



Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

May 27, 2020

Sent Via Email

Allison Lucas
Siri & Glimstad
200 Park Avenue, 17th Floor
New York, New York 10166
foia@sirillp.com

Dear Ms. Lucas:

This letter is regarding to your Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry (CDC/ATSDR) Freedom of Information Act (FOIA) request of January 3, 2020, assigned #20-00415-FOIA, seeking:

“Each and every email communication between January 1, 2019, and the present which includes Lauri Markowitz or her email address on the “To”, “From”, “Cc” or “Bcc” line and also includes Stanley Plotkin or his email address on the “To”, “From”, “Cc” or “Bcc” line.

Each and every email communication between January 1, 2019, and the present which includes James Sejvar or his email address on the “To”, “From”, “Cc” or “Bcc” line and also includes Stanley Plotkin or his email address on the “To”, “From”, “Cc” or “Bcc” line.

Each and every email communication between January 1, 2019, and the present which includes Skip Wolfe or his email address on the “To”, “From”, “Cc” or “Bcc” line and also includes Stanley Plotkin or his email address on the “To”, “From”, “Cc” or “Bcc” line.”

As a courtesy, note that email addresses for Stanley Plotkin include but are not limited to stanley.plotkin@sanofipasteur.com; stanley.plotkin@vaxconsult.com; admin@vaxconsult.com; CID.editorialoffice@oup.com; and Stanley.plotkin@sanofi.com.

We located 529 pages of responsive records of which 193 pages are being withheld in full. After a careful review of these pages, some information was withheld from release pursuant to 5 U.S.C. §552 Exemptions 5 and 6.

Exemption 5 protects inter-agency or intra-agency memorandums or letters which would not be available by law to a party other than an agency in litigation with the agency. Exemption 5 therefore incorporates the privileges that protect materials from discovery in litigation, including the deliberative process, attorney work-product, and attorney-client privileges. Information withheld under this exemption was protected under the deliberative process privilege. The deliberative process privilege protects the decision-making process of government agencies. The deliberative process privilege protects materials that are both predecisional and deliberative. The materials that have been withheld under the deliberative process privilege of Exemption 5 are both predecisional and deliberative, and do not contain or represent formal or informal agency policies or decisions. Examples of information withheld include documents in draft form, comments and opinions.

Exemption 6 which protects information in personnel and medical files and similar files when disclosure would constitute a clearly unwarranted invasion of personal privacy. The information that has been withheld under Exemption 6 consists of personal information, such as personal email addresses and photos. We have determined that the individuals to whom this information pertains has a substantial privacy interest in withholding it.

In accordance with the Department's implementing regulations, 45 CFR Part 5, a fee of \$92.00 is assessed (see attached invoice). Please follow mailing instructions on the invoice or your payment may not be credited.

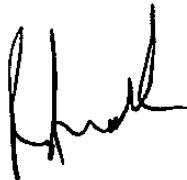
Please select the link below to obtain copies of your records (download access is open for 30 days).

<https://centersfordiseasecontrol.sharefile.com/d-s97c05297a4241888>

You may contact our FOIA Public Liaison at 770-488-6277 for any further assistance and to discuss any aspect of your request. Additionally, you may contact the Office of Government Information Services (OGIS) at the National Archives and Records Administration to inquire about the FOIA mediation services they offer. The contact information for OGIS is as follows: Office of Government Information Services, National Archives and Records Administration, 8601 Adelphi Road-OGIS, College Park, Maryland 20740-6001, e-mail at ogis@nara.gov; telephone at 202-741-5770; toll free at 1-877-684-6448; or facsimile at 202-741-5769.

If you are not satisfied with the response to this request, you may administratively appeal by writing to the Deputy Agency Chief FOIA Officer, Office of the Assistant Secretary for Public Affairs, U.S. Department of Health and Human Services, Hubert H. Humphrey Building, 200 Independence Avenue, Suite 729H, Washington, D.C. 20201. You may also transmit your appeal via email to FOIARequest@psc.hhs.gov. Please mark both your appeal letter and envelope "FOIA Appeal." Your appeal must be postmarked or electronically transmitted by August 25, 2020.

Sincerely,

A handwritten signature in black ink, appearing to read 'Roger Andoh', with a stylized, cursive script.

Roger Andoh
CDC/ATSDR FOIA Officer
Office of the Chief Operating Officer
Phone: (770) 488-6399
Fax: (404) 235-1852

Enclosures

#20-00415-FOIA

From: Admin
Sent: 26 Jul 2019 14:18:06 -0400
To: offit@email.chop.edu;Destefano, Frank
(CDC/DDID/NCEZID/DHQP);heidi.larson@lshtm.ac.uk;nkarora@incentrust.org;Zuber, Patrick (CDC who.int);fombonne@ohsu.edu;Sejvar, James (CDC/DDID/NCEZID/DHCPP);'Paul Henri Lambert';All@ssi.dk;nhalsey@jhsph.edu;nathalie.garcon@bioaster.org;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com;admin@vaxconsult.com
Subject: 2nd Draft - Summary of London Meeting
Attachments: Science of Vaccine Safety 7 17 2019.docx

Dear Speaker at the London meeting:

Here, finally, is the second draft of a summary of the meeting, with sections proposed by each of you. I have made some minor corrections for English and for quality, but these are your words. You can revise as you see fit.

I need you to provide affiliations, if you have not yet done so, to put on the title page of the attached draft. Of course, you are free to add or subtract, although the paper is already fairly large. Please reply both to admin@vaxconsult.com and to Stanley.plotkin@vaxconsult.com

Thank you, and once again I apologize for the delay.

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

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From: Heininger, Ulrich
Sent: 29 Aug 2019 04:36:51 +0000
To: Admin;nkarora@incentrust.org;fombonne@ohsu.edu;nathalie.garcon@bioaster.org;jason.m.glanz@kp.org;nhalsey@jhspk.edu;All@ssi.dk;paul.lambert@unige.ch;heidi.larson@lshtm.ac.uk;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber, Patrick (CDC who.int);Destefano, Frank (CDC/DDID/NCEZID/DHQP);kathryn.edwards@vumc.org;jim.buttery@monash.edu;(b)(6)
(b)(6) amy@vaccinateyourfamily.org;dsalmon1@jhu.edu;m.c.j.sturkenboom@umcutrecht.nl;priya.bahri@ema.europa.eu;(b)(6) bodenstabh@email.chop.edu;(b)(6)
(b)(6) hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;amyp@ecbt.org
Cc: 'Stanley Plotkin';Heininger, Ulrich
Subject: AW: Wellcome Trust - Summary of Ideas - Version 3
Attachments: London Ideas version 3_UH.docx

Dear Stanley and colleagues
thank you for the summary. I apologize for not having commented earlier, I was very busy with other projects but I followed the discussion.
Attached please find some critical - hopefully constructive - comments regarding the ideas that were brought forward.
I would be happy to be part of those projects that will be followed further on.

Best regards

Uli

(Ulrich Heininger)

Von: Admin <admin@vaxconsult.com>
Gesendet: Dienstag, 27. August 2019 21:02:39
An: nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhspk.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov; kathryn.edwards@vumc.org; jim.buttery@monash.edu; (b)(6) Heininger, Ulrich; amy@vaccinateyourfamily.org; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6) bodenstabh@email.chop.edu; (b)(6) hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; amyp@ecbt.org
Cc: 'Stanley Plotkin'
Betreff: Wellcome Trust - Summary of Ideas - Version 3

Dear Attendee at the London Vaccine Safety meeting:

I am sending again version 3 of ideas for new vaccine studies. The only comments I am aware of having received came from Frank Destefano, Nathalie Garcon and Helen Petousis-Harris. Before going ahead to a final revision I would appreciate your comments or at least your agreement with what is proposed.

The article summarizing the talks at the meeting is under review by the journal *Vaccine*.

Thanks,

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]

Sent: Monday, August 12, 2019 9:37 AM

To: 'Admin'

Subject: send to london attendees

Dear Attendee at the London Vaccine Safety meeting:

This is an updated version of the summary of ideas. Please review and comment as I plan to use this to start discussions with funders.

The article summarizing the talks at the meeting will be submitted to *Vaccine* today or tomorrow.

Stanley

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From: Robert Chen
Sent: 10 Aug 2019 11:57:29 -0400
To: Admin
Cc: nkarora@incentrust.org; Eric Fombonne; GARCON Nathalie; Jason M Glanz; nhalsey@jhsph.edu; Anders Peter Hviid; Paul Henri Lambert; Heidi Larson; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); Paul Offit; Peden, Keith (FDA/CBER); Andrew Pollard; Sejvar, James (CDC/DDID/NCEZID/DHCPP); Zuber, Patrick (CDC who.int); Destefano, Frank (CDC/DDID/NCEZID/DHQP); Stanley Plotkin; Edwards, Kathryn; jim.buttery@monash.edu; Heininger, Ulrich; Amy Pisani; Dan Salmon; Sturkenboom, M.C.J.; priya.bahri@ema.europa.eu; Steve Black; bodenstabh@email.chop.edu; (b)(6); hotez@bcm.edu; liz.miller@hpa.org.uk; Helen Petousis; Amy Pisani
Subject: Brighton Collaboration Membership
Attachments: Summary of changes from 2010 to 2019 Constitution.pdf, ConstitutionBC2019_05_15 SB approved.clean.pdf

Dear all,

Stan has kindly agreed for me to share this message with you. If you choose to sign up, this will allow you to receive future communications from Brighton Collaborations re: vaccine safety news and opportunities.

Robert (Bob) Chen MD MA
Scientific Director, Brighton Collaboration
Land: (b)(6) Cell: (b)(6)
email: (b)(6)

From: **Contact Brighton Collaboration** <contact@brightoncollaboration.org>
Date: Fri, Aug 9, 2019 at 7:15 AM
Subject: Brighton Collaboration Membership
To: (b)(6)

Dear Brighton Collaboration Partner,

We recently informed you of several new developments to strengthen the Brighton Collaboration, including our move to the Task Force for Global Health (TFGH; taskforce.org) in Decatur, GA, USA ([read the letter here](#)). We encourage you to maintain your active relationship with the Brighton Collaboration in helping build trust in safety of vaccines through rigorous science. In order to comply with new data privacy laws, we need you to signify this by completing the brief survey linked below.

By completing this survey, you acknowledge that you would like to join the new Brighton Collaboration 2.0 (based at the Task Force for Global Health), and have read

and understood the terms of reference (as detailed in the attached BC2.0 Constitution and Summary of Changes of new Constitution from 2010).

[Access the survey here](#)

Thank you!

Summary of changes from 2010 to 2019 Constitution

Throughout the document all references to Brighton Collaboration Foundation have been removed.

Section I – Legal nature, purpose and guiding principles: Articles 1-5

Article 1 Wording regarding being a partnership under Swiss code deleted, and description of Brighton Collaboration as a global network of partners combined with wording from article 2 regarding the nature of Brighton work.

Article 2 – deleted and replaced with a description of Brighton Collaboration being a program of the Task Force for Global health.

Article 3 – minor wording changes but no change in meaning to principles. Addition of a new principle, 12) Transparency – to provide transparency on all processes, work and products.

Article 4 – add ‘with logo’ to end of sentence.

Section II – Partners: Articles 6-12.

Article 6 Sentence added to end: “A list of partners and their contact details is kept by the Science Board.

Section III – Science Board: Articles 13-31 Substantively unchanged

Section IV - A new position, Scientific Director, is described in articles 32 and 33

Section V – Administration: new Articles 34 and 35

Article 34 – describes the role of the Task Force for Global Health

Article 35 Creates a standing committee to include Science Board Chair/Vice Chair, Scientific Director and TFGH Project Manager to ensure optimum efficiency, communication and transparency in terms of administration of the Brighton Collaboration.

Section VI Fund Raising: new Articles 36-38

Article 36 – notes importance of volunteer activity to the Brighton Collaboration, but also states the importance of funds for managing and supporting BC. Lists ways in which funds can be raised and notes that under TFGH BC will have a dedicated account.

Article 37 – notes that contracts for BC will be signed by Scientific Director and TFGH CEO once SB has approved the related project.

Article 38 – notes that TFGH will provide a comprehensive accounting of costs and income for BC to the Science Board each year.

Section VII –Compensation: Article 39 unchanged except to remove reference to BCF.

Section VIII - Conflicts of Interest: Articles 40-42 unchanged

Section IX – Brighton Documents: Articles 43-45 unchanged

Section X – Duties of confidentiality: Articles 46-50

Unchanged except to add TFGH personnel to Article 47 which described the agreement to maintain confidentiality with respect to confidential information shared by other Partners

Section XI – Final Provisions: Articles 51-52

Removed two articles concerned with constitution being governed by Swiss law as well as requirement that any legal action be brought to competent courts of Basel, Switzerland;

Removed article that required for constitutional change, agreement from 2/3 of partner votes cast. This process related to constitutional change will be addressed in the new regulations that will accompany the constitution.

Added new article 52 which states that the new constitution fully replaces the Constitution of 2010 and that the Regulations of 2010 are no longer effective and will be revised in line with this constitution.



Brighton

collaboration

Constitution
15-May-2019

Constitution

I) Legal nature, purpose and guiding principles

- Article 1.** The Brighton Collaboration (hereinafter referred to as "Collaboration") is a global network of partners with a shared commitment to facilitate the development, dissemination and evaluation of high quality information about the safety of human vaccines.
- Article 2.** The Brighton Collaboration is a program of the Task Force for Global Health (hereinafter referred to as Task Force). As such it complies with the rules and regulations of the Task Force's Bylaws and policies. The Task Force is a tax-exempt, non-profit corporation organized under the laws of the State of Georgia, USA. The Task Force serves as the legal entity for the Collaboration and as such takes on the fiduciary responsibilities for all contracts, grants, employer obligations, tax returns and a series of services among which are legal and financial management.
- Article 3.** The Collaboration abides by the following principles:
- 1) Altruism: To serve the needs of the global community concerned with immunization safety.
 - 2) Collaboration: To work together effectively by promoting good internal and external communications through open decision making and teamwork.
 - 3) Global Participation: To promote global participation.
 - 4) Independence: To keep the Brighton Collaboration scientifically independent
 - 5) Multidisciplinary Approach: To involve people of different skills and backgrounds, in order to benefit and build upon their contributions.
 - 6) Generalizability: To minimize bias by adhering to a strict scientific approach, ensuring broad participation, and avoiding conflicts of interest.
 - 7) Relevance: To maintain Brighton documents and tools up-to-date by identifying and incorporating the highest achievable quality of clinical evidence.
 - 8) Accessibility of Work: To facilitate access to Brighton Collaboration documents and tools through strategic alliances and choice of media.
 - 9) Responsiveness: To provide high quality information by being open and responsive to criticism.
 - 10) Continuity: To maintain continuity of responsibility for Brighton documents and tools and key functions.
 - 11) Accessibility: To allow broad participation in the work of the Brighton Collaboration by minimizing obstacles to contributing and promoting diversity.
 - 12) Transparency: To provide transparency on all processes, work and products
- Article 4.** The Collaboration performs its activities under the name and trademark: "Brighton Collaboration" with logo.

Article 5. The official language within the Collaboration is English. Any working language is permitted.

II) Partners

Article 6. The partners of the Collaboration (hereinafter referred to as "Partners") consist of individuals and legal entities that have agreed to be partners of the Collaboration. A list of partners and their contact details is kept by the Science Board.

Article 7. The Science Board has the right to admit any individual or legal entity that has suitable expertise or skills to contribute to the Collaboration's objectives as a Partner. The Science Board decides at its own discretion, but with view to the objectives and guiding principles of the Collaboration.

Article 8. Partner status is personal and cannot be transferred.

Article 9. The Science Board can exclude a Partner from the Collaboration for material violation of this Constitution or of any other rules or policies of the Collaboration adopted in accordance with it.

Article 10. A Partner can terminate its participation in the Collaboration at any time.

Article 11. The accession of new Partners or the departure of existing Partners does not affect the legal existence of the Collaboration or its identity.

Article 12. The Collaboration can be dissolved by the Science Board.

III) Science Board

Science Board Composition

Article 13. The Partners elect among themselves a Science Board consisting of 5 to 10 members (hereinafter referred to as "Board Members").

Article 14. New candidates for the Science Board are nominated by members of the existing Science Board after calling for recommendations of candidates among the Partners (as per Article 6). Then the Science Board chooses nominees with appropriate technical, strategic, policy and personal skills for a given position. The Science Board seeks to achieve a balanced composition of the Science Board as to the geographic and professional background of the Board Members. Further details of the voting procedure by Partners are laid down in the Regulations.

- Article 15.** The Science Board elects a chairperson ("the Chair") and a vice chairperson ("the Vice Chair") who shall act as chairperson in case of his/her absence. They may be removed from their office and replaced by other Board Members at any time.
- Article 16.** The Science Board can remove a Science Board Member from office for important reasons, such as a material violation of the Board Member's obligations, the Board Member's inability to work in a team, or the Board Member's incapability to properly perform its duties for health or other reasons.
- Article 17.** A Science Board member who does not participate in or otherwise contribute to three consecutive meetings can be replaced by decision of the other Science Board members.
- Article 18.** Board Members can resign from their office at any time.

Science Board Tasks

- Article 19.** The Science Board, within the framework of this Constitution, determines the scientific activities that the Collaboration engages in. It develops the Collaboration's scientific strategies and policies, and decides on new initiatives or the re-direction of current initiatives.
- Article 20.** The Science Board sets up the organizational structure for the scientific work of the Partners, such as working groups, committees and other units, and supervises the activities of the various units.
- Article 21.** The Science Board decides on the composition of the various organizational units. It chooses participants with suitable expertise or skills and seeks to ensure a balance of organizational affiliations as well as professional backgrounds. It takes into account possible conflicts of interest. Only Partners can participate in working groups, committees and other units of the Collaboration.

Science Board Meetings

- Article 22.** The Science Board convenes at least once per year. Meetings may be held in person, via teleconference or similar forums, provided that all participants can simultaneously communicate with each other.
- Article 23.** The invitations to the meetings have to be sent out timely enough to give the Board Members reasonable time for their time planning and for preparation of the meeting.
- Article 24.** The Chair convenes and presides over the Board meetings and is responsible for the implementation of the Board's decisions. In the event that the Chair is prevented from performing its duties, the Vice Chair will act as the Chair's substitute. In the event that

the Vice Chair is prevented as well, the Board members will elect an ad interim substitute.

- Article 25.** Meetings can also be convened by a certain number of Board Members. Unless otherwise specified in a Regulation, three Members are sufficient for this purpose.
- Article 26.** With the approval of the Science Board, temporary consultants can participate in Science Board sessions to provide input and perspective in discussions. Such consultants may not vote on Science Board decisions.
- Article 27.** With the approval of the Science Board, previous Board Members, liaisons of organizations and governmental agencies, associate partners of the Collaboration, and management team members can participate indefinitely in Science Board sessions as observers to provide input and perspective in discussions. Such observers may not vote on Science Board decisions.

Science Board Decisions

- Article 28.** Board decisions require a majority of 2/3 of the votes. The Board shall form a quorum whenever more than half of all members are present. In the event that a quorum is not formed, decisions must be confirmed by written procedure.
- Article 29.** The removal of a Board Member under Articles 16 and/or 17 requires that all of the votes cast are in favor of the exclusion of the Board member in question. If a Board member is proposed to be excluded, he or she will have to recuse himself or herself from the discussion of and decision on the removal. A vote for removal can only occur after giving notice of the intended removal prior to the meeting at which such vote shall take place.
- Article 30.** Decisions can also be adopted by written or electronic correspondence, unless one of the Board Members demands an oral discussion.
- Article 31.** The Science Board keeps records of all decisions adopted as well as minutes of all its meetings.

IV) Scientific director

- Article 32.** A Scientific Director is a Brighton Collaboration partner and will be appointed by the Science Board to represent the Brighton Collaboration and to ensure that key scientific programs and projects of the Collaboration progress. The Scientific Director will actively search for donations and/or scientific projects in the name of the Collaboration.

Article 33. The Scientific Director will attend the Science Board meetings and work closely with the Science Board to support its activities and to achieve the scientific priorities as developed with the Science Board.

V) Administration

Article 34. The Task Force supports the Collaboration with a variety of support services which may include: Facility services, Communications, Finance, Accounting, Fund Raising, and Information Technology.

Article 35. The Collaboration is administered by the Science Board, the Scientific Director and The Task Force. To ensure optimum efficiency, communication and transparency, a standing committee will be formed to include the Chair and Vice-Chair of the Science Board, the Scientific Director and the Representative of the Task Force.

VI) Fund Raising

Article 36. While reliance on volunteer activity is a major pillar of the Brighton Collaboration, funds are needed to manage and support the Collaboration. These funds can be raised from sources such as Governments or non-profit organizations; contracts regarding vaccine safety in the name of the Collaboration or its partners; services and donations through the Task Force (as per article 34). Funds will arrive at a dedicated Brighton Collaboration account.

Article 37. Contracts in the name of or with participation of the Collaboration will be reviewed and approved by the Science Board and Scientific Director, then signed by the Chief Operating Officer of The Task Force (as per article 34). .

Article 38. The Task Force (as per article 34) shall provide a complete and transparent accounting of expenses and revenue for the Brighton Collaboration to the Science Board at the end of each calendar year.

VII) Compensation

Article 39. The Science Board Members and Partners perform their duties under this Constitution on a voluntary basis. They are, however, entitled to reimbursement for reasonable travelling, hotel and other expenses properly incurred in connection with the performance of their duties conditional on prior approval by the Science Board.

VIII) Conflicts of Interest

Article 40. It is the interest of the Collaboration to protect and preserve public health. The decisions of the Partners shall not be influenced by any for-profit commercial concerns,

any biases or conflicting interests arising from an organizational or commercial affiliation or any financial interests.

- Article 41.** The development of any document must be free of any real or perceived bias due to the receipt of any benefit in cash or kind, any hospitality, or any subsidy derived from any source that may have or be perceived to have a financial interest or any other interest outside the scope of the purpose of the Collaboration in the outcome of the document.
- Article 42.** All Partners shall act at all times in a manner consistent with the best interests of the Collaboration. They shall fully disclose any conflict of interest. The Science Board shall exclude Board Members from its deliberations on the concerned matter in the case of a conflict of interest, if the affected Board Member does not abstain voluntarily.

IX) Brighton Documents

- Article 43.** Brighton Collaboration Documents include standardized case definitions for AEFI, guidelines for data collection, analysis, and presentation, template protocols, as well as other documents and tools developed within the framework and name of the Brighton Collaboration. In order to be presented as a Brighton Collaboration Document or tool, the document/tool must have been developed by Partners and approved by the Science Board.
- Article 44.** The Brighton Collaboration strives for the widest possible dissemination and accessibility of Brighton Collaboration documents and gives credit to participants and others where credit is due.
- Article 45.** Partners work under the understanding that, subject to the rules on authorship, Brighton Collaboration Documents will remain in the public domain and are not subject to any copyright.

X) Duties of Confidentiality

- Article 46.** Confidential Information is information that an individual has disclosed in a relationship of trust with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure. Confidentiality is the treatment of confidential information so that it is not divulged in ways that are inconsistent with the understanding of the original disclosure.
- Article 47.** The Partners and the Task Force personnel working with the Collaboration agree to hold information shared as confidential information by other Partners such as case information for case scenarios and organizational case definitions and protocols confidential. Unless otherwise provided by the person furnishing the information, the information may be shared with other Partners participating in the same working group, committee or other organizational unit or with Task Force personnel. With permission

of the Scientific Director, the information can also be shared with consultants and other collaborators.

- Article 48.** To protect the intellectual rights, confidential case information or protocols shall not be adapted or used by the Brighton Collaboration without permission of the Partner sharing this information.
- Article 49.** The meetings of the Science Board and any other discussions pertinent to the work of the Brighton Collaboration shall be confidential. The members of the Science Board shall not divulge to any third party information disclosed to them in the execution of their duties as members of the Science Board.
Observers or temporary participants attending a Science Board meeting shall agree to be bound by the Collaborations confidentiality rules.
- Article 50.** The Board Members shall keep in a proper manner all material provided to them by reason of their membership. When a Board Member retires, it shall return to the Chair all such material.

XI) Final Provisions

- Article 51.** This Constitution can only be amended by a written document approved by the Partners with a majority of at least 2/3 of the votes cast.
- Article 52.** This Constitution fully replaces the Constitution of 2010. The Regulations of 2010 are no longer effective and will be revised in line with this Constitution.

Approved May 15, 2019 by the Science Board (Barbara Law, Sonali Kochhar, Kathryn Edwards, Daniel Salmon, Nicholas Wood, Clare Cutland, Helen Petousis-Harris, Wan-Ting Huang, James Oleske, Delese Mimi Darko).

From: Admin
Sent: 3 Jun 2019 11:01:12 -0400
To: nkarora@incentrust.org; Destefano, Frank (CDC/DDID/NCEZID/DHQP); 'Eric Fombonne'; 'GARCON Nathalie'; jason.m.glanz@kp.org; All@ssi.dk; 'Paul Henri Lambert'; 'Heidi Larson'; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6) bod enstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6) 'Edwards, Kathryn'; ulrich.heininger@unibas.ch; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; 'Amy Pisani'; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; (b)(6)
Cc: 'Stanley Plotkin'
Subject: FW: A couple of ideas

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Eric Fombonne [mailto:fombonne@ohsu.edu]
Sent: Friday, May 31, 2019 1:57 PM
To: fxd1@cdc.gov; nhalsey1@jhu.edu; lem2@cdc.gov; offitt@email.chop.edu; 'Stanley Plotkin'
Subject: A couple of ideas

Hello,

I had these 2 ideas this afternoon. I am out of my league here, so I am unsure about their relevance.

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Thank you for an interesting meeting.

Regards,

Eric

From: Admin

Sent: 26 Jul 2019 09:54:18 -0400

To:

nkarora@incentrtrust.org;fombonne@ohsu.edu;nathalie.garcon@bioaster.org;jason.m.glanz@kp.org;nhalsey@jhsph.edu;All@ssi.dk;paul.lambert@unige.ch;heidi.larson@lshtm.ac.uk;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber, Patrick (CDC who.int);Destefano, Frank (CDC/DDID/NCEZID/DHQP);kathryn.edwards@vumc.org;jim.buttery@monash.edu;(b)(6)

(b)(6) ulrich.heininger@ukbb.ch;amy@vaccinateyourfamily.org;dsalmon1@jhu.edu;m.c.j.sturkenboom@umcutrecht.nl;priya.bahri@ema.europa.eu;(b)(6) bodenstabh@email.chop.edu;(b)(6)

(b)(6) hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;amyp@ecbt.org

Cc: stanley.plotkin@vaxconsult.com;Peden, Keith (FDA/CBER)

Subject: FW: Future Safety Studies - 2nd Version - Wellcome Trust Vaccine Safety Meeting - K. PEDEN Comments

Attachments: SUMMARY OF IDEAS FOR FUTURE STUDIES PROPOSED BY ATTENDEES AT THE WELLCOME TRUST LONDON VACCINE SAFETY MEETING[1]kp.docx

Dear all:

Below are Keith Peden's comments re above subject.

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

Dear Stanley and colleagues,

(b)(5)

(b)(5)

Best regards, Keith

Dear London Meeting Participant:

Attached is a second version of ideas for future safety studies. The goal is to create a document with which to seek funding. Feel free to comment, correct, elaborate or propose new ideas. This document is in evolution. The eventual purpose is to seek funding. Please send your comments to both myself and my admin at: Stanley.plotkin@vaxconsult and admin@vaxconsult.com.

Thanks,
Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902

215-297-9321

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(b)(5)

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(b)(5)

From: Stanley Plotkin
Sent: 15 Jul 2019 09:36:22 -0400
To: Wolfe, Skip (CDC/DDID/NCIRD/ISD)
Subject: FW: HPV article
Attachments: HPV Constable _20190715 (3).pdf

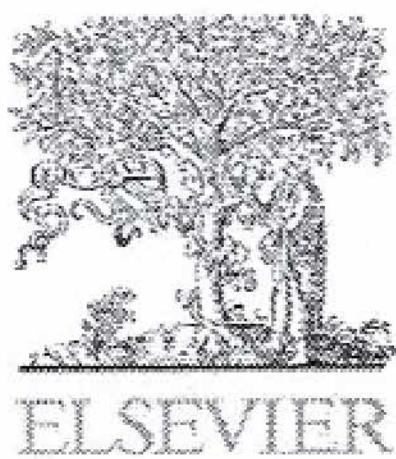
Dear Skip:

In case you missed this, I am not the only one concerned about the VIS, and I look forward to the review you mentioned.

Best wishes,
Stanley Plotkin

Scanned

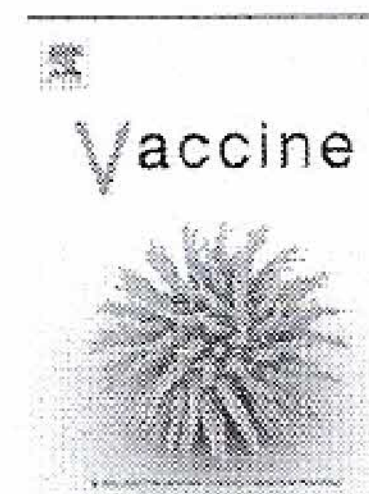
Vaccine 37 (2019) 4241–4242



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Commentary

Bolstering trust in the human papillomavirus vaccine through improved communication in the vaccine information statement



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Marking a major victory in public health, the FDA approved the first safe and effective vaccine for human papillomavirus (HPV) in 2006. HPV infects nearly all sexually active men and women, and causes approximately 5% of all cancers worldwide. Gardasil, the original vaccine developed by Merck, protects against the two HPV subtypes associated with the highest proportion of cancers in all regions of the world, HPV 16 and 18, as well as two types that cause most genital warts. Almost all cases of cervical cancer, over 90% of anal cancers, 70% of oropharyngeal cancers, 75% of vaginal cancers, 70% of vulvar cancers and over 60% of penile cancers are caused by high-risk HPVs [1]. The FDA granted marketing authorization to Cervarix and Gardasil 9, two additional HPV vaccines, in 2009 and 2014, respectively. Cervarix provides immunity against the HPV 16/18 types, but not against those associated with genital warts. Gardasil 9 expands on Gardasil with protection for five additional high-risk HPVs, and has replaced Gardasil in the U.S. HPV vaccination has already contributed to declines in genital warts [2] and cervical precancerous lesions [3].

However, hesitancy among parents has contributed to slow uptake. Current U.S. vaccination rates hover at around 53% for girls and 44% for boys [4], far below the targets of 80% for boys and girls ages 13–15 put forth by the U.S. government's HealthyPeople

initiative, which provides national objectives and establishes and monitors benchmarks to promote public health [5]. Although the safety profiles of HPV vaccines have stood up to scrutiny in post-marketing epidemiological studies [3], many factors have contributed to an erosion of trust in the HPV vaccines over and above historical hesitancy about childhood vaccines. These have included public resistance to state mandate proposals, given that HPV infection is transmitted sexually (a concern particularly prevalent among religious conservatives), and controversy surrounding the role of Merck in promoting mandates. To date, however, the two most commonly cited reasons for parental refusal are safety concerns and perceived lack of necessity [6].

Many researchers, including one of the authors of this Viewpoint, have been focused on improving provider communication strategies, which are known to be a major determinant of parental consent for the HPV vaccine [7]. At the same time, however, there is opportunity to improve the clarity of the CDC's HPV Vaccine Information Statement (VIS), which must be presented to parents prior to administration of the vaccine. Augmenting the information in the VIS would support clinicians in their communication efforts and better equip the person making the vaccination decision. Given that distrust of the safety and efficacy of the vaccine are major barriers to parental consent for adolescent vaccination, public health efforts to bolster public confidence in this vaccine should at minimum optimize the transparency and clarity of standardized communication of the vaccine's benefits and risks.

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E-mail address: catherine.constable@nyulangone.org (C. Constable).

In its current version, the HPV VIS does not present benefits and risks in forms that are easily compared. The VIS states that HPV infects 14 million Americans each year, and accurately lists the types of cancers caused by HPV. It also includes the annual incidence of cervical cancer diagnoses and deaths from cervical cancer, one of the most common cancers associated with HPV: “In the U.S., about 12,000 women get cervical cancer every year, and about 4,000 women die from it. HPV vaccine can prevent most of these cases of cervical cancer.” In contrast, the risks of the vaccine are presented as ratios: soreness (about 9 people in 10), redness or swelling (about 1 person in 3), mild fever (about 1 person in 10), moderate fever (about 1 person in 65) and headache (about 1 person in 3). Other problems are presented as well:

People sometimes faint after a medical procedure, including vaccination. . .

Some people get severe pain in the shoulder and have difficulty moving the arm where a shot was given. This happens very rarely. Any medication can cause a severe allergic reaction. Such reactions are very rare, estimated at about 1 in a million doses. . . As with any medicine, there is a very remote chance of a vaccine causing a serious injury or death.

From this sheet, a parent would be unable to determine whether the benefits of the vaccine justify its risks, since the probabilities of contracting an HPV-related disease and the probabilities of experiencing an adverse event from the vaccine are not presented in comparable formats. Given that the risks of the vaccine are listed as ratios, the risk of developing cervical cancer should also be expressed as a ratio (currently estimated at 1 in 161). For greater context, risk reduction data should be presented as well. While more time post-licensure is needed to establish cancer outcomes, what is currently known is that in young women and girls who are negative for high-risk HPV types prior to vaccination, risk of precancer from HPV 16/18 is reduced from 164/10,000 to 2/10,000. These ratios can be presented in the same format outlined above, i.e. “from 1 in 61 to 1 in 5000” [3]. Further, the risk of developing other cancers and the risk of contracting genital warts should be added and presented in the same fashion. While these disease risks are patently lower than the risks of mild or moderate adverse events specific to the HPV vaccine, a parent may reasonably judge them to be the more determining factors in their decision. Armed only with an incomplete presentation of benefits and risks, a parent’s decision to vaccinate—a prophylactic intervention on a healthy child—hinges on his or her trust of the healthcare provider and the medical community at large.

There is considerable variability in the way information is presented in VISs in general. For some vaccines (e.g. pneumococcus), information is presented the same way as for the HPV vaccine, with the risk of disease stated in absolute numbers and adverse reactions represented as ratios. Other VISs neglect to quantify the risk of adverse reactions (measles-mumps-rubella, hepatitis B, varicella). Indisputably, the VIS needs to be tailored to reflect the public health context for each vaccine. For diseases that are less prevalent in the U.S. (e.g. measles), the risk to the individual of contracting the disease may be negligible, but may increase sharply with the rise of unvaccinated pockets—a more than theoretical concern, as demonstrated by recent measles outbreaks in New York and several other states [8]. Where maintaining herd immunity is the priority, appeals to individual risk may be less to the point, given the low risk to the average American of contracting measles outside of outbreak zones. On the other hand, current prevalence of HPV-related disease should be a strong motivator

for parents considering the vaccine. This information should be coupled with rates of adverse reactions, in a comparable format.

To be sure, HPV vaccine uptake is impacted by a number of complex factors and interactions between stakeholders. These include government action such as state mandates, healthcare provider communication and support for the vaccine, as well as reactions from the parent community. Further research is needed to determine whether communicating the risks and benefits of vaccination in the format suggested will increase uptake. Notably, in a recent study, parents that accepted vaccination were more likely to report being offered the chance to ask questions about VISs, suggesting value in improved clarity [9]. Some parents will have concerns about possible harms that are not founded in existing biological and epidemiological evidence, which would not be appropriate to include in the VIS. However, it is the duty of government health agencies and healthcare providers to educate parents and supply factual information that supports the recommendation to vaccinate, especially in light of the abundance of misinformation and considerable distrust. To meet this goal, the HPV VIS must provide parents with clear and transparent risk/benefit information that demonstrates why it is in the interest of the public health—as well as of the individual—to get vaccinated.

Expressing the benefits and risks of the HPV vaccine in clear language and ratios that are directly comparable will better satisfy the requirements of informed and shared decision-making. There is an ethical duty to optimize clarity in health communication, apart from the public health objective of promoting recommended vaccines. Presenting evidence-based quantitative information in the HPV VIS more clearly and completely would be a positive step towards both dispelling misinformation and building up trust in the value of HPV vaccination.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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From: Admin
Sent: 15 Oct 2019 15:46:41 -0400
To: nkarora@incentrtrust.org;fombonne@ohsu.edu;nathalie.garcon@bioaster.org;jason.m.glanz@kp.org;nhalsey@jhsph.edu;All@ssi.dk;paul.lambert@unige.ch;'Heidi Larson';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);'Andrew Pollard';Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber, Patrick (CDC who.int);Destefano, Frank (CDC/DDID/NCEZID/DHQP);kathryn.edwards@vumc.org;jim.buttery@monash.edu;(b)(6);ulrich.heininger@ukbb.ch;dsalmon1@jhu.edu;m.c.j.sturkenboom@umcutrecht.nl;priya.bahri@ema.europa.eu;(b)(6);bodenstabh@email.chop.edu;(b)(6);hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz
Cc: 'Stanley Plotkin'
Subject: FW: London vaccines safety meeting

FYI. Disappointing response from the Wellcome Trust, but perhaps useful for studies done in LMIC.

Stanley

Sent on Behalf of Dr. Stanley Plotkin

Wendy D'Arcy
Assistant
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Divya Shah [<mailto:D.Shah@wellcome.ac.uk>]
Sent: Thursday, October 10, 2019 4:53 AM
To: Stanley Plotkin
Subject: RE: London vaccines safety meeting

Dear Stanley,

Thank for sending your paperwork through.

Wellcome has a variety of schemes available for funding, the most likely scheme that it seems you might be interested in is the Collaborative award scheme, please find more details here, including eligibility: <https://wellcome.ac.uk/funding/schemes/collaborative-awards-science>

With regards to where we fund, the lead PI for Collaborative awards must be based in the UK or LMIC, and as such we would not support someone in Denmark unless they are a co-PI. The centre of gravity of the work proposed must also be based in the UK/LMIC. All our other schemes have to be based in the UK or LMIC.

In terms of which proposal you take forward, that is entirely up to you, we do not advise on what work to do, as long as it fits within our science remit, please see more details here: <https://wellcome.ac.uk/funding/guidance/science-remit>

If you are interested in discussing a proposal, please send a 1-2 page outline and CVs of the co-PIs involved and we can find a suitable time and date to chat.

Best wishes,
Divya

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Sent: 09 October 2019 17:14
To: Divya Shah <D.Shah@wellcome.ac.uk>
Subject: RE: London vaccines safety meeting

Dear Divya:

Thank you for your contact. Please understand that the ideas mentioned in my summary (attached) do not yet have a proposal outline. The question is, would Wellcome accept proposals on the subjects mentioned in the summary, in which case I would request the scientists whose ideas are summarized to send you proposals. If only some of the ideas interest you it would be helpful to know which. I would suggest that the studies to be conducted in Denmark might particularly interest you, but it would also be helpful to know whether there are geographical restrictions to Wellcome funding.

Thank you,
Stanley

From: Divya Shah [<mailto:D.Shah@wellcome.ac.uk>]
Sent: Friday, October 04, 2019 9:51 AM
To: Stanley Plotkin
Subject: RE: London vaccines safety meeting

Dear Stanley,

I have been forwarded your email and would be happy to chat to you about potential funding options from our Science funding streams. If interested, please could you send a 2 page CV and 1-2 page proposal outline after which we can find a suitable time and date to chat.

Best wishes,
Divya

From: Charlie Weller
Sent: 04 October 2019 10:34
To: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Cc: Jeremy Farrar <J.Farrar@wellcome.ac.uk>; Divya Shah <D.Shah@wellcome.ac.uk>
Subject: RE: London vaccines safety meeting

Dear Stanley

I suggest that you connect the researchers directly with Divya Shah (cc'd) in our Infection and Immuno-biology team in Science. Divya will be best placed to discuss the research areas and what options and routes there may be among our different schemes for the researchers.

All the best
Charlie

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Sent: 28 September 2019 19:21

To: Charlie Weller <C.Weller@wellcome.ac.uk>
Cc: Jeremy Farrar <J.Farrar@wellcome.ac.uk>
Subject: RE: London vaccines safety meeting

Dear Charlie:

Thank you for this detailed reply, but let me see if I understand it. I realize that Wellcome cannot support the entire list of safety studies, but would it be open to specific proposals to study the issues outlined in my report? If so, can you refer me to the mechanism and to the Science team you refer to?

Best wishes,

Stanley

From: Charlie Weller [<mailto:C.Weller@wellcome.ac.uk>]
Sent: Friday, September 27, 2019 9:05 AM
To: Stanley Plotkin
Cc: Jeremy Farrar
Subject: London vaccines safety meeting

Dear Stanley

Jeremy shared the report from the London meeting with me and the proposed ideas for future studies of vaccines safety. A fantastic, comprehensive report and thank you for highlighting the current gaps in vaccine safety research.

There are no specific avenues for supporting the vaccines safety research areas you have highlighted within the Vaccines priority area at this moment in time. However there are different schemes that researchers can apply to within Wellcome and I suggest they speak to our Science team directly and I would be happy to connect them.

I can however update you on how we, in the Vaccine Priority Area, are thinking about Vaccine uptake and access issues, below.

In June 2019 we launched the results from the Wellcome Global Monitor which surveyed more than 140 countries and 140K people on their attitudes to research, science and vaccines.
<https://wellcome.ac.uk/what-we-do/our-work/wellcome-global-monitor>

We are investigating further with the Vaccines uptake and access community (including safety issues) to understand what the research needs are across the board, including behavioural and social sciences, vaccine acceptance and implementation research. We are also interested in better determining what the drivers of reduced uptake are and linking this to understanding what potential interventions could be used. All of this is context, country, community specific. Vaccine safety is integral to vaccine acceptance.

I can keep you updated on this piece of work, which my team is conducting, connecting and aligning with others such as WHO, the vaccines demand hub, which includes participants of the London vaccines safety meeting you led.

I think it is critical that you have identified the current research needs in Vaccine safety from a scientific perspective. To complement this I think it is also important to understand what 'hesitant people' want to know and what their concerns are so that the research conducted has the best chance to change attitudes and behaviours and ultimately increase uptake.

I hope this helps you understand our thinking,

All the best
Charlie

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From: Admin
Sent: 3 Jun 2019 11:04:56 -0400
To: nkarora@incentrust.org; Destefano, Frank (CDC/DDID/NCEZID/DHQP); 'Eric Fombonne'; 'GARCON Nathalie'; jason.m.glanz@kp.org; All@ssi.dk; 'Paul Henri Lambert'; 'Heidi Larson'; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6); 'Edwards, Kathryn'; ulrich.heininger@unibas.ch; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; 'Amy Pisani'; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; (b)(6)
Cc: 'Stanley Plotkin'
Subject: FW: Paul has Measles in Amazon

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Dr. Susana Lopez [mailto:susana@ibt.unam.mx]
Sent: Tuesday, May 21, 2019 8:44 AM
To: Stanley Plotkin
Subject: Paul has Measles in Amazon

Dear Stanley,

I hope you are fine.

Thanks to Paul Griffin, director of Parasites Without Borders (PWB), we were able to introduce the book in Amazon. It is available in paperback and in kindle version and it is available in Spanish, English, and French. I think this will be a good way to spread the book.

Could you please help me to spread the links to your friends?

Many thanks and Best regards,

Susana

Here are the links:

English

https://www.amazon.com/Paul-has-Measles-Susana-L%C3%B3pez/dp/1097510573/ref=sr_1_1?keywords=Paul+has+measles&qid=1558441916&s=gateway&sr=8-1-spell

French

https://www.amazon.com/Paul-Rougeole-French-Susana-L%C3%B3pez-ebook/dp/B07RTZVD6M/ref=sr_1_fkmrnull_1?keywords=Paul+a+la+rougeole&qid=1558441985&s=gateway&sr=8-1-fkmrnull

Spanish

https://www.amazon.com/Pablo-tiene-SARAMPI%C3%93N-Spanish-Susana/dp/1097516032/ref=sr_1_fkmrnull_2?keywords=Pablo+tiene+sarampion&qid=1558442059&s=gateway&sr=8-2-fkmrnull

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Dr. Susana Lopez
Instituto de Biotecnología/UNAM
Av. Universidad 2001,
Col. Chamilpa,
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Mexico

From: Admin
Sent: 3 Jun 2019 10:58:15 -0400
To: nkarora@incientrust.org;Destefano, Frank (CDC/DDID/NCEZID/DHQP);'Eric Fombonne';'GARCON Nathalie';jason.m.glanz@kp.org;All@ssi.dk;'Paul Henri Lambert';'Heidi Larson';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu;priya.bahri@ema.europa.eu;(b)(6);bodenstabh@email.chop.edu;jim.buttery@monash.edu;(b)(6);'Edwards, Kathryn';ulrich.heininger@unibas.ch;hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;'Amy Pisani';dsalmon1@jhu.edu;m.c.j.sturkenboom@umcutrecht.nl;(b)(6)
Cc: 'Stanley Plotkin'
Subject: FW: Vaccine Safety Reference Library website

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Bodenstab, Heather M [mailto:BODENSTABH@email.chop.edu]
Sent: Friday, May 31, 2019 11:10 AM
To: Stanley Plotkin
Cc: Offit, Paul; Bodenstab, Heather M
Subject: Re: Vaccine Safety Reference Library website

This is the link for the Vaccine Safety Reference Library website. Please note that the article summaries are very generalized for the website for usability by educators and health care professionals. The library is constantly evolving and numerous topics are to be added. Additionally, topics will be updated on a regular basis.

