From: Debora Rausch
Sent: 22 Feb 2018 14:43:47 +0000
To: Destefano, Frank (CDC/OID/NCEZID);Shimabukuro, Tom (CDC/OID/NCEZID);McNeil, Michael (CDC/OID/NCEZID);Weintraub, Eric (CDC/OID/NCEZID);Broder, Karen (CDC/OID/NCEZID);Wodi, Akpobome (CDC/OID/NCEZID);Harrington, Theresa (CDC/OID/NCEZID);Stanfill, Katherine (CDC/OID/NCEZID) (CTR);zqg1@cdc.gov;Grohskopf, Lisa A. (CDC/OID/NCIRD);Dooling, Kathleen L. (CDC/OID/NCIRD);Harpaz, Rafael (CDC/OID/NCIRD);Miller, Elaine R. (CDC/OID/NCEZID);Wharton, Melinda (CDC/OID/NCIRD);Cohn, Amanda (CDC/OID/NCIRD);dcn4@cdc.gov;nelson.jl@ghc.org;belongia.edward@marshfieldresearch.org;jackson.l@ghc.org;jackson.ml@ghc.org;ned.lewis@kp.org;Nicola.Klein@kp.org;kenneth.schmader@duke.edu;ktalaat@jhu.edu;Mary.Staat@cchmc.org;Elizabeth.Schlaudecker@cchmc.org;psl1@cumc.columbia.edu;aag1@cumc.columbia.edu;chip.walter@duke.edu;geeta.swamy@duke.edu;Neal Halsey
Cc: Cara Crumlish
Subject: GSK Presentation of Shingrix Post Licensure Safety Plans to CDC ISO and Partners (Presentation Attached)

Good Morning,
Please find attached the GSK Shingrix post-licensure safety monitoring presentation for tomorrow, Friday, February 23rd 2018 , 11 AM EST.
You should already have a calendar invite for this date and time.
In the event that you do not, please find the dial-in details below.
Please note, that we are required to conduct a quick attendance check concordant with already received CDAs.
To ensure a prompt start to the meeting, we would appreciate if participants begin to call in at 10:55 am.
Thank you,
Debora Rausch MD MA

Dial In Details

Name:	(b)(6)
Chairperson passcode:	
Participant passcode:	
GSK VPN number:	
USA toll (local dial-in):	
USA toll-free:	
UK toll (local dial-in):	
UK toll-free:	
Belgium (local dial-in):	
Belgium toll-free:	

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

From: Kuter, Barbara J.
Sent: 2 Nov 2015 17:47:07 -0500
To: Markowitz, Lauri (CDC/OID/NCIRD);Destefano, Frank (CDC/OID/NCEZID);Wharton, Melinda (CDC/OID/NCIRD)
Subject: HPV referral (EMA Article 20) - CRPS & POTS - CONFIDENTIAL

Lauri, Frank & Melinda,
I am sending this note to give you a heads-up that we are expecting a positive recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA/CHMP to conclude the referral that was conducted regarding the safety of HPV vaccines under Article 20. As you know, the PRAC was reviewing data on CRPS & POTS following HPV vaccination & it is our understanding that they have not found anything of concern. We have been informed that the PRAC is planning to have their Public Health Communication released to the public on Thursday, Nov 5th.
I will send along the notice as soon as it is received.
Please handle this information as CONFIDENTIAL until released.
Thanks.
Barb

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Sent: 2 Nov 2015 17:47:07 -0500
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I will send along the notice as soon as it is received.
Please handle this information as CONFIDENTIAL until released.
Thanks.
Barb

From: Kuter, Barbara J.
Sent: 5 Nov 2015 11:47:42 -0500
To: Markowitz, Lauri (CDC/OID/NCIRD);Destefano, Frank (CDC/OID/NCEZID);Wharton, Melinda (CDC/OID/NCIRD)
Subject: HPV referral (EMA Article 20) - Final Report on CRPS & POTS
Attachments: HPV - PRAC Final Report - CRPS & POTS - Nov 5, 2015.pdf

The PRAC has just issued a press release & final summary of the Article 20 referral related to CRPS & POTS and HPV vaccines.
The title of the summary report says "Review concludes evidence does not support that HPV vaccines cause CRPS or POTS.
Reports of CRPS and POTS after HPV vaccination are consistent with what would be expected in this age group."
Here is the link to the press release & a PDF of the actual report. Both can be found on the EMA/PRAC website.
http://www.ema.europa.eu/ema/index.jsp?
Barb

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 November 2015
EMA/714950/2015

Review concludes evidence does not support that HPV vaccines cause CRPS or POTS

Reports of CRPS and POTS after HPV vaccination are consistent with what would be expected in this age group

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a detailed scientific review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given human papillomavirus (HPV) vaccines. These vaccines are given to protect them from cervical cancer and other HPV-related cancers and pre-cancerous conditions. This review concluded that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil-9) and development of CRPS or POTS. Therefore there is no reason to change the way the vaccines are used or amend the current product information.

CRPS is a chronic pain syndrome affecting a limb, while POTS is a condition where the heart rate increases abnormally on sitting or standing up, together with symptoms such as dizziness, fainting and weakness, as well as headache, aches and pains, nausea and fatigue. In some patients they can severely affect the quality of life. The syndromes are recognised to occur in the general population, including adolescents, regardless of vaccination.

PRAC thoroughly reviewed the published research, data from clinical trials and reports of suspected side effects from patients and healthcare professionals, as well as data supplied by Member States. It also consulted a group of leading experts in the field, and took into account detailed information received from a number of patient groups that also highlighted the impact these syndromes can have on patients and families.

Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. However, available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. The review found no evidence that the overall rates of these syndromes in vaccinated girls were different from expected rates in these age groups, even taking into account possible underreporting. The PRAC noted that some symptoms of CRPS and POTS may overlap with chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME). Many of the reports considered in the review have features of CFS and some patients had diagnoses of both POTS and CFS. Results of a large published study that showed no link between HPV vaccine and CFS were therefore particularly relevant.

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

The PRAC concluded that the available evidence does not support that CRPS and POTS are caused by HPV vaccines. Therefore there is no reason to change the way the vaccines are used or amend the current product information.

The review recognised that more than 80 million girls and women worldwide have now received these vaccines, and in some European countries they have been given to 90% of the age group recommended for vaccination. Use of these vaccines is expected to prevent many cases of cervical cancer (cancer of the neck of the womb, which is responsible for tens of thousands of deaths in Europe each year) and various other cancers and conditions caused by HPV. The benefits of HPV vaccines therefore continue to outweigh their risks. The safety of these vaccines, as with all medicines, will continue to be carefully monitored.

The PRAC's recommendations will now be passed to the Committee for Medicinal Products for Human Use (CHMP) for adoption of the Agency's final position. The evidence supporting the PRAC review will be published in an assessment report following the CHMP opinion.

More about the medicine

HPV vaccines are available in the European Union under the names Gardasil/Silgard, Gardasil 9, and Cervarix. Gardasil has been authorised since September 2006, and is approved for use in males and females for preventing precancerous growths and cancer in the cervix and anus, and genital warts. It protects against 4 types of HPV (types 6, 11, 16 and 18). Gardasil 9 (approved in June 2015) is used similarly but protects against 9 types of the virus (types 6, 11, 16, 18, 31, 33, 45, 52 and 58). Cervarix has been approved since September 2007 for use in women and girls to protect against precancerous growths and cancer in the cervix and genital area. It is active against types 16 and 18 of the virus. Following their approval, the vaccines have been introduced in national immunisation programs in many countries. It is estimated that more than 63 million girls and women worldwide have been vaccinated with Gardasil/Silgard and more than 19 million with Cervarix.

More about the procedure

The review of HPV vaccines was initiated on 9 July 2015 by the European Commission at the request of Denmark, under Article 20 of Regulation (EC) No 726/2004.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. These PRAC recommendations will now be sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's final opinion. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.

Contact our press officer

Monika Benstetter

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.eu

From: Kuter, Barbara J.
Sent: 27 Mar 2014 11:37:43 -0400
To: Wharton, Melinda (CDC/OID/NCIRD);Destefano, Frank (CDC/OID/NCEZID)
Subject: HPV Vaccine - Japan
Attachments: 20140326 Eng MTPro.docx

Melinda and Frank,

We just received the attached English translation of a news item from Japan describing a preliminary study of patients with connective tissue disorder (rheumatoid arthritis and fibromyalgia) and their use of HPV vaccines. The information is based on a presentation made at a health seminar by a local investigator from the Japanese College of Fibromyalgia (JCFI), Tokyo Medical University. The JCFI has asked MHLW to conduct further research in this area.

We will be looking at our own pre & postlicensure safety data to address this question, but thought it would be helpful to find out if CDC has also been contacted to provide any data. Can you please tell me if you have looked at fibromyalgia in either VAERS or VSD or might be able to do so? We have not found any evaluation of this particular AE in the literature.

Any information you can share with us would be much appreciated.

Thanks.

Barb

Translation: MT Pro March 26, 2014

Pain after HPV vaccination caused by immune abnormalities in the brain – ASIA syndrome?

Japan College of Fibromyalgia Investigation conducts preliminary study

There are occasional reports of generalized pain similar to fibromyalgia mainly among junior and senior high school students in association with human papillomavirus (HPV) vaccination designed to prevent cervical cancer. At a health seminar held in Tokyo by the Japan Medical Research Foundation on March 23, Kusuki Nishioka, president of the Japan College of Fibromyalgia Investigation (JCFI) and director of Institute of Medical Science, Tokyo Medical University, said that the results of a preliminary study conducted by the JCFI indicate that the pain may be Autoimmune Syndrome induced by Adjuvants (ASIA), immune disorders in the brain induced by adjuvants that increase immune response after the vaccination. The JCFI announced that it will perform a full-scale study of HPV vaccine recipients.

Study finds immune disorder of anti-NMDA receptor antibodies

西岡 久寿樹 氏

Nishioka and the JCFI conducted a preliminary study of 96 patients with connective tissue diseases (89 females) including 12 cases of rheumatoid arthritis and 74 cases of fibromyalgia at three of 138 institutions in the JCFI network. Conducted between February 20 and March 20, the survey studied whether subjects have received the vaccination and whether they have adverse reactions. The results show that 55 among 96 patients have received HPV vaccination and 8 patients have suffered from unexplained generalized pain or severe arthritis after vaccination. Most of them were teenagers. While many of these patients sought medical attention suspecting fibromyalgia, pregabalin for the treatment of neuropathic pain was not effective in most cases.

One patient had positive tender points relating to juvenile fibromyalgia while no good result was attained with environmental isolate, which is considered effective. No abnormality was found in blood tests. Because the patient had auditory and visual hallucination, illusion, and personality disorder, physicians suspected acute encephalopathy. A detailed examination found significant increase in anti-N-methyl-D-aspartate receptor antibodies. The patient was diagnosed as having anti-NMDA receptor encephalitis under Shunpei Yokota, professor of pediatrics, Yokohama City University. The patient underwent steroid pulse therapy, which showed certain effect.

Nishioka further pointed out the possibility of ASIA, which shows symptoms such as severe muscle pain, arthritis, cognitive impairment, and sleeping disorder accompanied by neurological symptoms. The HPV vaccines contain aluminum and other materials as adjuvants to boost immune response. These new types of adjuvants may pass through blood-brain barrier using macrophage and cause autoimmune disorders in the brain.

At the end, Nishioka said that the JCFI had requested the Minister of Health, Labor and Welfare to conduct a survey after April to collect objective data on delayed adverse reactions that appear several months to several years after HPV vaccination as well as causal relationship with chronic pain and other symptoms.

According to Nishioka, Director-General of MHLW's Health Service Bureau visited him on March 24 to discuss various topics. He said that adverse reactions of the vaccination are not caused by mental factors and that it would be adequate to fully discontinue vaccination if any problem is found after serious investigations by the MHLW and relevant academic groups because there are quite a few reports of serious adverse reactions and there are many people who are suspicious about the benefit of the vaccination. Nishioka said that Director-General of Health Service Bureau indicated the intention to make reviews without delay.

From: Harry Seifert
Sent: 5 May 2015 13:49:19 +0000
To: McNeil, Michael (CDC/OID/NCEZID)
Cc: Destefano, Frank (CDC/OID/NCEZID);Brown, Harriet (CDC/OID/NCEZID);Jackson, Charla (CDC/ONDIEH/NCIPC);Roberts, Traci Sinetta (CDC/OID/NCEZID);Brown, Harriet (CDC/OID/NCEZID);Greg Powell
Subject: GSK presentation for May 7th ISO Hot Topics meeting

Dear Mike,
Attached is our PowerPoint presentation for Thursday's Hot Topics session. You are welcome to share these internally, but please regard the contents as proprietary and don't distribute them beyond the CDC.
I have included a conflict of interest slide. Our conflict of interest should be self-evident, but I ask that you please keep it in the presentation so there is no question about our transparency.
Looking forward to meeting with you and the team and hearing your thoughts.
Best regards,
Harry Seifert
Cell (b)(6)

From: Fernanda Tavares Da Silva
Sent: 18 Nov 2014 09:56:06 +0000
To: David Vaughn;Broder, Karen (CDC/OID/NCEZID);Valentina Attanasi;François P Roman;Destefano, Frank (CDC/OID/NCEZID);Gronostaj, Michael (CDC/OPHSS/CSELS/DSEPD);Clark, Thomas A. (CDC/ONDIEH/NCCDPHP)
Subject: RE: CDC-GSK Phase 3 and post-licensure PV
Attachments: CDC Ebola vaccine study - draft AEFI_Prevention Form 11 10 14-3pm1 dv+FT.docx

Dear Karen,
I also added a couple of comments for consideration.
Thanks!,
Best regards,
Fernanda

From: David Vaughn
Sent: Monday 17 November 2014 22:05
To: Broder, Karen (CDC/OID/NCEZID); Fernanda Tavares Da Silva; Valentina Attanasi; François P Roman; Destefano, Frank (CDC/OID/NCEZID); Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD)
Subject: RE: CDC-GSK Phase 3 and post-licensure PV

Karen,
See attached or two comments. Talk to you on Thursday. David.

From: Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
Sent: Friday, November 14, 2014 11:22 AM
To: David Vaughn; Fernanda Tavares Da Silva; Valentina Attanasi; François P Roman; Destefano, Frank (CDC/OID/NCEZID); Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD)
Subject: RE: CDC-GSK Phase 3 and post-licensure PV

David and Colleagues,
Here is the other draft AEFI prevention form. There is a section in yellow that would be good to update for accuracy re the GSK vaccine.
I am working on getting some schedule info from the CDC folks and will get back to David with some potential times for continued discussion.
Stay warm.
Thanks,
Karen

-----Original Appointment-----
From: David Vaughn [mailto:david.w.vaughn@gsk.com]
Sent: Friday, November 07, 2014 3:26 PM
To: David Vaughn; Fernanda Tavares Da Silva; Valentina Attanasi; François P Roman; Destefano, Frank (CDC/OID/NCEZID); Gronostaj, Michael (CDC/OID/NCEZID); Broder, Karen (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD)
Subject: CDC-GSK Phase 3 and post-licensure PV
When: Friday, November 14, 2014 10:00 AM-11:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: TC - see below

When: Friday, November 14, 2014 10:00 AM-11:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: TC - see below
Note: The GMT offset above does not reflect daylight saving time adjustments.
~~*~*~*~*~*~*~*~*~*

TC Details
Belgium Toll access n: (b)(6)
Belgium Toll-free access n: (b)(6)
Canada Toll access n: (b)(6)

Canada Toll-free access n: (b)(6)
US Toll-free access n: (b)(6)
Participant code: (b)(6)

Registered as GlaxoSmithKline Biologicals SA - Rue de l'Institut, (b)(6) Rixensart – TVA BE (b)(6) RPM Nivelles. Deutsche Bank AG Bruxelles (b)(6)

Ebola Candidate Vaccine Evaluation: Adverse Events Following Immunization (AEFI) Prevention Form -- DRAFT

AEFI	Description	Steps for Prevention/Immediate Management
Anaphylaxis	• Although anaphylaxis reactions are rare after vaccination their immediate onset (usually within minutes of vaccination) and life-threatening nature require all personnel and facilities providing vaccinations have procedures in place for anaphylaxis management. • Rapid recognition and initiation of treatment is needed to prevent possible progression to cardiovascular collapse. Symptoms include flushing, facial edema, urticaria, itching, swelling of mouth or throat, wheezing, dyspnea. Typically, the patient also has tachycardia; other symptoms may also occur. • Biphasic reactions where symptoms recur 8-12 hours after onset of the original attack may happen. • The Brighton Collaboration case definition for anaphylaxis should be consulted for a complete list of possible symptoms and signs of the condition, and subsequent review can ascertain if the case definition of anaphylaxis is met.	• If symptoms develop, the participant should be placed in recumbent position with legs elevated if possible. • Administration of intramuscular epinephrine is the treatment of choice. Intramuscular (IM) epinephrine should be kept readily accessible at location of vaccine administration • The expiry date of epinephrine should be checked before administering. It is important to note that health-care workers may misdiagnose a syncope attack as anaphylaxis and administer epinephrine as a part of emergency care. If the correct dose of epinephrine according to age and weight is administered via the IM route, no harm is likely to occur. • Particular attention should be paid to the maintenance of the participant's airway. • Participant should be referred for medical care.
Syncope (Fainting)	• Syncope (fainting, vasovagal reaction) can occur after vaccination and is most common among adolescents and young adults. • Of particular concern is the risk of serious secondary injuries from falling, including skull fracture and cerebral hemorrhage. • The patient may appear anxious and tense with pallor, and cool clammy diaphoresis, rapid breathing, normal or slow heart rate and be normo/hypotensive.	• The participant should be asked about history of fainting before vaccination. • All participants should be seated or lying down during vaccination. If patients have a history of fainting with shots or procedures consider vaccinating them lying down, ensure they are properly hydrated, and conduct closer observation. • All participants should be seated or lying down and observed for at least 15 minutes after vaccination.

Comment [FTDS]: Or clinical manifestations of shock including loss of consciousness

Comment [FTDS]: Vasovagal syncope

Comment [dwv]: Good that you do not need to be set up to treat cardiovascular collapse but only to prevent it with IM epi.

Comment [FTDS]: Difficulty in breathing or hyperventilation

Comment [FTDS]: Also limb jerking (often misinterpreted as a seizure or convulsion)

Ebola Candidate Vaccine Evaluation: Adverse Events Following Immunization (AEFI) Prevention Form -- DRAFT

AEFI	Description	Steps for Prevention/Immediate Management
Infections related to Injection	• Vaccine providers should follow appropriate precautions to minimize risk for injection site infections, self-injury and spread of disease. • Needles and syringes used for vaccination must be sterile and disposable. Infection at the injection site may be due to lack of awareness about proper injection protocol. • Vaccinator's careful attention to strict hand hygiene and skin disinfection prior to injection can prevent infection by skin colonizing bacteria (e.g., Staphylococcus aureus). Be sure to clean hands immediately before handling the medication. • Injection-site infections may also result because of improper reuse of single-dose vials which may contain slight excess of the vaccine following use for a single participant. Do not save leftover medication in them after use as harmful bacteria can grow and infect a participant. • Draw up vaccine in a clean medication preparation area. Read the vial label carefully before use and check the expiration date. • Vaccine vials for Ebola vaccine do not contain preservative. Follow the manufacturer recommended times for using the vaccine after it is thawed. These vials should not be used if at any time vial sterility is in question. Vaccine doses should not be drawn into a syringe until immediately before administration. Unused syringes filled by end user (not by the manufacturer) should be discarded at the end of the clinic day.	**Before the procedure** •Vaccinators should cleanse their hands with alcohol-based antiseptic hand rub or wash hands with soap and water before handling vaccine vials, preparing vaccine and between each participant contact. •Carefully read the label of the vaccine vial. •If vial says single use and has been accessed (needle punctured) throw it away. •If vial says multiple-dose, double check the expiration date and the beyond-use date if it was previously opened and visually inspect it to ensure no visible contamination. These vials should be discarded when the beyond-use date has been reached or at any time if the sterility of the vial is in question. Check the manufacturer instructions for use. •The injection site should be cleaned with soap and water or a single-use alcohol swab prior to injection to reduce risk of infection. **During and after the procedure** •Use aseptic technique. •A new needle and syringe should be used for each injection. •Disinfect the top of vaccine vial by rubbing the rubber stopper with alcohol. •Changing needles between drawing vaccine from the vial and injecting into the patient is not necessary unless the needle has been damaged or contaminated.

Comment [dwv]: Does "beyond-use date" refer to multi-use? Using after opened? If multi-dose may be a matter of hours rather than a date. TBD.

AEFI	Description	Steps for Prevention/Immediate Management
		• To prevent inadvertent needle-stick injury or reuse, used needles should not be recapped and needles and syringes should be discarded immediately in puncture-proof containers located in the same room where the vaccine is administered. Discard all used needles and syringes and single-use vials after the procedure is over. • Multiple-dose vials should be discarded when the beyond use date has been reached or any time vial sterility is in question.

References

1. Global manual on surveillance of adverse events following immunization. 2014. World Health Organization. Chapter 9. Actions and follow up to AEFI. http://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf?ua=1

2. CDC. General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices. MMWR 2011; 60: 1-62.

3. CDC. DHQP and One and Only Campaign Organization. One and only campaign for safe injection practices. at http://www.oneandonlycampaign.org/

4. Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, de Souza Brito G, Heininger U, Imoukhuede B, Khamesipour A, Erlewyn-Lajeunesse M, Martin S, Mäkelä M, Nell P, Pool V, Simpson N; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis and presentation of immunization safety data. Vaccine 2007; 25:5675-84. Also see https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions.html.

From: Francoise.Sillan@sanofipasteur.com
Sent: 19 Jun 2014 09:58:35 +0000
To: holmk@cioms.ch;maurec@who.int;Corinne.Jouquelet-Royer@sanofipasteur.com;Zuber, Patrick (CDC who.int);bergmanu@cioms.ch;(b)(6);Steven.R.Bailey@pfizer.com;Ayman.Ayoub@pfizer.com;Destefano, Frank (CDC/OID/NCEZID);novilia@biofarma.co.id;Harry.A.Seifert@gsk.com;Patricia.Mandali@anvisa.gov.br;ulrich.heininger@ukbb.ch;dongduo@cdr.gov.cn;Martin, David (FDA/CDER);KHGo@AIM.EDU;Dirk.Mentzer@pei.de;Doris.Oberle@pei.de;terhi.kilpi@thl.fi;Irina.Caplanusi@ema.europa.eu;Xavier.Kurz@ema.europa.eu
Cc: jiguete@who.int
Subject: RE: CIOMS TG2 Active Surv - Thursday, 19 June, 3pm
Attachments: TG2 TC June 19.pptx

Dear all
Please find enclosed the agenda for today's meeting and key elements of the business plan to guide our discussion
Thank you for your participation and talk to you soon!
Best regards / Bien cordialement,
Françoise

De : Holm Karin [mailto:holmk@cioms.ch]
Envoyé : lundi 16 juin 2014 15:36
À : 'MAURE, Christine'; Sillan, Francoise (sanofi pasteur); Jouquelet-Royer, Corinne (sanofi pasteur); Patrick Zuber (zuberp@who.int); Bergman Ulf;(b)(6)Bailey (Steven.R.Bailey@pfizer.com); Ayman.Ayoub@pfizer.com; fxd1@cdc.gov; Bachtiar (novilia@biofarma.co.id); Harry.A.Seifert@gsk.com; Patricia.Mandali@anvisa.gov.br; ulrich.heininger@ukbb.ch; dongduo@cdr.gov.cn; David.Martin@fda.hhs.gov; KHGo@AIM.EDU; Holm Karin; Dirk Mentzer; Oberle, Doris (alt2); 'Terhi Kilpi'; Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu); Xavier.Kurz@ema.europa.eu
Cc : JIGUET, Evelyn M. (jiguete@who.int)
Objet : CIOMS TG2 Active Surv - Thursday, 19 June, 3pm

Dear CIOMS TG2 Participants,
Please find the instructions below on how to join the teleconference call on THURSDAY, 19 JUNE, 3PM. (Thank you to WHO for arranging!)
Attached is the Arkadin list of toll-free or local numbers to call. NOTE! For participants from countries not listed in the attachment, they need to provide jiguete@who.int with the phone number at least 48 hours prior the call, and they will be connected through ARKADIN.
Attached also is the draft of the business plan for TG2 to discuss on the TC.
Thank you for your participation!
Karin

DIAL IN DETAILS:

-+-----+-----+-----+-----+-----+-----+-----+-----+-

JOIN AUDIO CONFERENCE:

Please open the attachment in order to find your international access toll free number.
Enter the participant PIN code:(b)(6) **followed by #**
It is recommended to mute your phone each time you're not speaking to avoid echo. For this purpose, please dial *1 to mute/unmute.

LIVE ASSISTANCE

Please first join the audio conference, then press ***0** to speak to an operator.

Please note: this conference may be recorded by the Moderator. By joining this meeting, you agree that your communication may be recorded at any time during the meeting..

More information at www.arkadin.com

Karin R. Holm
Publications Consultant, WG IX Risk Minimisation
Technical Coordinator, WG on Vaccine Safety
Council for International Organizations of Medical Sciences (CIOMS)
c/o WCC, P.O. Box 2100, CH-1211 Geneva 2, Switzerland
Phone: +41 22 791 6497 Website: www.cioms.ch
Email: holmk@cioms.ch
Associate partner of UNESCO
In official relations with WHO

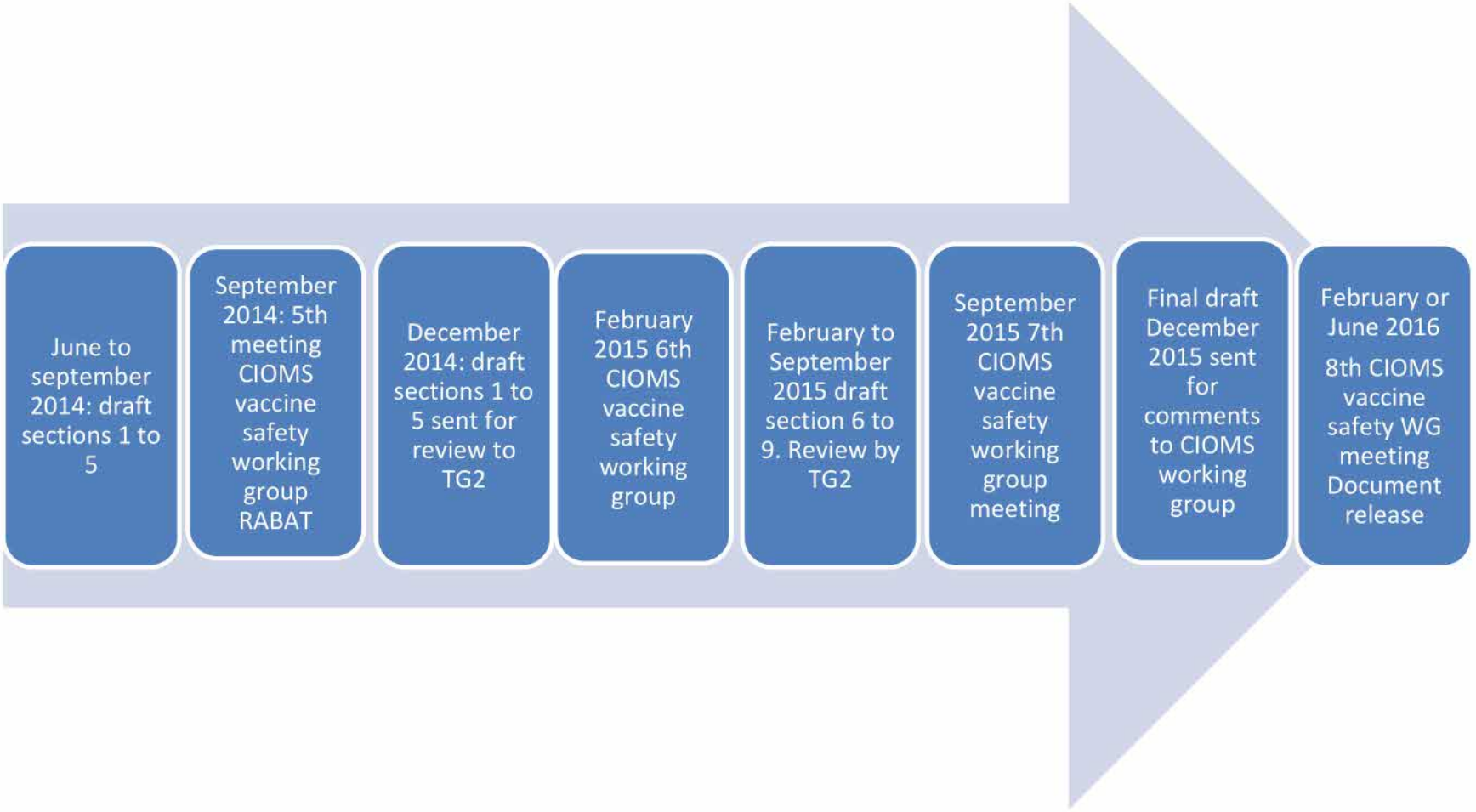
CIOMS VACCINE SAFETY WORKING GROUP

TOPIC GROUP 2Improvement of post marketing surveillance when launching a new vaccine in a LMIC

AGENDA

- Comments on draft business planReview of key stepsDefine leaders and contributors for sections 1 to 5

Key steps


June to september 2014: draft sections 1 to 5
September 2014: 5th meeting CIOMS vaccine safety working group RABAT
December 2014: draft sections 1 to 5 sent for review to TG2
February 2015 6th CIOMS vaccine safety working group
February to September 2015 draft section 6 to 9. Review by TG2
September 2015 7th CIOMS vaccine safety working group meeting
Final draft December 2015 sent for comments to CIOMS working group
February or June 2016
8th CIOMS vaccine safety WG meeting Document release

Key contributors sections 1 to 5

Section	Leader	Contributors
1-Glossary		
2-Abbreviations		
3-Purpose		
4-Post Marketing safety surveillance		
5-Establishing active safety surevillance		

From: Francoise.Sillan@sanofipasteur.com
Sent: 20 Jan 2014 10:41:31 +0000
To:
holmk@cioms.ch;(b)(6) alex.dodoo@umcafrica.org;owdena@cioms.ch;(b)(6) (b)(6) fr;Ayman.Ayoub@pfizer.com;William.Gregory@pfizer.com;Brigitte.Keller-Stanislawski@pei.de;maurec@who.int;Vellozzi, Claudia (CDC/OID/NCHHSTP);Martin, David (FDA/CDER);(b)(6) ;Dirk.Mentzer@pei.de;Destefano, Frank (CDC/OID/NCEZID);sjolinforsbergg@cioms.ch;Harry.A.Seifert@gsk.com;j.bonhoeffer@brightoncollaboration.org;KHGo@AIM.EDU;mceuppe1@its.jnj.com;Marie.Lindquist@who-umc.org;PatelMayur@MedImmune.com;BlumM@medimmune.com;(b)(6) (b)(6) novilia@biofarma.co.id;Patricia.Mandali@anvisa.gov.br;Zuber, Patrick (CDC who.int);Paulo.santos@bio.fiocruz.br;Peter.Arlett@ema.europa.eu;drpsk@seruminstitute.com;(b)(6) rroten@its.jnj.com;Rmenezes@bio.fiocruz.br;sidarta.silva@anvisa.gov.br;sten.olsson@who-umc.org;Steven.R.Bailey@pfizer.com;terhi.kilpi@thl.fi;ulrich.heininger@ukbb.ch;Xavier.Kurz@ema.europa.eu
Cc: Sabine.Garnier@sanofipasteur.com
Subject: RE: CIOMS vaccine safety TG2 surveillance TC 20Jan 2 to 4pm (French time)

Dear all
Please find enclosed the web link to the intercall service for more instructions.
If you don't find instructions for your country, you can call the phone number of the nearest country or let me know if there is a phone number were we can call you
http://www.intercall.com/sanofi/numbers/index.htm
I copy our assistant, Sabine, who will help me in the organization.
Talk to you soon,
Best regards / Bien cordialement,
Françoise

De : Holm Karin [mailto:holmk@cioms.ch]
Envoyé : lundi 20 janvier 2014 11:19
À : 'Alex Dodoo '; 'Alex Dodoo UMC'; Owden Amanda; 'Amina Tebaa '; Ayman.Ayoub@pfizer.com; 'Bill Gregory'; 'Brigitte Keller-Stanislawski'; 'Christine Maure (alt)'; 'Claudia Vellozzi '; 'David Martin '; 'Dawei, Liu'; Dirk Mentzer; Sillan, Francoise (sanofi pasteur); 'Frank DeStefano (alt)'; Sjolin_Forsberg Gunilla; 'Harry Seifert (alt)'; Holm Karin; 'Jan Bonhoeffer (alt)'; 'Kenneth Y. Hartigan-Go'; 'Marc Ceuppens '; 'Marie Lindquist '; 'Mayur Patel (alt)'; 'Michael Blum '; 'Mimi Darko Delese (alt)'; 'Mona Hassan Abu Youssef '; 'Novilia Sjafri Bachtiar'; 'Patricia Mandali de Figueiredo'; 'Patrick Zuber '; 'Paulo Gomes dos Santos (alt) '; 'Peter Arlett (alt)'; 'Prasad Kulkarni'; 'Raja Benkirane (alt)'; 'Raphaele Roten'; 'Reinaldo de Menezes Martins '; Silva Sidarta (sidarta.silva@anvisa.gov.br); 'Sten Olsson (alt)'; 'Steven Bailey'; 'Terhi Kilpi'; 'Ulrich Heininger '; 'Xavier Kurz '
Objet : CIOMS vaccine safety TG2 surveillance TC 20Jan 2 to 4pm (French time)

Dear WG members,
If you are interested in participating in the TC for Topic Group2 Surveillance Strategy, you are most welcome. Attached find the free or local call numbers. The participant's code will be: (b)(6) Thank you to Sanofi-Pasteur for sponsoring the TC.
Karin
The TC for Topic Group 2 will be on January 20 from 2 to 4 pm (French time); I send you enclosed the call numbers, the participant's code will be:(b)(6) Let me know the final list of participants and I will send the invitation.

Thank you,
Best regards / Bien cordialement,
Françoise

Topic Group 2: Surveillance Strategy

Leads: Françoise Sillan & Mimi Darko Delese
TC: Monday, January 20, 2:00pm Central European Time

Including: Amina Tebaa, Mona Youssef, Patrick Zuber, Harry Siefert, Christine Maure (alt), Novilia Bachtiar, Claudia Vellozzi, Alex Dodoo, Frank DeStefano (alt), Steven Bailey (alt), Bill Gregory, Harry Siefert (alt), David Martin, Michael Nguyen (alt)

Reps: Moroccan Centre PhV, EgyptVac, WHO, GSKBio, PT Bio Farma Indonesia, CDC, Ghana FDA,US FDA, GSKBio, Pfizer

Possible topics to discuss…

- Spontaneous reporting system improvements and post-marketing surveillance study: necessity to implement for new vaccines.
- Identification of new products and subsequent vaccine safety issues that will be generated when certain products are distributed for the first time in LMICs: a.)Spontaneous reporting system improvements, b.) Cohort Event Monitoring.
- CIOMS WG should define minimum capacity for post marketing surveillance.

From: Holm Karin
Sent: 5 Jul 2014 19:37:12 +0000
To: Jouquelet-Royer, Corinne;Harry.A.Seifert@gsk.com;Zuber, Patrick (CDC who.int);maurec@who.int;Winiecki, Scott (FDA/CDER);terhi.kilpi@thl.fi;Bachtiar (novilia@biofarma.co.id);Destefano, Frank (CDC/OID/NCEZID);Dawei, Liu (liudw929@126.com);Xavier.Kurz@ema.europa.eu;Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu);Martin, David (FDA/CDER);Bergman Ulf;Bailey (Steven.R.Bailey@pfizer.com);dongduo@cdr.gov.cn;Blum, Michael (BlumM@MedImmune.com)
Cc: Francoise.Sillan@sanofipasteur.com;Darko, Mimi (mimidarko66@yahoo.co.uk)
Subject: RE: CIOMS WG on VS TG2 chapter 5
Attachments: TG2 TC Section 5 June 27_kh.pptx

Dear Contributors to TG2 Chapter 5,
Additional contributors are needed, especially for section 5.2 and 5.4 --- for the later the public sector is key actor and also a regulator.
For the next TC, I am sending a doodle poll for 1.5 hour on the 8 , 9 or 10 of September in the afternoon.
Please note that Corinne and Harry need your drafts by September 3.
Please note that I am on vacation 7-28 July with only limited access to computers.
Best regards,
Karin

Karin R. Holm
Publications Consultant, WG IX Risk Minimisation
Technical Coordinator, WG on Vaccine Safety
Council for International Organizations of Medical Sciences (CIOMS)
Associate partner of UNESCO and in official relations with WHO
c/o WCC, P.O. Box 2100, CH-1211 Geneva 2, Switzerland
Ofc Phone: +41 22 791 6497 Website: www.cioms.ch
Email: holmk@cioms.ch

From: Holm Karin
Sent: 05 July 2014 21:33
To: Jouquelet-Royer, Corinne; Harry.A.Seifert@gsk.com; Patrick Zuber (zuberp@who.int); maurec@who.int; Winiecki, Scott; terhi.kilpi@thl.fi; Bachtiar (novilia@biofarma.co.id); fxd1@cdc.gov; Dawei, Liu (liudw929@126.com); Xavier.Kurz@ema.europa.eu; Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu); David.Martin@fda.hhs.gov; Bergman Ulf; Bailey (Steven.R.Bailey@pfizer.com); dongduo@cdr.gov.cn; Blum, Michael (BlumM@MedImmune.com)
Cc: Francoise.Sillan@sanofipasteur.com; Darko, Mimi (mimidarko66@yahoo.co.uk)
Subject: RE: CIOMS WG on VS TG2 chapter 5

Dear Contributors to TG2 Chapter 5,

Karin R. Holm
Publications Consultant, WG IX Risk Minimisation
Technical Coordinator, WG on Vaccine Safety
Council for International Organizations of Medical Sciences (CIOMS)
Associate partner of UNESCO and in official relations with WHO
c/o WCC, P.O. Box 2100, CH-1211 Geneva 2, Switzerland
Ofc Phone: +41 22 791 6497 Website: www.cioms.ch
Email: holmk@cioms.ch

From: Holm Karin
Sent: 24 June 2014 11:36
To: Jouquelet-Royer, Corinne; Harry.A.Seifert@gsk.com; Patrick Zuber (zuberp@who.int); maurec@who.int; Winiecki, Scott; terhi.kilpi@thl.fi; Bachtiar (novilia@biofarma.co.id); fxd1@cdc.gov; Dawei, Liu ((b)(6)); Xavier.Kurz@ema.europa.eu; Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu); David.Martin@fda.hhs.gov; Bergman Ulf; Bailey (Steven.R.Bailey@pfizer.com)
Cc: Francoise.Sillan@sanofipasteur.com; Darko, Mimi ((b)(6))
Subject: CIOMS WG on VS TG2 section 5 - Fri 27 June 12noon (French time)

Dear CIOMS TG2 Chapter 5 Contributors,
Corinne Jouquelet-Royer (Sanofi, who is new to the CIOMS WG but will eventually take over at some point in the future for Françoise, who is moving to a new area at Sanofi) and Harry Seifert (GSK) kindly offered to organize Chapter 5 of the Manual on Active Safety Surveillance. Ch.5 is the "meat of the manual" on Establishing Active Surveillance (see Table of Contents in business plan draft attached).
The best day/time was this Friday, 27 June, 12pm French time. Sanofi kindly will arrange TC and send instructions on how to access.
Agenda for TC

- Quick review of the section 5 to get alignment and shared understanding on what need to be achieved
- Agree on contributors to which sections
- And timelines for draft and reviews before September meeting

	June 2014
	Fri 27
	12:00 PM
Karin Holm	NO
corinne jouquelet royer	OK
Harry Seifert	OK
Patrick Zuber	OK
Christine Maure	OK
Scott Winiecki (FDA)	OK
Frank DeStefano	NO
Terhi Kilpi	OK
Novilia Sjafri Bachtiar	OK
Xavier Kurz	OK
Dawei Liu	?
Irina Caplanusi	?
David Martin	?
Steven Bailey	?
Ulf Bergman	NO
Count	8

Karin R. Holm
Technical Coordinator, Working Group on Vaccine Safety
Publications Consultant, Working Group IX Risk Minimization
Council for International Organizations of Medical Sciences (CIOMS)
Associate partner of UNESCO / In official relations with WHO
c/o WCC, P.O. Box 2100, CH-1211 Geneva 2, Switzerland

Phone: +41 22 791 6497 Website: www.cioms.ch
Email: holmk@cioms.ch

From: Holm Karin
Sent: 23 June 2014 16:05
To: 'Dawei, Liu (liudw929@126.com)'; 'Bachtiar (novilia@biofarma.co.id)'; 'Xavier.Kurz@ema.europa.eu'; 'Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu)'; 'David.Martin@fda.hhs.gov'; 'terhi.kilpi@thl.fi'; Bergman Ulf
Cc: 'Jouquelet-Royer, Corinne'; 'Francoise.Sillan@sanofipasteur.com'; 'Darko, Mimi (mimidarko66@yahoo.co.uk)'
Subject: RE: Doodle: Link for poll "CIOMS WG on VS TG2 section 5"

Dear Dawei Liu, Novi, Xavier, Irina, David, Terhi, Ulf…

We haven't yet heard from you if you are available at these times and we are trying to find the best time for a TC to work on Section 5 of the Manual on Active Safety Surveillance….

Hi, CIOMS WG on VS - TG2 Active Surveillance section 5
Corinne Jouquelet-Royer and Harry Seifert would like to have a TC to start the process moving on drafting section 5. Please let us know if you would be available any of these times by clicking on this doodle poll...
http://doodle.com/b6z8aicfaia92fbt
Thank you,
Karin

Most popular date: Friday, June 27, 2014 12:00 PM |

Top of Form

	June 2014	July 2014	
7 participants	**Fri 27 12:00 PM**	**Tue 1 5:00 PM**	**Wed 2 6:00 PM**
Karin Holm		✓	
corinne jouquelet royer	✓	✓	✓
Harry Seifert	✓	✓	✓
Patrick Zuber	✓		
Christine Maure	✓		
Scott Winiecki	✓		✓
Frank DeStefano			
	Friday, June 27, 2014 12:00 PM	Tuesday, July 1, 2014 5:00 PM	Wednesday, July 2, 2014 6:00 PM

Bottom of Form

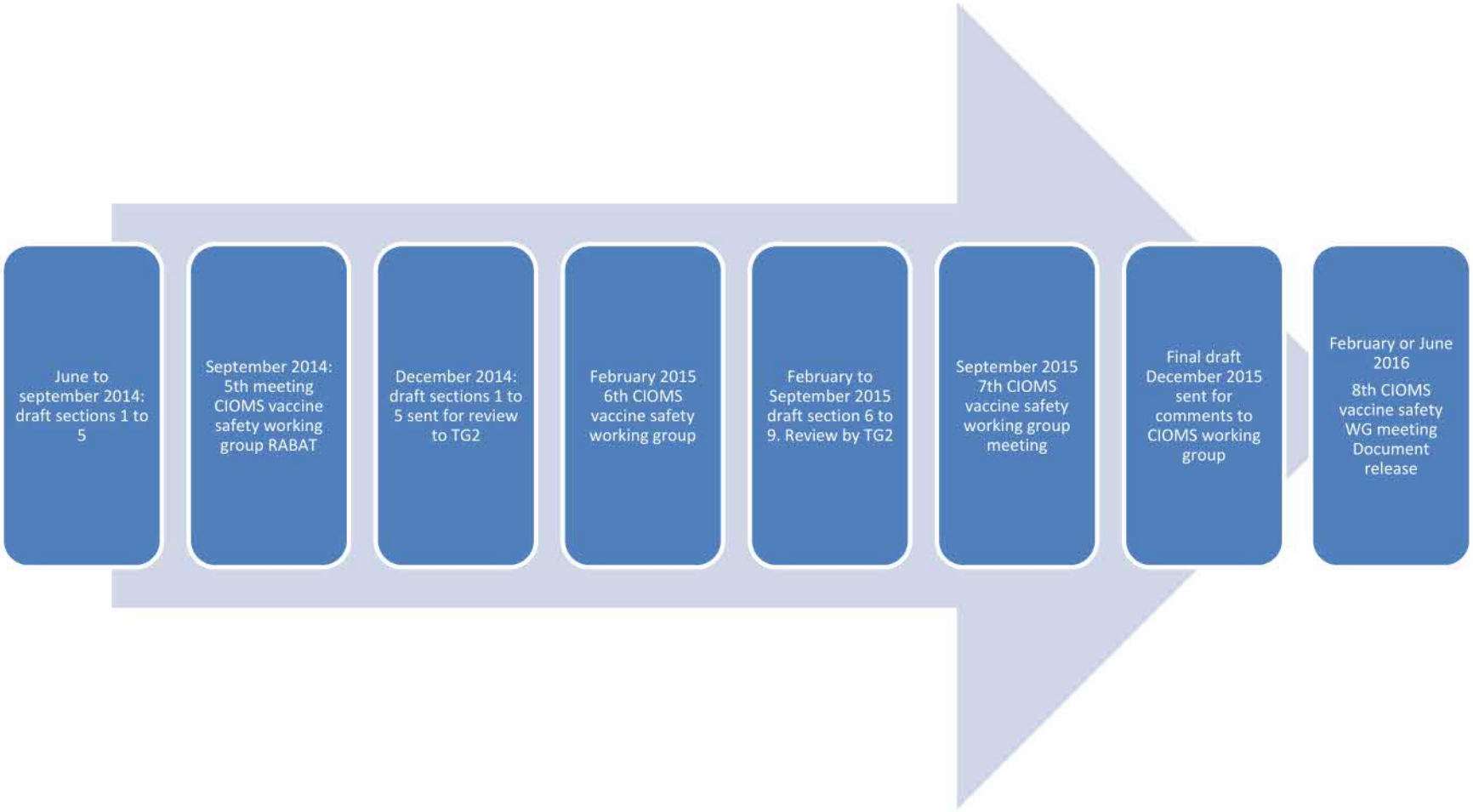
CIOMS VACCINE SAFETY WORKING GROUP

TOPIC GROUP 2Development of section 527 June 2014

AGENDA

- Review of the section 5 to get alignment and shared understanding on what need to be achieved Agree on contributors to which sections.Agree on How we will work together? And timelines for draft and reviews before September meeting

Key steps


June to september 2014: draft sections 1 to 5
September 2014: 5th meeting CIOMS vaccine safety working group RABAT
December 2014: draft sections 1 to 5 sent for review to TG2
February 2015 6th CIOMS vaccine safety working group
February to September 2015 draft section 6 to 9. Review by TG2
September 2015 7th CIOMS vaccine safety working group meeting
Final draft December 2015 sent for comments to CIOMS working group
February or June 2016
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Actions from Last Meetings

- Idea to add examples of successful and unsuccessful active surveillance systems throughout the text (not just in section 10). Suggestion to add a literature search for additional examples.Some examples at GAVCS included studies conducted in northern Ghana and India.Although example are essential to illustrate the topics, it is critical to provide as well clear criteria to set up and conduct active surveillance systems. This is what has been done in preparation of malaria vaccine introduction. Choose also examples of not successful active surveillanceSomething about MeninAfriVac seemed population-based but turned out to be case finding from sentinel sites (?)The links proposed to be provided (see section 3-Strategy of the Business plan) in the document should be accompanied by explanation.Think about the involvement of external experts at the time of the review of the draft document (additional funds needed).

List of volunteers

- Leaders : Harry Seifert , Corinne Jouquelet-Royer ContributorsDawei LiuNovilia BachtiarXavier Kurtz & Irina CaplanusiDavid Martin and Scott WinieckiFrank DestefanoTerhi Kilpi Other interested: Michael Blum, Stephen Bailey, Ayman Ayoub, Dong Duo

Section 5 Overview

Section & Sub sections	Key Content	Contributors	Action Items
5.1 . Rationale for ASS (fomer a)	• Need to define the scope	DavidXavier	• Reach out to section 4 leader End of July / Beginning Aug
5.2. Points to consider for setting up a ASS (former c, b, d)	1. Who ? When?Where?	1. NoviliaWHO representative (TBC) and FrancoiseTBC ???	
5.3 How (e) including examples	How?	Tehri	
5.4. Governance	Oversight of studyGovernance on decision making	Corinne WHO representative?	

Next steps

- Literature search : propose key words and ask the library (Sanofipasteur) : W 28 Corinne to circulate updated slides to people who did not attend and ask for additional contributors Scope of ASS: will be shared by Xavier and David end July early August First draft to be sent to Harry and Co by Week 36 (Sept 3) . Harry and Co to collate a doc for reveiw TC for review of comments on Week 37

From: Corinne.Jouquelet-Royer@sanofipasteur.com
Sent: 31 Jul 2014 09:16:17 +0000
To: holmk@cioms.ch;Harry.A.Seifert@gsk.com;Zuber, Patrick (CDC who.int);maurec@who.int;Winiecki, Scott (FDA/CDER);terhi.kilpi@thl.fi;novilia@biofarma.co.id;Destefano, Frank (CDC/OID/NCEZID);(b)(6) Xavier.Kurz@ema.europa.eu;Irina.Caplanusi@ema.europa.eu;Martin, David (FDA/CDER);bergmanu@cioms.ch;Steven.R.Bailey@pfizer.com;dongduo@cdr.gov.cn;BlumM@MedImmune.com
Cc: Francoise.Sillan@sanofipasteur.com;(b)(6)
Subject: RE: CIOMS WG on VS TG2 chapter 5
Attachments: Safety surveillance Literature search July 2014.docx

Dear all,
As agree you will find attached the result of the literature search. The search criteria included:
Pharmacovigilance
Safety . side effects. Adverse events
Monitoring
Post marketing
Observational study
Vaccine
Surveillance, active surveillance , passive surveillance
Network
LMIC (Low Middle Income Countries)
Feel free to add any reference when writing your section.
Kind regards
Co

From: Holm Karin [mailto:holmk@cioms.ch]
Sent: samedi 5 juillet 2014 21:37
To: Jouquelet-Royer, Corinne (sanofi pasteur); Harry.A.Seifert@gsk.com; Patrick Zuber (zuberp@who.int); maurec@who.int; Winiecki, Scott; terhi.kilpi@thl.fi; Bachtiar (novilia@biofarma.co.id); fxd1@cdc.gov; Dawei, Liu (b)(6) Xavier.Kurz@ema.europa.eu; Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu); David.Martin@fda.hhs.gov; Bergman Ulf; Bailey (Steven.R.Bailey@pfizer.com); dongduo@cdr.gov.cn; Blum, Michael (BlumM@MedImmune.com)
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corinne jouquelet royer	OK
Harry Seifert	OK
Patrick Zuber	OK
Christine Maure	OK

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Frank DeStefano	NO
Terhi Kilpi	OK
Novilia Sjafri Bachtiar	OK
Xavier Kurz	OK
Dawei Liu	?
Irina Caplanusi	?
David Martin	?
Steven Bailey	?
Ulf Bergman	NO
Count	8

Karin R. Holm
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Publications Consultant, Working Group IX Risk Minimization
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Email: holmk@cioms.ch

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http://doodle.com/b6z8aicfaia92fbt
Thank you,
Karin

Most popular date: Friday, June 27, 2014 12:00 PM |

Top of Form

	June 2014	July 2014	
7 participants	**Fri 27 12:00 PM**	**Tue 1 5:00 PM**	**Wed 2 6:00 PM**
Karin Holm		✓	
corinne jouquelet royer	✓	✓	✓
Harry Seifert	✓	✓	✓
Patrick Zuber	✓		
Christine Maure	✓		

Scott Winiecki	✓		✓
Frank DeStefano			
	Friday, June 27, 2014 12:00 PM	Tuesday, July 1, 2014 5:00 PM	Wednesday, July 2, 2014 6:00 PM

Bottom of Form

To:	Françoise Sillan, Corinne Jouquelet-Royer	**From:**	Anne-Céline Eydan
Request date:	July 8, 2014	Delivery date: July 23, 2014	

Subject: Safety surveillance: Observational Studies

Search strategy

Embase Session Results (23 Jul 2014)

No.	Query
#6	#1 AND #5
#5	'vaccine'/exp/dd_ae
#1	'observational study'/exp

Contenu

Low & Middle Income Countries

Children who received PCV-10 vaccine from a two-dose vial without preservative are not more likely to develop injection site abscess compared with those who received pentavalent (DPT-HepB-Hib) vaccine: A longitudinal multi-site study

Berhane Y., Worku A., Demissie M., Tesfaye N., Asefa N., Aniemaw W., Weldearegawi B., Kebede Y., Shiferaw T., Worku A., Olijira L., Merdekios B., Ashebir Y., Tadesse T., Dessie Y., Meseret S., Ayele G.
PLoS ONE 2014 9:6 Article Number e97376
Go to publisher for the full text

Background: The single dose pneumonia ten-valent vaccine has been widely used and is highly efficacious against selected strains Streptococcus pneumonia. A two-dose vial without preservative is being introduced in developing countries to reduce the cost of the vaccine. In routine settings improper immunization practice could result in microbial contamination leading to adverse events following immunization. Objective: To monitor adverse events following immunization recommended for routine administration during infancy by comparing the rate of injection-site abscess between children who received PCV-10 vaccine and children who received the Pentavalent (DPT-HepB-Hib) vaccine. Methods: A longitudinal population-based multi-site observational study was conducted between September 2011 and October 2012. The study was conducted in four existing Health and Demographic Surveillance sites run by public universities of Abraminch, Haramaya, Gondar and Mekelle. Adverse events following Immunization were monitored by trained data collectors. Children were identified at the time of vaccination and followed at home at 48 hour and 7 day following immunization. Incidence of abscess and relative risk with the corresponding 95% Confidence Intervals were calculated to examine the risk

difference in the comparison groups. Results: A total of 55, 268 PCV and 37, 480 Pentavalent (DPT-HepB-Hib) vaccinations were observed. A total of 19 adverse events following immunization, 10 abscesses and 9 deaths, were observed during the one year study period. The risk of developing abscess was not statistically different between children who received PCV-10 vaccine and those received Pentavalent (RR = 2.7, 95% CI 0.576-12.770), and between children who received the first aliquot of PCV and those received the second aliquot of PCV (RR = 1.72, 95% CI 0.485-6.091). Conclusion: No significant increase in the risk of injection site abscess was observed between the injection sites of PCV-10 vaccine from a two-dose vial without preservative and pentavalent (DPT-HepB-Hib) vaccine in the first 7 days following vaccination. © 2014 Berhane et al.

A prospective observational safety study on MF59® adjuvanted cell culture-derived vaccine, Celtura® during the A/H1N1 (2009) influenza pandemic

Reynales H., Astudillo P., de Vallière S., Hatz C., Schlagenhauf P., Rath B., Velentgas P., Fariña A., Sales-Carmona V., Groth N.