<https://www.chop.edu/centers-programs/vaccine-education-center/vaccine-safety-references>

From: Neal Halsey
Sent: 18 Jul 2019 15:07:07 +0000
To: Stanley
Plotkin;'Admin';nkarora@incentrust.org;fombonne@ohsu.edu;nathalie.garcon@bioaster.org;jason.m.glanz@kp.org;nhalsey@jhsph.edu;All@ssi.dk;paul.lambert@unige.ch;heidi.larson@lshtm.ac.uk;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber, Patrick (CDC who.int);Destefano, Frank (CDC/DDID/NCEZID/DHQP);Hotez, Peter Jay
Cc: kathryn.edwards@vumc.org;jim.buttery@monash.edu;(b)(6);ulrich.heininger@ukbb.ch;amy@vaccinateyourfamily.org;Daniel Salmon;m.c.j.sturkenboom@umcutrecht.nl;priya.bahri@ema.europa.eu;(b)(6);bodenstabh@email.chop.edu;(b)(6);liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;amyp@ecbt.org
Subject: Halsey comments London vaccine safety - Dr. Stanley Plotkin
Attachments: Halsey SUMMARY OF IDEAS FOR FUTURE STUDIES PROPOSED BY ATTENDEES AT THE WELLCOME TRUST LONDON VACCINE SAFETY MEETING.docx

Stan,

I have attached your list of studies with some written comments and suggestions. With regard to some of the comments that have been sent:

(b)(5)

Neal

From: "Hotez, Peter Jay" <hotez@bcm.edu>
Date: Thursday, July 18, 2019 at 9:53 AM
To: Stan Plotkin <stanley.plotkin@vaxconsult.com>, 'Admin' <admin@vaxconsult.com>, "nkarora@incentrust.org" <nkarora@incentrust.org>, "fombonne@ohsu.edu" <fombonne@ohsu.edu>, "nathalie.garcon@bioaster.org" <nathalie.garcon@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, JPIDS JPIDS <nhalsey@jhsph.edu>, "All@ssi.dk" <All@ssi.dk>, PAUL-hENRI LAMBERT <paul.lambert@unige.ch>, "heidi.larson@lshtm.ac.uk" <heidi.larson@lshtm.ac.uk>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <Keith.Peden@fda.hhs.gov>, "andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>, James Sejvar <zea3@cdc.gov>, Patrick Zuber <zuberp@who.int>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>
Cc: "kathryn.edwards@vumc.org" <kathryn.edwards@vumc.org>, "jim.buttery@monash.edu" <jim.buttery@monash.edu>, (b)(6)

"ulrich.heininger@ukbb.ch" <ulrich.heininger@ukbb.ch>, "amy@vaccinateyourfamily.org" <amy@vaccinateyourfamily.org>, Daniel Salmon <dsalmon1@jhu.edu>, "m.c.j.sturkenboom@umcutrecht.nl" <m.c.j.sturkenboom@umcutrecht.nl>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, (b)(6), (b)(6), "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, (b)(6) "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, "amyp@ecbt.org" <amyp@ecbt.org>
Subject: Re: HOTEZ COMMENTS London vaccine safety - Dr. Stanley Plotkin

(b)(5)

Peter Hotez, MD, PhD, FASTMH, FAAP

Dean, [National School of Tropical Medicine](#)

Professor, Pediatrics and Molecular & Virology and Microbiology

Co-Head, Section of Pediatric Tropical Medicine

Health Policy Scholar, Center for Medical Ethics and Health Policy

Baylor College of Medicine

Texas Children's Hospital Endowed Chair of Tropical Pediatrics

Co-Director, [Texas Children's Hospital Center for Vaccine Development](#)

University Professor

Department of Biology, Baylor University

Baker Institute Fellow in Disease and Poverty, Rice University

Founding Editor-in-Chief, PLoS Neglected Tropical Diseases

E-mail: hotez@bcm.edu

Twitter: [@peterhotez](https://twitter.com/peterhotez)

Skype: **p.hotez**

Executive Assistant: [Douglas Soriano](#)

Douglas.SorianoOsejo@bcm.edu

Phone: 713-798-1199

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Sent: Thursday, July 18, 2019 8:25:13 AM

To: Hotez, Peter Jay; 'Admin'; nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsph.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov

(b)(6) Cc: kathryn.edwards@vumc.org; jim.buttery@monash.edu; (b)(6) ulrich.heininger@ukbb.ch; amy@vaccinateyourfamily.org; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6) bodenstabh@email.chop.edu; (b)(6) liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; amyp@ecbt.org

Subject: RE: HOTEZ COMMENTS London vaccine safety - Dr. Stanley Plotkin

Dear Peter:

(b)(5)

Stanley

From: Hotez, Peter Jay [mailto:hotez@bcm.edu]

Sent: Thursday, July 18, 2019 8:02 AM

To: Admin; nkarora@incentrtrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhspk.edu; AII@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov

(b)(6) (b)(6) Cc: stanley.plotkin@vaxconsult.com; kathryn.edwards@vumc.org; jim.buttery@monash.edu; (b)(6) ulrich.heininger@ukbb.ch; amy@vaccinateyourfamily.org; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6) bodenstabh@email.chop.edu; (b)(6) liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; amyp@ecbt.org; Hotez, Peter Jay

Subject: Re: HOTEZ COMMENTS London vaccine safety - Dr. Stanley Plotkin

Dear Stanley et al: Thank you for addressing each of my four recommended points for further discussion. It was a real honor to attend the meeting.

(b)(5)

In the meantime thank you again for including me in these important discussions.

Title page affiliation: Peter Hotez MD PhD, Departments of Pediatrics and Molecular Virology & Microbiology, National School of Tropical Medicine, Baylor College of Medicine

Warm regards, Peter

Peter Hotez, MD, PhD, FASTMH, FAAP

Dean, [National School of Tropical Medicine](#)

Professor, Pediatrics and Molecular & Virology and Microbiology

Co-Head, Section of Pediatric Tropical Medicine

Health Policy Scholar, Center for Medical Ethics and Health Policy

Baylor College of Medicine

Texas Children's Hospital Endowed Chair of Tropical Pediatrics

Co-Director, [Texas Children's Hospital Center for Vaccine Development](#)

University Professor

Department of Biology, Baylor University

Baker Institute Fellow in Disease and Poverty, Rice University

Founding Editor-in-Chief, PLoS Neglected Tropical Diseases

E-mail: hotez@bcm.edu

Twitter: [@peterhotez](#)

Skype: **p.hotez**

Executive Assistant: [Douglas Soriano](#)

Douglas.SorianoOsejo@bcm.edu

Phone: 713-798-1199

From: Admin <admin@vaxconsult.com>

Sent: Wednesday, July 17, 2019 2:54 PM

To: nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org;
jason.m.glanz@kp.org; nhalsey@jhsp.h.edu; All@ssi.dk; paul.lambert@unige.ch;
heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov;
andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov

Cc: stanley.plotkin@vaxconsult.com; admin@vaxconsult.com; kathryn.edwards@vumc.org;
jim.buttery@monash.edu; [\[REDACTED\]](#) ulrich.heininger@ukbb.ch;
amy@vaccinateyourfamily.org; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl;

(b)(6)

priya.bahri@ema.europa.eu; (b)(6) bodenstabh@email.chop.edu;
alexooo@yahoo.com; Hotez, Peter Jay; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz;
amyp@ecbt.org
Subject: London vaccine safety - Dr. Stanley Plotkin

*****CAUTION:*** This email is not from a BCM Source. Only click links or open attachments you know are safe.**

Dear Attendees at the London Wellcome Trust Vaccine Safety Meeting:

I must begin with two apologies. First, for the delays in preparing the attached, caused by other projects I had to work on; second, for the fact that you have not received the slides from the meeting. With respect to the second, Wellcome promised to send them out weeks ago, but I have been unable to find out why the delay despite multiple attempts. I will not give up, but to avoid further delays I ask the speakers **to send me their slides and I will disseminate them to everybody else.**

With regard to the meeting report, what you have in this email is a first draft, subject to extensive polishing and to any changes you wish to make. The references will be incorporated into the mss. The authorship will be in the order of the text. I intend to submit it to Vaccine. Let me know if you have changes.

Important detail: Let me know how you want to be identified on the title page-affiliation, email.

With regard to the summary of ideas, please read and comment. I will enlarge and extend the summary beyond the outline and I welcome your additions. However, remember that this is about science, not public perception, so I have excluded ideas about vaccine hesitancy. My intention is to expand and hone this and to use it to seek funding.

By the way, Patrick Zuber is organizing a Global Vaccine Safety meeting in December.

Thank you so much for your help and your patience.

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

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modified or falsified. If you are not the intended recipient of this e-mail, please delete it immediately from your system and notify the sender of the wrong delivery and the mail deletion. Thank you.

(b)(5)

(b)(5)

(b)(5)

(b)(5)

(b)(5)

(b)(5)

From: Admin
Sent: 7 Jun 2019 09:28:08 -0400
To: nkarora@incentrust.org;Destefano, Frank (CDC/DDID/NCEZID/DHQP);'Eric Fombonne';'GARCON Nathalie';jason.m.glanz@kp.org;All@ssi.dk;'Paul Henri Lambert';'Heidi Larson';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu
Cc: 'Stanley Plotkin'
Subject: London Meeting Summary Request

Dear Speaker at the London Vaccine Safety Meeting:

Many of you have sent excellent ideas for future studies, as is not surprising from such a distinguished group. However, I have received few summaries of your talks. You will remember that I requested summaries of your talks of about 400 words each, stating explicitly your conclusions about specific safety issues relating to your subject for a summary publication.

Please return those to me as soon as possible.

**Thanks.
Stanley**

Wendy D'Arcy
Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Admin
Sent: 3 Jun 2019 09:17:05 -0400
To: nkarora@incentrust.org;Destefano, Frank (CDC/DDID/NCEZID/DHQP);'Eric Fombonne';'GARCON Nathalie';jason.m.glanz@kp.org;All@ssi.dk;'Paul Henri Lambert';'Heidi Larson';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu
Cc: 'Stanley Plotkin'
Subject: London Meeting

Dear Speaker:

As I said at the end of our conference in London, I would like to prepare a publication coming from the meeting and plan for further steps. To those ends, I beg of you to provide me within two weeks the following:

- 1) Approximately 400 words summarizing your talk. Please do not waste words with sentences beginning "We reviewed ten different reactions..." but rather "Multiple sclerosis after vaccination has been studied and no excess over unvaccinated people was found."
- 2) 200-300 words (or more if you like) about what additional studies you think are needed. These will NOT be published, but rather serve as the basis for funding proposals. As I think you will judge, I cannot promise anything but will do my best.
- 3) Up to 10 references to your subject

Please send your response to my e-mail: stanley.plotkin@vaxconsult.com

Thanks,

Stanley

Wendy D'Arcy
Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Stanley Plotkin
Sent: 17 May 2019 10:41:42 -0400
To: 'nk arora';fombonne@ohsu.edu;'GARCON Nathalie';'Jason M Glanz';aii@sii.dk;'Paul Henri Lambert';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);Peden, Keith (FDA/CBER);'Andrew Pollard';Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber, Patrick (CDC who.int)
Cc: 'Offit, Paul';Destefano, Frank (CDC/DDID/NCEZID/DHQP);'Heidi Larson'
Subject: london talks

Dear Speaker:

Just a reminder that your talk should be limited to about 25 minutes in order to leave plenty of time for discussion, during which you will be able to make additional points if you wish. Please emphasize what is known and what is not known.

Thanks,
Stanley Plotkin

From: Admin
Sent: 1 Oct 2019 10:02:04 -0400
To: offit@email.chop.edu;Destefano, Frank (CDC/DDID/NCEZID/DHQP);'Heidi Larson';nkarora@incitrust.org;Zuber, Patrick (CDC who.int);fombonne@ohsu.edu;Sejvar, James (CDC/DDID/NCEZID/DHCPP);paul.lambert@unige.ch;All@ssi.dk;nhalsey@jhsph.edu;nathalie.garcon@bioaster.org;Peden, Keith (FDA/CBER);'Andrew Pollard';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);jason.m.glanz@kp.org
Cc: 'Stanley Plotkin';admin@vaxconsult.com
Subject: London Vaccine Safety Article

Dear Co-Author:

The paper I put together summarizing your presentations at the London Wellcome Safety meeting has been reviewed and clearly will be published. However, as you can see from the extract below, they want tables and figures, specifically on:

WHO GACVS
Autoimmune mechanisms
HPV vaccine

(b)(5)

(b)(5)



Thanks, Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Bahri Priya
Sent: 23 Jul 2019 14:29:05 +0000

To: Admin;nkarora@incentrust.org;fombonne@ohsu.edu;nathalie.garcon@bioaster.org;jason.m.glanz@kp.org;nhalsey@jhspk.edu;All@ssi.dk;paul.lambert@unige.ch;heidi.larson@lshtm.ac.uk;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber, Patrick (CDC who.int);Destefano, Frank (CDC/DDID/NCEZID/DHQP)

Cc: stanley.plotkin@vaxconsult.com;kathryn.edwards@vumc.org;jim.buttery@monash.edu;(b)(6);ulrich.heininger@ukbb.ch;amy@vaccinateyourfamily.org;dsalmon1@jhu.edu;m.c.j.sturkenboom@umcutrecht.nl;(b)(6);bodenstabh@email.chop.edu;(b)(6);hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;amyp@ecbt.org

Subject: London Vaccine Safety Slide Presentations - EMA

Dear Wendy, Stanley, Heidi and All,

Many thanks again for the meeting.

With regard to the EMA receiving the slides, I had sent the email below to Stanley and Heidi but I am not sure whether all of you have received it. So I am recirculating it below.

In summary, we, at the EMA, will be grateful for receiving the slides, but please consider that once I have received them, I will forward them to the experts of the EU regulatory network. While we will not circulate them outside our network, I want to make you aware that the EMA is subject to transparency rules – please see the email below for our procedures in the case anybody asks us for access to documents we hold on a certain product or topic.

If you can share the slides with us under these conditions, please send them, otherwise, please understand that I cannot receive them.

The same goes for the manuscript.

I look very much forward to the meeting report and its publication in Vaccine. Your expertise, outside-the-box thinking, engagement and sharing is admirable and inspiring – many thanks! I hope for more work together!

With my kind regards, Priya

Dear Patrick,

Your slides can be exempted from Access to Documents requests if you tell me that they have been shared under the EMA-WHO Confidentiality Agreement.
Please let me know. Merci, P.

From: Bahri Priya
Sent: 26 June 2019 18:15
To: 'Stanley Plotkin' (stanley.plotkin@vaxconsult.com); Heidi Larson (Heidi.Larson@LSHTM.ac.uk)
Cc: Gonzalez-Quevedo Rosa; 'Kirstie Eaton'
Subject: The Science of Vaccine Safety, 30 - 31 May 2019 - Thank you and EMA Follow up regarding presentations

Dear Stanley and Heidi,

Thank you very much again for your invitation – it was a superbe meeting.

In the meantime, feedback could be provided to EMA colleagues, and I could check under which conditions the slides of the presenters could be accepted by the EMA, as the presenters had kindly offered to circulate them to all participants.

If the presenters agree to share the slides with the EMA, we will share them with the vaccine experts of the EU regulatory network, i.e. colleagues who work at the EMA or at/for a regulatory body in a member state of the EU. All these colleagues are bound to confidentiality. However, presenters should be aware that Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 applies to documents held by the EMA. This regulation allows stakeholders (i.e. any citizen of the EU and any natural or legal person residing or having its registered office in a member state) to request documents we hold on a topic the requester is interested in. If documents are authored by third parties, as it would be the case here, we would, should such a request be submitted to the EMA, consult the presenter before deciding on releasing or not the document. The consultation would also take into consideration the presence of private and personal data or commercially confidential information in a document. The fact that the document might include data or views not yet published, e.g. in a position paper or scientific journal as possibly intended by the presenters, cannot be the sole justification to refuse access. Hence, we will be grateful if these conditions would be brought by you to the attention of the presenters before they agree to share the slides with the EMA. Please feel free to forward my email to them. Of course we will be grateful if the presenters decide in favour of sharing the slides with us and express our thanks for their expertise and generosity in advance.

Looking forward to follow-up activities of the meeting,
with my best wishes,

Priya

Priya Bahri, Ph.D.

Principal Scientific Administrator

Surveillance & Epidemiology Service | Pharmacovigilance & Epidemiology Department

European Medicines Agency

Official address Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands

Address for visits and deliveries Refer to [How to find us](#)

Telephone: +31-(0)88 781 8454

Email: priya.bahri@ema.europa.eu

Website: <http://www.ema.europa.eu>



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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From: Admin [<mailto:admin@vaxconsult.com>]

Sent: 19 July 2019 17:44

To: nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org;

jason.m.glanz@kp.org; nhalsey@jhsph.edu; AII@ssi.dk; paul.lambert@unige.ch;
heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov;
andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov
Cc: stanley.plotkin@vaxconsult.com; kathryn.edwards@vumc.org; jim.buttery@monash.edu;
(b)(6) ulrich.heininger@ukbb.ch; amy@vaccinateyourfamily.org; dsalmon1@jhu.edu;
m.c.j.sturkenboom@umcutrecht.nl; Bahri Priya; (b)(6) bodenstabh@email.chop.edu;
(b)(6) hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz;
amyp@ecbt.org; admin@vaxconsult.com
Subject: London Vaccine Safety Slide Presentation - P. Zuber

Dear All:

I will forward slide presentations to you as I receive them from the speakers. Attached is Patrick Zuber's.

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

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This e-mail has been scanned for all known viruses by European Medicines Agency.

From: Admin
Sent: 12 Dec 2019 09:15:59 -0500
To: nkarora@incentrtrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsph.edu; All@ssi.dk; paul.lambert@unige.ch; 'Heidi Larson'; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); 'Andrew Pollard'; Sejvar, James (CDC/DDID/NCEZID/DHCPP); Zuber, Patrick (CDC who.int); Destefano, Frank (CDC/DDID/NCEZID/DHQP); kathryn.edwards@vumc.org; jim.buttery@monash.edu; (b)(6)
(b)(6) ulrich.heiningen@ukbb.ch; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); hotez@bcm.edu; li.z.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz
Cc: 'Stanley Plotkin'
Subject: London Vaccines Meeting - Funding

Dear All:

As promised I have been using the results of the London meeting to seek funding for vaccine safety studies. The response of the Wellcome Trust is that they would consider only studies by a UK investigator or by one associated with a UK investigator. The Gates Foundation is considering our proposals and it looks as if they may fund studies of HPV vaccine, and maybe maternal immunization. I will keep you posted.

Stanley

Sent on Behalf of Dr. Stanley Plotkin

Wendy D'Arcy
Assistant
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Wolfe, Skip (CDC/DDID/NCIRD/ISD)
Sent: 8 Mar 2019 17:24:24 +0000
To: Stanley Plotkin
Subject: MMR VIS Update

Dear Dr. Plotkin,

I've shared your specific questions with Frank DeStefano and others at CDC's Immunization Safety Office, and while I'm awaiting their response, here are some results of my own quick research, assumptions, and thoughts:

(b)(5)



Skip

From: Wolfe, Skip (CDC/DDID/NCIRD/ISD)
Sent: 15 Mar 2019 19:29:31 +0000
To: Stanley Plotkin
Subject: MMR VIS Update

Hello Dr. Plotkin,

Today we discussed

(b)(5)

(b)(5)

Skip

From: Wolfe, Skip (CDC/DDID/NCIRD/ISD)
Sent: 8 Mar 2019 20:41:05 +0000
To: Stanley Plotkin
Subject: MMR VIS

I just talked with Frank, and he said ISO doesn't have any more to add. Do you have enough information for your purposes? I think the major points are:

(b)(5)



I'll be around for another half hour (longer if necessary) if you need more.

Skip

From: Wolfe, Skip (CDC/DDID/NCIRD/ISD)
Sent: 8 Mar 2019 18:43:31 +0000
To: Stanley Plotkin
Subject: More MMR VIS Information

More comments from ISO.

I'm sending you information piecemeal, as I receive it. I hope that's okay.

Skip

From: Wodi, Akpobome (CDC/DDID/NCEZID/DHQP) <lgz1@cdc.gov>
Sent: Friday, March 8, 2019 12:59 PM
To: Destefano, Frank (CDC/DDID/NCEZID/DHQP) <fxd1@cdc.gov>
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <ayv6@cdc.gov>; Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <erm4@cdc.gov>
Subject: RE: Question about VIS Language

Frank,

(b)(6)

Thanks,
Patricia

1. Garcia Callejo, F. J., I. Costa Alcacer, C. De Paula Vernetta, and J. Marco Algarra. 2005. Sudden bilateral deafness after measles, mumps and rubella vaccination [4]. [Spanish]. *Anales de Pediatría* 62(5):482-483.
2. Healy, C. E. 1972. Mumps vaccine and nerve deafness. *American Journal of Diseases of Children* 123(6):612.
3. Nabe-Nielsen, J., and B. Walter. 1988a. Unilateral deafness as a complication of the mumps, measles, and rubella vaccination. *British Medical Journal* 297(6646):489-489.
4. Nabe-Nielsen, J., and B. Walter. 1988b. Unilateral total deafness as a complication of the measles-mumps-rubella vaccination. *Scandinavian Audiology Supplementum* 30:69-70.

From: Destefano, Frank (CDC/DDID/NCEZID/DHQP) <fxd1@cdc.gov>
Sent: Friday, March 8, 2019 11:45 AM
To: Wodi, Akpobome (CDC/DDID/NCEZID/DHQP) <lgz1@cdc.gov>
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <ayv6@cdc.gov>; Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <erm4@cdc.gov>
Subject: RE: Question about VIS Language

Patricia,

I just checked our SME roster and see that you are listed for MMR vaccine and the liaison to the ACIP workgroup. Let me know if you have anything to contribute to this question.

Thanks,

Frank

Frank DeStefano, MD, MPH

From: Eric Fombonne
Sent: 2 Aug 2019 00:16:09 +0000
To: Admin;offit@email.chop.edu;Destefano, Frank (CDC/DDID/NCEZID/DHQP);heidi.larson@lshtm.ac.uk;nkarora@incentrust.org;Zuber, Patrick (CDC who.int);Sejvar, James (CDC/DDID/NCEZID/DHCPP);'Paul Henri Lambert';All@ssi.dk;nhalsey@jhsph.edu;nathalie.garcon@bioaster.org;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com
Subject: RE: 2nd Draft - Summary of London Meeting
Attachments: Science of Vaccine Safety 7 17 2019_EFrevised August 1.docx

Hello Stanley,

I have made a few edits in my section and corrected one of the reference that was erroneous.

Regards,

Eric

From: Admin <admin@vaxconsult.com>
Sent: Friday, July 26, 2019 11:18 AM
To: offit@email.chop.edu; fxd1@cdc.gov; heidi.larson@lshtm.ac.uk; nkarora@incentrust.org; zuberp@who.int; Eric Fombonne <fombonne@ohsu.edu>; zea3@cdc.gov; 'Paul Henri Lambert' <Paul.Lambert@unige.ch>; All@ssi.dk; nhalsey@jhsph.edu; nathalie.garcon@bioaster.org; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; lem2@cdc.gov; jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com; admin@vaxconsult.com
Subject: 2nd Draft - Summary of London Meeting

Dear Speaker at the London meeting:

Here, finally, is the second draft of a summary of the meeting, with sections proposed by each of you. I have made some minor corrections for English and for quality, but these are your words. You can revise as you see fit.

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Thank you, and once again I apologize for the delay.

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road

Doylestown, PA 18902
215-297-9321

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From: Neal Halsey
Sent: 27 Jul 2019 16:03:26 +0000
To: Admin;offit@email.chop.edu;Destefano, Frank (CDC/DDID/NCEZID/DHQP);heidi.larson@lshtm.ac.uk;nkarora@incentrust.org;Zuber, Patrick (CDC who.int);fombonne@ohsu.edu;Sejvar, James (CDC/DDID/NCEZID/DHCPP);'Paul Henri Lambert';All@ssi.dk;nhalsey@jhsph.edu;nathalie.garcon@bioaster.org;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com
Subject: Re: 2nd Draft - Summary of London Meeting
Attachments: Science of Vaccine Safety 7 17 2019nh.docx

Stan suggested that if we have comments that go beyond our own sections we should copy everyone. I have made a few comments and suggestions in multiple sections. Since the text is a bit long, I made a few suggestions where wording could be more concise.

Neal

From: Admin <admin@vaxconsult.com>
Date: Friday, July 26, 2019 at 2:20 PM
To: Paul Offit <offit@email.chop.edu>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>, "heidi.larson@lshtm.ac.uk" <heidi.larson@lshtm.ac.uk>, "nkarora@incentrust.org" <nkarora@incentrust.org>, Patrick Zuber <zuberp@who.int>, "fombonne@ohsu.edu" <fombonne@ohsu.edu>, James Sejvar <zea3@cdc.gov>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, "All@ssi.dk" <All@ssi.dk>, JPIDS JPIDS <nhalsey@jhsph.edu>, "nathalie.garcon@bioaster.org" <nathalie.garcon@bioaster.org>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, "andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>, Lauri Markowitz <lem2@cdc.gov>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>
Cc: Stan Plotkin <stanley.plotkin@vaxconsult.com>, "admin@vaxconsult.com" <admin@vaxconsult.com>
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4650 Wismer Road
Doylestown, PA 18902
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From: Neal Halsey
Sent: 27 Jul 2019 16:35:43 +0000
To: Admin;offit@email.chop.edu;Destefano, Frank (CDC/DDID/NCEZID/DHQP);heidi.larson@lshtm.ac.uk;nkarora@incentrust.org;Zuber, Patrick (CDC who.int);fombonne@ohsu.edu;Sejvar, James (CDC/DDID/NCEZID/DHCPP);'Paul Henri Lambert';All@ssi.dk;nhalsey@jhsph.edu;nathalie.garcon@bioaster.org;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com
Subject: Re: 2nd Draft - Summary of London Meeting
Attachments: Salmon GBS 2013.pdf

I forgot to include the (b)(5)

(b)(5)

Neal

From: Neal Halsey <nhalsey1@jhu.edu>
Date: Saturday, July 27, 2019 at 12:03 PM
To: Admin <admin@vaxconsult.com>, Paul Offit <offit@email.chop.edu>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>, "heidi.larson@lshtm.ac.uk" <heidi.larson@lshtm.ac.uk>, "nkarora@incentrust.org" <nkarora@incentrust.org>, Patrick Zuber <zuberp@who.int>, "fombonne@ohsu.edu" <fombonne@ohsu.edu>, James Sejvar <zea3@cdc.gov>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, "All@ssi.dk" <All@ssi.dk>, JPIDS JPIDS <nhalsey@jhsph.edu>, "nathalie.garcon@bioaster.org" <nathalie.garcon@bioaster.org>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, "andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>, Lauri Markowitz <lem2@cdc.gov>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>
Cc: Stan Plotkin <stanley.plotkin@vaxconsult.com>
Subject: Re: 2nd Draft - Summary of London Meeting

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"jason.m.glanz@kp.org" <jason.m.glanz@kp.org>

Cc: Stan Plotkin <stanley.plotkin@vaxconsult.com>, "admin@vaxconsult.com" <admin@vaxconsult.com>

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Stanley

Wendy D'Arcy

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4650 Wismer Road
Doylestown, PA 18902
215-297-9321

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From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD)
Sent: 28 Jul 2019 21:34:13 +0000
To: Neal Halsey;Admin;offit@email.chop.edu;Destefano, Frank (CDC/DDID/NCEZID/DHQP);heidi.larson@lshtm.ac.uk;nkarora@incentrust.org;Zuber, Patrick (CDC who.int);fombonne@ohsu.edu;Sejvar, James (CDC/DDID/NCEZID/DHCPP);'Paul Henri Lambert';All@ssi.dk;nhalsey@jhsph.edu;nathalie.garcon@bioaster.org;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com
Subject: RE: 2nd Draft - Summary of London Meeting

I edited the HPV section and updated/corrected reference placement and other text. This will show up in next version distributed.

Lauri

From: Neal Halsey <nhalsey1@jhu.edu>
Sent: Saturday, July 27, 2019 12:36 PM
To: Admin <admin@vaxconsult.com>; offit@email.chop.edu; Destefano, Frank (CDC/DDID/NCEZID/DHQP) <fxd1@cdc.gov>; heidi.larson@lshtm.ac.uk; nkarora@incentrust.org; Zuber, Patrick (CDC who.int) <zuberp@who.int>; fombonne@ohsu.edu; Sejvar, James (CDC/DDID/NCEZID/DHCPP) <zea3@cdc.gov>; 'Paul Henri Lambert' <Paul.Lambert@unige.ch>; All@ssi.dk; nhalsey@jhsph.edu; nathalie.garcon@bioaster.org; Peden, Keith (FDA/CBER) <Keith.Peden@fda.hhs.gov>; andrew.pollard@paediatrics.ox.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) <lem2@cdc.gov>; jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com
Subject: Re: 2nd Draft - Summary of London Meeting

I forgot to include the (b)(5)

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Neal

From: Neal Halsey <nhalsey1@jhu.edu>
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To: Admin <admin@vaxconsult.com>, Paul Offit <offit@email.chop.edu>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>, "heidi.larson@lshtm.ac.uk" <heidi.larson@lshtm.ac.uk>, "nkarora@incentrust.org" <nkarora@incentrust.org>, Patrick Zuber <zuberp@who.int>, "fombonne@ohsu.edu" <fombonne@ohsu.edu>, James Sejvar <zea3@cdc.gov>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, "All@ssi.dk" <All@ssi.dk>, JPIDS JPIDS <nhalsey@jhsph.edu>, "nathalie.garcon@bioaster.org" <nathalie.garcon@bioaster.org>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, "andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>, Lauri Markowitz <lem2@cdc.gov>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>
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To: Paul Offit <offit@email.chop.edu>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>, "heidi.larson@lshtm.ac.uk" <heidi.larson@lshtm.ac.uk>, "nkarora@inclentrust.org" <nkarora@inclentrust.org>, Patrick Zuber <zuberp@who.int>, "fombonne@ohsu.edu" <fombonne@ohsu.edu>, James Sejvar <zea3@cdc.gov>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, "All@ssi.dk" <All@ssi.dk>, JPIDS JPIDS <nhalsey@jhsph.edu>, "nathalie.garcon@bioaster.org" <nathalie.garcon@bioaster.org>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, "andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>, Lauri Markowitz <lem2@cdc.gov>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>
Cc: Stan Plotkin <stanley.plotkin@vaxconsult.com>, "admin@vaxconsult.com" <admin@vaxconsult.com>
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Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Stanley Plotkin
Sent: 13 Jun 2019 09:01:15 -0400
To: 'Anders Peter Hviid'; 'Jason M Glanz'; 'Robert Chen'; 'Neal Halsey'
Cc: philippe.duclos@k-net.fr; 'Edwards, Kathryn'; nkarora@incentrust.org; 'Heidi Larson'; jim.buttery@monash.edu; 'Daniel Salmon'; 'Sturkenboom, M.C.J.'; 'Heininger, Ulrich'; 'Admin'; Destefano, Frank (CDC/DDID/NCEZID/DHQP); fombonne@ohsu.edu; 'GARCON Nathalie'; 'Paul Henri Lambert'; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); 'Andrew Pollard'; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); 'Ulrich Heininger'; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; 'Amy Pisani'
Subject: RE: A couple of ideas

Dear Anders:

Very interesting. Do you have ideas as to what additional reactions you would study?

Stanley

From: Anders Peter Hviid [mailto:API@ssi.dk]
Sent: Thursday, June 13, 2019 6:00 AM
To: Jason M Glanz; Robert Chen; Neal Halsey
Cc: philippe.duclos@k-net.fr; Edwards, Kathryn; nkarora@incentrust.org; Heidi Larson; jim.buttery@monash.edu; Daniel Salmon; Sturkenboom, M.C.J.; Heininger, Ulrich; Admin; fxd1@cdc.gov; fombonne@ohsu.edu; GARCON Nathalie; Paul Henri Lambert; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); Ulrich Heininger; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani; Stanley Plotkin
Subject: SV: A couple of ideas

Dear all,

(b)(5)

Sincerely,

Anders

Fra: Jason M Glanz [mailto:Jason.M.Glanz@kp.org]
Sendt: 12. juni 2019 17:07
Til: (b)(6); Neal Halsey <nhalsey1@jhu.edu>
Cc: philippe.duclos@k-net.fr; Edwards, Kathryn <kathryn.edwards@vumc.org>;

nkarora@incitrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; fombonne@ohsu.edu; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; Anders Peter Hviid <All@ssi.dk>; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsp.edu; priya.bahri@ema.europa.eu; (b)(6)
bodenstabh@email.chop.edu; (b)(6) Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Emne: RE: A couple of ideas

Hello,

Sorry to be late on this...I was out all last week. I too was honored to take part in the meeting in London.

I strongly support Dan's suggestion (b)(5)

(b)(5)

(b)(5)

Best,
Jason

From: (b)(6)
Sent: Sunday, June 9, 2019 2:48 PM
To: Neal Halsey <nhalsey1@jhu.edu>

Cc: philippe.duclos@k-net.fr; Edwards, Kathryn <kathryn.edwards@vumc.org>; nkarora@incitrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; fombonne@ohsu.edu; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; Jason M Glanz <Jason.M.Glanz@kp.org>; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov;

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priya.bahri@ema.europa.eu; (b)(6) bodenstabh@email.chop.edu;
(b)(6) Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu;
liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; Stanley Plotkin
<stanley.plotkin@vaxconsult.com>

Subject: Re: A couple of ideas

Caution: This email came from outside Kaiser Permanente. Do not open attachments or click on links if you do not recognize the sender.

Dear all,

Thanks to Stan and other organizers for bringing us together. Apologies for late input but wanted to reflect a bit before I shared my general and specific comments/suggestions (apologies if repetitive and if general, beyond scope for some attendees).

(b)(5)

(b)(5)

(b)(5)

Robert (Bob) Chen

(b)(6)

On Thu, Jun 6, 2019 at 9:16 AM Neal Halsey <nhalsey1@jhu.edu> wrote:

Attached, please find Philippe's presentation as per my email below.
Neal

From: Philippe Duclos <philippe.duclos@k-net.fr>

Date: Thursday, June 6, 2019 at 9:13 AM

To: Neal Halsey <nhalsey1@jhu.edu>, "Edwards, Kathryn" <kathryn.edwards@vumc.org>,

"nkarora@incentrust.org" <nkarora@incentrust.org>, 'Heidi Larson' <Heidi.Larson@lshtm.ac.uk>

Cc: "jim.buttery@monash.edu" <jim.buttery@monash.edu>, Daniel Salmon <dsalmon1@jhu.edu>, "'Sturkenboom, M.C.J.'" <M.C.J.Sturkenboom@umcutrecht.nl>, "'Heininger, Ulrich'" <ulrich.heininger@ukbb.ch>, 'Admin' <admin@vaxconsult.com>, 'DeStefano, Frank (NIP)' <fxd1@cdc.gov>, 'Eric Fombonne' <fombonne@ohsu.edu>, 'GARCON Nathalie' <Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, "All@ssi.dk" <All@ssi.dk>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, 'Andrew Pollard' <andrew.pollard@paediatrics.ox.ac.uk>, James Sejvar <zea3@cdc.gov>, JPIDS JPIDS <nhalsey@jhsph.edu>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, (b)(6)

(b)(6) "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, (b)(6) 'Ulrich Heininger' <ulrich.heininger@unibas.ch>, "hotez@bcm.edu" <hotez@bcm.edu>, "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, 'Amy Pisani' <amyp@ecbt.org>, (b)(6), Stan Plotkin <stanley.plotkin@vaxconsult.com>

Subject: RE: A couple of ideas

Dear Neal,

Of course please feel free to share my ADVAC safety presentation as you wish.

With kind regards,

Phil

De : Neal Halsey <nhalsey1@jhu.edu>

Envoyé : jeudi 6 juin 2019 14:59

À : Edwards, Kathryn <kathryn.edwards@vumc.org>; nkarora@incentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; Philippe Duclos <philippe.duclos@k-net.fr>

Cc : jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6) bodenstabh@email.chop.edu;

(b)(6) Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>;

(b)(6) Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Objet : Re: A couple of ideas

All of the ideas that have been proposed so far are worthwhile. I would like to reiterate the suggestion I made at the meeting. (b)(5)

(b)(5)

Neal

From: "Edwards, Kathryn" <kathryn.edwards@vumc.org>
Date: Thursday, June 6, 2019 at 7:22 AM
To: "nkarora@incentrust.org" <nkarora@incentrust.org>, Heidi Larson <Heidi.Larson@lshtm.ac.uk>
Cc: "jim.buttery@monash.edu" <jim.buttery@monash.edu>, Daniel Salmon <dsalmon1@jhu.edu>, "Sturkenboom, M.C.J." <M.C.J.Sturkenboom@umcutrecht.nl>, "Heininger, Ulrich" <ulrich.heininger@ukbb.ch>, Admin <admin@vaxconsult.com>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>, Eric Fombonne <fombonne@ohsu.edu>, GARCON Nathalie <Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, "All@ssi.dk" <All@ssi.dk>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>, James Sejvar <zea3@cdc.gov>, JPIDS JPIDS <nhalsey@jhsph.edu>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, (b)(6)
(b)(6) "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu> (b)(6) Ulrich Heininger <ulrich.heininger@unibas.ch>, "hotez@bcm.edu" <hotez@bcm.edu>, "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, Amy Pisani <amyp@ecbt.org>, (b)(6) Stan Plotkin <stanley.plotkin@vaxconsult.com>
Subject: RE: A couple of ideas

This is the letter that was recently published in CID and mentioned at the meeting on MHTFR.

From: Edwards, Kathryn
Sent: Thursday, June 6, 2019 5:57 AM
To: nkarora@incentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>
Cc: jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON

Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert
<Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov;
Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu;
priya.bahri@ema.europa.eu; (b)(6) bodenstabh@email.chop.edu;
(b)(6) Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu;
liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>;
(b)(6) Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Subject: RE: A couple of ideas

I was honored to participate in the Vaccine Safety Science meeting last week in London. The quality of the presentations, the subsequent discussions, and the email chains have been very stimulating. I would like to add a few perspectives and make several additional suggestions for studies to conduct. I will also comment on the suggestions of others.

(b)(5)

(b)(5)

Thanks again for a great meeting and I hope that the dialogue will continue.

Kathryn M. Edwards MD
Sarah Sell and Cornelius Vanderbilt Chair
Professor of Pediatrics
Vanderbilt University Medical Center

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5 Artillerivej | DK-2300 Copenhagen S | T +45 3268 3268 | F +45 3268 3868 | E serum@ssi.dk |
W ssi.dk

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From: Narendra Kumar Arora INCLEN
Sent: 6 Jun 2019 14:59:17 +0530
To: Heidi Larson
Cc: jim.buttery@monash.edu; Daniel Salmon; Sturkenboom, M.C.J.; Heininger, Ulrich; Admin; nkarora@inclentrust.org; Destefano, Frank (CDC/DDID/NCEZID/DHQP); Eric Fombonne; GARCON Nathalie; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); Andrew Pollard; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsph.edu; priya.bahri@ema.europa.eu (b)(6)
(b)(6) bodenstabh@email.chop.edu; (b)(6) Edwards, Kathryn; Ulrich Heininger; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani (b)(6) Stanley Plotkin
Subject: Re: A couple of ideas

Dear All
I strongly endorse prioritization of research questions.

(b)(5)

Warm wishes
Narendra Arora

On Thu, Jun 6, 2019 at 7:16 AM Heidi Larson <Heidi.Larson@lshtm.ac.uk> wrote:

Dear all,

I fully support Dan's points based on the questions and concerns we are hearing the most frequently, and particularly need for more research (and a summary of what research we do have) on the issue of vaccine ingredients.

Best, Heidi

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From: jim.buttery@monash.edu <jim.buttery@monash.edu>
Sent: Thursday, June 6, 2019 10:02:00 AM
To: 'Daniel Salmon'; 'Sturkenboom, M.C.J.'; 'Heininger, Ulrich'; 'Admin'
Cc: nkarora@inclentrust.org; fxdl@cdc.gov; 'Eric Fombonne'; 'GARCON Nathalie'; jason.m.glanz@kp.org; All@ssi.dk; 'Paul Henri Lambert'; Heidi Larson; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu (b)(6)
bodenstabh@email.chop.edu; (b)(6) 'Edwards, Kathryn'; 'Ulrich Heininger'; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; 'Amy Pisani'; (b)(6) 'Stanley Plotkin'
Subject: RE: A couple of ideas

In addition/support to what has already been discussed at the meeting or in the subsequent discussions, I would also suggest:

(b)(5)

Kind regards

Jim

From: Daniel Salmon <dsalmon1@jhu.edu>
Sent: Thursday, 6 June 2019 2:36 AM
To: Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>
Cc: nkarora@incitrust.org; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6) bodenstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6) Edwards, Kathryn <kathryn.edwards@vumc.org>; Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; (b)(6) Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Subject: Re: A couple of ideas

(b)(5)

(b)(5)

(b)(5)

From: "Sturkenboom, M.C.J." <M.C.J.Sturkenboom@umcutrecht.nl>
Date: Wednesday, June 5, 2019 at 11:39 AM
To: "Heininger, Ulrich" <ulrich.heininger@ukbb.ch>, Admin
<admin@vaxconsult.com>
Cc: "nkarora@inclentrust.org" <nkarora@inclentrust.org>, Frank Destefano
<fxdl@cdc.gov>, Eric Fombonne <fombonne@ohsu.edu>, GARCON Nathalie
<Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org"
<jason.m.glanz@kp.org>, "AII@ssi.dk" <AII@ssi.dk>, Paul Henri Lambert
<Paul.Lambert@unige.ch>, Heidi Larson <Heidi.Larson@lshtm.ac.uk>,
"lem2@cdc.gov" <lem2@cdc.gov>, "offit@email.chop.edu"
<offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>,
"andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>,
"zea3@cdc.gov" <zea3@cdc.gov>, 'Neal Halsey' <nhalsey@jhsp.edu>,
"priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>,
(b)(6) (b)(6) "bodenstabh@email.chop.edu"
<bodenstabh@email.chop.edu>, "jim.buttery@monash.edu"
<jim.buttery@monash.edu>, (b)(6) <alexooo@yahoo.com>,
"Edwards, Kathryn" <kathryn.edwards@vumc.org>, Ulrich Heininger
<ulrich.heininger@unibas.ch>, "hotez@bcm.edu" <hotez@bcm.edu>,
"liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-
harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, Amy Pisani
<amyp@ecbt.org>, Daniel Salmon <dsalmon1@jhu.edu>, (b)(6)
(b)(6) >, Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Subject: RE: A couple of ideas

Hi Ulli/Eric

(b)(5)

Best wishes, Miriam

From: Heininger, Ulrich [ulrich.heininger@ukbb.ch]

Sent: Tuesday, June 04, 2019 7:04 AM

To: Admin

Cc: nkarora@incitrust.org; fxd1@cdc.gov; Eric Fombonne; GARCON Nathalie; jason.m.glanz@kp.org; AI@ssi.dk; Paul Henri Lambert; Heidi Larson; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6); Edwards, Kathryn; Ulrich Heininger; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani; dsalmon1@jhu.edu; Sturkenboom, M.C.J.; (b)(6); Stanley Plotkin

Subject: Re: A couple of ideas

Dear Eric and colleagues

(b)(5)

Best regards

Uli

Am 03.06.2019 um 17:01 schrieb Admin <admin@vaxconsult.com>:

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin

4650 Wismer Road

Doylestown, PA 18902

215-297-9321

From: Eric Fombonne [<mailto:fombonne@ohsu.edu>]
Sent: Friday, May 31, 2019 1:57 PM
To: fxd1@cdc.gov; nhalsey1@jhu.edu; lem2@cdc.gov; offitt@email.chop.edu;
'Stanley Plotkin'
Subject: A couple of ideas

Hello,

I had these 2 ideas this afternoon. I am out of my league here, so I am unsure about their relevance.

(b)(5)



(b)(5)



Thank you for an interesting meeting.

Regards,

Eric

De informatie opgenomen in dit bericht kan vertrouwelijk zijn en is uitsluitend bestemd voor de geadresseerde. Indien u dit bericht onterecht ontvangt, wordt u verzocht de inhoud niet te gebruiken en de afzender direct te informeren door het bericht te retourneren. Het Universitair Medisch Centrum Utrecht is een publiekrechtelijke rechtspersoon in de zin van de W.H.W. (Wet Hoger Onderwijs en Wetenschappelijk Onderzoek) en staat geregistreerd bij de Kamer van Koophandel voor Midden-Nederland onder nr. 30244197.

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Narendra K. Arora
Executive Director
The INCLEN Trust International
F-1/5 Second Floor
Okhla Industrial Area Phase I
New Delhi - 110020, India
Tel no. +91-11-47730000 Fax: +91-11-47730001

From: Heidi Larson
Sent: 6 Jun 2019 01:46:07 +0000
To: jim.buttery@monash.edu; 'Daniel Salmon'; 'Sturkenboom, M.C.J.'; 'Heininger, Ulrich'; 'Admin'
Cc: nkarora@incentrust.org; Destefano, Frank (CDC/DDID/NCEZID/DHQP); 'Eric Fombonne'; 'GARCON Nathalie'; jason.m.glanz@kp.org; All@ssi.dk; 'Paul Henri Lambert'; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); Andrew Pollard; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsp.h.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); Edwards, Kathryn'; 'Ulrich Heininger'; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; 'Amy Pisani'; (b)(6); 'Stanley Plotkin'
Subject: Re: A couple of ideas

Dear all,
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Best, Heidi

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To: 'Daniel Salmon'; 'Sturkenboom, M.C.J.'; 'Heininger, Ulrich'; 'Admin'
Cc: nkarora@incentrust.org; fxd1@cdc.gov; 'Eric Fombonne'; 'GARCON Nathalie'; jason.m.glanz@kp.org; All@ssi.dk; 'Paul Henri Lambert'; Heidi Larson; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard; zea3@cdc.gov; nhalsey@jhsp.h.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); 'Edwards, Kathryn'; 'Ulrich Heininger'; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; 'Amy Pisani'; (b)(6); 'Stanley Plotkin'
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(b)(5)

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Subject: Re: A couple of ideas

(b)(5)

(b)(5)

(b)(5)

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(b)(6) "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, "jim.buttery@monash.edu" <jim.buttery@monash.edu>, (b)(6)
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Subject: Re: A couple of ideas

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Uli

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FYI

Wendy D'Arcy

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From: jim.buttery@monash.edu
Sent: 6 Jun 2019 11:02:00 +1000
To: 'Daniel Salmon'; 'Sturkenboom, M.C.J.'; 'Heininger, Ulrich'; 'Admin'
Cc: nkarora@incentrust.org; Destefano, Frank (CDC/DDID/NCEZID/DHQP); 'Eric Fombonne'; 'GARCON Nathalie'; jason.m.glanz@kp.org; All@ssi.dk; 'Paul Henri Lambert'; 'Heidi Larson'; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); 'Edwards, Kathryn'; 'Ulrich Heininger'; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; 'Amy Pisani'; (b)(6); 'Stanley Plotkin'
Subject: RE: A couple of ideas

In addition/support to what has already been discussed at the meeting or in the subsequent discussions, I would also suggest:

(b)(5)

Kind regards
Jim

From: Daniel Salmon <dsalmon1@jhu.edu>
Sent: Thursday, 6 June 2019 2:36 AM
To: Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>
Cc: nkarora@incentrust.org; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6); Edwards, Kathryn <kathryn.edwards@vumc.org>; Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; (b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Subject: Re: A couple of ideas

(b)(5)

(b)(5)

From: "Sturkenboom, M.C.J." <M.C.J.Sturkenboom@umcutrecht.nl>
Date: Wednesday, June 5, 2019 at 11:39 AM
To: "Heininger, Ulrich" <ulrich.heininger@ukbb.ch>, Admin <admin@vaxconsult.com>
Cc: "nkarora@inclentrust.org" <nkarora@inclentrust.org>, Frank Destefano <fxdl@cdc.gov>, Eric Fombonne <fombonne@ohsu.edu>, GARCON Nathalie

<Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, "AII@ssi.dk" <AII@ssi.dk>, Paul Henri Lambert <Paul.Lambert@unige.ch>, Heidi Larson <Heidi.Larson@lshtm.ac.uk>, "lem2@cdc.gov" <lem2@cdc.gov>, "offit@email.chop.edu" <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, "andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>, "zea3@cdc.gov" <zea3@cdc.gov>, 'Neal Halsey' <nhalsey@jhsph.edu>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, (b)(6) "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, "jim.buttery@monash.edu" <jim.buttery@monash.edu>, (b)(6) (b)(6), "Edwards, Kathryn" <kathryn.edwards@vumc.org>, Ulrich Heininger <ulrich.heininger@unibas.ch>, "hotez@bcm.edu" <hotez@bcm.edu>, "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, Amy Pisani <amyp@ecbt.org>, Daniel Salmon <dsalmon1@jhu.edu>, (b)(6) (b)(6) Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Subject: RE: A couple of ideas

Hi Ulli/Eric

(b)(5)

From: Heininger, Ulrich [ulrich.heininger@ukbb.ch]

Sent: Tuesday, June 04, 2019 7:04 AM

To: Admin

Cc: nkarora@incentrust.org; fxd1@cdc.gov; Eric Fombonne; GARCON Nathalie; jason.m.glanz@kp.org; AII@ssi.dk; Paul Henri Lambert; Heidi Larson; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6); Edwards, Kathryn; Ulrich Heininger; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani; dsalmon1@jhu.edu; Sturkenboom, M.C.J.; (b)(6); Stanley Plotkin

Subject: Re: A couple of ideas

Dear Eric and colleagues

(b)(5)

Best regards

Uli

Am 03.06.2019 um 17:01 schrieb Admin <admin@vaxconsult.com>:

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Eric Fombonne [<mailto:fombonne@ohsu.edu>]

Sent: Friday, May 31, 2019 1:57 PM

To: fxd1@cdc.gov; nhalsey1@jhu.edu; lem2@cdc.gov; offitt@email.chop.edu; 'Stanley Plotkin'

Subject: A couple of ideas

Hello,

(b)(5)



Thank you for an interesting meeting.

Regards,

Eric

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From: Daniel Salmon
Sent: 5 Jun 2019 16:36:01 +0000
To: Sturkenboom, M.C.J.;Heininger, Ulrich;Admin
Cc: nkarora@inclentrust.org;Destefano, Frank (CDC/DDID/NCEZID/DHQP);Eric Fombonne;GARCON Nathalie;jason.m.glanz@kp.org;All@ssi.dk;Paul Henri Lambert;Heidi Larson;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsp.h.edu;priya.bahri@ema.europa.eu;(b)(6) bod enstabh@email.chop.edu;jim.buttery@monash.edu;(b)(6) Edwards, Kathryn;Ulrich Heininger;hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;Amy Pisani;(b)(6);Stanley Plotkin
Subject: Re: A couple of ideas

(b)(5)

(b)(5)

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To: "Heininger, Ulrich" <ulrich.heininger@ukbb.ch>, Admin <admin@vaxconsult.com>
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Subject: Re: A couple of ideas

Dear Eric and colleagues

(b)(5)

Am 03.06.2019 um 17:01 schrieb Admin <admin@vaxconsult.com>:

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Eric Fombonne [<mailto:fombonne@ohsu.edu>]

Sent: Friday, May 31, 2019 1:57 PM

To: fxd1@cdc.gov; nhalsey1@jhu.edu; lem2@cdc.gov; offitt@email.chop.edu; 'Stanley Plotkin'

Subject: A couple of ideas

Hello,

I had these 2 ideas this afternoon. I am out of my league here, so I am unsure about their relevance.

(b)(5)

(b)(5)

Thank you for an interesting meeting.

Regards,

Eric

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From: Paul Henri Lambert
Sent: 5 Jun 2019 16:09:15 +0000
To: Sturkenboom, M.C.J.;Heininger, Ulrich;Admin
Cc: nkarora@incentrust.org;Destefano, Frank (CDC/DDID/NCEZID/DHQP);Eric Fombonne;GARCON Nathalie;jason.m.glanz@kp.org;All@ssi.dk;Heidi Larson;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu;priya.bahri@ema.europa.eu;(b)(6);bodenstabh@email.chop.edu;jim.buttery@monash.edu;(b)(6);Edwards, Kathryn;Ulrich Heininger;hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;Amy Pisani;dsalmon1@jhu.edu;(b)(6);Stanley Plotkin
Subject: RE: A couple of ideas
Attachments: Modulation of immune functions by measles virus-Ter Meulen.pdf, Long-term measles-induced immunomodulation-Mina2016.pdf

Dear all,
I attach the Mina paper as well as the older ter Meulen analysis on this topic
Best regards

Paul-Henri

De : Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>
Envoyé : mercredi, 5 juin 2019 17:37
À : Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>
Cc : nkarora@incentrust.org; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6); Edwards, Kathryn <kathryn.edwards@vumc.org>; Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; dsalmon1@jhu.edu;(b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Objet : RE: A couple of ideas

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Published in final edited form as:

Science. 2015 May 8; 348(6235): 694–699. doi:10.1126/science.aaa3662.

Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality

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¹Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ, USA

²Medical Scientist Training Program, School of Medicine, Emory University, Atlanta, GA, USA

³Fogarty International Center, National Institutes of Health, Bethesda, MD, USA ⁴Department of Viroscience, Erasmus University Medical Center, Rotterdam, Netherlands

Abstract

Immunosuppression after measles is known to predispose people to opportunistic infections for a period of several weeks to months. Using population-level data, we show that measles has a more prolonged effect on host resistance, extending over 2 to 3 years. We find that nonmeasles infectious disease mortality in high-income countries is tightly coupled to measles incidence at this lag, in both the pre- and post-vaccine eras. We conclude that long-term immunologic sequelae of measles drive interannual fluctuations in nonmeasles deaths. This is consistent with recent experimental work that attributes the immunosuppressive effects of measles to depletion of B and T lymphocytes. Our data provide an explanation for the long-term benefits of measles vaccination in preventing all-cause infectious disease. By preventing measles-associated immune memory loss, vaccination protects polymicrobial herd immunity.

Measles vaccines were introduced 50 years ago and were followed by striking reductions in child morbidity and mortality (1, 2). Measles control is now recognized as one of the most successful public health interventions ever undertaken (3). Despite this, in many countries vaccination targets remain unmet, and measles continues to take hundreds of thousands of lives each year (3). Even where control has been successful, vaccine hesitancy threatens the gains that have been made (1, 4). The introduction of mass measles vaccination has reduced childhood mortality by 30 to 50% in resource-poor countries (5–8) and by up to 90% in the most impoverished populations (9, 10). The observed benefits cannot be explained by the prevention of primary measles virus (MV) infections alone (11, 12), and they remain a central mystery (13).

*Corresponding author: michael.j.mina@gmail.com.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/348/6235/694/suppl/DC1

Materials and Methods

Supplementary Text

Figs. S1 to S13

Table S1

References (41–43)

Movies S1 to S3

MV infection is typified by a profound, but generally assumed to be transient, immunosuppression that renders hosts more susceptible to other pathogens (14–17). Thus, contemporaneous reductions in nonmeasles mortality after vaccination are expected. However, reductions in infectious disease mortality after measles vaccination can last throughout the first 5 years of life (5–10), which is much longer than anticipated by transient immunosuppression, which is generally considered to last for weeks to months (16, 17).

Proposed mechanisms for a nonspecific beneficial effect of measles vaccination range from suggestions that live vaccines may directly stimulate cross-reactive T cell responses or that they may train innate immunity to take on memory-like phenotypes (13, 18–21). Although well described by Aaby (11, 12) and others (22) in observational studies, primarily in low-resource settings, these effects may not fully explain the long-term benefits observed with measles vaccination and cannot explain the pre-vaccination associations of measles and infectious disease mortality we describe below. The World Health Organization (WHO) recently addressed this issue (22) and concluded that measles vaccination is associated with large reductions in all-cause childhood mortality but that there is no firm evidence to explain an immunological mechanism for the nonspecific vaccine benefits.

Recent work (17, 23) invoked a different hypothesis that a loss of immune memory cells after MV infection resets previously acquired immunity, and vaccination prevents this effect. de Vries *et al.* (17) reproduced transient measles immune suppression in macaques, characterized by systemic depletion of lymphocytes and reduced innate immune cell proliferation (24). Although peripheral blood lymphocyte counts were restored within weeks as expected (25), the authors hypothesized that rapid expansions of predominantly measles-specific B and T lymphocytes masked an ablated memory-cell population (17). In other words, MV infection replaced the previous memory cell repertoire with MV-specific lymphocytes, resulting in “immune amnesia” (17) to nonmeasles pathogens. Previous investigations of virus-induced memory-cell depletion suggest that recovery requires re-stimulation, either directly or via cross-reactive antigens (26–29).

We propose that, if loss of acquired immunological memory after measles exists, the resulting impaired host resistance should be detectable in the epidemiological data collected during periods when measles was common and [in contrast to previous investigations that focus on low-resource settings (5–12)] should be apparent in high-resource settings where mortality from opportunistic infections during acute measles immune suppression was low. Relatively few countries report the necessary parallel measles and mortality time series to test this hypothesis. National-level data from England, Wales, the United States, and Denmark [Fig. 1, A to C; see supplementary materials (SM) 1 for details], spanning the decades surrounding the introduction of mass measles vaccination campaigns, meet our data criteria.

To assess the underlying immunological hypothesis (Fig. 1D) using population-level data, we required that first, nonmeasles mortality should be correlated with measles incidence data, especially because the onset of vaccination reduces the latter. Second, an immune memory loss mechanism should present as a strengthening of this association when measles incidence data are transformed to reflect an accumulation of previous measles cases (a

measles “shadow”). For example, if immune memory loss (or more broadly, immunomodulation) lasts 3 years, the total number of immunomodulated individuals (S) in the n th quarter can be calculated as the sum of the measles cases (M) over the previous (and current) 12 quarters: $S_n = M_{n-11} + M_{n-10} + \dots + M_{n-1} + M_n$. In practice, we weighted the quarters using a gamma function. Dividing S by the total population of interest thus provides the prevalence of immunomodulation (see SM 2, and 3; fig. S1, A to C; and movie S1 for detailed methods). Third, the strength of this association should be greatest when the mean duration over which the cases are accumulated matches the mean duration required to restore immunological memory after MV infection. Fourth, the estimated duration should be consistent both with the available evidence of increased risk of mortality after MV, compared with uninfected children, and with the time required to build a protective immune repertoire in early life (Fig. 1D, fig. S2, and SM 5 and 6).

To explicitly address whether the observed nonspecific benefits of vaccination can be attributed to the prevention of MV immunomodulation, evidence for the four hypotheses must be present separately within the pre-vaccine eras.

Reductions in nonmeasles infectious disease mortality (SM 1) are shown in Fig. 1, for children aged 1 to 9 years in Europe and aged 1 to 14 years in the United States, shortly after the onset of mass vaccination in each country. The fall in mortality was later in Denmark, corresponding to the introduction of measles vaccination in the 1980s, as compared to the late 1960s for the United Kingdom and United States. In all locations, measles incidence showed significant ($P < 0.001$) associations with mortality (Fig. 1, E to G). However, effect sizes varied (fig. S3A), reflecting low reporting in the United States [fig. S3B and (30)] and changes in health care practice between eras. Adjusting for year as a covariate (SM 4) had little effect on the point estimates (fig. S3C). These associations could reflect transient measles immune suppression. Thus, to address our second hypothesis that MV immunomodulation can explain long-term increased mortality and, consequently, improved survival after vaccination, we transformed measles incidence into population prevalence of MV immunomodulation, with the duration of the immunomodulation (the time required to rebuild sufficiently protective immune memory) defined by a gamma distribution to weight the previous time points summed together, as discussed above and in SM 2 and movie S1.

When the gamma-distributed transformation was applied to the England and Wales measles data, the best-fit duration of MV immunomodulation, as determined by the linear fit of the corresponding prevalence of MV immunomodulation to the mortality data (SM 3), centered at a 28.3-month duration of measles-induced immunomodulation. This corresponded to a strong and significantly improved association between measles and all-cause infectious disease mortality [coefficient of determination (R^2) = 0.92 versus 0.37; $P < 0.00001$; Fig. 2, A to C]. Simpler additive transformations (SM 2 and movie S1) return the same qualitative pattern (Fig. 2D), and adjusting for year in the model had no effect (fig. S4). Figure 2, E and F, shows the time series for the actual and predicted mortalities (calculated from the linear fits), together with the prevalence of MV immunomodulation (see movie S2 for the full paths of these transformations). Overall, a simple weighted integral of measles incidence captures the nonmeasles mortality data remarkably well and more closely than the raw incidence.

To evaluate our fourth hypothesis, we compared the best-fit gamma distribution (indicating average time to return of full immunity) to (i) the previously observed (31) duration of elevated relative risk (RR) of all-cause mortality after intensive measles exposure (albeit in children exposed before 6 months of age) and (ii) to the global age distribution (fig. S2) of bacterial invasive disease in children under 5 years of age [an estimate for the time required to build protective immunity (32)]. Both the elevated RR of mortality after measles exposure and declines from peak rates of bacterial disease, indicating the development of sufficiently protective immunity, fell precisely along the gamma curve ($R^2 = 0.97$ and 0.99 , respectively; Fig. 2G).

We tested these results for nonspecific effects of vaccination (11) by applying the same procedures to the pre-vaccination data alone. Before vaccination, the best-fit duration of MV immunomodulation was no different (centered at 28.0 versus 28.3 months; Fig. 2, B to D, and fig. S5A) and closely matched the duration identified in the post-vaccine era as well (29.2 months; fig. S5A). Moreover, the coefficients describing the slope of mortality rate versus prevalence of immunomodulation were nearly identical (Fig. 2, B and I, and fig. S5B). This effect held regardless of which era's respective best-fit gamma transform was used (fig. S5, B to D), because optimizing the transformation using only the pre-vaccine data permitted accurate prediction of the post-vaccine era data that was not used to fit the model (known as out-of-sample prediction). The results are robust to the chosen focal age groups (1 to 4 and 5 to 9 years old age groups shown in fig. S6) and are sensitive to the specific order and magnitude of the measles epidemics, because randomizing the time series by year erased the above effects (fig. S7).

Furthermore, results were robust to individual disease classes (table S1), with best-fit durations of immunomodulation predisposing to individual classes of infectious disease mortality lasting between 18 and 30 months (mean, 27 months; median, 24 months). Exceptions were rubella [although rubella was not included in the primary analysis (SM 1)] and septicemia, which had best-fit durations of immune memory loss of approximately 12 and 3 months, respectively.

Many previous investigations described stronger nonspecific benefits of MV vaccination in females than males (7, 11, 13); thus, as an additional test of our hypotheses, we also compared genders. In agreement, we found consistently stronger associations among females (fig. S8). To test the England and Wales findings, we applied the full analysis to data from the United States (Fig. 3 and movie S3). Here, the optimized gamma transformation centered at 30.9 months (versus 28.3 for the United Kingdom) again greatly improved the fit of the data ($R^2 = 0.88$ versus 0.42 ; Fig. 3, A to F), showed very strong agreement with previously observed durations of mortality risk after intensive measles exposure ($R^2 = 0.999$, Fig. 3G), and was predicted by the age distribution of invasive bacterial infections in children under 5 ($R^2 = 0.921$; Fig. 3G).

We tested whether declines in mortality after vaccination were caused by nonspecific benefits of vaccination. Transformation of the data from the pre-vaccine era increased the strength of the association markedly ($R^2 = 0.87$ versus 0.07). As in the United Kingdom, very similar best-fit gamma transformations were obtained before (and after) vaccination

(centered at 30.3 and 29.2 months; Fig. 3C and fig. S9A); the coefficients of association (with mortality) across vaccine eras were again consistent (Fig. 3, B and I, and fig. S9); the results were robust across age groups (fig. S10); the strengths of association were stronger in females (fig. S11); and adjusting for year had no effect (fig. S12).

The data from Denmark (SM 1) were recorded at yearly rather than quarterly intervals and limited the scope of analyses. Furthermore, because measles vaccine introduction in Denmark in 1987 occurred as data became available and was so successful that within its first year, measles incidence was reduced by an order of magnitude (Fig. 1C), we were compelled to focus on the two decades that followed the logarithmic reduction of cases (1990–2010). Despite these limitations, transformation of the yearly data (using eqs. 3 and 8 in SM 2) led to steep peaks in model fit at 30 months duration of MV immunomodulation that predicted mortality ($R^2 = 0.77$; Fig. 4A). When we inferred quarterly incidence data from the annualized data [using monthly measles incidence data from a large population sample in Denmark (33) to estimate proportions of annual cases occurring each quarter; SM 1], the best fit indicated a 26.4-month duration of MV immunomodulation (Fig. 4, B and E), agreeing with the durations defined for England and Wales and the United States above, as well as the previously observed risk of mortality after measles (Fig. 4C).

These results provide population evidence for a generalized prolonged (roughly 2- to 3-year) impact of measles infection on subsequent mortality from other infectious diseases. Fluctuations in childhood mortality in the United Kingdom, the United States, and Denmark are explained by a simple weighted integral that describes the prevalence of measles immune memory loss and thus captures the impact of measles infection and immune depletion. We anticipate that morbidity data might show stronger effects.

As a further test of the immunosuppressive impact of measles, we carried out a similar analysis on pertussis. Pertussis is a vaccine-preventable disease that is not known to be immunosuppressive and for which high-quality weekly data (34) are available for England and Wales that were collected during the pre-measles vaccine years described above. We found no correlation (fig. S13) between pertussis incidence and non-pertussis infectious disease mortality. No correlation was observed even when the pertussis data were transformed to reflect the sum of previous pertussis cases (a pertussis “shadow”) extending over 48 months (fig. S13).

Our results show that when measles was common, MV infections could have been implicated in as many as half of all childhood deaths from infectious disease, thus accounting for nearly all of the interannual fluctuations in childhood infectious disease deaths. The reduction of MV infections was the main factor in reducing overall childhood infectious disease mortality after the introduction of vaccination.

Consistency in the best-fit duration of MV immunomodulation (the time required to restore protective immune memory) in all three countries, the close fit to observed durations of increased mortality after intensive MV exposure, and its correspondence to the early development of immunity (before 5 years of age) through exposure all provide strong evidence for a measles immune effect. The similarity in results obtained for both pre- and

post-vaccine eras, the qualitative consistency across ages, and the stronger associations in females (7) provide further support for an underlying immunomodulatory mechanism. Finally, these results are consistent with multiple immunoepidemiologic and case-controlled studies that show reduced or absent antigen-specific cellular responses lasting 3 years after measles (35, 36) and reduced atopy even 15 years after infection (37).

The correspondence between our results and previous epidemiological data by Aaby *et al.* (31) should be viewed with the caveat that the increased relative risk of mortality after intensive measles exposure was measured in children exposed before 6 months of age, not all of whom developed features of clinical measles infections. Other studies (12, 38, 39) have failed to detect long-term immunologic sequelae of measles. These previous cohort studies have focused on low-income countries, primarily in West Africa, where very high rates of death from opportunistic infections during acute measles immune suppression drive mortality dynamics and mask the pernicious long-term immunological effects of measles infection. For example, approximately 50% of all childhood deaths recorded over 5 years of follow-up occurred within only 2 months of measles infection, precluding the detection of long-term sequelae in those children.

MV infection and vaccination produce strong and durable herd immunity against subsequent epidemics (40). Our results thus suggest an extra dynamical twist: MV infections could also reduce population immunity against other infections in which MV immunomodulation could be envisioned as a measles-induced immune amnesia (17); hence, measles vaccination might also be preserving herd protection against nonmeasles infections.

Measles vaccination is one of the most cost-effective interventions for global health, and our results imply further immunological dividends: mortality (and probably morbidity) reductions linked to measles vaccination might be much greater than previously considered. This is of particular importance today where, especially in wealthy nations, reduced opportunistic infections during acute measles immunosuppression, added to the comparative rarity of infection, has led to a public view of measles as a benign childhood disease. Our findings help dispel the mystery surrounding the disproportionately large reductions in mortality seen after the introduction of measles vaccinations and reinforce the importance of measles vaccination in a global context.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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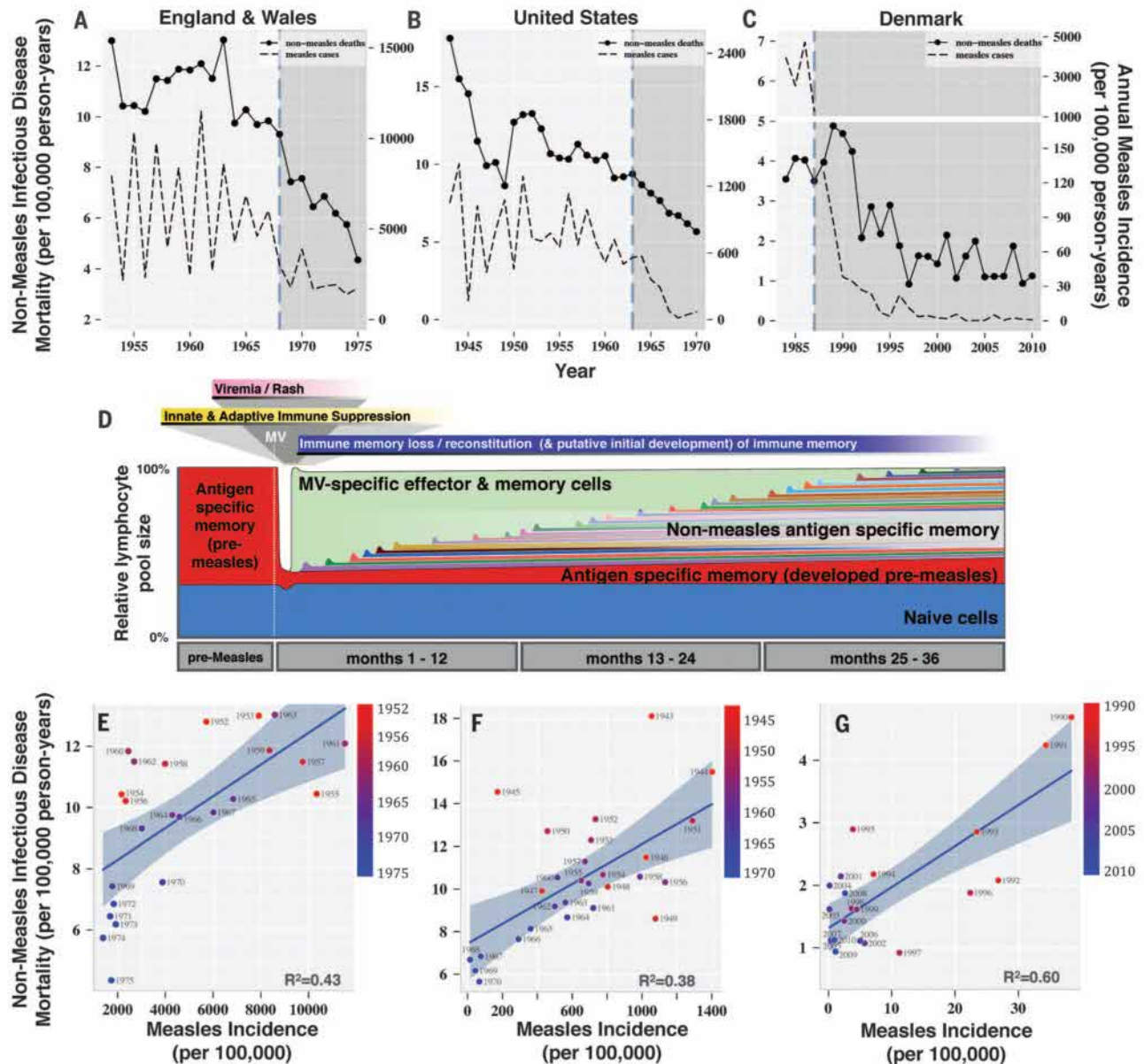


Fig. 1. Measles incidence, nonmeasles infectious disease mortality, and measles-induced immunomodulation

Nonmeasles infectious disease mortality and measles incidence time series (A to C) and regressions (E to G) are shown for England and Wales, the United States, and Denmark. The vertical dashed lines in (A) to (C) indicate the year of introduction of the measles vaccine. (D) Measles-induced lymphopenia and subsequent measles-specific lymphocyte expansion in the weeks after MV infection, as described in (17, 23), are shown, and time is extended to depict hypothesized long-term immunomodulatory effects of MV infection and reconstitution of the immune response through individual exposures. Scatter plots and best-fit regression curves (plotted with 95% confidence bands) are shown for nonmeasles infectious disease mortality versus measles incidence for England and Wales (E), the United States (F), and Denmark (G).

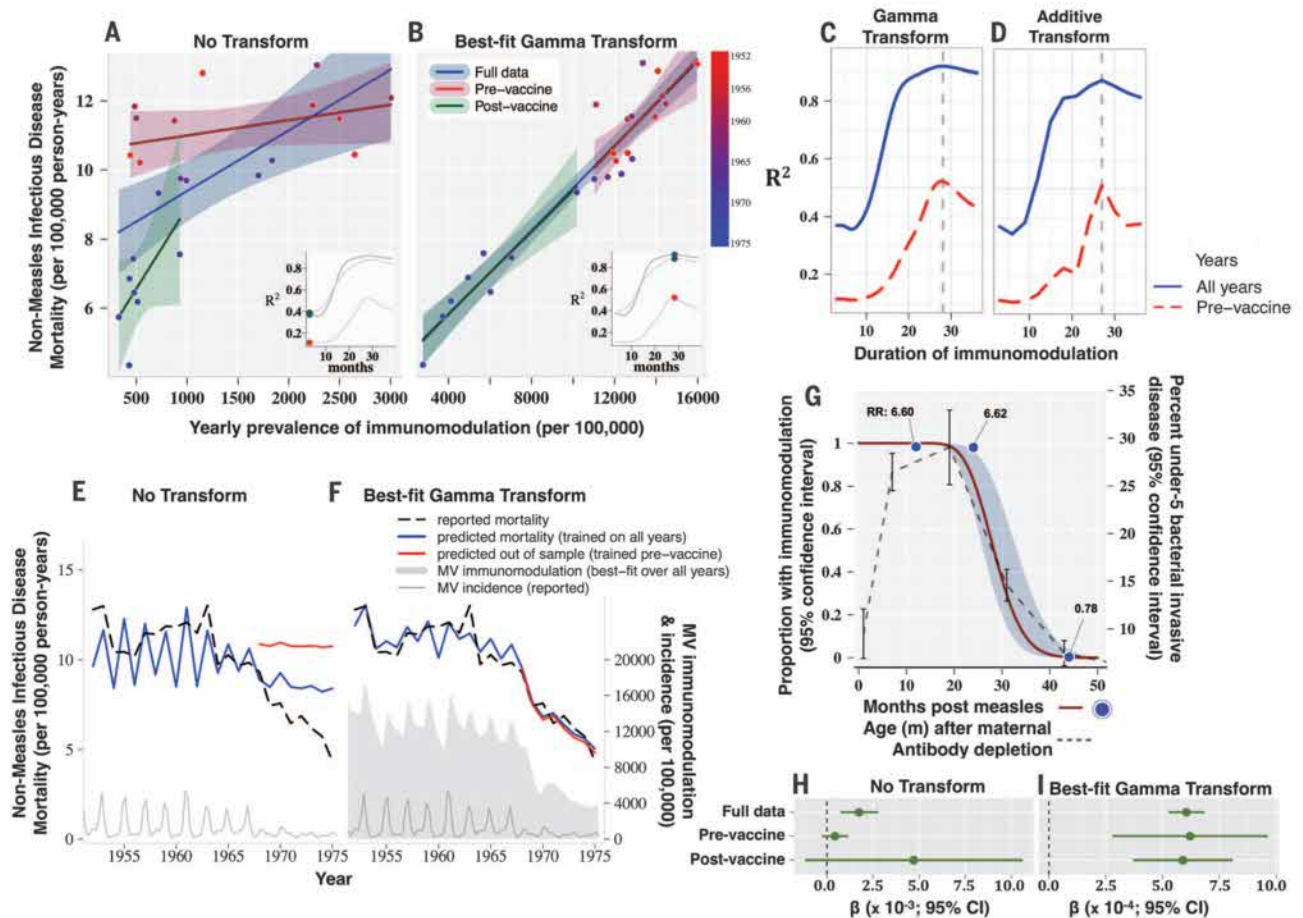


Fig. 2. England and Wales: Measles-induced immunomodulation and nonmeasles infectious disease mortality (1952–1975)

Annual incidence of nonmeasles infectious disease mortality regressed against the prevalence of MV immunomodulation, given (A) no transform or (B) the best-fit gamma transform (that provides the best linear fit, R^2 , to the data). Individual regression lines and 95% confidence intervals are plotted for regressions over the full data set (blue), the pre-vaccine era data only (green), and the post-vaccine era data only (red). R^2 is plotted against the mean duration of MV immunomodulation for the (C) gamma or (D) additive transformation for the full data set (blue lines) or the pre-vaccine data only (red lines). Inset graphs in (A) and (B) are the same as (C), and the location of the dots (color coded as per the regression lines) represent the duration of immunomodulation and the R^2 values associated with the scatter plot shown. In (E and F), the measured nonmeasles infectious disease mortality is plotted (broken line) along with the predicted annual mortalities (solid blue and red lines), predicted using the regression coefficients from the (H) untransformed or (I) best-fit transformed data. Predictions in (E) and (F) are either in sample and based on the full data set (blue line), or out of sample and based on the pre-vaccine data only (red line). In (F), for example, the in-sample mortality prediction is made from the regression coefficients (I) from the best-fit transformed data for the full data set (blue line), and mortality is also predicted entirely out of sample for the post-vaccine era by optimizing the

gamma transformation and calculating regression coefficients using only data from the pre-vaccine era (red line; fig. S5C). (G) The best-fit gamma distribution (optimized against the full data set) is shown (dark red line), along with the distribution of under-5 bacterial invasive disease versus age after the depletion of maternal antibodies (broken gray line), and the relative risk of non-MV mortality after MV infection, described in (31), is also shown plotted against time since MV infection (blue points). (H) and (I) The regression coefficients for the best-fit lines shown in (A) and (B) are plotted with 95% confidence intervals in (H) and (I), respectively.

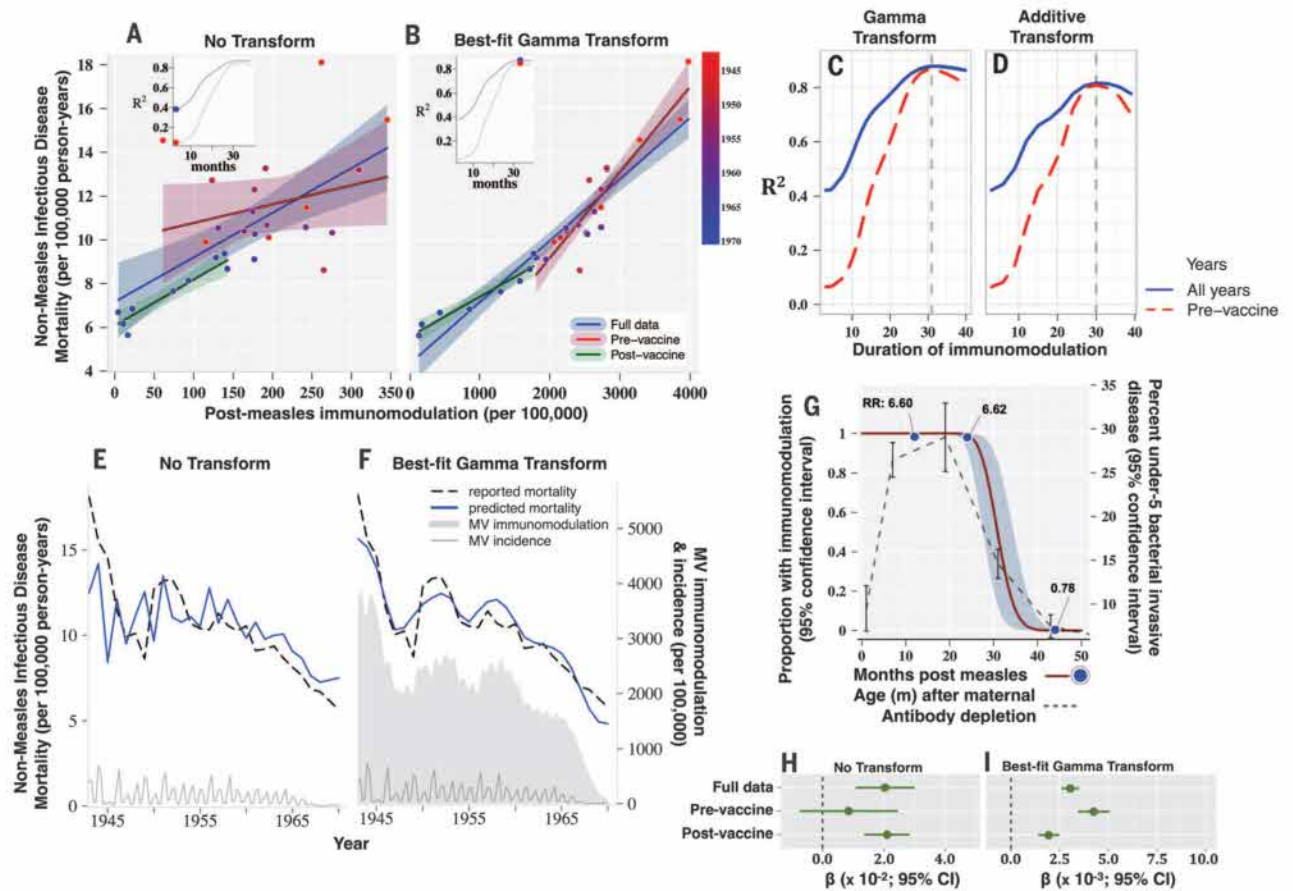


Fig. 3. USA: Measles-induced immunomodulation and nonmeasles infectious disease mortality (1943–1970)

(A to I) Plots are as described for England and Wales in Fig. 2.

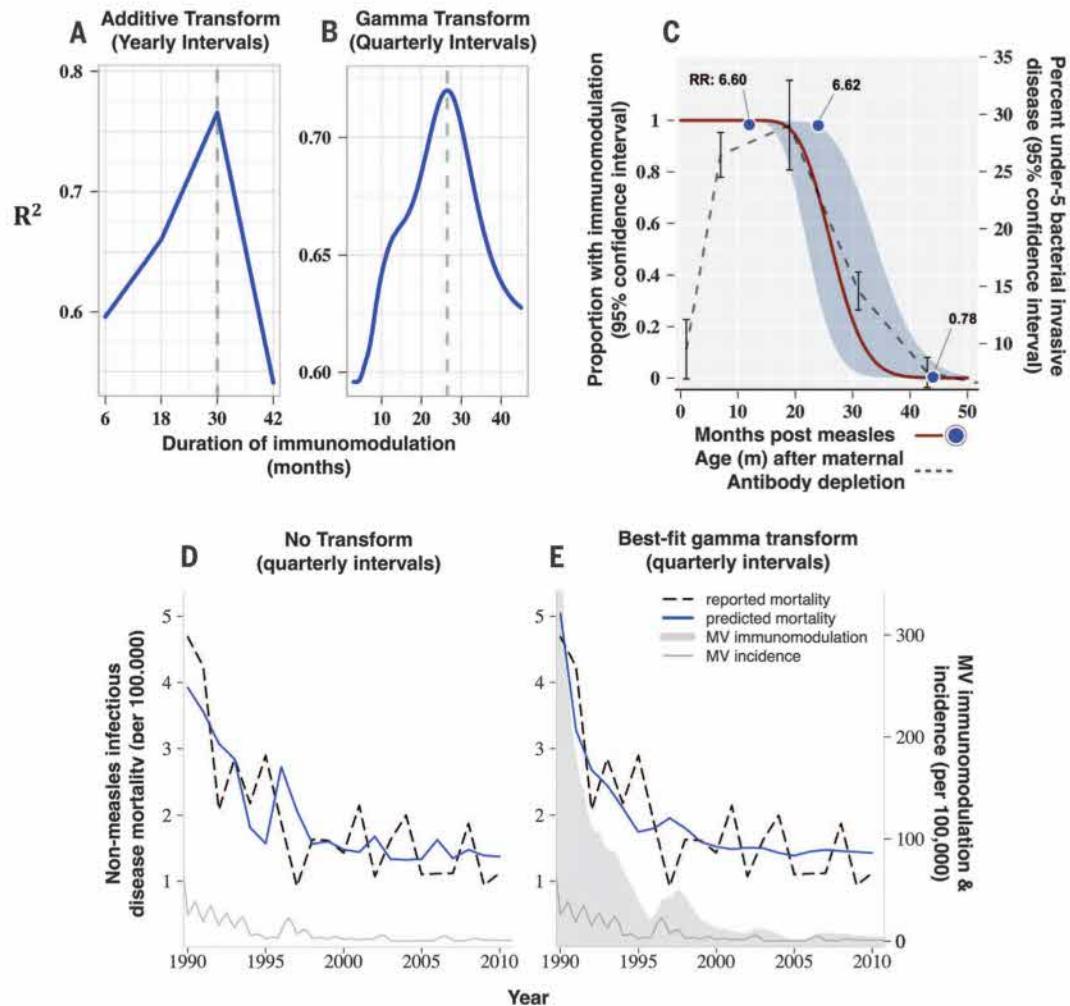


Fig. 4. Denmark: Measles-induced immunomodulation and non-MV infectious disease mortality (1990–2010)

R^2 versus duration of measles-induced immunomodulation when measles data are transformed using (A) the additive transformation with yearly intervals or (B) the gamma transform with quarterly intervals, where yearly measles incidence was converted to quarterly incidence based on (33). The best-fit gamma transform (C), as well as the predicted nonmeasles mortality, predicted from the untransformed (D) or the best-fit gamma transform (E) MV immunomodulation data, are shown and are described for the respective figures in Figs. 2 and 3.

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Subject: RE: A couple of ideas
Attachments: Gadroen_measles.pdf

Hi Ulli/Eric

(b)(5)

Best wishes, Miriam

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Subject: Re: A couple of ideas

Dear Eric and colleagues

(b)(5)

Best regards

Uli

Am 03.06.2019 um 17:01 schrieb Admin <admin@vaxconsult.com>:

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Eric Fombonne [<mailto:fombonne@ohsu.edu>]

Sent: Friday, May 31, 2019 1:57 PM

To: fxd1@cdc.gov; nhalsey1@jhu.edu; lem2@cdc.gov; offitt@email.chop.edu;
'Stanley Plotkin'

Subject: A couple of ideas

Hello,

(b)(5)



Thank you for an interesting meeting.

Regards,

Eric

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BMJ Open Impact and longevity of measles-associated immune suppression: a matched cohort study using data from the THIN general practice database in the UK

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DAMCV and RLS contributed equally.
KG and CND contributed equally.

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ABSTRACT

Objective To test the hypothesis that measles infection increases the incidence of non-measles infectious diseases over a prolonged period of time.

Design A population-based matched cohort study.

Data sources This study examined children aged 1–15 years in The Health Improvement Network UK general practice medical records database. Participants included 2228 patients diagnosed with measles between 1990 and 2014, which were matched on age, sex, general practitioner practice and calendar year with 19930 children without measles. All controls had received at least one measles vaccination. Children with a history of immune-compromising conditions or with immune-suppressive treatment were excluded.

Primary outcome measures Incidence rate ratio (IRR) of infections, anti-infective prescriptions and all-cause hospitalisations following measles in predetermined periods using multivariate analysis to adjust for confounding variables.

Results In children with measles, the incidence rate for non-measles infectious disease was significantly increased in each time period assessed up to 5 years postmeasles: 43% in the first month (IRR: 1.43; 95% CI 1.22 to 1.68), 22% from month one to the first year (IRR: 1.22; 95% CI 1.14 to 1.31), 10% from year 1 to 2.5 years (IRR: 1.10; 95% CI 1.02 to 1.19) and 15% (IRR: 1.15; 95% CI 1.06 to 1.25) in years 2.5 to 5 years of follow-up. Children with measles were more than three times as likely to receive an anti-infective prescription in the first month and 15%–24% more likely between the first month and 5 years. The rate of hospitalisation in children with measles was increased only in the month following diagnosis but not thereafter (IRR: 2.83; 95% CI 1.72 to 4.67).

Conclusion Following measles, children had increased rates of diagnosed infections, requiring increased prescribing of antimicrobial therapies. This population-based matched cohort study supports the hypothesis that measles has a prolonged impact on host resistance to non-measles infectious diseases.

Strength and limitations of this study

- Strength: cohort represents the full range of patients seen in routine clinical practice in a high-income country.
- Strength: the matched study design allowed estimation of the effect of measles on non-measles infections and anti-infective prescriptions over a prolonged period of time.
- Limitation: a key assumption of the study method is that children with measles and children free of measles are comparable. Although major confounders were adjusted for, there could potentially be residual confounding.
- Limitation: the cohort was assembled according to the Read diagnosis code for 'measles' from the electronic medical record. Laboratory confirmation is lacking for most of the identified cases. Validation studies to identify measles and assess the accuracy of the date of diagnosis using this type of database are also lacking. As a result, some patients may have been misclassified.

INTRODUCTION

Measles is a highly contagious childhood disease.¹ During the prevaccine era, nearly every child acquired measles before the age of 15 years.² A key characteristic of the disease is a transient immune suppression, causing increased susceptibility to opportunistic infections. As a result, measles is often complicated by pneumonia, diarrhoea or otitis media, which may lead to severe and even fatal disease.^{3 4} The introduction of measles-containing vaccines has reduced measles incidence¹ as well as childhood mortality.⁵ Interestingly, this reduction in childhood mortality is stronger than what would have been expected based on measles mortality in unvaccinated populations.⁶

Although measles virus is transmitted via the respiratory route, it predominantly infects immune cells and causes systemic disease.¹⁷ Recent studies into the mechanism of measles immune suppression, based on observations in experimentally infected non-human primates, showed that measles virus preferentially replicates in CD150⁺ memory lymphocytes.^{8–10} It was hypothesised that viral cytotoxicity and immune-mediated clearance resulted in depletion of these cells, leading to a loss of acquired immunological memory.^{4,9} Consistent with this hypothesis, a subsequent ecological study using population level data from England and Wales, the USA and Denmark found that rates of non-measles infectious disease mortality are tightly coupled to measles incidence—with a greater mortality rate at higher recent measles incidence. Mina *et al* measured a duration of measles-induced immunomodulation by assessing the association between measles incidence and childhood mortality. The results showed that measles was associated with increased mortality from other infectious diseases over a period of more than 2 years.¹¹ However, the study was based on population-level ecological association data, and the authors did not have access to case-based data.

Monovalent measles vaccination was introduced in England in 1968 and replaced in 1988 by the multivalent measles, mumps and rubella (MMR) vaccine. Initially, MMR was offered only as a single dose at the age of 12 months. In 1996, a second dose was introduced and offered at age of 40 months. From 1996 to 2004, the number of reported measles cases in the UK was small. Following the publication of a subsequently discredited study linking autism and measles vaccination in 1998, coverage dropped for several years below herd protection level, and in 2007, measles was re-established in the UK. In response, an MMR catch-up campaign targeting individuals up to 18 years of age was implemented in 2008. In response to a mumps outbreak, Wales had already implemented a national MMR vaccination campaign targeting individuals aged between 11 years and 25 years in 2005.

In the present study, we have used individual-level data from a UK database to test whether measles results in prolonged increased susceptibility to other infections. The aim of our study was to assess whether measles is associated with increased frequency of non-measles infectious disease, anti-infective prescriptions or hospitalisations over a prolonged period of time.

METHODS

Data source

For this matched-cohort study, we used data from The Health Improvement Network (THIN) database. THIN is a population-based general practice registry that contains prospectively collected, anonymised longitudinal electronic patient records from over 550 general practitioner (GP) practices across the UK, capturing healthcare data from more than 12 million patients (about 6% of the population).^{12,13} Data recorded in THIN include

demographic, socioeconomic and clinical information, including chief complaint, symptoms, test results, diagnoses, prescriptions and referrals to hospitals. The population covered has similar demographic characteristics to the national UK population, and the recording of consultations and prescriptions is comparable with national levels.^{14,15} Diagnoses and symptoms are recorded in Read codes, a standard terminology, maintained by the UK National Health Service Centre for Coding and Classification.¹⁶ Information on drug prescription is recorded using British National Formulary codes and the MULTILEX product dictionary. The specific codes used for this study were selected by a medical doctor and reviewed by a virologist, medical doctor and epidemiologist for their relevance (see online supplementary file S1 for selected read codes).

Study design and population

The source population consisted of all patients who had contributed longitudinal data to the database between 1 January 1990 to 30 September 2014, from the age of 6 months to 15 years. This study period captures the period of time when vaccination rates fell during the late 1990s, with increased measles cases in the following years. The measles group consisted of children with a measles diagnosis (whether or not laboratory confirmed) between the ages of 1 year and 15 years. The date of measles diagnosis was taken as the index date. To each child with a measles diagnosis, up to 10 children free of measles were matched on age in years, sex, GP practice and calendar time in years. Children free of measles were required to have had at least one dose of measles-containing vaccine, prior to the matched case's index date. We considered that having received at least one dose of measles-containing vaccine would reduce the chance that children included in the 'free of measles' group had ever had measles. Patients with a history of immune-compromising conditions (eg, HIV infection and organ or bone marrow transplantation), or with immune suppressive treatment prior to the index date were excluded (see supplementary file S2 Table for the STROBE statement of this study).

Patient involvement

No patient was involved in setting the research question, outcome measures, design or conduct of the study. The results were not disseminated to the patients, as the study was based on anonymised patient records.