Vaccine 2012 **30:45** (6436-6443)

Go to publisher for the full text

Background: The present study was a prospective observational study to evaluate the safety profile of Celtura®, a monovalent, cell culture-derived, inactivated subunit influenza vaccine prepared from A/California/07/2009(H1N1) with the adjuvant MF59®. Subjects were enrolled prospectively during the H1N1 2009 influenza pandemic at medical centres in **Colombia, Chile, Switzerland, and Germany** during the period December 2009 to June 2010. Methods: Subjects ages 18 and older were followed for the occurrence of adverse events (AEs) for six months after vaccination. Adverse events of special interest (AESIs) were neuritis, convulsion (seizure), anaphylaxis, encephalitis, vasculitis, Guillain-Barre syndrome, demyelinating conditions, Bell's palsy, and laboratory-confirmed vaccination failure. Results: Overall, 7348 AEs were reported in 2296 of 3989 enrolled subjects (57.6%). Only two AEs were considered related to injection site reactions. No laboratory-confirmed cases of influenza were reported. There were 108 medically confirmed serious adverse events (SAEs) reported among 73 subjects with 6 such SAEs described as possibly or probably related to vaccination. Three fatal cases were reported and assessed as not related to vaccination. Two AESIs classified as convulsion were reported and assessed as not related to vaccination. Both AESIs occurred well outside the pre-specified 7 day risk window representing the likely timeframe of the occurrence of seizure following vaccination. Conclusions: The results of this study support the overall good safety profile of MF59 adjuvanted cell culture-derived influenza vaccine as administered in adults during the 2009-2010 H1N1 influenza pandemic. No concern is raised regarding the occurrence of AESIs. © 2012 Elsevier Ltd.

Safety observation of influenza a H1N1 influenza vaccine vaccinations in 3300 medical workers

He X.-L., Kang S.-Q., Gong C.-Y., Jiang G.-Y.

Chinese Journal of Evidence-Based Medicine 2010 **10:4** (441-443)

Objective: To investigate safety of influenza A H1N1 vaccine vaccinations. Methods: A total of 3 300 medical workers were vaccinated by batch of 200909012 influenza A H1N1 vaccine produced by Shanghai Biological Products Corporation Limited according to the principle of voluntary and concentration. The adverse reactions were observed within half an hour, three days and a week after vaccinations, respectively. Results: The inoculators with local or systemic reaction reached 1.18% (39/3 300). There were 0.15% (5/3 300) of the inoculators with adverse reaction within half an hour; 0.70% (23/3 300) within 1 to 3 days after vaccination; and 0.33% (11/3 300) within 3 days to 1 week after vaccination. No severe adverse events were found. Conclusion: Influenza A H1N1 vaccine vaccinations is an economic and effective way of influenza A H1N1 prevention with mild reactions. © 2010 Editorial Board of Chin J Evid-based Med.

Active assessment of adverse events following yellow fever vaccination of persons aged 60 years and more

Miyaji K.T., Luiz A.M., Lara A.N., Chaves T.D.S.S., Piorelli R.D.O., Lopes M.H., Sartori A.M.C.

Human Vaccines and Immunotherapeutics 2013 **9:2** (277-282)

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Introduction: Older age has been associated to serious adverse events (AE) following yellow fever (YF) vaccination in passive surveillance studies, but few prospective studies involving seniors have been published. Results: Nine hundred and six persons were evaluated; 78 were not vaccinated and 828 received the vaccine; 700 (84.7%) were interviewed after vaccination: 593 (84.7%) did not report any symptoms or signs following YF vaccine; 107 (15.3%) reported at least one AE temporally associated to YF vaccination: 97 (13.9%) had systemic AE and 17 (2.4%) reported AE at the injection site (7 had both systemic and local AE). Data regarding previous vaccination was available for 655 subjects. Statistically significant higher rates of systemic AE were observed among subjects who received the first YF vaccination (17.5%) in comparison to persons who had been previously vaccinated (9.5%). Methods: This observational prospective study aimed to describe AE following YF vaccination in persons aged ≥ 60 y. From March 2009 to April 2010, seniors who sought YF vaccination at a reference Immunization Center in **Sao Paulo city, c Brazi**l, were included. Demographic and clinical data, previous YF vaccination, travel destination and the final decision regarding YF vaccination or not were collected from standardized medical records. Active AE assessment was done through telephone or electronic mail interview performed approximately 14 d after immunization. Conclusion: Most persons aged ≥ 60 y may be safely vaccinated against YF. Before vaccination, they must be carefully screened for conditions associated to altered immunocompetence and for risk of exposure to YF. © 2013 Landes Bioscience.

Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil™ in adult women

Luna J., Plata M., Gonzalez M., Correa A., Maldonado I., Nossa C., Radley D., Vuocolo S., Haupt R.M., Saah A.

PLoS ONE 2013 **8:12** Article Number e83431

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Background: Previous analyses from a randomized trial in women aged 24-45 have shown the quadrivalent HPV vaccine to be efficacious in the prevention of infection, cervical intraepithelial neoplasia (CIN) and external genital lesions (EGL) related to HPV 6/11/16/18 through 4 years. In this report we present long term follow-up data on the efficacy, safety and immunogenicity of the quadrivalent HPV vaccine in adult women. Methods: Follow-up data are from a study being conducted in 5 sites in **Colombia** designed to evaluate the long-term immunogenicity, effectiveness, and safety of the qHPV vaccine in women who were vaccinated at 24 to 45 years of age (in the original vaccine group during the base study [n = 684]) or 29 to 50 years of age (in the original placebo group during the base study [n = 651]). This analysis summarizes data collected as of the year 6 post-vaccination visit relative to day 1 of the base study (median follow-up of 6.26 years) from both the original base study and the Colombian follow-up. Results: There were no cases of HPV 6/11/16/18-related CIN or EGL during the extended follow-up phase in the per-protocol population. Immunogenicity persists against vaccine-related HPV types, and no evidence of HPV type replacement has been observed. No new serious adverse experiences have been reported. Conclusions: Vaccination with qHPV vaccine provides generally safe and effective protection from HPV 6-, 11-, 16-, and 18-related genital warts and cervical dysplasia through 6 years following administration to 24-45 year-old women. Trial Registration: Clinicaltrials.gov NCT00090220 © 2013 Luna et al.

Post-authorization safety surveillance of a liquid pentavalent vaccine in Guatemalan children

Asturias E.J., Contreras-Roldan I.L., Ram M., Garcia-Melgar A.J., Morales-Oquendo V., Hartman K., Rauscher M., Moulton L.H., Halsey N.A.

Vaccine 2013 **31:49** (5909-5914)

Go to publisher for the full text

Objective: Combination vaccines have improved the efficiency of delivery of new vaccines in low and middle-income countries. Post-authorization monitoring of adverse events (AEs) after vaccination with a liquid pentavalent DTwP-HepB-Hib combination vaccine was conducted in Guatemalan infants. Methods: A prospective observational safety study of the incidence of medical attended events (MAEs) and serious adverse events (SAEs) in children who received pentavalent and oral polio vaccines at 2, 4 and 6 months of age was conducted in two clinics at the Institute of Guatemala. Parents were contacted by telephone after each dose. All outpatient, emergency department visits, and hospitalizations were monitored. A self-controlled analysis was conducted to determine if there was evidence of increased risk of MAEs or SAEs following vaccines as compared to control time windows. Results: Of 3000 recruited infants, 2812 (93.7%) completed the third dose and 2805 (93.5%) completed follow-up. Ten AEs in eight infants, of which four SAEs in four infants, were classified as related to the vaccine. Thirteen deaths were reported due to

common illnesses of infancy, and none were judged to be related to the vaccine. The mortality rate (4.4 per 1000) was lower than expected for the population. The incidence-rate-ratio for healthcare visits was lower in post-vaccination time windows than for control windows; after the first vaccine dose, the rate ratios for the risk periods of 0-1, 2-6, and 7-30 days post-vaccination were 0.3, 0.5, and 0.7, respectively (all statistically significantly different from the reference value of 1.0 for the 31-60 day control period). Conclusion: The liquid pentavalent vaccine was associated with lower rates of health care visits and not associated with increases in SAEs or hospitalizations. Systems can be set up in low to middle income countries to capture all health care visits to monitor the safety of new vaccines. © 2013 Elsevier Ltd.

Long-term follow-up of study participants from prophylactic HIV vaccine clinical trials in Africa

Schmidt C., Jaoko W., Omosa-Manyonyi G., Kaleebu P., Mpendo J., Nanvubya A., Karita E., Bayingana R., Bekker L.-G., Chomba E., Kilembe W., Nchabeleng M., Nyombayire J., Stevens G., Chetty P., Lehrman J., Cox J., Allen S., Dally L., Smith C., Fast P.E.

Human Vaccines and Immunotherapeutics 2014 **10:3** (714-723)

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Long-term safety is critical for the development and later use of a vaccine to prevent HIV/AIDS. Likewise, the persistence of vaccine-induced antibodies and their impact on HIV testing must be established. IAVI has sponsored several Phase I and IIA HIV vaccine trials enrolling healthy, HIV-seronegative African volunteers. Plasmid DNA and viral vector based vaccines were tested. No vaccine-related serious adverse events were reported. After completion of vaccine trials conducted between 2001-2007, both vaccine and placebo recipients were offered enrolment into an observational long-term follow-up study (LTFU) to monitor potential late health effects and persistence of immune responses. At scheduled 6-monthly clinic visits, a health questionnaire was administered; clinical events were recorded and graded for severity. Blood was drawn for HIV testing and cellular immune assays. 287 volunteers were enrolled; total follow-up after last vaccination was 1463 person years (median: 5.2 years). Ninety-three (93)% of volunteers reported good health at their last LTFU visit. Infectious diseases and injuries accounted for almost 50% of the 175 reported clinical events, of which over 95% were mild or moderate in severity. There were 30 six pregnancies, six incident HIV infections and 14 volunteers reported cases of social harm. Persistence of immune responses was rare. No safety signal was identified. No potentially vaccine-related medical condition, no immune mediated disease, or malignancy was reported. HIV vaccines studied in these trials had a low potential of induction of persisting HIV antibodies. © 2014 Landes Bioscience.

Other countries

Prospective safety monitoring of Haemophilus influenzae type b and heptavalent pneumococcal conjugate vaccines in Kagoshima, Japan

Nishi J., Tokuda K., Imuta N., Minami T., Kawano Y.

Japanese Journal of Infectious Diseases 2013 **66:3** (235-237)

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Haemophilus influenzae type b (Hib) conjugate vaccine (PRP-T) and heptavalent pneumococcal conjugate vaccine (PCV7) were introduced in Japan in December 2008 and February 2010, respectively. The concurrent administration of these vaccines is routinely performed worldwide. However, the safety of the simultaneous administration of these vaccines has not been fully evaluated in Japan, because it has rarely been performed thus far.We conducted a 2-year prospective, observational, multicenter study on PRP-T and PCV7 safety from February 2009 through January 2011 in 29 facilities located in Kagoshima Prefecture, Japan. Objective severe adverse events included anaphylactoid reaction, encephalitis/encephalopathy, neurological events, severe focal reactions, systemic eruption/urticaria, fever above 399C within 2 days after inoculation, and other complications requiring hospitalization. The incidences of these events for PRP-T and PCV7 administration were 0.68z (76/11,197) and 0.92z (28/3,049), respectively. No deaths or subsequent complications were reported during the course of the study. There was no significant difference in the incidence of severe adverse events between the single and co-administration groups for both vaccines: PRP-T, 0.55z (31/5,662) versus 0.81z (45/5,535; P = 0.11); PCV7, 0.88z (11/1,247) versus 0.94z (17/1,802; P = 0.86). These results suggest that the simultaneous administration of vaccines including PRP-T and/or PCV7 does not increase the incidence of severe adverse events in Japanese children.

Monitoring adverse events of the vaccination campaign against influenza A (H1N1) in the Netherlands

Van Puijenbroek E.P., Broos N., Van Grootheest K.

Drug Safety 2010 **33:12** (1097-1108)

Go to publisher for the full text

Background: In November 2009, a vaccination campaign against Influenza A (H1N1) was started in the Netherlands. The accelerated registration procedure of the vaccines used in this campaign and the use of these vaccines on a large scale indicated a need for real-time safety monitoring. Objective: To describe the processing, analysing and performing of signal detection by the Netherlands Pharmacovigilance Centre (Lareb) on reports of adverse events following immunization (AEFI) with respect to the two pandemic influenza vaccines, Focetria® and Pandemrix®, used in the Netherlands. The secondary aim is to provide a summary of the results of the safety monitoring of both vaccines. Study Design: Description of the process of collecting information and analysis of the safety monitoring of the pandemic vaccines during the vaccination campaign against H1N1 in the Netherlands. An observational study on adverse events following immunization (AEFIs) associated with vaccines used in this campaign was conducted. Results: The use of a dedicated web form with predefined AEFIs enabled an efficient way of processing and analysing the reports, resulting in a close to real-time monitoring of the safety of the vaccines. From 1 November 2009 until 1 March 2010, 7534 reports concerning one or more AEFIs possibly related to the administration of both vaccines were

received. 2788 of the reports related to Focetria® and 4746 of the reports related to Pandemrix®. The total time between receiving the reports and completion was longer for the serious reports (average 2.8 days) compared with the non-serious reports (average 0.8 days). The profile of the reported adverse events is comparable with the information provided in the Summary of Product Characteristics (SPC). Differences in reported AEFIs between both vaccines may be caused by bias and confounding due to the different populations for which these vaccines have been used. No signals of possible batch-related problems were detected for either vaccine.

Safety of Zostavax™-A cohort study in a managed care organization

Baxter R., Tran T.N., Hansen J., Emery M., Fireman B., Bartlett J., Lewis N., Saddier P.

Vaccine 2012 **30:47** (6636-6641)

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Background: Zostavax™ is a live, attenuated varicella-zoster virus vaccine indicated for the prevention of herpes zoster (shingles). An observational post-licensure (Phase IV) study was conducted at Kaiser Permanente Northern California (KPNC), a US managed care organization, to assess the safety of zoster vaccine in people 60 years of age or older, vaccinated in routine medical care. Methods: We performed a cohort study, comparing rates of clinical events resulting in hospitalizations or emergency department visits in a 42-day risk time period immediately following vaccination with rates in the same cohort in a subsequent comparison time period. The study data were reviewed and interpreted by an external safety review committee of 3 independent experts. Results: Approximately 29,000 people ≥ 60 years of age were vaccinated with zoster vaccine from July 2006 to November 2007. Of the 386 comparisons performed for the main analysis, 4 had an increased relative risk with a nominal p-value. ≤ 0.05. After medical records review, the timing of these conditions and procedures was found to be often prior to vaccination, and no clear increase in health events was observed in the risk period following vaccination compared to later. Persons receiving zoster vaccine appeared to be in their optimal health at the time of vaccination, which led to an apparent protective effect of the vaccine for some health outcomes, due to the study design. Conclusions: There was no evidence of a safety concern for zoster vaccine. © 2012 Elsevier Ltd.

An early (3-6 weeks) active surveillance study to assess the safety of pandemic influenza vaccine Focetria® in a province of Emilia-Romagna region, Italy - Part One

Candela S., Pergolizzi S., Ragni P., Cavuto S., Nobilio L., Di Mario S., Dragosevic V., Groth N., Magrini N.

Vaccine 2013 **31:10** (1431-1437)

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Introduction: An observational, non-comparative, prospective, surveillance study of individuals vaccinated with the MF59-adjuvanted A/H1N1 influenza vaccine, Focetria®, (Novartis Vaccines & Diagnostics, Siena, Italy), was

performed in Italy during the 2009 A/H1N1 influenza pandemic. Method: This study assessed the short-term (six-week) safety profile of the investigational vaccine in real time. After vaccination (N=. 7943), adverse events (AE) were assessed using both active (telephone) and passive (healthcare database) follow-up in enrolled vaccinated subjects, including infants (6-23 months), pregnant women, and the immunosuppressed. The treating physicians of all subjects experiencing AEs post-vaccination were consulted for clinical information on the conditions reported. All AEs were coded according to ICD-10. Results: A total of 1583 AEs occurred during the study, 67 (4.2%) of which were serious adverse events (SAEs). One SAE was considered to be possibly related to vaccination (transitory and ill-defined neurologic disorder experienced by a 16-year-old asthmatic male). Three adverse events of special interest (AESI) were identified (convulsions experienced by two epileptic subjects), none of which were considered to be vaccine-related. Six individuals died during the study period, in each case the cause of death was not related to vaccination (four cases of severe underlying co-morbidity, one case of psychoactive drug misuse, and one case of acute myocardial infarction). Conclusions: No cases of clinically relevant AEs, SAEs, or AESI were observed within a six-week period of vaccine administration. In accordance with existing clinical and post-marketing safety data, the results of this active surveillance study demonstrate a good safety profile for the MF59-adjuvanted A/H1N1 vaccine, Focetria, within the general population. © 2012 Elsevier Ltd.

Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: A prospective cohort study

Nazareth I., Tavares F., Rosillon D., Haguinet F., Bauchau V.
BMJ Open 2013 **3:2** Article Number 001912
Go to publisher for the full text
Objectives: To assess the safety of an AS03- adjuvanted split virion H1N1 (2009) vaccine (Pandemrix) in persons vaccinated during the national pandemic influenza vaccination campaign in the UK. Design: Prospective, cohort, observational, postauthorisation safety study. Setting: 87 general practices forming part of the Medical Research Council General Practice Research Framework and widely distributed throughout England. Participants: A cohort of 9143 individuals aged 7 months to 97 years who received at least one dose of the AS03-adjuvanted H1N1 pandemic vaccine during the national pandemic influenza vaccination campaign in the UK was enrolled. 94% completed the 6-month follow-up. Exclusion criteria were previous vaccination with other H1N1 pandemic vaccine and any child in care. Primary and secondary outcome measures: Medically attended adverse events (MAEs) occurring within 31 days after any dose, serious adverse events (SAEs) and adverse events of special interest (AESIs) following vaccination were collected for all participants. Solicited adverse events (AEs) were assessed in a subset of participants. Results: MAEs were reported in 1219 participants and SAEs in 113 participants during the 31-day postvaccination period. The most frequently reported MAEs and SAEs were consistent with events expected to be reported during the winter season in this population: lower respiratory tract infections, asthma and pneumonia. The most commonly reported solicited AEs were irritability in young children aged <5 years (61.8%), muscle aches in children aged 5-17 years (61.9%) and adults (46.9%). 18 AESIs, experienced by 14 patients, met the

criteria to be considered for the observed-to-expected analyses. AESIs above the expected number were neuritis (1 case within 31 days) and convulsions (8 cases within 181 days). There were 41 deaths during the 181-day period after vaccination, fewer than expected. Conclusions: Results indicate that the AS03-adjuvanted H1N1 pandemic vaccine showed a clinically acceptable reactogenicity and safety profile in all age and risk groups studied.

A postlicensure evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 24-59 months of age

Toback S.L., Ambrose C.S., Eaton A., Hansen J., Aukes L., Lewis N., Wu X., Baxter R.

Vaccine 2013 **31:14** (1812-1818)

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Background: In the **United States**, live attenuated influenza vaccine (LAIV) was initially approved for use in individuals aged 5-49 years in 2003, which was extended to individuals aged 2-49 years in 2007. At that time, a postlicensure commitment was made to describe the safety of LAIV within a cohort of eligible children aged 2-5 years. Methods: A prospective observational postmarketing study was conducted to evaluate the safety of LAIV. Rates of medically attended events (MAEs) and serious adverse events (SAEs) in eligible children aged 24-59 months receiving LAIV as part of routine care from October 2007 to March 2010 were compared with rates in a within-cohort self-control, as well as matched unvaccinated and matched trivalent inactivated influenza vaccine (TIV)-vaccinated controls. Children with asthma and other high-risk medical conditions before vaccination were excluded. All MAEs and SAEs through 42 days postvaccination and all hospitalizations and deaths through 6 months postvaccination were analyzed. Statistical significance was declared without multiplicity adjustment. Results: A total of 28,226 unique LAIV recipients were matched with similar numbers of TIV-vaccinated and unvaccinated children. Of 4696 MAE incidence rate comparisons, 83 (1.8%) were statistically significantly higher and 221 (4.7%) were statistically significantly lower in LAIV recipients versus controls. No pattern of MAE rate differences suggested a safety signal with LAIV. Asthma/wheezing MAEs were not statistically increased in LAIV recipients. No anaphylaxis events occurred within 3 days postvaccination. Rates of SAEs were similar between LAIV and control groups. Conclusions: Results of this postlicensure evaluation of LAIV safety in US children are consistent with preapproval clinical studies and Vaccine Adverse Event Reporting System reports, both of which demonstrated no significant increase in asthma/wheezing events or other adverse outcomes among eligible children aged 24-59 months who received LAIV.

Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a united states health maintenance organization

Klein N.P., Hansen J., Lewis E., Lyon L., Nguyen B., Black S., Weston W.M., Wu S., Li P., Howe B., Friedland L.R.

Pediatric Infectious Disease Journal 2010 **29:7** (613-617)

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Background: Prelicensure clinical studies may not include sufficient numbers of subjects to assess the potential for rare postvaccination adverse events. The aim of this postlicensure study (NCT00297856) was to evaluate uncommon outcomes following vaccination with a tetanus, reduced-antigen-content diphtheria, and acellular pertussis vaccine (Tdap, Boostrix GlaxoSmithKline) in a large adolescent cohort. Methods: We monitored safety outcomes among 13,427 10 to 18-year-old adolescents enrolled in the Northern California Kaiser Permanente Health Care Plan who received Tdap vaccination as part of their normal health care. Subjects were evaluated using self-control analysis comparing days 0 to 29 to days 30 to 59 postvaccination for neurologic events, hematologic events and allergic reactions. We evaluated new onset chronic illnesses within 6 months of Tdap vaccination by comparing with historical Td controls matched for age at vaccination, season, sex, and geographic area. We also compared the incidence of events of interest between the Tdap and historical cohorts as exploratory analyses. Results: No increased risk for medically attended neurologic (odds ratio [OR], 0.962; 95% confidence interval [CI], 0.533-1.733) or allergic reactions (OR, 1.091; 95% CI, 0.441-2.729) was observed following Tdap vaccination when comparing the first 30 postvaccination days to the second 30 postvaccination days. There was one hematologic event within 30 days of Tdap, compared with 0 events within days 30 to 59 (P = 1.0). When compared with matched historical Td recipients, no increase in new onset chronic illnesses (OR, 0.634; 95% CI, 0.475-0.840) was seen after Tdap. No deaths occurred in the Tdap cohort during the study. Conclusions: This study provides no evidence for an increased risk for neurologic, hematologic, allergic events, or new onset of chronic illnesses among adolescents vaccinated with Tdap. © 2010 by Lippincott Williams & Wilkins.

Adverse events associated with pandemic influenza vaccines: Comparison of the results of a follow-up study with those coming from spontaneous reporting

Carvajal A., Ortega P.G., Sáinz M., Velasco V., Salado I., Martín Arias L.H., Eiros J.M., Pérez Rubio A., Castrodeza J.
Vaccine 2011 **29:3** (519-522)
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Prior to marketing of pandemic influenza vaccines, the only safety data were those from clinical trials. The objective of this study was to compare information coming from spontaneous reporting with that systematically collected in a formal observation study; this also permits to further evaluate safety of pandemic influenza vaccines in the targeted patients' population. Out of a sample of 507 vaccinated subjects, 103 (20.3%) developed some complication. In the same period 83 reports corresponding to all vaccinated people of **Castilla y León** (n=131,462) were collected. Severe cases were 1 (1%) and 7 (8.4%), respectively, with the two procedures. The spontaneous reporting rate was 322-fold lower than that identified through the follow-up study; when considered the severe cases, it was 37-fold lower. Under certain circumstances reporting might be performing better than usual due to strengthening of the surveillance system. Adverse events observed for the pandemic H1N1 vaccines lie within the expected safety profile for common

events with influenza vaccines. An overall benefit-risk assessment of these vaccines should be done. © 2010.

Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting

Jacobsen S.J., Ackerson B.K., Sy L.S., Tran T.N., Jones T.L., Yao J.F., Xie F., Craig Cheetham T., Saddier P.

Vaccine 2009 **27:34** (4656-4661)

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Background: A combined measles, mumps, rubella, varicella live vaccine (MMRV, Merck and Co., Inc., US) was recently licensed in **the US**. Pre-licensure clinical trial data showed a significant increase in fever in days 5-12 following MMRV vaccination as compared to the vaccines given separately (MMR + V). This post-licensure retrospective cohort study was undertaken to assess the incidence of febrile convulsion following MMRV. Methods: Children ages 12-60 months who received a first dose of MMRV in February 2006-June 2007 in a managed care organization were included in the study. Subjects were optimally matched on age, sex, and calendar date of vaccination to children who received MMR + V concomitantly in November 2003-January 2006, before MMRV licensure. Potential cases of febrile convulsion were identified through administrative data and adjudicated by expert panel, according to pre-specified criteria. Results: During the 30 days post-vaccination, there were 128 and 94 potential convulsion cases among the 31,298 children in the MMRV and MMR + V cohorts, respectively. After review of available medical charts and adjudication, there were 84 cases of confirmed febrile convulsion, 44 (1.41/1000) and 40 (1.28/1000) in the MMRV and MMR + V cohorts, respectively (RR = 1.10, 95% CI = 0.72, 1.69). In days 5-12 following vaccination, a pre-specified period of interest, the respective numbers were 22 (0.70/1000) and 10 (0.32/1000) (RR = 2.20, 95% CI = 1.04, 4.65). Conclusion: These data suggest that the risk of febrile convulsion is increased in days 5-12 following vaccination with MMRV as compared to MMR + V given separately during the same visit, when post-vaccination fever and rash are also increased in clinical trials. While there was no evidence of an increase in the overall month following vaccination, the elevated risk during this time period should be communicated and needs to be balanced with the potential benefit of a combined vaccine.

U.S. Postlicensure safety surveillance for adolescent and adult tetanus, diphtheria and acellular pertussis vaccines: 2005-2007

Chang S., O'Connor P.M., Slade B.A., Woo E.J.

Vaccine 2013 **31:10** (1447-1452)

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Background: Pre-licensure clinical trials for two U.S. licensed tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccines did not reveal any major safety concerns. However, routine use in large adolescent and adult populations could reveal rare and potentially serious adverse events (AEs). Methods: To characterize reported AEs following Tdap vaccination and identify potential safety concerns warranting further evaluation, we analyzed data from

the Vaccine Adverse Event Reporting System (VAERS) and assessed the frequency and proportions of AEs and reporting rates (reports per 100,000 vaccine doses distributed). Results: A total of 2090 reports (7% were serious; 55% listed Tdap alone) involving Tdap vaccines were submitted to VAERS May 2005-June 2007. The crude reporting rate was 10.2 per 100,000 vaccine doses distributed. The median age of vaccinees was 22 years, and the female to male ratio was about 2 to 1. The majority of reports described common local and systemic signs and symptoms, such as injection site reactions, fever, and headache. Rarely reported AEs included myopericarditis, demyelinating diseases of the central nervous system, Guillain-Barré Syndrome, syncope, encephalopathy/encephalitis, seizure, Bell's palsy, anaphylaxis, and thrombocytopenia. Conclusions: Because adolescents and adults were not routinely vaccinated against pertussis in the past, this surveillance summary provides important - and reassuring - information about the use of Tdap in these age groups. Although subject to the limitations of passive surveillance, the findings of this VAERS review support the pre-licensure clinical trial data with regard to the safety of the U.S. licensed Tdap vaccines. Continued monitoring of clinically significant AEs that are temporally associated with Tdap vaccination and further assessment of such events using controlled observational studies may provide additional information about the safety of these vaccines. © 2012.

Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: A prospective controlled observational cohort study

Heijstek M.W., Scherpenisse M., Groot N., Tacke C., Schepp R.M., Buisman A.-M., Berbers G.A.M., Van Der Klis F.R.M., Wulffraat N.M.

Annals of the Rheumatic Diseases 2014 **73:8** (1500-1507)

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Objectives: To compare the immunogenicity and safety of the bivalent human papillomavirus (HPV)16/18 vaccine between female patients with juvenile idiopathic arthritis (JIA) and healthy female adolescents. Methods: 68 patients and 55 healthy girls aged 12-18 years were included in a prospective controlled observational cohort and were vaccinated at 0, 1 and 6 months. Primary outcomes were immunogenicity expressed as seropositivity rate after three vaccine doses at 7 and 12 months and HPV-specific geometric mean antibody concentrations. Secondary outcomes were HPV16/18-specific memory B cell responses in a subset of participants and safety, defined as adverse events and the effect of vaccination on JIA disease activity. Results: All participants were seropositive for HPV16 and HPV18 at 7 months. One patient turned seronegative at 12 months for HPV16/18. No significant differences were found between patients and controls in HPV-specific antibody concentrations; however, antibody concentrations were consistently lower in patients. No effect of methotrexate on HPV16 antibodies (p=0.79) or HPV18 antibodies (p=0.37) was detected. All patients on anti-TNFα treatment were seropositive after vaccination. The kinetics of HPV16/18 memory B cell responses was comparable between patients and controls, but the magnitude of B cell responses at 7 and 12 months appeared lower in patients. No relevant differences in adverse events were found. HPV vaccination did not aggravate JIA disease. Conclusions: The bivalent HPV16/18 vaccine is immunogenic and well tolerated in JIA

patients. However, HPV-specific antibodies and B cell responses tended to be lower in patients compared with healthy controls.

General articles

Use of the self-controlled case-series method in vaccine safety studies: Review and recommendations for best practice

Weldeselassie Y.G., Whitaker H.J., Farrington C.P.
Epidemiology and Infection 2011 **139:12** (1805-1817)
Go to publisher for the full text
The self-controlled case-series method was originally developed to investigate potential associations between vaccines and adverse events, and is now commonly used for this purpose. This study reviews applications of the method to vaccine safety investigations in the period 1995-2010. In total, 40 studies were reviewed. The application of the self-controlled case-series method in these studies is critically examined, with particular reference to the definition of observation and risk periods, control of confounders, assumptions and potential biases, methodological and presentation issues, power and sample size, and software. Comparisons with other study designs undertaken in the papers reviewed are also highlighted. Some recommendations are presented, with the emphasis on promoting good practice. © 2011 Cambridge University Press.

Registration of observational studies: Is it time?

Williams R.J., Tse T., Harlan W.R., Zarin D.A.
CMAJ 2010 **182:15** (1638-1642)
Go to publisher for the full text
Observational studies form an important part of the medical evidence base, particularly for assessing rare adverse events and long-term effectiveness of medications and devices. 1 However, observational studies, like interventional studies (clinical trials), are subject to publication bias and reporting bias. 2–4 Registration of clinical trials is a widely recognized tool for facilitating complete public reporting. 5 Registration of observational studies has received less attention, although interest is growing. 6–8 Because existing registries (e.g., ClinicalTrials.gov) accommodate observational studies, and the rationale and benefits of registration are similar, we ask the scientific community and other stakeholders to consider the systematic, prospective registration of observational studies.

A scan statistic for identifying optimal risk windows in vaccine safety studies using self-controlled case series design

Xu S., Hambidge S.J., Mcclure D.L., Daley M.F., Glanz J.M.
Statistics in Medicine 2013 **32:19** (3290-3299)
Go to publisher for the full text

In the examination of the association between vaccines and rare adverse events after vaccination in postlicensure observational studies, it is challenging to define appropriate risk windows because prelicensure RCTs provide little insight on the timing of specific adverse events. Past vaccine safety studies have often used prespecified risk windows based on prior publications, biological understanding of the vaccine, and expert opinion. Recently, a data-driven approach was developed to identify appropriate risk windows for vaccine safety studies that use the self-controlled case series design. This approach employs both the maximum incidence rate ratio and the linear relation between the estimated incidence rate ratio and the inverse of average person time at risk, given a specified risk window. In this paper, we present a scan statistic that can identify appropriate risk windows in vaccine safety studies using the self-controlled case series design while taking into account the dependence of time intervals within an individual and while adjusting for time-varying covariates such as age and seasonality. This approach uses the maximum likelihood ratio test based on fixed-effects models, which has been used for analyzing data from self-controlled case series design in addition to conditional Poisson models. © 2013 John Wiley & Sons, Ltd.

Monitoring and assessing vaccine safety: A European perspective

Lopalco P.L., Johansen K., Ciancio B., De Carvalho Gomes H., Kramarz P., Giesecke J.

Expert Review of Vaccines 2010 **9:4** (371-380)

Go to publisher for the full text

The success of vaccination programs is an uncontroversial reality - in Europe as well as worldwide. On the other hand, the perceived risk of adverse events in the general public is the most important threat for implementing successful vaccination programs in Europe. For this reason, monitoring and assessing vaccine safety is a priority for public health. Vaccine safety is assessed both before and after vaccine authorization. In postmarketing settings, different activities related to vaccine safety usually involve several different stakeholders. In 2005, a new EU agency, the European Centre for Disease Prevention and Control, was established with the aim to strengthen Europes defences against infectious diseases. Implementing stable links between different stakeholders and defining clear roles in the EU is paramount in order to provide optimal and transparent information on adverse reactions following immunization, with the final goal of increasing compliance to safe and effective vaccination programs. © 2010 Expert Reviews Ltd.

A study of adverse drug reactions in patients admitted to intensive care unit of a tertiary care teaching rural hospital

Kathiria J.M., Sattigeri B.M., Desai P.M., Patel S.P.

International Journal of Pharmacy and Pharmaceutical Sciences 2013 **5:1** (160-163)

Adverse drug reactions (ADRs) are the common problems faced in the setups like ICU where the poly pharmacy is involved in treating the patients. Control of such events is possible if the culpable drug is known or if it is identified and

reported. However, reporting of adverse drug reactions still remains in its infancy for problems in many. Awareness about adverse drug reactions can decrease irrational use of medicines, poly pharmacy and adverse drug-drug interactions. A prospective, observational and non-interventional study was conducted over a period of 18 months in medical ICU of Dhiraj hospital, Piparia with the goal to highlight the responsibility of health care professionals in preventing, identifying, diagnosis, treating and reporting ADRs. The patients were monitored daily for ADRs. The data was analyzed for demographic parameters. The causality relationship between suspected drugs and the reactions were assessed by using various standard causality assessment scales. 1000 patients were enrolled for the study. Out of these 45 patients developed ADRs. Of these 27 males and 18 females developed ADRs showing male predominance (2. 7%). The ADRs increased with increasing number of drugs administered. The drug class most commonly implicated with ADRs was antibiotics 24(53. 33%). The system most commonly involved with an ADR was gastrointestinal tract 26. 67%. Most commonly reported reaction were hypoglycemia (13. 33%) and Rash (11. 11%).

Pregnancy

H1N1 influenza vaccination during pregnancy

Fell D.B., Dodds L., McNeil S., MacDonald N.E.
BMJ (Online) 2014 **348** Article Number g3500
Go to publisher for the full text

H1N1 safety data look reassuring, but we need ongoing surveillance of all influenza vaccines given to pregnant women
Risks to pregnant women from influenza infection have long been recognized.1 The recent 2009-10 H1N1 pandemic was no exception—pregnant women were at higher risk of severe H1N1 influenza illness compared with the general population,2 and those with H1N1 influenza had higher rates of adverse pregnancy outcomes than did uninfected pregnant women.3 Despite limited safety data for use of the monovalent H1N1 vaccines in pregnancy, pregnant women were widely prioritized for H1N1 vaccination programs.4 Fortunately, enhanced surveillance of pregnant women during the pandemic has enabled retrospective evaluation of the safety of monovalent H1N1 vaccine in obstetric populations around the world.

Influenza H1N1 vaccination and adverse pregnancy outcome

Ludvigsson J.F., Zugna D., Cnattingius S., Richiardi L., Ekbom A., Örtqvist Å., Persson I., Stephansson O.
European Journal of Epidemiology 2013 **28:7** (579-588)
Go to publisher for the full text
Although vaccines against influenza can reduce maternal morbidity and mortality, large-scale data on adverse effects in the offspring are scarce.

Historical cohort study in Stockholm County, Sweden. We linked H1N1 vaccination data (Pandemrix®, a mono-valent AS03 adjuvanted H1N1 vaccine) with pregnancy and birth data from 21,087 women with singleton offspring conceived between February 2009 and January 2010 (vaccinated during pregnancy: n = 13,297 vs. unvaccinated: n = 7,790). Data were analysed by conceptualizing the observational cohort as a series of nested cohorts defined at each week of gestation. Logistic regression estimated odds ratios (ORs) for low birth weight (LBW, <2,500 g), preterm birth (<37 completed weeks), small-for- gestational age (SGA, <10th percentile of the gestational age-specific birth weight within the cohort), low 5-min Apgar score (<7), and caesarean section. Data were adjusted for potential confounders, including maternal age, body mass index, smoking, parity, civil status and comorbidities. Compared with infants of non-vaccinated women, infants of vaccinated women had similar adjusted ORs (95 % CI) for LBW (0.91; 0.79-1.04), preterm birth (0.99; 0.89-1.10), SGA (0.97; 0.90-1.05), low Apgar score (1.05, 0.84-1.31), and a marginal risk reduction for caesarean section (0.94, 0.89-0.99). H1N1 vaccination during pregnancy, using an AS03-adjuvanted vaccine, does not appear to adversely influence offspring risks of LBW, preterm birth, SGA, or low Apgar score. Our results suggest that this vaccine is safe for the offspring when used in different stages of pregnancy. © 2013 Springer Science+Business Media Dordrecht.

Influenza H1N1 (swine flu) vaccination: A safety surveillance feasibility study using self-reporting of serious adverse events and pregnancy outcomes

Mackenzie I.S., Macdonald T.M., Shakir S., Dryburgh M., Mantay B.J., Mcdonnell P., Layton D.

British Journal of Clinical Pharmacology 2012 **73:5** (801-811)

Go to publisher for the full text

Aims: During the global H1N1 influenza A (swine flu) pandemic 2009-2010, swine flu vaccines were expeditiously licensed and a mass vaccination programme for high risk groups, including pregnant women, was introduced in the UK. This pilot active safety surveillance study was performed to establish the feasibility of rapidly monitoring the new swine flu vaccines in large patient numbers receiving or offered the vaccination under normal conditions of use within a short time frame. Methods: A cohort design with safety data capture through modern technologies was carried out in Scotland, UK during the winter swine flu vaccination programme 2009-2010 in individuals receiving or offered the swine flu vaccination. The main outcome measures were self-reported serious adverse events (SAEs) and pregnancy outcomes. Results: The cohort comprised 4066 people; 3754 vaccinated and 312 offered the vaccination but not vaccinated. There were 939 self-reported events (838 different events), 53 judged to fit SAE criteria by the investigators, with nine judged as possibly, probably or definitely vaccine related. None of the seven deaths (six in vaccinees) were judged as vaccine related. One hundred and twenty-eight women reported 130 pregnancies during the study with 117 pregnant at study start. There were reports of four miscarriages in three women and six possible congenital abnormalities in live births. Conclusions: Overall, no significant safety issues were identified. The methodology and use of modern technologies to collect safety data from large numbers of patients was successful and could

be used again in similar safety studies. © 2011 The Authors. British Journal of Clinical Pharmacology © 2011 The British Pharmacological Society.

A(H1N1)v2009: A controlled observational prospective cohort study on vaccine safety in pregnancy

Oppermann M., Fritzsche J., Weber-Schoendorfer C., Keller-Stanislawski B., Allignol A., Meister R., Schaefer C.
Vaccine 2012 **30:30** (4445-4452)
Go to publisher for the full text
Background: A(H1N1)v2009 influenza vaccination of pregnant women was a challenge for health care providers, as little safety data were available. Methods: We prospectively followed the pregnancies of women who were vaccinated at any time during pregnancy or ≤4 weeks prior to conception and compared these outcomes to a control cohort matched by the estimated date of birth. Primary endpoints: rate of spontaneous abortion and major malformations. Secondary endpoints: preeclampsia, gestational age at birth, and birth weight. Results: Pregnancy outcome of 323 women immunized with adjuvanted or non-adjuvanted A(H1N1)v2009 influenza vaccines from 2009-09-28 to 2010-03-31 were compared to 1329 control subjects. The risk for spontaneous abortions (HR 0.89; 95% CI 0.36-2.19) and the rate of major malformations (all trimesters: OR 0.87; 95% CI 0.38-1.77; preconception and first trimester exposure: OR 0.79; 95% CI 0.13-2.64) did not vary between the two cohorts. Furthermore, there was no increase in preeclampsia, prematurity, and intrauterine growth retardation in the vaccinated cohort. Conclusion: The results of our study do not indicate a risk for the pregnant woman and the developing embryo/fetus after H1N1 vaccination. We provide and apply methods novel in observational studies on pregnancy outcome, especially if a single dose exposure is investigated. © 2012 Elsevier Ltd.

Maternal safety of trivalent inactivated influenza vaccine in pregnant women

Nordin J.D., Kharbanda E.O., Benitez G.V., Nichol K., Lipkind H., Naleway A., Lee G.M., Hambidge S., Shi W., Olsen A.
Obstetrics and Gynecology 2013 **121:3** (519-525)
Go to publisher for the full text
OBJECTIVE: To estimate the risks for medically attended events occurring within 42 days of receiving trivalent inactivated influenza vaccine and to evaluate specific risks of first-trimester vaccination. METHODS: This retrospective observational cohort study compared rates of medically attended adverse events in trivalent inactivated influenza-vaccinated and unvaccinated pregnant women in the Vaccine Safety Datalink. Using a Poisson distribution and log link, we calculated maternal adjusted incident rate ratios for composite safety outcomes for the full cohort and the subset vaccinated during the first trimester. RESULTS: The cohort included 75,906 vaccinated (28.4% in the first trimester) and 147,992 unvaccinated women matched by age, site, and pregnancy start date. In the first 3 days after vaccination, trivalent inactivated influenza vaccine was not associated with increased risk of specified medically attended events, including allergic reactions, cellulitis, and seizures (full cohort

adjusted incident rate ratio 1.12, 95% confidence interval [CI] 0.81-1.55; P=.48; first-trimester adjusted incident rate ratio .97, 95% CI 0.53-1.78; P=.93). In the first 42 days, no incident cases of Guillain-Barré syndrome, optic neuritis, transverse myelitis, or Bells palsy were identified. Trivalent inactivated influenza vaccine was not associated with thrombocytopenia (full cohort adjusted incident rate ratio 0.90, 95% CI 0.68-1.19; P=.45; first-trimester adjusted incident rate ratio 0.56, 95% CI 0.22-1.39; P=.21) or an acute neurologic event (full cohort adjusted incident rate ratio 0.92, 95% CI 0.54-1.6; P=.75; first-trimester adjusted incident rate ratio 1.05, 95% CI 0.46-2.38; P=.91). CONCLUSIONS: Receipt of trivalent inactivated influenza vaccine during pregnancy was not associated with increased risk of adverse events in the 42 days after vaccination, supporting its safety for the mother. © 2013 by The American College of Obstetricians and Gynecologists.

Safety of seasonal influenza and influenza A (H1N1) 2009 monovalent vaccines in pregnancy

Moro P.L., Tepper N.K., Grohskopf L.A., Vellozzi C., Broder K.
Expert Review of Vaccines 2012 **11:8** (911-921)
Go to publisher for the full text
Inactivated influenza vaccines have been given to pregnant women since 1964. Since 2004, the Advisory Committee on Immunization Practices has recommended that pregnant women receive trivalent inactivated influenza vaccine at any time during pregnancy. Studies conducted before 2009 did not identify any safety concerns after trivalent inactivated influenza vaccine in mothers or their infants. During the 2009-2010 influenza A (H1N1) influenza vaccination program, several monitoring systems were established or enhanced to assess whether adverse events were associated with H1N1 2009 monovalent vaccines (2009 H1N1 influenza vaccines). Data from these systems did not identify any safety concerns in pregnant women who received 2009 H1N1 influenza vaccines or their infants. Although live attenuated influenza vaccines are not recommended in pregnant women, a small number of studies have not shown any safety concern among pregnant women or their infants who were inadvertently exposed to these vaccines. This review summarizes US and international safety data for influenza vaccines in pregnant women with an emphasis on 2009 H1N1 influenza vaccines. © 2012 2012 Expert Reviews Ltd.

Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: A comparative cohort study

Heikkinen T., Young J., Van Beek E., Franke H., Verstraeten T., Weil J.G., Della Cioppa G.
American Journal of Obstetrics and Gynecology 2012 **207:3** (177.e1-177.e8)
Go to publisher for the full text
Objective: The 2009-2010 A/H1N1 pandemic provided a unique setting to study the safety of MF59-adjuvanted vaccination in pregnancy. Study Design: This was an observational cohort study of the safety of an MF59-adjuvanted A/H1N1 vaccine (Focetria) conducted among 4508 pregnant women (2295 vaccinated vs 2213 unvaccinated), with 3 month follow-up of neonates. Results: No maternal

deaths or abortions occurred among the vaccinated women. No differences between the vaccinated and unvaccinated cohorts were observed for gestational diabetes, preeclampsia, stillbirth, low birthweight, neonatal deaths, or congenital malformations. The risk of premature birth was significantly decreased among the vaccinated women (adjusted proportional hazard, 0.69; 95% confidence interval, 0.51-0.92). No differences were observed in rates of congenital malformations after vaccination in the first (2.1%), second (2.7%), or third (2.1%) trimesters. Conclusion: There was no evidence of a safety risk for MF59-adjuvanted A/H1N1 vaccination in pregnant women; protection was observed against premature birth. © 2012 Mosby, Inc.

Pharmacovigilance monitoring of a cohort of pregnant women vaccinated against influenza A(H1N1) variant virus in the Nord-Pas de Calais region of northern France

Auffret M., Béné J., Gautier S., Moreau-Crépeaux S., Caron J.
European Journal of Obstetrics Gynecology and Reproductive Biology 2013 **170:1** (114-118)
Go to publisher for the full text
Objective During the 2009-2010 influenza A variant virus (A(H1N1)v) pandemic in France, a national pharmacovigilance program was set up to monitor vaccinated, pregnant women, especially the reactogenicity of the vaccine and its impact on the outcome of pregnancy and on the newborn. Here, we present the results for the cohort of pregnant women constituted in the Nord-Pas de Calais region of northern France. Study design Vaccinated pregnant women were included in the study by the region's vaccination centers between November 2009 and April 2010. Results Eight hundred and six pregnant women were included and 781 were followed up until delivery. The risk of adverse events after vaccination and the maternal, fetal and neonatal medical conditions in our cohort did not appear different from the risk observed in the general population. Conclusions Our results suggest that A(H1N1)v vaccination of pregnant women did not have an adverse

Epidemiology study

Prevalence of cervical human papillomavirus infection and types among women immigrated to Sicily, Italy

Giovannelli L., Vassallo R., Matranga D., Affronti M., Caleca M.P., Bellavia C., Perino A., Ammatuna P.
Acta Obstetricia et Gynecologica Scandinavica 2009 **88:6** (737-742)
Go to publisher for the full text
We determined the prevalence of human papillomavirus (HPV) cervical infection and HPV genotypes among 115 women immigrating to Sicily (Italy), with regard to abnormal cytology and socio-behavioral characteristics in a cross-sectional, observational study. Information was collected with the help of cultural mediators/translators. HPV-DNA was assayed by the INNOLiPA HPV

assay and a nested PCR/sequencing method. Sixty (52.2%) women came from sub-Saharan Africa and 55 (47.8%) from Eastern Europe. HPV infection was found in 55 (47.8%) women. The most frequent types were the oncogenic types HPV-16 (7.8%), HPV-18 and 51 (6.0% each), HPV-52 (5.2%), 31, 53, and 68 (4.3% each). Twenty-seven (23.5%) women had cytological abnormalities associated with HPV infection (p=0.04). Being single (OR = 2.98; 95%CI: 1.30-6.84) and parity (OR = 0.29; 95%CI: 0.12-0.65) were consistent predictors of HPV infection. Only 21 (18.2%) women returned to collect the results of their Pap and HPV tests. The high prevalence of HPV infection and oncogenic types among immigrant women make them a priority group for cervical cancer screening. Linguistically and culturally appropriate prevention efforts are needed to sensitize immigrant women regarding HPV-related issues and to conduct vaccine strategies for cervical cancer prevention.

Epidemiology of rotavirus gastroenteritis among children under 5 years of age in Tunisia - Results of sentinel hospital surveillance 2009 to 2011

Soltani M., Bouanene I., Trabelsi A., Harbi A., Hachicha M., Amri F., Boussnina S., Gueddiche M.N., Sfar M.T., Teleb N., Ben Ghorbel M., Ben Hamida E.

Revue d'Epidemiologie et de Sante Publique 2012 **60:6** (473-480)

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Background: Rotavirus is the major cause of severe acute gastroenteritis among young children. The objectives of this study were to assess the epidemiology, clinical and virological features of community-acquired rotavirus acute gastroenteritis, in children under 5 years of age, hospitalized in Tunisia. Methods: A multicenter prospective observational study was conducted from April 2009 to March 2011, in 11 sentinel pediatric departments. Clinical data and stool samples were collected for all children under 5 years, admitted for acute gastroenteritis. Rotavirus was detected by Elisa immunoassay test and genotyped for G and P by semi-nested multiplex RT-PCR. Result: A total of 621 children were enrolled in this study. Rotavirus was detected in 30.3% of cases (95% CI [26.7-33.9]). The estimated incidence rate of rotavirus acute gastroenteritis was 11 cases/100,000 child-years (95% CI [9.43-12.57]). This infection affected predominantly children aged under 24 months, and occurred mainly in winter (55.3%). Vomiting, fever and dehydration were observed in 79.6%, 69.5% and 57% respectively. Genotype analysis identified four G types (G1, G2, G3 and G4) and 4 P types (P[4], P[6], P[8] and P[9]). The most common G/P combination was G3P[8] (24.4%), followed by G4P[8] (13.3%) and G1P[8] (6.5%). Conclusion: These results highlight the frequency and potential severity of rotavirus acute gastroenteritis in pediatric hospital settings. The present study could provide a sufficient database to make a decision related to the introduction of rotavirus vaccine in Tunisian national immunization program. © 2012 Elsevier Masson SAS.

Epidemiology of HPV in HIV-positive and HIV-negative fertile women in cameroon, West Africa

Desruisseau A.J., Schmidt-Grimminger D., Welty E.

Infectious Diseases in Obstetrics and Gynecology 2009 **2009** Article Number 810596
Go to publisher for the full text
Background. HPV types vary by country and HIV status. There are no data on the prevalent HPV genotypes from Cameroon. Methods. We conducted a cross-sectional, observational study on 65 Cameroonian women. Samples were sent for HPV genotyping and Thin Prep analyses. Results. 41 out of 61 samples tested (67.2) had HPV subtypes detected. The most common high risk types encountered were: 45 (24.6) and 58 (21.5). HIV-positive women were more likely to test positive for any HPV (P=.014), have more than one HPV subtype (P=.003), and to test positive for the high risk subtypes (P=.007). Of those with high risk HPV, HIV-positive women were more likely to have Thin Prep abnormalities than HIV-negative women (P=.013). Conclusions. Oncogenic HPV subtypes 45 and 58 were more prevalent than those subtypes carried in the quadrivalent vaccine. Further studies are needed to assess whether the current vaccine will be effective in this region.

From: Holm Karin
Sent: 24 Jun 2014 15:35:37 +0000
To: 'Jouquelet-Royer, Corinne';'Harry.A.Seifert@gsk.com';Zuber, Patrick (CDC who.int);'maurec@who.int';Winiecki, Scott (FDA/CDER);'terhi.kilpi@thl.fi';'Bachtiar (novilia@biofarma.co.id)';Destefano, Frank (CDC/OID/NCEZID);'Dawei, Liu (b)(6) Xavier.Kurz@ema.europa.eu';'Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu)';Martin, David (FDA/CDER);Bergman Ulf;'Bailey (Steven.R.Bailey@pfizer.com)';Ayman.Ayoub@pfizer.com
Cc: 'Francoise.Sillan@sanofipasteur.com';'Darko, Mimi (mimidarko66@yahoo.co.uk)';Bergman Ulf
Subject: RE: CIOMS WG on VS TG2 section 5 - Fri 27 June 12noon (French time)
Attachments: business plan TG2_23june_kh.docx

Dear CIOMS TG2 section 5 Contributors:
Corinne and Harry are looking forward to talking with you on: **Fri 27 June 12noon (French time)**
Attached please find the latest version of the business plan (including the Manual Table of Contents) for discussion.

Agenda for TC

- Quick review of the section 5 to get alignment and shared understanding on what need to be achieved
- Agree on contributors to which sections
- And timelines for draft and reviews before September meeting

Sanofi Telecon dial in numbers
France : (b)(6) (toll free) or + (b)(6) (local)
Canada : (b)(6) (toll free) or + (b)(6) (local)
US : (b)(6) (toll free) or + (b)(6) (local)
Belgique (b)(6) (toll free) or + (b)(6) (local)
Singapore - (b)(6)
Mexique (b)(6) or (b)(6)

Participant code : (b)(6)

Code PIN (CP) : (b)(6)

Additional Numbers can be found here: http://www.intercall.com/sanofi/numbers/index.htm

Wishing you good connections and hope all try to speak clearly, loudly, slowly for optimal communication!
Karin

Karin R. Holm
Technical Coordinator, Working Group on Vaccine Safety
Publications Consultant, Working Group IX Risk Minimization
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From: Holm Karin
Sent: 24 June 2014 11:36
To: Jouquelet-Royer, Corinne; Harry.A.Seifert@gsk.com; Patrick Zuber (zuberp@who.int); maurec@who.int; Winiecki, Scott; terhi.kilpi@thl.fi; Bachtiar (novilia@biofarma.co.id); fxd1@cdc.gov; Dawei, Liu (b)(6) Xavier.Kurz@ema.europa.eu; Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu); David.Martin@fda.hhs.gov; Bergman Ulf; Bailey (Steven.R.Bailey@pfizer.com)

Cc: Francoise.Sillan@sanofipasteur.com; Darko, Mimi (mimidarko66@yahoo.co.uk)
Subject: CIOMS WG on VS TG2 section 5 - Fri 27 June 12noon (French time)

Dear CIOMS TG2 Chapter 5 Contributors,

Corinne Jouquelet-Royer (Sanofi, who is new to the CIOMS WG but will eventually take over at some point in the future for Françoise, who is moving to a new area at Sanofi) and Harry Seifert (GSK) kindly offered to organize Chapter 5 of the Manual on Active Safety Surveillance. Ch.5 is the "meat of the manual" on Establishing Active Surveillance (see Table of Contents in business plan draft attached). The best day/time was this Friday, 27 June, 12pm French time. Sanofi kindly will arrange TC and send instructions on how to access.

Agenda for TC

- Quick review of the section 5 to get alignment and shared understanding on what need to be achieved
- Agree on contributors to which sections
- And timelines for draft and reviews before September meeting

	June 2014
	Fri 27
	12:00 PM
Karin Holm	NO
corinne jouquelet royer	OK
Harry Seifert	OK
Patrick Zuber	OK
Christine Maure	OK
Scott Winiecki (FDA)	OK
Frank DeStefano	NO
Terhi Kilpi	OK
Novilia Sjafri Bachtiar	OK
Xavier Kurz	OK
Dawei Liu	?
Irina Caplanusi	?
David Martin	?
Ayman Ayoub	?
Steven Bailey	NO
Ulf Bergman	NO
Count	8

Karin R. Holm
Technical Coordinator, Working Group on Vaccine Safety
Publications Consultant, Working Group IX Risk Minimization
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Phone: +41 22 791 6497 Website: www.cioms.ch
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From: Holm Karin
Sent: 23 June 2014 16:05
To: 'Dawei, Liu ([redacted]; 'Bachtiar (novilia@biofarma.co.id)'; 'Xavier.Kurz@ema.europa.eu'; 'Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu)'; 'David.Martin@fda.hhs.gov'; 'terhi.kilpi@thl.fi'; Bergman Ulf
Cc: 'Jouquelet-Royer, Corinne'; 'Francoise.Sillan@sanofipasteur.com'; 'Darko, Mimi ([redacted]'
Subject: RE: Doodle: Link for poll "CIOMS WG on VS TG2 section 5"

Dear Dawei Liu, Novi, Xavier, Irina, David, Terhi, Ulf…
We haven't yet heard from you if you are available at these times and we are trying to find the best time for a TC to work on Section 5 of the Manual on Active Safety Surveillance….