Outcomes

Three clinical outcomes were considered: infections, anti-infective prescriptions and all-cause hospitalisations. The outcomes were defined by the relevant clinical codes for symptoms and diagnoses or drug codes. Infections included all communicable diseases other than measles. Infections were required to be 14 days apart to be considered a new event. Anti-infective prescriptions included all systemic antibiotics, antimycotic, antivirals and anti-parasitic medication. For anti-infective prescriptions and

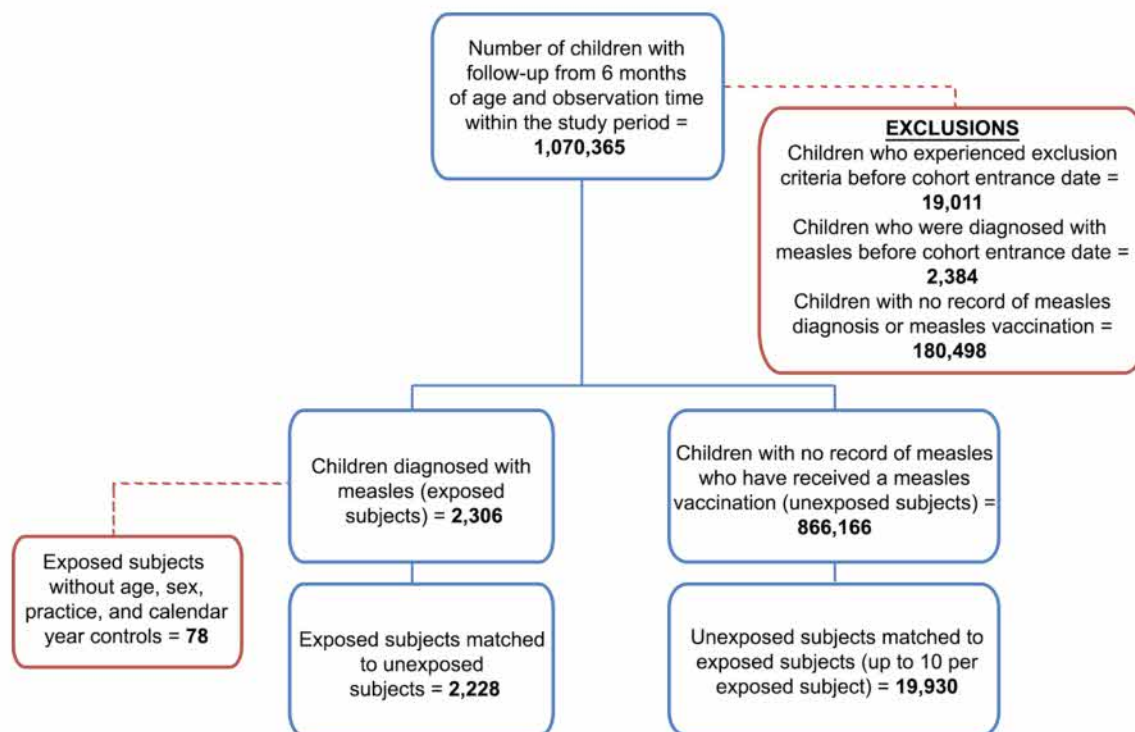


Figure 1 Flow chart of study cohort selection. Starting from 1 070 365 eligible children in the THIN database, 2228 measles patients and 19930 matched controls were selected for this study. THIN, The Health Improvement Network.

hospitalisations, any event occurring on a different day (at least 1 day apart) was considered a new event.

Follow-up

Follow-up started at the index date and continued for a period of 5 years, until date of transfer out the GP's practice, the 15th birthday or death, whichever came earliest. Each outcome was analysed in predetermined periods following measles diagnosis: within the first month; ≥ 1 month to < 1 year; ≥ 1 year to < 2.5 years; and ≥ 2.5 years to < 5 years, to observe changes over time. HRs for hospitalisation were calculated with follow-up starting at 30 days after the index date to avoid inclusion of hospitalisations due to initial complications related to measles.

Potential confounders and effect modifiers

We considered as potential confounders: chronic respiratory disease, cardiovascular disease, prior exposure to routine childhood vaccines other than measles containing vaccines, deprivation index, healthcare consumption and occurrence of each outcome of interest in the year prior to index. Potential confounders were assessed at the index date. Vaccine adherence was defined as exposure to any dose of other routine childhood vaccines such as pertussis-containing vaccines before the index date and coded as binary with vaccine adherence equal to one if any other childhood vaccine was received and zero otherwise. The Townsend deprivation score, a measure of social deprivation based on unemployment level, car ownership, home ownership and household overcrowding levels by area, was used within a particular zip code.¹⁷ Healthcare consumption, as a proxy for general health, was assessed

by the rate of GP consultations in the year prior to the index date¹⁸ and categorised using quintile cut-off points. For a list of various types of consultations included to calculate GP consultation rate, see online supplementary file S3. For each outcome, the event rate in the year prior to index was calculated.

Statistical analysis

Baseline characteristics were compared between children with measles and children free of measles using Student's t-test, Mann-Whitney U test, χ^2 test or Fisher's exact test as appropriate. Observed incidence rates of measles diagnosis codes as well as measles notification codes were estimated by dividing the number of cases by the number of person-years at risk within the database stratified by calendar year and were compared with expected incidence rates, derived from publicly available official statistics from the UK National Archives.¹⁹ The differences in incidence of the outcomes between children with measles and children free of measles were analysed for each period using Poisson regression. For this analysis, matching was relaxed due to uninformative matched strata for each outcome, with over 1000 uninformative strata for the hospitalisation outcome. A stratified analysis was therefore not conducted, and the analysis was adjusted for confounding using multivariable analysis. We submitted the following confounders: history of cardiovascular malformation, history of respiratory disease, exposure to childhood vaccinations other than measles containing vaccination, age, sex and GP consultation rate. Exposure to childhood vaccinations other

Table 1 Baseline characteristics of enrolled subjects

Variable	Category	Measles group (n=2228)		Non-measles group (n=19930)		P value
		Mean±SD or N (%)	Median (IQR)	Mean±SD or N (%)	Median (IQR)	
Age at case diagnosis		3.06±3.04	2 (1–4)	3.16±3.01	2 (1–4)	0.1264
Person time (days)		1379.9±595.33	1826 (849–1826)	1358.7±611.54	1826 (804–1826)	0.1186
Sex	Female	1038 (46.59)		9275 (46.54)		0.9643
Region	England	1816 (81.51)		16291 (81.74)		0.9871
	Northern Ireland	52 (2.33)		448 (2.25)		
	Scotland	167 (7.50)		1497 (7.51)		
	Wales	193 (8.66)		1695 (8.50)		
Experience of an excluding event during follow-up		125 (5.61)		898 (4.51)		0.0219
History of respiratory disease		84 (3.77)		737 (3.70)		0.8592
History of cardiovascular disease		18 (0.81)		124 (0.62)		0.3249
Townsend deprivation score	0	108 (4.85)		1001 (5.02)		0.1696
	1	482 (21.63)		4553 (22.84)		
	2	409 (18.36)		3483 (17.48)		
	3	422 (18.94)		3947 (19.80)		
	4	426 (19.12)		3727 (18.70)		
	5	381 (17.10)		3198 (16.05)		
	Missing	0 (0.00)		21 (0.11)		
Vaccine non-adherence	Yes	43 (1.93)		29 (0.15)		<0.0001
Measles vaccination before index date		1212 (54.40)		19930 (100.00)		<0.0001
Measles vaccination ever during observation		2044 (91.74)		19930 (100.00)		<0.0001
# Consults in the year before Index (continuous)		13.87±11.54	11 (6–19)	13.22±13.80	10 (5–17)	<0.0001
# Consults in the year before Index (categorical)	0–3	300 (13.46)		3731 (18.72)		<0.0001
	4–7	427 (19.17)		4193 (21.04)		
	8–11	443 (19.88)		3546 (17.79)		
	12–19	542 (24.33)		4406 (22.11)		
	>19	516 (23.16)		4054 (20.34)		
Infections in the year prior to index		0.86±1.27	1 (0–2)	0.87±1.58	1 (0–2)	0.7782
Anti-infectives in the year prior to index		1.58±1.97	0 (0–1)	1.53±2.41	0 (0–1)	0.2708
Hospitalisations in the year prior to index		0.11±0.51	0 (0–0)	0.07±0.41	0 (0–0)	0.0004

P values lower than 0.05 are shown in bold.

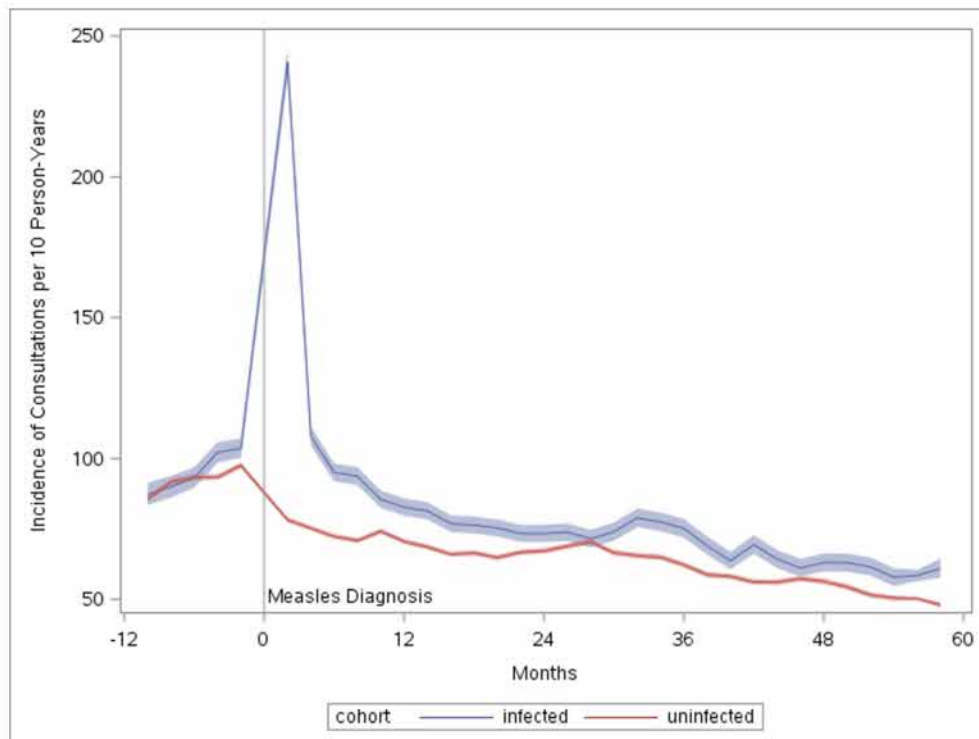


Figure 2 Consultations in measles patients and matched controls. Incidence rates of consultations in children diagnosed with measles (blue lines) or matched controls (red lines) per 10 person-years, plotted by time (in months) before or after diagnosis of measles. The vertical dotted line indicates the time point of diagnosis in the measles patients. The shaded areas represent 95% CIs.

than measles-containing vaccination was not retained in final models. In addition, per outcome, we submitted rate of the outcome in the year prior to the index date. Absolute rates of each outcome per 1000 person-days were calculated with covariates fixed as follows: cardiovascular and respiratory history=no; receipt of other childhood vaccines=yes; number of consults and events in the previous year=median; age=3 years; and sex=female. Kaplan-Meier curves and log-rank tests were used to compare time with first hospitalisation between measles infected and control individuals, with follow-up beginning at 30 days after the index date (to avoid including codes related to the initial measles infection). A stratified Cox proportional hazards model, stratified by matched set and adjusted for confounding variables, was applied to estimate HRs comparing children with measles and children free of measles. Assumptions of proportional hazards were assessed by inspecting the Kaplan-Meier curves and formally tested with inspection of a measles*time interaction term. Model selection was by backward covariate selection, with the criteria $p < 0.1$. Subsequently, we verified automatically selected models using minimisation of Akaike's Information Criterion (AIC). We also estimated the HRs for the outcomes first infection and first prescription.

Sensitivity analysis

Children who have received vaccinations may be different in their underlying health status, social background, lifestyle, healthcare-seeking behaviour and healthcare

utilisation from those who did not receive vaccinations. To examine the possible effect of these unmeasured confounders, we conducted a sensitivity analysis, stratifying the data into matched sets in which all measles cases had received (ie, non-measles group vaccinated vs measles group vaccinated) or had not received a measles-containing vaccine (ie, non-measles group vaccinated vs measles-group unvaccinated). In post hoc analyses, we assessed the incidence rate ratio (IRR) of each outcome over the entire study period in vaccine adherent versus non-adherent children for each outcome using Poisson regression. We also examined the correlation of the consultation rate the year before and after the index date in measles versus control groups using linear regression. For data management and analysis, we used SAS V.9.3.

RESULTS

From the database population of 1 070 365 children aged 1–15 years, we identified 2228 eligible children with a measles diagnosis. These children were matched to 19930 children free of measles. Figure 1 illustrates the composition of the study cohort. Table 1 describes baseline characteristics of children with measles and children free of measles. Median follow-up time was 5.0 years (IQR: 2.2–5.0). The incidence rate of measles and of measles notification as reported in the THIN database were similar to the expected overall confirmed measles incidence rate as reported by official UK Government

Table 2 Descriptive statistics of events in enrolled measles exposed and measles-non exposed children

Variable	Category	Measles group (n=2228)		Non-measles group (n=19930)		P values
		Mean±SD or N (%)	Median (IQR)	Mean±SD or N (%)	Median (IQR)	
# Infections (continuous)		1.61±2.17	1 (0–2)	1.28±1.85	1 (0–2)	<0.0001
# Infections (categorical)	0	864 (38.78)		9224 (46.28)		<0.0001
	1–2	856 (38.42)		7184 (36.05)		
	3–5	377 (16.92)		2852 (14.31)		
	6–10	115 (5.16)		591 (2.97)		
	>10	16 (0.72)		79 (0.40)		
# Anti-infective Rx (continuous)		4.58±5.45	3 (1–6)	3.35±4.43	2 (0–5)	<0.0001
# Anti-infective Rx (categorical)	0	326 (14.63)		5104 (25.61)		<0.0001
	1–2	631 (28.32)		6168 (30.95)		
	3–5	651 (29.22)		4617 (23.17)		
	6–10	393 (17.64)		2892 (14.51)		
	11–20	187 (8.39)		979 (4.91)		
	>20	40 (1.80)		170 (0.85)		
# Hospitalisations (continuous)		0.16±0.74	0 (0–0)	0.12±0.63	0 (0–0)	0.0001
# Hospitalisations (categorical)	0	1999 (89.72)		18369 (92.17)		0.0014
	1–2	204 (9.16)		1396 (7.00)		
	3–5	20 (0.90)		134 (0.67)		
	6–10	3 (0.13)		24 (0.12)		
	>10	2 (0.09)		7 (0.04)		

Rx, drug treatment.

statistics (see supplementary file S4 figure). However, between 1999 and 2006 diagnoses in THIN decrease while notifications and the population incidence increase. There was no significant difference in follow-up time between the children with measles and the children free of measles. Exposure to childhood vaccines other than measles-containing vaccines prior to the index date was lower among children with measles (98.1% vs 99.8%), but this difference was small compared with the difference in vaccination coverage of measles-containing vaccines prior to the index date (54.4% in children with measles vs 100% in children free of measles, due to inclusion criteria). GP consultation rate in the year prior to index date was slightly higher in the measles group than in the non-measles group: mean 13.87 versus 13.22 ($p<0.001$) consults in the year prior, respectively (figure 2). The Townsend deprivation index was similar in children with measles and children free of measles. The rate of infections and anti-infective prescriptions prior to index were similar between measles and non-measles subjects, while hospitalisations prior to index were more frequent for subjects subsequently diagnosed with measles. Table 2 describes events of interest occurring during follow-up in measles and non-measles subjects.

Infectious disease

The most frequently occurring infectious diseases were upper respiratory infectious diseases (for details see online Supplementary file S5 table). The IRR (table 3) of infections for children with measles compared with children free of measles was 43% higher in the first month (IRR: 1.43; 95% CI 1.22 to 1.68), 22% higher from the first month to the first year (IRR: 1.22; 95% CI 1.14 to 1.31), 10% higher from the first year to 2.5 years (IRR: 1.10; 95% CI 1.02 to 1.19) and 15% higher (IRR: 1.15; 95% CI 1.06 to 1.25) in the 2.5–5 years of follow-up (figure 3).

The absolute rate of infections per 1000 person-days in the first month to first year was 1.7 (95% CI 1.6 to 1.9) for children with measles and 1.33 (95% CI 1.29 to 1.36) for children free of measles. The adjusted HR for non-measles infectious disease over the full follow-up period starting 30 days after measles diagnosis was 1.20 (95% CI 1.13 to 1.28) (see online Supplementary file S6).

Prescriptions

Children with measles received more anti-infective prescriptions than children without measles in all periods (table 3, figure 4, online Supplementary file S5 and Supplementary file S7). The absolute rate of

Table 3 Incidence rate ratios (IRRs) of events of interest in predefined time periods following measles infection

Time period	Analysis*	IRR (95% CI)		
		Infections	Anti-infective prescriptions	Hospitalisation
Days 0–31	Primary	1.43 (1.22 to 1.68)	3.60 (3.31 to 3.91)	2.83 (1.72 to 4.67)
	Unadjusted	1.57 (1.34 to 1.84)	3.77 (3.48 to 4.08)	3.24 (2.03 to 5.19)
	Sensitivity (vaccinated measles subjects only)	1.47 (1.17 to 1.86)	4.65 (4.20 to 5.14)	1.92 (0.89 to 4.14)
	Sensitivity (unvaccinated measles subjects only)	1.33 (1.07 to 1.65)	2.45 (2.12 to 2.82)	3.30 (1.60 to 6.82)
Days 32–365	Primary	1.22 (1.14 to 1.31)	1.25 (1.18 to 1.32)	1.14 (0.88 to 1.48)
	Unadjusted	1.31 (1.21 to 1.41)	1.31 (1.24 to 1.39)	1.29 (0.94 to 1.77)
	Sensitivity (vaccinated measles subjects only)	1.15 (1.04 to 1.27)	1.25 (1.16 to 1.35)	0.95 (0.61 to 1.46)
	Sensitivity (unvaccinated measles subjects only)	1.26 (1.15 to 1.39)	1.24 (1.15 to 1.35)	1.29 (0.92 to 1.81)
Days 366–913	Primary	1.10 (1.02 to 1.19)	1.21 (1.13 to 1.29)	1.08 (0.80 to 1.47)
	Unadjusted	1.15 (1.06 to 1.24)	1.25 (1.17 to 1.34)	1.19 (0.85 to 1.66)
	Sensitivity (vaccinated measles subjects only)	1.10 (0.99 to 1.22)	1.21 (1.11 to 1.32)	1.26 (0.79 to 2.04)
	Sensitivity (unvaccinated measles subjects only)	1.09 (0.99 to 1.21)	1.22 (1.12 to 1.34)	0.93 (0.64 to 1.35)
Days 914–1826	Primary	1.15 (1.06 to 1.25)	1.15 (1.07 to 1.24)	1.24 (0.92 to 1.67)
	Unadjusted	1.23 (1.13 to 1.35)	1.22 (1.13 to 1.31)	1.38 (1.07 to 1.78)
	Sensitivity (vaccinated measles subjects only)	1.06 (0.94 to 1.20)	1.25 (1.13 to 1.37)	1.08 (0.76 to 1.54)
	Sensitivity (unvaccinated measles subjects only)	1.21 (1.07 to 1.35)	1.07 (0.96 to 1.19)	1.37 (0.87 to 2.17)

*Primary and sensitivity analyses were adjusted for: frequency of consultations in the year prior to index, frequency of the outcome of interest in the year prior to index, history of cardiovascular malformation, history of respiratory disease, age and sex.

anti-infective prescriptions per 1000 person-days in the first month to first year was 0.55 (95% CI 0.51 to 0.59) for children with measles and 0.45 (95% CI 0.43 to 0.47) for children free of measles. The adjusted HR for anti-infective prescription over the full follow-up period starting 30 days after measles diagnosis was 1.24 (95% CI 1.18 to 1.31). Within the first month of follow-up, children with measles had more than a threefold increase in use of anti-infective drugs as compared with controls (IRR: 3.60; 95% CI 3.31 to 3.91). Following the first month, children who had measles continued to use more anti-infective drugs over the entire duration of the follow-up: 1 month–1 year (IRR 1.24; 95% CI 1.18 to 1.32); 1 year–2.5 years (IRR 1.21; 95% CI 1.13 to 1.29) and 2.5 years–5 years (IRR 1.15; 95% CI 1.07 to 1.24).

Hospitalisation

Despite smaller sample sizes, the analysis on hospitalisations also showed increased IRRs, although these were significant during the first period only (figure 5). In the Cox proportional hazards model, confounder selection using either backward selection, or minimisation of the AIC resulted in the same model, namely control for the hospitalisation rate

prior to the index date, the GP consultation rate in the year prior to index date and history of cardiac malformation. The absolute rate of hospitalisations per 1000 person days in the first month to first year was equal at 0.2 (95% CI 0.1 to 0.2) for children with measles and children free of measles. The adjusted HR of hospitalisation for measles versus non-measles subjects was 1.12 (95% CI 0.96 to 1.31).

Sensitivity analysis

Results of the sensitivity analysis were partially in agreement with findings from the main analysis. When we restricted the analysis to only those children who had received measles vaccination prior to receiving a diagnosis of measles (54.4% of all eligible children with a measles diagnosis), differences to the main analyses were not observed for anti-infective prescriptions. However, an increased rate of hospitalisations was no longer detected in any time period and an increased rate of infections no longer extended beyond 1 year postdiagnosis. In the analysis restricted to those children who had not had a measles vaccination prior to receiving a diagnosis of measles (45.6% of all eligible children with a measles diagnosis), the results were in line with the main findings for hospitalisations, infections and anti-infective prescriptions

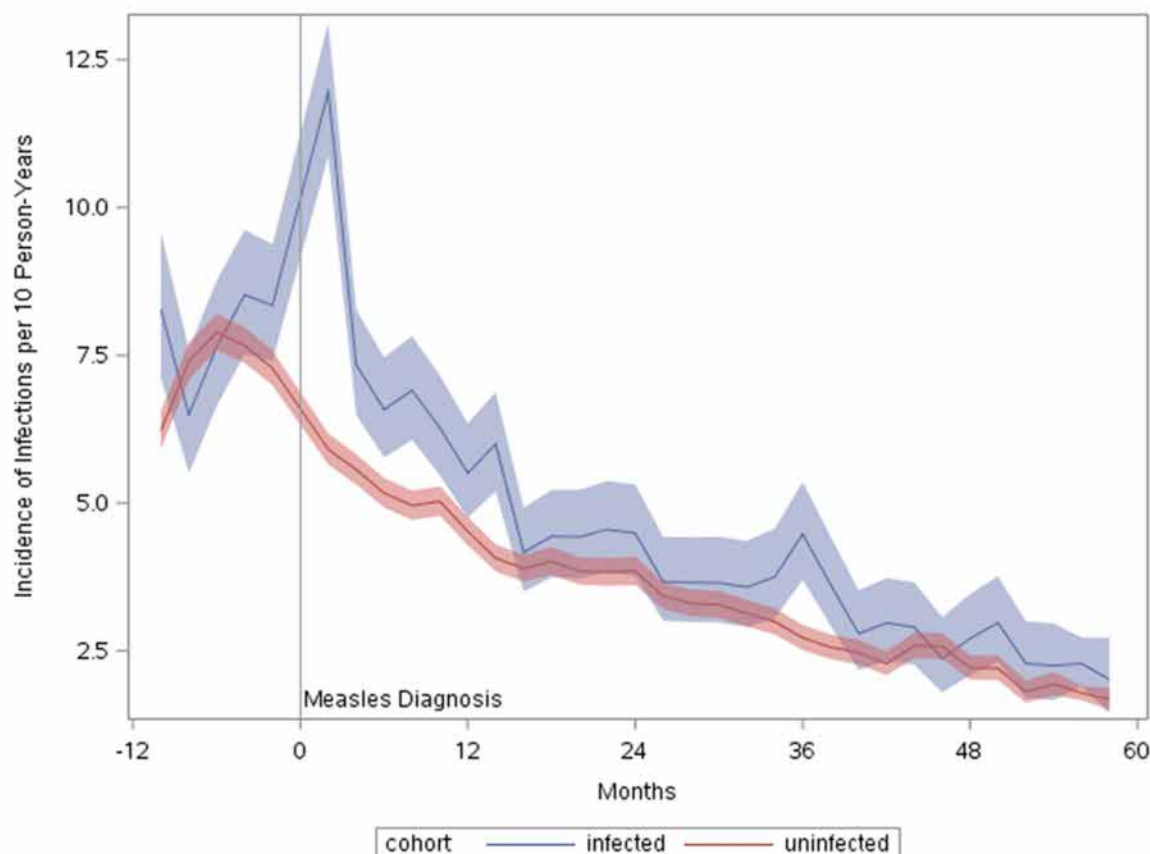


Figure 3 | Infections in measles patients and matched controls. Incidence rates of infections in children diagnosed with measles (blue lines) or matched controls (red lines) per 10 person-years, plotted by time (in months) before or after diagnosis of measles. The vertical dotted line indicates the time point of diagnosis in the measles patients. The shaded areas represent 95% CIs.

with the exception that increased risk for anti-infective prescriptions did not extend into the period 2.5–5 years following measles.

Post hoc analysis of the impact of vaccine adherence regardless of measles status revealed that vaccine non-adherent children were 42% more likely to receive an anti-infective prescription than vaccine-adherent children. There was no difference in risk of infections or hospitalisations. Regressing postindex consults on preindex consults and measles, or non-measles status revealed that both groups showed similar trends with the rate of consultation before index date higher than that after the index date.

DISCUSSION

To our knowledge, this is the first matched-cohort study to investigate the longevity of measles-associated immune suppression in a high-income country. The results of this study are in strong agreement with previous non-clinical and ecological studies also in high-income countries.¹¹ We found that rates of diagnosed infections and anti-infective prescriptions are elevated following measles infection for up to 5 years. While increased risk of infections and anti-infective prescriptions remained statistically significant over the full 5-year study period, the effect size diminished particularly after the first year, and statistical

significance is partly explained by our large sample size. Children diagnosed with measles were hospitalised more frequently than children free of measles, although this was only significant in the first month following infection. When we excluded the first month postmeasles, the time to first hospitalisation did not differ between the measles group and the non-measles group. This could be explained, at least in part, by a survival bias, whereby a disproportionately large number of measles cases entered the hospital during the first month, and these may have represented the most severe cases. Additionally, a lack of effect on hospitalisation after the first month was likely a result of the low overall number of hospitalisations in our cases and controls. We acknowledge that the first interval spanning 1 month–1 year postmeasles is wide and have conducted analysis using smaller intervals, the results of which can be found in the supplementary material (see online Supplementary file S8 table). These results are in agreement with our primary analysis, with risk of infections and anti-infectives remaining elevated throughout the entirety of the first year following measles and risk of hospitalisations elevated in the first month following measles only.

The incidence rates of infections, anti-infective prescriptions and hospitalisations in the measles group appear to

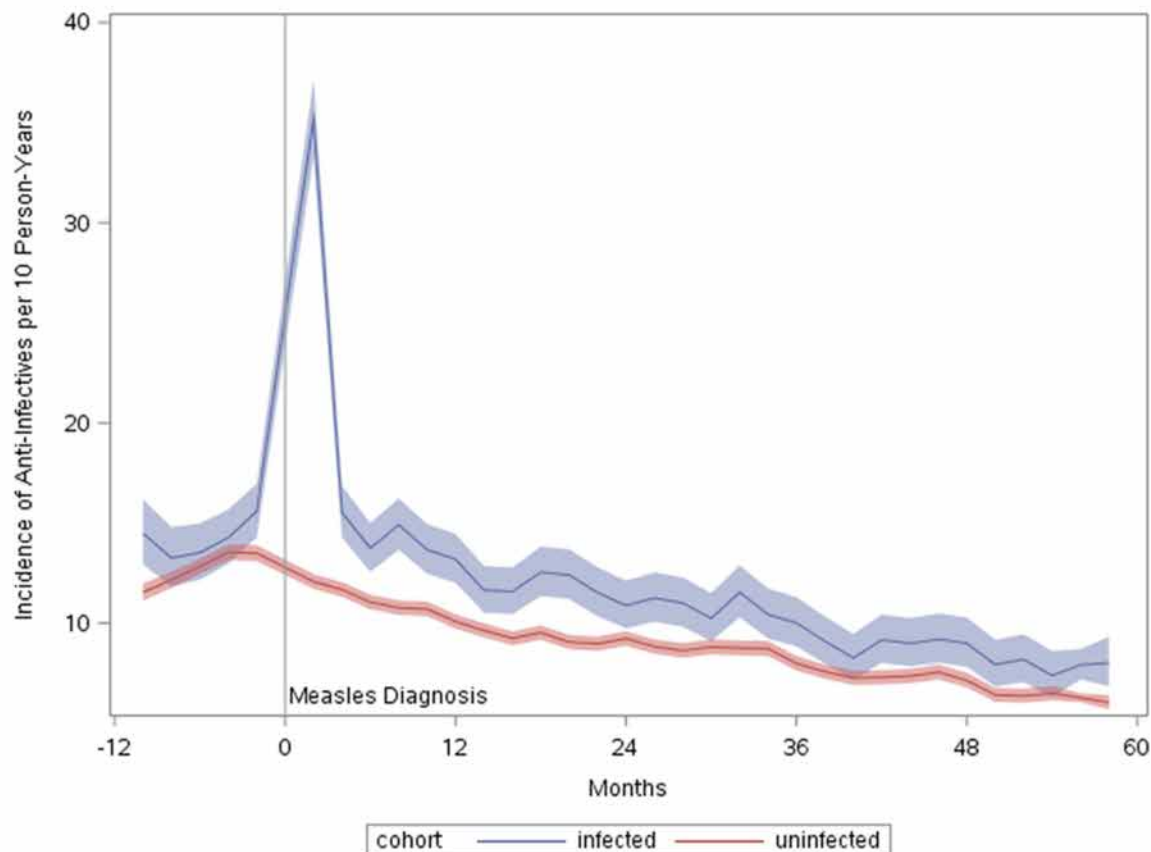


Figure 4 | Anti-infective prescriptions in measles patients and matched controls. Incidence rates of anti-infective prescriptions in children diagnosed with measles (blue lines) or matched controls (red lines) per 10 person-years, plotted by time (in months) before or after diagnosis of measles. The vertical dotted line indicates the time point of diagnosis in the measles patients. The shaded areas represent 95% CIs.

increase prior to the index date, that is, before they got measles (figures 3–5). This could partially be explained by a lag time between a suspected diagnosis and a definite diagnosis. In some instances, a GP may have coded a definite diagnosis on the date a confirmation had been received either from the lab or from the hospital. For some outcomes, however, the rise in incidence begins months before diagnosis. Validation studies to assess the accuracy of the date of diagnosis using this type of database are lacking.

To be considered a new event, prescriptions only had to be given on a different day. Acknowledging that a prescription can be changed if there is poor response or allergy to the first drug, we also examined the effect of anti-infective prescription, considering a 14-day interval between anti-infective prescriptions. This did not change the significance or direction of any result (results not shown). Both groups revealed similar trends with the rate of consultation before index date higher than after index date.^{20 21} This is most likely related to age. Although measles is a statutory notifiable infectious disease under EU legislation,²² an under-reporting of (severe) cases, who might have by-passed the GP and gone directly to the hospital, cannot be ruled out. Also, it is possible that a mild measles infection would not have prompted a visit to the GP and may have gone undetected as well.^{23 24} This means that we

may have missed some children with measles. It should be noted though that laboratory confirmation for most of the identified cases is lacking. As a result, some patients may have been misclassified. Validation studies to accurately identify measles using this type of database are also lacking. In case of non-differential misclassification, the direction of the bias is likely to be towards the null value, so one would expect to see a larger estimate if misclassification was absent. Differential misclassification however can inflate or attenuate the effect estimates. To minimise the impact of differential misclassification, we examined the consultation rate in both measles and non-measles groups. To provide additional assurance that controls were children truly free of measles, controls had to have at least one measles-containing vaccination prior to the index date. An advantage of this type of observational study is that it is not necessary to identify all outcomes in all children in order to obtain an unbiased estimate. A key assumption, however, is comparability of children with measles and children free of measles. In order to ensure that the children with measles and the children free of measles were comparable, we matched them on confounding factors such as age, sex, GP practice and calendar time. We also considered including experiencing an excluding event (ie, an immune-compromising condition or immune suppressive treatment) as a censoring

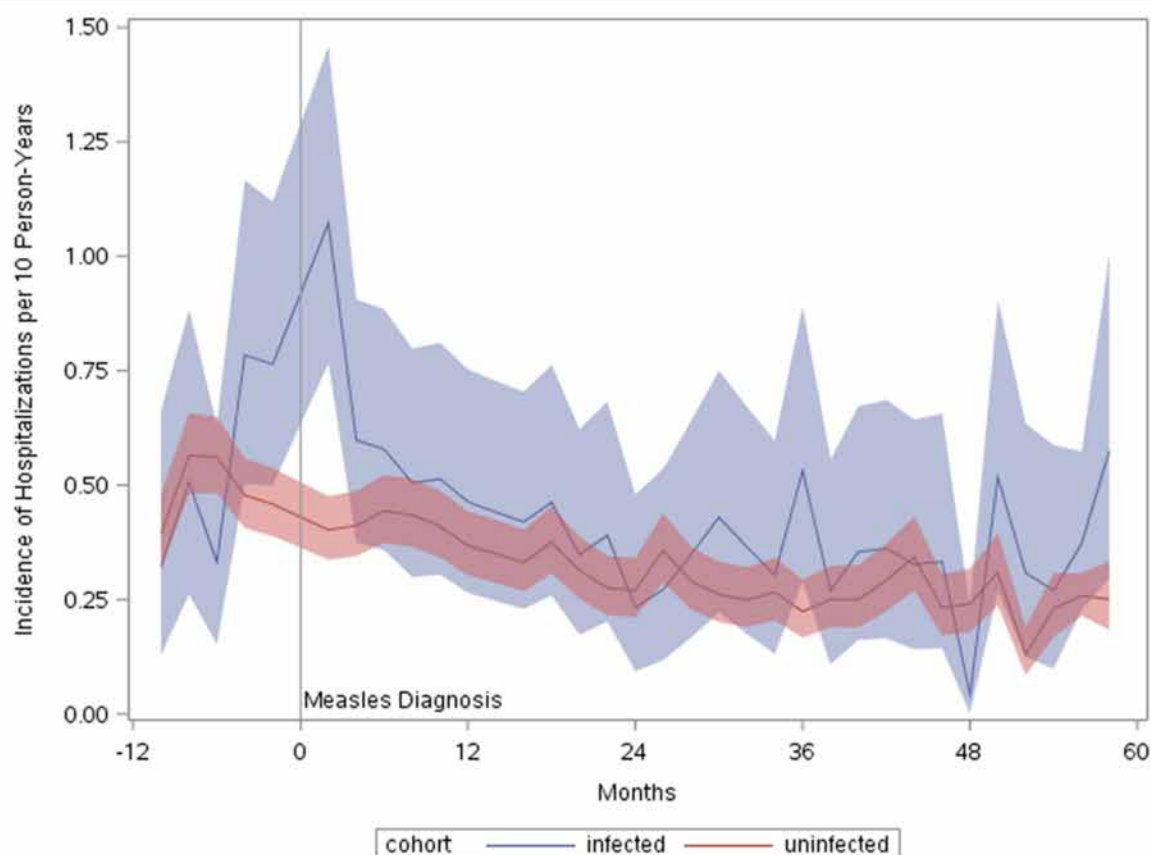


Figure 5 | Hospitalisations in measles patients and matched controls. Incidence rates of hospitalisations in children diagnosed with measles (blue lines) or matched controls (red lines) per 10 person-years, plotted by time (in months) before or after diagnosis of measles. The vertical dotted line indicates the time point of diagnosis in the measles patients. The shaded areas represent 95% CIs.

variable but determined this was not consistent with our matching strategy: the groups were matched to be comparable at index. Nevertheless, we acknowledge that it is possible that confounding due to differences in underlying health status, social background, lifestyle, health seeking behaviour and healthcare utilisation between children with measles and children free of measles may have occurred. The complexity of these factors makes them difficult to control. We attempted to overcome the confounding effect of underlying health status by excluding children with a history of immune-compromising conditions, and controlling for comorbidities such as cardiovascular disease, and respiratory disease. We assessed social background and lifestyle by testing for differences in social deprivation within a particular zip code and matching on practice. Certain children may have had a lower threshold for visiting the GP and therefore may have had a higher likelihood of receiving a diagnosis of measles (particular during an outbreak) and may also have been diagnosed more frequently with other infectious diseases and/or may have received a prescription for anti-infectives more frequently. To investigate this, we included GP consultation rate in the year prior to cohort entry as a covariate in each of our models. In the unmatched Poisson analyses, we did not control for all potential confounders. Because 472 unique practices

were represented in the cohort, it was impossible to control for practice. Similarly, the 25 years included in the study period make control for calendar year infeasible unless calendar year is treated as a continuous variable, which would require the assumption of a linear relationship between year and $\log(\text{events})$. To address the potential effect of calendar time, we have conducted analyses stratified by calendar period (before 2005 and after 2004) and included these results in supplementary material (see online Supplementary file S9 table).

Because vaccinated and unvaccinated children may differ in their health-seeking behaviour or likelihood of acquiring infectious disease, we conducted a sensitivity analysis in two strata: (1) restricting to only those children who had received a measles vaccination prior to the index date and (2) restricting to only those children who were unexposed to measles vaccination prior to the index date. Results from both subanalyses were in line with the findings from the main analysis with the exceptions that the period of increased risk for infections did not extend past 1 year and no increased risk for hospitalisations was detected when analysis was limited to measles-vaccinated children.

We did not adjust for measles vaccination after index date in the context of postexposure prophylaxis because many exposed persons are not identified until more

than 72 hours after initial exposure, which is too late for prophylaxis with measles vaccine.² Post hoc analysis of vaccine adherent versus non-adherent children revealed an increased rate of anti-infective prescriptions in non-adherent children but no difference for other outcomes.

We conclude that our results support the hypothesis that infection with measles is associated with long-term increased risk of other infectious diseases and that by preventing measles, vaccination is associated with non-specific heterologous improvements in health. However, because all of the non-measles controls received vaccination, we cannot rule out a direct benefit of vaccination to boost heterologous immune function, as has been suggested.^{25 26} Nonetheless, the results fit with what would be expected from animal models and what has been shown in ecological studies and warrant further investigation into the long-term consequences of viral infections, particularly those with heightened tropism for immune memory cells on host resistance.

Author affiliations

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Contributors Conceived and designed the study: MJM, BG, DAMCvdV and RLDS. Code selection: KG, GMC, DAMCvdV and RLDS. Data extraction and statistical analysis: CND, GMC and MdR. Interpretation of data: all authors. Authored draft paper: KG and CND. Critical revisions of manuscript: KG, CND, GMC, MdR, DAMCvdV, RLDS, MJM and BG. Study supervision: DAMCvdV, RLDS and MCJMS. Obtained funding: none.

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Competing interests None declared.

Patient consent Not required.

Ethics approval The study was approved by the independent THIN Scientific Review Committee (SRC reference number: 15-006).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional unpublished data from the study are available. All data are contained in the manuscript and the supplementary data files.

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From: Heining, Ulrich
Sent: 4 Jun 2019 05:04:22 +0000
To: Admin
Cc: nkarora@incentrust.org; Destefano, Frank (CDC/DDID/NCEZID/DHQP); Eric Fombonne; GARCON Nathalie; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert; Heidi Larson; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsp.h.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6); Edwards, Kathryn; Ulrich Heining; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; (b)(6); Stanley Plotkin
Subject: Re: A couple of ideas

Dear Eric and colleagues

(b)(5)

Best regards
Uli

Am 03.06.2019 um 17:01 schrieb Admin <admin@vaxconsult.com>:

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Eric Fombonne [<mailto:fombonne@ohsu.edu>]
Sent: Friday, May 31, 2019 1:57 PM
To: fxd1@cdc.gov; nhalsey1@jhu.edu; lem2@cdc.gov; offitt@email.chop.edu; 'Stanley Plotkin'
Subject: A couple of ideas

Hello,

I had these 2 ideas this afternoon. I am out of my league here, so I am unsure about their relevance.

(b)(5)

(b)(5)

Thank you for an interesting meeting.

Regards,

Eric

From: Andrew Pollard
Sent: 4 Jun 2019 10:05:37 +0000
To: Heininger, Ulrich;Admin
Cc: nkarora@incentrust.org;Destefano, Frank (CDC/DDID/NCEZID/DHQP);Eric Fombonne;GARCON Nathalie;jason.m.glanz@kp.org;All@ssi.dk;Paul Henri Lambert;Heidi Larson;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu;priya.bahri@ema.europa.eu;(b)(6);bod enstabh@email.chop.edu;jim.buttery@monash.edu;(b)(6);Edwards, Kathryn;Ulrich Heininger;hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;Amy Pisani;dsalmon1@jhu.edu;m.c.j.sturkenboom@umcutrecht.nl;(b)(6);Stanley Plotkin
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Mike Mina has a lot of data on the measles issues and so would be worth asking him

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Hot Topics In Infection And Immunity In Children
IIC - The ESPID-Oxford Course
1-3 July 2019 Oxford, UK www.oxfordiic.org



From: Heininger, Ulrich <ulrich.heininger@ukbb.ch>
Sent: 04 June 2019 06:04
To: Admin <admin@vaxconsult.com>
Cc: nkarora@incentrust.org; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard

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<stanley.plotkin@vaxconsult.com>

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Subject: A couple of ideas

Hello,

(b)(5)

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From: Neal Halsey
Sent: 4 Jun 2019 10:20:23 +0000
To: Andrew Pollard;Heininger, Ulrich;Admin
Cc: nkarora@inclentrust.org;Destefano, Frank (CDC/DDID/NCEZID/DHQP);Eric Fombonne;GARCON Nathalie;jason.m.glanz@kp.org;All@ssi.dk;Paul Henri Lambert;Heidi Larson;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu;priya.bahri@ema.europa.eu;(b)(6) bodenstabh@email.chop.edu;jim.buttery@monash.edu;(b)(6);Edwards, Kathryn;Ulrich Heininger;hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;Amy Pisani;Daniel Salmon;m.c.j.sturkenboom@umcutrecht.nl;(b)(6);Stanley Plotkin
Subject: Re: A couple of ideas

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Neal

From: Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>
Date: Tuesday, June 4, 2019 at 6:06 AM
To: "Heininger, Ulrich" <ulrich.heininger@ukbb.ch>, Admin <admin@vaxconsult.com>
Cc: "nkarora@inclentrust.org" <nkarora@inclentrust.org>, "DeStefano, Frank (NIP)" <fxdl@cdc.gov>, Eric Fombonne <fombonne@ohsu.edu>, GARCON Nathalie <Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, "All@ssi.dk" <All@ssi.dk>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, Heidi Larson <Heidi.Larson@lshtm.ac.uk>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, James Sejvar <zea3@cdc.gov>, JPIDS JPIDS <nhalsey@jhsph.edu>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, (b)(6) "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, "jim.buttery@monash.edu" <jim.buttery@monash.edu>, (b)(6), "Edwards, Kathryn" <kathryn.edwards@vumc.org>, Ulrich Heininger <ulrich.heininger@unibas.ch>, "hotez@bcm.edu" <hotez@bcm.edu>, "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, Amy Pisani <amyp@ecbt.org>, Daniel Salmon <dsalmon1@jhu.edu>, "m.c.j.sturkenboom@umcutrecht.nl" <m.c.j.sturkenboom@umcutrecht.nl>, (b)(6) Stan Plotkin <stanley.plotkin@vaxconsult.com>
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INFECTION AND
IMMUNITY IN
CHILDREN

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From: Heininger, Ulrich <ulrich.heininger@ukbb.ch>

Sent: 04 June 2019 06:04

To: Admin <admin@vaxconsult.com>

Cc: nkarora@incentrust.org; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; jim.buttery@monash.edu; (b)(6); Edwards, Kathryn <kathryn.edwards@vumc.org>; Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; (b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Subject: Re: A couple of ideas

Dear Eric and colleagues

(b)(5)

Best regards

Uli

Am 03.06.2019 um 17:01 schrieb Admin <admin@vaxconsult.com>:

FYI

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Eric Fombonne [<mailto:fombonne@ohsu.edu>]

Sent: Friday, May 31, 2019 1:57 PM

To: fxd1@cdc.gov; nhalsey1@jhu.edu; lem2@cdc.gov; offitt@email.chop.edu; 'Stanley Plotkin'

Subject: A couple of ideas

Hello,

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(b)(5)



Thank you for an interesting meeting.

Regards,

Eric

From: Jason M Glanz
Sent: 12 Jun 2019 15:07:20 +0000
To: Robert Chen; Neal Halsey
Cc: philippe.duclos@k-net.fr; Edwards, Kathryn; nkarora@inclentrust.org; Heidi Larson; jim.buttery@monash.edu; Daniel Salmon; Sturkenboom, M.C.J.; Heininger, Ulrich; Admin; Destefano, Frank (CDC/DDID/NCEZID/DHQP); fombonne@ohsu.edu; GARCON Nathalie; All@ssi.dk; Paul Henri Lambert; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); Andrew Pollard; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstah@email.chop.edu; (b)(6); Ulrich Heininger; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani; Stanley Plotkin
Subject: RE: A couple of ideas

Hello,

Sorry to be late on this...I was out all last week. I too was honored to take part in the meeting in London.

(b)(5)

Best,
Jason

From: (b)(6)
Sent: Sunday, June 9, 2019 2:48 PM
To: Neal Halsey <nhalsey1@jhu.edu>
Cc: philippe.duclos@k-net.fr; Edwards, Kathryn <kathryn.edwards@vumc.org>; nkarora@inclentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov;

fombonne@ohsu.edu; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; Jason M Glanz <Jason.M.Glanz@kp.org>; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Subject: Re: A couple of ideas

Caution: This email came from outside Kaiser Permanente. Do not open attachments or click on links if you do not recognize the sender.

Dear all,

Thanks to Stan and other organizers for bringing us together. Apologies for late input but wanted to reflect a bit before I shared my general and specific comments/suggestions (apologies if repetitive and if general, beyond scope for some attendees).

(b)(5)

(b)(5)

(b)(5)

Robert (Bob) Chen

Cell: (b)(6)

email: (b)(6)

On Thu, Jun 6, 2019 at 9:16 AM Neal Halsey <nhalsey1@jhu.edu> wrote:

Attached, please find Philippe's presentation as per my email below.
Neal

From: Philippe Duclos <philippe.duclos@k-net.fr>

Date: Thursday, June 6, 2019 at 9:13 AM

To: Neal Halsey <nhalsey1@jhu.edu>, "'Edwards, Kathryn'" <kathryn.edwards@vumc.org>, "nkarora@incentrust.org" <nkarora@incentrust.org>, 'Heidi Larson' <Heidi.Larson@lshtm.ac.uk>

Cc: "jim.buttery@monash.edu" <jim.buttery@monash.edu>, Daniel Salmon <dsalmon1@jhu.edu>, "'Sturkenboom, M.C.J.'" <M.C.J.Sturkenboom@umcutrecht.nl>, "'Heininger, Ulrich'" <ulrich.heininger@ukbb.ch>, 'Admin' <admin@vaxconsult.com>, 'DeStefano, Frank (NIP)' <fxd1@cdc.gov>, 'Eric Fombonne' <fombonne@ohsu.edu>, 'GARCON Nathalie' <Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, "All@ssi.dk" <All@ssi.dk>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, 'Andrew Pollard' <andrew.pollard@paediatrics.ox.ac.uk>, James Sejvar <zea3@cdc.gov>, JPIDS JPIDS <nhalsey@jhsph.edu>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, (b)(6)

(b)(6), "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, (b)(6) 'Ulrich Heininger' <ulrich.heininger@unibas.ch>, "hotez@bcm.edu" <hotez@bcm.edu>, "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, 'Amy Pisani' <amyp@ecbt.org>, (b)(6), Stan Plotkin <stanley.plotkin@vaxconsult.com>

Subject: RE: A couple of ideas

Dear Neal,

Of course please feel free to share my ADVAC safety presentation as you wish.

With kind regards,

Phil

De : Neal Halsey <nhalsey1@jhu.edu>

Envoyé : jeudi 6 juin 2019 14:59

À : Edwards, Kathryn <kathryn.edwards@vumc.org>; nkarora@incentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; Philippe Duclos <philippe.duclos@k-net.fr>

Cc : jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu;

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(b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Objet : Re: A couple of ideas

(b)(5)

Neal

From: "Edwards, Kathryn" <kathryn.edwards@vumc.org>
Date: Thursday, June 6, 2019 at 7:22 AM
To: "nkarora@incentrust.org" <nkarora@incentrust.org>, Heidi Larson <Heidi.Larson@lshtm.ac.uk>
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(b)(5)

(b)(5)

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Thanks again for a great meeting and I hope that the dialogue will continue.

Kathryn M. Edwards MD
Sarah Sell and Cornelius Vanderbilt Chair
Professor of Pediatrics
Vanderbilt University Medical Center

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From: Robert Chen
Sent: 9 Jun 2019 16:48:08 -0400
To: Neal Halsey
Cc: philippe.duclos@k-net.fr; Edwards, Kathryn;nkarora@inclentrust.org;Heidi Larson;jim.buttery@monash.edu;Daniel Salmon;Sturkenboom, M.C.J.;Heininger, Ulrich;Admin;Destefano, Frank (CDC/DDID/NCEZID/DHQP);Eric Fombonne;GARCON Nathalie;jason.m.glanz@kp.org;All@ssi.dk;Paul Henri Lambert;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);Andrew Pollard;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu;priya.bahri@ema.europa.eu;(b)(6) (b)(6);bodenstabh@email.chop.edu;(b)(6);Ulrich Heininger;hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;Amy Pisani;Stanley Plotkin
Subject: Re: A couple of ideas

Dear all,

Thanks to Stan and other organizers for bringing us together. Apologies for late input but wanted to reflect a bit before I shared my general and specific comments/suggestions (apologies if repetitive and if general, beyond scope for some attendees).

(b)(5)

(b)(5)

(b)(5)

Robert (Bob) Chen

Cell: (b)(6)

email: (b)(6)

On Thu, Jun 6, 2019 at 9:16 AM Neal Halsey <nhalsey1@jhu.edu> wrote:

Attached, please find Philippe's presentation as per my email below.

Neal

From: Philippe Duclos <philippe.duclos@k-net.fr>
Date: Thursday, June 6, 2019 at 9:13 AM
To: Neal Halsey <nhalsey1@jhu.edu>, "Edwards, Kathryn" <kathryn.edwards@vumc.org>, "nkarora@incletrust.org" <nkarora@incletrust.org>, 'Heidi Larson' <Heidi.Larson@lshtm.ac.uk>
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Dear Neal,

Of course please feel free to share my ADVAC safety presentation as you wish.

With kind regards,

Phil

De : Neal Halsey <nhalsey1@jhu.edu>

Envoyé : jeudi 6 juin 2019 14:59

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Professor of Pediatrics

Vanderbilt University Medical Center

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To: philippe.duclos@k-net.fr;'Edwards, Kathryn';nkarora@inclentrust.org;'Heidi Larson'
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Attachments: 1400_Philippe_Duclos_ADVAC_2019_Safety.pdf

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Immunization safety in low and middle income country vaccination programs

Philippe Duclos,
University of Geneva

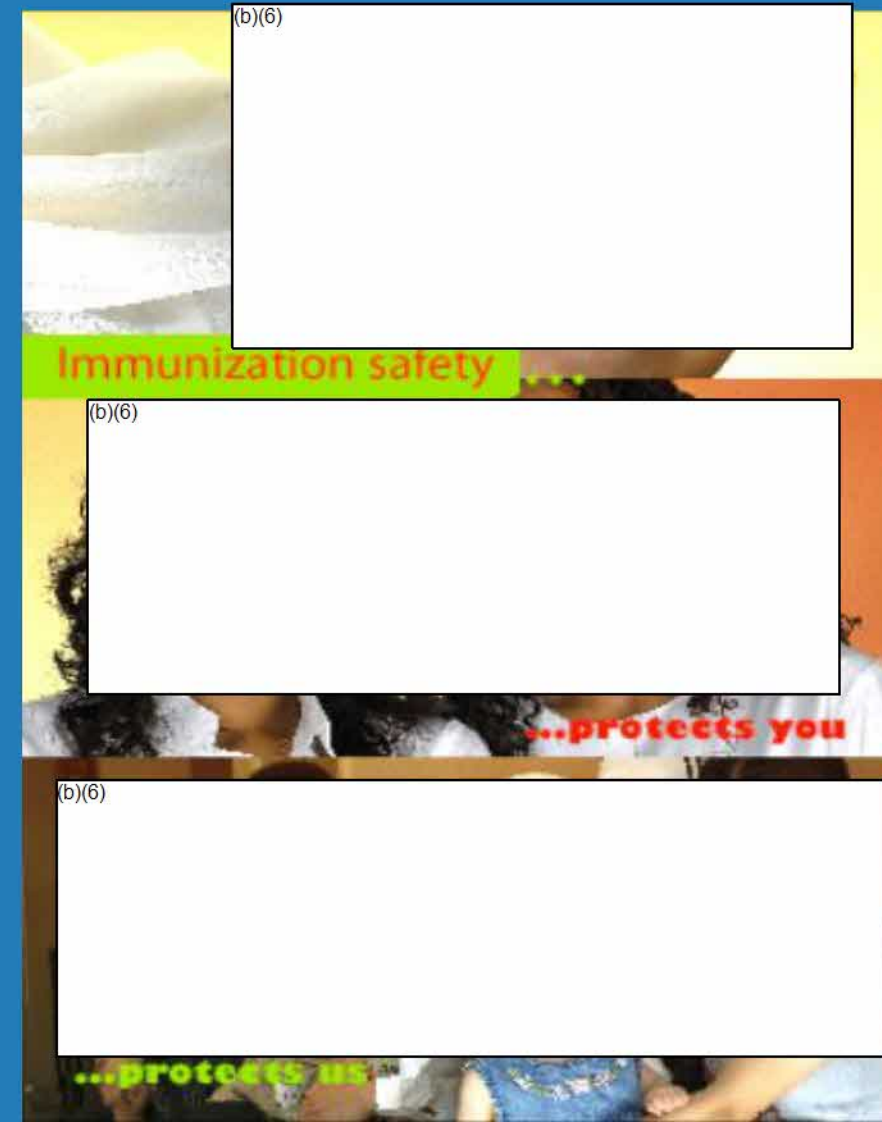
20th Advanced Vaccinology Course

17th May 2019

Veyrier-du-lac, France

With thanks to WHO colleagues and particularly to
Madhava Balakrishnan, Sophie Boisson, Diana
Chang-Blanc, Isaac Gobina, Alireza Khadem
Broojerdi, Ivana Knezevic, Margaret Montgomery,
Carmen Rodriguez-Hernandez, and Isabelle
Sahinovic.

With thanks to Ute Pieper.



Content

1. Range of immunization safety issues and what the real issues are

2. What should be done to ensure immunization safety and WHO's contribution (tools, guidance and initiatives)

Flag differences between low and middle income and high income countries

Examples of issues

- France 1998: allegation of link between hepatitis B vaccination and multiple sclerosis
- Egypt, 1999: 3 deaths labelled post DPT encephalopathy due to methanol impregnated compresses
- Algeria, 2001: 7 infants died from use of selenium vials instead of measles vaccine diluent
- Guinea, 2002: 2 adults died after YF vaccination due to vial contamination



Examples of issues

- Kenya: Higher risk of HIV-1 seropositivity in women who received TT*
- Rotavirus vaccines, 2010 detection of contamination with porcine circovirus
- Allegations of hormone contamination of vaccines in Nigeria, India and the Philippines (polio, TT)
- Vietnam, 2012: Suspended the use of pentavalent vaccine following coincidental occurrence of 9 deaths after vaccination

*Int J STD AIDS 2006;17:749-52.

Examples of issues

- Syria, 2014: 15 deaths and 50 hospitalizations following measles-rubella vaccination campaign. Use of Atracurium instead of proper diluent



AFP Photo / SANA
AFP

The UN has halted a measles vaccination campaign in northern Syria after at least 15 children died after receiving shots, the UN Children's Fund (UNICEF) and World Health Organization (WHO) confirmed in a joint statement. "UNICEF and WHO have been shocked and saddened to learn of the deaths of at least 15 young children in Idlib, Syria," the statement said. "The deaths of the children occurred in areas where a measles immunization campaign had been underway." The children were

- Kazakhstan, 2015: Cluster of anxiety reactions destroyed measles vaccination campaign



Examples of issues

- Coincidental deaths following vaccination with HPV (UK, Fiji, India, Ireland, Israel, Japan,...)
- South Sudan, 2017: 15 children died from contaminated measles vaccine
- 2019, Northern Pakistan, > 25,000 children rushed to hospital after spread of rumours that polio vaccine led to fainting and vomiting.

HOME > News

Peshawar hospital set on fire after parents panic over vaccine

Sohail Khattak

April 22, 2019

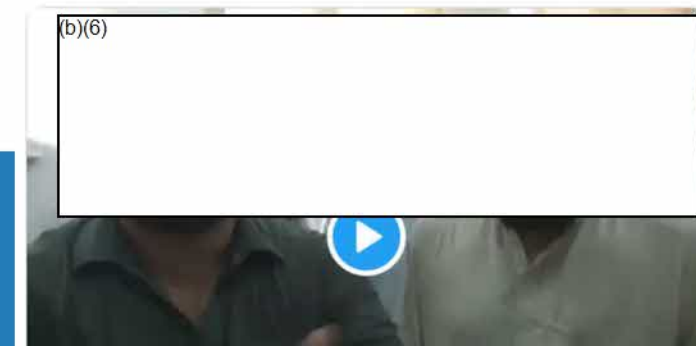


Doctors say their children are not sick, just panicked



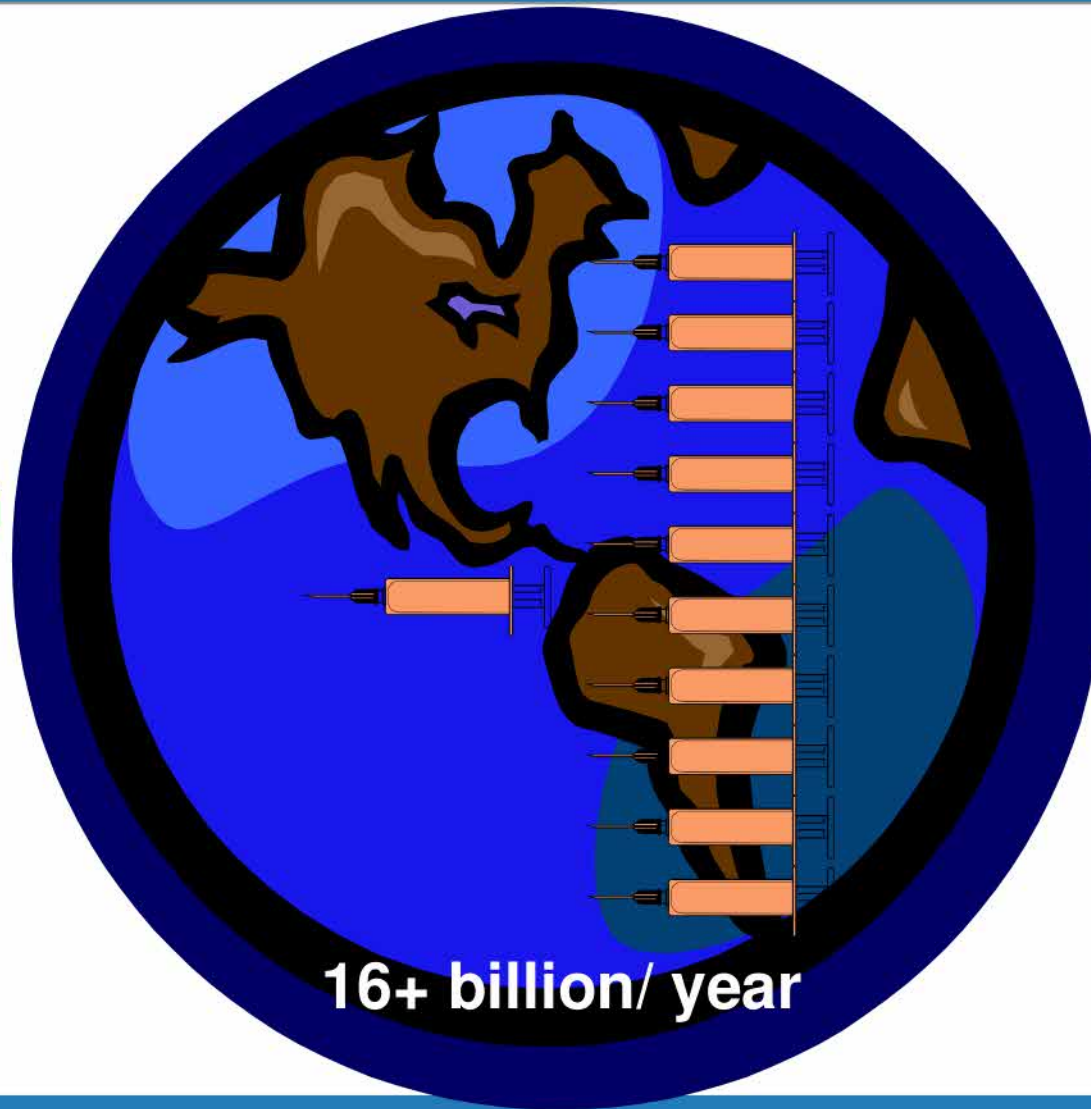
EXPOSED :: Watch how young innocent kids were made to lay down in hospital beds and pretend they're suffering due to Polio vaccination, to give a wrong message to masses regarding the #Polio campaign; SHAME on such people who're playing with the future of Pakistan !

#Peshawar



Use of injections worldwide

**Immunization
injections
5% to 10%**



**Therapeutic
injections
90 to 95%**

Global disease burden due to unsafe injections: situation and progress

■ In 2010:

- between 16734 and 33468 HIV infections, between 157592 and 315120 HCV infections, and 1.68 million HBV infections attributed to unsafe injections.

■ Between 2000 and 2010:

- reuse of injection devices dropped from 39.8% to 5.5%.
- reductions in unsafe therapeutic injections resulted in 87%, 83%, and 91% decrease in HIV, HCV, and HBV infections due to injections.

■ In 2008 it was estimated that:

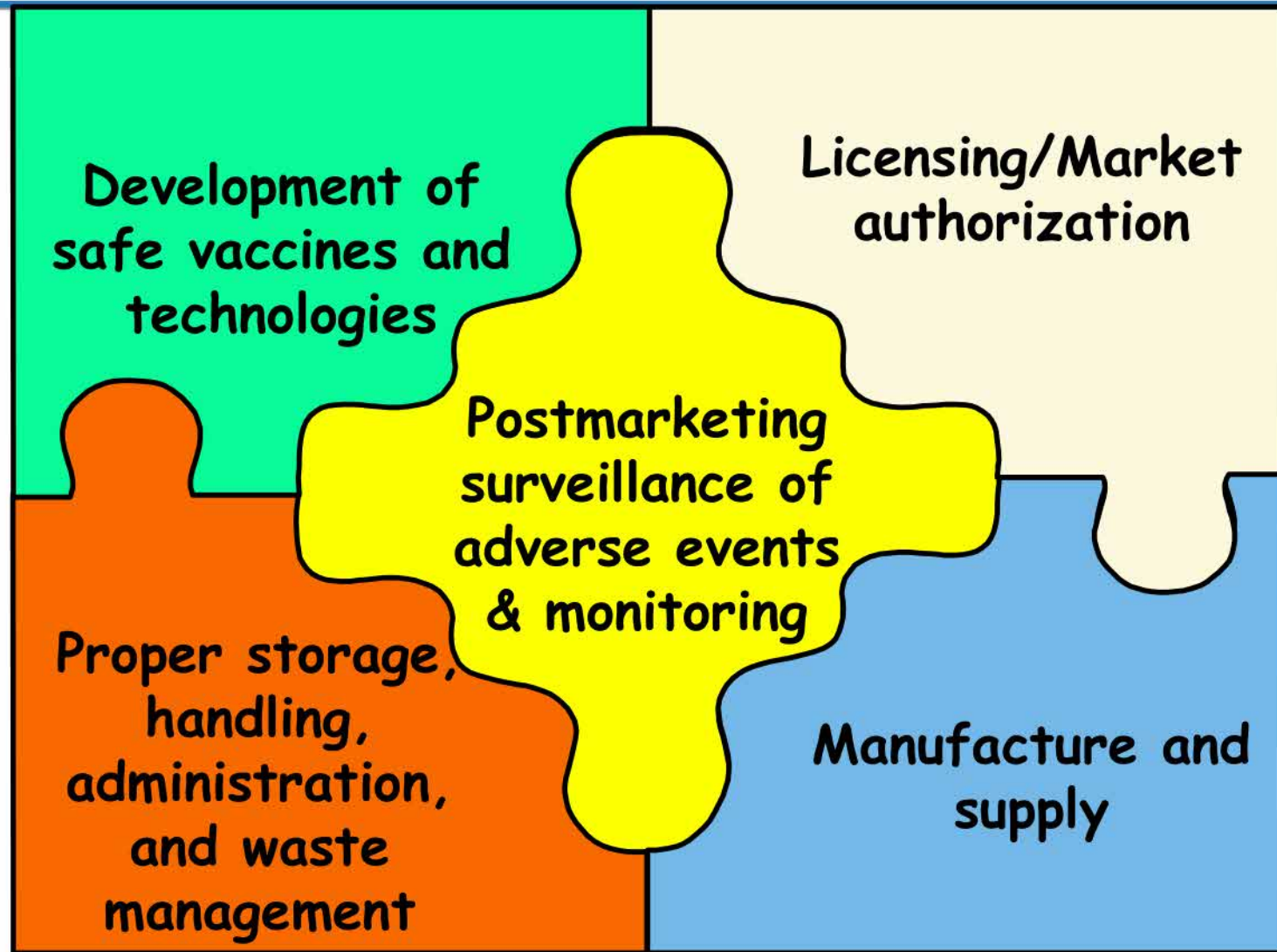
- use of auto-disable syringes for immunization prevented around 5500 HIV infections, 50000 HCV infections, 220000 HBV infections and 34000 injection site abscesses.
- hepatitis B vaccination prevented over 1.5 million infections from unsafe injections.

Immunization safety

"ensuring and monitoring the safety of **all** aspects of immunization, including:

- vaccine quality,
- transport, storage and handling,
- vaccine administration,
- and the disposal of sharps."

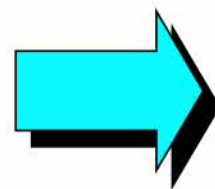
What makes a vaccination safe?



Vaccines of assured quality

WHO's Goal

Ensure that "100%" of vaccines used in all national immunization programmes are of assured quality



Definition of "Assured quality vaccines"

- ✓ National Regulatory Authority (NRA) independent from vaccine manufacturer
- ✓ NRA meeting maturity level 3 for required regulatory functions (*8 regulatory functions**)
- ✓ No unresolved reported problem with vaccine

Guided by Expert Committee on Biologicals Standardization (ECBS).
Recommendations on safety, efficacy and quality issued in WHO Technical Report Series (TRS)



This definition is based on the WHO Expert Committee on Biologicals Standardization and the revised WHO Global Benchmarking Tool (GBT) http://www.who.int/medicines/regulation/benchmarking_tool/en/ & www.who.int/biologicals/expert_committee/en/

WHO prequalification

Objectives

- Provide UN purchasing agencies (UNICEF and PAHO revolving fund) with an **independent opinion/ advice** on the quality, safety and efficacy of vaccines
- Ensure that candidate vaccines are **suitable for target population** and meet **programme needs (programmatic suitability)**
- Ensure **compliance with specifications and established standards of quality**

Principles

- **Reliance on a "functional" NRA**
- **Targeted testing** for compliance with specifications
- **Monitoring of complaints** from field

WHO Prequalified Vaccines

ions Browse Prequalified Vaccines Advanced Search

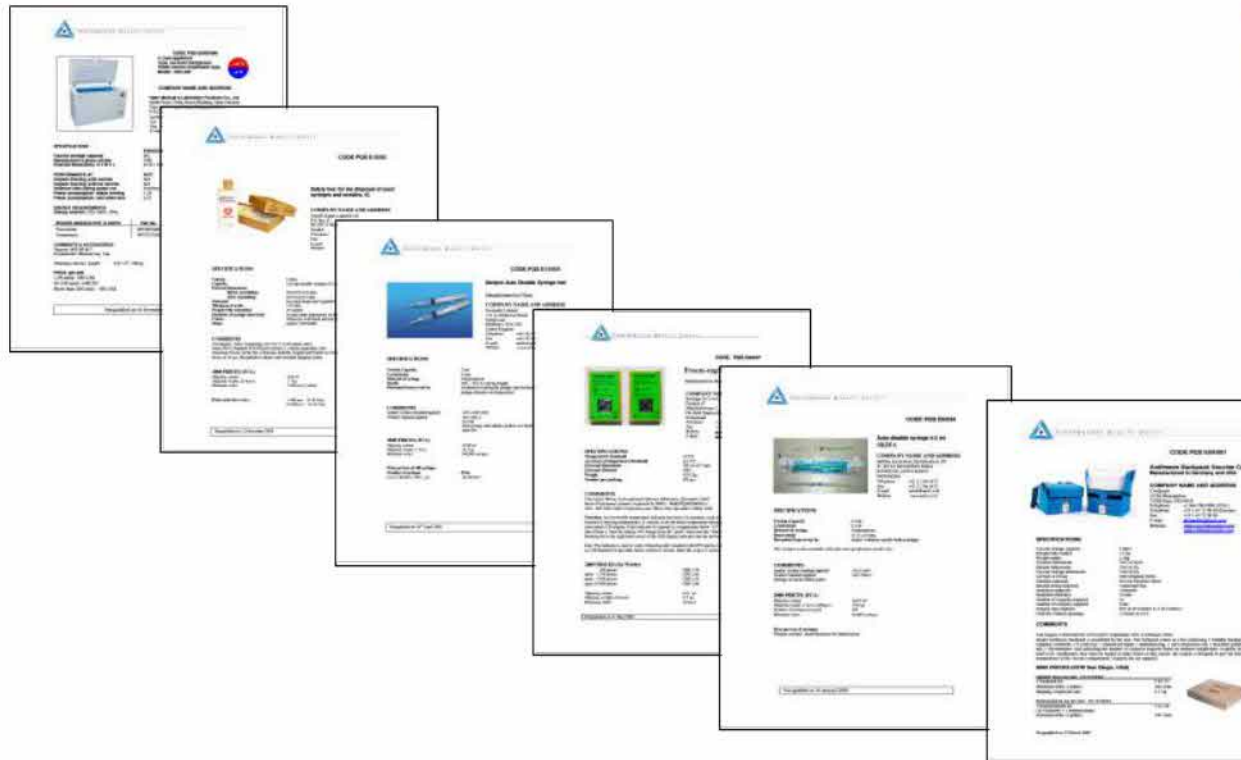
Last updated: 23/04/2019 235 presentation(s) for 147 vaccine(s)


Prequalified	Type	Commercial Name	Pharmaceutical Form	Presentation	No. of Doses	Manufacturer	Responsible NRA
26/09/2006	Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b	Quinvaxem	Liquid: ready to use	Vial	1	Janssen Vaccines Corp.	Ministry of Food and Drug Safety
11/03/1999	Diphtheria-Tetanus	Adsorbed DT Vaccine	Liquid: ready to use	Vial	10	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
06/04/2001	Diphtheria-Tetanus-Pertussis (whole cell)	DTP Vaccine	Liquid: ready to use	Vial	10	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
13/05/2004	Hepatitis B	Hepatitis B Vaccine Recombinant	Liquid: ready to use	Uniject	1	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
09/04/1997	Polio Vaccine - Oral (OPV) Trivalent	Oral polio	Liquid: ready to use	Vial	10	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
09/04/1997	Polio Vaccine - Oral (OPV) Trivalent	Oral polio	Liquid: ready to use	Vial	20	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
11/03/1999	Tetanus Toxoid	TT vaccine	Liquid: ready to use	Vial	10	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
11/03/1999	Tetanus Toxoid	TT vaccine	Liquid: ready to use	Vial	20	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
29/10/2003	Tetanus Toxoid	TT vaccine	Liquid: ready to use	Uniject	1	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
09/04/1997	Measles	Measles vaccine	Lyophilised active component to be reconstituted with excipient diluent before use	Vial + Ampoule	10	PT Bio Farma (Persero)	National Agency of Drug and Food Control Indonesia
17/10/2001	Yellow Fever	Yellow Fever	Lyophilised active component to be reconstituted with excipient diluent before use	Two vial set (active + excipient)	5	Bio-Manguinhos/Fiocruz	Agencia Nacional da Vigilância Sanitária
			Lyophilised active component	Two vial set			

https://extranet.who.int/gavi/PQ_Web/

Injection and other immunization related equipment: regulations and prequalification

Regulation of equipment and devices for immunization WHO prequalification Performance Quality and Safety project (PQS)



**World Health Organization**

عربي | 中文 | English | Français

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PQS Catalogue

The WHO Performance, Quality and Safety (PQS) process prequalifies devices so that member states and UN purchasing agencies are assured of suitability for use in immunization programs. The PQS process also provides a range of manufacturers to apply for prequalification so that a complete range of products develops.

The PQS website provides relevant documents, procedures, and data on currently prequalified products in the following equipment categories:

- E001: [Cold rooms, freezer rooms, and related equipment](#)
- E002: [Refrigerated vehicles](#)
- E003: [Refrigerators and freezers](#)
- E004: [Cold boxes and vaccine carriers](#)
- E005: [Coolant-packs](#)
- E006: [Temperature monitoring devices](#)
- E007: [Cold chain accessories](#)
- E008: [Injection devices for immunization](#)
- E010: [Waste management equipment](#)
- E013: [Injection devices for therapeutic purposes](#)

WHO PQS Devices Catalogue

The WHO PQS Devices Catalogue includes details of all immunization equipment currently pre-qualified by WHO for procurement by United Nations agencies. To comprehensive guidance notes to help purchasers make informed choices, the catalogue is updated whenever a change occurs with regards to a manufacturer or a laboratory. For assistance with the WHO PQS Devices Catalogue, please contact the PQS Secretariat at: gobinai@who.int

[WHO PQS Devices Catalogue](#) (PDF, version: 05 July 2018).

Feedback

User feedback supplies valuable information on equipment performance and conditions. It also facilitates identification of emerging vaccine transportation needs that are not met (fully) with the existing products on the market.

13 | http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/

A Safe Injection

- No harm to the recipient
- No harm to the health-care worker
- No harm to the community

Reuse of equipment



Unsafe collection



Unsafe disposal



Joint WHO/UNICEF 2019 policy statement promoting the exclusive use of injection safety devices for all immunization activities*

Policy on Injection Safety

All countries should use only auto-disable (AD) syringes for immunization injections (ISO 7886-3) and reuse prevention syringes (RUP) (ISO 7886-4) for vaccines reconstitution.

WHO & UNICEF: preference for AD mechanisms triggered at the start of injection.

Bundling Policy

Ensure sufficient number of AD syringes, reconstitution syringes and safety boxes for each vaccine dose.

Safety of injections

WHO-UNICEF-UNFPA joint statement[§] on the use of auto-disable syringes in immunization services

1. The issue of standard single-use disposable syringes and needles versus the potential



Joint Policy Statement[§]

Promoting the exclusive use of injection safety devices for all immunization activities

WHO and UNICEF strongly recommend the systematic and exclusive use of auto-disable (AD) syringes for the delivery of vaccines and reuse prevention syringes (RUP) for the reconstitution of vaccines during routine immunization services and mass vaccination campaigns.

This policy statement, which replaces the 1999 WHO/UNICEF/UNFPA joint policy statement on this subject, further re-affirms that:

- Auto-disable syringes, vaccines and safety boxes continue to be supplied as a "bundle"; and
- UNICEF will not procure standard disposable syringes for any immunization activities, including syringes used for reconstitution.

In addition, WHO and UNICEF:

Urge countries to:

- Develop a strategy for the exclusive procurement, training and education of health workers on the use of AD syringes and reuse prevention syringes for vaccine delivery and reconstitution, as well as their effective disposal and waste management;
- Evaluate the feasibility of adopting injection devices with sharps injury protection (SIP) technologies for vaccines; and
- Transition by 2020, to the exclusive procurement and use of AD syringes for vaccine administration and reuse prevention syringes for vaccine reconstitution that meet WHO quality standards.

Urge donors and development partners to:

- Exclusively fund vaccines bundled with WHO prequalified AD syringes and reuse prevention syringes for vaccine delivery and reconstitution, and sharps safety boxes for sharps disposal;
- Support health-worker training in the use of AD syringes and reuse prevention syringes for all immunization activities.

Urge manufacturers to:

Further develop and improve affordability of AD and RUP syringes and sharps injury protection (AD/SIP) technologies for both delivery and reconstitution devices.

Context

WHO, UNICEF and partners – including the Safe Injection Global Network (SIGN), have been working together for

more than two decades to promote safe injection practices with policy makers and programme managers, in making sterile injection equipment widely available, and in

[§] The joint policy statement revises and replaces the WHO-UNICEF-UNFPA policy statement on the use of auto-disable syringes in immunization services. WHO/V&B/99.2. It is issued by the World Health Organization, Geneva, Switzerland (Department of Immunization, Vaccines and Biologicals, and the Department for Essential Medicines and Health Products), the United Nations Children's Fund (UNICEF Programme Division, New York, USA and UNICEF Supply Division, Copenhagen, Denmark).

~40 WHO prequalified AD syringes (.05ml, .1ml, .25ml, .5ml) including some with sharps injury prevention (SIP) features and >50 WHO prequalified reuse prevention (RUP) injection devices for therapeutic use including a large number with SIP features



Disposable syringes: \pm 3 cents

ADs & RUPs: 3 to 5 cents per unit

SIPs a few cents more

Are AD & reuse prevention injection devices an answer to all injections safety issues?

NO,

AD does NOT stand for

Auto Destructible or Auto Disposable syringe



Are ADs & reuse prevention injection devices an answer to all injections safety issues?

NO,

AD does NOT stand for

Auto-Destructible or Auto-Disposable syringe

it stands only for

Auto-Disable syringe for fixed dose immunization

- **AD & reuse prevention injection devices prevent reuse problems and do not protect the vaccinator nor the community**



Reading labels?



Proper reconstitution?



Following the open vial policy?

DANGER

BCG Measles

freeze-dried Hib Vaccine

Freeze-dried Vaccine

Yellow Fever

Must be discarded 6 hours after reconstitution

Adapted from poster CCPS/21, (4031) Freeze-dried Vaccine, World Health Organization (WHO)

If Vaccine Vial Monitor (VVM), which is a thermochromic label, is on cap discard after 6 hours

If VVM on vial you can keep vaccine for 28 days as per Multi Dose Vial Policy



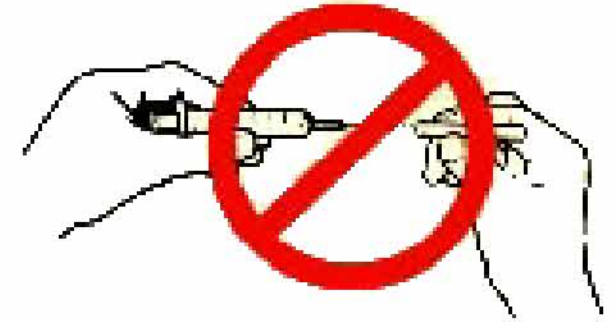
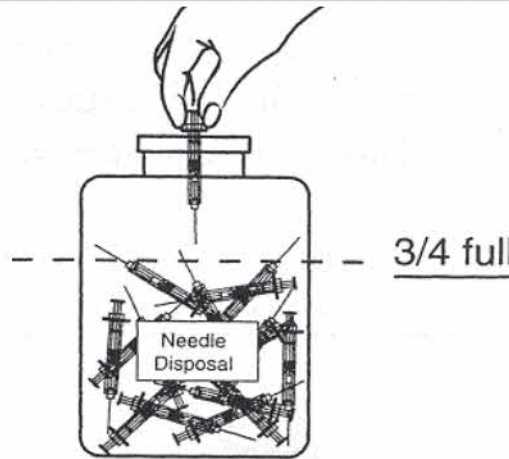
Using the proper technique?



Reprinted with permission from *Immunization in Practice*, WHO/EPI/TRAM/98.12

Collection of Sharp Waste

- Puncture proof
- Filled by max. $\frac{3}{4}$



Safety Box/
container



Needle & hub Cutters

Some good and some bad practices

Two-handed recapping is dangerous



Checking packages for breaks in integrity



The sharps box needs to be next to the patient care area



Needle left in the septum of a multi-dose diluent vial



Lots of progress... but work not finished yet !

Notes from the Field

Injection Safety and Vaccine Administration Errors at an Employee Influenza Vaccination Clinic — New Jersey, 2015

Laura Taylor, PhD¹; Rebecca Greeley, MPH¹; Jill Dinitz-Sklar, MPH¹;
Nicole Mazur, MPH¹; Jill Swanson, MPH²; JoEllen Wolicki, BSN³;
Joseph Perz, DrPH⁴; Christina Tan, MD¹; Barbara Montana, MD¹

On September 30, 2015, the New Jersey Department of Health (NJDOH) was notified by an out-of-state health services company that an experienced nurse had reused syringes for multiple persons earlier that day. This occurred at an

Training, advocacy and information, education and communication are essential and require continued attention and resources!

Waste Management

- **Stockholm and Basel conventions**
- **Environmental concerns, bans on burning in some countries**
- **Strategies**
 - No one-size-fits-all solution
 - Solutions do exist for many situations “non-availability” of technologies = “wrong problem”
 - Assessment and proper management using best option considering setting. Might be burying in pit or encapsulation in concrete
 - Identification and development of recycling options
 - All components same plastic, PVC free

Waste Treatment

- **International strategy: treatment of waste without generation of hazardous emissions like Dioxins and Furans:**

Movement from Small Scale Incineration towards environmental friendly high temperature incineration in accordance with Stockholm's Convention's best available techniques.

- **Basel Convention:**

Steam treatment by autoclaving is highlighted as the **PREFERRED METHOD** for the treatment of healthcare waste.

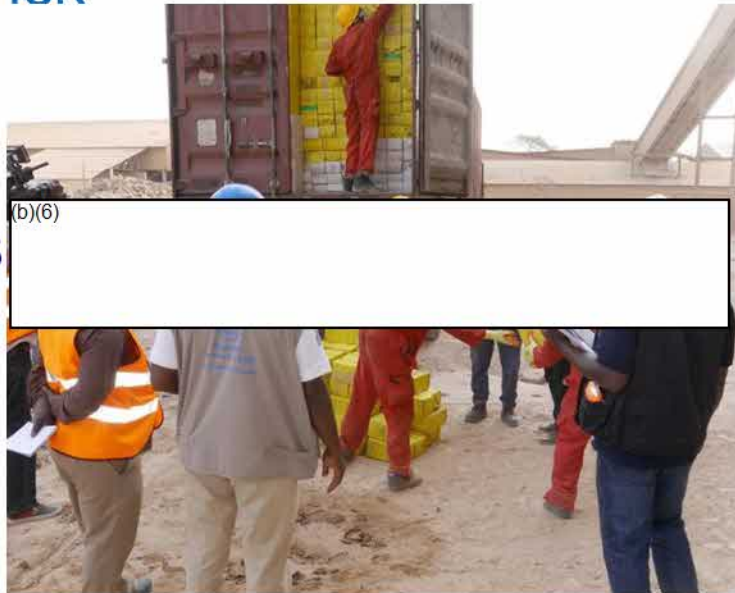
Incineration

Incineration is a wide spread method for burning infectious and sharp waste

Emissions should comply with national standards and the Stockholm's Convention if country signatory

Single-chamber, drum and brick incinerators not acceptable but transitional method

Ashes considered hazardous (heavy metals, dioxin and furans) → hazardous waste landfill, ash pit or treatment needed!



Steam based treatment: Autoclaving

■ Principles:

- based on a thermal decontamination process with high pressure and temperature (e.g. 121 or 134°C).
- waste can be disposed like normal non-general waste on a landfill / dumpsite

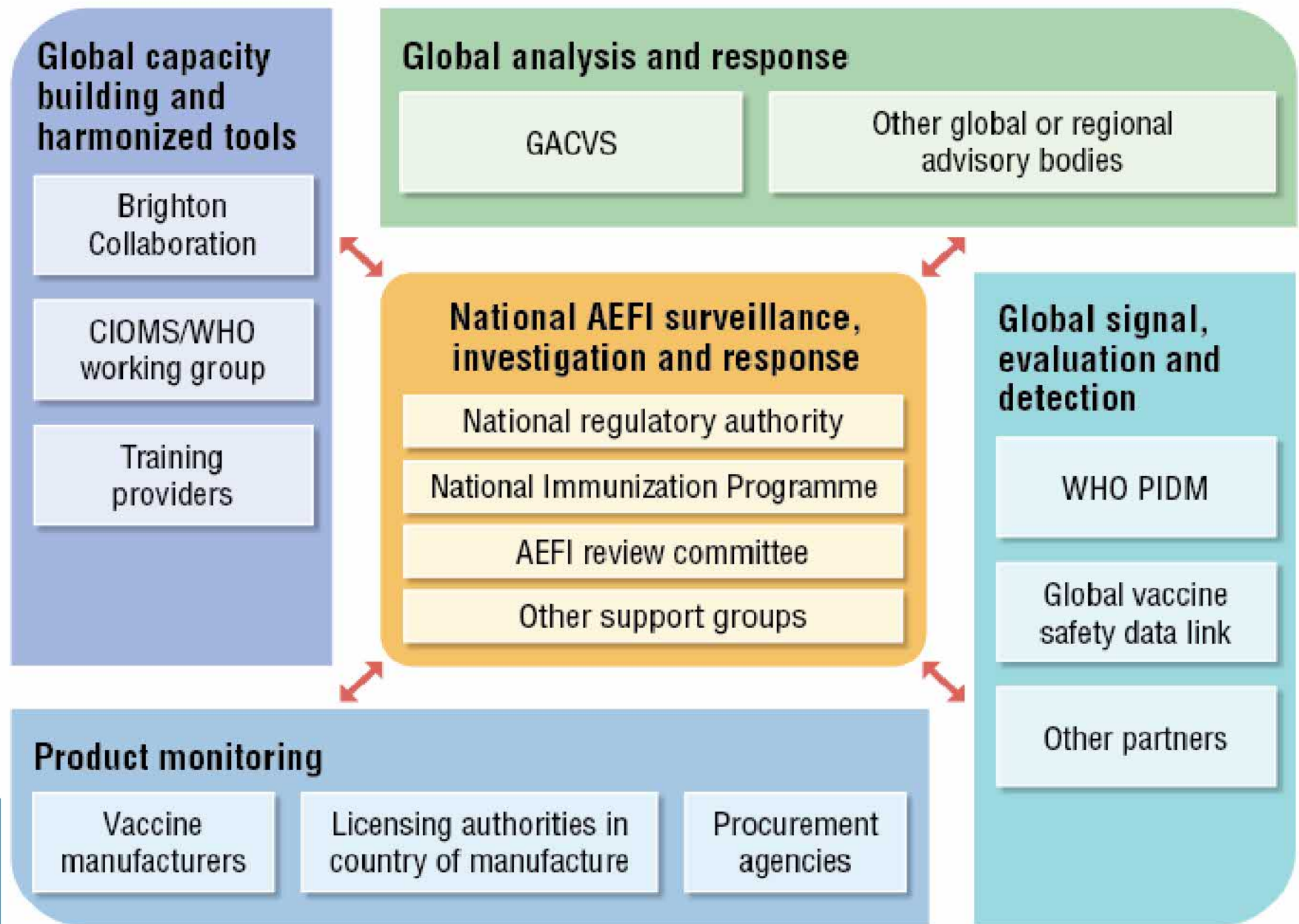
BUT autoclaves need reliable water and electricity connections and introduction not easy

Progress with international projects like Global Environment Facility financed ones in: Madagascar, Zambia, Ghana, Tanzania, Kenia, Egypt, Jordan, Kyrgyzstan*, Kazakhstan.



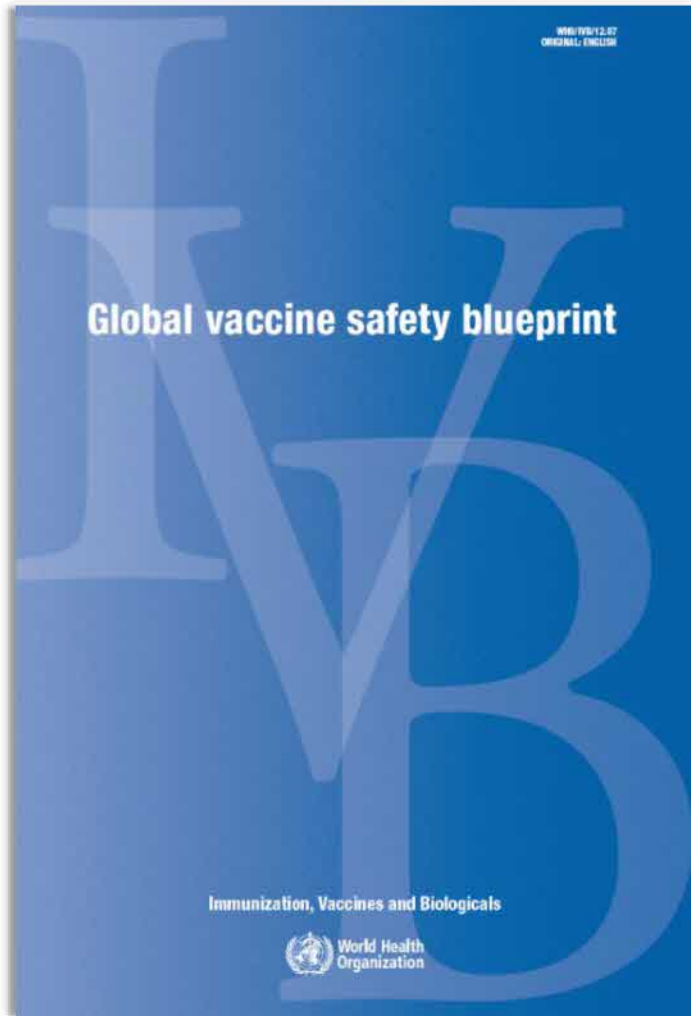
* In Kyrgyzstan the burning of HCW is prohibited – only autoclaving is supposed to be used.

Global vaccine safety, monitoring and response system



Global Vaccine Safety Blueprint

Developed with and for low and middle income countries



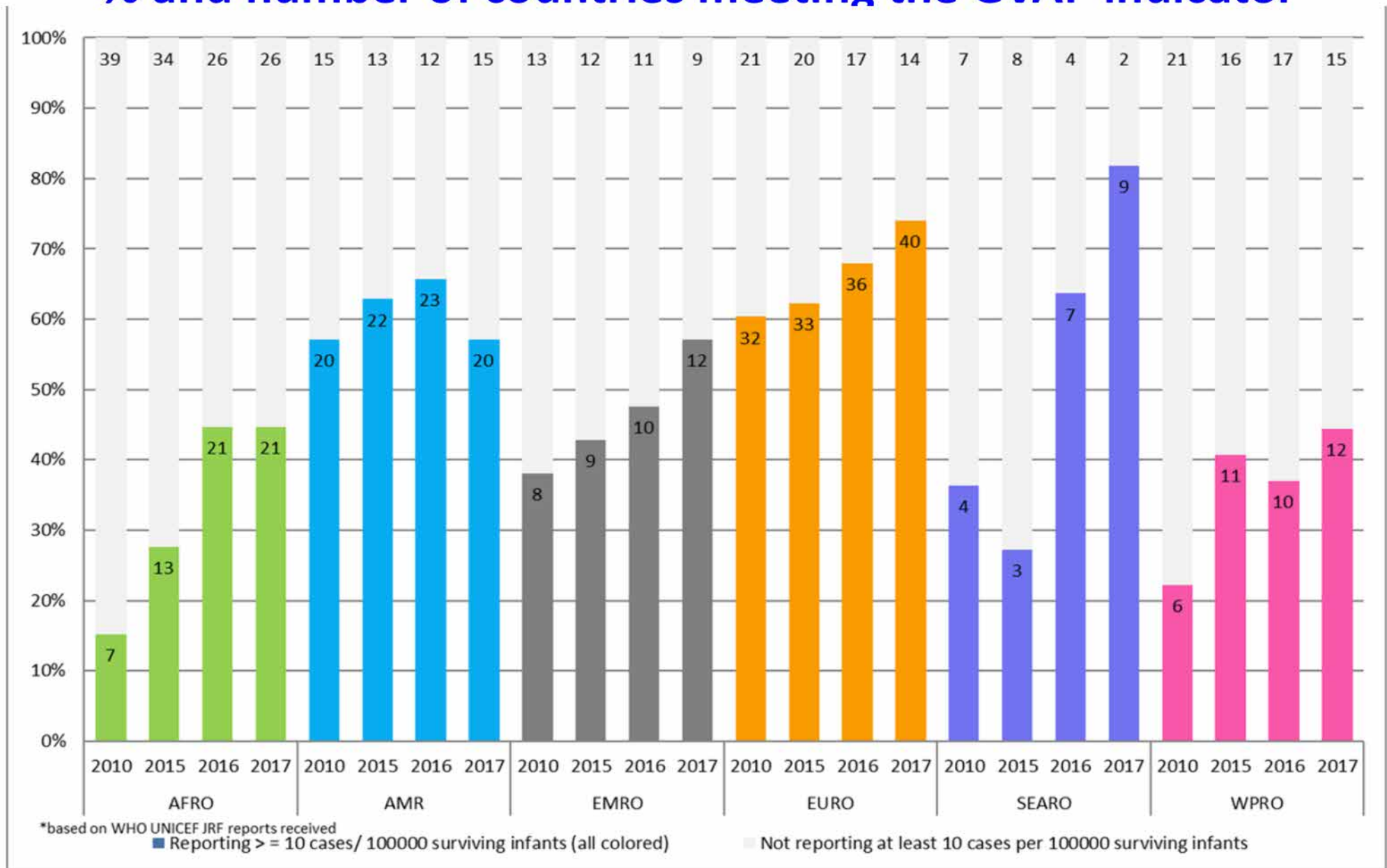
Capacity-building model towards, a **minimal capacity** for vaccine pharmacovigilance.