Hi, CIOMS WG on VS - TG2 Active Surveillance section 5
Corinne Jouquelet-Royer and Harry Seifert would like to have a TC to start the process moving on drafting section 5. Please let us know if you would be available any of these times by clicking on this doodle poll...
http://doodle.com/b6z8aicfaia92fbt
Thank you,
Karin

Most popular date: Friday, June 27, 2014 12:00 PM |

Top of Form

	June 2014	July 2014	
7 participants	**Fri 27 12:00 PM**	**Tue 1 5:00 PM**	**Wed 2 6:00 PM**
Karin Holm		✓	
corinne jouquelet royer	✓	✓	✓
Harry Seifert	✓	✓	✓
Patrick Zuber	✓		
Christine Maure	✓		
Scott Winiecki	✓		✓
Frank DeStefano			
	Friday, June 27, 2014 12:00 PM	Tuesday, July 1, 2014 5:00 PM	Wednesday, July 2, 2014 6:00 PM

Bottom of Form

MANUAL FOR IMPROVEMENT OF POST MARKETING (ACTIVE SAFETY) SURVEILLANCE IN LMIC BUSINESS PLAN

CIOMS VACCINE SAFETY WORKING GROUP

TOPIC GROUP 2

1. Executive summary

The objective is to provide a manual which can be a reference for all vaccine stakeholders who are involved in the launch of a new vaccine in a LMIC.

This Business plan describes the different steps for the preparation of this manual by the Topic group 2 from the CIOMS working group on vaccine safety.

The manual preparation will start in June 2014 and should be released by June 2016.

The different sections will be prepared outside CIOMS working group meetings, only the key sections will be discussed during meetings like establishing sentinel sites, governance, and above country-level (global) coordination.

2. Rationale and opportunities for improvement

Many on-going initiatives for improvement of post marketing surveillance have been initiated with GVSI. One of the main gaps identified is the lack of a guidance document to conduct active safety surveillance when a new vaccine is being launched in a LMIC.

Different scenarios are possible:

- The new vaccine is introduced in a LMIC by a vaccine manufacturer for public and private settings
- The new vaccine is supplied by a third party in a LMIC for a vaccination campaign and is not registered in the country

3. Strategy

Use the existing initiatives, do not reinvent the wheel. The manual will include useful links where the stakeholder can find the information on existing initiatives on improvement of post-marketing safety surveillance.

Select the sections which need to be discussed during CIOMS meeting, prepare the other sections between meetings.

Distribute the manual sections among TG2 members. Identify leaders for each section and contributors. The role of the contributors and the leaders is described in section 5.

4. Key steps and operational plan

The manual will be prepared by the contributors for topic 2, it will be a step wise approach, starting by the first 5 sections and then the section 6 to 10 although section 10, dedicated to examples, can be prepared in parallel with the other sections.

Between September 2013 and June 2014

- Review the purpose of the manual
- Preparation of the Table of Contents

Between June and September 2014:

- Circulate the business plan and have a final version- by end June 2014.
- Identify leaders and contributors for section 1 to 5-by end June 2014.
- Draft sections 1 to 5 by September 2014.

5th CIOMS vaccine safety working group September 2014 in Rabat, Morocco :

- Review the section drafted; work on section 5 (establishing active surveillance).

Between September 2014 and February 2015

- Finalize section 3 to 5 (sections 1&2 would need to be completed as the manual is being developed) based on discussion of 5th meeting.
- Identify leaders and contributors for section 6 to 9.

First draft document December 2014 sections 1 to 5 for comments to the CIOMS working group TG2

6th CIOMS vaccine safety working group February 2015

- Review of key comments from first review.
- Work on key sections on role and responsibilities of the stakeholders (7, work initiated during the 4th meeting should be fine-tuned with the updated sections), including funding (section 9), and on communication mechanism (8).
- Choose examples for section 10 (examples of active surveillance studies from literature).

Between February 2015, June 2015 and September 2015

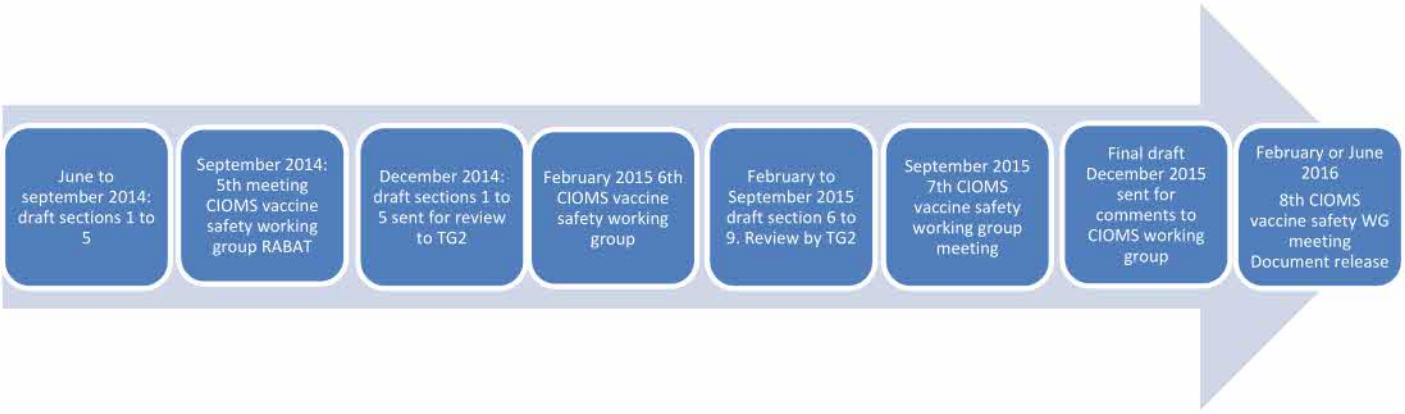
- Draft sections 6 to 10
- Circulate draft document within TG2

8th CIOMS vaccine safety working group September 2015

- Review of key comments

Final draft end of 2015 to be circulated to whole CIOMS working group + experts?

9th CIOMS vaccine safety working group February or June 2016
Final review of the manual
Document release : mid 2016



5. Management Key contributors

Each topic group 2 members will commit to the development and/or coordination of the various sections of the manual.

The section **leaders** will be responsible for coordinating the development of the designated section of the manual with the identified contributors, gathering comments and meeting deadlines.

Contributors will be responsible for providing inputs to the development of the section they committed to.

Editorial board will be responsible for coordinating and reviewing the different sections together to ensure consistency and harmonization of the whole manual.

To be completed during the TC June 19th....

Phase 1: development of section 1 to 5 (volunteers per TC on 19 June 2014)

Section	Leader	Contributors
1-Glossary	Novilia Bachtiar	Karin Holm
2-Abbreviations	Novilia Bachtiar	Karin Holm
3-Purpose	Françoise Sillan, Christine Maure	
4-Post Marketing safety surveillance	Christine Maure	Xavier Kurz, Irina Caplanusi, Terhi Kilpi
5-Establishing active safety surevillance	Corinne Jouqulet-Royer, Harry Seifert	Dawei Liu, Novilia Bachtiar, Xavier Kurz, Irina Caplanusi, David Martin/Scott Winiecki, Frank Destefano

Phase 2: development of section 6 to 9 (to be completed prior the February 2015 meeting)

Section	Leader	Contributors
6-Scientifc approach		
7-Role and responsibilities		
8-Communication mechanisme		
9-Funding		

6. Working Methods

All topic group member must be registered with SharePoint and have up-to-date info on the home page for contact info.

Teleconferences will be organized by section leaders at least once between each face to face meeting.

Lead :

Mimi Darko (alt)	Ghana WHO coll FDA
Françoise Sillan	Sanofi-Pasteur

Contribute :

Novilia Sjafri Bachtiar	Biofarma Indonesia
Frank DeStefano	CDC Atlanta
Amina Tebaa	Centre de PhV Morocco
Raja Benkirane (alt)	Centre de PhV Morocco
Dawei Liu	China CDC
Dong Duo	China Regulatory Authority
Ulf Bergman	CIOMS
Irina Caplanusi (alt)	EMA
Peter Arlett (alt)	EMA
Xavier Kurz	EMA
David Martin	
Scott Winiecki (alt)	FDA (but DM seconded to EMA jun-nov2014)
Alex Dodoo	Ghana WHO coll/ Food and Drugs Board
Harry Seifert	GSK
Mayur Patel (alt)	MedImmune/AstraZeneca
Michael Blum	MedImmune/AstraZeneca
Doris Oberle (Alt2)	Paul Erlich Institute (PEI), Germany
Dirk Mentzer (alt)	PEI
Keller-Stanislawski, Brigitte	PEI
Bill Gregory	Pfizer
Steven Bailey (alt)	Pfizer
Hanna Nohynek (alt)	THL,FI
Terhi Kilpi	THL,Finland
Sten Olsson (alt)	UMC WHO Collab Centre

Christine Maure (alt)	WHO
Patrick Zuber	WHO
Dr Fabien Diomande	WHO Intercountry Support Team for West Africa (but being seconded to CDC in Atlanta)

Additional Potential members ?:

Adrian Dana	Merck
Patricia Mandali de Figueiredo	ANVISA - Brazil
Sidarta Figueredo Silva (alt)	ANVISA- Brazil

Other key contributors ? (outside CIOMS working group?)

1. Needs (support and finance)
2. Support from CIOMS: share point, meetings
3. Support from WHO: consultant

Briefing -- CIOMS TG2 Active Surv - Thursday, 19 June, 3pm

Attending: Françoise Sillan, Corinne Jouquelet-Royer, Christine Maure, Karin Holm, Frank Destefano, Harry Seifert, Dong Duo, Terhi Kilpi, Novilia Bachtiar, Xavier Kurz, Irina Caplanusi, David Martin, Ulrich Heininger

Unable to join but wishing to be part of TG2: Mimi Darko (co-lead), Steven Bailey, Patricia Mandali, Sidarta Silva, Brigitte Keller-Stanislawski, Dirk Mentzer, Doris Oberle, Michael Blum, Mayur Patel, Dawei Liu (China CDC), Scott Winiecki (FDA).

Comments on draft business plan and Table of Contents.

- Idea to add examples of successful and unsuccessful active surveillance systems throughout the text (not just in section 10).
- Suggestion to add a literature search for additional examples.
- Some examples at GAVCS included studies conducted in northern Ghana and India.
- Although example are essential to illustrate the topics, it is critical to provide as well clear criteria to set up and conduct active surveillance systems. This is what has been done in preparation of malaria vaccine introduction. Choose also examples of not successful active surveillance
- Something about MeninAfriVac seemed population-based but turned out to be case finding from sentinel sites (?)
- The links proposed to be provided (see section 3-Strategy of the Business plan) in the document should be accompanied by explanation.
- Think about the involvement of external experts at the time of the review of the draft document (additional funds needed).

Review of key steps.

- Note usually 3 meetings per year (Jan-Feb, May-June, Sept-Oct). Usually two in Europe (which saves on expenses for us in general) and one farther afield.

- Everyone in the TG2 should identify relevant publications and examples and bring or send before Rabat.
- Note that the standard for CIOMS working groups, is that Contributors and Editorial Board are responsible for the actual writing.
- Karin can provide publication editing support but any external medical editing would need additional funding.
- Francoise will amend the business plan and the table of content based on the feedback received today, the document will be available for each leader in the sharepoint

Define leaders and contributors sections 1-5.

- 1&2 Glossary & Abbreviations – Lead Novilia (contrib. Karin)
- 3 Purpose – Lead Christine, Françoise
- 4 Post-marketing safety surv. – Lead Christine (contrib. Xavier&Irina, Terhi)
- 5 Estab. Active surv. – Lead Corinne and Harry (contrib. Dawei Liu, Novilia, Xavier&Irina, David& Scott, Frank, Terhi)

Next steps:
TC end of August beginning Sept.
Leads contact their contributors.

Table of Contents

1. Glossary
2. Abbreviations
3. Purpose

- To provide practical guidelines for implementing PV systems in LMIC
- To provide recommendations for roles and responsibilities for PV activities when a new vaccine is introduced into LMIC

Discussion:

- Economic consequences of surveillance – early detection and lower costs.
- To provide some ideas to address barriers.
- Have an effective system in place in advance.
- Discussion on programmatic questions.
- Document should provide an easy steps for conducting active surveillance.
- Should be a comprehensive document for all stakeholders.
- Should be a manual not a guideline.

---

4. Postmarketing safety surveillance.
    a. Rational for post marketing surveillance – Provide links to existing sources
        i. Definition - Provide links to existing definitions
        ii. Types of safety surveillance systems
            - Passive surveillance (spontaneous reporting)
              Decision to make mainly links to resources (WHO), discussion around the efficacy of this material.
                - Purpose for passive surveillance, link to WHO Global Immunization safety surveillance manual
                - List existing initiatives
            - Stimulated passive surveillance
              Discussion about different vocabulary possibilities: spontaneous targeted passive stimulated enhanced

surveillance (to be continuer post meeting).

- Purpose for stimulated passive surveillance, link to WHO Global Immunization safety surveillance manual.
- List existing initiatives

- Active surveillance

,

- Purpose for active surveillance
- list examples of types of active surveillance in use

5. Establishing active safety surveillance

a. Rational for active surveillance system (including the what: what vaccines and AEFI require active surveillance)

b. Who should set up active surveillance (list the different stakeholders)

c. When to set up active surveillance

d. Where to establish an active surveillance?
Discussion on conducting the surveillance in sentinel sites or the whole country: consensus to focus on good sustainable systems at a few sentinel sites.

- Needs for countries of reference for multicountry surveillance
- Minimum requirements for those countries of reference

e. How to establish an active surveillance system? List the requirements like:

- Establishing background rates

- Establishing sentinel sites (including how to select sentinel sites). Basic requirements for sentinel sites. Discuss limitations of sentinel sites (some would not be representative for the whole population).
  Presentation of one possible program from S. Black (Prevent)

  Expand on existing systems with broader possibilities, have permanent sentinel sites covering also vaccine surveillance, disease surveillance

- Tools, databases

Use of cell phones like in Nigeria

- Capture of exposure and of outcomes
- Methods for analysis
- Governance and Oversight, including monitoring

- Above Country Coordination
  To be developed, who should coordinate the whole safety surveillance system and how

6. Scientific approach of active safety surveillance
   - Different study designs
   - Analysis - Be able to pool the data, centralize results from different sources

7. Role and responsibilities of the Stakeholders

Three different scenarios for vaccine introduction in a LMIC:

A. Vaccine manufacturer introduce a new vaccine in a LMIC for public and private settings
B. The vaccine is supplied by a third party in a LMIC for vaccination campaign
C. Same as scenario 2 but the vaccine is not registered in the country

The role and responsibilities might be different from one scenario to another

- National Regulatory Agencies
- National committees for vaccines (if different from NRA)
- Regional and National Pharmacovigilance centers
- Sentinel sites
- Immunization programme
- Vaccine Manufacturers
- WHO and collaborating centers
- NGO and supply agencies (like GAVI)

- Immunization and health care providers
- Academia
- Community
- Media

8. Communication mechanism

Not limited to communication within the country but between each country involved in this program, to avoid redundancies and allow data pulling if appropriate

9. Funding

10. Examples of active surveillance studies from the literature

From: Corinne.Jouquelet-Royer@sanofipasteur.com
Sent: 27 Jun 2014 09:43:05 +0000
To: holmk@cioms.ch;Harry.A.Seifert@gsk.com;Zuber, Patrick (CDC who.int);maurec@who.int;Winiecki, Scott (FDA/CDER);terhi.kilpi@thl.fi;novilia@biofarma.co.id;Destefano, Frank (CDC/OID/NCEZID);(b)(6) Xavier.Kurz@ema.europa.eu;Irina.Caplanusi@ema.europa.eu;Martin, David (FDA/CDER);bergmanu@cioms.ch;Steven.R.Bailey@pfizer.com;Ayman.Ayoub@pfizer.com
Cc: Francoise.Sillan@sanofipasteur.com;(b)(6) ;bergmanu@cioms.ch
Subject: RE: CIOMS WG on VS TG2 section 5 - Fri 27 June 12noon (French time)
Attachments: TG2 TC Section 5 June 27.pptx

Dear all,
You will find attached the slides for our meeting today .
Sorry for the short notice
Regards
Corinne

Corinne Jouquelet-Royer, MD
Head Global Pharmacovigilance
TEL.: +33 (0)4.37.66.97.47 - CELL.: +33 (0)6.32.04.99.97
SIÈGE MONDIAL - 2, AVENUE PONT PASTEUR - 69367 LYON cedex 07 - France

From: Holm Karin [mailto:holmk@cioms.ch]
Sent: mardi 24 juin 2014 17:36
To: Jouquelet-Royer, Corinne (sanofi pasteur); 'Harry.A.Seifert@gsk.com'; 'Patrick Zuber (zuberp@who.int)'; 'maurec@who.int'; 'Winiecki, Scott'; 'terhi.kilpi@thl.fi'; 'Bachtiar (novilia@biofarma.co.id)'; 'fxd1@cdc.gov'; 'Dawei, Liu ((b)(6))'; 'Xavier.Kurz@ema.europa.eu'; 'Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu)'; 'David.Martin@fda.hhs.gov'; Bergman Ulf; 'Bailey (Steven.R.Bailey@pfizer.com)'; Ayman.Ayoub@pfizer.com
Cc: Sillan, Francoise (sanofi pasteur); 'Darko, Mimi ((b)(6) '; Bergman Ulf
Subject: RE: CIOMS WG on VS TG2 section 5 - Fri 27 June 12noon (French time)

Dear CIOMS TG2 section 5 Contributors:
Corinne and Harry are looking forward to talking with you on: **Fri 27 June 12noon (French time)**
Attached please find the latest version of the business plan (including the Manual Table of Contents) for discussion.

Agenda for TC

- Quick review of the section 5 to get alignment and shared understanding on what need to be achieved
- Agree on contributors to which sections
- And timelines for draft and reviews before September meeting

Sanofi Telecon dial in numbers
France : (b)(6) (toll free) or + (b)(6) (local)
Canada : (b)(6) (toll free) or + (b)(6) (local)
US : (b)(6) (toll free) or + (b)(6) (local)
Belgique : (b)(6) (toll free) or + (b)(6) (local)
Singapore : (b)(6)
Mexique - (b)(6)
Participant code : (b)(6)

Code PIN (CP) : (b)(6)

Additional Numbers can be found here: http://www.intercall.com/sanofi/numbers/index.htm

Wishing you good connections and hope all try to speak clearly, loudly, slowly for optimal communication!
Karin

Karin R. Holm
Technical Coordinator, Working Group on Vaccine Safety
Publications Consultant, Working Group IX Risk Minimization
Council for International Organizations of Medical Sciences (CIOMS)
Associate partner of UNESCO / In official relations with WHO
c/o WCC, P.O. Box 2100, CH-1211 Geneva 2, Switzerland
Phone: +41 22 791 6497 Website: www.cioms.ch
Email: holmk@cioms.ch

From: Holm Karin
Sent: 24 June 2014 11:36
To: Jouquelet-Royer, Corinne; Harry.A.Seifert@gsk.com; Patrick Zuber (zuberp@who.int); maurec@who.int; Winiecki, Scott; terhi.kilpi@thl.fi; Bachtiar (novilia@biofarma.co.id); fxd1@cdc.gov; Dawei, Liu (liudw929@126.com); Xavier.Kurz@ema.europa.eu; Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu); David.Martin@fda.hhs.gov; Bergman Ulf; Bailey (Steven.R.Bailey@pfizer.com)
Cc: Francoise.Sillan@sanofipasteur.com; Darko, Mimi (mimidarko66@yahoo.co.uk)
Subject: CIOMS WG on VS TG2 section 5 - Fri 27 June 12noon (French time)

Dear CIOMS TG2 Chapter 5 Contributors,

Corinne Jouquelet-Royer (Sanofi, who is new to the CIOMS WG but will eventually take over at some point in the future for Françoise, who is moving to a new area at Sanofi) and Harry Seifert (GSK) kindly offered to organize Chapter 5 of the Manual on Active Safety Surveillance. Ch.5 is the "meat of the manual" on Establishing Active Surveillance (see Table of Contents in business plan draft attached). The best day/time was this Friday, 27 June, 12pm French time. Sanofi kindly will arrange TC and send instructions on how to access.

Agenda for TC

- Quick review of the section 5 to get alignment and shared understanding on what need to be achieved
- Agree on contributors to which sections
- And timelines for draft and reviews before September meeting

	June 2014
	Fri 27
	12:00 PM
Karin Holm	NO
corinne jouquelet royer	OK
Harry Seifert	OK
Patrick Zuber	OK
Christine Maure	OK
Scott Winiecki (FDA)	OK
Frank DeStefano	NO
Terhi Kilpi	OK
Novilia Sjafri Bachtiar	OK
Xavier Kurz	OK
Dawei Liu	?

Irina Caplanusi	?
David Martin	?
Ayman Ayoub	?
Steven Bailey	NO
Ulf Bergman	NO
Count	8

Karin R. Holm
Technical Coordinator, Working Group on Vaccine Safety
Publications Consultant, Working Group IX Risk Minimization
Council for International Organizations of Medical Sciences (CIOMS)
Associate partner of UNESCO / In official relations with WHO
c/o WCC, P.O. Box 2100, CH-1211 Geneva 2, Switzerland
Phone: +41 22 791 6497 Website: www.cioms.ch
Email: holmk@cioms.ch

From: Holm Karin
Sent: 23 June 2014 16:05
To: 'Dawei, Liu (liudw929@126.com)'; 'Bachtiar (novilia@biofarma.co.id)'; 'Xavier.Kurz@ema.europa.eu'; 'Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu)'; 'David.Martin@fda.hhs.gov'; 'terhi.kilpi@thl.fi'; Bergman Ulf
Cc: 'Jouquelet-Royer, Corinne'; 'Francoise.Sillan@sanofipasteur.com'; 'Darko, Mimi (mimidarko66@yahoo.co.uk)'
Subject: RE: Doodle: Link for poll "CIOMS WG on VS TG2 section 5"

Dear Dawei Liu, Novi, Xavier, Irina, David, Terhi, Ulf…

We haven't yet heard from you if you are available at these times and we are trying to find the best time for a TC to work on Section 5 of the Manual on Active Safety Surveillance….

Hi, CIOMS WG on VS - TG2 Active Surveillance section 5
Corinne Jouquelet-Royer and Harry Seifert would like to have a TC to start the process moving on drafting section 5. Please let us know if you would be available any of these times by clicking on this doodle poll...
http://doodle.com/b6z8aicfaia92fbt
Thank you,
Karin

Most popular date: Friday, June 27, 2014 12:00 PM |

Top of Form

	June 2014	July 2014	
7 participants	**Fri 27 12:00 PM**	**Tue 1 5:00 PM**	**Wed 2 6:00 PM**
Karin Holm		✓	
corinne jouquelet royer	✓	✓	✓
Harry Seifert	✓	✓	✓
Patrick Zuber	✓		
Christine Maure	✓		
Scott Winiecki	✓		✓
Frank DeStefano			
	Friday, June 27, 2014 12:00 PM	Tuesday, July 1, 2014 5:00 PM	Wednesday, July 2, 2014 6:00 PM

Bottom of Form

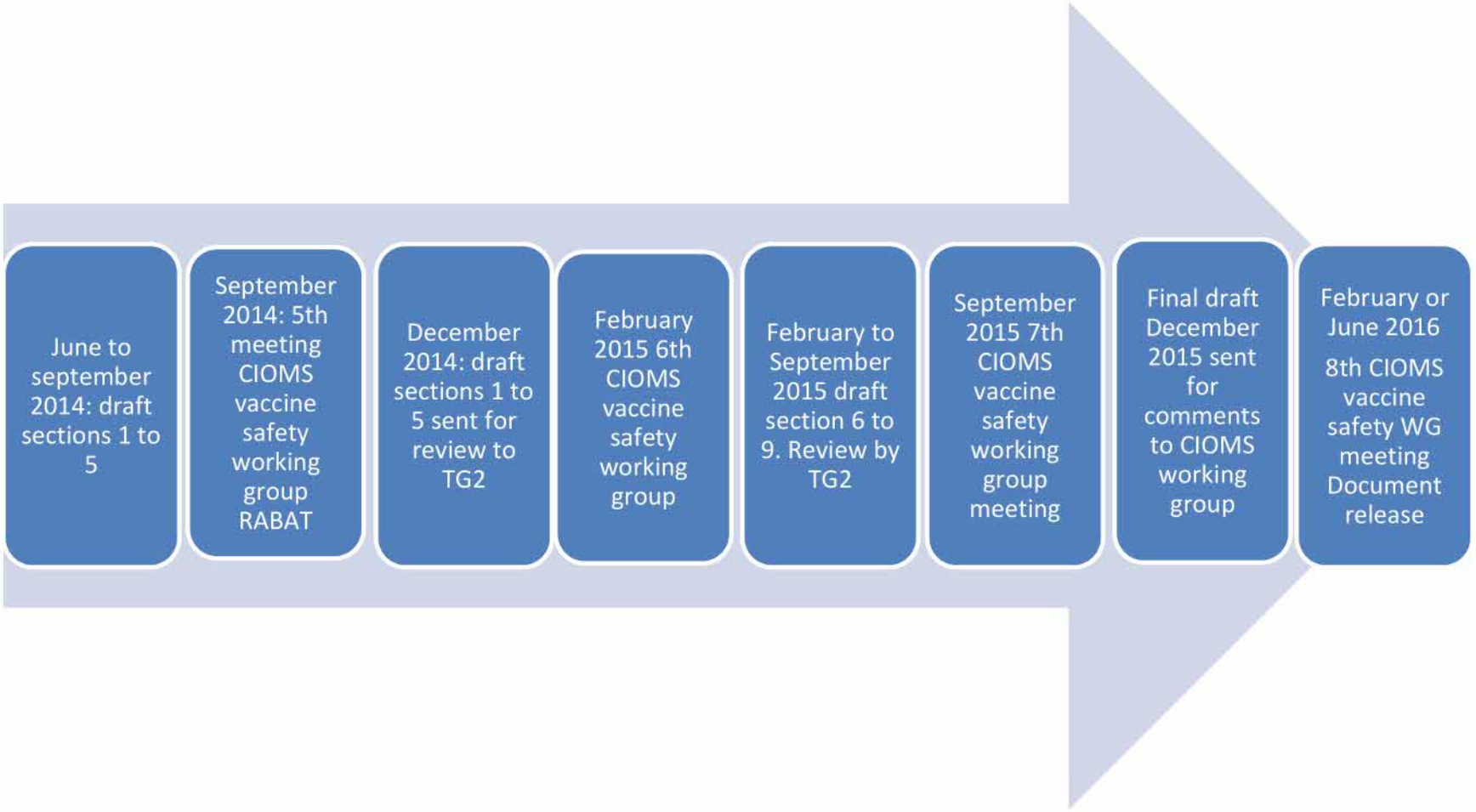
CIOMS VACCINE SAFETY WORKING GROUP

TOPIC GROUP 2Development of section 5

AGENDA

- Review of the section 5 to get alignment and shared understanding on what need to be achieved Agree on contributors to which sections.Agree on How we will work together? And timelines for draft and reviews before September meeting

Key steps


June to september 2014: draft sections 1 to 5
September 2014: 5th meeting CIOMS vaccine safety working group RABAT
December 2014: draft sections 1 to 5 sent for review to TG2
February 2015 6th CIOMS vaccine safety working group
February to September 2015 draft section 6 to 9. Review by TG2
September 2015 7th CIOMS vaccine safety working group meeting
Final draft December 2015 sent for comments to CIOMS working group
February or June 2016
8th CIOMS vaccine safety WG meeting Document release

Actions from Last Meetings

- Idea to add examples of successful and unsuccessful active surveillance systems throughout the text (not just in section 10). Suggestion to add a literature search for additional examples.Some examples at GAVCS included studies conducted in northern Ghana and India.Although example are essential to illustrate the topics, it is critical to provide as well clear criteria to set up and conduct active surveillance systems. This is what has been done in preparation of malaria vaccine introduction. Choose also examples of not successful active surveillanceSomething about MeninAfriVac seemed population-based but turned out to be case finding from sentinel sites (?)The links proposed to be provided (see section 3-Strategy of the Business plan) in the document should be accompanied by explanation.Think about the involvement of external experts at the time of the review of the draft document (additional funds needed).

List of volunteers

- Leaders : Harry Seifert , Corinne Jouquelet-Royer ContributorsLiu DaweiNovilia BachtiarXavier Kurtz & Irina CaplanusiDavid Martin and Scott WiniekyFrank DestefanoTehri Kilpi

Section 5 Overview

Section & Sub sections	Contributors	Key Content	Action Items
5.1 Rationale for ASS (a)			
5.2 Points to consider for setting up (c, b, d)			
5.3 How (e) including examples (?)			
5.4 Governance			

Section 5.1 Overview
Lead : ?

Contributors	Key Content	Action Items

Section 5.2 Overview
Lead: ?

Contributors	Key Content	Action Items

Section 5.3 Overview
Lead: ?

Contributors	Key Content	Action Items

Section 5.4 Overview
Lead: ?

Contributors	Key Content	Action Items

Next steps

From: Kuter, Barbara J.
Sent: 14 Jul 2015 18:27:34 -0400
To: Markowitz, Lauri (CDC/OID/NCIRD);Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Article 20 - EMA - HPV Vaccines - CONFIDENTIAL
Attachments: WC500189476.pdf0.pdf, WC500189477.pdf0.pdf, WC500189478.pdf0.pdf, WC500189479.pdf0.pdf

Lauri & Frank,
Here are all the documents that were posted on the EMA website in regards to this review.
Please let me know if you have any questions.
Thanks.
Barb

From: Kuter, Barbara J.
Sent: Friday, July 10, 2015 3:35 PM
To: Markowitz, Lauri (CDC/OID/NCHHSTP); Destefano, Frank (CDC/OID/NCEZID) (fxd1@cdc.gov)
Subject: Article 20 - EMA - HPV Vaccines - CONFIDENTIAL

Lauri & Frank,
Just a heads up. We were just informed that the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA will start a review of HPV vaccines to further clarify aspects of their safety profile. Specifically, the review will focus on rare reports of CRPS and POTS. The review does not question that the benefits of HPV vaccines outweigh their risks.
The official announcement from the EMA will be published online on Monday. I will send you a copy once available.
You may want to share with your colleagues as you may get questions or be asked for data.
Barb

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 July 2015
EMA/454979/2015

EMA to further clarify safety profile of human papillomavirus (HPV) vaccines

The European Medicines Agency (EMA) has started a review of HPV vaccines to further clarify aspects of their safety profile. These vaccines have been used in around 72 million people worldwide and their use is expected to prevent many cases of cervical cancer (cancer of the neck of the womb) and various other cancers and conditions caused by HPV. Cervical cancer is the 4th most common cause of cancer death in women worldwide, with tens of thousands of deaths in Europe each year despite the existence of screening programmes to identify the cancer early. The review does not question that the benefits of HPV vaccines outweigh their risks.

As for all licensed medicines the safety of these vaccines is monitored by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC). The current review will look at available data with a focus on rare reports of two conditions: complex regional pain syndrome (CRPS, a chronic pain condition affecting the limbs) and postural orthostatic tachycardia syndrome (POTS, a condition where the heart rate increases abnormally after sitting or standing up, causing symptoms such as dizziness and fainting, as well as headache, chest pain and weakness).

Reports of these conditions in young women who have received an HPV vaccine have been previously considered during routine safety monitoring by the PRAC but a causal link between them and the vaccines was not established. Both conditions can occur in non-vaccinated individuals and it is considered important to further review if the number of cases reported with HPV vaccine is greater than would be expected.

In its review the PRAC will consider the latest scientific knowledge, including any research that could help clarify the frequency of CRPS and POTS following vaccination or identify any causal link. Based on this review, the Committee will decide whether to recommend any changes to product information to better inform patients and healthcare professionals. While the review is ongoing there is no change in recommendations for the use of the vaccine.

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

More about the medicine

HPV vaccines are available in the European Union under the names Gardasil/Silgard, Gardasil 9, and Cervarix. Gardasil has been authorised since September 2006, and is approved in both males and females for preventing precancerous growths and cancer in the cervix and anus, and genital warts. It protects against 4 types of HPV (types 6, 11, 16 and 18). Gardasil 9 (approved in June 2015) is used similarly but protects against 9 types of the virus (6, 11, 16, 18, 31, 33, 45, 52 and 58). Cervarix has been approved since September 2007 for use in women and girls to protect against precancerous growths and cancer in the cervix and genital area. It is active against types 16 and 18 of the virus. Following their approval, the vaccines have been introduced in national immunisation programs in many countries worldwide.

More about the procedure

The review of HPV vaccines has been initiated by the European Commission at the request of Denmark, under Article 20 of Regulation (EC) No 726/2004.

The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations. The PRAC recommendations will then be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt a final opinion. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09 July 2015
EMA/PRAC/454436/2015

PRAC List of questions

To be addressed by the marketing authorisation holders

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Human papillomavirus (HPV) vaccines

Cervarix: EMEA/H/A20/1421/C/0721/0071

Gardasil: EMEA/H/A20/1421/C/0703/0060

Gardasil 9: EMEA/H/A20/1421/C/3852/0001

Silgard: EMEA/H/A20/1421/C/0732/0054

Marketing authorisation holders: GlaxoSmithKline Biologicals; Merck Sharp & Dohme Limited; Sanofi Pasteur MSD

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. Background

Human papillomavirus (HPV) vaccines have been authorised in Europe for prevention of cervical and various other cancers caused by HPV infection since 2006. Routine surveillance of suspected serious adverse drug reaction reports of the HPV vaccines have raised questions on the potential association between the use of the vaccines and in particular two syndromes, known as Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS).

The vast majority of the reported cases do not have a well-defined diagnosis. The need was identified that overall scientific evidence of a potential association between HPV vaccination and the two syndromes should be reviewed and methodologies to further investigate the concerns should be defined, if appropriate. In addition, discussion is needed on whether there is evidence of a causal association between HPV vaccination and CRPS and/or POTS, if research efforts should be strengthened, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures.

In that respect the marketing authorisation holders (MAHs) are requested to respond to the following questions.

2. Questions

Question 1

The MAHs should provide a cumulative review of available data from clinical trials, post-marketing and literature in order to evaluate the cases of CRPS and POTS with their product.

Review and case detection methods should be clearly described and the evaluation should discuss whether the reported cases fulfil published or recognised diagnostic criteria.

Question 2

Please provide an in depth review of cases of CRPS and POTS observed within all clinical studies; with comparison of HPV vaccine groups and control groups. If differences are observed, please discuss potential explanations including risk factors for the development of CRPS and POTS.

Question 3

The MAHs should provide an analysis of the observed number of post-marketing cases of CRPS and POTS in association with their HPV vaccine in comparison to those expected in the target population, stratified by region, if available. The analysis should discuss the assumptions made with respect to the background incidence in the target population and also the influence of potential under-reporting of cases in association with HPV vaccines.

Question 4

The MAHs should provide a critical appraisal of the strength of evidence for a causal association with HPV vaccine for CRPS and POTS. This should consider the available published literature, including epidemiological studies, and also the possible causes and pathophysiology of CRPS and POTS and discuss whether there is biological basis for a possible causal association.

Question 5

The MAHs should discuss the need for possible risk minimisation tools and provide proposals as appropriate.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 July 2015
EMA/PRAC/454661/2015

Timetable for the procedure

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Human papillomavirus (HPV) vaccines

Cervarix: EMEA/H/A20/1421/C/0721/0071

Gardasil: EMEA/H/A20/1421/C/0703/0060

Gardasil 9: EMEA/H/A20/1421/C/3852/0001

Silgard: EMEA/H/A20/1421/C/0732/0054

Procedural step:	**Date**
Notification:	09 July 2015
Start of the procedure (PRAC):	July 2015 PRAC
List of questions:	09 July 2015
Submission of responses:	20 August 2015
Re-start of the procedure:	27 August 2015
Rapporteur/co-rapporteur assessment reports circulated to PRAC and to CHMP[1]	25 September 2015
Comments:	01 October 2015

[1] Committee for Medicinal Products for Human Use

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Send a question via our website www.ema.europa.eu/contact

Procedural step:	Date
PRAC list of questions to Scientific advisory group	October 2015 PRAC
Scientific advisory group (SAG)	Exact date to be confirmed
Updated Rapporteur/co-rapporteur assessment reports circulated to PRAC and to CHMP	28 October 2015
PRAC list of outstanding issues or PRAC recommendation to CHMP	November 2015 PRAC

NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the PRAC made by the European Commission:

Product Name(s) Procedure name HPV vaccines	- Cervarix (Bivalent HPV vaccine (types 16, 18) - Gardasil (quadrivalent HPV vaccine (types 6, 11, 16, 18) - Gardasil 9 (9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52 and 58) - Silgard (quadrivalent HPV vaccine (types 6, 11, 16, 18)
Active Substance(s)	All
Pharmaceutical form(s)	All
Strength(s)	All
Route of administration(s)	All
Marketing Authorisation Holder(s)	GlaxoSmithKline Biologicals S.A. Merck Sharp & Dohme LTD Sanofi Pasteur MSD, SNC

Human papillomavirus (HPV) vaccines have been authorised in Europe for prevention of cervical and various other cancers caused by HPV infection since 2006. Following approval, these vaccines have been introduced in national immunisation programs worldwide, including in most EU member states.

The efficacy and safety of these medicinal products has been clearly demonstrated and the benefit of these vaccines in protecting against HPV related diseases is well established. Since launch, approximately 55 million subjects are estimated to have been vaccinated with Gardasil worldwide. Cumulative marketing exposure to Cervarix is estimated as being around 17 million subjects worldwide.

Routine surveillance of suspected serious adverse drug reaction reports have raised questions on the potential association between the use of the vaccines and two syndromes in particular, which are known as Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS). The vast majority of the reported cases do not have a well-defined diagnosis. These syndromes have been reviewed repeatedly by the PRAC within routine safety follow up procedures, and a relationship with vaccination has not been established in these previous procedures.

For CRPS most common symptoms are severe pain, swelling and changes in the skin temperature and colour of the arms or legs, but may also include amongst other symptoms headache, general fatigue, coldness of the legs, limb pain and weakness. POTS is characterised by an abnormally large increase in heart rate when changing from a lying down to a standing up position, without any orthostatic hypotension. In POTS, this excessive heart rate increase may be accompanied by a range of symptoms which may include light headedness, visual blurring, palpitations, tremulousness and weakness (especially of the legs), as well as fatigue, shortness of breath, chest pain, concentration difficulties, and headaches.

Individual case reports and case series of CRPS and POTS have been reported in the literature following HPV vaccination from several geographically distinct locations. Literature reports of CRPS come from Australia, Germany and Japan and reports of POTS originate from USA, Japan and Denmark.

The Danish Health and Medicines Authority drew the attention of the EMA and the Commission to the issue mentioned above in July 2015. It considers that in view of the seriousness and increasing number of reports and publications raising concern in EU Member States, this safety issue should be evaluated to ensure that sufficient scientific knowledge on the potential relationship is established.

There are uncertainties regarding the underlying pathogenesis for CRPS and POTS and an association between HPV vaccination and CRPS or POTS has also not been established. These conditions have been well known for a long time and before the introduction of the HPV vaccines.

It is recognised that these conditions can occur in the general non-vaccinated population and it is considered important to undertake further review to determine whether the number of cases reported with HPV vaccine is greater than would ordinarily be expected.

The Danish Health and Medicines Authority underlined that the objective with HVP vaccination is to prevent serious life-threatening disease, the exposure of healthy individuals

to the vaccine is extensive, the risk-benefit balance should be favourable and the risks effectively monitored and well characterized.

The persisting uncertainty with regard to causal association between CRPS/POTS and HPV vaccination may have a significant impact on the future confidence in national vaccination programs.

Overall scientific evidence of a potential association between HPV vaccination and the two syndromes should be reviewed and methodologies to further investigate the concerns should be defined, if appropriate.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns for the centrally authorised medicinal product(s) (mentioned above). The EC requests the Agency to give its opinion as soon as possible and not later than 31 May 2016 on whether there is evidence of a causal association between HPV vaccination and CRPS and/or POTS, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures on the marketing authorisations concerned.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

[redacted]

9/7/2015

Sabine Jülicher
Head of Unit
European Commission
DG Health and Food Safety
Unit D5 - Medicinal products - authorisations, European Medicines Agency

From: Fernanda Tavares Da Silva
Sent: 7 Nov 2014 20:21:20 +0000
To: Broder, Karen (CDC/OID/NCEZID)
Cc: François P Roman;David Vaughn;Gronostaj, Michael (CDC/OPHSS/CSELS/DSEPD);Clark, Thomas A. (CDC/ONDIEH/NCCDPHP);Destefano, Frank (CDC/OID/NCEZID);Valentina Attanasi
Subject: Re: Ebola vaccine pharmacovigilence

Hi Karen,
In my opinion, that schedule does not allow to detect early onset lab abnormalities.
In addition, any abnormality detected at Day 28 would be then difficult to interpret.
Regards,
Fernanda
Sent from my iPhone

On 7 nov. 2014, at 21:06, Broder, Karen (CDC/OID/NCEZID) <krb2@cdc.gov> wrote:

> So to clarify
> If the blood draw is day 0 and 28, is it worth pursuing?
> It seems that the issue of lab norms is less important if you have a baseline and post comparison for an individual.
> Thanks,
> Karen
>
> **From:** Fernanda Tavares Da Silva [mailto:FERNANDA.TAVARES@GSK.COM]
> **Sent:** Friday, November 07, 2014 3:01 PM
> **To:** François P Roman
> **Cc:** Broder, Karen (CDC/OID/NCEZID); David Vaughn; Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); Valentina Attanasi
> **Subject:** Re: Ebola vaccine pharmacovigilence
>
> Dear all,
> My idea was to have (ideally) a grading system for laboratory values but this is actually dependent upon country or institutional normal reference ranges. I agree, this is a 'nice to have'. It's actually not included in the protocol we sent you.
> I don't believe the safety lab assessment would be then valuable in the schedule you mentioned below.
> Thanks!,
> Fernanda
> Sent from my iPhone
>
> On 7 nov. 2014, at 20:36, François P Roman <FRANCOIS.P.ROMAN@GSK.COM> wrote:
>
> > Dear All,
> > I concur with David that Grade 4 reporting is not systematic practice at GSK.
> > The ChAd3-EBO-Z IB is in progress and should be available in the couple of weeks to come.
> > Thanks and regards,

Francois

François Roman
Director
Clinical Research & Translational Science
Vaccine Discovery & Development
GSK
89 Rue de l'Institut
Rixensart 1330, Belgium
Email FRANCOIS.P.ROMAN@GSK.COM
Mobile +32 472 900 494
Tel +32 2 656 6738
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From: Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
Sent: Friday 7 November 2014 20:32
To: David Vaughn
Cc: Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); François P Roman; Fernanda Tavares Da Silva; Valentina Attanasi
Subject: RE: Ebola vaccine pharmacovigilence

David,

Hi. I think since we get temperature data it could be re-coded later into a 3 and 4 severity – but I doubt there will be many grade 3 or 4 fevers. And since lab date would be numerical maybe this could be done as a second step. I think pre-defining lab categories might be hard, especially if we don't have country norms of lab values.

Also we realized that blood draws would be at baseline and day 28 for immunogencity if feasible in a sub-set, so I wanted to double check that the safety lab assessment would be valuable with this schedule. I think it would be more complex to add an NEW blood draw at day 2 or 3.

Thanks ,

Karen

From: David Vaughn [mailto:david.w.vaughn@gsk.com]
Sent: Friday, November 07, 2014 2:27 PM
To: Broder, Karen (CDC/OID/NCEZID)
Cc: Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); François P Roman; Fernanda Tavares Da Silva; Valentina Attanasi
Subject: RE: Ebola vaccine pharmacovigilence

Karen,

I contributed only to early versions of the protocol. Francois, Fernanda, or Valentina may be able to provide a better reply though it is now evening before a 4-day weekend in Belgium. I agree, no Grade 4 in the protocol. We sometimes have a Grade 4 for fever above 40 though this protocol fever is to be recorded as a continuous variable for assessment in half-degree intervals. There can be Grade 4 for laboratory abnormalities but I do not see that table in the protocol either.

I only have the VRC IB. One is being developed for the GSK-sponsored Phase 2 studies. Typically, CRFs are only constructed after concept protocol approval. David.

From: Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
Sent: Friday, November 07, 2014 2:11 PM
To: David Vaughn
Cc: Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A.

(CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); François P Roman; Fernanda Tavares Da Silva; Valentina Attanasi
Subject: RE: Ebola vaccine pharmacovigilence

David,

Thanks a lot; this is very helpful. We were wondering if it would also be possible see the Investigator's brochure or any associated forms?

Also we didn't see any mention of Grade 4 severity in the protocol. Let us know if we missed that

Thanks and have a nice weekend.

Karen

From: David Vaughn [mailto:david.w.vaughn@gsk.com]
Sent: Friday, November 07, 2014 1:37 PM
To: Broder, Karen (CDC/OID/NCEZID)
Cc: Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); François P Roman; Fernanda Tavares Da Silva; Valentina Attanasi
Subject: RE: Ebola vaccine pharmacovigilence

Karen,

Attached you should find the Phase 2 study protocol draft for adults; today's version. It should not be necessary to exceed (or even match) the safety surveillance found in this study for your Phase 3.

Tom Clark, Have you received a version of the NIH Phase 3 protocol from Barney Graham?

David.

From: Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
Sent: Thursday, November 06, 2014 10:14 AM
To: David Vaughn
Cc: Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Ebola vaccine pharmacovigilence

Hi David,

I hope you are well. We are working on the vaccine safety sections and forms for the draft CDC Expanded Access protocol for Tom Clark's team. The sections are still evolving as we get input from the staff in the field.

We have been trying to harmonize safety definitions, to the extent practical, with the last version of the NIH protocol we have (Oct 24). Is this the most recent version? Also do you have any of the vaccine safety forms from this study that could be shared with us?

Lastly, we are wondering if it might be helpful to have a short call with you regarding the materials we are developing for safety monitoring, perhaps tomorrow Friday November 7, to get some input?

Thanks,

Karen

From: David Vaughn [mailto:david.w.vaughn@gsk.com]
Sent: Friday, October 31, 2014 7:06 AM
To: Broder, Karen (CDC/OID/NCEZID)
Cc: Iris De Ryck
Subject: Ebola vaccine pharmacovigilence

Karen,

Do have time next Tuesday or Wednesday to discuss post-marketing (or emergency use) PV in Africa? As the MAH for an Ebola vaccine, we need a Risk Management Plan which includes a PV plan for countries where the

vaccine will be used. Capacity building in the affected countries would be challenging. Stand-alone PV studies could be done using sentinel sites. This would all be separate from Phase 3 activities. There is a possibility that GSK will seek EU funding for such efforts and we would like to have an informal discussion with you about what such an effort might look like. If the NIH/GSK vaccine is safe and effective, good PV is of importance to all (including BARDA, CDC, NIH, and DoD) as a bad PV program could derail a good vaccine or identify late a signal that reflects a real problem.
Iris is our clinical safety lead for Ebola vaccine. We are both available Tuesday, 4 November from 0800-0900 and from 1030-1100 and Wednesday 0900-1000 and after 1100 (Iris, recall that Europe falls back on Sunday and so CET is just 5 hours ahead of Philly and Atlanta for a couple weeks).
Thanks, David.

David W. Vaughn, MD, MPH
Head, External R&D, North America
Vaccines Discovery & Development
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From: David Vaughn
Sent: 7 Nov 2014 18:37:08 +0000
To: Broder, Karen (CDC/OID/NCEZID)
Cc: Gronostaj, Michael (CDC/OPHSS/CSELS/DSEPD);Clark, Thomas A. (CDC/ONDIEH/NCCDPHP);Destefano, Frank (CDC/OID/NCEZID);François P Roman;Fernanda Tavares Da Silva;Valentina Attanasi
Subject: RE: Ebola vaccine pharmacovigilence
Attachments: 202091 (EBOLA Z CHAD3-005) concept protocol (07-NOV-2014) clean.docx

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David W. Vaughn, MD, MPH
Head, External R&D, North America

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Clinical Study Concept Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'institut 89,
1330 Rixensart, Belgium

Primary Study vaccine and number	• GlaxoSmithKline (GSK) Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A)
Other Study vaccine	• Placebo
eTrack study number and Abbreviated Title	202091 (EBOLA Z CHAD3-005)
Investigational New Drug (IND) number	*To be decided*
Date of concept protocol	Final for Quintiles: 07 November 2014
Title	Safety and immunogenicity study of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (GSK3390107A) in adults in Africa.
Detailed Title	A Phase 2, randomised, observer-blind, placebo-controlled, multi-country study to assess the safety and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (ChAd3-EBO-Z) (GSK3390107A), in adults 18 years of age and older in Africa.
Co-ordinating author	Joke Debruyn (XPE Pharma & Science for GSK Biologicals)

eTrack study number and Abbreviated Title	202091 (EBOLA Z CHAD3-005)
Investigational New Drug (IND) number	*To be decided*
Title	Safety and immunogenicity study of GSK Biologicals' investigational recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine (GSK3390107A) in adults in Africa.
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Contributing authors	• François Roman, Paul Gillard and Johan Vekemans, Clinical Research and Development Leads • Ripley Ballou, Vice President, Clinical Research and Translational Science • Muriel Debois, Project Statistician • Bart Spiessens, Lead Statistician • Iris De Ryck, Safety Representative • Vanja Van Asch, Project Delivery Lead • Isabelle Benoot, Study Delivery Lead • Nathalie Vandenhoudt (CVO-Europe for GSK Biologicals), Vaccine Supply Coordinator • Justine Sirmel (Aixial Pharma for GSK Biologicals), Study Data Manager • Patricia Bourguignon, GVCL Project Manager • Myriam Acosta (Business & Decision Life Sciences for GSK Biologicals), GVCL Study Manager • Pascal Peeters, Global Regulatory Representative • Michael Conger, Global Patent Representative

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

Ad5:	Adenovirus type 5
AE:	Adverse event
AIDS:	Acquired immune deficiency disease
ALT:	Alanine aminotransferase
ATP:	According-to-protocol
BDBV:	Bundibugyo ebolavirus
CBC:	Complete blood count
CDC:	Centers for Disease Control and Prevention
ChAd3:	Chimpanzee adenovirus type 3
ChAd3-EBO-Z:	Investigational EBOV vaccine encoded by chimpanzee-derived adenovirus
CI:	Confidence interval
CMI:	Cell-mediated immunity
CRO:	Contract research organisation
EBOV:	Ebolavirus Zaire
ELISA	Enzyme-linked immunosorbent assay
EVD:	Ebola virus disease
GCP:	Good Clinical Practice
GMT:	Geometric meant tires
GP:	Glycoprotein
GSK:	GlaxoSmithKline
HIV:	Human immunodeficiency virus
IB:	Investigator brochure
ICF:	Informed consent form
ICH:	International Conference on Harmonisation
ICS:	intracellular cytokine staining
IDMC:	Independent data monitoring committee

IEC:	Independent ethics committee
IRB:	Institutional review board
MACDP:	Metropolitan Atlanta Congenital Defects Program
MedDRA:	Medical Dictionary for Regulatory Activities
RESTV:	Ebolavirus Reston
RNA:	Ribonucleic acid
SAE:	Serious adverse event
SmPC:	Summary of product characteristics
SOP:	Standard operating procedure
SUDV:	Ebolavirus Sudan
TAFV	Ebolavirus Taï Forest
TVC:	Total vaccinated cohort
UK:	United Kingdom
US:	United States
vp:	Viral particles
VRC/NIAID:	Vaccine Research Center of the National Institute of Allergy and Infectious Diseases
WHO:	World Health Organization

GLOSSARY OF TERMS

Adequate contraception:

Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- estrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the vaccination centre's personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of childbearing potential with same sex partners, when this is their preferred and usual lifestyle.

Adverse event:

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (*i.e.* lack of efficacy), abuse or misuse.

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. **Observer-blind** means that the subject and the vaccination centre and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment. **Single-blind** means that vaccination centre and sponsor personnel are aware of the treatment assignment but the subject is not. **Open-label** means that no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol analysis (see Sections 7.4.2, 7.5 and 9.6 for details on criteria for evaluability).
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age *e.g.* > 45 years.
Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol'. GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Solicited adverse event:	Adverse events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Subset:	A subset is defined as a group of subjects for which additional assays are planned as compared to other subjects.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

1. INDICATION

The investigational ChAd3-EBO-Z vaccine is developed for prevention of Zaire Ebola virus disease (EVD).

2. INTRODUCTION

2.1. Background

2.1.1. Ebolavirus Zaire outbreak 2014

The EVD outbreak In West Africa was first recognised on 22 March 2014 in Guinea. By 27 October 2014, the epidemic had spread to Sierra Leone and Liberia, with a total of 13 676 cases in those 3 countries (including 4 910 deaths). Travel-associated cases were observed in Mali, Senegal, Nigeria, Spain and United States (US), with localised transmission in Nigeria, Spain and US. The outbreaks of EVD in Senegal and Nigeria were declared over on 17 October and 19 October 2014, respectively.

2.1.2. Ebolavirus and Zaire Ebola virus disease

The genus Ebolavirus is one of three genera in the family Filoviridae, which along with the genera, Marburgvirus and Cuevavirus, are known to induce viral haemorrhagic fever. The 5 distinct species included in the genus Ebolavirus are Bundibugyo (BDBV), Reston (RESTV), Sudan (SUDV), Taï Forest (TAFV), and Zaire (EBOV).

Ebola virus is a large, negative-strand RNA virus composed of 7 genes encoding viral proteins, including a single glycoprotein (GP). The virus is responsible for causing EVD in humans. In particular, BDBV, EBOV, and SUDV have been associated with large outbreaks of EVD in Africa and reported case fatality rates of up to 90% [World Health Organization (WHO), 2014a]. Transmission of Ebola virus to humans is not yet fully understood, but is likely due to incidental exposure to infected animals. EVD then spreads through human-to-human transmission, with infection resulting from direct contact with blood, secretions, organs or other bodily fluids of infected people, and indirect contact with environments contaminated by such fluids.

EVD has an incubation period of 2 to 21 days (mean 4 – 10) which is followed by an abrupt onset of non-specific symptoms such as fever, chills, malaise, and myalgia. The subsequent signs and symptoms indicate multisystem involvement and include systemic (prostration), gastrointestinal (anorexia, nausea, vomiting, abdominal pain, diarrhoea), respiratory (chest pain, shortness of breath, cough, nasal discharge), vascular (conjunctival injection, postural hypotension, oedema), and neurological (headache, confusion, coma) manifestations. Haemorrhagic manifestations consistent with disseminated intravascular coagulation arise during the peak of the illness and include petechiae, ecchymoses, uncontrolled oozing from venepuncture sites, mucosal haemorrhages, and post-mortem evidence of visceral haemorrhagic effusions. A macropapular rash associated with varying severity of erythema and desquamate can

often be noted by day 5 – 7 of the illness; this symptom is a valuable differential diagnostic feature and is usually followed by desquamation in survivors. Abdominal pain is sometimes associated with hyperamylasaemia and true pancreatitis. In later stages, shock, convulsions, severe metabolic disturbances, and, in more than half the cases, diffuse coagulopathy supervene. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes. In general, the symptoms last for about 7 - 14 days, after which recovery may occur. Death can occur 6 to 16 days after the onset of symptoms [Feldmann, 2011]. People are infectious as long as their blood and secretions contain the virus; the virus was isolated from semen 61 days after onset of illness in a man who was infected in a laboratory [WHO, 2014b].