Solutions for **enhancing** vaccine pharmacovigilance capacity to adequately monitor newly available vaccine products.

Access to technical support from institutions with adequate expertise, cultural and geographical proximity through an integrated network.

Pharmacovigilance business models aligned with those for drugs and other medicinal products.

AEFI reporting 2010 through 2017: % and number of countries meeting the GVAP indicator



With thanks to Madhav Balakrishnan

Adverse Events Following Immunization (AEFI): Field Investigation Simulation

An innovative approach in capacity building for countries involves

- Creating an “artificial vaccine safety crisis” in a village, health centre, hospital and vaccine cold chain system
- This is “investigated”, causality assessment is done and crisis management is rehearsed in controlled conditions

Vaccine safety communications is rehearsed e.g. interpersonal communications, addressing the media and making a press statement



Global analysis and response

Global Advisory Committee on Vaccine Safety (GACVS)

- **Advisory body to WHO**
- **Response to vaccine safety issues of potential global importance**
 - promptly, efficiently, with scientific rigor
- **Broad expertise & Independence**
- **Decisions and recommendations based on best available evidence**

Folb 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: 1926-31.

Global Vaccine Safety

- Global Vaccine Safety Initiative
- Global Advisory Committee on Vaccine Safety**

Topics
Committee reports
Reference documents and publications


The Global Advisory Committee on Vaccine Safety


The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance.

The Committee provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short or long term national immunization programmes.

[GACVS - Terms of Reference](#) pdf, 20kb
 [Annex 1](#) pdf, 63kb
 [Annex 2](#) pdf, 22kb

GACVS areas


Working mechanisms


Members

Next meetings

7, 92, 13-20

No 2



Weekly epidemiological record Relevé épidémiologique hebdomadaire

13 JANUARY 2017, 92th YEAR / 13 JANVIER 2017, 92^e ANNÉE
No 2, 2017, 92, 13-20
<http://www.who.int/wer>

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- 13 Comité consultatif mondial pour la sécurité des vaccins, 30 novembre - 1^{er} décembre 2016

Global Advisory Committee on Vaccine Safety, 30 November – 1 December 2016

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.¹ GACVS held its 35th meeting in Geneva, Switzerland, 30 November – 1 December 2016.

Comité consultatif mondial pour la sécurité des vaccins, 30 novembre - 1^{er} décembre 2016

Le Comité consultatif mondial pour la sécurité des vaccins (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale.¹ Le GACVS a tenu sa 35^e réunion à Genève, Suisse, le 30 novembre – 1^{er} décembre 2016.

Vaccine Safety Net



■ GACVS endorsed criteria for evaluating websites

■ **Credibility**
■ **Content** } **Mandatory**

■ **Accessibility**
■ **Design** } **Desired**

■ Websites evaluations *with preliminary screening*



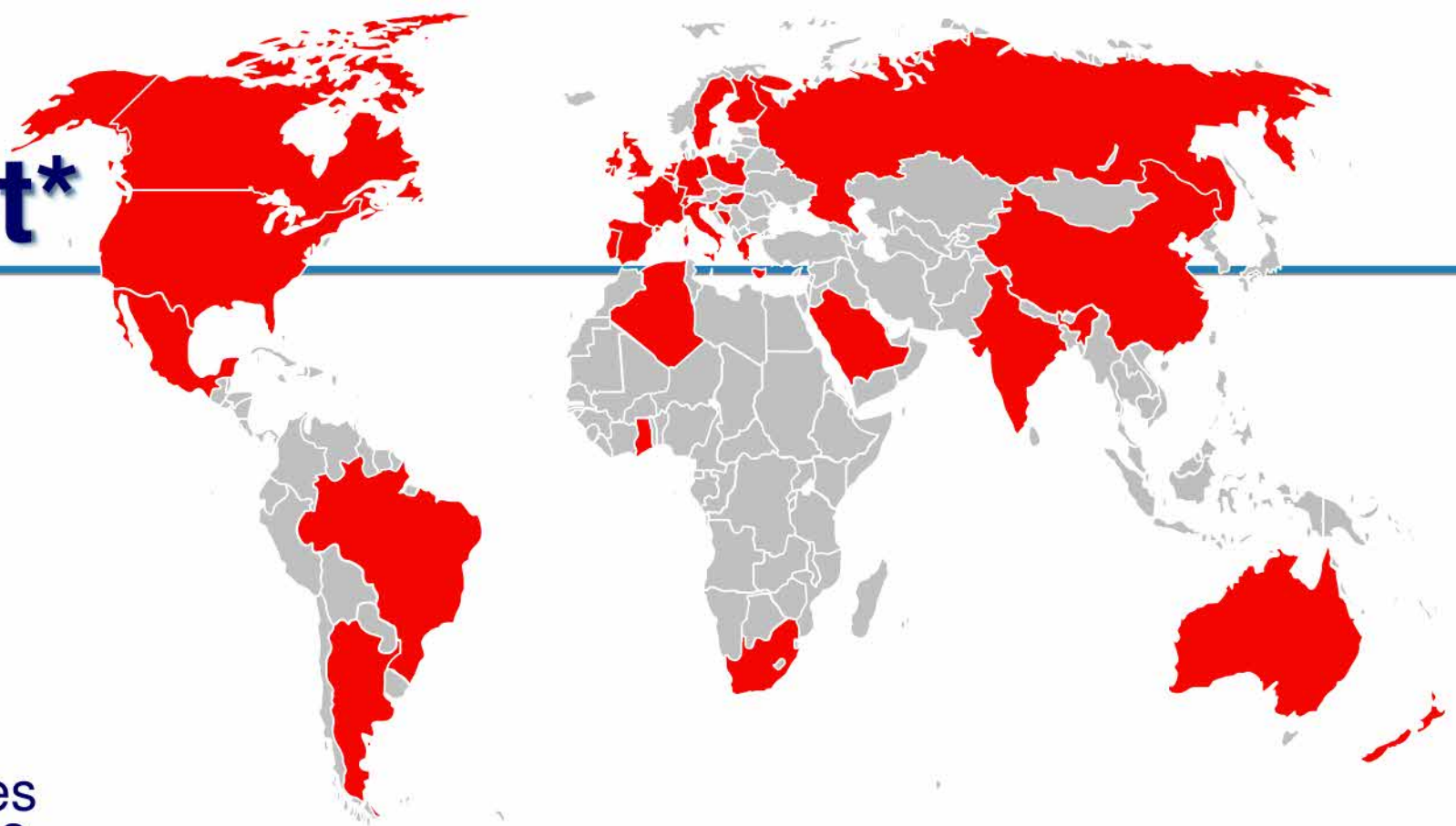
A global network of websites, **evaluated by WHO**, that provide reliable **information on vaccine safety**

Facilitate easy access to reliable, understandable, evidence-based information on the safety of vaccines for internet users, regardless of their geographic location and language

Vaccine Safety Net*

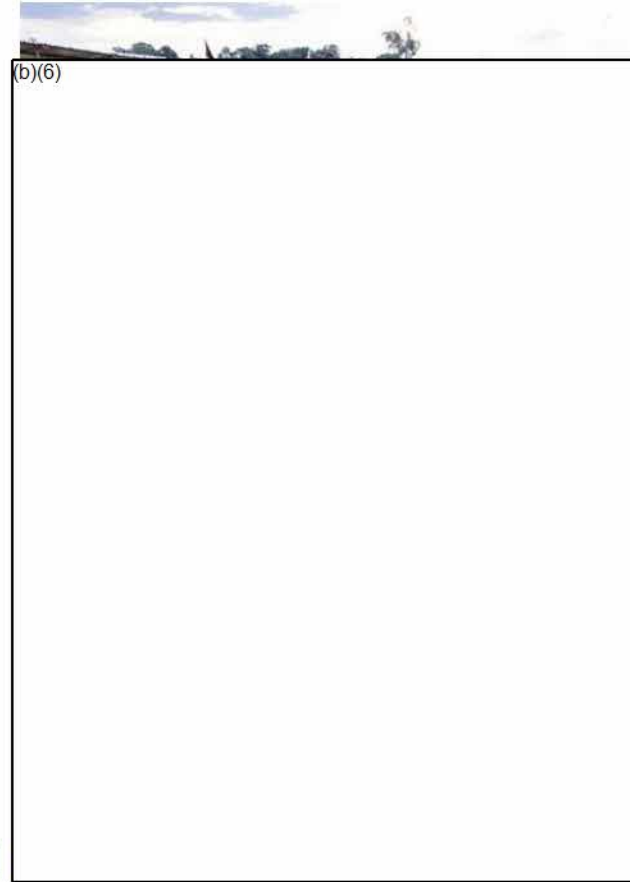
- Established in 2003
- Network of 69 websites from 33 countries
- 22 languages
- 34 candidate websites evaluated in the last 3 months (10 dropped from graduating process)
- Across the globe

Governmental agencies, professional associations, grass roots...



Mass vaccination campaigns - special issues

- **Impression of increase in adverse events**
 - many doses over short period of time
 - more vigilance/awareness
 - different age groups targeted
- **Real rise from programmatic errors**
 - pressure and fatigue result in normal safe injection practices not observed
 - new staff lack specific training and expertise
- **Increased risk of negative impact of rumours**
- **Mass Immunization Stress-Related Response**
- **Adverse events generate criticism of campaign**
- **Huge amount of waste to dispose of!!**



Immunization safety: What is needed?

- Exclusive use of vaccine of ensured quality
- Prevent reuse of needles/syringes (AD syringes)
- Proper disposal of immunization waste
- Appropriate waste management and treatment
- Training of staff and supervision
- Effective AEFI monitoring and management (background rates)
- Appropriate handling of safety issues and rumours
- Global collaboration

YOUR ADVOCACY





From: philippe.duclos@k-net.fr
Sent: 6 Jun 2019 15:12:04 +0200
To: 'Neal Halsey'; 'Edwards, Kathryn'; nkarora@inclentrust.org; 'Heidi Larson'
Cc: jim.buttery@monash.edu; 'Daniel Salmon'; 'Sturkenboom, M.C.J.'; 'Heininger, Ulrich'; 'Admin'; 'Destefano, Frank (CDC/DDID/NCEZID/DHQP)'; 'Eric Fombonne'; 'GARCON Nathalie'; 'jason.m.glanz@kp.org'; 'All@ssi.dk'; 'Paul Henri Lambert'; 'Markowitz, Lauri (CDC/DDID/NCIRD/DVD)'; 'offit@email.chop.edu'; 'Peden, Keith (FDA/CBER)'; 'Andrew Pollard'; 'Sejvar, James (CDC/DDID/NCEZID/DHCPP)'; 'nhalsey@jhsph.edu'; 'priya.bahri@ema.europa.eu'; '(b)(6)'; 'bodenstabh@email.chop.edu'; '(b)(6)'; 'Ulrich Heininger'; 'hotez@bcm.edu'; 'liz.miller@hpa.org.uk'; 'h.petousis-harris@auckland.ac.nz'; 'Amy Pisani'; 'rtchen1135@gmail.com'; 'Stanley Plotkin'
Subject: RE: A couple of ideas

Dear Neal,

Of course please feel free to share my ADVAC safety presentation as you wish.

With kind regards,

Phil

De : Neal Halsey <nhalsey1@jhu.edu>

Envoyé : jeudi 6 juin 2019 14:59

À : Edwards, Kathryn <kathryn.edwards@vumc.org>; nkarora@inclentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>; Philippe Duclos <philippe.duclos@k-net.fr>

Cc : jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; (b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Objet : Re: A couple of ideas

All of the ideas that have been proposed so far are worthwhile. I would like to reiterate the suggestion I made at the meeting. (b)(5)

(b)(5)

(b)(5)

Neal

From: "Edwards, Kathryn" <kathryn.edwards@vumc.org>
Date: Thursday, June 6, 2019 at 7:22 AM
To: "nkarora@incentrust.org" <nkarora@incentrust.org>, Heidi Larson <Heidi.Larson@lshtm.ac.uk>
Cc: "jim.buttery@monash.edu" <jim.buttery@monash.edu>, Daniel Salmon <dsalmon1@jhu.edu>, "Sturkenboom, M.C.J." <M.C.J.Sturkenboom@umcutrecht.nl>, "Heininger, Ulrich" <ulrich.heininger@ukbb.ch>, Admin <admin@vaxconsult.com>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>, Eric Fombonne <fombonne@ohsu.edu>, GARCON Nathalie <Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, "All@ssi.dk" <All@ssi.dk>, PAUL-HENRI LAMBERT <Paul.Lambert@unige.ch>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>, James Sejvar <zea3@cdc.gov>, JPIDS JPIDS <nhalsey@jhsph.edu>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, (b)(6), (b)(6), "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, (b)(6), Ulrich Heininger <ulrich.heininger@unibas.ch>, "hotez@bcm.edu" <hotez@bcm.edu>, "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, Amy Pisani <amyp@ecbt.org>, (b)(6), (b)(6), Stan Plotkin <stanley.plotkin@vaxconsult.com>
Subject: RE: A couple of ideas

This is the letter that was recently published in CID and mentioned at the meeting on MHTFR.

From: Edwards, Kathryn
Sent: Thursday, June 6, 2019 5:57 AM
To: nkarora@incentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>
Cc: jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; (b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>
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(b)(5)

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Kathryn M. Edwards MD
Sarah Sell and Cornelius Vanderbilt Chair
Professor of Pediatrics
Vanderbilt University Medical Center

From: Amy Pisani
Sent: 6 Jun 2019 13:00:01 +0000
To: Edwards, Kathryn;nkarora@incitrust.org;Heidi Larson
Cc: jim.buttery@monash.edu;Daniel Salmon;Sturkenboom, M.C.J.;Heininger, Ulrich;Admin;Destefano, Frank (CDC/DDID/NCEZID/DHQP);Eric Fombonne;GARCON Nathalie;jason.m.glanz@kp.org;All@ssi.dk;Paul Henri Lambert;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);Andrew Pollard;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu;priya.bahri@ema.europa.eu;(b)(6);bod enstabh@email.chop.edu;(b)(6);Ulrich
Heininger;hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;(b)(6);Stanley Plotkin
Subject: RE: A couple of ideas
Attachments: Religious Views of Vaccination At-a-Glance.pdf, SOTIReport_2019_Final.pdf

I want to once again thank Stanley for convening this meeting and all of the presenters for offering in-depth research summaries on vaccine safety. As I mentioned in the introduction time on day one, I have been reading your research for my entire public health career and to be present at the meeting to hear you all present in person was akin to meeting my favorite rock stars.

I left the meeting with even greater confidence that the vaccines offered to the children of this world are indeed safe and incredibly well monitored. That being said, I continue to work with my colleagues in the U.S. to push for policies that will ensure the ongoing ability to oversee vaccine safety and communicate to the public. I have a big idea swirling around in my head regarding a way to share the scientific evidence presented at the meeting to the public in a weekly social media post, along with accompanying graphics. I do believe that if we can find a way to share the data, parents can make informed decisions based on real science...the trick is to understand the algorithms that allow our posts to be heard among all of the "noise".

In the meantime, I have attached a resource on the religious views of vaccination which we use quite often at Vaccinate Your Family when addressing legislators. It is also used by our partners at the state and local level who must respond to legislative attempts to weaken vaccine requirements for school and daycares. We are planning to add additional resources to address the recent attempts to dissuade some Jewish populations from vaccinating. Also attached is our "State of ImmUnion" report which we present to the Congress the week of our President's "State of the Union" address each year.

I am truly enjoying this follow up thread and working to improve the safety information presented on our Vaccinate Your Family website based on all of your work.

Most Sincerely,

Amy Pisani, MS
Executive Director
(202) 277-7587



The Next Generation of Every Child By Two

From: Edwards, Kathryn [mailto:kathryn.edwards@vumc.org]

Sent: Thursday, June 6, 2019 7:22 AM

To: nkarora@inclentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>

Cc: jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amy@vaccinateyourfamily.org>; (b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>

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Kathryn M. Edwards MD
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Religious Views of Vaccination At-A-Glance

- While there is a minority of **Amish** parents who do not vaccinate their children, vaccination is not prohibited by their religion.¹
- In 2010, Tibetan **Buddhist** spiritual leader and Nobel laureate the Dalai Lama helped vaccinate and launch a polio eradication drive in India.²
- There are some faith-healing groups—of which the **Church of Christ, Scientist (Christian Science)** is the most prominent—that believe they can heal all things through prayer rather than through medicine. Therefore, many of these worshippers strongly oppose vaccinations.^{3, 4, 5}
- The **Church of Jesus Christ of Latter-day Saints** has supported childhood vaccination for over 30 years. In July 1978 they stated, “We urge members of The Church of Jesus Christ of Latter-day Saints to protect their own children through immunization. Then they may wish to join other public-spirited citizens in efforts to eradicate ignorance and apathy that have caused the disturbingly low levels of childhood immunization.”⁶
- There is no formal statement from **Hindu** authorities on vaccination, as Hinduism has several hundreds of sects, each with its own traditions and rules. Many areas of the world with large Hindu populations, such as India which is 80.5% Hindu, have taken proactive efforts to eradicate vaccine-preventable diseases like polio.^{7, 8}
- Many imams and other **Islamic** leaders have issued clear statements commenting that vaccination is consistent with Islamic principles.^{9, 10, 11} In particular, a 1995 conference of Islamic scholars concluded, “The transformation of pork products into gelatin alters them sufficiently to make it permissible for observant Muslims to receive vaccines containing pork gelatin.”¹² However, some specific select Muslim communities throughout the world have opposed vaccinations, including the Nation of Islam, whose leader Minister Louis Farrakhan once said that the 2009 H1N1 flu vaccine was designed to kill people.¹³
- According to The Watch Tower Bible and Tract Society of Pennsylvania, the main legal entity that organizes worldwide activities by **Jehovah’s Witnesses**, “We have no objection to vaccines in general.”¹⁴
- While there is no single voice for **Jewish** communities, many rabbis have spoken out in favor of vaccinations noting the importance of preserving life (*pikuakh nefesh*) and that, according to Jewish law, there is no objection to porcine or other animal-derived ingredients in vaccines.¹⁵
- There is no official statement on immunization from **Sikh** authorities. But generally, Sikhs do not have religious or societal issues against vaccination.
- The **Roman Catholic Church** recognizes the importance of vaccinations and their use in the fight against infectious disease to protect both individuals and the larger community. It advocates use of alternatives, if available, of certain viral vaccines manufactured in cell lines with remote fetal

origins.¹⁶ Additionally, in a 2006 journal article it is stated, “Those who use... vaccines... do not cooperate with the destruction of life and arguably do not facilitate it, nor do they intend the destruction. Further... using cell lines for vaccines... does not deplete the cell supply in a significant way and thus does not necessitate or encourage further destruction of human life.”¹⁷

¹ Grens, K. (June 27, 2011). Amish Parents Mirror Wider Concerns over Vaccines. *Reuters Health*. Retrieved from <http://www.reuters.com/article/2011/06/27/us-amish-parents-idUSTRE75Q5SO20110627>

² Reuters. (January 10, 2010). Video: Dalai Lama Launches polio vaccine. Retrieved from <http://www.reuters.com/video/2010/01/10/dalai-lama-launches-polio-vaccine?videoId=26160277>

³ The College of Physicians of Philadelphia. (2012). Cultural Perspectives on Vaccination. *The History of Vaccines*. Retrieved from <http://www.historyofvaccines.org/content/articles/cultural-perspectives-vaccination>

⁴ GOOD.is. (February 3, 2011). Should Parents Be Allowed to Pray Their Children Healthy? Retrieved from <http://www.good.is/posts/should-families-that-believe-in-faith-healing-be-prosecuted-when-their-children-die>

⁵ Rodgers, D.V., Gindler, J.S., Atkinson, W.L., & Markowitz L.E. (1993). High Attack Rates and Case Fatality During a Measles Outbreak in Groups with Religious Exemption to Vaccination. *Pediatric Infectious Disease Journal*, 12(4): 288-292. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8483622>

⁶ The Church of Jesus Christ of Latter-day Saints. (July 1978). Immunize Children, Leaders Urge. *Liahona*. Retrieved from <http://www.lds.org/liahona/1978/07/immunize-children-leaders-urge?lang=eng>

⁷ Memon, A. (September 20, 2012). Opinion: Cross-border Lessons in Saving Lives. *The Hindu*. Retrieved from <http://www.thehindu.com/todays-paper/tp-opinion/article3916454.ece>

⁸ Office of the Registrar General and Census Commissioner, India under Ministry of Home Affairs, Government of India. (2010-2011). Distribution of Population by Religions. Retrieved from http://censusindia.gov.in/Census_And_You/religion.aspx

⁹ Yahya M. (2006). Polio vaccines—Difficult to Swallow. The Story of a Controversy in Northern Nigeria. Institute of Development Studies. Retrieved from www.ids.ac.uk/files/Wp261.pdf

¹⁰ Kaufmann, J.R., & Feldbaum, H. (2009). Diplomacy and the Polio Immunization Boycott in Northern Nigeria. *Health Affairs*, 28(July-August)(4):1091-101. Retrieved from <http://content.healthaffairs.org/content/28/4/1091.full.html>

¹¹ Jegede, A.S. (2007). What Led to the Nigerian Boycott of the Polio Vaccination Campaign? *PLoS Med*, 4(Mar):e73. Retrieved from <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0040073>

¹² Institute for Vaccine Safety. (2010). Religious Leaders Approval of Use of Vaccines Containing Porcine Gelatin. Retrieved from <http://www.vaccinesafety.edu/Porcine-vaccineapproval.htm>

¹³ United Press International, Inc. (October 19, 2009). Farrakhan Suspicious of H1N1 Vaccine. Retrieved from http://www.upi.com/Top_News/US/2009/10/19/Farrakhan-suspicious-of-H1N1-vaccine/UPI-63931256011008/

¹⁴ Watch Tower Bible and Tract Society of Pennsylvania. (2012). Our View of Medical Care: Health Choices. Retrieved from <http://www.jw-media.org/aboutjw/article02.htm>

¹⁵ Institute for Vaccine Safety. (2010). Religious Leaders Approval of Use of Vaccines Containing Porcine Gelatin. Retrieved from <http://www.vaccinesafety.edu/Porcine-vaccineapproval.htm>

¹⁶ Pontifical Academy for Life. (2005) “Moral Reflections on Vaccines Prepared from Cells Derived from Aborted Human Foetuses” Retrieved from <http://www.academiavita.org/publications.php>

¹⁷ Sujdak Mackiewicz, Birgitta N. “Can Catholic Facilities Justify The Use Of Embryonic Stem Cell Therapies Developed From The Destruction Of Human Embryos?” *Health Care Ethics USA*. 14.2 (2006).



2019

STATE OF THE **IMM**UNION

A REPORT ON VACCINE-PREVENTABLE DISEASES IN THE U.S.



2018 PROVED VACCINE-PREVENTABLE



DISEASES ARE STILL A THREAT TO THE U.S.

2018 marked a difficult year in our fight against vaccine-preventable diseases. The country experienced a record number of flu deaths, measles cases and hepatitis A cases across the U.S. A lack of sufficient federal and state funding, barriers to vaccine access and a lack of understanding of the need for timely vaccines is helping to fuel the rise of vaccine-preventable diseases.

The Centers for Disease Control and Prevention (CDC) reported that the 2017-2018 influenza season resulted in approximately 79,000 deaths,¹ including 185 children, most of whom were unvaccinated.² That's more deaths from the flu than we have seen in any single season since the 1970s. Only 37% of adults³ and 58% of children⁴ received the flu vaccine during the season, despite the fact that vaccination is the best way to avoid serious

illness and complications from flu. As a result, flu and pneumonia remain the eighth most common killer of adults in the U.S.⁵

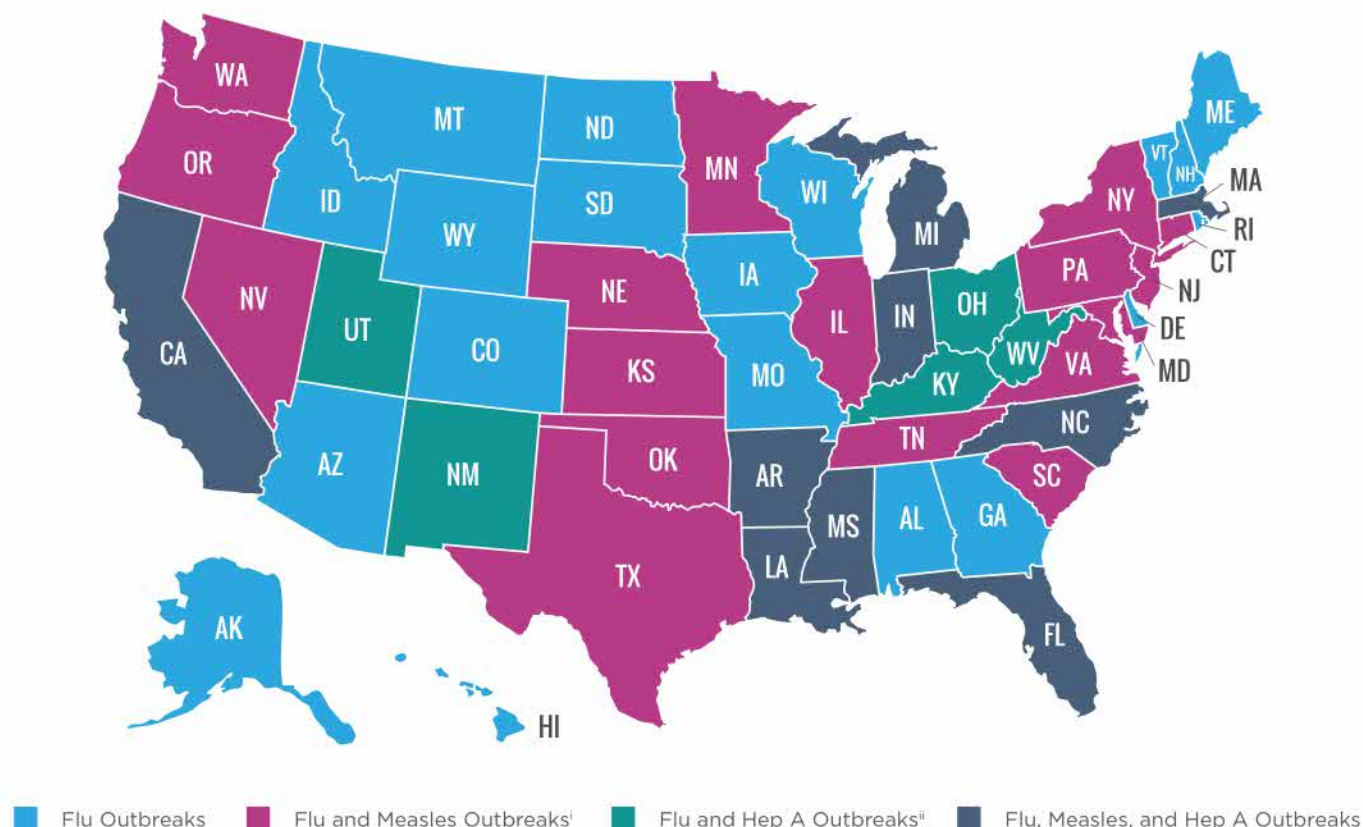
Meanwhile, measles cases are once again on the rise. After major, single source outbreaks in 2015 and 2017, multiple cases were imported to the U.S. by travelers with measles over the course of 2018. In 2018, 349 individual cases of measles were confirmed in 26 states and the District of Columbia. This is the second-greatest number of annual cases reported since measles was eliminated in the U.S. in 2000. (The greatest was 667 cases reported in 2014). The majority of people who got measles were unvaccinated.⁶

Compounding these issues are ongoing outbreaks of hepatitis A. Beginning in the spring of 2017, hepatitis A outbreaks began primarily among people who use drugs and/or are experiencing homelessness.⁷ These groups can be difficult for public health workers to reach, straining resources that were already spread thin due to the serious flu season. In states such as California, funding was quickly expended responding to these public health crises, and the CDC had no further funding for the year to support the state's efforts.

How did we get here? Throughout this report, we examine the reasons why children, adolescents and adults including pregnant women may not be receiving timely vaccinations. Most importantly, we put forward several policy solutions to stop the needless loss of lives due to vaccine-preventable diseases.

The CDC has declared vaccines to be the single greatest public health intervention of the 20th century, second only to clean water. Furthermore, we know that for every \$1 spent on childhood vaccination, our country saves \$10.10 Together, we can ensure we're saving both lives and money.

Are Disease Outbreaks Affecting Your State?



Honoring a Policy Pioneer

In November 2018, Vaccinate Your Family co-founder Betty Bumpers, wife of the late Senator Bumpers and former first lady of Arkansas, passed away. Working alongside Former First Lady Rosalynn Carter for over thirty years, Betty was the driving force behind many of the nation's most effective federal and state immunization policies, including kindergarten and daycare vaccine-entry requirements and the Vaccines for Children program. Learn more about her legacy saving children from vaccine-preventable diseases at www.vaccinateyourfamily.org/in-memory-of-betty-bumpers/.



PROTECTING CHILDREN IS

ALL OF OUR RESPONSIBILITY

Vaccination rates are beginning to decline among children in some communities. Some parents are choosing to exempt their children from school vaccination requirements, but their reasons vary. While some are concerned about the safety of vaccines, others simply do not have the means to access them.

Vaccines protect both the individuals vaccinated and those around them from dangerous diseases (a concept known as “community protection,” “community immunity” or “herd immunity”). That’s because most vaccine-preventable diseases are transmitted from person to person. If a high proportion of the population is vaccinated and immune to a disease then the chains of transmission are broken. So, for example, a child can be indirectly protected against diseases like measles and whooping cough even if they are not fully vaccinated because enough people around them were immunized, making those people less likely to carry or spread the diseases.

Community Protection Thresholds

A community protection threshold is the percentage of vaccinated individuals needed in a population to prevent a disease from spreading.^{23,1}



MEASLES: 83-94%



WHOOPIING COUGH: 92-94%



VARICELLA: 90%



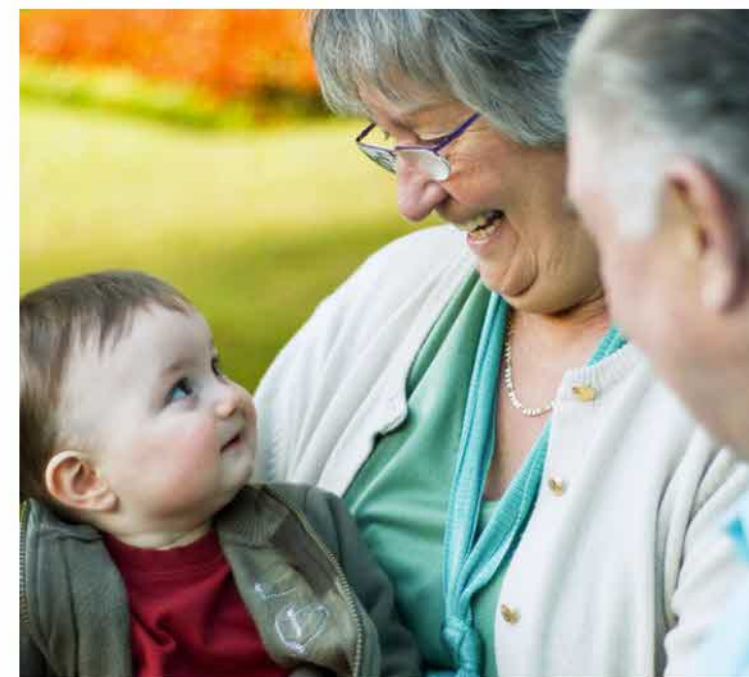
MUMPS: 75-86%

Thus, those children who are not yet fully vaccinated are indirectly protected because they are not exposed to the vaccine-preventable infectious germ when immunity levels induced by vaccination are high in the community. It’s therefore critical that we vaccinate a certain percentage of the population to prevent vaccine-preventable diseases from circulating. This percentage, known as a “community protection threshold,” varies from disease to disease based on its infectivity and is by no means a perfect number. We must continually strive toward high vaccination rates, because even a small drop in vaccination rates within a community can lead to a disease outbreak.

Overall vaccination rates remain high in the U.S.; however, we do continue to see groups of children who remain unprotected against vaccine-preventable diseases. Children who live outside metropolitan areas as well as those who are on Medicaid are less likely to be fully vaccinated by as much as 15% for some vaccines.⁶ Uninsured children are also less likely to be protected than those who are privately insured. **The difference is startling: over 7% of uninsured children receive no vaccines, compared to less than 1% of privately insured children.**⁷ This is particularly concerning since the Vaccines for Children Program (VFC) was created just for this reason and provides

vaccines at no cost to qualifying children whose families otherwise may not be able to afford them. More research is being conducted by the CDC and others to pinpoint the exact barriers preventing these children from receiving vaccines, particularly recommended booster doses.

We have also begun to see an increase in the percentage of children who receive no vaccines. Normally, we see variations in immunization rates from vaccine to vaccine, but **since 2011, the rate of children who received no vaccines increased from 0.9% to 1.3%, which translates to approximately 18,400 children at risk of serious disease and even death.**⁸



Families who choose not to vaccinate tend to cluster together in communities, which means the high vaccination rates necessary for community protection may not have been reached. We saw this happen in 2017, when a measles outbreak swept through a community in Hennepin County, Minnesota. Those families had chosen not to vaccinate their children against measles due to disinformation about the safety of the vaccine from activists who are opposed to immunizations. During the outbreak, which lasted several months, more than 8,000 people were exposed.⁹ Seventy-three of the 79 people who contracted the disease were children under 10, and 22 were hospitalized.¹⁰ Luckily, no one died as a result of this outbreak, but it's important to realize that measles can be very serious in people of all ages. The disease can also result in long-term consequences, such as subacute

sclerosing panencephalitis, a rare but fatal disease of the central nervous system that can develop seven to 10 years after a person has measles.¹¹ While the condition is rare, it is more likely to occur in children who get measles before two years of age.¹²

Disease outbreaks among unprotected children can also be an enormous burden on a family's financial stability. Children with vaccine-preventable illnesses are not permitted to attend school in order to avoid further spreading the diseases, and children who have not been vaccinated may be excluded from school for weeks during an outbreak to ensure they are not exposed to the diseases. During this time, parents will likely miss work to remain home with their children, which can translate to costs that add up quickly. Parents also risk missing even more days if they or other family members contract the disease as well.

DID YOU KNOW?

Parents Miss Work When Children are Ill

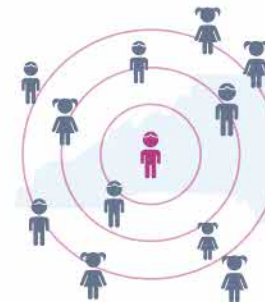
When children are sick with vaccine-preventable diseases, parents have to stay at home for extended periods of time.^v

INCUBATION PERIODS BY DISEASE

Chickenpox 10-21 days	Measles 8-12 days	Rubella 14-21 days
Diphtheria 2-5 days	Influenza 1-6 days	Whooping Cough 7-10 days
Hepatitis A 14-50 days	Mumps 12-25 days	Meningitis (bacterial) 2-10 days

A Chickenpox Outbreak in Asheville

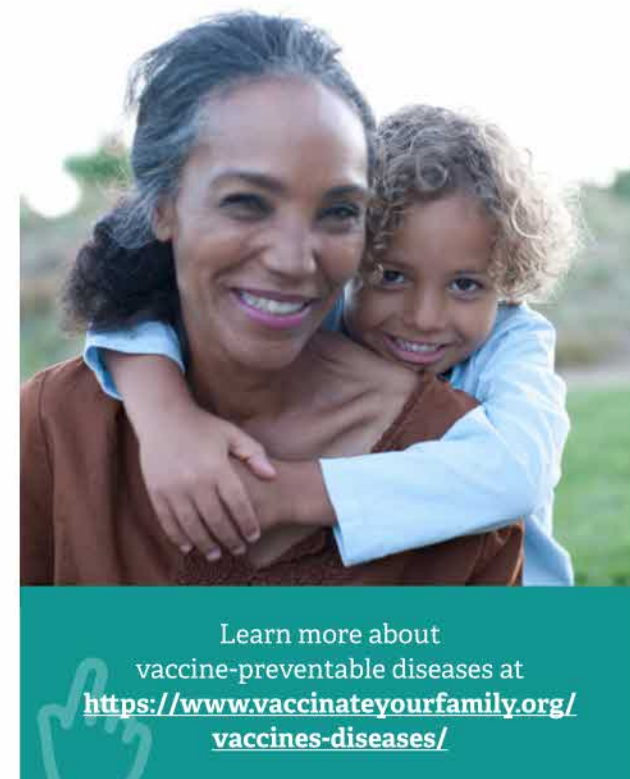
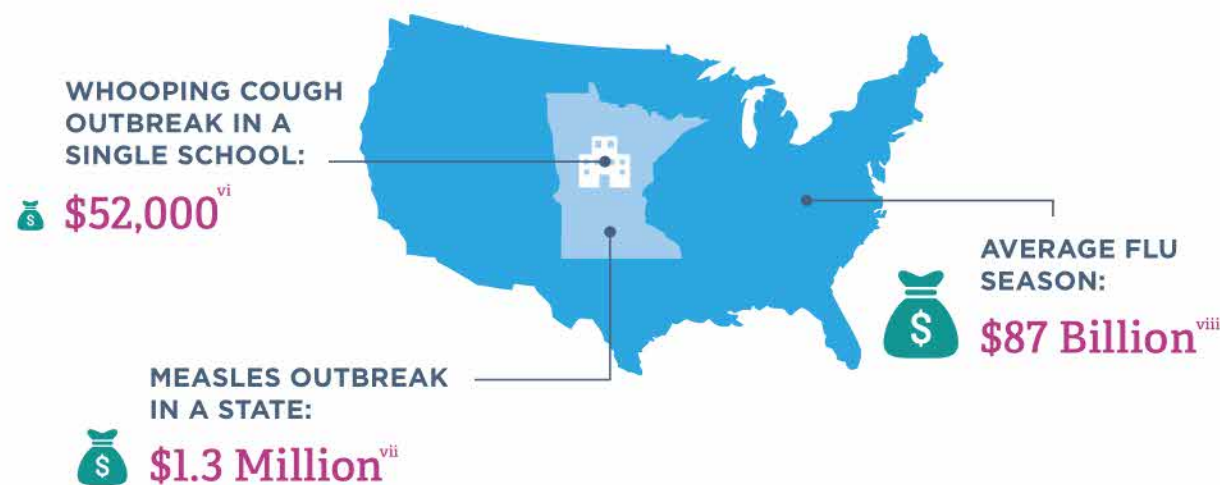
Chickenpox is not an innocent childhood disease. **Prior to the vaccine, between 100 and 150 people died of the disease each year and nearly 11,000 children were hospitalized due to serious complications.**ⁱⁱⁱ Unfortunately, a large group of parents in Asheville, North Carolina, have decided not to vaccinate their children against several diseases, including chickenpox, also known as varicella. As a result, nearly 40 children had contracted the disease as of November 2018. It is the state's largest outbreak of the disease since the vaccine was introduced in 1995.^{iv}



NEARLY 40 CHILDREN contracted chickenpox in Asheville, North Carolina.

The Economic Burden of Vaccine-Preventable Diseases

While vaccines save money, treating vaccine-preventable diseases can be expensive for local, state and national authorities:



These costs are not limited to individual families. Disease outbreaks require a huge investment of public health staff and financial resources to control and contain outbreaks once they have begun. The Minnesota measles outbreak cost Hennepin County and the State Department of Health \$1.3 million to contain.¹³ These costs do not include the amounts incurred by private insurance or the in-direct costs incurred by families due to lost days of work or ongoing care.

States are doing their best to address the threat of outbreaks through a combination of policy and funding solutions. For instance, each state has different laws pertaining to vaccinations required for school entry, vaccine exemption rules, and exclusion

policies during outbreaks. However, the one thing that all states struggle with is a lack of sufficient funding to respond to outbreaks. This is where the federal government's financial support is critical, as diseases know no borders.

It's far better to vaccinate children to prevent these diseases than to have to treat the illnesses. In fact, **vaccines given to children born between 1994-2016 will prevent an estimated 381 million illnesses, 24.5 million hospitalizations, 855,000 deaths, and \$1.65 trillion in total societal costs.**¹⁴ It is essential that states work in tandem with the federal government to support our nation's public health infrastructure and ensure everyone has equal access to vaccines.



ADOLESCENTS ARE AT RISK FROM SERIOUS VACCINE-PREVENTABLE DISEASES

Just because children are getting older doesn't mean they've outgrown vaccines. Preteens and teens are being exposed – and exposing others – to vaccine-preventable diseases that could impact their health now and for many years to come.

Adolescents are learning to make their own choices, but they still need guidance in a number of areas – specifically around their personal health. Preteens and teens are at risk of contracting certain vaccine-preventable diseases as they engage in common activities such as sharing drinks and utensils, kissing, and attending summer camps. There are now five vaccines recommended for adolescents. Unfortunately, since teens have fewer well visits with providers, missed opportunities to vaccinate can cause this population to remain undervaccinated and thus at risk of deadly diseases.

The Tdap (tetanus-diphtheria-pertussis) vaccine is recommended for all 11-12 year olds in order to boost the immunity they received from their DTaP vaccination series as young children. The booster shot not only extends their own protection, but also helps protect those around them from diseases including pertussis (whooping cough). This disease can cause illness in adolescents, but the greater concern is that they can pass this disease onto their siblings and other young children, who are more likely to suffer serious consequences. Infants, for example, are most likely to be hospitalized or die from whooping cough. Studies show that when a source of whooping cough among infants could be identified, family members were the source of the infections 85% of the time.¹⁵

Adolescents may also need two meningococcal vaccines, which together cover serogroups A, B, C, Y, and W135. Meningococcal disease will kill nearly 15% of those infected, and leave nearly 20% of survivors permanently disabled.¹⁶ Preteens and teens are recommended to receive a MenACWY vaccine at 11 or 12 years of age with a booster at 16 years. Parents can also ask their children's healthcare providers about a vaccine against meningitis B which is recommended for some adolescents, and can be given to anyone 16 through 23 years old. While rare, meningitis B has been associated with outbreaks of serious disease and deaths, particularly in colleges.¹⁷

For some illnesses, the importance of the vaccines received as an adolescent may not be revealed until later in life. Consider the human papillomavirus (HPV) vaccine, a two-dose immunization recommended by the CDC that can prevent several forms of cancer in adulthood.

According to the CDC, nearly all men and women will get at least one type of HPV at some point in their lives.¹⁸ In fact, HPV causes over 33,700 cases of cancer in men and women every year in the U.S.¹⁹ The HPV vaccine is vital to ensuring the health of adolescents as they grow to adulthood, and could result in the annual prevention of up to 31,200 cases (90%) of related cancers in both men and women as well as cost savings for years to come.²⁰



DID YOU KNOW?

We could eliminate nearly all cervical cancers, and other HPV-associated cancers, with **two doses of the HPV vaccine.**

4 in 5 

people in the U.S. will be infected with HPV at some point.^{ix}



31,200 OF 33,700 HPV-RELATED CANCERS could be prevented each year in the U.S.^x

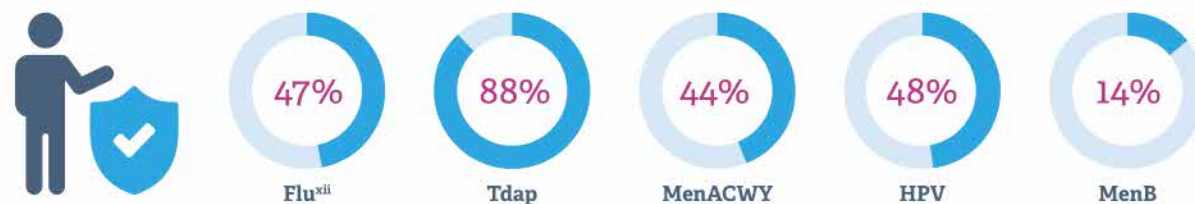
Despite the incredible benefits of this cancer prevention vaccine, many parents are still failing to understand the lifelong value of the vaccine and the importance of getting their preteens vaccinated at ages 11-12, before the risk of exposure to the virus and when the vaccine is most effective. Until we can raise the HPV vaccination rates, we will be failing to prevent thousands of cases of HPV-related cancers among tomorrow's adults.

Finally, adolescents also need to receive a yearly flu vaccine. Influenza can spread quickly in schools, and a typical case of flu can result in a week or more of missed classes.²¹ Teens, even those who are otherwise healthy, can also have severe illness from influenza, which has resulted in several deaths in recent years. Once a preteen or teen is infected, he or she can also spread the infection to their parents, siblings, and other vulnerable family and community members.²²

Unfortunately, rates for all five of these vaccines remain alarmingly low. More research needs to be done to understand why there is a disparity between vaccine rates when the Tdap, MenACWY and HPV vaccines should be recommended together. The CDC has determined that the way healthcare providers are recommending HPV vaccine has left parents with doubts as to whether it's necessary for their preteens. Other disparities, however, such as a gap between Tdap and MenACWY vaccination rates in rural areas, need further exploration.

Adolescent vaccinations enable parents to protect their children in ways that were unimaginable just 10 years ago, yet without sufficient public health funding to support educational programs and other efforts, many children will remain vulnerable to preventable infectious diseases.