2.1.3. GSK Biologicals' investigational ChAd3-EBO-Z vaccine

The replication deficient investigational EBOV vaccine encoded by chimpanzee-derived adenovirus (ChAd3-EBO-Z) was developed by the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (VRC/NIAID) in the US using the Okairos adenovirus vaccine platform technology, which was acquired by GlaxoSmithKline (GSK) Biologicals in May 2013. The DNA fragment inserted in the ChAd3 vector encodes the EBOV GP, which is expressed on the virion surface and is critical for attachment to host cells and catalysis of membrane fusion. A single dose of 10^{10} viral particles (vp) of ChAd3-EBO-Z provided 100% protection 4 - 5 weeks after vaccination in cynomolgous macaques [Stanley, 2014].

Serological studies showed a low seroprevalence in human sera for antibodies to ChAd3, and when present, antibody titres were low [Colloca, 2012]. Adenovirus type 5 (Ad5; a common adenovirus infection of humans) pre-existing immunity did not appear to cross-react with ChAd3 in mice [Peruzzi, 2009]. ChAd3-based vaccines were capable of inducing an immune response and protection comparable to human Ad5 vectored vaccine even in those with pre-existing immunity against Ad5.

2.2. Rationale for the study and study design

2.2.1. Rationale for the study

On 7 August 2014, WHO requested that GSK "fully engages in WHO-coordinated efforts to test, license and make available safe and effective Ebola interventions" to assist in the control of the outbreak in Western Africa. Given the severity of the situation, time to vaccine deployment was an important aspect of the WHO request. In response to this call, an accelerated Phase 1/2, dose-finding vaccine development effort was initiated mid-August that involved WHO, GSK, VRC/NIAID, the University of Oxford, the University of Maryland and the University of Lausanne and the Centre for Vaccine Development in Mali.

Using the ChAd3-EBO-Z dose selected during the Phase 1/2 stage, the present Phase 2, randomised, placebo-controlled trial will aim at collecting robust safety and immunogenicity data following a single injection of the investigational ChAd3-EBO-Z vaccine.

The study will be conducted in adults living in multiple countries from Western to Central Africa, which are adjacent to the current Ebola outbreak zones.

2.2.2. Rationale for the study design

The ChAd3-EBO-Z dose will be selected based on the safety, reactogenicity and immunogenicity data collected in Phase 1/2 studies.

In this Phase 2 study in ~3 000 adults in Africa, the safety and immunogenicity of the selected investigational ChAd3-EBO-Z vaccine will be assessed. The investigational vaccine will be administered as a single intramuscular injection seeking to induce rapid, potentially protective, immune responses.

Considering the risk of exposure to Ebola and the potential (based on animal data) for the investigational ChAd3-EBO-Z vaccine to afford at least partial protection, all subjects in the study will receive the investigational ChAd3 EBO-Z vaccine. The subjects in the Group EBO-Z will receive the vaccine at Day 0 of the study, whereas the subjects in the Group Placebo/ EBO-Z will receive a placebo at Day 0 (as a control) and will receive the investigational ChAd3-EBO-Z vaccine at Month 6 (provided that no safety concerns are raised by the independent data monitoring committee (IDMC) [refer to Section 8.5 for more information on the IDMC]). In addition, vaccinating all subjects in the study with the investigational ChAd3-EBO-Z vaccine will allow to increase the safety database of the investigational vaccine. In case the geographic range of EBOV transmission expands to encompass any of the regions where this trial is conducted, earlier administration of the investigational ChAd3-EBO-Z vaccine to the subjects in the Group Placebo/ EBO-Z will be considered in that region.

2.2.3. Rationale for the use of placebo

There is no known active, licensed comparator for the investigational ChAd3-EBO-Z vaccine.

The use of a placebo control is therefore considered as an acceptable approach to have an unbiased estimation of the safety and tolerability in the vaccine in a population with high rates of co-morbidities.

2.3. Risk: Benefit Assessment

All subjects in the study will receive a single dose of the investigational ChAd3-EBO-Z vaccine (either at Day 0 or at Month 6 of the study).

Please refer to the current investigator brochure (IB) for general information on potential risks and benefits of the investigational ChAd3-EBO-Z vaccine. The following section outlines the risk assessment and mitigation strategy for this study protocol.

2.3.1. Risk Assessment

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. These are however very rare and are estimated to occur once per 450 000 vaccinations to once per 1 000 000 for vaccines which do not contain allergens such as gelatine or egg protein [Zent, 2002]. In order to be able to treat subjects with an immediate systemic allergic reaction to vaccination, all subjects will need to remain under observation (*i.e.* visibly followed; no specific procedure) at the vaccination centre for at least 30 minutes after vaccination.

Local adverse events (AEs) observed in Phase 1 trials with dosages equal to or higher to the dosage that will be used in the current study were mostly mild and included local injection site pain, swelling, redness, warmth and itch as for any intramuscular vaccination. General AEs observed to date include malaise, myalgia, arthralgia, headache, fatigue, chills, feverishness or fever and nausea. The general AEs rarely exceeded mild to moderate severity. Most AEs occurred within the first 2 days after vaccination and were self-limiting within 48 hours. In addition to the local and general AEs described above, some mild to moderate self-limiting lymphopenia and transient (mostly self-limiting within 7 days) decrease in haemoglobin levels have been observed. To mitigate the risks linked to lymphopenia and decrease in haemoglobin levels, subjects with clinically significant abnormal haematology (including lymphocyte count and haemoglobin levels) or biochemistry parameters will be excluded from trial participation. In addition, haematology and biochemistry parameters will be closely followed up after vaccination at Day 0 (assessment on day 3 and day 6 after vaccination).

2.3.2. Benefit Assessment

Benefits linked to the investigational ChAd3-EBO-Z vaccine

The subjects in this study may not directly benefit from vaccination with the investigational ChAd3-EBO-Z vaccine as the vaccine has not been assessed in subjects exposed to EVD yet and it is hence not known whether it is effective in protecting against EVD. Moreover, this study will be conducted in countries adjacent to the current Ebola outbreak zone and the subjects in this study possibly may never come in contact with EBOV.

An indirect benefit is that the information obtained in this study will aid the development of a vaccine against EVD.

Other benefits

Another benefit for the subjects may include the gaining of information about their general health status through the medical evaluations/ assessments associated with this study (physical examination, HIV serostatus, blood testing [haematology and biochemistry data]). All subjects participating to the Screening Visit of this study will be medically examined including testing for haematological (complete blood count [CBC]) and biochemical (alanine aminotransferase [ALT] and creatinine).Those subjects with clinically significant disease who are not eligible for study participation will be referred for medical care to local facilities. Those subjects who are eligible and participate in the

study will receive medical follow-up during the study. Costs for diagnosis and acute care according to local standards will be covered during the study.

2.3.3. Overall Risk: Benefit Conclusion

The investigational ChAd3-EBO-Z vaccine is currently in an early stage of clinical development and no vaccine efficacy has been demonstrated. Measures are taken to minimise the risk to subjects participating in this study.

3. OBJECTIVES

3.1. Primary objective

- To assess the safety and reactogenicity of a single intramuscular dose of the ChAd3-EBO-Z vaccine.

Refer to Section 9.1 for the definition of the primary endpoints.

3.2. Secondary objective

- To assess the humoral immunogenicity of a single intramuscular dose of the ChAd3-EBO-Z vaccine, in terms of anti- GP EBOV antibody responses.

Refer to Section 9.2 for the definition of the secondary endpoint.

3.3. Tertiary objectives

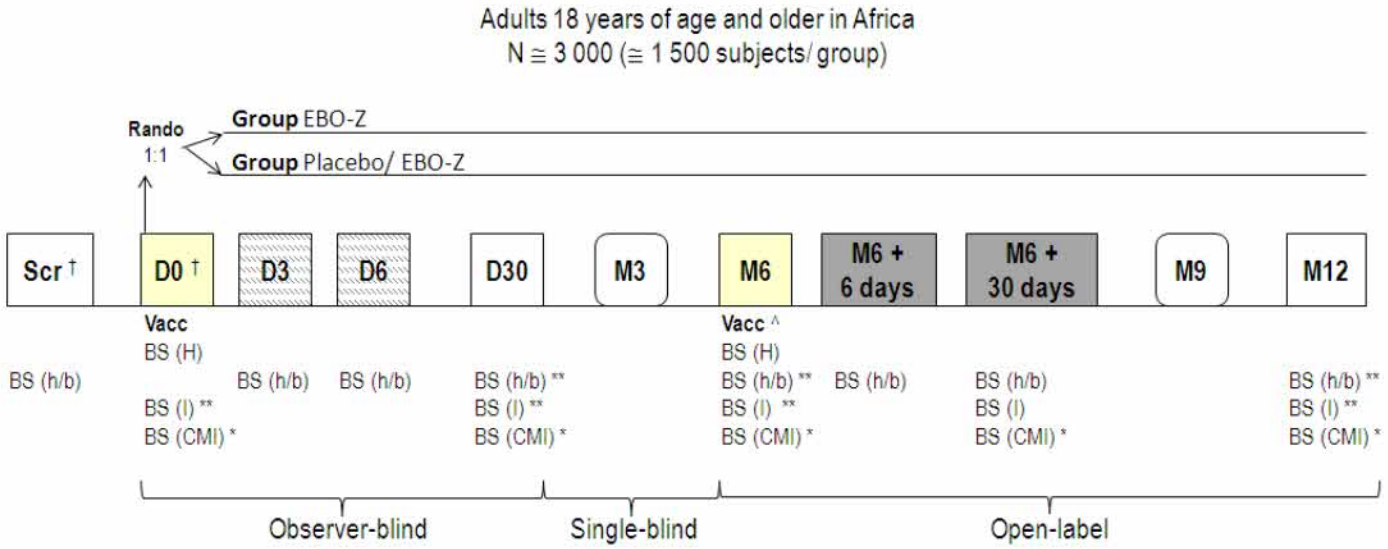
- To assess the persistence of the humoral response induced by a single intramuscular dose of the ChAd3-EBO-Z vaccine, in terms of anti-GP EBOV antibody responses.
- To assess the humoral immunogenicity and the persistence of the humoral immune response induced by a single intramuscular dose of the ChAd3-EBO-Z vaccine, in terms of anti-GP SUDV antibody responses.
- To assess EBOV- and SUDV-specific cell-mediated immunity (CMI) of a single intramuscular dose of the ChAd3-EBO-Z vaccine.
- To assess the pre-existing immunity to the ChAd3 virus vaccine vector prior vaccination, ChAd3-specific immune responses after vaccination and explore its potential impact on Ebola-specific immune responses.
- If deemed necessary, to further characterise the immune response to/ the safety profile of the investigational ChAd3-EBO-Z vaccine.

Refer to Section 9.3 for the definition of the tertiary endpoints.

4. STUDY DESIGN OVERVIEW

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 6.3), are essential and required for study conduct.

Figure 1 Study design overview



Scr = Screening; **D** = Day; **M** = Month; **Rando** = randomisation; **BS (h/b)** = blood sample for haematology/ biochemistry parameters; **BS (H)** = blood sample for determination of HIV serostatus; **BS (I)** = blood sample for humoral immunity; **BS (CMI)** = blood sample for cell-mediated immunity.
Squares indicate visits to the vaccination centre. Rounded rectangles indicate study contacts (home visit or phone call).
Yellow-coloured visits indicate vaccination visits. At the Day 0 visit, subjects in Group EBO-Z receive the investigational ChAd3-EBO-Z vaccine and subjects in Group placebo/ EBO-Z receive a placebo. At the Month 6 visit, subjects in Group Placebo/ EBO-Z receive the investigational ChAd3-EBO-Z vaccine.
Dashed visits are only applicable for subjects in the sub-cohort for follow-up of adverse events (AEs) and assessment of humoral immunity.
Grey coloured visits are only applicable for subjects in the sub-cohort for follow-up of AEs and assessment of humoral immunity in the Group Placebo/ EBO-Z.
The subjects in the sub-cohort for follow-up of AEs and assessment of humoral immunity will be followed up for AEs on a daily basis during the 7-day follow-up period after vaccination (day 0 to 6). During this period, AEs will be recorded on a Diary Card. For subjects who have difficulties completing a Diary Card, Home visits will be scheduled on those days that no study visit is planned.
† The Screening Visit and the Day 0 visit may take place on the same day (allowed interval 0 - 30 days).
^ Only for subjects in Group Placebo/ EBO-Z.
* Only for subjects in the sub-cohort for CMI.
** Only for subjects in the sub-cohort for follow-up of AEs and assessment of humoral immunity.

- **Experimental design:** Phase 2, randomised, observer-blind, placebo-controlled, multi-country study with 2 groups.
- **Duration of the study** for each subject enrolled will be approximately 12 months from the Day 0 visit.
  - Epoch 001: Primary starting at Screening and ending at the Month 12 visit.
- **Study groups**:
  - **Group EBO-Z**: ~1 500 adults.
  - **Group Placebo/ EBO-Z**: ~1 500 adults.

Table 1 Study groups and epochs foreseen in the study

Study group	Number of subjects	Age	Epochs
			Epoch 001
EBO-Z	~1500	18 years of age and older	x
Placebo/ EBO-Z	~1500	18 years of age and older	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		EBO-Z	Placebo/ EBO-Z
ChAd3-EBO-Z	ChAd3-EBO-Z	x (Day 0)	x (Month 6)
Placebo	PBS (Formulation buffer S9b)		x (Day 0)

PBS = phosphate-buffered saline

- **Control**: Placebo control.
- **Vaccination schedule**:
  - Subjects in Group EBO-Z will receive 1 vaccination: the investigational ChAd3-EBO-Z vaccine at the Day 0 visit.
  - Subjects in Group Placebo/ EBO-Z will receive 2 vaccinations: a placebo at the Day 0 visit and the investigational ChAd3-EBO-Z vaccine at the Month 6 visit.
- **Treatment allocation**: Subjects will be randomised (1:1) at Day 0. The randomisation will use a minimisation procedure accounting for age, gender, occupation and centre.
- **Blinding**:
  - **Observer-blind** from study start until the interim analysis that will be conducted when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0 (refer to Section 9.10.1 for more information on this interim analysis).
  - **Single-blind** from interim analysis until vaccination at Month 6.
  - **Open-label** as of vaccination at Month 6.

- **Sampling schedule**:
  - A blood sample for **determination of HIV serostatus** will be taken from all subjects at the Day 0 and the Month 6 visits.
  - Blood samples for **haematology/ biochemistry** assessment will be taken:
    - From all subjects at Screening.
    - From a sub-cohort of 750 subjects per group at the Day 3, Day 6, the Day 30, the Month 6 and the Month 12 visits.
    - From a sub-cohort of 750 subjects in the Group Placebo/ EBO-Z at the Month 6+ 6 days and the Month 6 + 30 days visit.
  - Blood samples for **humoral immunity** will be taken:
    - From a sub-cohort of 750 subjects per group at the Day 0, the Day 30, the Month 6 and the Month 12 visits.
    - From a sub-cohort of 750 subjects in the Group Placebo/ EBO-Z at the Month 6 + 30 days visit.
  - Blood samples for **CMI** will be taken:
    - From a sub-cohort of 100 subjects per group at the Day 0, the Day 30, the Month 6 and the Month 12 visits.
    - From a sub-cohort of 100 subjects in the Group Placebo/ EBO-Z at the Month 6 + 30 days visit.
- **Type of study**: self-contained.
- **Data collection**: eSource.

5. STUDY COHORT

5.1. Number of subjects/ centres

The target is to enrol approximately 3 000 eligible adults (approximately 1 500 per group). Refer to Section 9.4 for a detailed description in the criteria used in the estimation of sample size.

This study will be conducted in multiple countries in West and Central Africa.

5.2. Sub-cohorts

A sub-cohort is defined as a group of subjects for whom specific procedures are planned as compared to other subjects. There will be 2 sub-cohorts in this study:

- The first ~750 subjects enrolled in each group (~1 500 subjects in total) will be part of the sub-cohort for follow-up of AEs and assessment of humoral immunity. For these subjects:

  - Solicited AEs will be recorded during a 7-day follow-up period and unsolicited AEs will be recorded during a 30-day follow-up period after vaccination.
  - Haematology/ biochemistry parameters will be assessed throughout the study.
  - A blood sample for assessment of humoral immunity will be taken at certain study visits.
- The first ~100 subjects enrolled in each group (~200 subjects in total) will be part of the sub-cohort for CMI. A blood sample for assessment of CMI should be taken from these subjects at certain study visits.

Table 3 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
Sub-cohort for follow-up of AEs and assessment of humoral immunity	For these subjects: • Solicited AEs will be recorded during a 7-day follow-up period and unsolicited AEs will be recorded during a 30-day follow-up period after vaccination. • Haematology/ biochemistry parameters will be assessed throughout the study. • A blood sample for assessment of humoral immunity will be taken at certain study visits.	~750 subjects per group (~1 500 subjects in total)
Sub-cohort for CMI	A blood sample for assessment of CMI will be taken from these subjects at certain study visits.	~100 subjects per group (~200 subjects in total)

5.3. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (*e.g.* capability of or availability for Diary Card completion, return for follow-up visits, availability for clinical follow-up throughout the study period).
- Written/ thumb printed informed consent obtained from the subject prior to performing any study specific procedure.
- A male or female aged 18 years of age or older at the time of first study vaccination.
- Healthy subjects as per investigator judgement, as established by medical history, clinical examination and haematology/ biochemistry laboratory parameters screening before entering into the study.

- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the glossary of terms for the definition of menarche and menopause.

- Female subjects of childbearing potential may be enrolled in the study, if the subject:
  - has practiced adequate contraception for 30 days prior to the Day 0 visit, and
  - has a negative pregnancy test at the Day 0 visit, and
  - has agreed to continue adequate contraception until 30 days after the Month 6 visit.

Please refer to the glossary of terms for the definition of adequate contraception.

5.4. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the Day 0 visit, or planned use during the study period.
- Previous vaccination with an investigational EBOV or Marburg vaccine, or previous vaccination with a chimpanzee adenoviral vectored investigational vaccine.
- Known prior EBOV or SUDV disease.
- History of any reaction or hypersensitivity (such as anaphylaxis, urticaria (hives), respiratory difficulty, angioedema, or abdominal pain) likely to be exacerbated by any component of the study vaccine
- Planned administration/ administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after each vaccination visit.
- Serious acute or chronic illness determined by medical history and clinical examination including, but not limited to:
  - Clinically significant immunosuppressive or immunodeficient condition (*e.g.* clinical AIDS).
  - Any clinically significant haematological (CBC) and biochemical (ALT, creatinine) laboratory abnormality.
  - Any chronic illness with recent signs of exacerbation, or imposing a change in the chronic treatment regimen, within 3 months prior to the Day 0 visit.

  - Any unstable chronic medical condition (*e.g.* uncontrolled asthma).

- Pregnant female.

6. CONDUCT OF THE STUDY

6.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK Biologicals/ the contracted research organisation (CRO) engaged to conduct the study will obtain favourable opinion/ approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a vaccination centre initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) review and favourable opinion/ approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK Biologicals/ the CRO will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject prior to participation in the study.

GSK Biologicals/ the CRO will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's/ the CRO's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/ IEC.

6.2. Method of blinding

The blinding level will change in the course of the study:

- **Observer-blind** from study start until the interim analysis that will be conducted when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0 (refer to Section 9.10.1 for more information on this interim analysis). Given the different appearance of the investigational ChAd3-EBO-Z vaccine and the placebo, double-blinding is not possible and this part of the study will be conducted in an observer-blind manner. By observer-blind, it is meant that the vaccine recipient and those responsible for the evaluation of any study endpoint will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration at Day 0 will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays.
- **Single-blind** as of the interim analysis until vaccination at Month 6. At the time of the interim analysis, the study will become single-blind to ensure full data availability. By single-blind, it is meant that vaccination centre and sponsor personnel are aware of the treatment assignment but the subject is not. Note that the blind will be kept as much as possible at the vaccination centre, including for the vaccination centre staff.
- **Open-label** as of Month 6.

For samples collected during the observer-blind part of the study, the laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

6.3. Outline of study procedures

6.3.1. List of study procedures

6.3.1.1. Visits to the vaccination centre

Table 4 List of study procedures during visits to the vaccination centre

Type of contact	Visit	Visit	Visit	Visit	Visit	Contact *	Visit	Visit	Visit	Contact *	Visit
Timepoint	**Screening [1]**	**Day 0 [1]**	**Day 3 [2]**	**Day 6 [2]**	**Day 30**	**Month 3**	**Month 6**	**Month 6 + 6 days [2,3]**	**Month 6 + 30 days [2,3]**	**Month 9**	**Month 12**
Subjects participating to this visit/ contact	**All**	**All**	**Sub-cohort ******	**Sub-cohort ******	**All**	**All**	**All**	**Group Placebo/ EBO-Z in sub-cohort ******	**Group Placebo/ EBO-Z in sub-cohort ******	**All**	**All**
Informed consent	●										
Inclusion/exclusion criteria	●	O									
Demographic data	●										
Medical history	O	●									
Physical examination (including vital signs) [4]	●	● [5]	●	●	●		●	●	●		●
Unblinding							O				
Urine pregnancy test [6]	●	● [7]					● [3]				
Pre-vaccination body temperature		●					● [3]				
Check contraindications to vaccination		O					O [3]				
Study group and treatment number allocation [8]		O					O [3]				
Vaccination		●					● [3]				
Recording of administered treatment number		O					O [3]				
30 minutes post-vaccination observation		O					O [3]				
Blood sampling											
HIV testing [9]		●					●				

Type of contact	Visit	Visit	Visit	Visit	Visit	Contact *	Visit	Visit	Visit	Contact *	Visit
Timepoint	**Screening [1]**	**Day 0 [1]**	**Day 3 [2]**	**Day 6 [2]**	**Day 30**	**Month 3**	**Month 6**	**Month 6 + 6 days [2,3]**	**Month 6 + 30 days [2,3]**	**Month 9**	**Month 12**
Subjects participating to this visit/ contact	**All**	**All**	**Sub-cohort ******	**Sub-cohort ******	**All**	**All**	**All**	**Group Placebo/ EBO-Z in sub-cohort ********	**Group Placebo/ EBO-Z in sub-cohort ********	**All**	**All**
Blood for haematology/ biochemistry (~x mL)	●		●	●	● [2]		● [2]	●	●		● [2]
Blood for humoral immunity (~x mL) [2]		●			●		●		●		●
Blood for CMI (~x mL) [10]		●			●		●		●		●
Safety follow-up											
Record solicited AEs Record solicited AEs (day 0 - day 6) [2]		●	●	●			● [2]	●			
Record unsolicited AEs (day 0 - day 29) [2]		●	●	●	●		● [2]	●	●		
Evaluate if subject is capable of completing Diary Card	O										
Distribution of Diary Card [11]		O					O [2]				
Return of Diary Card [11]				O				O			
Diary Card transcription by investigator				●				●			
Record serious adverse events (SAEs)	● [12]	●	●	●	●	●	●	●	●	●	●
Record pregnancies		●	●	●	●	●	●	●	●	●	●
Record concomitant medications/ products/ vaccinations [13]		●	●	●	●	●	●	●	●	●	●
Screening Conclusion	●										
Study Conclusion											●

Note: The double-line borders following Month 1 and Month 12 indicate analyses which will be performed.
● is used to indicate a study procedure that requires documentation in eSource.
O is used to indicate a study procedure that does not require documentation in eSource.
* Home visit by field worker or phone call.
** Sub-cohort for follow-up of AEs and humoral immunity.
[1] The Screening visit and the Day 0 visit may take place on the same day (allowed interval 0 - 30 days).

[2] Only for subjects in the sub-cohort for follow-up of AEs and assessment for humoral immunity.
[3] Only for subjects in the Group Placebo/ EBO-Z.
[4] Height, weight, systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature.
[5] Only if Visit 1 and Screening take place on a different day.
[6] Only for women of childbearing potential.
[7] Only if Visit 1 takes place more than 1 week after the Screening Visit.
[8] Treatment number allocation with randomisation at Day 0; treatment number allocation without randomisation at Month 6.
[9] HIV pre- and post-test counselling will be provided. HIV positive subjects will be referred for confirmatory HIV diagnosis/ management as per vaccination centre standard operating procedure (SOP).
[10] Only for subjects in the sub-cohort for CMI.
[11] Only for subjects who are capable of completing a Diary Card.
[12] From Screening to Day 0, only those SAEs that are considered related to study participation or to concurrent use of GSK medication/ vaccine need to be recorded.
[13] Concomitant medications/ products/ vaccinations as described in Section 7.4.1 and 7.4.2 need to be recorded in eSource.

6.3.1.2. Diary Card for follow-up adverse events occurring from day 0 to day 6 after vaccination

Subjects in the sub-cohort for follow-up of AEs and assessment of humoral immunity will be followed up for AEs on a daily basis during the 7-day follow-up period after vaccination. During this period, AEs will be recorded on a Diary Card.

Subjects who are capable of completing a Diary Card will be provided with one on the day of vaccination. On this Diary Card, the subject will record solicited and unsolicited AEs experienced and concomitant medications/ products/ vaccinations received from day 0 to day 6 after vaccination. The subject will be instructed to return the completed Diary Card at the visit at 6 days after vaccination.

Subjects who have difficulties completing a Diary Card will not be provided with one and their Diary Card will be managed/ completed by the investigator at the vaccination centre (at study visits during the 7-day follow-up period), or by a field worker (at home visits during the 7-day follow-up period; on those days that no study visit is planned). The home visits will be conducted by a trained field worker under the supervision of the principal investigator. During these home visits, the field worker will record information on solicited AEs, unsolicited AEs and on medication taken on a paper Diary Card. In the event that the field worker finds any Grade 3 AE, the subject will be brought to the vaccination centre for examination by a study clinician. Any further clinical data, including treatment provided, will be documented on the paper Diary Card and on specific clinic forms and transcribed in eSource. If the physician finds that the subject has experienced a serious adverse event (SAE), the appropriate measures will be taken to report this.

Diary Cards will be checked and verified by the principal investigator or his/ her designate before transcription in eSource. The principal investigator has a primary responsibility for the data transcribed in eSource. Unresolved AEs will be followed-up by field workers until resolution under the supervision of the principal investigator and data will be entered in eSource. The procedures and frequency of visits will be outlined in an standard operating procedure (SOP) at the vaccination centre. Analgesics/ antipyretics will be provided to field workers for the treatment of subjects with injection site pain and fever and their use will be documented. Subjects will not routinely be provided with these medications.

6.3.1.3. Retrospective follow-up for unsolicited adverse events occurring from day 7 to day 29 after vaccination

For subjects in the sub-cohort for follow-up of AEs and assessment of humoral immunity, unsolicited AEs occurring from day 7 up to day 29 after vaccination and medications taken in this period will be captured retrospectively during the study visit at 30 days after vaccination.

6.3.2. Intervals between study visits

Table 5 Intervals between study visits

Interval	Allowed interval
Screening → Visit Day 0	0 - 30 days
Visit Day 0 → Visit Day 3	3 days
Visit Day 0 → Visit Day 6	6 - 8 days
Visit Day 0 → Visit Day 30	30 - 44 days [1]
Visit Day 0 → Contact Month 3	3 months ± 30 days
Visit Day 0 → Visit Month 6	6 months ± 30 days [1]
Visit Month 6 → Visit Month 6 + 6 days	6 - 8 days
Visit Month 6 → Visit Month 6 + 30 days	30 - 44 days [1]
Visit Month 6 → Contact Month 9	3 months ± 30 days
Visit Month 6 → Visit Month 12	6 months ± 30 days [1]

[1] Subjects will not be eligible for inclusion in the ATP cohort for immunogenicity if they make the study visit outside this interval.

6.4. Biological sample handling and analysis

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed, will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Collected samples will be stored for a maximum of 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

6.4.1. Biological samples

Table 6 Biological samples

Sample type	Quantity	Unit	Timepoint	Sub-cohort *	Number of subjects
Blood for HIV serostatus	x	mL	Day 0	All enrolled subjects	~3 000
	x	mL	Month 6	All enrolled subjects	~3 000
Blood for haematology/ biochemistry	x	mL	Screening	All screened subjects	>3 000
	x	mL	Day 3	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	x	mL	Day 6	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	x	mL	Day 30	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	x	mL	Month 6	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	x	mL	Month 6 + 6 days	Subjects in the sub-cohort for follow-up of AEs and assessment of humoral immunity in Group Placebo/ EBO-Z	~750
	x	mL	Month 6 + 30 days	Subjects in the sub-cohort for follow-up of AEs and assessment of humoral immunity in Group Placebo/ EBO-Z	~750
	x	mL	Month 12	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
Blood for humoral immunity	x	mL	Day 0	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	x	mL	Day 30	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	x	mL	Month 6	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	x	mL	Month 6 +30 days	Subjects in Group Placebo/ EBO-Z in sub-cohort for follow-up of AEs and assessment of humoral immunity	~750
	x	mL	Month 12	Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
Blood for CMI	x	mL	Day 0	Sub-cohort for CMI	~200
	x	mL	Day 30	Sub-cohort for CMI	~200
	x	mL	Month 6	Sub-cohort for CMI	~200
	x	mL	Month 6 + 30 days	Subjects in Group Placebo/ EBO-Z in the sub-cohort for CMI	~100
	x	mL	Month 12	Sub-cohort for CMI	~200

* Refer to Section 5.2 for the description of the different sub-cohorts.

6.4.2. Laboratory assays

In addition to the assays described below, other tests to characterise the safety and/ or the immunogenicity of the investigational ChAd3-EBO-Z vaccine may be performed if deemed necessary for accurate interpretation of the data and/ or should such test(s) become available.

6.4.2.1. HIV serostatus

Two different HIV rapid test will be used sequentially at the investigator's laboratory. HIV positive subjects will be referred for confirmatory HIV diagnosis/ management as per vaccination centre SOP.

6.4.2.2. Haematology/ biochemistry

Haematology (CBC) and biochemistry (ALT and creatinine) assessments will be performed at investigator's laboratory as per local practice, or at a central laboratory (to be determined).

6.4.2.3. Immune response against Ebola

Table 7 Humoral Immunity against Ebola

System	Component	Method	Kit/ Manufacturer	Laboratory
Serum	anti-GP EBOV	ELISA	TBD	Laboratory designated by GSK Biologicals (TBD)
Serum	anti-GP SUDV	ELISA	Commercial Kit /Alpha Diagnostics	Laboratory designated by GSK Biologicals (TBD)

ELISA = enzyme-linked immunosorbent assay; **TBD** = to be determined

Table 8 Cell-Mediated Immunity against Ebola

System	Component	Challenge	Method	Kit/ Manufacturer	Laboratory
PBMCs	ChAd3-EBO-Z-specific $CD4^+$ or $CD8^+$ T-cell responses	Zaire or Sudan Gulu GP antigens	ICS	In-house	NVITAL

PBMCs = peripheral blood mononuclear cells; **ICS** = intracellular cytokine staining; **NVITAL** = NIAID Vaccine Immune T-cell and Antibody Laboratory (NIH)

6.4.2.4. Immune response against ChAd3

Table 9 Humoral Immunity against ChAd3

System	Component	Method	Kit/ Manufacturer	Laboratory
Serum	ChAd3 neutralising antibody	neutralisation	In-house	NVITAL

NVITAL = NIAID Vaccine Immune T-cell and Antibody Laboratory (NIH)

6.4.3. Biological sample evaluation

Table 10 Immunological read-outs

Timepoint	Component	Subset/ Sub-cohort *	No. subjects
Day 0	Anti-GP EBOV	• Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	Anti-GP SUDV	• Subset for additional humoral immunogenicity assays	~200
	ChAd3-EBO-Z-specific $CD4^+$ or $CD8^+$ T-cell responses	• Sub-cohort for CMI	~200
	ChAd3 neutralising antibody	• Subset for additional humoral immunogenicity assays	~200
Day 30	Anti-GP EBOV	• Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	Anti-GP SUDV	• Subset for additional humoral immunogenicity assays	~200
	ChAd3-EBO-Z-specific $CD4^+$ or $CD8^+$ T-cell responses	• Sub-cohort for CMI	~200
	ChAd3 neutralising antibody	• Subset for additional humoral immunogenicity assays	~200
Month 6	Anti-GP EBOV	• Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	Anti-GP SUDV	• Subset for additional humoral immunogenicity assays	~200
	ChAd3-EBO-Z-specific $CD4^+$ or $CD8^+$ T-cell responses	• Sub-cohort for CMI	~200
	ChAd3 neutralising antibody	• Subset for additional humoral immunogenicity assays	~200
Month 6 + 30 days	Anti-GP EBOV	• Sub-cohort for follow-up of AEs and assessment of humoral immunity in the Group Placebo/ EBO-Z	~750
	Anti-GP SUDV	• Subset for additional humoral immunogenicity assays in the Group Placebo/ EBO-Z	~100
	ChAd3-EBO-Z-specific $CD4^+$ or $CD8^+$ T-cell responses	• Sub-cohort for CMI in the Group Placebo/ EBO-Z	~100
	ChAd3 neutralising antibody	• Subset for additional humoral immunogenicity assays in the Group Placebo/ EBO-Z	~100
Month 12	Anti-GP EBOV	• Sub-cohort for follow-up of AEs and assessment of humoral immunity	~1 500
	Anti-GP SUDV	• Subset for additional humoral immunogenicity assays	~200
	ChAd3-EBO-Z-specific $CD4^+$ or $CD8^+$ T-cell responses	• Sub-cohort for CMI	~200

* Refer to Section 5.2 for the description of the different sub-cohorts and to Section 9.4 for the description of the subset for additional humoral immunogenicity assays.

7. STUDY VACCINES AND ADMINISTRATION

7.1. Description of study vaccines

The investigational ChAd3-EBO-Z vaccine has been developed by the VRC/NIAID using the Okairos adenovirus vaccine platform technology, which was acquired by GSK Biological in May 2013.

The Quality Control Standards and Requirements for the investigational vaccine are described in separate Quality Assurance documents (*e.g.* release protocols, certificate of analysis) and the required approvals have been obtained.

Table 11 Study vaccines

Treatment name	Vaccine/ Product name	Formulation	Presentation	Volume to be administered	Number of doses
ChAd3-EBO-Z	ChAd3-EBO-Z	ChAd3-EBO-Z=$5*10^{10}$vp/mL	Liquid in vial	0.2 - 1 mL *	1
Placebo	PBS (Formulation buffer S9b)	Na_2HPO_4=1.3mg; KH_2PO_4=186µg; NaCl=3.85mg; KCl=100µg; $MgCl_2$=50µg	Liquid in vial	0.2 - 1 mL *	1

PBS = phosphate-buffered saline
* The volume to be administered will depend on the dose ChAd3-EBO-Z selected based on Phase 1/2 data and will be described in the study procedures manual.

7.2. Dosage and administration of study vaccines

Table 12 Dosage and administration

Type of contact and timepoint	Volume to be administered	Treatment name	Study group	Route	Site	Side *
Visit Day 0	0.2 - 1 mL **	ChAd3-EBO-Z	Group EBO-Z	IM	Deltoid	Non-Dominant
	0.2 - 1 mL **	Placebo	Group Placebo/ EBO-Z	IM	Deltoid	Non-Dominant
Visit Month 6	0.2 - 1 mL **	ChAd3-EBO-Z	Group Placebo/ EBO-Z	IM	Deltoid	Non-Dominant

IM = intramuscular
* In case of anatomical features or medical indication preventing vaccination in the non-dominant arm, the vaccine may be administered in dominant arm.
** The volume to be administered will depend on the dose ChAd3-EBO-Z selected based on Phase 1/2 data and will be described in the study procedures manual.

7.3. Contraindications to vaccination

The following event constitutes a contraindication to study vaccination at that point in time; if this event occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the allowed time window:

- Acute disease and/ or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be axillary.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can receive study vaccination.

The following events constitute absolute contraindications to subsequent vaccination. If any of these events are applicable at Month 6 for the subjects in the Group Placebo/ EBO-Z, the subject must not receive the investigational vaccine , but may continue other study procedures at the discretion of the investigator:

- Anaphylaxis following vaccine administration.
- Clinically significant immunosuppressive or immunodeficient condition (*e.g.* AIDS).
- Pregnancy (see Section 8.2).

7.4. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator should question the subject about any medications/ products taken and vaccinations received by the subject, with a focus on the medications listed in the Section 7.4.1 and 7.4.2, which need to recorded in eSource.

7.4.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medications/ products/ vaccinations must be recorded in eSource:

- All concomitant medications/ products, except vitamins and dietary supplements, administered as of study vaccination up to 29 days after (30-day follow-up period).
- Any concomitant vaccination administered as of the Day 0 visit up to study conclusion (Day 0 to Month 12).
- Prophylactic medication (*i.e.* medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/ 100.4°F for rectal route).

- Any concomitant medications/products/vaccines relevant to an SAE to be reported as per protocol or administered at any time during the study period for the treatment of a SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.
- Any concomitant medications/products/vaccines listed in Section 7.4.2 during the period specified in that section.

7.4.2. Concomitant medications/ products/ vaccines that may lead to the elimination of a subject from according-to-protocol analyses

The use of the following concomitant medications/ products/ vaccinations will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 9.6 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- A vaccine* not foreseen by the study protocol administered within 30 days of a vaccination visit.

  * In case an emergency mass vaccination for an unforeseen public health threat (*e.g.* a pandemic) is organised by the public health authorities, outside the routine immunisation programme, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SmPC or Prescribing Information and according to the local governmental recommendations and provided a written approval of the sponsor is obtained.
- Any immunosupressive medication used during the study period.
- Any immunoglobulins and/ or any blood products administered during the study period.

7.5. Intercurrent medical conditions that may lead to elimination of a subject from according-to-protocol analyses

At each study visit subsequent to the first vaccination/the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in eSource.

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or if they are diagnosed with an immunological disorder.

8. SAFETY

The investigator or vaccination centre staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should he/ she manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (*i.e.* lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/ or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/ SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (*i.e.* invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (*e.g.* endoscopy, appendectomy); the condition that leads to the procedure is an AE/ SAE.
- Situations where an untoward medical occurrence did not occur (*e.g.* social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to study vaccination. These events will be recorded in the medical history section of eSource.

8.1.2. Definition of a serious adverse event

An SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/ incapacity, OR

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Solicited adverse events

Solicited local and general AEs occurring during a 7-day follow-up period after vaccination (*i.e.* the day of vaccination and 6 subsequent days) will be recorded via paper Diary Cards, which will be completed either by the subject him/herself, or by a trained field worker/ the investigator (see Section 6.3.1.2).

8.1.3.1. Solicited local adverse events

The following local (injection-site) AEs will be solicited:

Table 13 Solicited local adverse events

Pain at injection site
Redness * at injection site
Swelling at injection site

* In case it is not possible to determine the extent of redness on darkly pigmented skin, it will be reported as uninterpretable on the Diary Card and in eSource.

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 14 Solicited general adverse events

Fatigue
Fever *
Gastrointestinal symptoms **
Headache

* Fever is defined as temperature ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C / 100.4°F for rectal route. The preferred route for recording temperature in this study will be axillary.
** Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/ or abdominal pain.

8.2. Events or outcomes not qualifying as adverse events or serious adverse events (Pregnancy)

Female subjects who become pregnant after completion of study vaccination may continue the study at the discretion of the investigator.

Female subjects in the Group Placebo/ EBO-Z who are pregnant or lactating at the time of the vaccination at Month 6 must not receive the investigational ChAd3-EBO-Z vaccine, but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on a paper pregnancy report/ electronic pregnancy report.

The following should always be considered as SAE:

- Spontaneous pregnancy loss, including:
  - Spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation).
  - Ectopic and molar pregnancy.

– Stillbirth (intrauterine death of foetus after 22 weeks of gestation).

Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognised that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine will be reported. While the investigator is not obligated to actively seek this information from former study participants, he/ she may learn of a pregnancy through spontaneous reporting.

8.3. Detecting and recording adverse events, serious adverse events and pregnancies

8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

An overview of the protocol-required reporting periods for AEs, SAEs and pregnancies is given in Table 15.

Adverse events

All AEs starting in the 30-day follow-up period following administration of each dose of study vaccine must be recorded onto/ into the appropriate section of eSource, irrespective of intensity or whether or not they are considered vaccination-related.

Serious adverse events

The time period for collecting and recording SAEs will begin at study vaccination at Day 0 and will end at study conclusion for each subject.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (*i.e.* protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/ vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

Pregnancies

The time period for collecting and recording pregnancies will begin at study vaccination and will end at study conclusion for each subject.

Table 15 Reporting periods for collecting safety information

Event	Screening*	Vacc	end 7-day follow-up	end 30-day follow-up	Vacc	end 7-day follow-up	end 30-day follow-up	Study Conclusion
Timepoint		**D0**	**D6**	**D29**	**M6**	**M6 + 6 days**	**M6 + 29 days**	**M12**
Solicited local and general AEs								
Unsolicited AEs								
SAEs								
SAEs related to study participation or concurrent GSK medication/ vaccine								
Pregnancies								

Vacc = vaccination; **D**= Day, **M** = Month
Light grey highlighted reporting periods are for all subjects. Dark grey highlighted reporting period are for subjects with a vaccination at Month 6 only (*i.e.* subjects in the Group Placebo/ EBO-Z).
* *i.e.* consent obtained.

8.3.2. Evaluation of adverse events and serious adverse events

8.3.2.1. Assessment of adverse events

8.3.2.1.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described below.

Table 16 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness * at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever **		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

* In case it is not possible to determine the extent of redness on darkly pigmented skin, it will be reported as uninterpretable on the Diary Card and in eSource.
** Fever is defined as temperature ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C / 100.4°F for rectal route. The preferred route for recording temperature in this study will be axillary.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0 : ≤ 20 mm
1 : > 20 mm to ≤ 50 mm
2 : > 50 mm to ≤ 100 mm
3 : > 100 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

0	:	< 37.5 °C
1	:	≥ 37.5 °C to ≤ 38.5 °C
2	:	> 38.5 °C to ≤ 39.5°C
3	:	> 39.5°C

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities Such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.3.2.1.2. Assessment of causality

The investigator is obligated to assess the relationship between the study vaccination and the occurrence of each AE/ SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine will be considered and investigated.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/ her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccine administered.

The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the study vaccine?

YES : There is a reasonable possibility that the study vaccine contributed to the AE.

NO : There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

8.3.2.2. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.4. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to local standard of care.

8.5. Safety monitoring by the independent Data Monitoring Committee

An IDMC will be appointed to monitor the safety and tolerability of the investigational ChAd3-EBO-Z vaccine. and, if necessary, make recommendations to the sponsor concerning the modification or termination of the study. The IDMC will consist of clinical experts who are not involved in the conduct of the study and an independent statistician.

The IDMC will review, in an unblinded manner, safety and reactogenicity data from the current study, and from the study EBOLA Z CHAD3-004, which will be conducted in parallel with the current study.

In the study EBOLA Z CHAD-004, the safety, reactogenicity and immunogenicity of the investigational ChAd3-EBO-Z vaccine will be assessed when administered to children aged 1 to 17 years, divided into 3 age strata (1 to 6 years, 7 to 12 years and 13 to 17 years of age). As this will be the first time the investigational ChAd3-EBO-Z vaccine is administered to children, the study EBOLA Z CHAD3-004 will be conducted in a staggered manner, starting with vaccination of the oldest children and requiring an IDMC review of safety data up to at least 7 days after vaccination from 50 subjects (25/ group) to continue vaccination and to start with vaccination of younger children (if applicable). During these IDMC reviews, all available safety data from the current study in adults will be reviewed in addition to the safety and reactogenicity data from the study EBOLA Z CHAD3-004. For each of these IDMC reviews, interim unblinded IDMC reports including all available safety and reactogenicity data will be produced by an independent statistician according to an agreed pre-defined Report and Analysis Plan.

In addition, the following IDMC evaluations will take place:

- IDMC review of all safety and reactogenicity data included in the interim analysis that will be conducted when data is available from all subjects up to 30 days after vaccination at Day 0 (refer to Section 9.10.1 for more information on this interim analysis).
- *Ad hoc* IDMC meetings may be held if any safety concern is raised. For example, the principal investigator may, using discretion, ask for the study vaccination to be put on hold and an *ad hoc* IDMC meeting to be held for any single event or combination of multiple events which, in his/ her professional opinion, jeopardise the safety of the subjects or the reliability of the data.

9. STATISTICAL METHODS

9.1. Primary endpoints

- Occurrence of each solicited local and general AE, during a 7-day follow-up period after each vaccination (*i.e.* the day of vaccination and 6 subsequent days), in a sub-cohort of 750 subjects per group.
- Occurrence of any unsolicited AE, during a 30-day follow-up period after each vaccination (*i.e.* the day of vaccination and 29 subsequent days), in a sub-cohort of 750 subjects per group.
- Occurrence of haematological (CBC) and biochemical (ALT, creatinine) laboratory abnormalities at Screening, Day 3, Day 6, Day 30, Month 6 and Month 12 in a sub-cohort of 750 subjects per group, and at Month 6 + 6 days and Month 6 + 30 days in a sub-cohort of 750 subjects in the Group Placebo/ EBO-Z.
- Occurrence of any SAE, in all subjects, in both groups.

9.2. Secondary endpoint

- Anti-GP EBOV antibody titres, as measured by ELISA:
  - At Day 0 and Day 30, in a sub-cohort of 750 subjects per group.
  - At Month 6 and Month 6 + 30 days, in a sub-cohort of 750 subjects in the Group Placebo/ EBO-Z.

9.3. Tertiary endpoints

- Anti-GP EBOV antibody titres, as measured by ELISA:
  - At Month 6, in a sub-cohort of 750 subjects in the Group EBO-Z.
  - At Month 12, in a sub-cohort of 750 subjects per group.
- Anti-GP SUDV antibody titres, as measured by ELISA:
  - At Day 0, Day 30, Month 6 and Month 12, in a subset of 100 subjects per group.
  - At Month 6 + 30 days, in a subset of 100 subjects in the Group Placebo/ EBO-Z.
- Magnitude, breadth and cytokine co-expression profile of ChAd3-EBO-Z-specific $CD4^+$ or $CD8^+$ T-cell responses, as assessed by intracellular cytokine staining (ICS) after stimulation with Zaire or Sudan Gulu GP antigens:
  - At Day 0, Day 30, Month 6, and Month 12, in a sub-cohort of 100 subjects per group.
  - At Month 6 + 30 days, in a sub-cohort of 100 subjects in the Group Placebo/ EBO-Z.
- ChAd3 neutralising antibody titres, as measured by a neutralisation assay:
  - At Day 0, Day 30and Month 6, in a subset of 100 subjects per group.
  - At Month 6 + 30days, in a subset of 100 subjects in the Group Placebo/ EBO-Z.

9.4. Randomisation

Allocation ratio: 1:1

Over-randomisation of subjects:

☐ **No**

☒ **Yes, description:**
20% over-randomisation

Subset:

☐ **No**

☒ **Yes, description:**
A subset is defined as a group of subjects for which additional assays are planned as compared to other subjects. Approximately 100 subjects per group will be part of the subset for additional humoral immunogenicity assays. These will be the same subjects as the subjects in the sub-cohort for CMI.

Stratification/ randomisation:

☐ **No**

☒ **Yes, minimisation factors:**

- Age
- Gender
- Occupation
- Centre

9.5. Determination of sample size

The primary objective of this study is to assess the safety of the investigational ChAd-EBO-Z vaccine.

Considering the target sample size of 1 500 subjects to be enrolled in the Group EBO-Z and 1 500 subjects to be enrolled Group Placebo/ EBO-Z, Table 17 shows the true proportions associated with a 90% probability to observe a certain number of SAEs.

Table 17 True proportions associated with a 90% probability to observe a certain number of serious adverse events within a group (1 500 subjects)

True proportion	Number of adverse events observed with > 90% probability
0.002	>0
0.003	>1
0.004	>2
0.005	>3
0.006	>4
0.007	>5
0.015	>15
0.026	>30
0.076	>100

Table 18 illustrates the 95% exact confidence intervals (CI) for different possible observed number of AEs within the sub-cohort for follow-up of AEs and assessment of humoral immunity before vaccination at Month 6 (administration of the investigational ChAd3-EBO-Z vaccine to the subjects in the Group Placebo/ EBO-Z).

Table 18 95% exact Confidence Intervals for the true adverse event rate at different possible observed adverse event rates within the sub-cohort for follow-up of AEs and assessment of humoral immunity (750 subjects)

Observed number of adverse events	Observed adverse event proportion	95% Exact Confidence Interval	
		Lower Bound	Upper Bound
0	0.0000	0.0000	0.0049
1	0.0013	0.0000	0.0074
5	0.0067	0.0022	0.0155
10	0.0133	0.0064	0.0244
25	0.0333	0.0217	0.0488
50	0.0667	0.0499	0.0870
100	0.1333	0.1098	0.1598
250	0.3333	0.2996	0.3683
500	0.6667	0.6317	0.7004

9.6. Cohorts for Analyses

9.6.1. Total vaccinated cohort

The Total vaccinated cohort (TVC) will include all subjects with at least one vaccine administration documented:

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.

The TVC will be performed per study group as treated.

9.6.2. According-to-protocol cohort for analysis of safety

The ATP cohort for analysis of safety will include all vaccinated and eligible subjects who have received at least one dose of study vaccine according to protocol procedures and to their random assignment, who have not received a concomitant vaccine that may lead to elimination from an ATP analysis, and for whom the randomisation code has not been broken.

9.6.3. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects (*i.e.* those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, meeting none of the criteria for elimination from analysis) for whom data concerning immunogenicity endpoint measures are available.

9.7. Derived and transformed data

Immunogenicity

- A seronegative subject is a subject whose titre is below the cut-off value (to be determined).
- A seropositive subject is a subject whose titre is greater than or equal to the cut-off value (to be determined).
- Seroconversion is defined as the appearance of antibodies (*i.e.* titre greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.
- Response is defined as greater than or equal to a X-fold (*to be determined*) increase in previously positive titre for seropositive subjects or seroconversion in subjects seronegative before vaccination.
- The Geometric Mean Titres (GMTs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT calculation.
- Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Reactogenicity and Safety

- Handling of missing data: subjects who missed reporting events (unsolicited or concomitant medications) will be treated as subjects without event (unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.

- For the analysis of solicited symptom, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only subjects/doses with documented safety data (*i.e.* symptom screen/sheet completed).

9.8. Statistical analyses

All analyses will be descriptive. Depending on the endpoint, data will be presented overall or for a sub-cohort of subjects. In a first step, the safety and immunogenicity results will be presented by treatment administered at Day 0 (ChAd3-EBO-Z vaccine *vs.* Placebo). In a second step, all data post-vaccination with the investigational ChAd3-EBO-Z vaccine (ChAd3-EBO-Z vaccine at Day 0 *and* ChAd3-EBO-Z vaccine at Month 6) will be pooled. The latter aggregated data cannot be presented *vs.* Placebo patients because of the administration of the investigational ChAd3-EBO-Z vaccine to the subjects in the Group Placebo/ EBO-Z, who initially received placebo (population overlap).

9.8.1. Analysis of Demography

Demographic characteristics (age at study vaccination in years, gender, ethnicity,…) and withdrawal status will be summarised by group in the TVC, using descriptive statistics:

- Frequency tables will be generated for categorical variable such as centre.
- Mean, median, standard deviation will be provided for continuous data such as age.

9.8.2. Analysis of Safety

The primary analysis will be performed on the TVC. If in any study group, 5% or more of the vaccinated subjects are eliminated from the ATP cohort for analysis of safety, a second analysis will be performed on the ATP cohort for analysis of safety.

Within group assessment

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for symptoms rated as Grade 3.

The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for Grade 3 AEs and for AEs with relationship to vaccination.

Duration and prevalence of fever will be presented.

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects with at least one report of unsolicited

AE classified by the MedDRA and reported up to 29 days after vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.

SAEs will be described in detail.

9.9. Analysis of Immunogenicity

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If, in any study group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC will be performed to complement the ATP analysis.

Humoral immune response

Within group assessment

For each study group, each antigen, at each timepoint where a blood sample result is available:

- Seropositivity rates (with exact 95% CI) will be calculated by group.
- GMTs with 95% CI will be tabulated.
- Vaccine responses to the antigen (with exact 95% CI) will be calculated.
- Reverse cumulative distribution curves will display antibody titres distributions

The same analyses will be done by baseline anti-GP EBOV serological status.

Cell-mediated immune response

For each study group, at each timepoint where a blood sample result is available, the frequency of specific $CD4^+$/ $CD8^+$ T-cells will be summarised (descriptive statistics).

If number allow, the same analysis will be done by baseline anti-GP EBOV serological status.

9.10. Interpretation of analyses

Comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/ safety/ immunogenicity investigational ChAd3-EBO-Z vaccine and placebo.

9.10.1. Sequence of analyses

All analyses (including the interim analysis) will be conducted on data as clean as possible.

The analyses will be performed stepwise:

- An interim analysis will be performed when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0. The interim analysis will be conducted on all safety, reactogenicity and immunogenicity data available at that time.
- A final analysis of all data will be performed when all data up to study conclusion will be available.

9.10.2. Statistical considerations for interim analyses

In order to obtain early data on the investigational ChAd3-EBO-Z vaccine, an interim analysis will be performed when safety, reactogenicity and immunogenicity (including at least anti-GP EBOV data at Day 30) data is available from all subjects up to 30 days after vaccination at Day 0. The interim analysis will be conducted on all safety, reactogenicity and immunogenicity data available at that time. This analysis will present a descriptive summary of safety, reactogenicity and immunogenicity. As the study does not include any confirmatory objective, no statistical adjustment will be made.

10. REFERENCES

Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf

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From: David Vaughn
Sent: 31 Oct 2014 17:59:36 +0000
To: Broder, Karen (CDC/OID/NCEZID)
Cc: Iris De Ryck;Destefano, Frank (CDC/OID/NCEZID);Shimabukuro, Tom (CDC/OID/NCEZID);Gronostaj, Michael (CDC/OPHSS/CSELS/DSEPD);Clark, Thomas A. (CDC/ONDIEH/NCCDPHP);Gargiullo, Paul (CDC/OID/NCIRD)
Subject: RE: Ebola vaccine pharmacovigilence

Thanks. Meeting invitation sent.

From: Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
Sent: Friday, October 31, 2014 1:47 PM
To: David Vaughn
Cc: Iris De Ryck; Destefano, Frank (CDC/OID/NCEZID); Shimabukuro, Tom (CDC/OID/NCEZID); Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Gargiullo, Paul (CDC/OID/NCIRD)
Subject: RE: Ebola vaccine pharmacovigilence

Hi David and Iris,

Thanks for your invitation to participate in a PV call regarding Ebola Vaccines. The best time on your list is Tuesday November 4 from 8a-9a EST. In additional to me, please invite the other colleagues cced from CDC: Immunization Safety Office - Frank Destefano (ISO director), Tom Shimabukuro, Mike Gronostaj and from the CDC Ebola Response Vaccine Team - Tom Clark and Paul Gargiullo.

Frank reminded me that there is a CIOMS WG on developing recommendations and materials for improving PV (passive and active) in low and middle income countries. Frank (who is serving on that WG) suggested it might also be helpful for Harry Seifert from GSK to be involved in the Ebola vaccine PV discussion call, since he is also on the CIOMS WG. Here is some further information:
http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/

Have a nice weekend.

Sincerely,
Karen R. Broder, MD
Captain, United States Public Health Service
Team Lead
Clinical Immunization Safety Assessment (CISA) Project
Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Phone: 404-639-8538 Fax: 404-639-8834
email: Kbroder@cdc.gov

From: David Vaughn [mailto:david.w.vaughn@gsk.com]
Sent: Friday, October 31, 2014 7:06 AM
To: Broder, Karen (CDC/OID/NCEZID)
Cc: Iris De Ryck
Subject: Ebola vaccine pharmacovigilence

Karen,

Do have time next Tuesday or Wednesday to discuss post-marketing (or emergency use) PV in Africa? As the MAH for an Ebola vaccine, we need a Risk Management Plan which includes a PV plan for countries where the vaccine will be used. Capacity building in the affected countries would be challenging. Stand-alone PV studies could be done using sentinel sites. This would all be separate from Phase 3 activities. There is a possibility that GSK will seek EU funding for such efforts and we would like to have an informal discussion with you about what such an effort might look like. If the NIH/GSK vaccine is safe and effective, good PV is of importance to all (including BARDA, CDC, NIH, and DoD) as a bad PV program could derail a good vaccine or identify late a signal that reflects a real problem.