Preteens & Teens Aren't Getting the Protection They Deserve^{xi}



 Vaccination Rates for the 5 Recommended Adolescent Vaccines





ENSURING ACCESS TO AFFORDABLE

An investment in vaccinating adults could help eliminate the nearly \$27 billion spent annually while treating four vaccine-preventable diseases in adults over the age of 50.²³

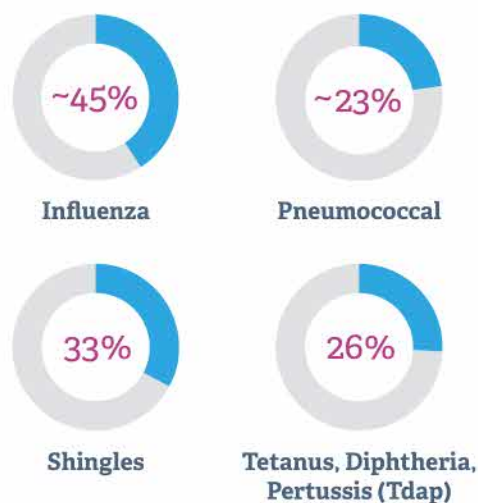
VACCINES FOR ADULTS

Influenza and pneumonia together are the eighth leading causes of death of adults in this country.²⁴ Low vaccination rates contribute to substantial, yet preventable, national healthcare expenses and productivity losses. The nearly \$27 billion that is spent each year treating four vaccine-preventable diseases (flu, pneumococcal disease, shingles and whooping cough) in adults includes the cost of medical visits, hospitalizations and

Adults are Missing Critical Vaccinations

Vaccination rates among U.S. adults are well below the targets established in the Healthy People 2020 report.^{18, ix}

■ Real vaccination rate among U.S. adults



prescription coverage. This does not cover the astronomical costs of absenteeism and short-term disability from work.

As the country's population ages, we can expect that by 2020, one of every four workers will be over the age of 55.²⁵ The costs for addressing the health challenges within this segment of the workforce are massive, as treatments for conditions like diabetes and heart disease number in the hundreds of billions of dollars annually.²⁶ Many current vaccines, as well as those in development pipelines, prevent diseases that can cause dangerous illnesses, and lead to severe and sometimes deadly complications in individuals with chronic conditions. Vaccines are a proven means of preventing and reducing the inevitably huge cost of maintaining the health of our aging workforce.

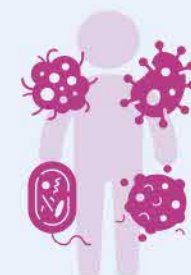
Unfortunately, older adults and those with chronic health conditions are not the only groups at high risk of contracting vaccine-preventable diseases. The opioid epidemic ravaging many parts of our country has had yet another unintended consequence: an uptick in hepatitis B cases. In Kentucky, Tennessee and West Virginia alone there has been a 114% increase in hepatitis B cases from 2006 to 2013.²⁷ That number is expected to increase across the country as opioid dependence has become even more common over the past five years.

DID YOU KNOW?

The Costs of Vaccine-Preventable Disease

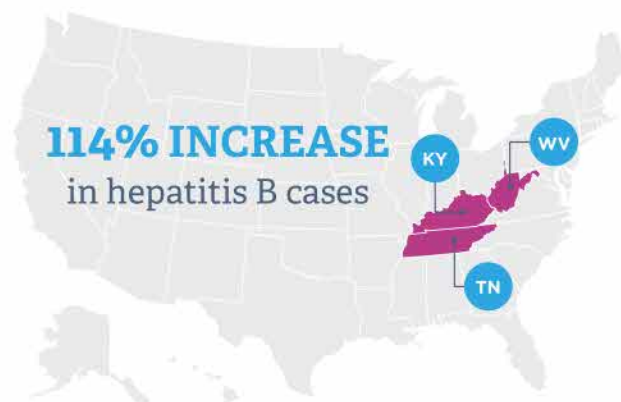
Flu, pneumococcal disease, shingles and whooping cough cost \$27 billion to treat each year in adults over the age of 50.

**\$27
BILLION**
in treatment



Vaccines & the Opioid Epidemic

The opioid epidemic has led to a 114% increase in hepatitis B cases in Kentucky, Tennessee and West Virginia.



Racial and ethnic disparities also continue in vaccination coverage among adult populations, as whites are consistently better vaccinated than minority groups.²⁸ People of color have traditionally been at disproportionate risk for being underinsured, lacking access to quality treatment, and preventive care through health insurance coverage.

In fact, first dollar coverage of vaccines can greatly improve the likelihood that an adult will be immunized.²⁹ Without it, we can expect more adults to be required to pay out-of-pocket expenses for vaccines. Expanding first dollar coverage of vaccines to Medicare Part D and encouraging Medicare Advantage and stand-alone Medicare Prescription Drug Plans to include immunizations in the zero-cost sharing tier is also critical to reducing the barriers to access for all adults. Influenza and pneumococcal vaccines, which are both covered by Part B, have been received by 71.5% and 61.3% of seniors over the age of 65, respectively. This same population must spend between \$14 and \$102, on average to receive either the shingles or the Tdap vaccine. These two vaccines that protect against four diseases have only been received by 27.9% and 14% of seniors, respectively.³⁰ The cost savings for our economy, coupled with increased workplace productivity, are well worth the investment.

In addition to coverage, access to immunization providers in a wide array of community settings, such as a healthcare provider office, health clinic, pharmacy, employer-sponsored clinic or other site is also essential to improving adult immunization rates. Incentivizing a robust network of community providers who support and carry out adult immunization standards in their practices has been proven to be a strong driver of improved adult immunization rates.

Future healthcare reform could therefore have a deep impact on vaccination rates and consequently serious illness, hospitalizations and deaths due to vaccine-preventable diseases, both among vulnerable populations and the general public, and will require careful Congressional consideration.

PPHF is Not “Extra” Money

Since the introduction of the Prevention & Public Health Fund (PPHF), Congress has been redirecting core funding for immunizations under this line item.

PPHF now provides half of all immunization funding. If PPHF were cut:



Local immunization programs would be **CUT BY 45%**



Fewer children, adolescents, adults and pregnant women would be vaccinated, **RESULTING IN DISEASE OUTBREAKS**

Learn more at: immunizationmanagers.org/page/Publication



DID YOU KNOW?



Disparities in Adult Vaccination Rates

Adult vaccination rates for shingles, as seen in the following statistics from 2016, varied greatly among racial/ethnic groups:^{xiii}

Whites	Blacks	Hispanics & Asians
38%	16%	22%



PROTECTING PREGNANT WOMEN

ALSO EXTENDS PROTECTION

TO THEIR BABIES

A single vaccine can protect both a pregnant woman and her baby.

Maternal vaccinations protect both pregnant women and their babies, both before they are born and during the first few months of life.

Almost all vaccines for infants start at two months of age or later, so the only protection for newborns from vaccine-preventable diseases is through vaccination of their mothers, who transfer protective proteins called antibodies to their babies across the placenta. These antibodies protect the infants until they can develop their own immunity through vaccination.

The stakes are high. Pregnant women and their unborn babies have a greater risk of influenza complications than the general population. Due to changes in the immune system, heart, and lungs during pregnancy, pregnant women are more prone to severe illness from flu, which has been known to result in premature delivery, low birth weight babies, miscarriage, hospitalization and even death. Fortunately, babies whose mothers got the seasonal flu vaccine during pregnancy were 70% less likely to get the flu than babies born to unimmunized mothers.³¹ Since infants do not begin receiving their own annual influenza vaccinations until they are six months of age, they rely on the protection they get from their mothers; however, only about half of pregnant women are getting flu vaccines in pregnancy.³²

Infants also comprise the largest share of pertussis-related deaths. Half of the infants who get pertussis, also known as whooping cough, will be hospitalized, and one in 100 will die.³³ Studies show that when a source of whooping cough among infants could be identified, family members were the source of the infections 85% of the time.³⁴ The Tdap vaccine, which should be administered to women during weeks 27-36 of every pregnancy,³⁵ is therefore critical for protecting newborns.

While currently only influenza, pertussis, diphtheria, and tetanus are preventable through maternal vaccination, researchers are working to discover scientific breakthroughs for many other devastating infant conditions. Maternal vaccines may soon be used to protect infants from respiratory syncytial virus (RSV), cytomegalovirus (CMV), and group B streptococcus (GBS).

Our country's future rests in the hands of our young. Here in the U.S. we have the technology to prevent suffering among some of our most vulnerable citizens—our infants. Through public health efforts to educate all maternal providers, and by working together to ensure access to and delivery of vaccines to pregnant women, we can prevent the suffering of families who could otherwise lose their precious newborns to vaccine-preventable diseases.

DID YOU KNOW?

Receiving Flu and Tdap Vaccines During Pregnancy Protects Mom & Baby



DURING PREGNANCY:

Changes in immune, heart & lung functions make pregnant women more susceptible to disease and pregnancy complications.

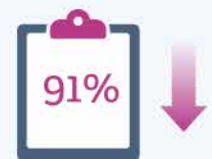
POST DELIVERY: Moms pass protective antibodies on to their babies, which helps protect them from dangerous infections until they can receive their flu and Tdap vaccines.



Vaccines Given in Pregnancy Protect Babies

Pertussis

When mothers get Tdap vaccine in pregnancy, they **reduce infants risk of pertussis by^{xiii}:**



Flu

When mothers get flu vaccine in pregnancy, they **reduce infant risk of flu by:**





A QUICK REFERENCE GUIDE TO VACCINE SAFETY AND OVERSIGHT

Questions about the safety of vaccines are common. Vaccinate Your Family is dedicated to breaking down the complex science so everyone can understand why vaccines are the best option for protecting you, your family and your constituents from serious infectious diseases.

Vaccines are one of the most thoroughly tested medical products available in the U.S. Before a vaccine can be considered for approval by the FDA, a vaccine manufacturer must show it is safe and effective through clinical trials. Developing a new vaccine begins with an exploratory stage and a pre-clinical stage before advancing to three stages of clinical trials. Together, this scientific process can take over a decade and cost millions of dollars.³⁶ The FDA then examines these studies and determines whether a vaccine is safe, effective, and ready to be licensed for use. The FDA only licenses vaccines that have data that shows that the vaccines' benefits outweigh the potential risks. If there is any question or concern about the data, the FDA will request further studies before approving the vaccine.³⁷

After a vaccine is licensed for use in the U.S., there are four systems in place that work together to help scientists monitor the safety of vaccines and identify any rare side effects that may not have been found in clinical trials. Even large clinical trials may not be big enough to find very rare side effects. For example, some side effects may only happen in 1 in 100,000 or 1 in 500,000 people. In addition, vaccine trials may not include certain populations like pregnant women or people with specific medical conditions who might have different types of side effects or who might have a higher risk of side effects than the volunteers who got the vaccine during clinical trials. These four systems are:



- 1 Vaccine Adverse Events Reporting System (VAERS)³⁸:** VAERS is a passive reporting system. That means it relies on individuals to report vaccine reactions. Anyone can report a reaction or injury, including healthcare providers, patients and patients' representatives, such as caregivers or attorneys. The system is co-managed by the FDA and the CDC. However, it is important to note that VAERS data alone can't be used to answer the question, "Does a certain vaccine cause a certain side effect?" This is because adverse events (health problems) reported to VAERS may or may not be caused by vaccines. There are reports in VAERS of common conditions that occur just by chance after vaccination. Further investigation may find no medical link between vaccination and these conditions. Instead, the purpose of VAERS is to see if unexpected or unusual patterns emerge, which may indicate an issue that needs to be researched further.
- 2 Vaccine Safety Datalink (VSD)³⁹:** Established in 1990, VSD is a collaboration between the CDC's Immunization Safety Office and eight healthcare organizations across the country. It conducts studies based on questions or concerns raised from the medical literature and reports to VAERS. In addition, when new vaccines are recommended or if changes are made in how a vaccine is recommended, VSD will monitor the safety of these vaccines.

3 Clinical Immunization Safety Assessment Project (CISA)⁴⁰: CISA, which was created in 2001, is a national network of vaccine safety experts from the CDC's Immunization Safety Office, seven medical research centers and other partners. CISA addresses vaccine safety issues, conducts high quality clinical research and assesses complex clinical adverse events following vaccination. CISA also helps to connect clinicians with experts who can help consult on vaccine safety questions related to individual patients.

4 Post-Licensure Rapid Immunization Safety Monitoring System (PRISM)⁴¹: PRISM is a partnership between the FDA's Center for Biologics Evaluation and Research and leading health insurance plans. It actively monitors and analyzes data from a representative subset of the general population. PRISM links data from health plans with data from state and city immunization information systems (IIS). PRISM has access to information for over 190 million people allowing it to identify and analyze rare health outcomes that would otherwise be difficult to assess.

In summary, because vaccines are given to the entire population, they are one of the most scrutinized and well-tested products on the U.S. market. The systems that have been put in place to ensure their ongoing safety are expansive and have time and again proven to be effective at determining any safety signals that require further investigation. For more information on how the U.S. healthcare system collaborates with the federal government on these endeavors or for answers to a particular vaccine-related concern from your constituents, please visit the *Questions About Vaccines* section of our website at vaccinateyourfamily.org/questions-about-vaccines.





THE STATE

OF OUR IMMUNION IS UNCERTAIN

2019 will mark the 25th anniversary of the Vaccines for Children program, yet outbreaks of some vaccine-preventable diseases are now on the rise. As a result, even seemingly unrelated policy decisions regarding healthcare can have unintended consequences on vaccination rates.

Legislators can play an important role in ensuring that public health professionals are prepared to face the threats of disease outbreaks and that their constituents are protected from dangerous infectious diseases. Please consider:

- **Increasing the federal appropriations to the CDC, states and territories** so that they are prepared to respond to existing and potential emerging vaccine-preventable disease outbreaks and can conduct community outreach, educate providers and the public, maintain immunization registries, and offer vaccine services to the community.

Historically, federal vaccine appropriations have not met the levels requested in CDC's

Congressional budget justifications, and state budgets for vaccine infrastructure are nearly non-existent. This has resulted in a loss of essential immunization program personnel and the disbanding of several highly effective statewide immunization coalitions, which supported vaccination programs for decades.

Furthermore, it's important to note that the Prevention & Public Health Fund (PPHF) currently provides 53% of the CDC's Immunization Program funding. Proposals to cut PPHF or use PPHF as a budgetary offset for other programs could place your constituents' health in further danger when compounded with the current funding gap.

- **Also increasing funding to the Indian Health Service that includes a specific line item for immunizations** to support immunization activities, clinical service delivery and electronic health record systems.
- **Expanding funding to include pressing research into access barriers.** There is an increasing disparity between those who receive vaccines in rural areas and those who live in suburban and urban areas. Children without private health insurance are also less likely to be vaccinated, despite programs in place such as VFC, which are meant to address this gap. In order to ensure equal access to life-saving vaccines, CDC and other agencies require additional funding to further explore and address the specific barriers.

- **Supporting healthcare payment measures that expand access, protect first dollar coverage and essential health benefits.**

For example, Medicare immunization coverage is divided between Medicare Part B and Medicare Part D and often results in prohibitive cost sharing for beneficiaries who wish to access recommended vaccines such as shingles and Tdap under the Part D program. Recommended vaccines should be widely available to people of all ages at no additional cost, regardless of insurance program, as they are cost-saving preventive care.

Also consider other avenues through which vaccines can be helpful, such as in policies and funding packages meant to address the opioid epidemic. By ensuring young adults are vaccinated against hepatitis B, we can prevent long-term costs associated with treating the diseases as they recover from their addictions.

- **Learning more about the science behind vaccines and supporting the CDC-recommended immunization schedule.** The public must be reassured that the timing of vaccines is carefully considered prior to CDC's recommendations and that prior to and following licensure, vaccine safety is heavily monitored by various departments within HHS, CDC, and FDA, and through long-term health plan collaboratives. There are many disproven myths about the safety of vaccines that continue to circulate, negatively impacting your constituents' understanding of the safety and value of vaccines, and threatening the health of your communities. You can be an immunization champion simply by knowing how to respond to your constituents' concerns and offering science-based responses.
- **Reaching out to your local immunization advocates** including hospitals, leading healthcare providers, colleges and universities, and immunization coalitions, to support their efforts and gather feedback on the impact that policies have on their ability to protect your constituents from deadly diseases.
- **Connecting with your fellow legislators** to sponsor legislation in support of federal, state and local efforts.





RESOURCES AND USEFUL LINKS

Commonly Requested Information for Constituents

- Vaccinate Your Family: The Next Generation of Every Child By Two is a leading source of evidence-based vaccine information. You can find information on common questions about vaccines, vaccine safety oversight, disease outbreaks and other topics on our website and social media channels. Learn more at:
 - www.vaccinateyourfamily.org
 - www.shoto prevention.com blog
 - And on Facebook (facebook.com/VaccinateYourFamily) and Twitter ([@vaxyourfam](https://twitter.com/vaxyourfam))

Policy Resources

- [Trust for American's Health: Ready or Not?](#) examines the nation's ability to respond to public health emergencies, tracks progress and vulnerabilities, and includes a review of state and federal public health preparedness policies and a state-by-state map rating of preparedness.
- [317 Coalition](#) is solely focused on advocating for increased federal funding for the National Center for Immunization and Respiratory Diseases at

the Centers for Disease Control and Prevention, and as such will focus on implementing the policies of the Advisory Committee on Immunization Practices and other relevant policy making bodies.

- [Adult Vaccine Access Coalition](#) is fostering an inclusive partnership of organizations to inform and engage federal policymakers in working towards common legislative and regulatory solutions that will strengthen and enhance access to and utilization of adult immunization services across the health care system.
- [Association of Immunization Managers](#) enables immunization program managers to work together to effectively prevent and control vaccine-preventable diseases and improve immunization coverage in the United States and its territories.
- [Association of State and Territorial Health Officials](#) is the national nonprofit organization representing public health agencies in the United States, the U.S. Territories, and the District of Columbia, and over 100,000 public health professionals these agencies employ.
- [Immunization Coalitions Network of the Immunization Action Coalition](#) offers a searchable database to locate state and local

immunization coalitions and a host of state policy resources.

- [National Association of County & City Health Officials](#) is comprised of over 2,800 Local Health Departments across the United States.
- [American Academy of Pediatrics](#) offers an overview of recent disease outbreaks and vaccination rates.
- [The Centers for Disease Control and Prevention](#) has created an infographic outlining the country's process for vaccine approval and ongoing oversight.

Annual Vaccination Rate Data

- Child Rates: <https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/data-reports/index.html>
- School Rates: <https://www.cdc.gov/vaccines/imz-managers/coverage/schoolvaxview/data-reports/index.html>
- Teen Rates: <https://www.cdc.gov/vaccines/imz-managers/coverage/teenvaxview/index.html>
- Adult Rates: <https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/index.html>
- Flu Rates: <https://www.cdc.gov/flu/fluview/index.html>

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The Next Generation of Every Child By Two

Vaccinate Your Family: The Next Generation of Every Child By Two

Our mission is to protect people of all ages from vaccine-preventable diseases by raising awareness of the critical need for timely immunizations, increasing the public's understanding of the benefits of vaccines, increasing confidence in the safety of vaccines, ensuring that all families have access to life-saving vaccines, and advocating for policies that support timely vaccination.

From: Neal Halsey
Sent: 6 Jun 2019 12:58:48 +0000
To: Edwards, Kathryn;nkarora@incentrust.org;Heidi Larson;Philippe Duclos
Cc: jim.buttery@monash.edu;Daniel Salmon;Sturkenboom, M.C.J.;Heininger, Ulrich;Admin;Destefano, Frank (CDC/DDID/NCEZID/DHQP);Eric Fombonne;GARCON Nathalie;jason.m.glanz@kp.org;All@ssi.dk;Paul Henri Lambert;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);Andrew Pollard;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsp.h.edu;priya.bahri@ema.europa.eu;(b)(6);bodenstabh@email.chop.edu;(b)(6);Ulrich
Heininger;hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz;Amy Pisani;rtchen1135@gmail.com;Stanley Plotkin
Subject: Re: A couple of ideas

All of the ideas that have been proposed so far are worthwhile. I would like to reiterate the suggestion I made at the meeting. (b)(5)

(b)(5)

Neal

From: "Edwards, Kathryn" <kathryn.edwards@vumc.org>
Date: Thursday, June 6, 2019 at 7:22 AM
To: "nkarora@incentrust.org" <nkarora@incentrust.org>, Heidi Larson <Heidi.Larson@lshtm.ac.uk>
Cc: "jim.buttery@monash.edu" <jim.buttery@monash.edu>, Daniel Salmon <dsalmon1@jhu.edu>, "Sturkenboom, M.C.J." <M.C.J.Sturkenboom@umcutrecht.nl>, "Heininger, Ulrich" <ulrich.heininger@ukbb.ch>, Admin <admin@vaxconsult.com>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>, Eric Fombonne <fombonne@ohsu.edu>, GARCON Nathalie <Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, "All@ssi.dk" <All@ssi.dk>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>, James Sejvar <zea3@cdc.gov>, JPIDS JPIDS <nhalsey@jhsp.h.edu>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, (b)(6)
(b)(6), "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, (b)(6), Ulrich Heininger <ulrich.heininger@unibas.ch>, "hotez@bcm.edu" <hotez@bcm.edu>, "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, Amy Pisani <amyp@ecbt.org>, (b)(6)

(b)(6)

, Stan Plotkin <stanley.plotkin@vaxconsult.com>

Subject: RE: A couple of ideas

This is the letter that was recently published in CID and mentioned at the meeting on MHTFR.

From: Edwards, Kathryn

Sent: Thursday, June 6, 2019 5:57 AM

To: nkarora@incentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>

Cc: jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu;

(b)(6); Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>;

(b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Subject: RE: A couple of ideas

I was honored to participate in the Vaccine Safety Science meeting last week in London. The quality of the presentations, the subsequent discussions, and the email chains have been very stimulating. I would like to add a few perspectives and make several additional suggestions for studies to conduct. I will also comment on the suggestions of others.

(b)(5)

(b)(5)

Thanks again for a great meeting and I hope that the dialogue will continue.

Kathryn M. Edwards MD
Sarah Sell and Cornelius Vanderbilt Chair
Professor of Pediatrics
Vanderbilt University Medical Center

From: Edwards, Kathryn
Sent: 6 Jun 2019 11:21:45 +0000
To: nkarora@incentrust.org; Heidi Larson
Cc: jim.buttery@monash.edu; Daniel Salmon; Sturkenboom, M.C.J.; Heininger, Ulrich; Admin; Destefano, Frank (CDC/DDID/NCEZID/DHQP); Eric Fombonne; GARCON Nathalie; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); Andrew Pollard; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); Ulrich Heininger; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani (b)(6); Stanley Plotkin
Subject: RE: A couple of ideas
Attachments: Reif-2019-Inappropriate-citation-of-vaccine-a.pdf

This is the letter that was recently published in CID and mentioned at the meeting on MHTFR.

From: Edwards, Kathryn
Sent: Thursday, June 6, 2019 5:57 AM
To: nkarora@incentrust.org; Heidi Larson <Heidi.Larson@lshtm.ac.uk>
Cc: jim.buttery@monash.edu; Daniel Salmon <dsalmon1@jhu.edu>; Sturkenboom, M.C.J. <M.C.J.Sturkenboom@umcutrecht.nl>; Heininger, Ulrich <ulrich.heininger@ukbb.ch>; Admin <admin@vaxconsult.com>; fxd1@cdc.gov; Eric Fombonne <fombonne@ohsu.edu>; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert <Paul.Lambert@unige.ch>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; Andrew Pollard <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; alexooo@yahoo.com; Ulrich Heininger <ulrich.heininger@unibas.ch>; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani <amyp@ecbt.org>; (b)(6); Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Subject: RE: A couple of ideas

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(b)(5)

(b)(5)

(b)(5)



Thanks again for a great meeting and I hope that the dialogue will continue.

Kathryn M. Edwards MD
Sarah Sell and Cornelius Vanderbilt Chair
Professor of Pediatrics
Vanderbilt University Medical Center

Title: Inappropriate Citation of Vaccine Article

Dear Editor:

We wish to call attention to an unfortunate misuse of our 2008 article published in *the Journal of Infectious Diseases*, entitled “Genetic basis for adverse events in smallpox vaccination.”¹ Our manuscript is being used by some to support medical exemptions to vaccination in children with a common genetic polymorphism in the methylenetetrahydrofolate reductase gene (*MTHFR*-known as C677T), particularly to measles vaccine. The citation of this exploratory report, which addressed a unique set of phase 1 studies of a candidate smallpox vaccine, should not constitute an exemption from formal vaccination recommendations issued by the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP). There is no published evidence to suggest that the likelihood of an adverse reaction to one vaccine implies that one is expected to have a reaction to other unrelated vaccines. In this regard, the results observed with a vaccine that is not FDA-approved and that targets an infectious pathogen against which people are no longer vaccinated, do not have any implications for the risk of FDA-approved vaccines against other infectious pathogens.

The limitations of our study in assessing adverse reactions to smallpox vaccine and other vaccines, particularly measles, are several. The study was a small, underpowered, exploratory, candidate gene study conducted more than 15 years ago in a special population, *i.e.*, participants in two small phase 1 studies of smallpox vaccines. This article does not meet the standards for establishing a robust genetic association. It is most likely that the reported relation to a common variant within the (*MTHFR*) gene (known as C677T) is due to chance. In fact, the article clearly states: “*It is possible that our findings could be due to chance*” and “*follow-up replication and functional studies are needed to establish the plausibility of the association*”. The findings presented have not been replicated in additional settings of individuals receiving a smallpox vaccine or in any other setting testing for genetic modifiers of vaccine response or adverse events. In this regard, we wish to emphasize that this use of *MTHFR* gene polymorphisms to support medical exemptions to vaccination in children represents an inappropriate and unsubstantiated use of direct-to-consumer genetic testing. The policy statement of the American Academy of Pediatrics and the American College of Medical Geneticists and Genomics strongly discourages the use of DTC because of the risk of inaccurate interpretation as well as a potentially harmful intervention (*e.g.*, avoidance of a medically indicated vaccine)².

In conclusion, the invalid interpretation that the determination of the *MTFHR* variant is an acceptable reason for vaccine exemptions is not based on the precepts of replication and rigorous clinical testing. It is unfortunate that the loose application of our exploratory report has been misinterpreted and used to inappropriately justify exemption of children from medically indicated vaccines.

Sincerely,

David M. Reif, Ph.D.
N.C. State University

Stephen J. Chanock, M.D.
National Institutes of Health

Kathryn M. Edwards, M.D.
James E. Crowe, Jr., M.D.
Vanderbilt University Medical Center

References

¹Reif DM, McKinney BA, Motsinger AA, Chanock SJ, Edwards KM, Rock MT, Moore JH, Crowe JE. Genetic basis for adverse events after smallpox vaccination. *J Infect Dis.* 2008; 198:16-22.

²Ross LF, Saal HM, David KL, Anderson RR; American Academy of Pediatrics; American College of Medical Genetics and Genomics. Technical report: Ethical and policy issues in genetic testing and screening of children. *Genet Med.* 2013;15:234-45. Erratum in: *Genet Med.* 2013;15:321. Ross, Laine Friedman [corrected to Ross, Lainie Friedman].

From: Edwards, Kathryn
Sent: 6 Jun 2019 10:57:20 +0000
To: nkarora@incientrust.org; Heidi Larson
Cc: jim.buttery@monash.edu; Daniel Salmon; Sturkenboom, M.C.J.; Heininger, Ulrich; Admin; Destefano, Frank (CDC/DDID/NCEZID/DHQP); Eric Fombonne; GARCON Nathalie; jason.m.glanz@kp.org; All@ssi.dk; Paul Henri Lambert; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); Andrew Pollard; Sejvar, James (CDC/DDID/NCEZID/DHCPP); nhalsey@jhsph.edu; priya.bahri@ema.europa.eu; (b)(6); bodenstah@email.chop.edu; (b)(6); Ulrich Heininger; hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; Amy Pisani; (b)(6); Stanley Plotkin
Subject: RE: A couple of ideas

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(b)(5)

(b)(5)

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Kathryn M. Edwards MD
Sarah Sell and Cornelius Vanderbilt Chair
Professor of Pediatrics
Vanderbilt University Medical Center

From: Stanley Plotkin
Sent: 16 Aug 2019 11:00:15 -0400
To: Destefano, Frank (CDC/DDID/NCEZID/DHQP); 'Admin'
Cc: Markowitz, Lauri (CDC/DDID/NCIRD/DVD); Sejvar, James (CDC/DDID/NCEZID/DHCPP)
Subject: RE: Final - The Science of Vaccine Safety

OK, will do

From: Destefano, Frank (CDC/DDID/NCEZID/DHQP) [mailto:fxd1@cdc.gov]
Sent: Friday, August 16, 2019 10:51 AM
To: Admin; stanley.plotkin@vaxconsult.com
Cc: Markowitz, Lauri (CDC/DDID/NCIRD/DVD); Sejvar, James (CDC/DDID/NCEZID/DHCPP)
Subject: RE: Final - The Science of Vaccine Safety

Hi Stanley,
I know you are probably familiar with CDC clearance of manuscripts and some of the challenges that may present. We have submitted The Science of Vaccine Safety into clearance and have received feedback that the following sentence in the summary is problematic:

(b)(5)

I'm sorry about this complication, but hope that you understand.

Thanks for your consideration and best regards,
Frank

Frank DeStefano, MD, MPH

From: Admin <admin@vaxconsult.com>
Sent: Tuesday, August 13, 2019 11:37 AM
To: offit@email.chop.edu; Destefano, Frank (CDC/DDID/NCEZID/DHQP) <fxd1@cdc.gov>; heidi.larson@lshtm.ac.uk; nkarora@inclentrust.org; Sejvar, James (CDC/DDID/NCEZID/DHCPP) <zea3@cdc.gov>; fombonne@ohsu.edu; Zuber, Patrick (CDC who.int) <zuberp@who.int>; paul.lambert@unige.ch; All@ssi.dk; nhalsey@jhsph.edu; nathalie.garcon@bioaster.org; Peden, Keith (FDA/CBER) <Keith.Peden@fda.hhs.gov>; andrew.pollard@paediatrics.ox.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) <lem2@cdc.gov>; jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com
Subject: Final - The Science of Vaccine Safety

Dear All:

The attached manuscript will be submitted to *Vaccine* on Monday, August 19.

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: Destefano, Frank (CDC/DDID/NCEZID/DHQP)
Sent: 16 Aug 2019 14:50:41 +0000
To: Admin;stanley.plotkin@vaxconsult.com
Cc: Markowitz, Lauri (CDC/DDID/NCIRD/DVD);Sejvar, James (CDC/DDID/NCEZID/DHCPP)
Subject: RE: Final - The Science of Vaccine Safety

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Thanks for your consideration and best regards,
Frank

Frank DeStefano, MD, MPH

From: Admin <admin@vaxconsult.com>
Sent: Tuesday, August 13, 2019 11:37 AM
To: offit@email.chop.edu; Destefano, Frank (CDC/DDID/NCEZID/DHQP) <fxd1@cdc.gov>; heidi.larson@lshtm.ac.uk; nkarora@inclentrust.org; Sejvar, James (CDC/DDID/NCEZID/DHCPP) <zea3@cdc.gov>; fombonne@ohsu.edu; Zuber, Patrick (CDC who.int) <zuberp@who.int>; paul.lambert@unige.ch; All@ssi.dk; nhalsey@jhsphe.edu; nathalie.garcon@bioaster.org; Peden, Keith (FDA/CBER) <Keith.Peden@fda.hhs.gov>; andrew.pollard@paediatrics.ox.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) <lem2@cdc.gov>; jason.m.glanz@kp.org
Cc: stanley.plotkin@vaxconsult.com
Subject: Final - The Science of Vaccine Safety

Dear All:

The attached manuscript will be submitted to *Vaccine* on Monday, August 19.

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

From: jim.buttery@monash.edu
Sent: 19 Jul 2019 15:16:52 +1000
To: 'Neal Halsey'; 'Stanley Plotkin'; 'Admin'; nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhspk.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); Zuber, Patrick (CDC who.int); Destefano, Frank (CDC/DDID/NCEZID/DHQP); 'Hotez, Peter Jay'
Cc: kathryn.edwards@vumc.org; (b)(6); ulrich.heininger@ukbb.ch; amy@vaccinateyourfamily.org; 'Daniel Salmon'; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; amyp@ecbt.org
Subject: RE: Halsey comments London vaccine safety - Dr. Stanley Plotkin
Attachments: Halsey SUMMARY OF IDEAS FOR FUTURE STUDIES PROPOSED BY ATTENDEES AT THE WELLCOME TRUST LONDON VACCINE SAFETY MEETING_Mod_JB.docx

Dear Stanley

Thanks for the opportunity to comment- I have added to Neal's document

The last in "other" I have added (around signal detection/validation/investigation) may be too general but thought worth including given discussion around Frank's and Ander's presentations

Kind regards
Jim

From: Neal Halsey <nhalsey1@jhu.edu>
Sent: Friday, 19 July 2019 1:07 AM
To: Stanley Plotkin <stanley.plotkin@vaxconsult.com>; 'Admin' <admin@vaxconsult.com>; nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhspk.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; Keith.Peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov; Hotez, Peter Jay <hotez@bcm.edu>
Cc: kathryn.edwards@vumc.org; jim.buttery@monash.edu; (b)(6); ulrich.heininger@ukbb.ch; amy@vaccinateyourfamily.org; Daniel Salmon <dsalmon1@jhu.edu>; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; amyp@ecbt.org
Subject: Halsey comments London vaccine safety - Dr. Stanley Plotkin

Stan,
I have attached your list of studies with some written comments and suggestions. With regard to some of the comments that have been sent:

(b)(5)

(b)(5)

Neal

From: "Hotez, Peter Jay" <hotez@bcm.edu>

Date: Thursday, July 18, 2019 at 9:53 AM

To: Stan Plotkin <stanley.plotkin@vaxconsult.com>, 'Admin' <admin@vaxconsult.com>, "nkarora@incentrust.org" <nkarora@incentrust.org>, "fombonne@ohsu.edu" <fombonne@ohsu.edu>, "nathalie.garcon@bioaster.org" <nathalie.garcon@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, JPIDS JPIDS <nhalsey@jhsph.edu>, "All@ssi.dk" <All@ssi.dk>, PAUL-hENRI LAMBERT <paul.lambert@unige.ch>, "heidi.larson@lshtm.ac.uk" <heidi.larson@lshtm.ac.uk>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <Keith.Peden@fda.hhs.gov>, "andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>, James Sejvar <zea3@cdc.gov>, Patrick Zuber <zuberp@who.int>, "DeStefano, Frank (NIP)" <fxd1@cdc.gov>
Cc: "kathryn.edwards@vumc.org" <kathryn.edwards@vumc.org>, "jim.buttery@monash.edu" <jim.buttery@monash.edu>, (b)(6) <(b)(6)>, "ulrich.heininger@ukbb.ch" <ulrich.heininger@ukbb.ch>, "amy@vaccinateyourfamily.org" <amy@vaccinateyourfamily.org>, Daniel Salmon <dsalmon1@jhu.edu>, "m.c.j.sturkenboom@umcutrecht.nl" <m.c.j.sturkenboom@umcutrecht.nl>, "priya.bahri@ema.europa.eu" <priya.bahri@ema.europa.eu>, Steve Black <(b)(6)>, "bodenstabh@email.chop.edu" <bodenstabh@email.chop.edu>, (b)(6) <(b)(6)>, "liz.miller@hpa.org.uk" <liz.miller@hpa.org.uk>, "h.petousis-harris@auckland.ac.nz" <h.petousis-harris@auckland.ac.nz>, "amyp@ecbt.org" <amyp@ecbt.org>
Subject: Re: HOTEZ COMMENTS London vaccine safety - Dr. Stanley Plotkin

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Executive Assistant: [Douglas Soriano](#)

Douglas.SorianoOsejo@bcm.edu

Phone: 713-798-1199

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Sent: Thursday, July 18, 2019 8:25:13 AM

To: Hotez, Peter Jay; 'Admin'; nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsph.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov

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From: Stanley Plotkin
Sent: 18 Jul 2019 09:25:13 -0400
To: 'Hotez, Peter

Jay'; 'Admin'; nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhspk.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); Zuber, Patrick (CDC who.int); Destefano, Frank (CDC/DDID/NCEZID/DHQP)

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From: Amy Pisani
Sent: 25 Jul 2019 19:17:12 +0000
To: Hotez, Peter Jay; Stanley Plotkin; 'Admin'; nkarora@inclentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsp.h.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); Zuber, Patrick (CDC who.int); Destefano, Frank (CDC/DDID/NCEZID/DHQP)
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Subject: RE: HOTEZ COMMENTS London vaccine safety - Dr. Stanley Plotkin

Great news! Skeptical Raptor has countered RFK Jr's points on his blog. Please take a look at the attached links. Vaccinate Your Family will be adding them to our partner portal as well as sharing them widely with partners.

<https://www.skepticalraptor.com/skepticalraptorblog.php/gardasil-vaccine-rfkjr-false-unscientific-claims-part-1/>

<https://www.skepticalraptor.com/skepticalraptorblog.php/hpv-vaccine-facts-refuting-rfkjr-false-claims-part-2/>

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Sent: Thursday, July 18, 2019 9:53 AM
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Executive Assistant: [Douglas Soriano](#)

Douglas.SorianoOsejo@bcm.edu

Phone: 713-798-1199

From: Admin <admin@vaxconsult.com>

Sent: Wednesday, July 17, 2019 2:54 PM

To: nkarora@inclentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsph.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov

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(FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James
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From: Stanley Plotkin
Sent: 18 Jul 2019 09:25:13 -0400
To: 'Hotez, Peter

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priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu;

(b)(6); Hotez, Peter Jay; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; amyp@ecbt.org

Subject: London vaccine safety - Dr. Stanley Plotkin

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Thank you so much for your help and your patience.

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
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215-297-9321

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From: Helen Petousis-Harris
Sent: 18 Jul 2019 22:37:01 +0000
To: Hotez, Peter Jay; Stanley Plotkin; 'Admin'; nkarora@inclentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhspk.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); Zuber, Patrick (CDC who.int); Destefano, Frank (CDC/DDID/NCEZID/DHQP)
Cc: kathryn.edwards@vumc.org; jim.buttery@monash.edu; (b)(6); ulrich.heininger@ukbb.ch; amy@vaccinateyourfamily.org; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); liz.miller@hpa.org.uk; amyp@ecbt.org
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Also agree.

I think that rebuttals/debunking are extremely valuable, in particular to those who are directly engaged in vaccine communications. Often those engaged in conversations may not be versed on all the arguments, especially the latest 'twists'. Having a scientific rebuttal serves to provide them both with the confidence and the information they need in order to formulate suitable messages to their audience. Also, as Peter notes, these are great for identifying the gaps.

However, where to host these is a good question as indeed you do not want to draw attention to something if it is not on a radar, you also want the rebuttals to be from an established reputable source. In NZ these have resided [on the Immunisation Advisory Centre \(part of the University of Auckland\)](#) website but not in the pages about the vaccines and diseases. They are placed where people looking can find them in the pages targeting health professionals. They are developed based on requests from the front line vaccinators and highly valued. Refuting this stuff is really important but you need to get it to where it is needed.

Kind regards
Helen

From: Hotez, Peter Jay <hotez@bcm.edu>
Sent: Friday, 19 July 2019 1:53 AM
To: Stanley Plotkin <stanley.plotkin@vaxconsult.com>; 'Admin' <admin@vaxconsult.com>; nkarora@inclentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhspk.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov
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Department of Biology, Baylor University

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E-mail: hotez@bcm.edu

Twitter: [@peterhotez](#)

Skype: [p.hotez](#)

Executive Assistant: [Douglas Soriano](#)

Douglas.SorianoOsejo@bcm.edu

Phone: 713-798-1199

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Sent: Thursday, July 18, 2019 8:25:13 AM

To: Hotez, Peter Jay; 'Admin'; nkarora@inclentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsph.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov

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Title page affiliation: Peter Hotez MD PhD, Departments of Pediatrics and Molecular Virology & Microbiology, National School of Tropical Medicine, Baylor College of Medicine

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E-mail: hotez@bcm.edu

Twitter: [@peterhotez](#)

Skype: **p.hotez**

Executive Assistant: [Douglas Soriano](#)

Douglas.SorianoOsejo@bcm.edu

Phone: 713-798-1199

From: Admin <admin@vaxconsult.com>

Sent: Wednesday, July 17, 2019 2:54 PM

To: nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org;
jason.m.glanz@kp.org; nhalsey@jhspk.edu; All@ssi.dk; paul.lambert@unige.ch;
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From: Amy Pisani
Sent: 22 Jul 2019 20:43:44 +0000
To: Hotez, Peter Jay; Stanley Plotkin; 'Admin'; nkarora@inclentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsp.h.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); Zuber, Patrick (CDC who.int); Destefano, Frank (CDC/DDID/NCEZID/DHQP)
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Subject: RE: HOTEZ COMMENTS London vaccine safety - Dr. Stanley Plotkin

I have been out of town so apologize for chiming in late. I am asking around to determine if there is already a response to the RFK claims that we can utilize. That being said I am planning to update a post on our blog which is one of the top three MOST READ POSTs since we launched Shot of Prevention in 2008. I can envision developing a post like this without mentioning RFK.

[Questioning Whether To Get Your Child the HPV Vaccine? Read This](#)

<https://shotofprevention.com/2016/01/21/questioning-whether-to-get-your-child-the-hpv-vaccine-read-this/>

From: Hotez, Peter Jay [mailto:hotez@bcm.edu]
Sent: Thursday, July 18, 2019 9:53 AM
To: Stanley Plotkin <stanley.plotkin@vaxconsult.com>; 'Admin' <admin@vaxconsult.com>; nkarora@inclentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsp.h.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; andrew.pollard@paediatrics.ox.ac.uk; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov
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Executive Assistant: [Douglas Soriano](#)
Douglas.SorianoOsejo@bcm.edu

Phone: 713-798-1199

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Sent: Thursday, July 18, 2019 8:25:13 AM

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Doylestown, PA 18902
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From: Wolfe, Skip (CDC/DDID/NCIRD/ISD)
Sent: 15 Jul 2019 20:38:44 +0000
To: Stanley Plotkin
Subject: RE: HPV article

Thanks. We received a copy of this, and will be having a meeting this week to discuss changes we've been discussing in VIS format and content, and to plan for the future.

By the way, I watched the video you made explaining the use of fetal tissue in the production of rubella vaccine. I'd hope it should persuade any but the hardest core anti-vaxxers that it has saved and improved countless lives while doing virtually no harm to anyone. Very fascinating historically.

Skip

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Sent: Monday, July 15, 2019 9:36 AM
To: Wolfe, Skip (CDC/DDID/NCIRD/ISD) <crw4@cdc.gov>
Subject: FW: HPV article

Dear Skip:

In case you missed this, I am not the only one concerned about the VIS, and I look forward to the review you mentioned.

Best wishes,
Stanley Plotkin

From: Edwards, Kathryn
Sent: 16 Sep 2019 14:13:09 +0000

To:

Admin;nkarora@incentrust.org;fombonne@ohsu.edu;nathalie.garcon@bioaster.org;jason.m.glanz@kp.org;nhalsey@jhspk.edu;All@ssi.dk;paul.lambert@unige.ch;'Heidi Larson';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);'Andrew Pollard';Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber, Patrick (CDC who.int);Destefano, Frank (CDC/DDID/NCEZID/DHQP);jim.buttery@monash.edu;(b)(6);ulrich.heininger@ukbb.ch;dsalmon1@jhu.edu;m.c.j.sturkenboom@umcutrecht.nl;priya.bahri@ema.europa.eu;(b)(6);(b)(6);bodenstabh@email.chop.edu;(b)(6);hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz

Cc: 'Stanley Plotkin'
Subject: RE: London Ideas - Version 4
Attachments: London Ideas version 3 fxdke.docx

I have added a few comments to the document. I am not sure that we have generated a very robust list of research ideas. Vaccine safety research is extraordinarily difficult. The adverse events are uncommon and not always seen by the same people, so the recognition of patterns is problematic. But there are examples in drug adverse events that could be used as models for vaccine adverse events. I challenge all of us to think about this and engage new colleagues with new ideas to work on this. My best. K

From: Admin <admin@vaxconsult.com>
Sent: Tuesday, September 3, 2019 10:41 AM
To: nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhspk.edu; All@ssi.dk; paul.lambert@unige.ch; 'Heidi Larson' <Heidi.Larson@LSHTM.ac.uk>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; 'Andrew Pollard' <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov; Edwards, Kathryn <kathryn.edwards@vumc.org>; jim.buttery@monash.edu; (b)(6); ulrich.heininger@ukbb.ch; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz
Cc: 'Stanley Plotkin' <stanley.plotkin@vaxconsult.com>
Subject: London Ideas - Version 4

Dear Attendee at the London Vaccine Safety meeting:

I have prepared a fourth version based on your comments. If you have further comments they must be received by September 15, after which I will be using it to seek funding. Please send comments to stanley.plotkin@vaxconsult.com

Thank you,
Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
Doylestown, PA 18902
215-297-9321

(b)(5)

(b)(5)

(b)(5)

(b)(5)

From: Neal Halsey
Sent: 10 Jun 2019 15:50:39 +0000
To: Admin;nkarora@inclentrust.org;Destefano, Frank (CDC/DDID/NCEZID/DHQP);'Eric Fombonne';'GARCON Nathalie';jason.m.glanz@kp.org;All@ssi.dk;'Paul Henri Lambert';'Heidi Larson';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);andrew.pollard@paediatrics.ox.ac.uk;Sejvar, James (CDC/DDID/NCEZID/DHCPP);nhalsey@jhsph.edu
Cc: 'Stanley Plotkin'
Subject: Re: London Meeting

Stan,
How do you want the references listed in the text, or are you planning to just list the references by the section? Many of the references I will list are applicable to multiple statements I make, not just individual points.
Neal

From: Admin <admin@vaxconsult.com>
Date: Monday, June 3, 2019 at 9:18 AM
To: "nkarora@inclentrust.org" <nkarora@inclentrust.org>, "DeStefano, Frank (NIP)" <fxdl@cdc.gov>, 'Eric Fombonne' <fombonne@ohsu.edu>, 'GARCON Nathalie' <Nathalie.GARCON@bioaster.org>, "jason.m.glanz@kp.org" <jason.m.glanz@kp.org>, "All@ssi.dk" <All@ssi.dk>, PAUL-hENRI LAMBERT <Paul.Lambert@unige.ch>, 'Heidi Larson' <Heidi.Larson@LSHTM.ac.uk>, Lauri Markowitz <lem2@cdc.gov>, Paul Offit <offit@email.chop.edu>, "keith.peden@fda.hhs.gov" <keith.peden@fda.hhs.gov>, "andrew.pollard@paediatrics.ox.ac.uk" <andrew.pollard@paediatrics.ox.ac.uk>, James Sejvar <zea3@cdc.gov>, JPIDS JPIDS <nhalsey@jhsph.edu>
Cc: Stan Plotkin <stanley.plotkin@vaxconsult.com>
Subject: London Meeting

Dear Speaker:

As I said at the end of our conference in London, I would like to prepare a publication coming from the meeting and plan for further steps. To those ends, I beg of you to provide me within two weeks the following:

1. Approximately 400 words summarizing your talk. Please do not waste words with sentences beginning "We reviewed ten different reactions..." but rather "Multiple sclerosis after vaccination has been studied and no excess over unvaccinated people was found."
2. 200-300 words (or more if you like) about what additional studies you think are needed. These will NOT be published, but rather serve as the basis for funding proposals. As I think you will judge, I cannot promise anything but will do my best.
3. Up to 10 references to your subject

Please send your response to my e-mail: stanley.plotkin@vaxconsult.com

Thanks,

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin

4650 Wismer Road

Doylestown, PA 18902

215-297-9321

From: Steve Black
Sent: 18 Jul 2019 08:56:29 +0200
To: Admin
Cc: Narendra K Arora;Eric Fombonne;GARCON
Nathalie;jason.m.glanz@kp.org;Neil Halsey;Anders Peter
Hviid;paul.lambert;<heidi.larson@lshtm.ac.uk>;Markowitz, Lauri (CDC/DDID/NCIRD/DVD);Paul
Offit;Peden, Keith (FDA/CBER);Andrew Pollard;Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber,
Patrick (CDC who.int);Destefano, Frank (CDC/DDID/NCEZID/DHQP);Stan Plotkin;Edwards,
Kathryn;Jim Buttery;Robert Chen;Heininger, Ulrich;amy@vaccinateyourfamily.org;Daniel
Salmon;Miriam
Sturkenboom;priya.bahri@ema.europa.eu;bodenstabh@email.chop.edu;Alexander
Dodoo;Peter Hotez;Liz Miller;Helen Petousis;Amy Pisani
Subject: Re: London vaccine safety - Dr. Stanley Plotkin

Thank you for the opportunity to comment.