Iris is our clinical safety lead for Ebola vaccine. We are both available Tuesday, 4 November from 0800-0900 and from 1030-1100 and Wednesday 0900-1000 and after 1100 (Iris, recall that Europe falls back on Sunday and so CET is just 5 hours ahead of Philly and Atlanta for a couple weeks).

Thanks, David.

David W. Vaughn, MD, MPH
Head, External R&D, North America
Vaccines Discovery & Development
GSK
2301 Renaissance Boulevard, RN0220
King of Prussia, PA 19406-2772, USA
Email David.W.Vaughn@gsk.com
Mobile +1 267-355-2160
Tel +1 610-787-3907
Admin. Support Elaine Slavish +1 610-787-3102
gsk.com | Twitter | YouTube | Facebook | Flickr

From: Fernanda Tavares Da Silva
Sent: 7 Nov 2014 20:22:18 +0000
To: David Vaughn
Cc: Broder, Karen (CDC/OID/NCEZID);François P Roman;Gronostaj, Michael (CDC/OPHSS/CSELS/DSEPD);Clark, Thomas A. (CDC/ONDIEH/NCCDPHP);Destefano, Frank (CDC/OID/NCEZID);Valentina Attanasi
Subject: Re: Ebola vaccine pharmacovigilence

I agree :-)
Fernanda

Sent from my iPhone

On 7 nov. 2014, at 21:18, David Vaughn <david.w.vaughn@gsk.com> wrote:

> I agree with Fernanda that Day 0 – Day 28 safety labs are unlikely to be helpful and will be collected during Phase 1 and Phase 2 under more controlled circumstances.
> The consideration might be more of a public-reassurance strategy to have a safety lab analysis after a month to show that as many measured values went up at Day 28 as went down.
> A serum specimen at baseline can be useful to evaluate AEs later but this would generally be the case only for rare serious events and the likelihood that the 100-200 subjects you follow more closely for reacto and immuno will be the ones to have such events is low. Still, good to have an extra aliquot if drawing blood for serology.
>
> **From:** Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
> **Sent:** Friday, November 07, 2014 3:07 PM
> **To:** Fernanda Tavares Da Silva; François P Roman
> **Cc:** David Vaughn; Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); Valentina Attanasi
> **Subject:** RE: Ebola vaccine pharmacovigilence
>
> So to clarify
> If the blood draw is day 0 and 28, is it worth pursuing?
> It seems that the issue of lab norms is less important if you have a baseline and post comparison for an individual.
> Thanks,
> Karen
>
> **From:** Fernanda Tavares Da Silva [mailto:FERNANDA.TAVARES@GSK.COM]
> **Sent:** Friday, November 07, 2014 3:01 PM
> **To:** François P Roman
> **Cc:** Broder, Karen (CDC/OID/NCEZID); David Vaughn; Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); Valentina Attanasi
> **Subject:** Re: Ebola vaccine pharmacovigilence
>
> Dear all,
> My idea was to have (ideally) a grading system for laboratory values but this is actually dependent upon country or institutional normal reference ranges. I agree, this is a 'nice to have'. It's actually not included in the protocol we sent you.
> I don't believe the safety lab assessment would be then valuable in the schedule you mentioned below.

Thanks!,
Fernanda
Sent from my iPhone

On 7 nov. 2014, at 20:36, François P Roman <FRANCOIS.P.ROMAN@GSK.COM> wrote:

> Dear All,
> I concur with David that Grade 4 reporting is not systematic practice at GSK. The ChAd3-EBO-Z IB is in progress and should be available in the couple of weeks to come.
> Thanks and regards,
> Francois
> **François Roman**
> **Director**
> Clinical Research & Translational Science
> Vaccine Discovery & Development
> **GSK**
> **89 Rue de l'Institut**
> **Rixensart 1330, Belgium**
> **Email** FRANCOIS.P.ROMAN@GSK.COM
> **Mobile** +32 472 900 494
> **Tel** +32 2 656 6738
> gsk.com | Twitter | YouTube | Facebook | Flickr
>
> **From:** Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
> **Sent:** Friday 7 November 2014 20:32
> **To:** David Vaughn
> **Cc:** Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); François P Roman; Fernanda Tavares Da Silva; Valentina Attanasi
> **Subject:** RE: Ebola vaccine pharmacovigilence
>
> David,
> Hi. I think since we get temperature data it could be re-coded later into a 3 and 4 severity – but I doubt there will be many grade 3 or 4 fevers. And since lab date would be numerical maybe this could be done as a second step. I think pre-defining lab categories might be hard, especially if we don't have country norms of lab values.
> Also we realized that blood draws would be at baseline and day 28 for immunogencity if feasible in a sub-set, so I wanted to double check that the safety lab assessment would be valuable with this schedule. I think it would be more complex to add an NEW blood draw at day 2 or 3.
> Thanks ,
> Karen
>
> **From:** David Vaughn [mailto:david.w.vaughn@gsk.com]
> **Sent:** Friday, November 07, 2014 2:27 PM
> **To:** Broder, Karen (CDC/OID/NCEZID)
> **Cc:** Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); François P Roman; Fernanda Tavares Da Silva; Valentina Attanasi
> **Subject:** RE: Ebola vaccine pharmacovigilence
>
> Karen,
> I contributed only to early versions of the protocol. Francois, Fernanda, or Valentina may be able to provide a better reply though it is now evening

before a 4-day weekend in Belgium. I agree, no Grade 4 in the protocol. We sometimes have a Grade 4 for fever above 40 though this protocol fever is to be recorded as a continuous variable for assessment in half-degree intervals. There can be Grade 4 for laboratory abnormalities but I do not see that table in the protocol either.
I only have the VRC IB. One is being developed for the GSK-sponsored Phase 2 studies. Typically, CRFs are only constructed after concept protocol approval. David.

From: Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
Sent: Friday, November 07, 2014 2:11 PM
To: David Vaughn
Cc: Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); François P Roman; Fernanda Tavares Da Silva; Valentina Attanasi
Subject: RE: Ebola vaccine pharmacovigilence

David,
Thanks a lot; this is very helpful. We were wondering if it would also be possible see the Investigator's brochure or any associated forms?
Also we didn't see any mention of Grade 4 severity in the protocol. Let us know if we missed that
Thanks and have a nice weekend.
Karen

From: David Vaughn [mailto:david.w.vaughn@gsk.com]
Sent: Friday, November 07, 2014 1:37 PM
To: Broder, Karen (CDC/OID/NCEZID)
Cc: Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID); François P Roman; Fernanda Tavares Da Silva; Valentina Attanasi
Subject: RE: Ebola vaccine pharmacovigilence

Karen,
Attached you should find the Phase 2 study protocol draft for adults; today's version. It should not be necessary to exceed (or even match) the safety surveillance found in this study for your Phase 3.
Tom Clark, Have you received a version of the NIH Phase 3 protocol from Barney Graham?
David.

From: Broder, Karen (CDC/OID/NCEZID) [mailto:krb2@cdc.gov]
Sent: Thursday, November 06, 2014 10:14 AM
To: David Vaughn
Cc: Gronostaj, Michael (CDC/OID/NCEZID); Clark, Thomas A. (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Ebola vaccine pharmacovigilence

Hi David,
I hope you are well. We are working on the vaccine safety sections and forms for the draft CDC Expanded Access protocol for Tom Clark's team. The sections are still evolving as we get input from the staff in the field.
We have been trying to harmonize safety definitions, to the extent practical, with the last version of the NIH protocol we have (Oct 24). Is this the most recent version? Also do you have any of the vaccine safety forms from this study that could be shared with us?

Lastly, we are wondering if it might be helpful to have a short call with you regarding the materials we are developing for safety monitoring, perhaps tomorrow Friday November 7, to get some input?
Thanks,
Karen

From: David Vaughn [mailto:david.w.vaughn@gsk.com]
Sent: Friday, October 31, 2014 7:06 AM
To: Broder, Karen (CDC/OID/NCEZID)
Cc: Iris De Ryck
Subject: Ebola vaccine pharmacovigilence

Karen,
Do have time next Tuesday or Wednesday to discuss post-marketing (or emergency use) PV in Africa? As the MAH for an Ebola vaccine, we need a Risk Management Plan which includes a PV plan for countries where the vaccine will be used. Capacity building in the affected countries would be challenging. Stand-alone PV studies could be done using sentinel sites. This would all be separate from Phase 3 activities. There is a possibility that GSK will seek EU funding for such efforts and we would like to have an informal discussion with you about what such an effort might look like. If the NIH/GSK vaccine is safe and effective, good PV is of importance to all (including BARDA, CDC, NIH, and DoD) as a bad PV program could derail a good vaccine or identify late a signal that reflects a real problem.
Iris is our clinical safety lead for Ebola vaccine. We are both available Tuesday, 4 November from 0800-0900 and from 1030-1100 and Wednesday 0900-1000 and after 1100 (Iris, recall that Europe falls back on Sunday and so CET is just 5 hours ahead of Philly and Atlanta for a couple weeks).
Thanks, David.

David W. Vaughn, MD, MPH
Head, External R&D, North America
Vaccines Discovery & Development
GSK
2301 Renaissance Boulevard, RN0220
King of Prussia, PA 19406-2772, USA
Email David.W.Vaughn@gsk.com
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From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 24 Jun 2015 14:04:38 +0000
To: 'Harry Seifert';McNeil, Michael (CDC/OID/NCEZID)
Cc: Martin, David (FDA/CDER);Nguyen, Michael D. (FDA/CDER);'Jens-Ulrich Stegmann';'Greg Powell';'Leonard Friedland'
Subject: RE: Follow-up from GSK presentation at May 7th ISO Hot Topics meeting

Hi Harry,
Thanks again for presenting to our group and this interesting follow-up information.
Best regards,
Frank

From: Harry Seifert [mailto:Harry.A.Seifert@gsk.com]
Sent: Wednesday, June 24, 2015 8:28 AM
To: Destefano, Frank (CDC/OID/NCEZID); McNeil, Michael (CDC/OID/NCEZID)
Cc: Martin, David (FDA/CBER); Nguyen, Michael D. (FDA/CDER); Jens-Ulrich Stegmann; Greg Powell; Leonard Friedland
Subject: Follow-up from GSK presentation at May 7th ISO Hot Topics meeting

Dear Frank and Mike,
The attached slides summarize our findings to answer your question about how the social media AEFIs compared to what has been reported to VAERS.
Methods: We used the CDC Wonder web tool to obtain VAERS public release data for HEP, HEPA, and HEPAB. For hep B vaccine, we obtained data cumulatively through February 2015 and from Oct 2013 through Feb 2015; for the other hep vaccines, we obtained only cumulative data through Feb 2015. The data (PTs and number of events reported) were downloaded into Excel and percentages of the total number of events reported were calculated. We obtained GSK data by querying our global safety database for all spontaneously-reported events from launch through Feb 2015 and performing similar operations in Excel as we did for the VAERS data.
Conclusions: We believe that any comparisons among the datasets must be made extremely cautiously, because of the nature of the underlying data [e.g., the company database contains all events, regardless of seriousness/expectedness, whereas Sponsor (expedited) reports to VAERS are required only for serious/unexpected reports for US-licensed vaccines], differences in coding conventions and practices, the absence of possible "filtering" of AEFIs in social media by HCPs or regulatory authorities , the limitations of small numbers, and possible differences in MedDRA versions. With those caveats in mind, we note that social media have different reporting patterns than traditional PV methods, but detect no signals for these vaccines among AEFIs from social media.
We have copied Drs. Nguyen and Martin from OBE/CBER/FDA to ensure transparency. We ask that you please regard the content of these slides as sensitive and proprietary, and that you do not share them beyond the relevant groups within CDC and CBER.
Of course, we would be happy to discuss these data and conclusion further with your group and/or CBER, and would be interested in the CDC and/or CBER's views on the data. We are still discussing, internally, what steps to take next in our exploration of social media for vaccine safety, and your input would be welcome.
Thank you for inviting us to present our work, and for the interesting discussions and useful suggestions.
Best regards,
Harry

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 14 Aug 2015 13:42:51 +0000
To: Bailey, Steven R.;Winiecki, Scott (FDA/CDER)
Subject: RE: CIOMS WG Updated distribution list for TG2 manual

Steven,
The version of Chapter 3 that you have is the most recent. I think the first 70% is in pretty good shape and the remaining comments are mostly issues with harmonization with other chapters or for general discussion. By the time I got to "Table 3, Summary of steps, activities and resources in the establishment of ActSS systemes" I ran out of steam and have not been able to get motivated to edit the sections on the more day-to-day processes of establishing and running a surveillance system. If someone is willing to pick up the baton from there it would be a big help. Also, only one person has responded to the draft that I distributed in June. It would be helpful if we got more input, especially from other LMIC representatives. Perhaps at the meeting in September what is needed is to give people some protected time (either individually or in small groups) to review and comment on the document rather than spending too much time on presentations and group processes.
Thanks,
Frank

From: Bailey, Steven R. [mailto:Steven.R.Bailey@pfizer.com]
Sent: Thursday, August 13, 2015 5:21 PM
To: Winiecki, Scott (FDA/CBER); Destefano, Frank (CDC/OID/NCEZID)
Cc: Bailey, Steven R.
Subject: FW: CIOMS WG Updated distribution list for TG2 manual

Frank/Scott:
As we get ready for our next meeting here in Philadelphia (I certainly hope you are joining us), Karin is beginning to organize where each group stands. I will work with her to ready WG2 (apparently I am now the lead), and will meet with her on Tuesday.
Ahead of my talking with her, could you just update me where we are with Chapters 2 and 3? Karin has attached what she believes is the latest version, but I would assume you might have already addressed the comments you have received, and might have a more updated version than what has been passing through the e-mail ether.
More importantly, could you give me your perspective of what the next steps are (from you perspective) for your chapters, and how we can best use the 2 days together to move them to completion? That way I can build an agenda that can productively give you all the feedback/additional materials/etc. to finish our work.
Thanks in advance your consideration, and if you could send an update before I meet with Karin on Tuesday morning it would be appreciated.
Regards,
Steven

Steven R. Bailey, MD MPH MBA
Vice President, Worldwide Safety and Regulatory
SSRM RU/Vaccines Group Head
Pfizer
Steven.R.Bailey@Pfizer.com
484 865 3670

From: Holm Karin [mailto:holmk@cioms.ch]
Sent: Thursday, August 13, 2015 5:43 AM
To: Bailey, Steven R.
Subject: FW: CIOMS WG Updated distribution list for TG2 manual

Dear Steven,

Thanks for everything you have been doing to ensure a good meeting in September!
I am trying to find out where we stand on TG2 the manual and wonder if you could give me an overview on where we stand and where I can help over the next week or so to get things ready for the Philly meeting? We need to think of how to structure the agenda to be most productive. We have no outside speakers planned, except you are welcome to invite a senior Pfizer person to open, if you wish. We must obviously focus on making most use of our face-to-face to progress on deliverables.
Attached please find the latest versions as I understand for the various sections of the entire WG:*

1. WG Combined Business Plan (incl. Chart of Chapters)
2. TG1 Essential Vaccine Information Document
3. TG2 Manual on Active Safety Surveillance
    a. Chapter 1
    b. Chapter 2
    c. Chapter 3
    d. Other Sections Drafts
4. TG3 Vaccine Safety Communication

*Please note that the person responsible may not as yet have incorporated all comments received from WG members in the version attached.
After I hear from you on any updates for TG2, I will send the same complete group of files to the heads of topic group 1 (Uli Heininger) and topic group 3 (Priya Bahri). If you would like to discuss by phone, let me know a good date/time for you?
Kind regards,
Karin

Karin R. Holm
Technical Collaboration Coordinator, CIOMS WG on Vaccine Safety
CIOMS IX Risk Minimisation and CIOMS X Meta-Analysis
Council for International Organizations of Medical Sciences (CIOMS)
c/o WCC, P.O. Box 2100, CH-1211 Geneva 2, Switzerland
Phone: +41 22 791 6497 Website: www.cioms.ch
Email: holmk@cioms.ch
Associate partner of UNESCO
In official relations with WHO

From: Holm Karin [mailto:holmk@cioms.ch]
Sent: Tuesday, August 04, 2015 4:39 PM
To: Novilia; Bailey (Steven.R.Bailey@pfizer.com); Blum, Michael (BlumM@MedImmune.com); Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu); Chandler, Rebecca (alt) (rebecca.chandler@who-umc.org); Darko, Mimi (b)(6); Dawei, Liu (b)(6); DeStefano, Frank (fxd1@cdc.gov); Duo, Dong (dongduo@cdr.gov.cn); Holm Karin; Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com); Kilpi, Terhi (terhi.kilpi@thl.fi); Kurz, Xavier (Xavier.Kurz@ema.europa.eu); Martin (David.Martin@fda.hhs.gov); Maure, Christine (maurec@who.int); Nishioka, Sergio (sergio.de.andrade.nishioka@gmail.com); Seifert, Harry (Harry.A.Seifert@gsk.com); Sillan, Françoise (Francoise.Sillan@sanofipasteur.com); Sjolin_Forsberg Gunilla; Tebaa, Amina (atebaa@yahoo.fr); Ulf Bergman (ulf.bergman@karolinska.se); Winiecki, Scott (alt) (Scott.Winiecki@fda.hhs.gov); Zuber, Patrick (zuberp@who.int); Heiles, Bernhard (bernhard.heiles@merck.com)
Cc: Le_Roux Susanne
Subject: CIOMS WG Updated distribution list for TG2 manual

My updated distribution list for CIOMS WG on Vaccine Safety, topic group 2 on the manual for active safety surveillance.
Adding to distribution: Rebecca Chandler (new UMC), Bernard Heiles (new merck), Karin Holm (I didn't have myself on it!), Sue le Roux (CIOMS new administrative person)
Removing due to leaving WG: Fabio Leviano, Sten Olsson

Karin R. Holm
Publications Consultant, WG IX Risk Minimisation
Technical Coordinator, WG on Vaccine Safety
Council for International Organizations of Medical Sciences (CIOMS)
c/o WCC, P.O. Box 2100, CH-1211 Geneva 2, Switzerland
Phone: +41 22 791 6497 Website: www.cioms.ch
Email: holmk@cioms.ch
Associate partner of UNESCO
In official relations with WHO

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 19 Mar 2015 16:13:26 +0000
To: 'Harry.A.Seifert@gsk.com'
Subject: Re: dinner

Dinner near the hotel sounds good to me. Shall we meet in the lobby at 7 pm?

From: Harry Seifert [mailto:Harry.A.Seifert@gsk.com]
Sent: Thursday, March 19, 2015 05:07 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: dinner

Steve proposed that we take a taxi and meet home near the old town (where we had dinner last night) at around 7:00. We had not fixed a meeting or dinner location.
I am starting to crash, so I could easily be convinced to stay closer to our hotel and get dinner someplace very nearby – or even in the hotel restaurant. Let me know what you'd prefer and we'll go from there. I am going to take a shower and will check my email thereafter. Or, you can text me at (b)(6) whatever is easiest for you.
Harry

From: Straus, Walter L.
Sent: 5 Feb 2015 11:36:42 -0500
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Intro Frank Destefano and Walter Straus

That's great. Would you like for me to call you (if so, what#)? Otherwise, my # is (b)(6)

Walter

Walter L. Straus, MD, MPH, FCPP, FACP Executive Director, Global Director for Scientific Affairs / Merck Research Laboratories, Merck & Co., Inc., 351 North Sumneytown Pike, North Wales, PA 19454 / Tel: 267-305-7143 /Fax: 215-616-1095
Assistant: Betsy Panacio betsy_panacio@@merck.com Tel: 267-305-2541

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Thursday, February 05, 2015 8:49 AM
To: Straus, Walter L.
Subject: RE: Intro Frank Destefano and Walter Straus

Hi Walter,
I am available on 2/11 at 4pm.
Frank

-----Original Message-----
From: Straus, Walter L. [mailto:walter_straus@merck.com]
Sent: Tuesday, February 03, 2015 2:45 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Intro Frank Destefano and Walter Straus

Frank,
Do you have a few minutes any of the dates: 2/10, 11 or 12 after 3 PM?

Walter

Walter L. Straus, MD, MPH, FCPP, FACP Executive Director, Global Director for Scientific Affairs / Merck Research Laboratories, Merck & Co., Inc., 351 North Sumneytown Pike, North Wales, PA 19454 / Tel: 267-305-7143 /Fax: 215-616-1095
Assistant: Betsy Panacio betsy_panacio@@merck.com Tel: 267-305-2541

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Tuesday, February 03, 2015 10:52 AM
To: Straus, Walter L.
Subject: RE: Intro Frank Destefano and Walter Straus

CISA is a formal project. It conducts clinical research in addition to providing consultation on individual cases. I'd be happy to discuss further if you like.

-----Original Message-----
From: Straus, Walter L. [mailto:walter_straus@merck.com]

Sent: Tuesday, February 03, 2015 8:37 AM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Intro Frank Destefano and Walter Straus

Hi Frank,
I've had a chance to look at the slides. It's a tremendous help.
One question I had concerned the CISA project. Is this a formal project, or simply a mechanism for CDC to engage academicians, in an ad hoc manner, on consultations when questions arise regarding safety of a vaccine?
If easiest, can we find a few minutes to chat by phone?
Again, MANY thanks. I will, of course, acknowledge you in the presentation.
Best,

Walter

Walter L. Straus, MD, MPH, FCPP, FACP Executive Director, Global Director for Scientific Affairs / Merck Research Laboratories, Merck & Co., Inc., 351 North Sumneytown Pike, North Wales, PA 19454 / Tel: 267-305-7143 /Fax: 215-616-1095
Assistant: Betsy Panacio betsy_panacio@@merck.com Tel: 267-305-2541

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Monday, February 02, 2015 4:29 PM
To: Straus, Walter L.
Subject: RE: Intro Frank Destefano and Walter Straus

Hi Walter,
Good to hear from you. Attached are slides from a general vaccine safety talk that I gave at the NFID Vaccinology course recently. You can borrow at will.
Best regards,
Frank

-----Original Message-----
From: Straus, Walter L. [mailto:walter_straus@merck.com]
Sent: Monday, February 02, 2015 3:42 PM
To: Chen, Robert (Bob) (CDC/OID/NCHHSTP)
Cc: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Intro Frank Destefano and Walter Straus

Thanks, Bob.
I've known Frank for years, but hadn't had a chance to speak recently. Any publicly available slides re VAERS/VSD would be great. We can also easily chat by phone.
Many thanks to both of you.

Walter

Walter L. Straus, MD, MPH, FCPP, FACP Executive Director, Global Director for Scientific Affairs / Merck Research Laboratories, Merck & Co., Inc., 351 North Sumneytown Pike, North Wales, PA 19454 / Tel: 267-305-7143 /Fax: 215-616-1095
Assistant: Betsy Panacio betsy_panacio@@merck.com Tel: 267-305-2541

-----Original Message-----
From: Chen, Robert (Bob) (CDC/OID/NCHHSTP) [mailto:rtc1@cdc.gov]
Sent: Monday, February 02, 2015 3:20 PM
To: Straus, Walter L.
Cc: Destefano, Frank (CDC/OID/NCEZID)
Subject: Intro Frank Destefano and Walter Straus

Walter,

Good to chat. The recent review paper on VSD is PMID: 25108215. There is one on VAERS too but it's still under peer review. So PMID: 15071280 probably best stand in in the interim.

Frank,

Walter Straus (EIS 1990) now at Merck is giving a talk and was wondering if CDC has slides re: VAERS and VSD that he can borrow.

Bob

-----Original Message-----
From: Straus, Walter L. [mailto:walter_straus@merck.com]
Sent: Monday, February 02, 2015 1:47 PM
To: Chen, Robert (Bob) (CDC/OID/NCHHSTP)
Subject: RE: Chat next week?

Bob,
Thanks for this, and for the call.

Best,

Walter

Walter L. Straus, MD, MPH, FCPP, FACP Executive Director, Global Director for Scientific Affairs / Merck Research Laboratories, Merck & Co., Inc., 351 North Sumneytown Pike, North Wales, PA 19454 / Tel: 267-305-7143 /Fax: 215-616-1095
Assistant: Betsy Panacio betsy_panacio@@merck.com Tel: 267-305-2541

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From: Catherine Cohet (Biologicals, BE)
Sent: 29 Feb 2012 17:16:24 +0000
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Vellozzi, Claudia (CDC/OID/NCEZID);Vivek Shinde (Biologicals, BE)
Subject: RE: Question from GSK Biologicals

Claudia, Frank,
Thanks a lot for a great discussion today!
We'll be happy to stay in touch.
Catherine & Vivek
+32 1085 9084 (office)
(b)(6) (mobile)
catherine.cohet@gskbio.com
vivek.shinde@gskbio.com

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Wednesday 29 February 2012 15:23
To: Catherine Cohet (Biologicals, BE)
Cc: Vellozzi, Claudia (CDC/OID/NCEZID)
Subject: RE: Question from GSK Biologicals

Thank you. We'll talk with you soon.

From: Catherine Cohet (Biologicals, BE) [mailto:CATHERINE.X.COHET@GSKBIO.COM]
Sent: Wednesday, February 29, 2012 9:04 AM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Question from GSK Biologicals

Great.
You can use the following TC details:

US	Toll	(b)(6)
	Toll Free	

PIN : (b)(6)
Talk to you at 11am,
Catherine

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Tuesday 28 February 2012 15:41
To: Catherine Cohet (Biologicals, BE)
Cc: Vellozzi, Claudia (CDC/OID/NCEZID)
Subject: RE: Question from GSK Biologicals

Let's leave it as 11 am EST on 2/29. We'll talk with you tomorrow.
Frank

From: Catherine Cohet (Biologicals, BE) [mailto:CATHERINE.X.COHET@GSKBIO.COM]
Sent: Tuesday, February 28, 2012 5:48 AM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Question from GSK Biologicals

We can change the timing, no problem. Thursday or next week work too.
Thanks!

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Friday 24 February 2012 20:37
To: Catherine Cohet (Biologicals, BE); Vellozzi, Claudia (CDC/OID/NCEZID)
Subject: RE: Question from GSK Biologicals

That tentatively works for me, but now I may have to rearrange another meeting that has come up in the interim.
Thanks,

Frank

From: Catherine Cohet (Biologicals, BE) [mailto:CATHERINE.X.COHET@GSKBIO.COM]
Sent: Friday, February 24, 2012 1:10 PM
To: Destefano, Frank (CDC/OID/NCEZID); Vellozzi, Claudia (CDC/OID/NCEZID)
Subject: RE: Question from GSK Biologicals

Wednesday 29 would work for us. How about 11am EST. I'll send call in details next week.

Thanks,

Catherine

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Tuesday 21 February 2012 15:48
To: Vellozzi, Claudia (CDC/OID/NCEZID); Catherine Cohet (Biologicals, BE)
Subject: RE: Question from GSK Biologicals

O.K. Let's try next week: mon afternoon or wed morning (except 930 to 1030).

From: Vellozzi, Claudia (CDC/OID/NCEZID)
Sent: Tuesday, February 21, 2012 9:07 AM
To: Destefano, Frank (CDC/OID/NCEZID); Catherine Cohet (Biologicals, BE)
Subject: RE: Question from GSK Biologicals

Unfortunately I am out of the office this Friday.

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: Tuesday, February 21, 2012 9:06 AM
To: Catherine Cohet (Biologicals, BE)
Cc: Vellozzi, Claudia (CDC/OID/NCEZID)
Subject: RE: Question from GSK Biologicals

Friday morning looks like the best option for us this week.

Thanks,

Frank

From: Catherine Cohet (Biologicals, BE) [mailto:CATHERINE.X.COHET@GSKBIO.COM]
Sent: Wednesday, February 15, 2012 10:37 AM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Question from GSK Biologicals

Dear Frank,

Thanks for your answer. Which days would work best for a call with you and Claudia next week? I'll then check availabilities here (I can make it most days next week).

Regards,

Catherine

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Friday 10 February 2012 22:30
To: Catherine Cohet (Biologicals, BE); Bruce Innis; Vellozzi, Claudia (CDC/OID/NCEZID)
Cc: David Vaughn; Huebner, Robert (OS); Stuart Burstin; Vivek Shinde (Biologicals, BE)
Subject: RE: Question from GSK Biologicals

Dear Catherine,

I agree that a teleconference to brief each other on activities related to narcolepsy would be helpful and I will take you up on your offer to arrange the call. In addition to me, Claudia Vellozzi will participate from our office.

Thanks,

Frank

From: Catherine Cohet (Biologicals, BE) [mailto:CATHERINE.X.COHET@GSKBIO.COM]
Sent: Friday, February 10, 2012 10:38 AM
To: Bruce Innis; Destefano, Frank (CDC/OID/NCEZID)
Cc: David Vaughn; Huebner, Robert (OS); Stuart Burstin; Vivek Shinde (Biologicals, BE)
Subject: RE: Question from GSK Biologicals

Dear Frank,

I'm following up on Bruce's email regarding the CDC-sponsored analysis of pandemic vaccination and narcolepsy in the VSD.
As you certainly know, GSK is supporting a study in Canada, as well as interacting with the European Medicines Agency to explore further avenues to assess the narcolepsy signal. Options include implementing studies in settings where a non-adjuvanted pandemic vaccine was used; assessing the impact of other vaccines (e.g. seasonal TIV) or natural infection (using proxies such as records of influenza-like illness, lab-confirmed infection, or surveillance data on circulating strains).
The study in the VSD provides an opportunity to touch these different aspects. This type of research would supplement existing independent initiatives (such as the ECDC sponsored multi-country VAESCO study in Europe) and could shed light on the role of the vaccine antigen vs. virus infection vs. the adjuvant.
That said, small numbers and need for in-depth case adjudication are indeed a challenge! We have regular contacts with Emmanuel Mignot, sleep expert from the Stanford University Center for narcolepsy; he could probably provide advice (he recently mentioned having heard anecdotal evidence of increased incidence of diagnosis in children in the US…).
In the context of regulatory discussions on the submission of future adjuvanted (pre)pandemic vaccines in the US, we also feel that the VSD analysis could contribute addressing a mutually important question.
We'd be happy to set up a teleconference to share our experience so far and discuss how we can help, as well as discuss ongoing and planned research (I heard that VAESCO are considering extending the study to include countries outside of Europe, incl. the US…)..
Best regards,
Catherine

Catherine Cohet, PhD
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GlaxoSmithKline Biologicals | Global Vaccine Development | Avenue Fleming 20 | 1300 Wavre | Belgium
☎ +32 1085 9084 (office) | +32 488 157 317 (mobile)
catherine.cohet@gskbio.com

From: Bruce Innis
Sent: Tuesday 20 December 2011 19:51
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: David Vaughn; Huebner, Robert (OS); Stuart Burstin; Catherine Cohet (Biologicals, BE)
Subject: RE: Question from GSK Biologicals

Dear Frank:
Tx for the prompt reply. I use this email to introduce you to Catherine Cohet, GSK's epidemiologist in Belgium for the pandemic influenza vaccine project team. Catherine, who works for Vivek Shinde (ex-CDC) whom you might know, may wish to f/u with you in early 2012.
Best wishes,
Bruce

Bruce L. Innis, MD
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MOBILE: +1 484 802 6098
bruce.2.innis@gsk.com

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Tuesday, December 20, 2011 1:36 PM
To: Bruce Innis

Cc: David Vaughn; Huebner, Robert (OS); Stuart Burstin
Subject: RE: Question from GSK Biologicals

Bruce,

Yes, we are conducting an exploratory analysis of narcolepsy and the H1N1 vaccine. Thus far, we only have data from computerized diagnostic codes and are in the process of trying to validate those codes by medical chart reviews. I suspect that we may have too few cases to draw any firm conclusions.

I hope this helps,

Frank

Frank DeStefano, MD, MPH
Director
Immunization Safety Office
MS D-26
Centers for Disease Control and Prevention
1600 Clifton Rd., NE
Atlanta, GA 30333

From: Bruce Innis [mailto:Bruce.2.Innis@gsk.com]
Sent: Tuesday, December 20, 2011 11:54 AM
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: David Vaughn; Huebner, Robert (OS); Stuart Burstin
Subject: Question from GSK Biologicals

Dear Frank:

Hi. I am writing to f/u on an email that you sent to Guillermo Herrera Taracena on 25 Aug (see below in red text). May I ask if CDC plans have advanced to explore a potential link between narcolepsy and H1N1 infection or vaccination? GSK has briefly discussed the potential value of such an investigation with Robert Heubner from HHS/BARDA in the context of our contract with HHS/BARDA to develop adjuvanted pandemic vaccines.

(From Frank Destefano to Guillermo): Yes, VSD plans to do an analysis of narcolepsy. The first step will be to determine how many cases there may be. Narcolepsy is rare and VSD may not have sufficient cases to do any meaningful analysis. Unfortunately, I will be out of the country on September 22nd and will miss the opportunity to see you then. I hope all is well.

With best wishes,

Bruce

Bruce L. Innis, MD
Vaccines for Influenza, MMR, Varicella and Dengue
VP, Global Vaccine Development
GSK Biologicals
King of Prussia, PA, USA
TEL: +1 610 787 3105/3110
MOBILE: (b)(6)
bruce.2.innis@gsk.com

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 17 Jan 2014 14:43:15 +0000
To: 'Leonard Friedland';Weintraub, Eric (CDC/OID/NCEZID)
Cc: 'Dominique Rosillon'
Subject: RE: question from GSK: NEJM Weintraub 2014 publication

Len and Dominique,
I am referring your question to Eric Weintraub, the first author and primary analyst on the manuscript. The comparison of RV1 and RV5 was based on Brighton chart-confirmed cases. Eric will be better able to address if you may be able to use the chart-confirmed cases in your meta-analysis.
Thanks,
Frank

From: Leonard Friedland [mailto:Leonard.R.Friedland@gsk.com]
Sent: Friday, January 17, 2014 9:29 AM
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Dominique Rosillon
Subject: question from GSK: NEJM Weintraub 2014 publication

Dear Dr. DeStefano
Congratulations on the VSD-rotavirus vaccine publication in NEJM (Weintraub et al. 2014).
As you are aware from prior discussions with me, GSK is performing a meta-analysis of the risk of intussusception after vaccination with Rotavirus Vaccines. The inclusion criteria for studies to be included in the meta-analysis are the following criteria :

1. postmarketing study;
2. risk estimated for the 7-day period after vaccination;
3. risk estimated for dose 1 and dose 2, separately;
4. data obtained through active and/or passive surveillance for "confirmed" cases of intussusception cases (Brighton or other method of case confirmation);
5. full publically available study report or peer-reviewed publication.

I highlight in yellow inclusion criteria #4: data obtained through active and/or passive surveillance for "confirmed" cases of intussusception cases (Brighton or other method of case confirmation).
In the NEJM paper, intussusception case confirmation using Brighton Collaboration definition is described in the methods yet in the discussion use of unconfirmed cases is presented as a limitation. Specifically, in the discussion: "*A potential limitation of the study is the use of unconfirmed cases of intussusception in the sequential analyses. However, both the background rates used to calculate the expected number of cases and the observed cases were restricted to inpatient and emergency department settings. When limited to such settings, cases based on these ICD-9-CM codes had previously been shown to have a positive predictive value of approximately 75% in the VSD data7 and in the current study*".
In order for GSK to conduct the meta-analysis, it is important that we ask the authors of the NEJM paper whether the analysis (Observed/Expected results presented in tables 1-2) meets the above-listed criteria #4 for inclusion in the GSK meta-analysis, namely if the cases presented in tables 1 and 2 are all confirmed by Brighton or other methods of case confirmation.
Dr. DeStefano, we greatly appreciate your timely response.
Thank you very much,
Len and Dominique
Leonard Friedland, MD, Scientific Affairs and Public Health
Dominique Rosillon, Ph.D., Epidemiology – Statistics
GlaxoSmithKline

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 8 Jan 2014 22:07:31 +0000
To: 'Cristina Masseria';'Shanthy Krishnarajah';Broder, Karen (CDC/OID/NCEZID)
Cc: 'Leonard Silverstein';Weinbaum, Cindy (CDC/OID/NCIRD)
Subject: RE: Safety of Boostrix during pregnancy

Ideally, we would prefer to meet with you during the 9-12 pm meeting with Dr. Clark's group, but unfortunately Dr. Broder and I are not available that morning. Would you and your colleagues be able to stay on for a separate meeting with us from 1-2 pm that day?
Thanks,
Frank

From: Cristina Masseria [mailto:cristina.x.masseria@gsk.com]
Sent: Tuesday, January 07, 2014 9:36 PM
To: Destefano, Frank (CDC/OID/NCEZID); Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

Thank you for your flexibility.
Do you prefer to set up a separate meeting or to have our discussion during the 9-12pm meeting with Dr Clark and his colleagues?
I am still working on the final agenda. We have 3 hours and therefore there should be enough time to cover both epidemiology/health economics studies and safety studies in case you prefer the second option.
Best regards,
Cristina

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Tuesday, January 07, 2014 4:30 PM
To: Cristina Masseria; Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

Sorry that we got the date wrong. I have some availability on 1/23.
Thanks,
Frank

From: Cristina Masseria [mailto:cristina.x.masseria@gsk.com]
Sent: Tuesday, January 07, 2014 4:11 PM
To: Destefano, Frank (CDC/OID/NCEZID); Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

Dear Dr De Sterfano,

That's great news. However, the meeting with Dr Clark is scheduled for January 23rd from 9-noon and not for the 22nd. Sorry for the confusion.

Are you and Dr Broder available for January 23rd?
Thank you and happy New Year,
Cristina

Cristina Masseria, PhD
GlaxoSmithKline
US Health Outcomes and Medical Policy - Vaccines
Phone: +1.215.751.4960

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Tuesday, January 07, 2014 3:53 PM
To: Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Cristina Masseria; Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

Dear Ms. Krishnarajah,

Thank you again for your request for consultation and for your patience in waiting for our response. We have a mutual interest in gaining more data on the safety of Tdap vaccines administered to pregnant women. Dr. Broder and I could be available to meet with GSK colleagues to discuss maternal Tdap safety issues on January 22 when you are at CDC. Dr. Cindy Weinbaum, in the Division of Healthcare Quality Promotion (copied here), will follow-up with you in the near future on the logistics for the safety meeting. We can further discuss your other questions during that time.

Best wishes for the New Year,

Frank DeStefano, MD, MPH
Director
Immunization Safety Office
Centers for Disease Control and Prevention
Atlanta, GA

From: Shanthy Krishnarajah [mailto:girishanthy.x.krishnarajah@gsk.com]
Sent: Monday, December 16, 2013 10:15 PM
To: Destefano, Frank (CDC/OID/NCEZID); Broder, Karen (CDC/OID/NCEZID)
Cc: Cristina Masseria; Leonard Silverstein
Subject: RE: Safety of Boostrix during pregnancy

Dear Dr. Destefano and Dr. Broder,

Thank you for your time on Dec 5th call.

Pursuant to teleconference, we wanted to follow up on some specific questions we have on the potential safety study using Boostrix among Pregnant women that we are currently evaluating. I am not sure if I mentioned that GSK is interested in including the results of the study proposed by GSK for safety and regulatory purposes.

In addition I wanted to follow up on the following questions

a/ Are you able to recommend other sites than Duke and Vanderbilt which would be able to recruit pregnant women vaccinated with Boostrix that are part of the CISA network?

b/ Are there any lessons learnt from implementing a safety study around pregnant women you are currently planning

c/ How are you adjusting for women who would have received flu vaccine when looking at adverse events

We are still in the process of drafting a concept design and would like to see if you would be open to reviewing the protocol.

And finally we are having a face to face meeting with Tom and his colleagues the morning of Jan 22nd. Let us know if you would also be open to meeting us that day.

Thanks very much and Happy Holidays

Shanthy Krishnarajah, MPH, MBA/MS
Head US HO/Epidemiology Vaccines
USHO and MP
Work Tel: 215 751-3267
Cell : (b)(6)
Pls Note my new office number

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 7 Jan 2014 21:29:33 +0000
To: 'Cristina Masseria';'Shanthy Krishnarajah';Broder, Karen (CDC/OID/NCEZID)
Cc: 'Leonard Silverstein';Weinbaum, Cindy (CDC/OID/NCIRD)
Subject: RE: Safety of Boostrix during pregnancy

Sorry that we got the date wrong. I have some availability on 1/23.
Thanks,
Frank

From: Cristina Masseria [mailto:cristina.x.masseria@gsk.com]
Sent: Tuesday, January 07, 2014 4:11 PM
To: Destefano, Frank (CDC/OID/NCEZID); Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

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Cristina

Cristina Masseria, PhD
GlaxoSmithKline
US Health Outcomes and Medical Policy - Vaccines
Phone: +1.215.751.4960

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Tuesday, January 07, 2014 3:53 PM
To: Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Cristina Masseria; Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

Dear Ms. Krishnarajah,

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Frank DeStefano, MD, MPH
Director
Immunization Safety Office
Centers for Disease Control and Prevention
Atlanta, GA

From: Shanthy Krishnarajah [mailto:girishanthy.x.krishnarajah@gsk.com]
Sent: Monday, December 16, 2013 10:15 PM
To: Destefano, Frank (CDC/OID/NCEZID); Broder, Karen (CDC/OID/NCEZID)
Cc: Cristina Masseria; Leonard Silverstein
Subject: RE: Safety of Boostrix during pregnancy

Dear Dr. Destefano and Dr. Broder,

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Shanthy Krishnarajah, MPH, MBA/MS
Head US HO/Epidemiology Vaccines
USHO and MP
Work Tel: 215 751-3267
Cell : (b)(6)
Pls Note my new office number

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 9 Jan 2014 16:59:30 +0000
To: 'Cristina Masseria';'Shanthy Krishnarajah';Broder, Karen (CDC/OID/NCEZID)
Cc: 'Leonard Silverstein';Weinbaum, Cindy (CDC/OID/NCIRD);Clark, Thomas A. (CDC/ONDIEH/NCCDPHP);Liang, Jennifer L. (CDC/OPHSS/CSELS/DSEPD)
Subject: RE: Safety of Boostrix during pregnancy

That sounds good. It would be helpful if we could receive a brief concept document that we could review before the meeting. Please let me know who from GSK will be attending so that we can arrange suitable meeting space.
Thanks,
Frank
P.S. Tom and Jennifer – You are welcome to attend if you are available.

From: Cristina Masseria [mailto:cristina.x.masseria@gsk.com]
Sent: Thursday, January 09, 2014 10:40 AM
To: Destefano, Frank (CDC/OID/NCEZID); Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

Dear Dr De Stefano,
1-2 is good for us.
Regarding the logistics, Jennifer Liang and Renalda Barlatier are organizing our CDC passes. I am going to find out if it is ok for us to stay until 2 or if we need an extension.
We are at the moment working on the concept protocol for the GSK safety study and, if you agree, I would like to send you the document before the meeting (one week in advance) to facilitate our discussion.
Thank you again for your availability.
Best regards
Cristina

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Wednesday, January 08, 2014 5:08 PM
To: Cristina Masseria; Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

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From: Cristina Masseria [mailto:cristina.x.masseria@gsk.com]
Sent: Tuesday, January 07, 2014 9:36 PM
To: Destefano, Frank (CDC/OID/NCEZID); Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
Cc: Leonard Silverstein; Weinbaum, Cindy (CDC/OID/NCEZID)
Subject: RE: Safety of Boostrix during pregnancy

Thank you for your flexibility.
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Sent: Tuesday, January 07, 2014 4:30 PM
To: Cristina Masseria; Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
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To: Destefano, Frank (CDC/OID/NCEZID); Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
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To: Shanthy Krishnarajah; Broder, Karen (CDC/OID/NCEZID)
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Director
Immunization Safety Office
Centers for Disease Control and Prevention
Atlanta, GA

From: Shanthy Krishnarajah [mailto:girishanthy.x.krishnarajah@gsk.com]
Sent: Monday, December 16, 2013 10:15 PM
To: Destefano, Frank (CDC/OID/NCEZID); Broder, Karen (CDC/OID/NCEZID)
Cc: Cristina Masseria; Leonard Silverstein
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Shanthy Krishnarajah, MPH, MBA/MS
Head US HO/Epidemiology Vaccines
USHO and MP
Work Tel: 215 751-3267
Cell : (b)(6)
Pls Note my new office number

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 30 Oct 2015 14:51:51 +0000
To: Winiecki, Scott (FDA/CDER);'Bailey, Steven R.';Holm Karin;Bachtiar, Novilia (novilia@biofarma.co.id);Bergman, (b)(6) Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu);Darko, Mimi (mimidarko66@yahoo.co.uk);Duo, Dong (dongduo@cdr.gov.cn);Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com);Maure, Christine (maurec@who.int);Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br);Nishioka, Sergio (sergio.de.andrade.nishioka@gmail.com);Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br);Seifert, Harry (Harry.A.Seifert@gsk.com);Sjolin_Forsberg Gunilla;Tebaa, Amina (atebaa@yahoo.fr);Zuber, Patrick (CDC who.int)
Cc: Ashley Wivel (ashley.wivel@merck.com);Maroko, Robert;dongduo@cdr-adr.org.cn
Subject: RE: Some Meeting Follow Up
Attachments: 1 CIOMS Manual on Vaccine Active Safety Surveillance - AD fxd.docx

Here are my edits on the chapters. They include Mimi's and Steven's edits, but I did it before I received Scott's edits.
Thanks,
Frank
Frank DeStefano, MD, MPH

From: Winiecki, Scott (FDA/CBER)
Sent: Thursday, October 29, 2015 3:26 PM
To: 'Bailey, Steven R.' ; Holm Karin ; Bachtiar, Novilia (novilia@biofarma.co.id) ; Bergman, Ulf (b)(6) ; Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu) ; Darko, Mimi (b)(6) ; Destefano, Frank (CDC/OID/NCEZID) ; Duo, Dong (dongduo@cdr.gov.cn) ; Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com) ; Maure, Christine (maurec@who.int) ; Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br) ; Nishioka, Sergio (b)(6) ; Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br) ; Seifert, Harry (Harry.A.Seifert@gsk.com) ; Sjolin_Forsberg Gunilla ; Tebaa, Amina (atebaa@yahoo.fr) ; Zuber, Patrick (CDC who.int)
Cc: Ashley Wivel (ashley.wivel@merck.com) ; Maroko, Robert ; dongduo@cdr-adr.org.cn
Subject: RE: Some Meeting Follow Up
Dear Working Group members,
I have added my edits to the Manual; for Chapters 1-3. Steve's edits are on this version, but Mimi's are not, as I started before I received her update. I have also added in the expanded Section 3.6 that I agreed to work on at the Philadelphia meeting.
Thanks,
Scott

From: Bailey, Steven R. [mailto:Steven.R.Bailey@pfizer.com]
Sent: Friday, October 23, 2015 4:22 PM
To: Holm Karin; Bachtiar, Novilia (novilia@biofarma.co.id); Bergman, Ulf (b)(6) ; Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu); Darko, Mimi (b)(6) Destefano, Frank (CDC); Duo, Dong (dongduo@cdr.gov.cn); Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com); Maure, Christine (maurec@who.int); Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br); Nishioka, Sergio (b)(6) ; Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br); Seifert, Harry (Harry.A.Seifert@gsk.com); Sjolin_Forsberg Gunilla; Tebaa, Amina (b)(6) ; Winiecki, Scott; Zuber, Patrick (zuberp@who.int)
Cc: Ashley Wivel (ashley.wivel@merck.com); Maroko, Robert; dongduo@cdr-adr.org.cn

Subject: RE: Some Meeting Follow Up
Importance: High

All:

We are just 1 week away from our first set of deadlines for TG2 (November 1st if a week from this Sunday), and I want to make sure we were moving along, and either encourage everyone to provide updates, or, if necessary, rework our deliverable date.

From our business plan, here is what is due by November 1st:

- Thorough review of Chapters 1, 2 and 3, with track changes/comments to Chapter owners **(ALL)**
- Chapter 3: Table 3.3, Section 3.4: Update/Write: **(Novi/Irina)**
- Chapter 3: Sections 3.5 and 3.6: Update/Write: **(Scott)**
- Introduction: Update/Write section 1 (intro), section 2 (algorithm), section 3 (RACI): **(Steven)**
- Introduction: Write Section 4 (structure approach to reviewing data) **(Ashley/Rob (draft 1)**
- Ethical Section (end of chapter 3 now): Carefull Review/update: **(ALL)**

Per previous e-mail, I have already completed bullet 4 and circulated. I am now providing my thorough review of the first 3 chapters, with special attention to the ethical section (see attached).

Hoping this encourages everyone to move forward with the above. However, I do understand how busy schedules are, so let's see how everyone does over the coming week, and we can consider moving our deadlines as needed. Also, based on where we are, I would like to set up a telecon of the group in mid November or so to go over any open items or issues.

Regards,

Steven.

Steven R. Bailey, MD MPH MBA
Vice President, Worldwide Safety and Regulatory
SSRM RU/Vaccines Group Head
Pfizer
Steven.R.Bailey@Pfizer.com
484 865 3670

From: Bailey, Steven R.
Sent: Monday, October 12, 2015 12:58 PM
To: Holm Karin; Bachtiar, Novilia (novilia@biofarma.co.id); Bergman, Ulf (b)(6); Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu); Darko, Mimi (b)(6); DeStefano, Frank (fxd1@cdc.gov); Duo, Dong (dongduo@cdr.gov.cn); Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com); Maure, Christine (maurec@who.int); Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br); Nishioka, Sergio (b)(6); Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br); Seifert, Harry (Harry.A.Seifert@gsk.com); Sjolin_Forsberg Gunilla; Tebaa, Amina (b)(6); Winiecki, Scott (alt) (Scott.Winiecki@fda.hhs.gov); Zuber, Patrick (zuberp@who.int)
Cc: Ashley Wivel (ashley.wivel@merck.com); Maroko, Robert; 'dongduo@cdr-adr.org.cn'
Subject: RE: Some Meeting Follow Up
Importance: High

All:

Hope everyone is well. I wanted to make sure we were still keeping up the momentum for TG2. So I have gone ahead an completed one of my deliverables for the project. Please find attached a DRAFT of an update to the Introduction. It include 3 of the 4 pieces: the opening, the RACI, and the Algorithm. The last piece of the intro is the "Structured Approach to Gap Identification, Evaluation, and Determination". Ashley and Rob have agree to take a stab at adding this piece (first draft), and my hope is that by providing this it will be helpful in moving this forward. Ashely/Rob: please reach out if needed as we move this forward.

Please keep in mind the remaining activities per our business plan:

For November 1st:

- All to review Chapters 1, 2, and 3 very carefully. Please send your comments to all, and the owner of each section will consolidate those comments and provide the next draft. Please note the revised drafts are due November 23rd, so it is very important that you provide your comments by NOVEMBER 1st, as discussed. [as a reminder, Chapter Owners are Chapter 1: Steven, Chapter 2: Scott, Chapter 3: Frank]
- Novi/Irina/Scott: Chapter 3 has some sections that still need to be completed, and you all kindly "volunteered" to work on these sections (Table 3.3/section 3.4 (Irina/Novi) and section 3.5/3.6 (Scott)
- All: Review the "ethical section" of chapter 3, with an eye towards how it fits with the rest of the chapter, and any required changes.

I know we committed to tight timelines, but it would be great if we can deliver. If we can work on the 3 bullets above by the 1st of November, we really will be in good shape to have all of our deliverable finalized (per our group) before the year-end holidays, and allow review by the larger group before we all meet in Ghana.

If anyone feels a telecon would be helpful at any point in the process (this entire group, or a subset), please let me know and we will work to arrange.

Kind regards,

Steven.

Steven R. Bailey, MD MPH MBA
Vice President, Worldwide Safety and Regulatory
SSRM RU/Vaccines Group Head
Pfizer
Steven.R.Bailey@Pfizer.com
484 865 3670

From: Bailey, Steven R.
Sent: Wednesday, September 30, 2015 4:48 PM
To: Holm Karin; Bachtiar, Novilia (novilia@biofarma.co.id); Bergman, Ulf (b)(6); Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu); Darko, Mimi (b)(6); DeStefano, Frank (fxd1@cdc.gov); Duo, Dong (dongduo@cdr.gov.cn); Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com); Maure, Christine (maurec@who.int); Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br); Nishioka, Sergio (b)(6); Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br); Seifert, Harry (Harry.A.Seifert@gsk.com); Sjolin_Forsberg Gunilla; Tebaa, Amina (b)(6); Winiecki, Scott (alt) (Scott.Winiecki@fda.hhs.gov); Zuber, Patrick (zuberp@who.int)
Cc: Ashley Wivel (ashley.wivel@merck.com); Maroko, Robert; Bailey, Steven R.
Subject: Some Meeting Follow Up

All (Primarily TG 2 members and key stakeholders)

Please find attached some promised documents (sorry for the delay).

Attached are:

1) The Updated Business Plan for TG2. Please pay special attention to your assignments and due dates in the business plan I will send reminders in about 2 weeks to try to keep us on track. Please feel free to offer updates or suggestions if I missed anything
2) Attached is our preliminary RACI. Will require more work as we move forward, but a good start.
3) The latest draft of the Introduction that we discussed at the meeting. Ashley, Rob, Scott and others who offered to work on this (including myself), please compare against the business plan for what we agreed to as next steps. If anyone feels a small telecon to further discuss the intro is needed, do not hesitate to request, and I can arrange.

It was a pleasure seeing most of you in Collegeville, and for those who could not attend, look forward to seeing you in Ghana. I will trust everyone will move forward with our work as outlined in the business plan, and will check in in a few weeks. If any questions, please reach out.

Regards,

Steven

Steven R. Bailey, MD MPH MBA
Vice President, Worldwide Safety and Regulatory
SSRM RU/Vaccines Group Head
Pfizer
Steven.R.Bailey@Pfizer.com
484 865 3670

From: Holm Karin [mailto:holmk@cioms.ch]
Sent: Thursday, September 24, 2015 11:03 AM
To: Abdoellah, Siti (alt) (b)(6); Arlett, Peter (Peter.Arlett@ema.europa.eu); Ayoub, Ayman; Bachtiar, Novilia (novilia@biofarma.co.id); Bahri, Priya (Priya.Bahri@ema.europa.eu); Bailey, Steven R.; Benkirane, Raja (b)(6); Bergman, Ulf (b)(6); Blum, Michael (BlumM@MedImmune.com); Bonhoeffer, Jan (alt) (j.bonhoeffer@brightoncollaboration.org); Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu); Ceuppens, Marc (mceuppe1@its.jnj.com); Chandler, Rebecca (alt) (rebecca.chandler@who-umc.org); Darko, Mimi (b)(6); Dawei, Liu (b)(6); DeStefano, Frank (fxd1@cdc.gov); Dodoo, Alex (alex.dodoo@umcafrica.org); Duo, Dong (dongduo@cdr.gov.cn); Gregory, William (NYC); Gunale, Bhagwat (alt) (bhagwat.gunale@seruminstitute.com); HAMID, T. Bahdar Johan (b)(6); Heiles, Bernhard <bernhard.heiles@merck.com>; Heininger, Ulrich (ulrich.heininger@ukbb.ch); Holm Karin; Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com); Keller-Stanislawski (Brigitte.Keller-Stanislawski@pei.de); Kilpi, Terhi (terhi.kilpi@thl.fi); Kulkarni, Prasad (drpsk@seruminstitute.com); Kurz, Xavier (Xavier.Kurz@ema.europa.eu); Lindquist, Marie (Marie.Lindquist@who-umc.org); Martin, David (David.Martin@fda.hhs.gov); Maure, Christine (maurec@who.int); Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br); Mentzer, Dirk (Dirk.Mentzer@pei.de); Nishioka, Sergio (b)(6); Nohynek Anna (Hanna.Nohynek@thl.fi); Oberle, Doris (alt2) (Doris.Oberle@pei.de); Patel, Mayur (alt) (PatelMayur@MedImmune.com); Ramkishan, Ajmeer (b)(6); Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br); Seifert, Harry (Harry.A.Seifert@gsk.com); Shimabukuro, Tom (alt) (ayv6@cdc.gov9); Sjolin_Forsberg Gunilla; Srivastava, Swati (alt) (b)(6); Tebaa, Amina (b)(6); Winiecki, Scott (alt) (Scott.Winiecki@fda.hhs.gov); Youssef, Mona (b)(6); Zuber, Patrick (zuberp@who.int)
Cc: Le_Roux Susanne; Habersaat, Katrine (DCE-VPI); Ashley Wivel (ashley.wivel@merck.com); Maroko, Robert
Subject: Philly meeting group photo

Dear All,

Sending you the group photo from the Philadelphia meeting, which I think reflects on our faces the positive feelings we had about what we achieved at this meeting.

I will also shortly be sending you information about how to access the SharePoint website in an easier manner to get the latest drafts and background documents (I have not yet posted all the updates but shall in coming few weeks).

You will also receive within the coming few weeks, the Philly meeting report so that everyone will feel up-to-date and ready to contribute to this next phase of further writing and editing. Even if you have had little time to involve yourself until now, the Editorial Team can really use your help, expertise, and support to produce a useful guide to Vaccine Safety for new and new-to-you (as we were calling them for short) vaccines.

Please be already planning on attending the next 8th meeting to be hosted in Accra, Ghana by the Ghana Food and Drugs Authority, in March or April 2016, as announced by Mimi Darko on the second day of our meeting. We will be sending out a doodle to help determine the best date.

Best regards,

Karin

Karin R. Holm
Technical Collaboration Coordinator, Working Group on Vaccine Safety
Publications Coordinator, CIOMS X Meta-Analysis
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(CIOMS is an Associate Partner of UNESCO and in Official Relations with WHO.)

CIOMS Manual for Active Vaccine Safety Surveillance

Comment [DF(]: I thought this was not going to be a "manual'.

303
304

Chapter 1. When ~~a~~ knowledge gaps exist requiring additional safety surveillance

When is additional study/action necessary at introduction of a new vaccine in a country or in the context of emerging information?

- Identifying gaps in knowledge of the vaccines benefit-risk profile that require active surveillance, with special reference to low- and middle-income countries.

1.1. Introduction

The present manual focuses on *Active* Safety Surveillance that may be needed in special circumstances, including its rationale, implementation and requirements. Basic and routine pharmacovigilance (PhV) activities, needed for any vaccine in any geographical context, including low and middle income countries (LMICs), is described in a global manual for safety surveillance of vaccines, and published by the WHO in 2014.[1]

The purpose of this first chapter is to introduce and discuss the key points to consider when determining *whether* active safety surveillance is necessary, such as at launch of a ~~new~~ vaccine newly authorized for introduction into a country, or when an important safety issue has emerged for a vaccine that is on the market. ~~This question will be addressed particularly~~The focus will be in the context of resource-limited countries (RLCs), including LMICs, ~~resource-limited countries (RLCs),~~ and other countries introducing new vaccines directly without the traditional safety data from extended experience in the International Conference of Harmonization (ICH) countries. For ease of description in this document, these countries will collectively be referred to as "RLCs."

This chapter will highlight instances that may justify additional safety surveillance (SS) beyond routine pharmacovigilance (PhV). It will ~~focus on describing~~describe the types of knowledge gaps that may exist at the time of vaccine introduction, or during usage, and will provide a list of potential gaps that could be pertinent to RLCs especially. It is not expected that this list will be exhaustive, and stakeholders may indeed find other situations requiring additional action. However, the types of gaps described will provide an important starting point.

1.2. Points to Consider

The need for additional study of vaccine safety ~~needs to be carefully considered. It~~ should only be considered if there is a specific knowledge gap (and thus, a specific question has been identified). The gap must be substantive enough to justify formal additional study, and there must be confidence that the question can be answered by the action chosen. This need for rigor and caution in launching and performing surveillance studies of vaccines is emphasized for several reasons, including:

[1] Global Manual on Surveillance of Adverse Events Following Immunization, Sept 2014, http://www.who.int/vaccine_safety/publicatio ns/aefi_surveillance/en

Comment [DF(]: delete

Comment [DF(]: I think the Introduction would benefit by inclusion of the definitions that we will be using for "surveillance", "passive surveillance", "active surveillance", "routine pharmacovigilance", etc.

Comment [MD]: 'THIS" manual sounds better

Comment [DF(]: I thought we were not going to call this a "manual".

Comment [MD]: not necessary to italicize this word.

Comment [MD]: There is still a gap here as I have always said: 1. New vaccine. 2. Pre-exixting vaccine on that market. 3?? Vaccine is not new globally, BUT is NEW on that market/country. Please can we include this.

Comment [MD]: Points should be brought ot clearly as indicated by the title 1.2. These **Points** are not clearly evident as being part of 1.2, especially in the sections in green

- The introduction of additional safety surveillance (~~included~~ including active safety surveillance) could potentially lead to negative impact on the public's confidence in the vaccines and the willingness to participate in vaccination programs;
- There are real implications for resource usage from these additional activities; While they should certainly be undertaken if determined to necessary, careful consideration of appropriate use of limited resources should be undertaken;
- A qualified person or body (text should define criteria and resources!) should be available to appropriately analyze the data; and
- The results should be obtained in a manner to allow effective communication of results.

The overall positive benefit-risk (B-R) profile of the vaccine is established when the Market Authorization (MA), according to regulations in the particular country or region, is granted by the competent regulatory agency or other authority, based on the submitted regulatory dossier. As part of the MA, there may already be conditions for active safety surveillance through studies in the postmarketing setting, e.g. by means of risk management requirements, see below. In particular, for vaccines newly deployed, there may be the need to quickly generate real-life data from the local population to assure policy makers and to give a guarantee of safety especially since data from routine spontaneous reporting systems are likely to be very few.

This paragraph may be placed under the "Introduction" not "Points to Consider"
Thus, Chapter 1 describes the identification of a potential knowledge gap that may impact on the understanding of B-R profile in the postmarketing setting for a vaccine that has been newly authorized for marketing in a RLC. Of course, if an important gap is identified later after the introduction, much if this chapter, and manual, may still be of use. If no such gap with relevance for the specific country is identified, (i.e., no important serious identified or potential risks or missing information are known), or known risks can be appropriately mitigated, ~~at the time of licensing, no proactive measures through~~ active safety surveillance would not be needed. If so, routine PhV would suffice provided an adequate PhV system is in place in the country.[2] However, if a relevant gap is identified, and if this gap could be important for the B-R of the vaccine and the safety of the vaccinated subjects, then actions and tools for active safety surveillance should be considered.

It should also be emphasized that once a gap has been identified, that does not necessarily mean that active SS is based available tool. Numerous tools for closing a gap can be considered, and active SS should only be undertaken if it is determined that this is the appropriate tool. The various tools available and when they may be used, including active safety surveillance, will be introduced in Chapter 2.

There must be a rigorous review of all available data to confirm there is truly a gap. Within the context of this manual, an Essential Vaccine Information Document (EVID) has been developed to help build a standard "dossier" of available information to guide the stakeholder in vaccine introduction. It is only in reviewing this extensive set of data

[2] WHO manual, see above.

Comment [MD]: I don't agree to this statement. I don't see how additional studies will lead to negative impact. If anything at all, it will rather provide more confidence

Comment [MD]: This point is ambiguous and could be rephrased. Yes, in RLCs there are limitations with resources – but assuming it must be done as pointed out, what does "appropriate use of limited resources" mean? It could be restricted to caution on the resource implications of active studies and only to do when necessary.

Comment [DF(]: Not sure what this mean. I don't think a "guarantee" is possible.

Comment [MD]: ??

that one might determine whether an important knowledge gap actually exists. But even after reviewing the comprehensive set of available data, before actually instituting additional surveillance activities the stakeholder is encouraged to be very diligent to refer to all available data to ensure these is not data already available to fill the gap. Some additional sources of information are provided in that chapter.

The gaps to be considered should be relevant and specific to the country/region where the vaccine product is being introduced. However, it should be considered whether this gap ~~may~~might be seen across countries or regions. Before undertaking the additional activities, the stakeholders should consider whether other countries or regions ~~may~~might have similar concerns. It may prove beneficial, and should be encouraged, that there be communications with other stakeholders, as they may work together to close the gaps in the most efficient and robust manner. Thus, information sharing and cooperation between RLCs and other countries should be developed.

1.3. Structured approach for assessing existing vaccine safety data

Information on new vaccines from regulatory agencies in developed countries may be accessed by stakeholders in RLCs. Agencies in the European Union (national regulatory authorities - NRAs and the European Medicines Agency -- EMA), and the US Food and Drug Administration (USFDA) require extensive documentation and assessment of safety data in application dossiers for licensing, i.e. from pre-licensing studies (and perhaps postmarketing experience). Submitted dossiers for new products or new chemical entities as well as for new indications of licensed products provide extensive safety data and analyses of gaps in knowledge. Such gaps may lead to regulatory requirements for additional PhV activities in the postmarketing setting. In the EU system legislation requires that the applicant manufacturer submits a Risk Management Plan (RMP) as part of the application dossier.[3]

The RMP as used in the EU system is considered as a useful guidance for the present manual on safety surveillance in RLCs, for several reasons:

- First, it provides a systematic and comprehensive model for RLCs, i.e. for an analysis of gaps in safety data on new vaccines, and for determining the need for additional PhV studies in the postmarketing setting.
- Second, stakeholders in RLCs would benefit from using regulatory, and assessed, information on safety issues and PhV requirements in the RMP dossiers for new vaccines (provided the particular vaccine has been approved in the EU or US).
- It documents all key risk mitigations, including ongoing registries (disease or product), post authorization safety or efficacy studies, and other post marketing commitments.

1.4. Specific topics to consider that might justify the need for additional studies in RLCs: examples of the types of gaps specific to RLCs.

[3] Guideline on good pharmacovigilance practices, EMA April 2014, see the EMA website: ema.europa.eu/Human regulatory/Pharmacovigilance/Risk-management plans.

Comment [DF(]: I think that something more needs to be said about the EVID. Pointing to the appendix I don't think is sufficient. As I understand it, the EVID doesn't really exist at the moment; it is something that we are proposing be put together. Not clear whose responsibility this would be. The statement that "an EVID has been developed", I don't think is accurate. My understanding is that the appendix will provide a template for an EVID that will then have to be "developed" or completed for a specific vaccine in a specific country.

Comment [MD]: Which chapter are we referring to? Can we point it out as this is the beginning of the manual.

Comment [MD]: Can we please discuss this "structured approach" as its not very clear here. Is it 1) review of MA data. 2) Review of RMP?

Comment [DF(]: I agree. Pointing to these two processes without further description is not very helpful.

1.4.1. Broad consideration regarding type of introduction and potential knowledge gaps

In broad terms, there are two major types of vaccine introductions into an RLC that may occur, and each may require a different consideration regarding knowledge gaps, and methods for evaluation. The first ~~group are~~group is vaccines with a significant history of post marketing usage. These are vaccines that have, generally, long history of use in developed countries, including the European Union or United States. These vaccines have well established use in large patient populations ~~in the real world~~ . However, they are now being introduced for the first time in a particular RLC country or region. The second ~~group are~~group is vaccines that are not only introduced in a particular RLC, but are being introduced for the first time globally within an RLC. These vaccines, which would have limited use in real world setting, could be vaccines with indications specifically pertinent to RLCs, such a Dengue Fever, malaria or Ebola.

The first type of vaccine introduction has previously been the norm, and there are numerous examples of such introductions. Generally, they represent vaccines that were first introduced in developed countries, and thus have a long history of use. Besides the initial authorization data and dossiers, these vaccines will have extensive post marketing data available. This could include, in addition to post marketing reports, completed or ongoing active safety surveillance and other additional pharmacovigilance activities. For these vaccines, the safety profile in the general population will have been well established, and there would be significant data ~~to leverage~~. The considerations in introducing them into an RLC would generally be around items specific to an RLC, and usage that may be different (e.g., population, vaccination schedules, etc). The examples below may be especially helpful in understanding the types of gaps that may still exist.

The second type of vaccine introduction will be very different in terms of the types, and number of gaps that may be seen at introduction into an RLC. In essence, these vaccines will have limited or no significant history of use in a real world setting. This will limit available safety data generally to the clinical data used for registration. Therefore, the types of gaps that might exist in terms of data could be much more basic. Instead of ~~only looking~~ gaps due to items specific to the concerned RLC, there may be much larger, basic gaps in knowledge. In the same way a vaccine being introduced into the EU or US for the first time ~~globally~~ is more likely to require formal postmarketing study, the likelihood of need for active safety surveillance is much higher for these types of vaccines when introduced to RLC.

1.4.2. Specific types of gaps: Examples of potential gaps related to the vaccine or usage in an RLC

Whether a vaccine is being used for the first time in an RLC after extensive usage/ experience globally, or is basically being used for the first time anywhere in the world, it is critical to identify those knowledge gaps that may require additional post authorization study. These gaps will be dependent not just upon the vaccine itself, its properties, and available data, but especially upon factors specific to an RLC, and the usage of the vaccine in that country. The specific gaps that may thus arise from a combination of these factors cannot be predicted for all situations, and will require

Comment [MD]: What is "real world" with respect to RLCs

Comment [DF(]: See above.

careful consideration ~~from the stakeholders using this manual~~ to determine if additional post authorization study is warranted.

While each potential gap cannot be outlined in this manual ~~for this reason~~, there are a variety of different *types* of gaps, as described below, that might be considered~~, and could be helpful in considering appropriate action~~. ~~It~~ The following list is by no means comprehensive, and the stakeholders may certainly find gaps outside of these categories.

1.4.2.1. Novelty of the vaccine

Notable would be a vaccine that has not been used in other countries or is still in development, but is being used in a crisis situation in a RLC. An example of such a vaccine introduction might be the initial use of a new or evolving Ebola vaccine. In such a case, the vaccine, which may be specific to certain RLCs will not have global usage and a long safety history. Nor would significant parallel use in a developed country be expected at introduction. In a case such as this, there would of course be limited or no post authorization safety information upon which to rely. In fact, in a crisis situation, even the clinical data may be relatively limited.

In such a case, the expected potential gaps would be much broader, and could in fact include a need to further characterize the safety profile generally of the vaccine. In ~~these case~~these cases, the stakeholder will need to consider the totality of their knowledge of the safety profile of the vaccine, and whether the key areas that are not known would warrant formal additional study. Such a case would not be dissimilar to first introduction in any country, and consideration of the need for post authorization study would be similar to that undertaken in Europe or the US at first introduction ~~globally~~. This will depend, again, on factors specific to the vaccine and the country in which it is being introduced. The example below (XXX-XXX) should be considered against the backdrop of the more general lack of safety experience for these types of introductions.

It may also be the case that a novel vaccine may have a first introduction in a RLC but with limited or no use in other countries or limited number of countries at the time of introduction. As opposed to the RLC doing so under emergent conditions, this may occur as part of a global introduction in which many countries are introducing the vaccine at the same time. This could include a mix of developed and RLC nations. In many ways, such a large, simultaneous introduction is similar to the above example. The nature and types of gaps in knowledge might be very similar. However, contextually, they might need to be assessed in a different way. Because in this case a number of ~~introduction~~introductions are going on in similar time frames, the gaps themselves could be answered in many different ways. The various countries involved could certainly work together to determine the best way to close the gaps, and could certainly share studies and approaches.

The remaining examples of potential gaps are more specific in scope. Generally they pertain to vaccines with more extensive post authorization usage (and thus available safety data). Generally, they represent potential gaps that are specific to situations that

Comment [MD]: Emergency is a better word

Comment [MD]: If the example being used is Ebola, then this should be deleted as its not a correct assumption to put in the manual

Comment [DF(]: ?

Comment [DF(]: ?

Comment [DF(]: I don't see the example.

would generally occur in an RLC, and related to issues specific to the usage or situation in these countries.

1.4.2.2. Change in the use of the vaccine

This could regard the dosing schedule or regimen, or dose of the vaccine to be used. For various reasons, the dosing schedule for a well-established vaccine might be altered for introduction in a new country (for instance, to match a general vaccination initiative). Or a more abbreviated or accelerated vaccination schedule may be being used for the first time. For instance, in the past, many countries have chosen to provide pneumococcal vaccination on a two dose (plus booster) regimen, rather than a three dose (plus booster) regimen. This type of change in vaccination schedule, especially if there is limited experience, *may* warrant the need for additional pharmacovigilance activities, which could include active SS.xxx??

1.4.2.3. Changes/differences in the vaccine product

Issues may include a new formulation or serotype, a new adjuvant, or formulation. For instance, a vaccine may have a long history of use in single dose vials, or pre-filled syringes. However, in order to expand vaccination into a larger population, the vaccine may be reformulated to be provided in a multi-use vial. In this case, not only would the vaccine product be reformulated, but the usage pattern (repeated insertions into a single vial) would change. Dependent on the experience and clinical data supporting the change in formulation, a stakeholder could determine that active SS might be warranted in order to ensure these new usage patterns lead to no new safety concerns.

1.4.2.4. Related to the target population

Underlying conditions that are especially prevalent in the target population may be of importance for ~~the~~ safety, e.g. HIV, malnutrition or the vulnerability in the population, (e.g., neonates, pregnant women, geriatric individuals) can play a role. These can be especially true if these conditions are not as common in those regions/countries where the bulk of the safety experience has been garnered globally. Thus, while a vaccine may have been used by millions of patients prior to roll out in an RLC for the first time, there may still be a gap to be considered if there ~~is~~are not a large number of exposed patients previously with these conditions.

Also differences in ethnic makeup in the population being targeted in the RLC could be important to consider. Again, it may certainly be the case that even though a vaccine has many years and millions of exposures in the real world setting, there could still be particular populations that do not have significant history of use. This could also be related to the usage patterns that may occur in the RLC pattern. For instance, both MMR and influenza vaccines can be???? used extensively in pregnant women in many RLCs. However, there is often little clinical or even post marketing experience in a controlled setting on such use.

1.4.2.5. Concomitant vaccine or other medication with the present vaccine

Comment [DF(]: ?

Comment [DF(]: The format here and elsewhere assumes the section heading is a topic sentence. It might read more clearly if the intent of the section is repeated in the text of the section rather than using ambiguous terms such as "this", "issues", etc.

Comment [DF(]: ?

Comment [DF(]: ?

Comment [DF(]:

Comment [MD]: These products are never used in Africa! Rarely are they used

The consideration of other products being used by the populations receiving a vaccine at rollout can be very important to consider. Often, the types of vaccines (and pharmaceuticals) used in RLCs may differ from the countries where the greatest experience in use exists. This may be related to disease patterns requiring different vaccinations can differ between them. It may also be due to delivery systems that may cause vaccines that may not otherwise be given together in developed settings to be given together as part of a mass campaign.

For instance, stakeholders may be considering the use of a live, attenuated rotavirus vaccine. In looking at introducing this in their country, they could be concerned that the same population is also receiving the Oral Poliovirus Vaccine. When they explore this concern, they could come to realize that the vast majority of countries where there is experience with the rotavirus vaccine was in the context of IPV. This could be considered something that could require additional pharmacovigilance, such as active SS, if no data are available

1.4.2.6. Different age groups being targeted

For various reasons, a vaccine may be introduced into an RLC in which patients receiving vaccines may have slightly different age ranges than previous usage. For instance, the disease may be more common in a wider range age than where it has been previously used. Therefore, a medical decision may be reached that the vaccine will be given to a larger range of patients than previously exposed (for instance, rather than use in just 0 to 2 year olds that due to higher disease rates, in lack of herd immunity, vaccination for up to year 5). Again, this could represent an important gap.

1.4.2.7. Related to the target disease, or differences in local, serotypes, mutations, virulence factors

While many of these aspects may have a bigger effect on the potential ~~efficacy~~ effectiveness of the vaccine when used in a new setting, there are potential safety issues that could ~~be raised~~arise if the target disease has significant differences in the country of introduction. And, of course, a change in benefit could affect the overall benefit-risk ratio of the product, which could lead to the need to ensure the safety profile is understood in this particular setting.

Also, the vaccine itself may be changed based on ~~the~~ local differences in the target ~~local~~ vaccine preventable disease (or changes in the disease over time). For instance, influenza strains change on a yearly basis, and along with the strain changes, the vaccine~~s~~ is updated. These changes could warrant the need for some additional postmarketing surveillance, depending upon the nature of the change. Similar changes could occur based on local disease epidemiology. For instance, it is possible that a multi-serotype pneumococcal vaccine could be modified to add a serotype specific to an RLC/region, or have a serotype not found in that region to be removed. Again, such chance could warrant consideration of additional pharmacovigilance. Xxx really. This is a new product not just a PV issue (like synflorix and Prevenar 13

1.4.2.8. Disease burden significantly different by country/region

Comment [DF(]: ?

Comment [MD]: And?

As with issues related to local differences in the target disease organism, the overall burden of disease can play a role in the effectiveness and overall Benefit Risk of a vaccine being introduced into an RLC. When introduced into a country with a significant burden of disease, there could be issues that could require additional study. Again, many of these issues may center on efficacy, but there could be safety implications as well. This is especially true during the initial introduction when herd immunity has not yet been established, and the possibility of partial protection exists.

Comment [DF(]: An example or two might be helpful.

1.4.2.9. Related to the health care setting ~~for use~~

If the vaccine is being given in a setting that differs significantly from the previous experience upon which the safety profile is based, additional surveillance may be considered. For example, a vaccine may have been given to a significant number of patients in other developed countries, but the majority of this use may have been in the setting of provision of vaccine by physicians in a medical office. This may allow for specific monitoring, and availability of medical facilities in the event of adverse events, including expected events such as syncope with HPV vaccine.

With introduction into a RLC, the vaccine provider may differ significantly. It may not be given by a fully trained Healthcare Professional. And even with appropriate training, the vaccine provider may be doing so in a setting outside of a healthcare facility. While this may require additional training/resource availability, it could certainly require additional pharmacovigilance to understand the potential implications. Also, if not being performed by HCPs, the ability to actually perform active SS could be compromised.

1.4.2.10. Is the vaccination initiative part of a mass vaccination campaign?

If the vaccine is being introduced for the first time in an RLC, and is being done so through a mass vaccination program, this could increase the need to consider active SS. If there are open questions or gaps, the provision of vaccination within a mass campaign can magnify the issue. If there is a realistic possibility of a safety issue arising, the rapid update and exposure of mass vaccination campaign could increase the potential impact. In such a setting, it would be particularly important to consider systems to rapidly identify any emerging issues, and this could include formal active SS. At the same time, a formal mass vaccine campaign may actually allow for effective and efficient active SS.

1.4.2.11. Are there issues with the cold chain storage or stability?

A last specific example for consideration is around technical issues with vaccine storage and logistics. Especially noteworthy for many vaccines is the maintenance of the cold chain. This can be especially challenging in many RLCs, where cold chain maintenance is especially challenging, and where appropriate storage facilities may not ~~exists~~exist . If the potential loss of cold chain integrity is an issue, active SS may be appropriate to monitor potentially related issues ~~that may be related~~.

The above examples of the types of gaps/issues that could lead an RLC to consider additional study, and potentially active SS, ~~is~~ are by no means exhaustive. ~~The identification of knowledge gaps specific to an RLC, the vaccine, and the nature of the introduction.~~ The above are meant ~~as guides, and to provide~~to illustrate some of the more common types of gaps that have been seen previously encountered, or that are important theoretical concerns and issues. However, it is likely that other gaps could be identified beyond ~~these~~ those above, and certainly one should not only consider these gaps in identifying the needs ~~to~~ for additional study.

1.5 Conclusions

The focus of this first chapter has been to introduce and discuss the key points to consider when determining *whether* active safety surveillance is necessary at launch of a new vaccine or when an important safety issue has emerged for a vaccine that is on the market. The focus is to help the user identify potential gaps in knowledge that could impact the need for additional study, ~~but~~ and to also put these gaps into context of whether such study is needed, and when.

It should be noted that in most cases, existing routine pharmacovigilance is generally sufficient for monitoring the launch of a vaccine within an RLC, especially if there is significant experience with the vaccine in other countries and the safety profile is well established. However, it is equally noteworthy to state that the existing routine pharmacovigilance systems in most RLC are very weak and active SS may be the only way to obtain any safety information on new or newly introduced vaccines. For vaccines being introduced for the first time globally into an RLC setting, there may be an increased need for additional study, including active SS. But even for such vaccines, careful consideration of whether this additional study is necessary should be undertaken. The actual need will depend on the knowledge gaps identified, the impact of these potential gaps on public safety and the Benefit Risk balance of the vaccine, and the ability to identify a particular question that can be answered with the appropriate tool.

To assist in reviewing the available data (see Appendix X) to identify such gaps, a number of examples have been provided. As cautioned, this list is not exhaustive; stakeholders will need to review the particular situation of their vaccine introduction to identify key gaps that may exist.

Notably, this is only the first step in a process. Once a gap is identified, it needs to be confirmed. Further data search should be undertaken to confirm the gap is indeed an open question. If it is determined the gap does indeed exist, it then needs to be confirmed that the gap is significant enough to warrant further study. If both of these steps conclude that there is a significant knowledge gap warranting further study in the postmarketing setting, then stakeholders need to work together to determine which tools can be used to close the gap. Active safety surveillance, while a powerful pharmacovigilance and public health tool, is not the only method available to help close key gaps in knowledge. In Chapter 2, the key available tools will be reviewed to help the stakeholders begin the process of matching the right tool the identified gap/question.

Comment [MD]: I think this can be removed as this has been clearly stated several times and does not make a good point following all the examples given in 1.4.2.1 -1.4.2.10

734
735

Chapter 2. Forms of Safety Surveillance

2.1. Introduction

In this chapter, we will highlight various methods of post-marketing surveillance, including passive and active safety surveillance methods. If a confirmed gap in knowledge has been identified, and deemed critical enough to warrant additional study (see Chapter 1), one of these tools *may* be appropriate to close the gap. ~~The~~The methods to be discussed are shown in Table 2.1.

Table 2.1.: Tools for Performing Additional P~~M~~ost-Marketing Review

Passive Safety Surveillance	**Active Safety Surveillance**	**Active Interventional Safety Surveillance**
Spontaneous reporting	Sentinel Sites	Clinical study
Stimulated Reporting	Drug Event Monitoring -cohort event monitoring	
Sentinel Sites	Registries	
Enhanced Passive Surveillance • On-line reporting • systematic stimulation • additional training	Comparative Observational Study • cross sectional • cohort • case-control • case only study	

When a vaccine is introduced into an RLC, safety surveillance is a shared responsibility between numerous stakeholders: the vaccine manufacturer and distributor, regulatory agency ~~or agencies~~, WHO, Health Ministries, National Immunisation Programmes, organizations that administer~~ring the~~ vaccines (NGOs, hospitals, clinics, etc.), healthcare providers, and ~~patients~~vaccinees. Safety surveillance can only be effective if all groups work together cooperatively.

The Essential Vaccine Information Document (EVID) provides a summary of key information about a product in a user-friendly format. The EVID is designed to serve as a first source of information and a quick reference. Using the EVID, along with the information in Chapter 1, an assessment can be made to identify substantial safety information gaps about the use of a vaccine in a particular country or region. Also recall from Chapter 1 that information may be available from other sources and that a thorough search for relevant information is an important step prior to deciding ~~an~~ if additional surveillance activity is needed. Whether an information gap is truly important depends on many factors but can be summed up by asking the question: "Does this gap potentially affect the benefit-risk balance of the use of this vaccine in this country?" Active safety surveillance is a powerful tool, but it is also expensive and resource intensive. It should only be undertaken when other forms of surveillance will

Comment [MD]: I think this point has been made several times in Chapter one and to make less reading, we should restrict this chapter to just the forms of surveillance

Comment [srb]: Added as transition between the two chapters and to re-enforce messaging (just a suggestion)

Comment [srb]: Would spell out

Comment [DF(]: See comment in chapter 1 about the EVID. Should emphasize here that perhaps the first step will be to develop the EVID for the specific local situation, but perhaps I don't fully understand what the EVID would be.

Comment [DF(]: Seems repetitive of Chapter 1.

not address the information gap *and* the information gained would potentially influence the benefit-risk balance.

This chapter will review several forms of safety surveillance (SS) and the type of information each can generate. It is important to select the appropriate type of surveillance to address areas of missing information. While active SS is the subject of this manual and a very powerful tool, it isn't always ~~the correct method to choose~~most appropriate. ~~Again, t~~The least resource-intensive approach which can address the information gap is likely the most appropriate. In this chapter, we will discuss passive approaches, which are less resource-intensive, followed by active surveillance.

2.2. Passive Safety Surveillance

Passive safety surveillance (passive SS) implies that no active measures are taken to search for adverse effects other than voluntary, spontaneous reports on safety concerns from health professionals and others. Passive SS is the routine~~, basic,~~ and often sole resource for pharmacovigilance (PhV) in many countries. The practice of routine PhV is described in detail in the WHO manual of 2014 and focuses on the application of passive surveillance in RLCs.[4] ~~Several~~ Several methods of passive surveillance are discussed below.

2.2.1. Spontaneous reporting

Pharmacovigilance using a spontaneous reporting system is a first line system designed to detect AEFIs not previously observed in preclinical or clinical studies. The purpose is to detect signals that may generate hypotheses for possibly causally related AEFIs that need to be assessed or investigated further.

The systems rely on health professionals or the general public reporting any suspected AEFIs in connection with vaccine exposure. This system is simple, relatively inexpensive, and does not limit the population from which reports are accepted. Because of the broad pool of reporters, it offers the potential for detecting rare events. However, limitations of passive spontaneous surveillance systems include variability in reporting standards, reporter bias, and significant under-reporting of events.

Using a passive surveillance system, a case series can be assembled to detect patterns and possible associations between a vaccine and an adverse event.

In some situations, ~~S~~spontaneous reporting may be the only surveillance needed. This would be particularly true if a vaccine has been used in multiple ICH countries or over a long period of time and has a well-known safety profile with few serious adverse events. For example, injectable polio vaccine has been given in hundreds of millions of doses and typically causes only mild injection site reactions. However, as stated above the operation of most passive surveillance systems in RLC is associated with extremely high under-reporting. In fact, very little data on safety is reported from RLC to the global

[4] Global Manual on Surveillance of Adverse Events Following. Immunization, Sept 2014, http://www.who.int/vaccine_safety/publications/aefi_surveillance/en

Comment [MD]: This has been mentioned and cautioned several times and almost seems like this manual is serves to deter form performing ASS. It can be moved to Chapter 1 so that this Chapter 2 focuses on forms of SS

Comment [srb]: As discussed at our meeting, would this be a good place to also say one needs to confirm that the tool (or any tool) needs to actually be able to close, the gap, and that in some cases the gap cannot be readily closed by these tools, and if assessment shows this it should not b undertaken.

Comment [DF(]: Pre-licensure?

Comment [srb]: Consider stressing that SR is not for signal generation, but can help close a gap depending on the nature of the gap [this is where we want people to land in most cases, so might want to stress it has potential to close gaps, even with newish vaccines if the gap amenable to be picked up in a spont. System.

database of safety of all medical products including vaccines. Spontaneous reporting may therefore not be feasible ~~nor realistic~~ in ~~several~~some RLSC.

2.2.2. Stimulated Reporting

Several approaches have been used to encourage and facilitate reporting in specific situations (e.g., for new products and for limited time periods). Such methods could include publicizing the need to report AEFI to the public or providing information on what and how to report at the time of vaccination. It could also include systematic stimulation of reporting and frequent reminders to vaccine administrators based on a pre-designed case definition. Although these methods have been shown to improve reporting, they are still subject to the limitations of spontaneous reporting, especially selective reporting and incomplete information.

2.2.3. Sentinel Sites

In some instances, it may be useful to limit stimulated passive reporting to a few sites. This could reduce the amount of data gathered and allow a more focused effort to increase reporting in the sentinel sites. An advantage of this approach is that the number of sites can be selected based on available resources and that the focused efforts at increasing reporting may be more effective. The most important disadvantage is that selection bias may be introduced, if the population of the sentinel sites differs from the general population to be vaccinated.

2.2.4. Enhanced Passive Surveillance

Any intervention that increases the likelihood that more reports will be submitted via a passive surveillance system could be considered an "enhancement." Thus, stimulated reporting and sentinel sites as described above are forms of "enhanced passive surveillance." There are a variety of methods by which reporting can be enhanced:

2.2.4.1. On-line reporting

The electronic submission of AEFI reports can be a convenient way for patients and providers to submit information on AEFI. This also allows the structuring of the collected information, which should increase the quality and quantity of the collected information. The website can be provided to patients and providers during immunization campaigns as well as advertised in different forms (print, public service announcements on broadcast media).

On-line reporting should also facilitate analysis of AEFI data, as large numbers of reports can be compiled and examined for patterns.

2.2.4.2. Systematic stimulation

It is possible, via publications, email reminders, letters, or personal visits to stimulate reporting over an entire area. The effect on increasing reporting will likely diminish with time, so this method is probably best used for a limited time, such as following the introduction of a new vaccine in a mass vaccination campaign.

Comment [DF(]: Needs a reference.

Comment [DF(]: Is this because it is not possible to improve reporting?

Comment [srb]: A thought, and it might fit here is worthwhile (many of my thoughts are not worth-while). Would it be worth noting that one could stimulate reporting specifically around the gap, and the stimulated reporting can be more that generally more reporting; it could include having specific questionnaires for follow up of certain types of events, or stimulating reporting in certain condtions (say, malnutrition or SGA). Just a thought.

(perhaps this is what you mean by pre-designed case definitions)

Comment [DF(]: Need some distinction on how sentinel sites for passive surveillance would differ from sentinel sites for active surveillance.

Comment [DF(]: Then why not include them under this section?

Comment [DF(]: Should you include caveats about the feasibility of on-line reporting in RLC?

Comment [DF(]: Stimulated reporting also discussed above.

One example of systematic stimulation was during the introduction of MenAfriVac in Burkina Faso.[5] In this case, the Ministry of Health developed a field guide, case definitions, a case notification form, and an investigation form for serious cases. Additional training, updated AEFI monitoring guidelines, and reminders about AEFI reporting were distributed. Again, this will increase the number of reports but does not eliminate the difficulties common to passive surveillance, such as under-reporting, report quality issues (missing information, lack of details), and biases (events closer in time to vaccination are more likely to be reported, etc.)

2.2.4.3. Additional Training

Another approach to enhance passive reporting is to provide additional training about suspected events and how to respond to AEFI to healthcare providers. Brazil has used this approach to increase the reporting of viscerotropic disease after yellow fever vaccine. Viscerotropic disease is rare (0.11 – 0.31 cases/100,000 doses) but has a high mortality rate (92.3%). Brazil has stimulated the reporting of this particular event by distributing a manual on AEFIs for health professionals and a Guideline for Investigation of Serious Adverse Events. At the time of Yellow Fever vaccination campaigns, a kit is sent to hospitals instructing how to collect and transport patient samples, increasing the likelihood a case of viscerotropic disease will be diagnosed and reported.[6] Again, this approach may result in more reports and reports of better quality, but it is best used for a short period. The effect of any training likely decreases significantly with time.

2.3. Active Safety Surveillance

Active safety surveillance, in contrast to spontaneous reporting, is characterized by systematic patient follow-up, seeking to ascertain completely the number of adverse events via a continuous pre-organized process in defined (vaccine) exposed populations. Common, too, is the active enrollment of vaccine exposed individuals and follow-up of events (AEFIs) that are detected by asking patients directly, searching registries, or obtaining information from medical records in clinical care. This surveillance is best done prospectively. The most comprehensive approach is through different types of observational, epidemiological studies.

The general concept is an observational, prospective, non-interventional, post-authorization study.

One possible scenario would be a situation where a vaccine has not been licensed in another country or has been in limited use, and there is incomplete information available about serious adverse events or a potential safety signal was detected in the ~~clinical~~ pre-licensure trial. In such a ~~case~~situation, an observational study in the post-

[5] Ouandaogo CR, Yaméogo TM, Diomandé FV, et al. Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010. *Vaccine*. 2012 May 30;30 Suppl 2:B46-51. doi: 10.1016/j

[6] de Menezes Martins R, de Lourdes de S. Maia M, Matos dos Santos E, *et al*. Yellow Fever Vaccine Post-Marketing Surveillance in Brazil. *Procedia in Vaccinology* 2(2010)178-83.

Comment [DF(]: A reference would be helpful to support this statement.

Comment [DF(]: Not sure what this means.

Comment [srb]: Should this be separated like this as its own paragraph?

Comment [DF(]: Not sure this is necessary.

market environment may be deemed appropriate. (This would depend on the frequency of the event, the seriousness of the event, and potential biologic plausibility).

Participants can be enrolled in the study and monitored for adverse event(s) of interest. The adverse event could be monitored by an in-person follow-up, a telephone call, or some other means. Active SS studies are best utilized to monitor for one or a few adverse events of interest. The complexity increases greatly if a large number of events or endpoints are selected.

Since all patients require enrollment and follow-up, active SS ~~is a very~~can be a resource-intensive approach. Active SS should only be used if the adverse event of interest has the potential to ~~effect~~affect the benefit-risk balance of the vaccine and a passive SS method will be inadequate to address the safety issue. ~~Such studies are resource intensive, and should not be undertaken lightly.~~

Active safety surveillance can be accomplished via a number of approaches:

2.3.2. Sentinel Sites

Active safety surveillance can be achieved by compiling and reviewing medical records or interviewing patients and/or physicians in a sample of chosen sentinel sites, i.e. centers identified and designated to participate in a scheme for active SS. The idea is to ensure complete and accurate data on AEFIs in a complete set of vaccine exposed individuals attending these sites. Active surveillance with sentinel sites is most effective for those drugs/vaccines that are used in specific institutions or administered in specific clinical settings, e.g. vaccines in vaccination centers.

While this can be very resource intensive, it is less so than attempting to monitor all patients at all sites, and therefore more easily practiced in RLCs. In addition, the effort can be reduced if sites are carefully selected based on staff training, patient flow, availability of records for review, or other factors. The disadvantage of sentinel sites is the potential for the population at the sentinel sites to differ from the population as a whole, ~~introducing bias and~~potentially limiting the generalizability of the results.

2.3.3. Drug Event Monitoring or Cohort Event Monitoring

In this method, a group of patients with a particular exposure (to a vaccine) are followed for a period of time, during which adverse events are recorded. The cohort may be identified via prescription files, billing data, or a roster of vaccinated individuals. Adverse events are recorded by conducting periodic follow up of all individuals in the cohort. This may be accomplished via questionnaires sent at predetermined intervals to collect information on the adverse event(s) of interest. It may be of use to collect information before vaccination or after the risk interval for the event of interest, to establish a period for comparison. Cohort Event Monitoring can be used to generate new signals or strengthen existing signals, although the complexity of the information increases rapidly with the number of adverse events monitored.

2.3.4. Registries

Comment [srb]: Should we limit to AE? Couldn't a gap be something more "vague", such as the efficacy/sfety of a diferent vaccine schedule, the affects of malnutrion, etc.)

Comment [DF(]: Should mention the need for a comparison (i.e., unvaccinated group or comparison of risk versus non-risk time intervals.)

Comment [DF(]: Not clear how this is different from the sentinel sites approach described above.

Registries are built from data on patients with a disease/AEFI (disease registry), with a biological exposure (e.g. vaccine registry), or with a particular condition (e.g., pregnancy registry). Patients can be followed over time and included in a cohort study collecting safety data with questionnaires. Incidence rates among the exposed can be calculated, and thereby be valuable for investigation of a signal or creating new hypotheses. This method can also be used to examine longer term outcomes of patients with a particular AEFI. In the case of a pregnancy registry, follow up must be of sufficient duration to detect the event of interest in the infant. Thus, if vaccination occurs early in pregnancy and the plan is to follow the infant until one year of age, each mother-infant pair may need to be followed for almost two years.

2.3.5. Comparative Observational Studiesy

Traditional epidemiologic methods are a key component in the evaluation of adverse events following immunization. There are different observational study designs that could be used to validate signals from spontaneous reports or case series and to estimate risk of AEFIs. Major design types are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective) and case-only studies.

2.3.5.1. Cross-sectional study

A cross sectional study collects data on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status. These types of studies are primarily used to gather data for surveys or for ecological analyses. Their major drawback is that the temporal relationship between vaccine exposure and AEFI outcome cannot be directly addressed. These studies are best used to examine the prevalence of an AEFI at one time point or to examine trends over time, when data for serial time points can be captured.

2.3.5.2. Cohort Studies

In a cohort study, a vaccination exposed population at-risk for the disease (or AEFI) is followed over time for the occurrence of the disease (or AEFI). Information on vaccine exposure status is known throughout the follow-up period for each patient. Since the exposed population is known, incidence rates can be calculated. Ideally in cohort studies involving vaccine exposure, comparison cohorts of interest, i.e. without vaccine exposure, should be established and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events (AEFIs). Multiple AEFIs can be investigated using the same data source in a cohort study. A disadvantage is that it can be difficult to enroll a sufficient number of patients who are exposed to a vaccine of interest or to study very rare outcomes (as for some AEFIs). The identification of vaccinated patients and unvaccinated subjects for cohort studies can be accomplished in large automated databases or from special efforts to collect data for the study at hand. Another disadvantage is the difficulty involved in tracking patients over time, to minimize loss to follow up. These challenges increase greatly with longer-term studies.

2.3.5.3. Case-control study

In a case-control study, cases with an event of interest are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The vaccine exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of an AEFI in association with the vaccine exposure. Patients can be identified using data collected specifically for the purpose of the study of interest. For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time. The case-control study design may, however, ~~be unsuitable for vaccine safety studies since it allows only for the study of~~may not be well-suited for studying more than one AEFI at a time. On the other hand, this design allows risk factors other than the vaccine to be studied.

2.3.5.4. Case Only Study

Case Only Designs, as opposed to cohort or case-control designs, focus only on cases (those vaccinated and with the AEFI of interest) and are self-controlled. In a self-controlled case series, a risk and control period is defined and the incidence of the AEFI within each period is calculated. The risk period is the biologically plausible time frame after vaccination when an AEFI might occur. Control periods can be before vaccination and after vaccination, at a time when the AEFI would not ~~longer~~ be plausibly caused by the vaccine (and the patient is at baseline risk). Since each patient serves as their own control, factors which do not vary with time are implicitly controlled for. If the risk and control windows are short, time varying confounders are minimized. The use of administrative databases can facilitate this study design, since it allows the automated identification of cases following a particular exposure.

2.4. Active Intervention Safety Surveillance (e.g. Clinical Trials)

Active, interventional studies (such as clinical trials) can be performed in the post-market environment. However, this approach is seldom employed for vaccines. Typically, vaccine safety (and efficacy) has been established prior to licensure. Therefore, it would be unethical to conduct a trial with a placebo or control (unvaccinated) group. Theoretically, if there were 2 vaccines with similar safety profiles and a comparator trial was needed to establish which product had superior efficacy, a blinded study could be conducted. However, such post-marketing trials are more common in areas where there are multiple therapeutic options for the same disease, such as oncology.

2.5. Conclusions

Gaps in ~~the~~ knowledge ~~regarding of~~ safety of vaccines at the time of authorization or when safety issues emerge during post-marketing monitoring render pharmacovigilance systems crucial for assuring their safety ~~and safe use~~. Passive, spontaneous reporting, systems are most commonly used and constitute a basic resource for PhV that is available in most countries. In some circumstances, active SS approaches will be needed, e.g. when there is a signal of an AEFI for a vaccine or when there is real uncertainty about the safety of a vaccine in clinical use due to its properties or introduction into a new population.

Comment [DF(]: I don't think these should be considered "surveillance". Could mention for completeness, but note that they will not be considered further. I would just call them "clinical trials".

Comment [srb]: Should we note specifically that these are not covered in Chapter 3? (both here and below)

This chapter ~~considers what~~provided an overview of available tools for ~~PhV~~ active safety surveillance ~~are available~~ in different situations and settings. Active safety surveillance is a powerful tool, but should be employed only if passive surveillance methods are inadequate to address the safety issue and the issue has the potential to impact the benefit-risk balance of the vaccine. In general, the least resource intensive study that addresses the identified knowledge gap is the most appropriate approach to use. Details on how these approaches might be utilized in RLCs are presented in Chapter 3.

Comment [srb]: As above, we may need to specically state that PSS and Interventional CTs not covered in Chptr 3

Chapter 3. Active safety surveillance

~~How can a system for active safety surveillance be established?~~
~~- With special reference to resource-limited countries (RLCs)~~

3.1. Rationale for active surveillance systems

~~Safety surveillance systems for medicines and vaccines have traditionally been passive, relying upon spontaneous reporting (See Chapters 1 and 2). Experience from low- and middle-income countries (LMICs) and resource-limited countries (RLCs) shows that few data are generally collected by this approach due to logistics, resource constraints and cultural backgrounds.~~ Passive safety surveillance has an important limitation because it does not allow for a measurement of the frequency of an adverse event in the population as it is subject to underreporting and the number of reports cannot be directly related to the number of persons exposed. ~~Despite these limitations, passive safety surveillance is, in most situations, sufficient to close most knowledge gaps in the post authorization setting (see chapter [ ]).~~

Even though the most commonly-used approach for safety surveillance (SS) in the majority of countries is passive safety surveillance (passive SS), methods of active safety surveillance (active SS) are increasingly used to monitor the safety of vaccines and vaccination programs, especially in high income countries.

The purpose of this chapter is to present principles, steps and approaches to establish active SS systems, with special reference to LMICs, RLCs, and other countries introducing new vaccines directly without the traditional safety data from extended experience in the International Conference of Harmonization (ICH) countries. For ease of description in this document, these countries will collectively be referred to as "RLCs."

3.1.1. Definition and objective of active safety surveillance

Active safety surveillance is a data collection system that seeks to completely ascertain the number of adverse events following immunization (AEFIs) in a given population via a continuous organized process [7] ~~(see also Chapter 2)~~.

The main purpose of active SS is to provide adequate information to guide public health interventions in a timely manner, such as interventions minimizing risks associated with vaccines or vaccination programs. The design and implementation of an active SS system should be driven by the public health objectives and the acquisition of information needed to take successful actions, including the need to initiate epidemiological investigations. [8] It must be recognized, however, that available local resources and capabilities, such as databases and technical expertise, may have a determining influence on the type of active surveillance system that feasibly can be implemented.

[7] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 1). Appendix I.http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf.
[8] Dean T. Jamison et al. Disease Control Priorities in Developing Countries, 2nd edition. Washington, 2006, 53

Comment [srb]: We need a summary (and perhaps even a specific TOC) for this chapter to make it easier for the reader to follow thorugh the chapter and go to the part they need.

Comment [srb]: See above. Should we state "non-interventinal" (just once, don't mean to beat a dead hourse.

Comment [srb]: Try to provide consistent messaging as we move through. While we want to provide rationale for ACTIVE SAFETY SURVEILLANCE, we don't want to make passive SS sound useless for most situation

Comment [MD]: Why are we discussing passive surveillance here again. Can this be moved to the PS portion of Chapter 2 to make less reading and avoid repetition and the impression that this manual serves to deter ASS

Comment [DF(]: I believe that at the beginning we said we would use the term "RLC". Should stick with one.

Comment [DF(]: Is there a reference for this?

Comment [DF(]: I think this was already stated in Chapter 1.

Comment [DF(]: My preference would be to avoid the "SS" acronym and similar acronyms.

Active safety surveillance is a population-based type of surveillance in which the information is collected with defined objectives to investigate one or several predefined primary hypothesis/es of potential adverse effects emanating from passive safety surveillance or other well-grounded concerns (see Chapter 12). Various objectives and hypotheses may be pursued.

Active safety surveillance can also be carried out to complement passive safety surveillance, but with a specific objective to monitor targeted AEFIs, often denoted as Adverse Events of Special Interest (AESIs) and for a specified time period. Active safety surveillance is generally not designed to identify unexpected AEFIs (signal generation).

A primary aim of active SS systems is to estimate the risk of an AEFI in a population exposed to a vaccine. To evaluate if a vaccine increases the risk of a particular AE requires determination of relative risks. ~~in relation to a comparison population not exposed to the vaccine~~. Usually, relative risk estimation involves the comparison with background rates of such events in the underlying population or rates in a comparison cohort, although other methods are available to estimate relative risks, as detailed below.

Estimation of risk, or incidence rates, requires data on the number of exposed individuals in a defined cohort (denominator) and on the subset of these who present an AEFI or condition of ~~of~~ interest over a defined time period (numerator). Whilst denominators may come from aggregated population-level data, the numerator requires the ascertainment of all exposed individuals presenting the event of interest through direct follow-up, review of health records, or use of clinical information in databases when available.[9,10] Examples of different active SS methodologies are provided below.

~~Active safety surveillance can also be carried out to complement passive safety surveillance, but with a specific objective to monitor targeted AEFIs, often denoted as Adverse Events of Special Interest (AESIs) and for a specified time period.[11] Active safety surveillance is generally *not* designed to identify unexpected AEFIs (signal generation).~~

3.2. Points to consider for setting up an active safety surveillance system

An active SS system should have specific objectives with specified milestones during a predefined time period. Immunization safety surveillance needs to be a collaborative venture between several stakeholders, e.g. the immunization programme, national regulatory authority (NRA), PhV Center, or other appropriate stakeholders. [12]

Comment [srb]: Is this true of things like pregnancy registries?

[9] London School of Hygiene and Tropical Medicine. The use of epidemiological tools in conflict-affected populations: open –access educational resources for policy-makers (conflict.lshtm.ac.uk).

[10] World Health Organization. Global Vaccine Safety Blueprint (www.who.int/vaccines-documents). Geneva, 2012, v (Glossary).

~~[11] Nigel.W.Crawford et al. Active Surveillance for adverse events following immunization. Expert Rev Vaccines. 2014 Feb; 13(2):265-76.~~

[12] WHO Global manual on surveillance of adverse events following immunization, *Draft v 6,* 27 August 2014.

Depending on the country situation, implementation of the surveillance system can be delegated to an independent organization such as an academic pharmacovigilance center.

3.2.1. Which stakeholders may be involved in active safety surveillance?

A list of potential, relevant, parties include (see ~~also Chapter 4~~Introduction):

- Immunization programme center
- National Regulatory Agency
- Pharmacovigilance center
- Immunization service (center)
- Academia
- Manufacturer
- Other research centers

Although implementation and direct operation of the surveillance system will likely rest with one stakeholder, all stakeholders should be consulted and given the opportunity to provide input on the objectives, design, and oversight of the system and the interpretation and communication of the findings.

3.2.2. Reasons to use active safety surveillance?

Active safety surveillance is best suited to investigate AEFIs of special interest (AESIs) for specific vaccines, especially those newly introduced. Circumstances where active SS could be useful include (See also Chapter 1):

- ~~A significant gap in knowledge (see Chapter 1) that requires additional study in the post authorization setting. These gaps in knowledge can be to an introduction of a vaccine with limited experience in ICH countries, or due to issues specific to an LMIC and its specific vaccination plan.~~
- Investigation of safety signals arising from clinical trials (e.g. AEFI where there was a non-statistically significant imbalance perhaps related to inadequate sample size) or from postmarketing passive safety surveillance or other sources (e.g., case reports in the medical literature).
- Events (AESIs) too rare to occur in pre-marketing clinical trials, including events that were suggested to carry increased risks in the trials but that did not have statistical power for detection
- ~~Safety concerns that have been identified in the Risk Management Plan (i.e. in the Safety Specification of the RMP: important identified risks, important potential risks, important missing information. See Chapter 1).~~ Potential risks anticipated from experience with similar vaccines and vaccine ingredients or due to particular biological properties of the vaccine, in terms of manufacturing process, composition (e.g. adjuvants), or immunogenicity.
- Potential risks associated with concomitant administration of several vaccines
- A mass vaccination programme where it is expected that a large number of adverse reactions may be reported and their processing may need to be prioritized.

Comment [DF(]: Seems to repeat the second bullet.

Comment [srb]: For discussion: I am not sure we should bring in the EU RMP. If something is identified in an EU RMP, it will likely already have appropriate study in place (or appropriately resort to passive surveillance.

We have already removed the RMP references from chapter 1.

Knowledge gaps or aAdverse events of special interest (AESIs) to be assessed with high priority are those representing potential risks that would need immediate investigation or regulatory action, i.e. AEFIs that could lead to a change in the benefit-risk balance of the vaccine, or require prompt communication to the public.

3.2.3. When to set up an active safety surveillance system?

Situations that should be considered for setting up of a system for active SS include introduction of a new vaccine, or modification in the composition, formulation or conditions of use (e.g. target population, immunization schedule) of an existing vaccine, or introduction of a vaccine with a well-established safety profile into a new, specific population/country (see Chapter 1).

Examples of situations when active SS may be justified

- The introduction of a new dengue or malaria vaccine for primary use in LMICs
- The switch from OPV to IPV within an LMIC,
- The introduction of rotavirus vaccine in a new population (e.g., that uses OPV or has different risks of GI infections)

Ideally, an active surveillance system should be set up in the country in which the vaccine is being introduced. This may not always be feasible due to resource or other logistical constraints. ~~in~~ In some countries, data could be accepted from another country of reference which is producing safety data within the region and serving as a sentinel surveillance system. Selected countries for sentinel surveillance sites would be those where there is an existing infrastructure to conduct an active SS and where the population exposed to the vaccine is sufficiently large. Some countries, however, may not find it acceptable to rely on safety information from other countries and would require a plan for active SS before new vaccine introduction ~~(e.g. Brazil)~~.

In ~~both~~ either situation~~s~~ there ~~would~~ may be a need for capacity building in the respective country, e.g. in terms of PhV centers, sentinel sites, etc.

3.3. How to establish active safety surveillance systems, with special reference to RLCs?

~~- Methodological aspects~~

3.3.1. What are the scientific features of active safety surveillance studies?

Overall, active safety surveillance through observational studies should be able to:

- Quantify risk of AEFIs/AESIs: i.e. incidence rates;
- Provide quantitive or qualitative data to allow assessment of the knowledge gap of focus.
- Provide measures of association between a vaccine and AEFI in terms of relative risks and attributable risk;
- Ascertain risk factors for AEFI (e.g., age, underlying health status);
- Provide supportive evidence of possible causal association between the vaccine and occurrence of AEFIs/AESIs;

Comment [DF(]: Where?

Comment [DF(]: Not clear why this is separate from 3.2.2.

- Address the possible impact of methodological issue; and/or
- Consider the possible public health impact of risk relationships for specific AEFIs/AESIs.

Key to active SS is the observational nature of studies, meaning that they are "non-interventional" and undertaken in real-life situations. Drug treatment/vaccination is given according to the usual local guidelines. Thus, all patients who receive treatment/vaccination can be included until the desired sample size is achieved, including patients of all ages, with other diseases and taking other medicines.

As will be discussed later in this chapter, various types of designs may be used for active surveillance, but prospective observational studies may be considered the prototype and provide the most complete data. Prospective observational studies are:

- Planned before the patients are treated/vaccinated.
- Inceptional (i.e. every patient is followed-up for adverse events from the time of commencement of their treatment/vaccination).
- Longitudinal (i.e. the occurrence of any events in patients are observed over a period of time until the end of the programme/study ~~or until they cease to receive treatment with the monitored vaccines/medicines~~).
- Usually dynamic (i.e. new subjects are added as the study progresses until such time as there are sufficient numbers in the cohort), but sometimes a fixed number of subjects may be recruited at the same time.

Methods for vaccine pharmacovigilance studies have been developed, among others, by the Brighton Collaboration (Link), providing advice for data collection, analysis and presentation of vaccine safety data, including case definitions, an electronic tool to help the classification of reported signs and symptoms, template protocols and guidelines. Further, module 4 (Surveillance)[13] of the e-learning training course Vaccine Safety Basics of the World Health Organization[14] describes pharmacovigilance principles, causality assessment procedures, surveillance systems and factors influencing the risk-benefit balance of vaccines.

3.3.2. How should active safety surveillance be planned for?

Advance planning of an active SS system for new vaccines/new safety issues is essential so that well-functioning systems are in place before the vaccine is introduced. The planning should generate a protocol that describes comprehensively all important components of the targeted active SS system, such as:

- Definition of objectives to be pursued and of hypotheses to be tested;
- Definition of exposure, with a clear description of whether the surveillance will concern a specific vaccine, the vaccination process or the vaccination programme; this distinction is needed to identify the range of data which will need to be collected
- Definition of vaccination outcomes, AEFIs/AESIs (providing standard definitions to be used by health care professionals);

[13] http://www.vaccine-safety-training.org/overview-and-outcomes-4.html

[14] http://www.vaccine-safety-training.org/home.html

- Definition of other data to be collected (e.g. socio-demographic data, morbidities);
- Identification of a geographical area (e.g. a district) and population where adequate health care infrastructure and data processing capability are available;
- Identification of relevant available data sources, if any, that could be used to collect data on exposure and outcomes;
- Description of processes and schedule of data collection, considering simplicity, feasibility, acceptability by the health care professionals and the patients, timeliness and data quality;
- Preparation of data collection forms and quality control procedures;
- Plans for statistical analyses of data, and strategies for addressing methodological issues and for interpretation;
- Roles and responsibilities of different stakeholders;
- Information to health care providers and the population about the objective of the active SS project, describing approaches for ~~exhaustive~~ enrolment of vaccine exposed individuals and for active screening of AEFIs/AESIs;[15]
- Plans for communicating findings.

Useful information for planning safety surveillance systems is available in three WHO handbooks on the PhV of ~~three important groups of~~ medicines ~~(Anti-malarials, Anti-TB and ARV),~~ published by WHO (see Chapter 2, Links).

These handbooks present practical steps to establish and conduct different types of safety surveillance, especially in LMIC and RLC environments. Further, detailed guidelines for the conduct of pharmacoepidemiological studies can be consulted, e.g. ENCePP Guide on Methodological Standards in Pharmacoepidemiology (Link: http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml)

3.3.3. What are the basic study approaches that can be used?

Three main overall approaches can be used to estimate risks associated with a vaccine through active SS:

- Cohort studies ~~that~~ can be used to determine risks (i.e., incidence rates) of AEFIs in vaccinated individuals, as well as relative risks by ~~compare~~ comparing AEFI/AESI incidence rates in vaccinated and, as available, non-vaccinated persons or persons vaccinated with another vaccine whose exposure and outcomes have been measured concomitantly;
- Self-controlled case series (SCCS) ~~analyses where~~designs use the cases to act as their own controls and relative risk is estimated by comparing the incidence in risk periods ~~is compared~~ to the incidence in control periods; and
- Observed versus Expected (O/E) is an approach in which the calculated rates following current vaccination are compared to historical (unvaccinated) baseline/ background rates.

In situations in which it is not possible to identify a suitable cohort of vaccinated individuals, a case-control design may be an appropriate alternative for estimating relative risks, as described below.

[15] Nigel.W.Crawford et al. Active Surveillance for adverse events following immunization. Expert Rev Vaccines. 2014 Feb; 13(2):265-76.

Comment [srb]: For discussion by group: do we want to determining the estimate of risk, which may not always be the objective (as set up earlier). This is a messaging question that deserves some discussion at next meeting.

3.3.4. What are the data requirements for establishing useful active safety surveillance systems (in RLCs)?

The goal of public health surveillance systems is to obtain data that can be used to monitor and evaluate health conditions or interventions. Establishing an effective active SS, however, requires more than just data. The acquisition, analysis, interpretation, and communication of surveillance data is dependent on a number of different resources and initiatives by stakeholders for building ~~up~~ capacity and ~~for~~ using ~~any~~ existing healthcare and public health infrastructure. Critical to these activities is expert and trained staff with the knowledge and experience to design and implement active surveillance systems and to analyze and interpret the surveillance system data. This would include personnel with expertise in public health, medicine, vaccinology, epidemiology, and statistics. Attempting to establish and conduct active surveillance for AEFI without the requisite expertise and experience is not advisable and prone to errors from inexperience.

Three main types of data are required for an active surveillance system of vaccine safety:

- Vaccination data for individuals in vaccinated cohorts;
- Health events (or outcomes), i.e. adverse events following immunization (AEFIs) or adverse events of special interest (AESIs); and
- Demographic and background information on age, gender, domicile, and on relevant background medical factors, ideally available for both vaccinated and unvaccinated cohorts.

Generally, these data would need to be complete and representative of the studied populations/cohorts. The types and quality of the information collected from the sources will determine what methodological approaches that that can be employed.

3.3.5. What are the specific requirements for the source data?

3.3.5.1. Vaccination data

Specific aspects of vaccines to be considered in pharmacovigilance and pharmacoepidemiology have been highlighted in several documents. The report of the CIOMS/WHO Working Group on Definition and Application of Terms for Vaccine Pharmacovigilance emphasizes that characteristics of the vaccine and the vaccinated population, settings and circumstances of vaccine administration and data analysis are issues worthy of special attention in vaccine safety monitoring (Link).

Complete, reliable and unbiased data on vaccinations in a defined population is essential for epidemiologic evaluations of associations between specific vaccines and specific AEFIs.

Thus, an active SS system would benefit from access to readily-retrievable, documented data on every individual vaccinated concerning:

- Individual identifier
- Place of vaccination
- Vaccine type
- Vaccine presentation, single or multiple dose
- Manufacturer
- Lot number
- Date of vaccination (and perhaps time)
- Vaccine injection site
- Number of dose

Ideally, vaccination data for exposed individuals should be maintained in a computerized database or registry.

In some predominantly high-income countries, national or regional registries have been used *ad hoc* in connection with vaccination campaigns, e.g. for vaccinations during the H1N1 pandemic in Europe (e.g. Sweden, Finland) or are used on a regular basis for routine vaccination programs (e.g. Sweden). Vaccination data may also be maintained by medical practices, health plans, clinics or hospitals. In the U.S., health plan or health insurance data provide the source of vaccination data for the two main vaccine safety active surveillance systems (VSD and PRISM).

In reality, it may not be feasible in some countries to establish and maintain immunization registry resources (computerized or paper-based). Alternatives may be considered, e.g.:

- Data on the numbers of distributed vaccine doses could be maintained by the manufacturer, NGO, or NRA, and include as much detail as possible, especially lot numbers. Such data could be used in epidemiological approaches using an observed versus expected outcome type of design (O/E)~~, see below;~~.
- ~~T~~The main limitations would be that not all distributed doses are actually administered and also that there will be no data on the characteristics of vaccinated subjects (age, etc~~);~~).
- Individual vaccination cards, maintained by the person vaccinated or a parent of a vaccinated child. This approach could be useful for case-based studies (e.g., case-control or self-controlled case series studies~~;~~.
- However, problems with lost cards, lack of participation, etc, ~~would~~ can be anticipated~~;~~.
- Immunization coverage surveys could provide data on the proportion of the population that is vaccinated with further coverage estimates in various demographic categories (sex and age) and different geographic regions. Unless everyone in a specific area is surveyed, sample survey methods can be used to extrapolate the proportions into estimated number of people vaccinated. The survey approach could provide data for epidemiological O/E approaches, using background rates or in concurrent analyses of AEFI/AESI rates in vaccinated versus unvaccinated groups. Limitations of this approach include that they are time-consuming and expensive and not likely to provide timely data unless the surveys are routinely conducted in an ongoing basis, and further there may be recall bias if the surveys rely on self-reports~~;~~.

- Self-reports could be used but only as a last resort due to potential problems with erroneous recall by the individual, and as a consequence possible biases. Self-reports could be used in coverage surveys or case-based studies in which efforts should be made to validate the self-reported data.

3.3.5.2. Health events/outcomes data

For information on health events or outcomes, the source of data to be used will depend on type and severity of the health event (AEFI/AESI) of interest. Generally, serious events that require medical care would be better suited for active SS, since the events have a greater chance of being recorded in medical institutions.

Ideally, the source of event data should contain information on all medical encounters by all individuals, independently of vaccination status. The source should be able to capture data from in-patient care hospital admissions emergency departments, as well as outpatient/primary care clinics. The data should be readily retrievable (i.e., computerized) and ideally include:

- Patient identifier (to allow for linkage to other data)
- Place of care
- Diagnosis(es) (ideally standardized)
- Date (and time?) of onset of first symptom of the event
- Other relevant medical information

In RLC settings, access to medical care may be limited and medical care settings may not provide complete ascertainment of the health event of interest. Even if data sources for the ascertainment of AFFIs/AESIs are deemed to be complete, the possibility for health-care seeking bias should be considered. Individuals being vaccinated could be more or less likely to seek medical attention in the presence of symptoms. Further, they may have a different propensity to develop the event in question as compared with non-vaccinated individuals, due to pre-existing medical conditions (being healthier or less healthy).

The difficulties in ascertaining AEFI is illustrated by an enhanced active surveillance project during a yellow fever vaccination campaign in several countries in Africa (See Case Study 1). Although extensive efforts were initiated to actively find cases of AEFI in multiple settings, underreporting remained a major limitation (e.g., ~~more than 38,000~~substantially fewer deaths than expected were ascertained~~ deaths within one month of vaccination would be expected in the eight countries; however, only 33 deaths were reported~~). Incomplete AEFI identification and investigation in hospitals resulted from some cases not being investigated because doctors assumed that they were due to other causes (e.g., malaria) or not associated with vaccination (e.g., traffic accidents). The study also illustrates the importance of local background rates; they were lacking in this study and AEFI rates had to be compared to US and European rates which may have been very different populations (e.g., pre-existing YF immunity).

Comment [srb]: Suggest we soften to make it clear these are not vaccine related deaths: otherwise this number appears quite shocking as written)

Case study 1: Enhanced surveillance for AEFI in multi-country vaccination campaigns in Africa

Reference: Breugelmans JG, Lewis RF, Agbenu E, Veit O, Jackson D, Domingo C, et al. Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010. Vaccine 2013;31:1819-1829.

Issue: To assess the safety of yellow fever vaccine in mass vaccination campaigns in Africa

Locations: Benin, Burkina Faso, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone, and Togo

Data sources: Not reported.

Vaccine: Voluntarily reported or ascertained for AEFI cases.

Total vaccine doses administered was known.

Outcomes: All eight countries established enhanced case-finding for AEFI in addition to the existing routine AEFI reporting system integrated into the Expanded Programme on Immunization.

Health workers were trained to identify any adverse events during the vaccination campaign, to complete case report forms, and to send forms weekly to the national level.

Dedicated and trained staff identified potential cases in regional and national referral hospitals by means of daily review of hospital registries, medical charts and interviews with emergency room staff.

Population: Not reported.

Design: Enhanced passive surveillance with active case-finding

Methods: This project used active surveillance only to the extent that it involved more active case finding. All eight countries established enhanced case-finding for AEFI and included standard operating procedures (SOPs) for collection of biological specimens and a customized data entry tool for data management and analysis. A national expert committee (NEC) was created and convened by each Ministry of Health. Workers were trained to identify and report adverse events during the vaccination campaign, including routine surveillance in regional and national referral hospitals. Data were entered into country-specific databases.

Findings: Rates of AEFI (YEL-AVD and YEL-AND) were much lower than in studies of US and European travelers.

Lessons: Initiated extensive efforts to actively find cases of AEFI in multiple settings.

The effort supported development of NECs and raised awareness of AEFIs in countries with limited pharmacovigilance experience.

Underreporting was a limitation (e.g., ~~more than 38,000~~only 33 deaths within one month of vaccination ~~would be expected~~were identified in the eight countries; however, ~~only 33 deaths were reported~~many more were expected).

Importance of local background rates – AEFI rates had to be compared to US and European rates which may have been very different populations (e.g., pre-existing YF immunity).

Lack of individual data on immunization status – voluntary reporting and incomplete ascertainment of vaccination status of cases contributed to underestimates of AEFI rates.

Incomplete AEFI identification and investigation – in hospitals some cases were not investigated because doctors assumed that they were due to other causes (e.g., malaria) or not associated with vaccination (e.g., traffic accidents).

Organizers of an active SS system will have to adapt to existing medical care infrastructures and availability of medical information. In some circumstances event data may be only available from hospitals, on paper logs or in computerized registries. In other situations there will be a need for individual follow-up through home visits. Focused examinations by trained examiners may be feasible for selected conditions/events. In case self-reporting by patients would be applied, such events would have to be of a fairly general nature.

Other possibilities could be telephone follow-up calls (cell/smartphones, text messaging) or scheduled clinic follow-up visits. Safety surveillance could also be managed in a setting of a special clinical study (e.g. in an established Health and Demographic Surveillance System (HDSS) (Sankoh and Byass 2012). Individual follow-up would be better suited for focused research studies on specific AEFIs rather than an ongoing active SS system.

In considering the important choices of source and approach, the costs and efforts should be weighed against the expected yield and quality of information that could be collected in the specific setting.

3.3.5.3. Population demographic data

Demographic information is important at both a population and individual level.

3.3.5.3.1. Population level

First, there is a need to define the population under surveillance (at risk). Usually this population is based on administrative boundaries (country, region, province, etc.) or the

catchment area of a particular health care provider, assuming residents of the catchment area would seek care predominantly at a particular hospital or other local health care service.

At a minimum, the total number of people (population) in the particular surveillance system should be ascertained. Also, data on other demographic variables, especially gender and age should be obtained.

Sources of population data could emanate from:

- Census and vital statistics, as available, including births and deaths;
- Hospital or clinic patient reference populations (especially primary care), although these could be unrepresentative particularly if healthcare utilization is low; and
- Special projects (e.g., HDSS).

For safety monitoring, aggregate population-level data can be useful in epidemiological approaches using O/E analyses or ecological analyses (see below). Population-level data can also be used to estimate vaccination coverage and background rates.

3.3.5.3.2. Individual-level demographic and medical information

For more advanced epidemiologic study approaches, i.e., cohort studies, there is a need for individual-level demographic data.

It may however be difficult to obtain demographic information on individuals, unless already available in a record system, e.g. population registries or hospital or primary care clinic registries (e.g., patient panels).

If available, it is often helpful to have health information on individuals in the population. In epidemiological studies, such as cohort or case-based studies, information on the health status of vaccinated and non-vaccinated individuals can help address possible biases due to selection on account of the indication for vaccination and pre-existing medical conditions. The health information may be available from health care registries in some countries, but in most situations it may have to be collected from the individuals within a particular study.

3.3.6. What methodological approaches can be used?

Overall, the analytical approaches that can be used depend on the types of data that are available on vaccinations, health events, and population demographic and medical characteristics. It is decisive for the choice of methodological approach whether these data are available on the individual or at a population (aggregate) level. Individual-level data tend to be richer and amenable to more advanced analytical designs, whereas population-level aggregate data are more restricted and subject to a greater degree of biases and confounding.

3.3.6.2. Individual-level linked data ~~(Table 1)~~

If vaccination, health events, and demographic data are available for individuals, then a broad spectrum of epidemiologic study approaches is possible, including cohort, case-control, and case-only designs (Table 1). These have been described in Chapter 2 and are summarized below with reference to how the different data sources apply to the various methodologic designs. Many textbooks and tutorials are available on epidemiologic methods. For example, a free on-line tutorial (ActiveEpi Web) is available from Emory University at: http://activepi.herokuapp.com.

Table 3.1. Possible study methods for individual-level data

Data Type			Methods
Vaccine	Health Event	Population/Demographic*	
Available	Available	Available	Cohort Case-control Self-control
Available	Available	Not available	Self-control
Available	Not available	+/- Available	none
Not available	+/- Available	+/- Available	none

*Available for both vaccinated and unvaccinated individuals

3.3.6.2.1. Cohort studies

Design features.

In a ~~pharmacoepidemiological~~ cohort study, a defined population-at-risk (cohort) for the disease (or event) is followed over time for the occurrence of the disease or events of interest (AEFI/AESI). ~~In a situation w~~When individual data on vaccine exposed individuals, and data on unexposed subjects, together with their individual follow-up of events, are available, then ~~full-scale or simplified~~comparative cohort studies can be performed. The necessary data for cohort studies can be time-consuming and laborious to collect, whether relying on existing health care databases or ~~household surveys~~direct participant follow-up.

Information on vaccine exposure status is ascertained before start of follow-up and thus known throughout the follow-up period for each patient. In a comparative cohort study, a population unexposed to the vaccine is defined and followed in a similar manner. Enrollment of vaccinated subjects could be achieved through ad hoc registration at vaccination centers at one or several sites, or be obtained from vaccination registries in countries that offer such resources. The follow-up of AEFIs/AESIs could likewise be managed through vaccination centers by means of questionnaire or interview-based collection of event data, or when available from health registries.

The ~~occurrence of (~~number~~)~~ of observed cases of a disease/event of interest (AEFIs/AESIs) is ~~related~~ divided ~~to~~ by the number of subjects in the populations at risk

and time period of observation (person-years). These data are used to generate incidence rates as the direct measure of occurrence over a defined study period.

Full-scale cohort studies

In a situation when individual data on vaccine exposed individuals, and data on unexposed subjects, together with their individual follow-up of events, are available, then full-scale or simplified cohort studies can be performed. The necessary data for cohort studies can be time-consuming and laborious to collect, whether relying on existing health care databases or household surveys.

3.3.6.2.2. Simple uncontrolled cohort design.

Cohort event monitoring (CEM), a simplified cohort method of active SS. In CEM patients are identified from prescribing physicians' (electronic) prescription data or automated health insurance claims data. A follow-up questionnaire is sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information on new events. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire (Ref12[151617]).
CEM studies could be useful to generate signals of new AEFIs/AESIs among vaccine exposed cohorts that could give rise to new hypotheses on adverse events. Limitations of CEM include varying physician and patient response rates and an unfocused nature of data collection, which can obscure important signals.

Examples
Reports from numerous CEM studies are available from centers in e.g. New Zeeland (Intensive Medicines Monitoring Programme) and the UK (Prescription Event Monitoring) where such systems are part of routine safety surveillance of drugs (Ref).
Provide concrete examples, UMC database. See Chapter 2.

Methodological considerations for cohort studies.

Methodological requirements need to be carefully considered before planning a cohort study, especially in relation to circumstances in RLCs. For a cohort study to be meaningful and effective, i.e. to be able to detect a change in the risk at a pre-specified level, the cohorts need to have sufficient numbers of subjects enrolled. For rare but serious events, the necessary cohort sample sizes can be substantial and demanding. The follow-up of vaccine exposed and non-exposed subjects need to be as complete as possible for all studied events, and the degree of completeness should be similar in the exposed and non-exposed cohorts. Further, full-scale vaccinewell-conducted cohort studies would need to collect data on other characteristics of the study participants. Data on age, gender and socioeconomic features would be useful for analyses of risk in subgroups of participants in a vaccination programme. These factors and data on medical background factors need to be mapped evaluated in order to address the problems of selection bias and confounding in the risk estimates.

3.3.6.2.3. Special resources to consider

Automated databases

Comment [DF(]: This is already addressed in Chapter 2.

The identification of large numbers of patients for cohort studies could be facilitated if data can be derived from large automated databases. There are several automated databases available for pharmacoepidemiological studies (Ref 12,[15,18]). They contain automated medical records or automated accounting/billing systems. Vietnam provides an example of a study using a large linked database system for active surveillance in an RLC setting (see Case Study 2). This study demonstrates the feasibility of establishing a large linked database system for active surveillance in an RLC setting. The study was aided by an existing infrastructure that included data from a pre-existing census and a well-defined population. Coding and transcription of medical diagnoses had been in place before the study started. The surveillance system provides all necessary data to conduct active surveillance and can serve as an infrastructure to address many immunization safety issues, as well as other issues (e.g., vaccine coverage and effectiveness). Census, coding and community participation may be costly and time-consuming activities. An active surveillance system that can serve a variety of public health purposes, including vaccine safety monitoring, may be more likely to obtain support from public health agencies and other policy makers.

Case study 2: A large linked database approach for active surveillance in Vietnam

Reference: Ali M et al. The use of a computerized database to monitor vaccine safety in Viet Nam. Bulletin of the World Health Organization 2005;83:604-610.

Issue: To monitor adverse events during a measles mass vaccination campaign. There were concerns that measles immunizations, administered to children across a broad age range of 9 months to 10 years, irrespective of earlier measles immunization status, might trigger adverse events.

Location: Vietnam

Data sources:

Vaccine: All vaccinations and vaccine lots used were recorded on an individual vaccination card and in a logbook which were stored at the vaccination center.

Outcomes: All admissions to polyclinics, district hospitals or the provincial hospital were recorded by the surveillance system

Population: A dynamic study cohort of children under 15 years of age was assembled based on a census conducted in 2002.

Records of births during the study period were collected monthly and used to update the population database.

Emigrations and deaths of cohort members were recorded during quarterly visits to the community.

Design: Self-control design for safety assessment (cohort design for vaccine coverage)

Methods: The study was conducted in two provinces in Vietnam. A dynamic relational database was used, containing data on population, vaccination history and medical events. The Commune Health Centre (CHC) system was the primary source of data. Routine vaccinations were usually administered at CHC. The data were linked through a unique identification number assigned to each individual in the study area. An interactive system was designed to enter data collected from health care providers. All medical encounter diagnoses were coded by a trained team of physicians according to ICD-10 guidelines. The project staff visited the vaccination centers every month to record vaccination information (i.e. patient identifiers, vaccine types, vaccination dates and vaccine lots used). SCCS analysis was performed for the most frequent medical events comparing rates during the 14 days after vaccination with a pre-vaccination period. (In addition to relative rates of AEFIs, vaccine coverage was calculated using a cohort design based on the vaccination and population denominator data.)

Findings: No increased risk was found for any of the medical events evaluated.

Lessons: This study demonstrates the feasibility of establishing a large linked database system for active surveillance in an RLC setting.

The surveillance system provides all necessary data to conduct active surveillance and can serve as an infrastructure to address many immunization safety issues, as well as other issues (e.g., vaccine coverage and effectiveness).

An active surveillance system that can serve a variety of public health purposes, including vaccine safety monitoring, affords considerable efficiencies and can leverage public health resources and support.

The study was aided by an existing infrastructure that included data from a pre-existing census and a well-defined population. Coding and transcription of medical diagnoses had been in place before the study started.

Census, coding and community participation may be costly and time-consuming activities which could complicate the establishment of surveillance networks in other areas.

Sentinel sites

Active safety surveillance can be achieved by using medical record or interview data on patients collected through ~~selected, targeted~~specially established surveillance areas or centers, so called Sentinel Sites. As a strength, such Sentinel Sites could be organized to ensure complete and accurate data on reported AEFIs/AESIs, from specific patient subgroups. Further, information on the use of a drug/vaccine can be targeted. Some of the major weaknesses of Sentinel Sites are problems with selection bias, small numbers of patients, and increased costs. Active SS through Sentinel Sites could be efficient for vaccines since they are prescribed and administered in special settings, such as vaccination centers where an infrastructure for dedicated reporting can be created.

In RLC settings, established Health and Demographic Surveillance Systems (HDSS) sites may be considered to serve as regional sentinel sites, particularly in areas that lack administrative data on the population (reference). An example of conducting cohort-based active surveillance in a HDSS setting is provided by a study in Ethiopia (see Case Study 3). The study illustrates the use of data on immunization history linked to data on health events ascertained from home visits, clinic visits, hospital admissions and demographic observations of mortality using a common individual ID number assigned to all HDSS residents. As may be often required for active monitoring or follow-up of individuals, informed consent was obtained. Utilization of healthcare was limited, requiring ascertainment of health events of interest through structured interviews by trained study personnel at home visits. The study utilized verbal autopsies to determine general causes of death (refs). HDSSs exist in several RLC countries, particularly in Africa and Asia, and provide a potential existing infrastructure to serve as sentinel sites for conducting active surveillance of AEFIs. HDSSs are most suitable for locations that lack reliable population-based data; however, establishing and maintaining an HDSS is resource and labor intensive.

Case study 3: A cohort study utilizing Health and Demographic Surveillance Systems (HDSS) in Ethiopia

Reference: Berhane Y, Worku A, Demissie M, Tesfaye N, Asefa N, Aniemaw W, et al. Children Who Received PCV-10 Vaccine from a Two-Dose Vial without Preservative Are Not More Likely to Develop Injection Site Abscess Compared with Those Who Received Pentavalent (DPT-HepB-Hib) Vaccine: A Longitudinal Multi-Site Study. PLOS ONE 2014;9(6): e97376. doi:10.1371/journal.pone.0097376.

Issue: To monitor AEFI comparing the rate of injection-site abscess following PCV-10 and the pentavalent vaccine (DTP-HepB-Bib)

Location: Ethiopia

Vaccine: Vaccination cards that specified type of vaccine and site of injection plus vaccine registration books maintained at vaccination centers.

Outcomes: Household-based surveillance -- at 48 hours and 7 days after vaccination by trained interviewers using uniform follow up visit form.
Hospital-based surveillance – study personnel visited healthcare facilities weekly.

Population: House-to-house survey in all the study sites enumerated eligible study population. Photo ID with unique identification number was issued to mothers of eligible infants.

Design: Cohort study

Methods: The study was conducted in existing Health and Demographic Surveillance Systems (HDSS) in Ethiopia. Household population records are updated annually. Data on vaccines received and AEFI were collected systematically and prospectively at vaccination centers, households, and clinics/hospitals. Verbal autopsies were conducted

for any deaths identified. Unique identification number allowed linkage between data sources. Informed consent was obtained.

Findings: No significant differences were observed

Lessons: The study illustrates the use of data on immunization history linked to data on health events ascertained from home visits, clinic visits, hospital admissions and demographic observations of mortality using the common individual ID number assigned to all HDSS residents.

HDSSs exist in several RLC countries, particularly in Africa and Asia, and provide a potential existing infrastructure to serve as sentinel sites for conducting active surveillance of AEFIs. HDSSs are most suitable for locations that lack reliable population-based data; however, establishing and maintaining an HDSS is resource and labor intensive.

Overall considerations

In summary, cohort studies can be useful for active SS of vaccines since direct incidence rates of vaccine adverse events, in addition to absolute risk (AR) and relative risk estimates (RR), can be produced. Further, multiple AEFIs/AESIs can be investigated using the same cohorts. However, cohort studies are demanding in terms of logistics and ~~resources due~~may require large ~~to~~ sample size~~s requirements~~, rendering it difficult, especially for rare/serious events to enroll sufficient numbers of vaccine exposed patients. ~~An alternative to full-scale comparative cohort studies could be the Cohort-Event-Monitoring approach, especially when the aim is signal generation or strengthening.~~

3.3.6.2.2. Case-control studies

Design

Detailed description of the case-control methodology can be found in various guidance documents (Link).

In a case-control study, cases with a disease or experienced event (AEFIs/AESIs) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio (OR), which is an estimate of the relative risk (RR) of disease in the two groups (if the disease is not common).

Methodological considerations

Depending on the condition of interest, identifying a sufficient and representative number of case subjects and collecting needed data from medical records or by interviewing can be laborious and time-consuming. The availability of large population-based databases are especially useful to provide efficient means for ~~enrolling~~ identifying a sufficient number of cases and determining their vaccine exposure and medical outcome data in a relatively short period of time.

Case-control studies are particularly valuable when investigating whether there is an association between a drug/vaccine and *one* specific rare and serious disease/adverse event, as well as to identify a number of other risk factors in addition the vaccine. Data on both vaccine exposure and presence of risk factors need to be collected from cases and controls retrospectively, implying that accurate personal recall is necessary when interview data are used. Risk factors important to include concern other predisposing or triggering factors relevant for the outcome under study.

Selection bias, in addition to recall bias, and confounding due to underlying differences in health profiles and risk factors of case and control subjects, need to be addressed in the design (by matching) or the analyses (by statistical adjustment).

The major drawback of the case-control design is that only one AEFI/AESI can be examined for a particular vaccine, rendering this design less practical for active SS. An example of a case-control study for AEFI monitoring, is a study conducted in Mexico and Brazil to evaluate the risk of intussusception following monovalent rotavirus vaccine (RV1) ~~RV1~~ (Rotarix) vaccination (see Case Study 4). Although from relatively more advanced settings, the study illustrates the basic principles of conducting a case-control study. Use of hospital-based surveillance would be applicable only in settings where the particular AEFI (intussusception in this case) would have come to medical attention. Matching controls to cases based on area of residence is a useful strategy which could be applied in settings without a well-enumerated population database or register from which to select controls. This type of study, however, is resource-intensive, requiring trained study personnel to conduct periodic monitoring and review of records at several hospitals.

Case study 4: A case-control study of a rare AEFI in Mexico and Brazil

Reference: Manish M. Patel, Vesta Richardson López-Collada, Marília Mattos Bulhões, Lucia Helena De Oliveira, Aurora Bautista Márquez, et al. Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil. N Engl J Med 2011;364:2283-92.

Issue: To assess the association of a newly introduced monovalent rotavirus vaccine (RV1) with intussusception

Locations: Mexico and Brazil

Vaccine: Review of vaccination cards and provider records plus parent interviews.

Outcomes: Hospital-based surveillance with review of clinical records by trained study personnel

Population: Controls were identified from the same population as the controls by matching on neighborhood of residence

Design: Case-control study (in addition to self-control case series)

Methods: The study was conducted in 53 hospitals in 7 states in Brazil and 16 hospitals in 10 states in Mexico. Cases of intussusception were identified independently of their vaccination status through prospective enrollment at the participating hospitals. Informed consent was obtained. In addition to the case-control analysis, a self-controlled case series analysis was also performed.

Findings: A small increased risk of intussusception was found.

Lessons: Although not strictly from RLC settings, the study illustrates the basic principles of conducting a case-control study.

Use of hospital-based surveillance would be applicable only in settings where the particular AEFI (intussusception in this case) would have come to medical attention.

Matching controls to cases based on neighborhood of residence is a useful strategy which could be applied in settings without a well-enumerated population database or register from which to select controls.

This type of study could be relatively expensive as trained study personnel were employed to conduct periodic monitoring and review of records at several hospitals

Overall consideration

In summary, the case-control epidemiological design has a major disadvantage in that only one AEFI/AESI can be examined at a time. It is therefore not used much as a first line approach for active SS. It should be considered to formally test the hypothesis of an association between the vaccination and a specific AEFI following detection of a strong and serious signal that has been generated through routine safety surveillance.

3.3.6.2.3. Self-control designs

In recent years, the development and adoption of self-control designs have expanded the capabilities of epidemiologic research on vaccine safety (Ref). Variations on self-control designs exist, but probably the best known is the Self-Controlled-Case-~~Study~~ Series (SCCS) (Ref).

Design, methodology

These types of designs use a person as their own control by comparing the risk of a health event during a time period shortly following vaccination with other time windows before and/or after vaccination in the same individual. Thus, the self-control design implicitly adjusts for all factors that do not vary with time (e.g., sex, ethnicity, and

genetics) even if they have not been measured in the study. Also, these designs allow for analyses in highly vaccinated populations since time periods shortly after vaccination are being compared with other time periods, rather than relying on comparing risks in groups of vaccinated individuals with unvaccinated individuals (which may be few in some populations). Thus, these designs can be conducted using vaccinated cases only and therefore ~~be~~ are efficient and feasible in settings in which data are not available on unvaccinated individuals. The design requires ascertainment of all (or a representative sample of) vaccinated cases during the study period. ~~In special situations, however, self-control designs have been applied to spontaneous reporting systems in which completeness of case reporting varies with time from vaccination (refs).~~

Methodological considerations

The main limitation of ~~these S~~self-~~C~~controlled designs is they are methodologically appropriate only for relatively acute events (AEFIs/AESIs). In events that have a long and variable latency period for development~~,~~ follow-up may be difficult and specification of an appropriate risk interval may not be possible. ~~potential underlying risk factors may change in presentation and severity over time in the individual.~~ ~~Further~~Another concern is the appropriateness of including pre-vaccination time periods within the comparison interval~~,~~ ~~the presence of some factors in a pre-vaccination interval~~ especially if occurrence of the outcome of interest may affect likelihood of future vaccination and bias the association between the vaccine and the event. Nevertheless, the SCCS method has been successfully used to assess several vaccine adverse effects.

An example of the self-control methodology applied in an RLC setting is provided by a study in Guatemala (See Case Study 5). This type of active surveillance system in an RLC country could serve as a model for other countries. The use of a self-control methodology meant that data was only needed on vaccinated infants and an unvaccinated comparison group was not needed. The feasibility of ascertaining all AEFI through multi-source active follow up was demonstrated. Although the study recruited only parents with access to telephones, 95% of the population of Guatemala City owns a mobile phone and the methodology may be applicable in other RLC settings with relatively high mobile phone coverage.

Case study 5: Active vaccine safety surveillance using a self-control analysis in Guatemala

Reference: Asturias EJ, Contreras-Roldan IL, Ram M, Garcia-Melgar JA, Morales-Oquendo B, Hartman K, et al. Post-authorization safety surveillance of a liquid pentavalent vaccine in Guatemalan children. Vaccine 2013; 31:5909-5914.

Issue: To study the safety of DTwP-HepB-Hib combination vaccine (Quinvaxem®)

Location: Guatemala

Vaccine: Documented at study enrollment at two pediatric clinics

Outcomes: Parents reported possible AEFIs.
Routine telephone contact with parents.

Reviewed medical records of any health care encounters.
Active daily monitoring of electronic database of pediatric emergency room and hospital.

Population: Healthy infants who received study vaccine at well-child care visits at two pediatric clinics in Guatemala City
Parents accessible by telephone

Design: Self-control case series

Methods: Only vaccinated infants were studied to determine relative risk of AEFI occurring within 30 days of vaccination compared with days 31-60. Informed consent was obtained. Parents/guardians were asked to report any possibly serious symptoms to study physician or nurse, being contacted by telephone at regular intervals to inquire about symptoms and healthcare visits. The research nurse completed AEFI form and reviewed medical records of healthcare visits. AEFIs were also captured through active daily monitoring at the pediatric emergency room and hospital using an electronic database (matched using unique identification number). Post-neonatal mortality rate was compared with the rate for the department of Guatemala in 2008-2009.

Findings: The liquid pentavalent vaccine was not associated with increases in SAEs or hospitalizations.

Lessons: This was a comprehensive active surveillance system in an RLC country that could serve as a model for other countries.

The use of a self-control methodology meant that data was only needed on vaccinated infants and an unvaccinated comparison group was not needed.

The feasibility of ascertaining all AEFI through multi-source active follow up was demonstrated.

Although the study recruited only parents with access to telephones, 95% of population of Guatemala City owns a mobile phone and the methodology may be applicable in other RLC settings with relatively high mobile phone coverage.

Overall consideration.

In summary, a self-controlled case-based design provides a mechanism to monitor defined AEFIs and to ~~quantify~~ evaluate in a timely and cost-effective way a vaccine safety signal. Since exposure and outcome data are only required on the vaccinated population, the self-controlled design could be considered for active SS of acute AEFIs vaccines in the RLC setting in which unexposed population data would be difficult to obtain.

3.3.6.1. Aggregate data without individual-level linkage (Table 2).

In the absence of individual-level data, summary or aggregate data on a population or group of patients may still provide useful information in monitoring vaccine safety. Three types of aggregate summary data may be considered: the number of vaccinations, the number of health events, and population characteristics. These data may be available from separate sources. Depending on which data sources are available different types of study approaches and analyses are possible (Table 2).

Table 3.2. Possible study methods for aggregate data without individual-level linkage.

Data Type			Methods
Vaccine	Health Event	Population/Demographic	
Available	Available	Available	O/E Ecological
Available	Available	Not available	O/E (need BG rates) Ecological
Not available	Available	Available	BG rates
+/- Available	Available	+/- Available	Ecological
+/- Available	Not available	+/- Available	none
Not available	~~+/-~~ Not ~~A~~available	+/- Available	none

If all three types of data are available only at an aggregate level, observed-to-expected (O/E) analyses can be performed to estimate relative risks associated with vaccination. The results may only be approximations since the sequence of vaccinations and health events may not be known (i.e., may be mixing individuals who had the health event prior to vaccination with individuals who experienced the health event after vaccination). To be most informative, the number of individuals that experienced a health event after vaccination is needed in calculating O/E ratios. ~~The calculation of rates of occurrence of the health event of interest (AEFIs/AESIs) in vaccinated people presupposes data on the number of cases that were vaccinated, as well as the total number of people who were vaccinated. Then, the number of vaccinated subjects can be subtracted from the total population to estimate a denominator of unvaccinated people, and if the number of vaccinated cases is known then a similar calculation can performed to estimate number of cases that were not vaccinated and the rate in the unvaccinated can be calculated and compared to the rate in the vaccinated. The rates in the vaccinated divided by the rates in the unvaccinated population provides an estimate of the relative risk (RR) and the difference in the two rates provides an attributable risk (AR).~~ The O/E ratio is calculated by applying the rate in the unvaccinated to the number of vaccinated people to obtain the expected number of cases among the vaccinated (E) and this is compared with the observed number of cases among the vaccinated (O). Availability of demographic data will allow stratification of the analyses by relevant characteristics (e.g., sex, age).

If all three types of data are available only at an aggregate level, observed-to-expected (O/E) analyses can be performed to estimate relative risks associated with vaccination. The results may only be approximations since the sequence of vaccinations and health events may not be known (i.e., may be mixing individuals who had the health event prior to vaccination with individuals who experienced the health event after vaccination). To be most informative, the number of individuals that experienced a health event after vaccination is needed in calculating O/E ratios. The calculation of rates of occurrence of the health event of interest (AEFIs/AESIs) in vaccinated people presupposes data on the number of cases that were vaccinated, as well as the total number of people who were vaccinated. Then, the number of vaccinated subjects can be subtracted from the total population to estimate a denominator of unvaccinated people, and if the number of vaccinated cases is known then a similar calculation can performed to estimate number of cases that were not vaccinated and the rate in the unvaccinated can be calculated and compared to the rate in the vaccinated. The rates in the vaccinated divided by the rates in the unvaccinated population provides an estimate of the relative risk (RR) and the difference in the two rates provides an attributable risk (AR). The O/E ratio is calculated by applying the rate in the unvaccinated to the number of vaccinated people to obtain the expected number of cases among the vaccinated (E) and this is compared with the observed number of cases among the vaccinated (O). Availability of demographic data will allow stratification of the analyses by relevant characteristics (e.g., sex, age).

If only aggregate vaccination and health events data are available without available population data (i.e., including number of unvaccinated), it may still be possible to perform an O/E calculation if the number of vaccinated cases is known and a background rate for the AE of interest is available from other sources (e.g., from prior years, from other comparable countries, or from the literature). If retrospective unvaccinated rates are used to estimate the O/E ratio, the interpretation of the results must consider possible temporal trends in the health condition interest.

Ecological analyses can also be performed using aggregate data. Ecological analyses attempt to correlate changes in one factor (e.g., vaccinations) in a population with changes in another factor (e.g., health event). Since they involve population-level correlations, ecological analyses are subject to confounding by many other unaccounted for factors that may have also changed in the population. Thus, ecological analyses tend to be most suitable for hypothesis generation. Nonetheless, they are often used in studies of immunization programs, including for vaccine safety issues. Probably the best known use of ecological analyses is in demonstrating the effectiveness of immunization programs; for example, graphs that show how the incidence of a vaccine preventable disease decreases as vaccination coverage increases. In vaccine safety, Gangarosa used ecological graphs particularly effectively in illustrating how vaccine scares about pertussis vaccines in the 1970's and 1980's led to decreasing acceptance of pertussis vaccination with consequent increases in pertussis disease (ref: Ganagrosa). Another example involves analyses that have shown that autism continued to increase in countries after they had eliminated thimerosal-containing vaccines from their vaccination schedules, thus providing persuasive evidence against an association between thimerosal and autism (refs). If aggregate data are available on vaccinations, health events, and population characteristics, ecological analyses can be performed

comparing vaccine coverage with disease rates. If vaccination coverage data are not available, sometimes ecological analyses may simply compare disease trends relative to the date when a vaccine was introduced (or discontinued).

Essential for many types of vaccine safety analyses is the availability of background rates of potential AEFIs (ref: Black). Background rates are especially valuable for evaluating reports from spontaneous reporting systems to determine if the number of cases that are reported following vaccination is more than would be expected by chance. Background rates may be available from the literature or from other countries, but having background rates from the local population provides the most valid data for comparisons with AEFI reports in a particular country or area. Calculation of background rates requires data on the total number of health events in the defined population, as well as the size and other demographic characteristics of the population.

A study from Tunisia provides an example of how a hospital-based network was used to establish disease background rates in an RLC setting (see Case Study 6). Although not a safety study, this study demonstrates how a sentinel hospital surveillance system can be used to ascertain and provide background rates of cases of specific health conditions. It could be adapted to provide background rates for possible AEFI (e.g., intussusception). The study highlights the need for complete case ascertainment and estimates of population denominators for determining background rates.

Case study 6: Background rates from active hospital-based surveillance in Tunisia

Reference: Soltani M, Bouanene I, Trabelsi A, Harbi A, Hachicha M, Amri F, et al. Epidemiology of rotavirus gastroenteritis among children under 5 years of age in Tunisia – Results of sentinel hospital surveillance 2009 to 2011. Revue d'Epidemilogie et de Sante Publique 2012;60:473-80.

Issue: To assess the epidemiology, clinical and laboratory features of rotavirus acute gastroenteritis in children less than 5 years of age

Locations: Tunisia

Vaccine: Not applicable

Outcomes: Cases identified in 11 sentinel pediatric departments

Population: Population data provided by the national institute of statistics

Design: Multicenter prospective observational study

Methods: Clinical data and stool samples collected for children admitted for acute gastroenteritis. Stool samples were tested for rotavirus. Incidence rates calculated using estimated population denominators.

Findings: Estimated incidence rate of rotavirus acute GE was 11 cases/100,000 child-years

Lessons: Although not a safety study, this study demonstrates how a sentinel hospital surveillance system can be used to ascertain and provide background rates of cases of specific health conditions. It could be adapted to provide background rates for possible AEFI (e.g., intussusception).

Highlights the need for complete case ascertainment and estimates of population denominators for determining background rates.

Comment [srb]: Is this the beginning of a whole new section on Steps: Should there be a header/introduction.

Table 3.3. Summary of steps, activities and resources in the establishment of active safety surveillance systems.

STEPS	ACTIVITIES	RESOURCES
Planning	See 3.3.2	PhV study center, trained team, adequate resources
Study design and preparations	- Expert advice on possible design options for active SS - Consult field investigators on practicalities/ feasibility/ acceptability of different options - Choose best option with scientific committee - Write study protocol - Organize peer review of study protocol	Same
Study implementation	- Appoint study coordinator - Identify study sit(s) - Run study pilot exercise	Monitoring Center, Sentinel Site, trained team, adequate resources
Establishing cohort or case material:	- Determine sample size: cohort, comparative cohort, case-control, SCCS	Study center and team, consultations
Data acquisition: - Data base - Reporting rates - Advice on good practice	- Collect: details on vaccines, other medicines, reports on all events after vaccination, background medical data	- Study center - Reporters, clinicians - UMC database available

	- Organize data base - Promote high reporting - Data collection to be selective	
Data analysis: - Data entries - Strategies for analyses - Incidence, risk estimation	-Entry data be reviewed -Staff trained, motivated - Questions on causality - Decide strategy: Signal detection/strengthening, risk estimation - Develop incidence rates and risk estimates for vaccine and other risk factors.	- Study center scientific staff - Biostatistical expertise

3.4.1. Planning and study implementation

The study protocol needs to be carefully planned, see above. Guiding documents should be consulted, e.g. the EU template for study protocol and ENCePP Checklist for study protocols might be used and adapted (Link). As regards estimates on sample size requirements for different designs and circumstances, consultation with statistical literature and expertise is recommended.

The implementation step has to be well prepared if an active SS study is to succeed. To ensure this it is necessary to, as a first action, appoint a full-time study coordinator and a study team. A second step would be to conduct a pilot exercise aiming at running an initial pilot phase of a planned study programme. Third, appropriate collaborative units, so called Sentinel Sites, should be selected that have adequate resources to perform the study, and the teams should be together.

3.4.2. Establishing cohort or case materials.

If aiming for a cohort study, the desirable cohort size should be determined. If a comparative cohort study is being undertaken, greater numbers will be needed. Likewise, if performing a case-control or SCCS special considerations of sample size are needed.

3.4.3. Data collection

- Detailed data on vaccine exposure: to be collected is information on the identity of the patient, name of the vaccine, site and time of first and repeat vaccinations, dose, lot number, etc., and data on other concomitant medicines.

- Data on AEFIs/AESIs: All adverse events are requested to be recorded and not just suspected adverse reactions. Health professionals should be asked to record the following types of events: all new events even if minor, change in a pre-existing

condition, abnormal changes in laboratory tests compared with a previous examination, lack of effectiveness, admission to hospital with date and cause, the first observation of pregnancy of any duration, all deaths with date and cause. Also, relevant background medical information should be collected, as needed in a particular study.
Special reporting forms should be used; questionnaires for routine monitoring forms are available.

- Data storage: An appropriate database software should be chosen. For instance, the Uppsala Monitoring Center (UMC) has developed 'CemFlow' for storage of study data (cohort data and also statistical analysis functions), which can be accessed via a broadband internet connection.

- Maximizing reporting rates: in the planning phases and at communications with potential reporters (health professionals, health workers and public health staff), it is important to promote willingness for collaboration, and to remove barriers.

- Advice building on experience: With the awareness that increased data requests increase the workload and the cost, the data collected should be carefully selected and weighed. Some study data may be best requested in the follow-up phase when there is opportunity for further personal contacts.

- The entry of data should meet a number of requirements: data must be accurate (standardized/coded and checked for quality), data processors must be adequately trained, be supervised, and have good tools. This staff should be well informed on the scientific development in the project in order for them to share the vision.

3.4.4. Data analysis

- As a first step, a clinical review of all reported, observed, cases is necessary.
At the monitoring center this involves, for the purpose of epidemiological studies, assessing the clinical details in the reports and determining the appropriate event terms, assessing the duration to onset of each event, the severity and seriousness, and further recording the outcome of each event.

- The entry of data should meet a number of requirements: data must be accurate (standardized/coded and checked for quality), data processors must be adequately trained, be supervised, and have good tools. This staff should be well informed on the scientific development in the project in order for them to share the vision.

- The analyses should address two basic questions:
- Is there a convincing relationship between the vaccine and the AEFI/AESI?
- Is it likely that the vaccine that the vaccine actually caused the event?

- When considering the relationship between the vaccine and event, some questions should be considered:
- Did the event begin before the patient was vaccinated?
- Is there any other possible cause for the event?
- Could the event be due to some other co-existent medical condition, or medicine?

- Is the duration to onset of the event biologically plausible (e.g. in case of an allergic or immune related event, or a cancer)?

- The analytical work will be governed by the general strategy of the active SS.
A common scenario for an active SS will be to evaluate signals identified by passive safety surveillance at PhV centers in separate countries, in the WHO system through signal detection approaches at the UMC or in the EU by regulatory agency EMA. This effort may also may also be denoted as "strengthening" of the signal. The process entails a number of possible steps, e.g. reviewing other experience, searching for non-random patterns, consulting experts, and undertaking epidemiological studies for active SS.

- Another situation is when the risk for an AEFI/AESI in association with a particular vaccine, or other risk factor(s), is to be carefully investigated and quantified, i.e. for the purpose of risk estimation. A risk factor is a characteristic associated with an increased probability of occurrence of an event. In the presence of a risk factor, a patient is more likely to develop an adverse reaction.
The importance of knowledge on risk factors is because it provides a means of avoiding or minimizing the number of AEFIs/ AESIs.
Risk factors may be linked to the patient, the vaccine or the environment. The strategy is here to produce valid risk estimates - with a main focus on the vaccine - for each risk factor and in for subgroups of the vaccine exposed population.

- The biostatistical analyses aim to produce incidence rates for exposed and non-exposed cohorts, together with relative risks and absolute. Likewise, risk estimates are produced in other study designs, as relative risks in case-control and (odds ratios) SCCS approaches. In the full-scale epidemiological studies, bias and confounding issues need to be addressed to ensure results to be as valid as possible, through strategies in data collection and data analysis.

- In the conduct of such epidemiological studies for active SS there is need for special expertise in epidemiology and biostatistics, within the study centers.

3.5 ?

3.6. Oversight of the active safety surveillance studies (to be expanded?)

3.6.1. Protocol and design
3.6.2. Review of the protocol
3.6.3. Approval of the study
3.6.4. Monitoring

The first consideration is who will be the formal sponsor of the study, i.e. who will pay for the study (MAH? NGO? Academic Center, Regulatory body, other party, shared cost)? Second to consider, who will be in the lead (implementation team) of actively running the study (MAH, NGO, CRO, Academic Institution)?

As to the design considerations and establishment of the protocol, all stakeholders should participate in the review (e.g. sponsor, implementation team). The ultimate oversight of the proposed protocol should be managed by the Sponsor.

The final "internal" approval of the active SS would be by the sponsor, who should have reached alignment amongst all the stakeholders. Approval would also have to be sought from the NRA or other National Authorities.

The practical work on monitoring of the study procedures would generally fall on the implementing team of the study, whereas oversight of the monitoring would be in the remit of the sponsor.

Given the multiple stakeholders in a study of this type, a shared "ownership" or "sponsorship" could be preferred, rather than the traditional, separate, roles in trials. Creation of a cross stakeholder oversight committee might best serve these type of studies the best. If this is deemed to be an option there would be a need to create a structure for how this would work. Given multiple stakeholders, an external Data Monitoring Committee would be highly advisable for these studies.

~~**Global Advisory Committee on Vaccine Safety (GACVS)**~~

~~The rapid detection of vaccine safety signals of global importance should be complemented by a scientifically sound assessment of the signals through studies which are analyzed and evaluated by global experts. To respond promptly, efficiently and with scientific rigor, to vaccine safety issues of potential global importance, WHO established the Global Advisory Committee on Vaccine Safety (GACVS) in 1999[1,2].~~

~~GACVS has 14 members, who serve in their personal capacity and represent a broad range of disciplines covering immunization activities. GACVS members are acknowledged experts from around the world selected from, but not necessarily restricted to, disciplines such as epidemiology, statistics, pediatrics, internal medicine, pharmacology and toxicology, infectious diseases, public health, immunology and autoimmunity, vaccinology, pathology, ethics, neurology, drug regulation and vaccine safety.~~

~~GACVS is responsible for risk assessment by considering the evidence on vaccine safety issues, and complements other bodies, such as Strategic Advisory Group of Experts (SAGE) on Immunization[3], which deal with the mitigation of risk. GACVS discusses vaccine safety issues that are either causing public concern, or have the potential to do so. These include general safety issues that are relevant to all vaccines, some vaccine-specific concerns and safety issues related to new vaccines, or vaccines still in development.~~

~~WHO through the GACVS maintains the global safety profile of all vaccines, advises on the conduct of studies for assessing vaccine safety signals of global importance and review the results of those studies.~~

~~The Advisory Committee's assessments of vaccine safety are published regularly, both in print and on the WHO web site.~~

~~Safety Expert Group: The Safety Expert Group is a review committee consisting in independent senior pharmacovigilance experts and experts of other disciplines involved in the research of vaccine safety and/or with vaccine research experience. The primary purpose of the Safety Expert Group is to assess scientific evidence related to adverse events following immunization. This includes rigorous reviews of the latest knowledge, in all fields ranging from basic sciences to epidemiology, concerning any aspect of vaccine safety of global or regional interest, in close collaboration with all parties involved, including experts from national governments, academia and industry. Those groups are also expected to determine causal relationships between vaccines and/or their components and adverse events attributed to them.~~

~~Safety Expert Group membership consists but is not limited to, vaccine safety experts, regulatory and public health agencies representatives, and specialists in epidemiology, biostatistics, pediatrics, internal medicine, pharmacology and toxicology, infectious diseases, public health, immunology, vaccinology, pathology, ethics, neurology and drug regulation.~~

~~[1] Global Advisory Committee on Vaccine Safety (http://www.who.int/vaccine_safety/en/).~~
~~[2] Folb PI et al. A global perspective on vaccine safety and public health: the Global Advisory Committee on Vaccine Safety. American Journal of Public Health, 2004, 94:1926–1931~~
~~[3] Strategic Advisory Group of Experts (http://www.who.int/immunization/sage/en/). /~~

3.7. Ethical conduct, patient and data protection

All research involving human subjects, regardless of the study design, should be carried out in accordance with international ethical principles and high medical and scientific standards. Requirements would be similar in RLCs as in high-income countries.

3.7.1. Ethical issues ([i])

Ethical principles must be applied consistently to all types of pharmacovigilance methods. The ethics of collecting data for active SS after immunization, in particular, has special features since it is a methodology which may, depending on design option, require the collection of detailed personal data and sometimes stores these data for indefinite periods. There may often be a need for follow-up at a later date for the further study of any safety concerns identified, at which time there will be a need to conduct investigations such as a more detailed cohort study, nested case–control studies, comparative safety studies, subgroup investigations (e.g. in children) or even a full clinical trial.

Before starting an active safety surveillance programme, there must be open discussions with all the stakeholders including patients. Most importantly, early in the planning

Comment [srb]: Is this really true? Or practical? For many observational studies, the patients do not have open discussion; they may (or may not) be informed their data will be used in a stuy and promised data will be protected, but usually not a open discussion.

Comment [MD]: Vaccinees not patients

stage, endorsement must be sought from the health ministry/health authorities without whose support little will be achieved. Open communication must follow with professional organizations, all health providers, the pharmaceutical industry, the general public, community leaders and the media.

3.7.2. Prerequisites to collecting patient data

It is important to seek the required approval of the highest appropriate authority in the country in which the active safety surveillance is going to be performed. This may be the Minister of Health or the national regulatory authority (NRA). Also approval on the basis of ethics principles in the Declaration of Helsinki should be sought from Ethics Review Boards of the relevant university/ies in the country.

It is important to declare publicly what data are being collected and why. The stated purposes should be broad enough to include:

- ~~long-term follow-up looking for or investigating signals of delayed reactions;~~
- use of the data to enable follow-up investigations such as cohort studies and case–control studies nested in cohorts to be undertaken to identify risk factors. It is not always possible to predict what additional studies might be needed for the investigation of safety issues that are identified during monitoring, and so approval should be sought for storage of the data to enable further investigations if necessary;
- follow-up studies required to validate signals;
- comparative studies with new vaccines or regimens.

Security and confidentiality arrangements should be publicized and should conform to any national legislative requirements.

3.7.3. Training of staff

Staff members responsible for pharmacovigilance need to be trained in the strict maintenance of security and confidentiality.

After appropriate instruction they should be required to sign a document ~~saying~~ stating ~~that~~that they understand the privacy issues and agree to maintain security and confidentiality.

3.7.4. Security issues

Because it is essential to record personal identifiers, the security, privacy and confidentiality of personal data need to be strenuously maintained. ~~Pharmacovigilance will not work properly if personal identifiers are not available.~~ With both passive safety surveillance (spontaneous reporting) and active SS programs, the ability to follow up specific patients on important outcomes is essential. With active SS, which can measure ~~risk (~~incidence~~)~~ and estimate risk for a number of factors, it is essential that duplicate entries are avoided so that the accuracy of these findings is not compromised by an inflated denominator, and this can only be done if patients can be correctly identified. This necessity for recording patient identifiers therefore imposes strict conditions on maintaining data security. These are outlined below:

- Data that might identify patients should be stored on computers that have no Internet link. This prevents access by hackers. This precaution will be impractical and unnecessary for those using VigiFlow or CemFlow.

Comment [srb]: Is this entire paragraph really appropriate for section on ethical issues?

Comment [MD]: Maybe this can be moved to the communication section of the manual as pre introduction communication

Comment [srb]: Shouldn't we just state the appropriate required approval: it is often delegated, and the high authority will be determined by local policy.

Comment [MD]: Ministry

Comment [srb]: Would it really be the Minister of Health. Or Minestry of Health.

Comment [MD]: Delete relevant universities

Comment [srb]: What if the universities have nothing to do with the study? Shouldn't it be the ERB of whatever entities are responsible for the study.

Comment [srb]: Who is this? We need to define what we mean by staff, I think.

Comment [MD]: Staff of NRAs and their expert committees already have signed confidentiality and code of conduct documents on employment

Comment [srb]: Many observational studies will not record or even collect this data.

Comment [srb]: Personal identifiers now are not included in most pharmacovigilance (CIOMS/AERS).

At first line, this data may be captured, but we need to be clearer at what level this is true/how it can be handled.

Comment [MD]: Most of our NRAs who have this data are part of the WHO Programme for IDM

• Access to a computer that has identifiable data on persons should be controlled by password.
• Password access should be given only to those people involved in the particular pharmacovigilance activity.
• Access to the premises should be security controlled.

3.7.5. Use of data

• The data collected should be used only for the purposes declared.
• Personal identifiable data should not be given to any other parties including pharmaceutical companies, government or ministry officials, agencies and research groups. This includes personal details of patients or reporters. Only anonymized data may be shared.

Confidentiality

• No published data, including reports, should contain any information that could identify patients.
• Staff should not take any identifiable data home or to other places outside the pharmacovigilance center or monitoring center.
• Staff should not discuss information outside the monitoring center that could lead to the identification of any patient.

3.7.6. Informed consent

If pharmacovigilance activities, spontaneous reporting and active SS, are authorized or required by law, informed consent from individual patients may not be required for the collection of not publically available data required for safety monitoring. However, all the privacy conditions outlined above should be strictly observed.

To clarify, the above would apply only to studies and investigations of e g health related registers being part of an active SS performed within the scope of regulatory authorities. Studies being part of an active SS but performed by other stakeholders using data from e.g. health-related registries that involves the use of data that have been compiled without the informed consent of individuals should be submitted to an ethical committee.

Obtaining individual informed consent if at all possible can be time-consuming in order to try to explain the concepts of pharmacovigilance (which will often be culturally strange) to each patient, it will increase complexity and add to the cost, and could potentially compromise the validity of the results if many patients refuse to be enrolled. Studies included in an active SS programme performed within the scope of a regulatory/public health is a process of observation of normal practice and data collection in the interests of public health and should not interfere with the treatment in any way. In this perspective it is not equal to a clinical trial or research study.
An alternative to obtaining informed consent from individual patients is to provide information publicly and to give patients leaflets which they can study, ([ii]) or have explained to them away from the pressure of the clinics, and which provide them with contact details for the health facility and pharmacovigilance center so that they can

Comment [srb]: What premises are we talking about? Data collection points? Central database? How will we handle data being transferred from the field to central? Will this need secutiry?

Comment [srb]: This sentence is just too complex. Is the key point that often IC is not necessary, and when it is, it need to be done?

Comment [srb]: Where does this come from? This point does not make sense to me and I do not think it is true, or not true in all countires: we need to clarify this

Comment [srb]: Do we mean a formal ERB?

Comment [srb]: Perhaps I am missing something, but this whole discussion of IC is not making sense to me, esp. in the context of the vast majority of active safety surveillance. I am not fmailiar with conduct in LMICs, but we need to check with local expertise to see if this all makes sense.

object to having their data stored if this is their decision. Their data can then not be entered or if they have already been entered, they will be deleted. This is called the "opt out principle" which operates in a number of countries and, if needed, is much more practical than individual informed consent.
This approach has been endorsed by competent authorities internationally. ([iii]) and be in line with local legislation.

Comment [srb]: Once chapter has been completed, we may need to update this section to be consistent with entire chapter, and to bring home key messages.

3.8. Conclusions

When stakeholders in a RLC have decided to launch an Active Safety Surveillance study for a particular vaccine and setting, a design needs to be determined that can achieve the objectives and build on existing resources. A number of steps need to be taken, e.g. involving meticulous planning, consultation with expertise and securing adequate infrastructure and funding. This chapter describes methodological considerations and approaches, illustrated through examples of vaccine safety studies and refers to other, relevant, manuals with special focus on RLCs.

Links (to be completed)

References (to be completed)

[i] For the section on Ethics 3.5, the text may need to be edited for vaccines since it is taken from: A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: enhancing the safety of the TB patient, **World Health Organization, 2012.** ISBN 978 92 4 150349 5, pp 71-73.
[ii] In the U.S. the Vaccine Information Statement (VIS) is legally mandated and necessary to provide to individuals for any licensed vaccine. REFERENCE needed.
[iii] Council for International Organizations of Medical Sciences. *International ethical guidelines for epidemiological studies.* Geneva, CIOMS, 2009: pp. 37, 42–43.

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 18 Nov 2015 14:26:28 +0000
To: Bailey, Steven R.;Winiecki, Scott (FDA/CDER);Corinne.Jouquelet-Royer@sanofipasteur.com;holmk@cioms.ch;novilia@biofarma.co.id;(b)(6) Irina.Caplanusi@ema.europa.eu;(b)(6) dongduo@cdr.gov.cn;maurec@who.int;Rmenezes@bio.fiocruz.br;(b)(6) ;Paulo.santos@bio.fiocruz.br;Harry.A.Seifert@gsk.com;sjolinforsbergg@cioms.ch;(b)(6) Zuber, Patrick (CDC who.int)
Cc: ashley.wivel@merck.com;Maroko, Robert;dongduo@cdr-adr.org.cn;董铎
Subject: RE: Some Meeting Follow Up

Mid-December should work for me. Thanks.
Frank DeStefano, MD, MPH

From: Bailey, Steven R. [mailto:Steven.R.Bailey@pfizer.com]
Sent: Wednesday, November 18, 2015 9:10 AM
To: Winiecki, Scott (FDA/CBER) ; Corinne.Jouquelet-Royer@sanofipasteur.com; Destefano, Frank (CDC/OID/NCEZID) ; holmk@cioms.ch; novilia@biofarma.co.id;(b)(6) Irina.Caplanusi@ema.europa.eu; (b)(6) dongduo@cdr.gov.cn; maurec@who.int; Rmenezes@bio.fiocruz.br;(b)(6) Paulo.santos@bio.fiocruz.br; Harry.A.Seifert@gsk.com; sjolinforsbergg@cioms.ch; (b)(6) Zuber, Patrick (CDC who.int)
Cc: ashley.wivel@merck.com; Maroko, Robert ; dongduo@cdr-adr.org.cn; 董铎
Subject: RE: Some Meeting Follow Up

Thanks Scott. December 1st should be fine; in fact, depending on the answers from everyone else, I think if we have updated versions of everything by mid-December we should be good. But the sooner the better, of course, but let's not strain our work life balance.
I'll wait until we hear from everyone and then send out some new timelines.
Regards,
Steven.

Steven R. Bailey, MD MPH MBA
Vice President, Worldwide Safety and Regulatory
SSRM RU/Vaccines Group Head
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Steven.R.Bailey@Pfizer.com
484 865 3670

From: Winiecki, Scott [mailto:Scott.Winiecki@fda.hhs.gov]
Sent: Wednesday, November 18, 2015 7:59 AM
To: Bailey, Steven R.; Corinne.Jouquelet-Royer@sanofipasteur.com; Destefano, Frank (CDC); holmk@cioms.ch; novilia@biofarma.co.id;(b)(6) Irina.Caplanusi@ema.europa.eu; (b)(6) dongduo@cdr.gov.cn; maurec@who.int; Rmenezes@bio.fiocruz.br; (b)(6) Paulo.santos@bio.fiocruz.br; Harry.A.Seifert@gsk.com; sjolinforsbergg@cioms.ch; (b)(6) zuberp@who.int
Cc: ashley.wivel@merck.com; Maroko, Robert; dongduo@cdr-adr.org.cn; 董铎
Subject: RE: Some Meeting Follow Up

Steven,
Thanks for keeping all of us on track.
Frank and Scott: what is the status for Chapter 2 and 3?
I still have some comments to review and updates to make for Chapter 2.
I might be able to complete by Nov 23 but can certainly complete this work by December 1.
Thanks,
Scott

From: Bailey, Steven R. [mailto:Steven.R.Bailey@pfizer.com]
Sent: Tuesday, November 17, 2015 5:43 PM
To: Corinne.Jouquelet-Royer@sanofipasteur.com; Destefano, Frank (CDC); Winiecki, Scott; holmk@cioms.ch; novilia@biofarma.co.id; (b)(6) Irina.Caplanusi@ema.europa.eu; (b)(6); dongduo@cdr.gov.cn; maurec@who.int; Rmenezes@bio.fiocruz.br; (b)(6) Paulo.santos@bio.fiocruz.br; Harry.A.Seifert@gsk.com; sjolinforsbergg@cioms.ch; (b)(6) zuberp@who.int
Cc: ashley.wivel@merck.com; Maroko, Robert; dongduo@cdr-adr.org.cn; Bailey, Steven R.; 董铎
Subject: RE: Some Meeting Follow Up

All:

Just taking a status check to see where everything stands, and everyone's preferred next steps. I think we will need to adjust our business plan a bit (which is fine, we will still be ready for Ghana)

Here is current status of each item:

1) Thorough review of Latest Draft of All Chapters: Largely Complete: comments received from Corinne, Duo Dong, Steven, Frank, Scott, Mimi, and, perhaps someone I am missing.
2) Chapter 3, Table 3.3, Section 3.4: Novi has provided text to Irina. Awaiting further edits from Irina
3) Chapter 3, 3.5/3.6: Done. Scott provided to the entire group
4) Introduction: Intro/Algorithm/RACI: Complete and Circulated to Team. Comments Received
5) Introduction: Structured Approach: Ashley has comleted a draft. Rob Maroko to review (and then I will review)
6) Ethical Section: Comments Received along with the comments (item 1 above).

Thanks to everyone who has provided authorship/comments to date. We are making good progress. If my summary above is up to date, the following are our next steps:

1) **Steven/Scott/Frank**: Update Chapters 1/2/3 with comments from others. I have not had time to complete this yet. **Frank** and **Scott**: what is the status for Chapter 2 and 3? We had originally said these would be complete by Nov 23rd. I will need at least until December 1st. Frank/Scott: is this workable for you? If not, simply propose a date and I will re-work our timelines appropriately (and Frank: see item 3 below)
2) **Irina**: Awaiting final text for section 3.4 and table 3.3. When do you think that will be ready? Once ready, we can circulate to the larger group.
3) **Frank**: once we have text from Irina (item 2), will you be able to incorporate this and the text from Scott for 3.6 into a final version of Chapter 3?
4) **Steven/Ashley/Rob**: **Rob**: when will you have reviewed the draft that Ashley provided? When comlete, I will review and incorporate into a comlete introduction. I will circulate to all at this point. I will aim for December 1st for this as well, or whatever data we land on for completion of all chapters.
5) **Someone (Volunteer Please)**: The ethical section needs to be re-worked with all the comments received. While this currently sits in Chapter 3, but not sure it belongs there. It was not originally authored by Frank, and he has so much on his plate, that it would be helpful if someone else would take on the rework of this section (and leading a discussion of where it best belongs).

Once I hear from everyone (and especially those **bolded** with todo items, including myself), I will re-work our business plan and dates for next steps. Ideally we will get everything roughly into the same timelines (Intro/Chapters 1-3/Additional Chapter 3 material/Ethical Section) probably by December 15th (earlier if everyone agrees, but hopefully before Christmas). If we can do this, then we will be able to relax over the holiday season, and we can circulate everything in the new year for one last look to our group and get this to everyone at least a month ahead of the meeting in Ghana.

Regards, and thanks,

Steven.

All:

We are just 1 week away from our first set of deadlines for TG2 (November 1st if a week from this Sunday), and I want to make sure we were moving along, and either encourage everyone to provide updates, or, if necessary, rework our deliverable date.

From our business plan, here is what is due by November 1st:

- Thorough review of Chapters 1, 2 and 3, with track changes/comments to Chapter owners **(ALL)**
- Chapter 3: Table 3.3, Section 3.4: Update/Write: **(Novi/Irina)**
- Chapter 3: Sections 3.5 and 3.6: Update/Write: **(Scott)**
- Introduction: Update/Write section 1 (intro), section 2 (algorithm), section 3 (RACI): **(Steven)**
- Introduction: Write Section 4 (structure approach to reviewing data) **(Ashley/Rob (draft 1)**
- Ethical Section (end of chapter 3 now): Carefull Review/update: **(ALL)**

Per previous e-mail, I have already completed bullet 4 and circulated. I am now providing my thorough review of the first 3 chapters, with special attention to the ethical section (see attached).

Hoping this encourages everyone to move forward with the above. However, I do understand how busy schedules are, so let's see how everyone does over the coming week, and we can consider moving our deadlines as needed. Also, based on where we are, I would like to set up a telecon of the group in mid November or so to go over any open items or issues.

Regards,

Steven.

Steven R. Bailey, MD MPH MBA
Vice President, Worldwide Safety and Regulatory
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Steven.R.Bailey@Pfizer.com
484 865 3670

From: Bailey, Steven R.
Sent: Monday, October 12, 2015 12:58 PM
To: Holm Karin; Bachtiar, Novilia (novilia@biofarma.co.id); Bergman, Ulf (b)(6); Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu); Darko, Mimi (b)(6); DeStefano, Frank (fxd1@cdc.gov); Duo, Dong (dongduo@cdr.gov.cn); Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com); Maure, Christine (maurec@who.int); Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br); Nishioka, Sergio (b)(6) Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br); Seifert, Harry (Harry.A.Seifert@gsk.com); Sjolin_Forsberg Gunilla; Tebaa, Amina (b)(6); Winiecki, Scott (alt) (Scott.Winiecki@fda.hhs.gov); Zuber, Patrick (zuberp@who.int)
Cc: Ashley Wivel (ashley.wivel@merck.com); Maroko, Robert; 'dongduo@cdr-adr.org.cn'
Subject: RE: Some Meeting Follow Up
Importance: High

All:

Hope everyone is well. I wanted to make sure we were still keeping up the momentum for TG2. So I have gone ahead an completed one of my deliverables for the project. Please find attached a DRAFT of an update to the Introduction. It include 3 of the 4 pieces: the opening, the RACI, and the Algorithm. The last piece of the intro is the "Structured Approach to Gap Identification, Evaluation, and Determination". Ashley and Rob have agree to take a stab at adding this piece (first draft), and my hope is that by providing this it will be helpful in moving this forward. Ashely/Rob: please reach out if needed as we move this forward.

Please keep in mind the remaining activities per our business plan:

For November 1st:

- All to review Chapters 1, 2, and 3 very carefully. Please send your comments to all, and the owner of each section will consolidate those comments and provide the next draft. Please note the revised drafts are due November 23rd, so it is very important that you provide your comments by NOVEMBER 1st, as discussed. [as a reminder, Chapter Owners are Chapter 1: Steven, Chapter 2: Scott, Chapter 3: Frank]
- Novi/Irina/Scott: Chapter 3 has some sections that still need to be completed, and you all kindly "volunteered" to work on these sections (Table 3.3/section 3.4 (Irina/Novi) and section 3.5/3.6 (Scott)
- All: Review the "ethical section" of chapter 3, with an eye towards how it fits with the rest of the chapter, and any required changes.

I know we committed to tight timelines, but it would be great if we can deliver. If we can work on the 3 bullets above by the 1st of November, we really will be in good shape to have all of our deliverable finalized (per our group) before the year-end holidays, and allow review by the larger group before we all meet in Ghana.

If anyone feels a telecon would be helpful at any point in the process (this entire group, or a subset), please let me know and we will work to arrange.

Kind regards,

Steven.

Steven R. Bailey, MD MPH MBA
Vice President, Worldwide Safety and Regulatory
SSRM RU/Vaccines Group Head
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Steven.R.Bailey@Pfizer.com
484 865 3670

From: Bailey, Steven R.
Sent: Wednesday, September 30, 2015 4:48 PM
To: Holm Karin; Bachtiar, Novilia (novilia@biofarma.co.id); Bergman, Ulf (b)(6); Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu); Darko, Mimi (b)(6); DeStefano, Frank (fxd1@cdc.gov); Duo, Dong (dongduo@cdr.gov.cn); Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com); Maure, Christine (maurec@who.int); Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br); Nishioka, Sergio (b)(6); Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br); Seifert, Harry (Harry.A.Seifert@gsk.com); Sjolin_Forsberg Gunilla; Tebaa, Amina (b)(6); Winiecki, Scott (alt) (Scott.Winiecki@fda.hhs.gov); Zuber, Patrick (zuberp@who.int)
Cc: Ashley Wivel (ashley.wivel@merck.com); Maroko, Robert; Bailey, Steven R.
Subject: Some Meeting Follow Up

All (Primarily TG 2 members and key stakeholders)

Please find attached some promised documents (sorry for the delay).

Attached are:

1) The Updated Business Plan for TG2. Please pay special attention to your assignments and due dates in the business plan I will send reminders in about 2 weeks to try to keep us on track. Please feel free to offer updates or suggestions if I missed anything
2) Attached is our preliminary RACI. Will require more work as we move forward, but a good start.
3) The latest draft of the Introduction that we discussed at the meeting. Ashley, Rob, Scott and others who offered to work on this (including myself), please compare against the business plan for what we agreed to as next steps. If anyone feels a small telecon to further discuss the intro is needed, do not hesitate to request, and I can arrange.

It was a pleasure seeing most of you in Collegeville, and for those who could not attend, look forward to seeing you in Ghana. I will trust everyone will move forward with our work as outlined in the business plan, and will check in in a few weeks. If any questions, please reach out.

Regards,

Steven

Steven R. Bailey, MD MPH MBA
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484 865 3670

From: Holm Karin [mailto:holmk@cioms.ch]
Sent: Thursday, September 24, 2015 11:03 AM
To: Abdoellah, Siti (alt) (asfyabd@hotmail.com); Arlett, Peter (Peter.Arlett@ema.europa.eu); Ayoub, Ayman; Bachtiar, Novilia (novilia@biofarma.co.id); Bahri, Priya (Priya.Bahri@ema.europa.eu); Bailey, Steven R.; Benkirane, Raja ((b)(6)); Bergman, Ulf ((b)(6)); Blum, Michael (BlumM@MedImmune.com); Bonhoeffer, Jan (alt) (j.bonhoeffer@brightoncollaboration.org); Caplanusi, Irina (alt) (Irina.Caplanusi@ema.europa.eu); Ceuppens, Marc (mceuppe1@its.jnj.com); Chandler, Rebecca (alt) (rebecca.chandler@who-umc.org); Darko, Mimi ((b)(6)); Dawei, Liu ((b)(6)); DeStefano, Frank (fxd1@cdc.gov); Dodoo, Alex (alex.dodoo@umcafrica.org); Duo, Dong (dongduo@cdr.gov.cn); Gregory, William (NYC); Gunale, Bhagwat (alt) (bhagwat.gunale@seruminstitute.com); HAMID, T. Bahdar Johan ((b)(6)); Heiles, Bernhard <bernhard.heiles@merck.com>; Heininger, Ulrich (ulrich.heininger@ukbb.ch); Holm Karin; Jouquelet-Royer, Corinne (Corinne.Jouquelet-Royer@sanofipasteur.com); Keller-Stanislawski (Brigitte.Keller-Stanislawski@pei.de); Kilpi, Terhi (terhi.kilpi@thl.fi); Kulkarni, Prasad (drpsk@seruminstitute.com); Kurz, Xavier (Xavier.Kurz@ema.europa.eu); Lindquist, Marie (Marie.Lindquist@who-umc.org); Martin, David (David.Martin@fda.hhs.gov); Maure, Christine (maurec@who.int); Menezes, Reinaldo de (Rmenezes@bio.fiocruz.br); Mentzer, Dirk (Dirk.Mentzer@pei.de); Nishioka, Sergio ((b)(6)); Nohynek Anna (Hanna.Nohynek@thl.fi); Oberle, Doris (alt2) (Doris.Oberle@pei.de); Patel, Mayur (alt) (PatelMayur@MedImmune.com); Ramkishan, Ajmeer ((b)(6)); Santos, Paulo (alt) (Paulo.santos@bio.fiocruz.br); Seifert, Harry (Harry.A.Seifert@gsk.com); Shimabukuro, Tom (alt) (ayv6@cdc.gov9); Sjolin_Forsberg Gunilla; Srivastava, Swati (alt) ((b)(6)); Tebaa, Amina ((b)(6)); Winiecki, Scott (alt) (Scott.Winiecki@fda.hhs.gov); Youssef, Mona ((b)(6)); Zuber, Patrick (zuberp@who.int)
Cc: Le_Roux Susanne; Habersaat, Katrine (DCE-VPI); Ashley Wivel (ashley.wivel@merck.com); Maroko, Robert
Subject: Philly meeting group photo

Dear All,

Sending you the group photo from the Philadelphia meeting, which I think reflects on our faces the positive feelings we had about what we achieved at this meeting.

I will also shortly be sending you information about how to access the SharePoint website in an easier manner to get the latest drafts and background documents (I have not yet posted all the updates but shall in coming few weeks).

You will also receive within the coming few weeks, the Philly meeting report so that everyone will feel up-to-date and ready to contribute to this next phase of further writing and editing. Even if you have had little time to involve yourself until now, the Editorial Team can really use your help, expertise, and support to produce a useful guide to Vaccine Safety for new and new-to-you (as we were calling them for short) vaccines.

Please be already planning on attending the next 8th meeting to be hosted in Accra, Ghana by the Ghana Food and Drugs Authority, in March or April 2016, as announced by Mimi Darko on the second day of our meeting. We will be sending out a doodle to help determine the best date.

Best regards,

Karin

Karin R. Holm
Technical Collaboration Coordinator, Working Group on Vaccine Safety
Publications Coordinator, CIOMS X Meta-Analysis
Council for International Organizations of Medical Sciences (CIOMS)
c/o WCC, P.O. Box 2100 CH-1211 Geneva 2, Switzerland
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Email: holmk@cioms.ch
(CIOMS is an Associate Partner of UNESCO and in Official Relations with WHO.)

From: Whary, Maryellen
Sent: 14 May 2013 14:03:58 -0400
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: RE: Teleconf. w/Frank DeStefano from the CDC re presentation at June ACIP on rotavirus vaccines and intussusception

Please forward call details. Thank you.
Maryellen Whary (works Monday, Tuesday, Wednesday)
Robyn Mowrer (works Thursday, Friday)
WP97-A345 - phone: 215-652-9445/fax: 215-993-1848
maryellen_whary@merck.com/robyn_mowrer@merck.com
-----Original Appointment-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Tuesday, May 14, 2013 2:02 PM
To: Whary, Maryellen
Subject: Accepted: Teleconf. w/Frank DeStefano from the CDC re presentation at June ACIP on rotavirus vaccines and intussusception
When: Friday, May 31, 2013 10:30 AM-11:30 AM (UTC-05:00) Eastern Time (US & Canada).
Where: Frank to provide teleconf. info.--will forward once I receive

From: Cristina Masseria
Sent: 20 Nov 2013 18:54:40 +0000
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Leonard Silverstein;Shanthy Krishnarajah
Subject: Safety of Boostrix during pregnancy

Dear Dr De Stefano,
GSK is assessing the feasibility of conducting a ph4 safety study of Boostrix during pregnancy in the US. Would you be able to meet with us in order to discuss several technical issues, as we would greatly appreciate your advice.
Please let us know your availability.
Thank you very much.
Best regards,
Cristina
Cristina Masseria, PhD
GlaxoSmithKline
US Health Outcomes and Medical Policy - Vaccines
Phone: +1.215.751.4960

From: Holm Karin
Sent: 4 Sep 2014 14:07:48 +0000
To: Jouquelet-Royer, Corinne;Sillan, Françoise;Darko, Mimi ([redacted]);Seifert, Harry;Bergman Ulf;Maure, Christine;Zuber, Patrick (CDC who.int);Bailey (Steven.R.Bailey@pfizer.com);Nishioka, Sergio;Blum, Michael (BlumM@MedImmune.com);Tebaa, Amina;Bachtiar, Novilia;terhi.kilpi@thl.fi;Winiecki, Scott (FDA/CDER);sten.olsson@who-umc.org;Duo, Dong;Destefano, Frank (CDC/OID/NCEZID);Caplanusi, Irina (Irina.Caplanusi@ema.europa.eu);Xavier.Kurz@ema.europa.eu;Dawei, Liu [redacted]david.martin@ema.europa.eu
Cc: Sjolin_Forsberg Gunilla
Subject: The two TCs for TG2: Overall Fri, 3pm, Ch.5 Only Tues, 1pm
Attachments: image002.png, CIOMS TG2 business plan TG2_18july_fs-cgm.docx, TG2 business plan 19 Aug.pptx

Dear CIOMS Topic Group 2 members:

Please note the upcoming TC's: (1) tomorrow Friday 5 September 3pm (Eurotime) with the Overall issues (chapters 1-5)

And (2) Tuesday 9 September 1pm (Eurotime) with only Chapter 5.

Here is who is expected to be on the calls according to Doodle responses. I think Mimi Darko will also try to patch in, if connections are possible.

Attached please find latest documents for discussion.

Thank you to Sanofi for arranging the TCs!

Fri. 5 Sept 15h (3pm) CIOMS TC TG2 on Active Safety Surveillance Overall Ch.1-5

Lyon, France will set up (thank you Sanofipasteur)

Françoise Sillan, Corinne Jouquelet-Royer, and Harry Seifert invite your participation in a TC concerning the whole Active Safety Surveillance (AcSS) manual, where we stand, and what needs to be completed for Rabat. We request active participation from all. When you write your name in the doodle, please add your country so that Sanofi can send you the correct toll-free or local number to call and participation. I will shortly send out the latest draft of the manual and business plan for your review.

12 participants responded Fri 5 Sept, 15:00

Karin Holm (Switzerland) ✓
Patrick Zuber (Brazil on 5, Switz on 9) ✓

Sergio Nishioka (Brazil)	✓
Christine Maure (Switzerland)	✓
Steven Bailey	✓
Michael Blum (US)	✓
tebaa amina	✓
Novilia Sjafri Bachtiar	✓
Terhi Kilpi	✓
Scott Winiecki (USA)	✓
Sten Olsson, Sweden	X regrets
Dong Duo (China)	✓

Tues 9 Sept., 13h (1pm) CIOMS TG2 Active Safety Surveillance Chapter 5

TC arranged by Sanofi in Lyon, France

Corinne and Harry are calling this CIOMS TG2 TC for the subsections of Chapter 5. Please indicate whether you can join at these times. The call is scheduled for 1.5 hours in order to cover all topics. Thank you for your time and thank you to Sanofi for arranging the TC.

8 participants responded 13:00

Karin Holm	✓
corinne jouquelet royer	✓
Christine maure	✓
Scott Winiecki	✓
Frank DeStefano	✓
Irina Caplanusi	X regrets
Françoise Sillan	X regrets
Dong Duo	✓

Karin R. Holm
Technical Coordinator, Working Group on Vaccine Safety
Publications Consultant, Working Group IX Risk Minimization
Council for International Organizations of Medical Sciences (CIOMS)
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Email: holmk@cioms.ch
(CIOMS is an Associate Partner of UNESCO and in Official Relations with WHO.)

✓

CIOMS manual on establishing active safety surveillance systems for newly introduced vaccines

CIOMS VACCINE SAFETY WORKING GROUP

TOPIC GROUP 2

1. Executive summary

The objective is to provide a manual, which can be a reference for all vaccine stakeholders who are involved in the introduction of a new vaccine in a LMIC.

This Business plan describes the different steps for the preparation of this manual by the Topic group 2 from the CIOMS working group on vaccine safety.

The manual preparation will start in June 2014 and should be released by June 2016.

The different sections will be prepared outside CIOMS working group meetings, only the key sections will be discussed during meetings like establishing sentinel sites, governance, and above country-level (global) coordination.

2. Rationale and opportunities for improvement

Many on-going initiatives for improvement of post marketing surveillance have been initiated within GVSI. One of the main gaps identified is the lack of a guidance document to conduct active safety surveillance when a new vaccine is being introduced in a LMIC.

Different scenarios are possible:

- The new vaccine is registered and introduced in a LMIC by a vaccine manufacturer for public and private settings
- The new vaccine is supplied by a third party (GAVI, UNICEF..) in a LMIC and is not registered in the country
- Vaccine is being supplied to EPI program by direct procurement (prequalified vaccines) without prior registration by NRA.

3. Strategy

This manual should provide practical guidelines for implementing PV systems and recommendations for roles and responsibilities for PV activities when a new vaccine is introduced in LMIC. The different sections should be illustrated with examples from available publications or country/study experiences and references made to existing guidelines where the

stakeholders can find information on prevailing initiatives for improvement of post-marketing safety surveillance.

The overall governance and the coordination of active surveillance programs should also be addressed. In addition to examples, it is critical to provide clear criteria to set up appropriate sustainable systems and conduct active surveillance (example of preparation of malaria vaccine introduction)

The manual sections will be distributed among TG2 members for write up. For each section, leaders and contributors will be identified. The role of the contributors and the leaders is described in section 5.

The preparation of the manual will progress between each CIOMS meeting, usually three per year. (Jan-Feb, May-June, Sept-Oct). During the meetings, the TG2 contributors will review the progress of the manual, only selected sections will be discussed.

4. Key steps and operational plan

The manual will be prepared by the contributors for topic 2, in a step wise approach, starting with the first 5 sections and then the section 6 to 10. While examples will be given to illustrate the different sections of the manual, section 10 can be used to detail most representative publications.

Between September 2013 and June 2014

- Review the purpose of the manual
- Preparation of the Table of Contents

Between June and September 2014:

- Circulate the business plan and have a final version- by end June 2014.
- Identify leaders and contributors for section 1 to 5-by end June 2014.
- Draft sections 1 to 5 by September 2014.
- Everyone in the TG2 should identify relevant publications and examples and bring/send before Rabat

5th CIOMS vaccine safety working group September 2014 in Rabat, Morocco :

- Review the section drafted; work on section 5 (establishing active surveillance).

Between September 2014 and February 2015

- Finalize section 3 to 5 (sections 1&2 would need to be completed as the manual is being developed) based on discussion of 5th meeting.
- Identify leaders and contributors for section 6 to 9.

- First draft document December 2014 sections 1 to 5 for comments to the CIOMS working group TG2

6th CIOMS vaccine safety working group February 2015

- Review of key comments from first review.
- Work on key sections on role and responsibilities of the stakeholders (7, work initiated during the 4th meeting should be fine-tuned with the updated sections), including funding (section 9), and on communication mechanism (8).
- Choose examples for section 10 (examples of active surveillance studies from literature).

Between February 2015, June 2015 and September 2015

- Draft sections 6 to 10
- Circulate draft document within TG2

8th CIOMS vaccine safety working group September 2015

- Review of key comments

Final draft end of 2015 to be circulated to whole CIOMS working group + experts (through the WHO Global Advisory Committee on Vaccine Safety GACVS ?) and representatives of manual users (regulators and EPI managers from LMIC, vaccine supplied agencies, ..)

9th CIOMS vaccine safety working group February or June 2016
Final review of the manual
Document release : mid 2016

5. Management Key contributors

Each topic group 2 members will commit to the development and/or coordination of the various sections of the manual.

The section **leaders** will be responsible for coordinating the development of the designated section of the manual with the identified contributors, gathering comments and meeting deadlines.

Contributors will be responsible for providing inputs to the development of the section they committed to.

Editorial board will be responsible for coordinating and reviewing the different sections together to ensure consistency and harmonization of the whole manual. (will the Editorial Board be established at any point or does it exist already)

Phase 1: development of section 1 to 5 (volunteers per TC on 19 June 2014)

Section	**Leader**	**Contributors**
1-Glossary	Novilia Bachtiar	Karin Holm
2-Abbreviations	Novilia Bachtiar	Karin Holm
3-Purpose	Françoise Sillan, Christine Maure	Mimi Darko
4-Post Marketing safety surveillance	Christine Maure	Xavier Kurz, Irina Caplanusi, Terhi Kilpi
5-Establishing active safety surveillance	Corinne Jouquelet-Royer, Harry Seifert	Dawei Liu, Novilia Bachtiar, Xavier Kurz, Irina Caplanusi, David Martin/Scott Winiecki, Frank Destefano, Mimi Darko, Patrick Zuber

Phase 2: development of section 6 to 9 (to be completed prior the February 2015 meeting)

Section	Leader	Contributors
6-Scientifc approach		
7-Role and responsibilities		
8-Communication mechanism		
9-Funding		

6. Working Methods

All topic group member must be registered with SharePoint and have up-to-date info on the home page for contact info.

Teleconferences will be organized by section leaders at least once between each face to face meeting.

7. Topic group 2 members :

TG2 Leaders

Mimi Darko (alt)	Ghana FDA
Françoise Sillan	Sanofi-Pasteur

TG2 members :

Novilia Sjafri Bachtiar	Biofarma Indonesia

Frank DeStefano	CDC Atlanta
Amina Tebaa	Centre de PhV Morocco
Raja Benkirane (alt)	Centre de PhV Morocco
Dawei Liu	China CDC
Dong Duo	China Regulatory Authority
Ulf Bergman	CIOMS
Irina Caplanusi (alt)	EMA
Peter Arlett (alt)	EMA
Xavier Kurz	EMA
David Martin	
Scott Winiecki (alt)	FDA (but DM seconded to EMA jun-nov2014)
Alex Dodoo	Ghana WHO coll/ Food and Drugs Board
Harry Seifert	GSK
Mayur Patel (alt)	MedImmune/AstraZeneca
Michael Blum	MedImmune/AstraZeneca
Doris Oberle (Alt2)	Paul Erlich Institute (PEI), Germany
Dirk Mentzer (alt)	PEI
Keller-Stanislawski, Brigitte	PEI
Bill Gregory	Pfizer
Steven Bailey (alt)	Pfizer
Hanna Nohynek (alt)	THL,FI
Terhi Kilpi	THL,Finland
Sten Olsson (alt)	UMC WHO Collab Centre
Christine Maure (alt)	WHO
Patrick Zuber	WHO

1 Additional Potential members ?:

Adrian Dana	Merck
Patricia Mandali de Figueiredo	ANVISA - Brazil
Sidarta Figueredo Silva (alt)	ANVISA- Brazil

2 Other key contributors ? (outside CIOMS working group?)

1. Needs (support and finance)
2. Support from CIOMS: share point, meetings
3. Support from WHO: consultant

Table of Contents

1. Glossary
2. Abbreviations
3. Purpose

- To provide practical guidelines for implementing active PV systems in LMIC
- To provide recommendations for roles and responsibilities for PV activities when a new vaccine is introduced into LMIC

Discussion:

- Economic consequences of surveillance – early detection and lower costs.
- To provide some ideas to address barriers.(Immunisation Programme vrs NRA)
- Have an effective system in place in advance.
- Discussion on programmatic questions.
- Document should provide an easy steps for conducting active surveillance.
- Should be a comprehensive document for all stakeholders.
- Should be a manual not a guideline.

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4. Postmarketing safety surveillance.

4.1. Rational for post marketing surveillance – Provide links to existing sources

4.1.1. Definition - Provide links to existing definitions

4.1.2. Types of safety surveillance systems

- Passive surveillance (spontaneous reporting)
  Decision to make mainly links to resources (WHO), discussion around the efficacy of this material.
  - Purpose for passive surveillance, link to WHO Global Immunization safety surveillance manual
  - List existing initiatives
- Stimulated passive surveillance
  Discussion about different vocabulary possibilities: spontaneous targeted passive stimulated enhanced surveillance (to be continued post meeting).
  - Purpose for stimulated passive surveillance, link to WHO Global Immunization safety surveillance manual.
  - List existing initiatives
- Active surveillance

,

  - Purpose for active surveillance
  - list examples of types of active surveillance in use (strategies?)

5. Establishing active safety surveillance

5.1. Rational for active surveillance system

Including the what: what vaccines and AEFI require active surveillance and in what settings?)

5.2. Point to consider for setting an Active Surveillance System

Who should set up active surveillance (list the different stakeholders), When to set up active surveillance

Where to establish an active surveillance?
Discussion on conducting the surveillance in sentinel sites or the whole country (or multi country /regional studies): consensus to focus on good sustainable systems at a few sentinel sites.

- Needs for countries of reference for multicountry surveillance (is this what the country wants? Or what it needs to have in place as below) Minimum requirements for those countries of reference (available capacity building for reference country)

5.3. How to establish an active surveillance system?

List the requirements like:

- Establishing background rates (the process of piloting the use of Electronic Health Records has begun in some LMIC countries, and software for this system has been fully developed. May soon become relevant so could be included in TG1 document. Good background data source for epi studies and data analysis)

- Establishing sentinel sites (including how to select sentinel sites Explore the use of DSS sites that exist in countries in Africa/Asia already, trained and capacity built to collect data.). Basic requirements for sentinel sites. Discuss limitations of sentinel sites (some would not be representative for the whole population).
  Presentation of one possible program from S. Black (Prevent)

  Expand on existing systems with broader possibilities, have permanent sentinel sites covering also vaccine surveillance, disease surveillance

- Tools, databases

Use of cell phones like in Nigeria (mobile phone apps, social media approaches, to actively collect data) Vaccine PV Tool kit??

- Capture of exposure and of outcomes

- Methods for analysis

5.4. Oversight of study Governance

- Governance and Oversight, including monitoring

- Above Country Coordination
  To be developed, who should coordinate the whole safety surveillance system and how

6. Scientific approach of active safety surveillance

- Different study designs

- Analysis - Be able to pool the data, centralize results from different sources

7. Role and responsibilities of the Stakeholders

Three different scenarios for vaccine introduction in a LMIC:

A. Vaccine manufacturer introduce a new vaccine in a LMIC for public and private settings
B. The vaccine is supplied by a third party in a LMIC for vaccination campaign
C. Same as scenario 2 but the vaccine is not registered in the country

The role and responsibilities might be different from one scenario to another

- National Regulatory Agencies
- National committees for vaccines (if different from NRA)
- Regional and National Pharmacovigilance centers
- Sentinel sites
- Immunization programme
- Vaccine Manufacturers
- WHO and collaborating centers
- NGO and supply agencies (like GAVI)
- Immunization and health care providers
- Academia
- Community
- Media

Activities	Responsible	Accountable	Consulted	Informed
Background rates events of interest	NRA, MOH	Hospitals, Health care system	Expert Committees, PhV Centers MAH	Vaccine manufacture
Sentinel Sites	MOH, Medical Association, NRA, Vaccine Manufacturers	Hospitals (Public and private)	Expert Committees, PhV Centers	
Decision to conduct a study	NRA, Vaccine Manufacturers, « Coordination Committee (TBD) MOH (CDC-PH Agency)	NRA, Vaccine Manufacturers, MOH (CDC-PH Agency)	GACVS, EMA (Art 58), CDC PhV centers	Public
Design study	Vaccine Manufacturers, MAH, sponsor, NRA, Academics	MAH, sponsor*	Sentinel sites, PhV centers « Coordination Committee (TBD)	Public
Study Implementation (Conducting the study)	Sponsor*, Sentinel sites	Sponsor, Sentinel sites, NRA	WHO, PhV centers	Public/subje
High Level Coordination	WHO(GACVS)	WHO(GACVS)		Vaccine MAH MOHs, Publi

8. Communication mechanism

Not limited to communication within the country but between each country involved in this program, to avoid redundancies and allow data pulling if appropriate

9. Funding

10. Examples of active surveillance studies from the literature

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 13 Mar 2015 17:09:03 +0000
To: Harry Seifert
Cc: Shimabukuro, Tom (CDC/OID/NCEZID);Pryzby, Rachel (CDC/OID/NCEZID) (CTR)
Subject: RE: GSK social listening slides

Hi Harry,
Thanks again for sharing the slides. I am not sure if your offer to meet was intended for FDA, but a few of us at CDC would be interested in meeting with you (either in person or by phone). Let us know if that would be possible.
I hope to see you in Lyon,
Frank

From: Harry Seifert [mailto:Harry.A.Seifert@gsk.com]
Sent: Friday, March 13, 2015 7:45 AM
To: Nguyen, Michael D. (FDA/CBER); Martin, David (FDA/CBER); Destefano, Frank (CDC/OID/NCEZID)
Cc: Greg Powell
Subject: RE: GSK social listening slides

All,
We were invited to return to White Oak to present again in early summer. By then, we will have actual data for the vaccine pilot explorations. I'll keep you in the loop for that presentation, too, and our offer to meet with you stands.
As a sneak peek and reassurance: Our superficial look at the data for the GSK-trade name vaccines, on Facebook and Twitter, revealed very few public posts (over the past 2 years) and no signals.
Best regards,
Harry

Harry Seifert, MD, MSCE
Executive Director
Vaccine Clinical Safety & Pharmacovigilance
GlaxoSmithKline Biologicals
2301 Renaissance Blvd.
Mail Code RN-0220
King of Prussia, PA 19406
USA
Email: harry.a.seifert@gsk.com
Office: +1 610 917 4177
Fax: +1 610 787 7055

From: Nguyen, Michael D. [mailto:Michael.Nguyen@fda.hhs.gov]
Sent: Monday, March 02, 2015 2:50 PM
To: Harry Seifert; Martin, David; Destefano, Frank (CDC)
Cc: Greg Powell
Subject: RE: GSK social listening slides

Thank you. I was not aware that GSK was engaging in this type of work. Michael

---

From: Harry Seifert [mailto:Harry.A.Seifert@gsk.com]
Sent: Monday, March 02, 2015 12:54 PM
To: Martin, David; Nguyen, Michael D.; Destefano, Frank (CDC)
Cc: Greg Powell
Subject: GSK social listening slides

Dear David, Michael, and Frank,

Attached are the slides that GSK will present at the meeting with the FDA data mining task force on Wednesday. The vaccine slides are #15-19. Although these should not be publically disclosed, you may share them freely within your organizations.
I would be happy to discuss the content of the slides, or GSK's project, or GSK's plans with you, either by phone or in person.
Best regards,
Harry

Harry Seifert, MD, MSCE
Executive Director
Vaccine Clinical Safety & Pharmacovigilance
GlaxoSmithKline Biologicals
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Mail Code RN-0220
King of Prussia, PA 19406
USA
Email: harry.a.seifert@gsk.com
Office: +1 610 917 4177
Fax: +1 610 787 7055

From: Destefano, Frank (CDC/OID/NCEZID)
Sent: 24 Mar 2015 15:08:38 +0000
To: 'Harry Seifert'
Cc: Shimabukuro, Tom (CDC/OID/NCEZID);Pryzby, Rachel (CDC/OID/NCEZID) (CTR);'Greg Powell'
Subject: RE: GSK social listening slides

Hi Harry,
I think that we should be able to schedule a 90 minute time slot on any of the dates in May.
Thanks,
Frank

From: Harry Seifert [mailto:Harry.A.Seifert@gsk.com]
Sent: Monday, March 23, 2015 8:47 AM
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Shimabukuro, Tom (CDC/OID/NCEZID); Pryzby, Rachel (CDC/OID/NCEZID) (CTR); Greg Powell
Subject: RE: GSK social listening slides

Dear Frank,
Thanks for your interest. Because of the challenges with teleconferences or Web-Ex meetings and the GSK IT infrastructure, we would prefer to meet in person. We estimate that this would take only an hour, although it might be safer to schedule 90 minutes to allow more discussion – we'll defer to you on that.
Please let us know if any of the following dates would work for your team:
April 29
May 5, 6, 7, 12, 13, 14.
If none of these work, we could propose dates in June.
Best regards,
Harry

From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Friday, March 13, 2015 1:09 PM
To: Harry Seifert
Cc: Shimabukuro, Tom (CDC/OID/NCEZID); Pryzby, Rachel (CDC/OID/NCEZID) (CTR)
Subject: RE: GSK social listening slides

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King of Prussia, PA 19406
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Email: harry.a.seifert@gsk.com
Office: +1 610 917 4177
Fax: +1 610 787 7055

From: Kuter, Barbara J.
Sent: 28 Mar 2014 15:50:21 -0400
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Frank,

Thanks for these numbers - this is very helpful. Would it be appropriate to compare the reporting rate of fibromyalgia in VAERS (based on doses distributed) to a background rate of fibromyalgia in this age group (with the appropriate caveats)? If so, what background rate would you use, please?

And by any chance do you know the age range for the 41 cases reported?

Thanks again,

Barb

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Friday, March 28, 2014 12:57 PM
To: Kuter, Barbara J.
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

The HPV/Fibromyalgia search includes all reports in VAERS from the time HPV4 vaccine was originally licensed (6/8/06) to reports received and processed (some reports received may not have been processed/entered yet) as of 3/27/14.

From the time of HPV4 vaccine licensure on 6/8/06 to 3/27/14, VAERS has received and processed a total of 27,300 US primary reports for HPV2, HPV4 or HPVx(HPV brand unknown) when given alone or in combination with other vaccines; 1971 (7.2%) were serious reports and 25,329 (92.78%) were non serious. A serious report is one in which at least one of the following was reported: death, life threatening illness, hospitalization, prolongation of an existing hospitalization or permanent disability.

From 6/8/06 to 3/27/14, VAERS has received and processed a total of 219,447 US primary reports after ALL vaccines. Of those 10,659 (4.86%) were serious and 208,788 (95.14%) were non serious.

-----Original Message-----
From: Kuter, Barbara J. [mailto:barbara_kuter@merck.com]
Sent: Friday, March 28, 2014 12:05 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Thanks, Frank, for the rapid response. I assume this search covered the period from 2006 to date. Can you please remind me of the total number of VAERS reports received over that period?

Barb

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Friday, March 28, 2014 9:59 AM
To: Kuter, Barbara J.
Cc: Wharton, Melinda (CDC/OID/NCIRD)

Subject: RE: HPV Vaccine - Japan

Barb,
We searched VAERS for US primary reports coded as "FIBROMYALGIA" after HPV2, HPV4 or HPVx(HPV brand unknown) when given alone or in combination with other vaccines. VAERS contains 41 reports. Of those, 33 were for cases in which HPV4 was the only vaccine administered. Of the 41 reports, 25 were serious. Among the 25 serious reports, 5 were reported as a life threatening illness, 12 required hospitalization and 8 resulted in permanent disability.

I hope this helps,
Frank

-----Original Message-----
From: Kuter, Barbara J. [mailto:barbara_kuter@merck.com]
Sent: Thursday, March 27, 2014 2:40 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Frank,

Thanks for your rapid response. If you could take a quick look at this in VAERS, that would be helpful. Of course, we recognize the limitations of doing so.

Thanks again,

Barb

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Thursday, March 27, 2014 1:51 PM
To: Kuter, Barbara J.; Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Barb,
We have not been contacted about this. We also are not aware of any literature or other data on HPV vaccine and CTD's. We have not looked at fibromyalgia in VSD or VAERS. This is a complex diagnosis and does not lend itself to a quick analysis in either system, but for what it would be worth (which may be little) we could take a look at reports submitted to VAERS.
Thanks for bringing this to our attention, Frank

-----Original Message-----
From: Kuter, Barbara J. [mailto:barbara_kuter@merck.com]
Sent: Thursday, March 27, 2014 11:38 AM
To: Wharton, Melinda (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID)
Subject: HPV Vaccine - Japan

Melinda and Frank,

We just received the attached English translation of a news item from Japan describing a preliminary study of patients with connective tissue disorder (rheumatoid arthritis and fibromyalgia) and their use of HPV vaccines. The information is based on a presentation made at a health seminar by a local investigator from the Japanese College of Fibromyalgia (JCFI), Tokyo Medical University. The JCFI has asked MHLW to conduct further research in this area.

We will be looking at our own pre & postlicensure safety data to address this question, but thought it would be helpful to find out if CDC has also been contacted to provide any data.   Can you please tell me if you have looked at fibromyalgia in either VAERS or VSD or might be able to do so? We have not found any evaluation of this particular AE in the literature.

Any information you can share with us would be much appreciated.

Thanks.

Barb

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From: Kuter, Barbara J.
Sent: 28 Mar 2014 16:34:51 -0400
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Frank,

Thanks for all your work in the last 24 hours! I think the information you have provided thus far is sufficient. Let's see if a formal request comes from Japan. Then a comparison to background rates might be needed.

Have a great weekend!

Barb

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Friday, March 28, 2014 4:16 PM
To: Kuter, Barbara J.
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Barb,
The age range of the 41 cases is 12 to 27 years (median 16). A comparison of VAERS reporting rates for fibromyalgia would require a lot of caveats, but it could be done. I am not sure what the background rate is for fibromyalgia or if there is even a reliable estimate. If you would like to discuss further, I could put you in contact with the medical officer in our office that deals with HPV vaccine, but she is out of the office until next week.
Frank

-----Original Message-----
From: Kuter, Barbara J. [mailto:barbara_kuter@merck.com]
Sent: Friday, March 28, 2014 3:50 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Frank,

Thanks for these numbers - this is very helpful. Would it be appropriate to compare the reporting rate of fibromyalgia in VAERS (based on doses distributed) to a background rate of fibromyalgia in this age group (with the appropriate caveats)? If so, what background rate would you use, please?

And by any chance do you know the age range for the 41 cases reported?

Thanks again,

Barb

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Sent: Friday, March 28, 2014 12:57 PM
To: Kuter, Barbara J.
Cc: Wharton, Melinda (CDC/OID/NCIRD)

Subject: RE: HPV Vaccine - Japan

The HPV/Fibromyalgia search includes all reports in VAERS from the time HPV4 vaccine was originally licensed (6/8/06) to reports received and processed (some reports received may not have been processed/entered yet) as of 3/27/14.

From the time of HPV4 vaccine licensure on 6/8/06 to 3/27/14, VAERS has received and processed a total of 27,300 US primary reports for HPV2, HPV4 or HPVx(HPV brand unknown) when given alone or in combination with other vaccines; 1971 (7.2%) were serious reports and 25,329 (92.78%) were non serious. A serious report is one in which at least one of the following was reported: death, life threatening illness, hospitalization, prolongation of an existing hospitalization or permanent disability.

From 6/8/06 to 3/27/14, VAERS has received and processed a total of 219,447 US primary reports after ALL vaccines. Of those 10,659 (4.86%) were serious and 208,788 (95.14%) were non serious.

-----Original Message-----
From: Kuter, Barbara J. [mailto:barbara_kuter@merck.com]
Sent: Friday, March 28, 2014 12:05 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Thanks, Frank, for the rapid response. I assume this search covered the period from 2006 to date. Can you please remind me of the total number of VAERS reports received over that period?

Barb

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Friday, March 28, 2014 9:59 AM
To: Kuter, Barbara J.
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Barb,
We searched VAERS for US primary reports coded as "FIBROMYALGIA" after HPV2, HPV4 or HPVx(HPV brand unknown) when given alone or in combination with other vaccines. VAERS contains 41 reports. Of those, 33 were for cases in which HPV4 was the only vaccine administered. Of the 41 reports, 25 were serious. Among the 25 serious reports, 5 were reported as a life threatening illness, 12 required hospitalization and 8 resulted in permanent disability.

I hope this helps,
Frank

-----Original Message-----
From: Kuter, Barbara J. [mailto:barbara_kuter@merck.com]
Sent: Thursday, March 27, 2014 2:40 PM
To: Destefano, Frank (CDC/OID/NCEZID)
Cc: Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Frank,

Thanks for your rapid response. If you could take a quick look at this in VAERS, that would be helpful. Of course, we recognize the limitations of doing so.

Thanks again,

Barb

-----Original Message-----
From: Destefano, Frank (CDC/OID/NCEZID) [mailto:fxd1@cdc.gov]
Sent: Thursday, March 27, 2014 1:51 PM
To: Kuter, Barbara J.; Wharton, Melinda (CDC/OID/NCIRD)
Subject: RE: HPV Vaccine - Japan

Barb,
We have not been contacted about this. We also are not aware of any literature or other data on HPV vaccine and CTD's. We have not looked at fibromyalgia in VSD or VAERS. This is a complex diagnosis and does not lend itself to a quick analysis in either system, but for what it would be worth (which may be little) we could take a look at reports submitted to VAERS.
Thanks for bringing this to our attention, Frank

-----Original Message-----
From: Kuter, Barbara J. [mailto:barbara_kuter@merck.com]
Sent: Thursday, March 27, 2014 11:38 AM
To: Wharton, Melinda (CDC/OID/NCIRD); Destefano, Frank (CDC/OID/NCEZID)
Subject: HPV Vaccine - Japan

Melinda and Frank,

We just received the attached English translation of a news item from Japan describing a preliminary study of patients with connective tissue disorder (rheumatoid arthritis and fibromyalgia) and their use of HPV vaccines. The information is based on a presentation made at a health seminar by a local investigator from the Japanese College of Fibromyalgia (JCFI), Tokyo Medical University. The JCFI has asked MHLW to conduct further research in this area.

We will be looking at our own pre & postlicensure safety data to address this question, but thought it would be helpful to find out if CDC has also been contacted to provide any data. Can you please tell me if you have looked at fibromyalgia in either VAERS or VSD or might be able to do so? We have not found any evaluation of this particular AE in the literature.

Any information you can share with us would be much appreciated.

Thanks.

Barb

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From: Destefano, Frank (CDC/OID/NCEZID)
To: "Leonard Friedland"
Subject: RE: GSK - transaction with Novartis
Date: Tuesday, March 3, 2015 9:04:00 AM
Attachments: image001.png

Dear Len,

Thank you for sharing this exciting news. Congratulations to GSK on this acquisition. I confirm that I will continue to be the main point of contact for vaccine safety topics.

Best regards,

Frank

Frank DeStefano, MD, MPH
Director
Immunization Safety Office
Centers for Disease Control and Prevention
Atlanta, GA

From: Leonard Friedland [mailto:Leonard.R.Friedland@gsk.com]
Sent: Tuesday, March 03, 2015 8:09 AM
To: Destefano, Frank (CDC/OID/NCEZID)
Subject: GSK - transaction with Novartis

Dear Dr. DeStefano,
I want to share some important news about the future of our company and, in particular, of our global vaccines business.
As you may have heard, today GSK announced the conclusion of its three-part transaction with Novartis involving the Consumer Healthcare, Vaccines and Oncology businesses.

The acquisition of Novartis' global vaccines business (excluding influenza vaccines[1]) provides GSK with an exciting opportunity to build an even stronger, sustainable global vaccines business while remaining true to our commitments to access, innovation, quality and collaboration.
The transaction will enhance our vaccines portfolio and strengthen our presence around the world, enabling us to deliver more vaccines where they are needed. It will bring together our expertise in virology, bacterial infection and technological platforms, to drive innovation in areas of unmet medical need. And it will strengthen our manufacturing network and capacity, increasing our ability to deliver a reliable supply of high quality vaccines.
We are currently working to complete the integration as quickly and as smoothly as possible and to maintain 'business as usual' wherever we can. With that in mind, I would like to confirm that I will remain your key contact for medical vaccine topics.
Dr. DeStefano, please feel free to distribute this letter to CDC Immunization Safety Office staff.
I look forward to keeping you informed as we move forward. In the meantime, if you have any questions, please don't hesitate to let me know.
With kind regards,
Len

Leonard Friedland, MD
VP, Scientific Affairs and Public Health

Vaccines, North America
GSK
Leonard.R.Friedland@gsk.com
484 620 9540

[1] Except in China.

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[1] Except in China.