(b)(5)

Take care all

steve

On Wed, Jul 17, 2019 at 9:54 PM Admin <admin@vaxconsult.com> wrote:

Dear Attendees at the London Wellcome Trust Vaccine Safety Meeting:

I must begin with two apologies. First, for the delays in preparing the attached, caused by other projects I had to work on; second, for the fact that you have not received the slides from the meeting. With respect to the second, Wellcome promised to send them out weeks ago, but I have been unable to find out why the delay despite multiple attempts. I will not give up, but to avoid further delays I ask the speakers **to send me their slides and I will disseminate them to everybody else.**

(b)(5)

By the way, Patrick Zuber is organizing a Global Vaccine Safety meeting in December.

Thank you so much for your help and your patience.

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin

4650 Wismer Road

Doylestown, PA 18902

215-297-9321

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you.

From: Admin
Sent: 26 Jul 2019 14:42:30 -0400
To: nkarora@incentrust.org; fombonne@ohsu.edu; nathalie.garcon@bioaster.org; jason.m.glanz@kp.org; nhalsey@jhsphe.edu; All@ssi.dk; paul.lambert@unige.ch; heidi.larson@lshtm.ac.uk; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); offit@email.chop.edu; Peden, Keith (FDA/CBER); andrew.pollard@paediatrics.ox.ac.uk; Sejvar, James (CDC/DDID/NCEZID/DHCPP); Zuber, Patrick (CDC who.int); Destefano, Frank (CDC/DDID/NCEZID/DHQP)
Cc: stanley.plotkin@vaxconsult.com; kathryn.edwards@vumc.org; jim.buttery@monash.edu; (b)(6); (b)(6); ulrich.heininger@ukbb.ch; amy@vaccinateyourfamily.org; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); (b)(6); hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz; amyp@ecbt.org
Subject: RE: London vaccine safety - IDEAS SUMMARY addition - A. Pollard
Attachments: Pollard summary 7 26 19.docx

Dear All:

Andy Pollard had made suggestions for the Idea Document that I had failed to include in my mailing summarizing the ideas. I have attached those suggestions and will include them in the next version of the ideas document.

Stanley

Wendy D'Arcy

Assistant to Dr. Stanley Plotkin
4650 Wismer Road
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215-297-9321

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Study proposals [Pollard]

Given the above comments, it seems prudent to

(b)(5)

(b)(5)

From: Eric Fombonne
Sent: 14 Jan 2020 06:35:09 +0000
To: Admin;offit@email.chop.edu;Destefano, Frank
(CDC/DDID/NCEZID/DHQP);'Heidi Larson';nkarora@inclentrust.org;Zuber, Patrick (CDC
who.int);Sejvar, James
(CDC/DDID/NCEZID/DHCPP);paul.lambert@unige.ch;All@ssi.dk;nhalsey@jhsph.edu;nathalie.gar
con@bioaster.org;Peden, Keith (FDA/CBER);'Andrew Pollard';Markowitz, Lauri
(CDC/DDID/NCIRD/DVD);jason.m.glanz@kp.org
Cc: 'Stanley Plotkin'
Subject: RE: London Vaccine Safety Article
Attachments: Fombonne et al_Vaccine_2020_Beliefs in vaccine in SPARK.pdf

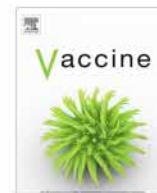
FYI
Regards,

Eric Fombonne



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Beliefs in vaccine as causes of autism among SPARK cohort caregivers

Eric Fombonne^{a,*}, Robin P. Goin-Kochel^b, Brian J. O'Roak^c, the SPARK Consortium^a Departments of Psychiatry, Pediatrics & Behavioral Neuroscience - Oregon Health & Science University, Portland, OR, USA^b Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA^c Department of Molecular & Medical Genetics, Oregon Health & Science University, Portland, OR, USA

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Ethnicity

Social factors

ABSTRACT

Background: Fear of autism has led to a decline in childhood-immunization uptake and to a resurgence of preventable infectious diseases. Identifying characteristics of parents who believe in a causal role of vaccines for autism spectrum disorder (ASD) in their child may help targeting educational activities and improve adherence to the immunization schedule.

Objectives: To compare caregivers of children with ASD who agree or disagree that vaccines play an etiological role in autism for 1) socio-demographics characteristics and 2) developmental and clinical profiles of their children.

Methods: Data from 16,525 participants with ASD under age 18 were obtained from SPARK, a national research cohort started in 2016. Caregivers completed questionnaires at registration that included questions on beliefs about the etiologic role of childhood immunizations and other factors in ASD. Data were available about family socio-demographic characteristics, first symptoms of autism, developmental regression, co-occurring psychiatric disorders, seizures, and current levels of functioning.

Results: Participants with ASD were 80.4% male with a mean age of 8.1 years (SD = 4.1). Overall, 16.5% of caregivers endorsed immunizations as perceived causes of autism. Compared to caregivers who disagreed with vaccines as a cause for ASD, those who believed in vaccine causation came disproportionately from ethnic minority, less educated, and less wealthy backgrounds. More often their children had experienced developmental regression involving language and other skills, were diagnosed earlier, had lost skills during the second year of life, and had worse language, adaptive, and cognitive outcomes.

Conclusion: One in six caregivers who participate in a national research cohort believe that child immunizations could be a cause of autism in their child. Parent social background (non-White, less educated) and child developmental features (regression in second year, poorer language skills, and worse adaptive outcomes) index caregivers who are more likely to harbor these beliefs and could benefit from targeted educational activities.

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder manifesting in the first years of life with a combination of developmental impairments in communication and reciprocal social interactions and atypical patterns of play, behavior, and sensorimotor responses. Although improvements occur as a function of maturation and early behavioral interventions, ASD is a lifelong disorder with persisting long-term impairments in core-symptom domains of ASD, especially social functioning [26]. Current epidemiological estimates for ASD in the US child population range between 1.7% [2] and 2.5% [24].

In the late 1990s, claims that childhood vaccinations accounted for upward trends in autism prevalence were widely publicized despite weak, if any, supporting empirical evidence. One purported mechanism incriminated the measles component of the triple MMR vaccine, arguing that in children previously normally developing, a regression and loss of skills occurred 5 to 6 days after vaccination, leading to autism associated with gastrointestinal symptoms and inflammatory pathology [45]. The second one implicated the cumulative dose of thimerosal (ethylmercury) received through other childhood vaccines up to age 2 that was deemed to be too high and possibly exceeding safety thresholds.

Numerous controlled observational studies (case-control and cohort studies) failed to show that exposure to MMR vaccination [40] or to thimerosal-containing vaccines in various doses raised the risk of autism [21], findings that extended to their high-risk

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siblings [22,48]. The convergence of negative studies across investigators, study designs, samples and countries has been impressive and the absence of association between MMR and autism confirmed in several meta-analyses [23,42].

Further claims were subsequently made that the risk could be confined to a small, vulnerable, subgroup that epidemiological studies would not be capable to detect. Limited evidence was brought forward to describe this group (defined by regression/loss of skills days following the MMR vaccine, association with gastrointestinal symptoms, and demonstrated abnormal persistence of the measles virus in the gut and other biological specimens). A systematic search for this hypothetical phenotype failed to validate its existence [10,15]. Regression/loss of skills in the developmental trajectory of autism had been described since the 1940s in up to 30% of children with ASD, and there is no evidence that this regressive phenotype has increased recently or in post-MMR years [10]. Comparative studies showed that children exposed to MMR were not more likely than unexposed children to experience regression, or a combination of regression and GI symptoms [10]. Moreover, studies of peripheral blood mononuclear cells RNA and measles antibodies titers [6] and measles RNA in gut specimen [20] all failed to document the presumed persistence of the measles virus in biological compartments of children with autism exposed to MMR. Of note, the initial research was shown to be fraudulent and the original paper was retracted by the *Lancet* [13].

Despite the strong convergence of negative scientific findings on this issue, fears that vaccines might cause ASD have persisted in the community of individuals with autism and their caregivers, as well as the lay public. In fact, misperception about an ASD-vaccine link has been proposed as a leading explanation behind increases in vaccine delays and refusals [30], the public-health consequences of which are evident in increased outbreaks of vaccine-preventable diseases [32]. These outbreaks and steadily declining immunization rates prompted the World Health Organization to identify vaccine hesitancy as one of the 10 greatest threats to global health in 2019 [47], as well as the publication of The Salzburg Statement on Vaccine Acceptance [35], which appeals to social media, government, healthcare, education, and families to actively promote confidence in vaccines. A public health focus is increasingly centered on parents who are *vaccine hesitant* (VHPs), which refers to a continuum of vaccine concerns that may include delaying/refusing one or more vaccines; however, VHPs are more amenable to vaccination compared to parents who refuse vaccines entirely.

Prevalence of parental vaccine hesitancy varies geographically, but in the general population, estimates range from 9 to 15% [18,31,19]. However, emerging evidence suggests that this rate is much higher among parents of children with ASD. Two recent studies on vaccine hesitancy and beliefs about causes of autism/developmental delays among parents of chi at approximately 28% of parents were vaccine hesitant [28,17]. Not surprisingly, the bulk of these parents endorsed vaccines as a cause for their children's ASD. Considering that (a) children later diagnosed with ASD are well-vaccinated for childhood vaccines recommended during the first two years of life [15,48] and (b) the median age of ASD diagnosis in the U.S. is four years, it is possible that many of these families become vaccine hesitant and endorse vaccines as a cause for ASD only *after* receiving the autism diagnosis. Unfortunately, once these beliefs are founded, they can be difficult to change and easy to disseminate, and little is known about the content and format of vaccine-information delivery that resonates most with parents who have concerns about vaccine safety [29].

As part of the Simons Foundation Autism Research Initiative, the SPARK cohort was recently initiated nationwide to increase genetic discovery and research capacity in ASD (SPARK, 2018). Since April 2016, recruitment from academic sites and the public

at large has allowed for rapid accrual of a very large sample of individuals with ASD of all ages and from all US regions. A majority of these individuals and their parents consented to provide saliva samples for genetic characterization (<https://www.sfari.org/resource/spark/>). Data were collected on family background, medical and social history, and specific autism symptom patterns. As part of these baseline data, caregivers were asked questions about their beliefs about causes of autism in their child. We dichotomized the group into those participants who either did or did not identify immunizations as a possible cause of autism. We compared the two groups of participants with respects to familial socio-demographics and index child developmental and clinical profiles. Our objectives were to identify: (1) characteristics of caregivers and households associated with belief in immunizations as a potential cause of autism; and (2) features of developmental trajectories and clinical profiles of children with ASD whose parents are most vulnerable to endorsing such beliefs.

1. Material and methods

1.1. SPARK cohort

In April 2016, SPARK began nationwide recruitment with 21 clinical sites, stakeholder partner organizations, and a multi-pronged social media strategy. Any individual living in the US with a professional diagnosis of ASD (by provider or school), alongside their parents (or legal guardians) and an unaffected sibling, are eligible to participate in SPARK. SPARK collects phenotypic data and biospecimens remotely so that participants can complete the study protocol online at their convenience, usually from home.

As part of participation in SPARK, individuals are also asked to complete a battery of online questionnaires (<https://www.sfari.org/resource/spark/>). For children under age 18, all questionnaires are completed by parents/caregivers.

Although phenotypic information and ASD diagnoses in SPARK are self- or parent-reported, past research on the first web-based registry for ASD, the Interactive Autism Network [25], as well as recent analyses of the dependent adults SPARK participants [11] suggest that parent-reported diagnosis of ASD is valid. Participants consent to share their de-identified data and to be contacted about future ASD research studies for which they may be eligible. Participants can also consent to contribute a saliva sample for genetic analysis and have the option to receive individual genetic results related to ASD should a primary genetic cause of ASD be identified. Detailed aspects of genetic material collection, genomic analyses, and return of results to participants are described elsewhere [39,11,9]. In SPARK's first 32 months of recruitment, through December 2018, SPARK enrolled 150,064 participants, including 59,218 individuals with ASD.

1.2. Data and instruments

Online registration requires completing a basic set of registration questions about each individual who enrolls, and a series of supplementary questionnaires.

• Registration Questions

The registration questions (hereafter referred to as 'Registration Questions') for individual participants with ASD cover: age at registration, sex, ASD diagnosis, professional/s who made the ASD diagnosis, age at first diagnosis, lifetime receipt of any services or therapies specifically for ASD, presence of an individualized education program/plan (IEP), lifetime diagnosis of intellectual disability or cognitive impairment, and current everyday language level

(coded on 4 levels: *No words/does not speak, Uses single words meaningfully (for example, to request), Combines 3 words together into short sentences, Uses longer sentences of his/her own and is able to tell you something that happened*). From this, we generated a dichotomous variable for current language functioning with: 0 = Sentence speech, 1 = Minimally or non-verbal (3 other levels).

• Medical questionnaire

Respondents can endorse any of the 5 following medical domains questions for diagnoses made by a professional: Birth or pregnancy complications, Neurological conditions, Growth conditions (e.g., obesity, head size), Vision or Hearing conditions, and Birth defects. A positive answer for any domain leads to more detailed follow-up questions. From these, we selected the following variables for subsequent analyses. We constructed a variable *Any birth defect* that was scored 1 when any of the 25 birth defects was endorsed and 0 otherwise. The five birth/pregnancy complications were similarly summarized in a binary variable *Any birth problem* scored 1 (=Any complications) or 0 (=No complications). Sleep disorder and Seizure disorder or epilepsy were similarly coded 1 for Yes and 0 for No. For psychiatric disorders, we created summary binary variables for *Any disruptive disorder*, *Any emotional disorder*, and *Any psychiatric disorder*. We also examined specific disorders for their particular relevance—ADHD because of its high prevalence and impact on management and caregivers [38], and Tics because of prior concerns about an increased risk of tics following vaccine exposure [44,3]. ADHD and Tics were included in *Any psychiatric disorder* but not in *Any disruptive disorder*. Questions on psychiatric disorders apply retrospectively to the lifetime period and no data were collected about date of onset, duration, or treatment.

• Background history

This questionnaire covered socio-demographic information about the parents (marital status, race/ethnicity, annual household income, education level, occupation/employment status) and current living arrangements. From the child's developmental history, the following variables were used: *Motor delay* (0 = No; 1 = Sat after 8 months or walked after 18 months), *Delay in 1st words* (0 = No; 1 = >= 24 months), *Delay in first phrases* (0 = No; 1 = >=33 months), *Age of parental recognition of 1st symptoms*, *Type of parental concern*, *Stopped progressing or "plateaued"* (0 = No, 1 = yes), *Stopped talking, lost language* (0 = No, 1 = yes), *Loss of other skills* (0 = No, 1 = yes), *Age at diagnosis*, *Diagnosed with Asperger/PDDNOS* (0 = No, 1 = yes), *Ever diagnosed with cognitive impairment/intellectual disability* (0 = No, 1 = yes), and *Presence of a sibling with ASD* (0 = No; 1 = Yes). Cut points for delays in milestones were selected to be similar to those of the *Autism Diagnostic Interview-Revised*, a widely used caregiver interview for the diagnosis of autism. In the current functioning questions, parents were asked to rate the level of functioning of their child as compared to same-age peers. Questions covered the level of support required, general understanding of concepts and problem-solving capacity, daily functioning, and current level of spoken language. For each domain, parents indicated if their child was functioning above or at age level, slightly below age, or significantly below age. A composite variable was generated by calculating the *Number of areas* where the child was most behind his peers (significantly below age or very substantial support required), with a range from 0 to 4.

One final question was about the caregiver's perceptions about the causes of ASD: "What is your opinion as to what may have caused X's ASD?". Nine options were listed: Genetic causes, Other medical conditions, Environmental exposures, Problems during pregnancy, Drug or alcohol exposure in pregnancy, Birth or

delivery complication, Infection in infancy or early childhood, Immunizations, Don't know/Other. Parents could select as many responses as they liked. A positive response to the 'Immunizations' modality was used to stratify the sample into caregivers who endorsed immunizations (EI) or not (NEI) as a cause of ASD.

• Other SPARK data

Other questionnaire data used were:

- The *Social Communication Questionnaire* (SCQ) is a parent-report questionnaire that evaluates 3 major aspects of ASD: communication, social interaction, and repetitive behaviors. The development of the SCQ was modeled after the *Autism Diagnostic Interview* to generate a brief, parent-completed, screening tool (Berument et al., 1999). The questionnaire exists in two forms: lifetime and current. The "lifetime" version (used in this study) evaluates the child's developmental history as well as current behaviors. It comprises 40 questions with "yes" or "no" responses. Each item is scored as 0 or 1, and the sum of 39 items yields a total SCQ score ranging from 0 to 39 (the first item documents whether or not the child has phrase speech and is not scored). Total scores are prorated when there are 3 items or less missing; with 4 or more items missing, total score is set to missing. Cutoffs of 15 and 22 were initially proposed to select children likely to have a broader or narrower form of ASD, with a cut-off of 12 recommended in subsequent epidemiologic studies.

- The *Repetitive Behavior Scale-Revised* (RBS-R) is a caregiver completed rating scale that evaluates 43 restricted, repetitive, self-injurious behaviors rated on a zero (Behavior does not occur) to 3 (Behavior occurs and is a severe problem) scale as observed during the last month. An overall score is derived from the sum of items scores, and scale-specific scores can also be derived for six dimensions (Stereotyped behavior; Self-injurious behavior; Compulsive behavior; Ritualistic behavior; Sameness behavior; Restricted behavior). The RBS-R overall score was dichotomized by using the 75th (47) and 90th (65) centiles of the whole sample distribution.

The SCQ and the RBS-R were examined both as continuous and categorical scores.

1.3. Sample selection

Data for participants registered in the SPARK cohort were downloaded December 20, 2018, from the SFARI website (<https://www.sfari.org>). There were 59,218 participants with an ASD diagnosis, of whom 50,505 were under age 18 at registration. Of these, 18,480 had Background history data with the vaccine-belief question answered. We further excluded 1,955 subjects who were siblings or half-siblings of an already registered child in order to maintain independence of observations, leaving a sample of 16,525 participants under age 18 with available data. They were comparable to participants without Background history data for sex, age, cognitive and language levels, and history of ASD services.

1.4. Ethical approval

All recruiting sites for SPARK delegated institutional oversight of the study to a central institutional review board (Western IRB). Only de-identified data were used in this study.

1.5. Statistical analyses

Data were analyzed in SPSS v25 and conventional statistical tests for categorical (Fisher exact test; chi-square) and continuous variables (t-tests, Pearson or Spearman correlation coefficients)

were used. Binary and multivariate logistic regression was used to evaluate predictors of binary dependent variables. In line with current recommendations [34,37], we did not use Bonferroni's adjustment for multiple tests. Owing to the large sample size, a p-value of ≤ 0.01 was retained throughout as a pre-set level of statistical significance.

2. Results

The SPARK-participant sample was 80.4% male (male:female ratio: 4.1), and the mean age was 8.1 years ($SD = 4.1$) at registration. Overall, 2,730 caregivers (16.5%) endorsed immunizations as a possible cause of ASD in their child; this was the fourth most frequent potential etiology endorsed by respondents, preceded by genetic causes ($N = 9,650$, 58.4%), environmental exposures ($N = 3,611$; 21.9%) and birth or delivery complications ($N = 2,796$, 16.9%).

2.1. Attributions to immunizations versus other causes

EI and NEI caregivers were compared with respect to other endorsed etiologic beliefs (Table 1). Genetic causes were the most frequently endorsed etiology, with no difference between the EI and NEI groups in likelihood of endorsing that cause. For 6 of the remaining 7 potential causes, the EI group had significantly higher levels of endorsement than the NEI group. When causes were added up, EI caregivers endorsed a higher number of causes than NEI caregivers (2.8 vs 1.3; $p < 0.001$).

2.2. Socio-demographic characteristics by caregiver-belief status

Sociodemographic characteristics are summarized in Table 2. Children did not differ by gender but were significantly older in the EI group compared to the NEI group. There was a marked tendency for children from ethnic minority backgrounds (with the exception of Native Americans) to have parents belonging to the EI group. Compared to NEI caregivers, EI caregivers were significantly less often married, had lower income, were less educated, less often employed, and more likely to be full-time caregivers for their child. Sibling recurrence of ASD had no impact on beliefs.

2.3. Developmental and clinical profiles by caregiver belief status

Children from NEI caregivers had slightly higher rates of birth problems; otherwise, the 2 groups were comparable for the incidence of birth defects, motor delay, and language delay when estimated by first-word onset (Table 3). However, phrase-speech delay was significantly more frequent in the EI group. The EI caregivers also differed from their NEI counterparts in their reports of first

ASD symptoms in their child. EI caregivers less often reported early (< 12 months) or late (> 36 months) recognition of first symptoms but identified them more frequently during the second year of life. The type of first ASD symptom recognized by parents significantly differed across groups, with EI caregivers reporting a change or loss of skills three times more frequently than NEI parents. Irrespective of age at symptom identification, over half the EI caregivers reported a loss of language in their child and over two fifths reported a loss of another skill, with both reports occurring about twice as frequently in the EI compared to the NEI group. Similarly, reports of plateauing in development was much more frequent in the EI than the NEI group. In addition, when language loss occurred, children from the EI group lost language skills at an earlier age than in the NEI group (21.0 vs 23.1 months; $p < 0.001$). When asked if speech ever came back to the level it was just before the loss, NEI caregivers had more frequent positive answers than EI caregivers (69.5% vs 59.7%; $p < 0.001$) and the reported duration of the loss (< 1 year) was significantly different across the two groups and shorter in the NEI group (NEI: 34.3%; EI: 18.8%; $p < 0.001$).

A similar pattern was observed for loss of other skills (i.e., non-language skills), which occurred at a significantly younger age in the EI group compared to the NEI group (27.5 vs 37.5 months; < 0.001). The return to pre-loss skill level was endorsed by 51.1% of NEI and 44.0% of EI caregivers ($p < 0.001$) and a duration of loss < 1 year was reported by 29.4% of NEI and 16.4% of EI caregivers ($p < 0.001$).

The mean age at diagnosis in this sample was 4.4 years ($SD = 2.7$; IQR: 2.5–5.5). The age at diagnosis was significantly lower in the EI group than in the NEI group (3.7 vs 4.5 years; $p < 0.001$), with higher proportion of children diagnosed before age 3 and the opposite pattern after age 6 (Table 3). Severity was more pronounced in children of the EI group, with a higher rate of lifetime diagnosis of intellectual disability, similarly indexed by less reliance on 'high-functioning' diagnostic categorization.

With the exception of Tics, lifetime prevalence of psychiatric disorders was slightly higher among NEI compared to EI offspring. By contrast, other indicators of clinical severity were significantly raised in the EI group, including sleep disorders, epilepsy, as well as minimally verbal status (currently, no sentence speech). Likewise, when asked about the level of support currently required by their child, findings were consistent across the 4 areas investigated, with EI children endorsing a higher number of areas with significant needs than NEI children by a factor that ranged from 1.3 (Spoken language) to 1.6 (Support required) (Fig. 1).

Finally, levels of autistic symptomatology, whether measured by the general autism SCQ questionnaire or by the more symptom-domain specific RBS-R scale, showed consistently higher levels of symptoms in the EI compared to the NEI group. This was true when scores were examined both continuously or categorically (Table 3).

Table 1
Vaccines versus other etiologic beliefs.

What is your opinion as to what may have caused your child's ASD...	Immunizations				p-value
	No (NEI) N = 13,795		Yes (EI) N = 2,730		
	N	%	N	%	
Genetic causes	8,099	58.7	1,551	56.8	0.066
Other medical conditions	980	7.1	359	13.2	<0.001
Environmental exposures	2,408	17.5	1,203	44.1	<0.001
Problems during pregnancy	2,186	15.8	540	19.8	<0.001
Drug or alcohol exposure in pregnancy	348	2.5	80	2.9	0.22
Birth or delivery complication	2,166	15.7	630	23.1	<0.001
Infection in infancy or early childhood	473	3.4	261	9.6	<0.001
Other causes	1081	7.8	308	11.3	<0.001

Table 2

Sociodemographic characteristics, by belief status.

	Immunizations may have caused my child's ASD...				
	No (NEI)		Yes (EI)		p-value
	N	%	N	%	
Child					
Gender male	11,045	80.1	2,233	81.8	0.038
Age at joining the study					
• Under 3 years	916	6.6	172	6.3	<0.001
• 3–5 years	3,647	26.4	696	25.5	
• 6–11 years	6,118	44.3	1,094	40.1	
• 12–17 years	3,114	22.6	768	28.1	
Ethnicity					
• African-American	617	4.5	219	8.1	<0.001
• White	10,902	79.3	1,921	70.7	
• Native American	83	0.6	10	0.4	
• Asian	258	1.9	87	3.2	
• Other	1,892	13.8	479	17.6	
Living arrangements					
• With both parents	9,697	70.4	1,893	69.5	0.001
• With mother	3,466	25.2	749	27.5	
• With father	155	1.1	28	1.0	
• Adopted/foster home/relatives	424	3.1	50	1.8	
• Residential	26	0.2	2	0.1	
Has a sibling with ASD	1,680	12.2	333	12.2	0.98
Family					
Marital status biological parents					
• Married	8,770	65.4	1,645	62.4	0.003
• Never married	2,369	17.7	544	20.6	
• Divorced and remarried	977	7.3	186	7.1	
• Divorced/separated	1,286	9.6	263	10.0	
Household income/year					
• <\$20,000	1,552	11.5	381	14.4	<0.001
• \$20,000 to \$50,000	3,729	27.7	760	28.7	
• \$51,000 to \$80,000	2,834	21.0	607	22.9	
• \$80,000 to \$130,000	3,209	23.8	579	21.9	
• Over \$131,000	2,152	16.0	318	12.0	
	Immunizations may have caused my child's ASD...				
	No (NEI)		Yes (EI)		p-value
	N	%	N	%	
Mother's education					
• Did not complete high school	728	5.3	192	7.0	<0.001
• High school	1,271	9.2	278	10.2	
• Trade or Associate degree	2,854	20.7	631	23.2	
• Some college	2,370	17.1	530	19.4	
• Bachelor degree	3,697	26.8	652	23.9	
• Professional degree	2,854	20.7	442	16.2	
Mother's occupation					
• Employed	6,360	46.4	1,130	41.5	<0.001
• Home carer	4,801	35.0	1,076	39.6	
• Temporary or Part-time	1,410	10.3	271	10.0	
• Unemployed	1,129	8.2	243	8.9	

Thus, children from parents endorsing immunization as a potential cause of ASD had a developmental course marked on average by an 'onset' in the second year of life, a regressive pattern involving language and other skills, an earlier (<3) age at diagnosis, and greater clinical severity as shown by heightened developmental language and cognitive impairments, as well as more pronounced deficits in current level of functioning across key areas. Moreover, parents in the EI group more frequently tended to come from minority, less educated, and less wealthy backgrounds. The findings on psychiatric disorders ran in the opposite direction; however, previous analyses [11] showed that psychiatric prevalence is decreased among individuals with lower levels of language and cognitive functioning, likely indicating under-detection among those who are more severely impaired.

Because factors associated with vaccine-belief status were intercorrelated, we employed multiple logistic regression analyses to obtain a more parsimonious set of correlates of such beliefs. Using belief in immunization as a dependent variable, three *a priori*

defined blocks of variables with a significant ($p < 0.01$) association with belief status were entered as predictors as follows: (a) demographic characteristics (child ethnicity, living arrangements, parent's marital status, annual household income, mother's education, and mother's occupation; see Table 2 variables); (b) developmental trajectory characteristics (sex, age, any birth problems, cognitive impairment, motor delay, phrase-speech delay, age at first ASD symptoms, type of parental concern, plateau, any regression [language or other skill], age at diagnosis, Asperger/PDDNOS diagnosis; see Table 3 variables, Section Early Development); (c) current behavioral/adaptive functioning (history of seizures, any lifetime psychiatric disorder, diagnosed sleep problems, minimally verbal status, total SCQ score [continuous], total RBS-R score [continuous], and number [0–4] of areas [support required, understanding concepts/problem solving, daily functioning, spoken language] with significantly below-age functioning; see Table 3 variables, section on Current behavioral/adaptive functioning). Gender was initially forced in the models because of its

Table 3
Developmental and clinical characteristics, by belief status.

	Immunizations may have caused my child's ASD...				
	No (NEI)		Yes (EI)		p-value
	N	%	N	%	
Early development					
Any birth defect	446	3.2	65	2.4	0.019
Any birth problems	4,230	30.7	751	27.5	0.001
Motor delay (sitting > 8 or walking > 18 mos)	2,894	21.2	519	19.2	0.02
Delay in 1st words (>=24 mos)	4,936	37.0	977	36.9	0.96
Delay in 1st phrases (>=33 mos)	6,722	50.9	1,595	61.7	<0.001
Age at parental recognition of 1st symptoms					
• <12 months	4,782	34.9	738	27.2	<0.001
• 13–24 months	5,304	38.7	1,370	50.4	
• 25–36 months	2,054	15.0	433	15.9	
• >36 months	1,571	11.5	176	6.5	
First parental concern					
• Motor or language delay	5,446	39.8	970	35.7	<0.001
• Loss or change in abilities	1,029	7.5	623	22.9	
• Atypical social interaction	2,631	19.2	463	17.0	
• Unusual speech or habits	1,608	11.7	238	8.8	
• Other	2,981	21.8	423	15.6	
Stopped progressing or “plateaued”	6,967	50.7	1,972	72.3	<0.001
Stopped talking, lost language	3,950	28.7	1,561	57.3	<0.001
Loss of other skills	3,457	25.1	1,194	43.9	<0.001
Age diagnosis					
• <3 years	4,781	34.7	1,300	47.6	<0.001
• 3–5 years	5,739	41.6	1,099	40.3	
• >= 6 years	3,273	23.7	331	12.1	
Asperger or PDDNOS diagnosis	2,237	16.2	368	13.5	<0.001
Cognitive impairment/ID (ever diagnosed with)	2,100	15.2	546	20.0	<0.001
Current behavioral/adaptive functioning					
Seizure disorder or epilepsy (lifetime)	683	5.0	179	6.6	0.001
Psychiatric comorbidity (lifetime)					
• ADHD	5,129	37.2	856	31.4	<0.001
• Any disruptive disorder	5,319	38.6	910	33.3	<0.001
• Any emotional disorder	3,881	28.1	652	23.9	<0.001
• Tics	512	3.7	105	3.8	0.74
• Any psychiatric disorder	7,670	55.6	1,402	51.4	<0.001
Sleep Disorder/problem diagnosed by a professional	2,542	18.4	606	22.2	<0.001
Minimally or non verbal	5,463	39.6	1,521	55.7	<0.001
Level of support required					
• No or minimal support	1,388	10.1	187	6.9	<0.001
• Some support	5,677	41.3	883	32.5	
• Substantial	4,691	34.1	1,029	37.8	
• Very substantial	1,998	14.5	620	22.8	
General understanding of concepts/problem-solving					
• At age or above age level	6,352	47.0	861	32.6	<0.001
• Slightly below age	3,712	27.5	779	29.4	
• Significantly below age	3,443	25.5	1,006	38.0	
Daily functioning					
• At age or above age level	3,189	23.3	534	19.7	<0.001
• Slightly below age	6,634	48.4	1,206	44.4	
• Significantly below age	3,885	28.3	979	36.0	
Current level of spoken language					
• Above age level	2,383	17.4	261	9.6	<0.001
• At age level	2,658	19.4	344	12.7	
• Slightly below age	3,604	26.4	643	23.7	
• Significantly below age	5,031	36.8	1,461	53.9	
Number of areas with lowest functioning					
• 0	7,688	45.9	1,029	30.6	<0.001
• 1	4,168	24.9	853	25.4	
• 2	2,190	13.1	589	17.5	
• 3	1,571	9.4	499	14.8	
• 4	1,141	6.8	394	11.7	
Autism symptomatology measures					
<i>Categorical scores</i>					
SCQ					
• >=15	11,504	83.4	2,379	87.1	<0.001
• >=22	7,445	54.0	1,696	62.1	<0.001
RBS-R					
• >75 h centile	3,265	23.7	775	28.4	<0.001
• >=90th centile	1,287	9.3	310	11.4	0.001
<i>Continuous scale scores</i>					
SCQ total score, X (SD)	22.2	6.8	23.7	6.7	<0.001
RBS-R total score, X (SD)	34.77	20.6	37.30	21.8	<0.001

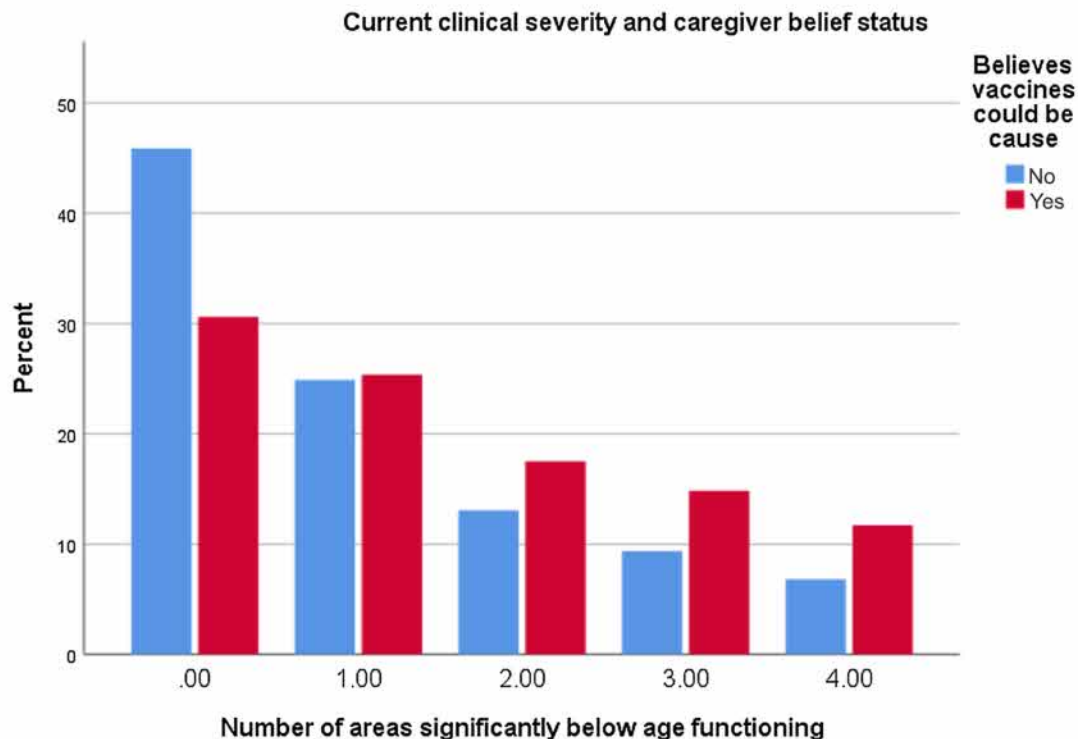


Fig. 1. Current clinical severity and caregiver belief status.

general developmental and biological significance. Results of the three resulting logistic models are provided in the Supplement alongside rules for recoding variables. In summary, of the 25 variables tested as predictors in the 3 models, 11 no longer significantly contributed to the model (- marital status, living arrangements, household income; - sex, cognitive impairment, motor delay, Asperger/PDDNOS diagnosis; - seizure history, any psychiatric disorder, RBS-R total score) and were not further considered. The remaining 14 variables were entered into a stepwise logistic regression with forward selection procedure and a

$p = 0.01$ for inclusion in the model. Results are shown in Table 4. Three variables (total SCQ score, mother's occupation, and delay in phrase speech) were not retained in the final model. The model fit was good (Hosmer-Lemeshow $\chi^2 = 3.7$; $df = 8$; $p = 0.89$). The 11 predictors remaining in the model reflected the role of both socio-demographic (child's race, child age, maternal education), developmental (regression, plateau, age at diagnosis, age and type of symptom for parental recognition, birth problems), and current functioning (language deficits, number of areas with significant below age functioning) factors. Interestingly, levels of autistic

Table 4

Predictors of belief in the role of immunizations: multiple logistic regression model (N = 16,239).

	B	S.E.	Wald	df	Sig.	Odds-ratio	95%CI lower	95%CI upper
Minimally or non verbal	0.322	0.062	26.863	1	0.000	1.379	1.221	1.558
Number of significantly below age areas	0.077	0.021	13.947	1	0.000	1.080	1.037	1.124
Child race	0.420	0.050	70.619	1	0.000	1.522	1.380	1.678
Mother's education: College/Professional	-	-	20.307	2	0.000	[Ref]	-	-
Some college	0.199	0.049	16.585	1	0.000	1.220	1.109	1.343
High school or less	0.217	0.065	11.231	1	0.001	1.242	1.094	1.411
Any birth problems	-0.163	0.049	10.901	1	0.001	0.849	0.771	0.936
Stopped progressing or "plateaued"	0.374	0.055	45.357	1	0.000	1.453	1.303	1.620
Any regression/loss of skills	0.600	0.055	118.462	1	0.000	1.822	1.635	2.029
Age at diagnosis	0.313	0.050	38.719	1	0.000	1.367	1.239	1.509
Age at parental recognition	0.298	0.046	42.054	1	0.000	1.347	1.231	1.473
First parental concern	0.702	0.062	128.158	1	0.000	2.018	1.787	2.279
Age at registration under 3 years	-	-	163.513	3	0.000	[Ref]	-	-
3-5 years	0.352	0.099	12.546	1	0.000	1.421	1.170	1.727
6-11 years	0.666	0.101	43.244	1	0.000	1.946	1.596	2.373
12-17 years	1.113	0.107	107.148	1	0.000	3.042	2.465	3.756
Constant	-3.611	0.116	962.297	1	0.000	0.027		

Variables were coded: Minimally or non verbal: 0 = No, 1 = Yes; - Number of significantly below age areas: 0 = Does not require very substantial support or is significantly below age in either general understanding of concepts/problem-solving or in daily functioning or for current level of spoken language, 1 = meets criteria for 1 area, 2 = meets criteria for 2 areas, 3 = meets criteria for 3 areas, 4 = meets criteria for 4 areas; - Child race: 0 = White, 1 = Otherwise; - Mother's education: 0 = Bachelor/professional, 1 = Some college, Trade/Associate degree, 2 = High school or less; - Any birth problems: 0 = No, 1 = Yes; - Stopped progressing or "plateaued": 0 = No, 1 = Yes; - Any regression/loss of skills: 0 = No language regression or loss of other skills, 1 = Language regression or loss of other skill; - Age at diagnosis: 0 = after age 3, 1 = under age 3; - Age at parental recognition: 0 = before 1 or after 2 years, 1 = between 13 and 24 months; - First parental concern: 0 = Other concerns than change or loss in abilities, 1 = Change or loss in abilities; - Age at registration: 0 = Under 3 years, 1 = 3-5 years, 2 = 6-11 years, 3 = 12-17 years.

symptomatology (other than language deficits) were no longer contributory.

3. Discussion

In this large community sample of caregivers of children with ASD under age 18, one in six participants believed immunizations could be a cause of ASD in their child; this was the fourth most frequently endorsed cause. Caregivers who endorsed vaccinations as a potential cause also more frequently endorsed other external, environmental causes and came from more adverse social backgrounds; their children had developmental trajectories characterized by skill loss in the second year of life and long-term, persisting impairments in language and overall functioning.

In our sample, beliefs in vaccines as a cause for ASD was not associated with a lessened endorsement of genetic factors as causal, as well; rather, it was paralleled with more frequent endorsement of multiple, additional, putative environmental causes. As the SPARK cohort relies on voluntary research participation in a cohort with strong underpinning of genetic research, our observed proportion of caregivers harboring vaccine beliefs is likely to be an underestimate of the true frequency among the population of caregivers of children with ASD. Data were not available on actual vaccine uptake of the children concerned, thus caution is needed in extrapolating from parental beliefs to actual opting out of the vaccination schedule. However, previous studies have shown that parents of children with ASD are more likely to be vaccine-hesitant [28,36] and parental beliefs in vaccine causation is associated with lower immunization rates of ASD children at later ages [4,48] and lower rates of immunizations in unaffected younger siblings compared to their peers [1,4,12,48]. Taken all together, the results of these studies strongly suggest that parental beliefs in vaccine causation lead to delays or declines in vaccine uptake in both children with ASD and their unaffected siblings.

Interestingly, the proportion of EI believers was higher in caregivers of older children. This might reflect a cohort effect in which parents of children born around 2000 may have been more affected by the vaccine controversy in general, or by earlier concerns arising from the use of thimerosal that have subsided following discontinuation of the preservative in vaccine preparation since 2004. Alternatively, it may reflect an age effect by which the persistence of substantial impairments at older ages may be associated with different patterns of parental beliefs. The cross-sectional and retrospective nature of the data did not permit further investigation of these competing hypotheses.

The sociodemographic factors related to parental beliefs showed that parents from ethnic minority and less-educated backgrounds were more prone to endorse these beliefs, findings that are consistent with previous results [4]. Already, ethnic minority and underserved social groups have well-established decreased access to diagnostic and early intervention services [2,7]. Our findings show that they also are more vulnerable to embracing unproven attributions that may, in turn, result in increased medical risk or morbidity associated with preventable infectious diseases. In multivariate analysis, both ethnicity and lower maternal education increased significantly the odds of erroneous vaccine beliefs beyond the effect of individual clinical characteristics, suggesting that preemptive educational efforts should be specially targeted at caregivers with these social risk characteristics. Moreover, it is worth noting that minority groups have been specifically targeted by anti-vaccine movements [46,8], which makes preventative education within these subgroups even more necessary.

Both early developmental and current clinical characteristics influenced the likelihood of vaccine beliefs. In the early developmental period, both the emergence of specific symptoms and their

timing separately increased odds of belief in vaccine causation. A first parental concern about a change or loss of abilities in the child and report of regression or loss of language/other skills were the two developmental features with the strongest association with vaccine causation beliefs. With respect to timing, parental recognition of first alarming symptoms during the second year of life and a diagnosis before age 3 were predictive of later antivaccine sentiment. In addition, loss of skills occurred earlier in that group and lasted longer. Loss of skills occurs in 20–40% of children with ASD, usually during the second year of life, and is associated in several studies with more severe language, adaptive behavior and cognitive outcomes [10,14,27,33,43]. The origin of the regressive pattern is unknown but has been associated with increased frequency of *de novo* variants in genes encoding for post-synaptic density proteins [16] or in a few specific genes involved in chromatin remodeling or synapse formation and adhesion [41].

Belief in a vaccine-based etiology was also associated with increased overall current severity of the child at SPARK registration. In particular, risk was increased in parents of children with current language limitations, either being non-verbal or having single words or word combinations, as well as those functioning below chronological age in multiple areas. Interestingly, when past and current delays in milestones or functioning were adjusted for, autism symptomatology scores no longer contributed to the prediction of parental beliefs. Thus, it appears that severity as indexed by non specific delays in development, especially in language and communication, rather than autism specific symptoms is the most predictive characteristic.

It is worth noting that the type, and more so the timing, of first autism symptoms identified in our sample make the measles-mumps-rubella (MMR) immunization a more likely target for parental causal attribution, as MMR is usually given during ages 12–18 months, a period that coincides with the emergence of parental concerns in a high proportion of families [5]. In an earlier study, when parents harboring anti-vaccine beliefs were asked to compare different vaccines, MMR came well ahead of other vaccines or vaccine combinations (49% vs <26%) as the culprit for ASD [4].

Taken together, our results suggest that preemptive educational activities should preferentially target families from ethnic minority and less educated backgrounds and whose children exhibit loss of skills in the second year of life. Professionals involved in multidisciplinary specialist teams who diagnose ASD may not always have enough time to educate parents about what ASD is *not* caused by. Additionally, teams led by nonmedical professionals may feel less competent to talk through medical matters and may refer families to later discussions with their community providers, which may or may not occur. Because of the recent resurgence of measles outbreaks, it is important that professionals tackle this information gap. There is a need to develop evidence-based tools for practitioners and families to facilitate this process.

4. Limitations

This cohort comprises participants who volunteered for research, with special emphasis on genetic research, and the representativeness of the SPARK cohort cannot be fully assessed. Data, including those on diagnosis, are reported by parents online and no independent validation is yet available. However, preliminary phenotypic [11] and genetic [9] data provide indirect evidence for diagnostic validity among affected SPARK participants. Data on early developmental trajectories of ASD was retrospectively collected. Beliefs in vaccine causation of ASD were investigated globally and no analysis could be done for beliefs relating to specific childhood vaccines. We did not have vaccination records and could not test if parents who hold beliefs that vaccines can cause ASD

were also less likely to have their child with ASD up-to-date with the vaccination schedule or whether their younger offspring were under-vaccinated.

CRedit authorship contribution statement

Eric Fombonne: Conceptualization, Data curation, Formal analysis, Methodology, Writing original draft, Writing-review & editing. **Robin P. Goin-Kochel:** Formal analysis, Methodology, Writing-review & editing. **Brian J. O'Roak:** Formal analysis, Methodology, Writing-review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. E. Fombonne was a paid expert witness in litigation involving autism and vaccines between 2004 and 2011 for Glaxo Smith & Kline. He was an expert witness for the US Department of Justice in the class action litigation before the Vaccine Compensation Injury Court in Washington DC (2005–2009). Drs B. J. O'Roak and R. P. Goin-Kochel have no conflict of interest to declare.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.12.026>.

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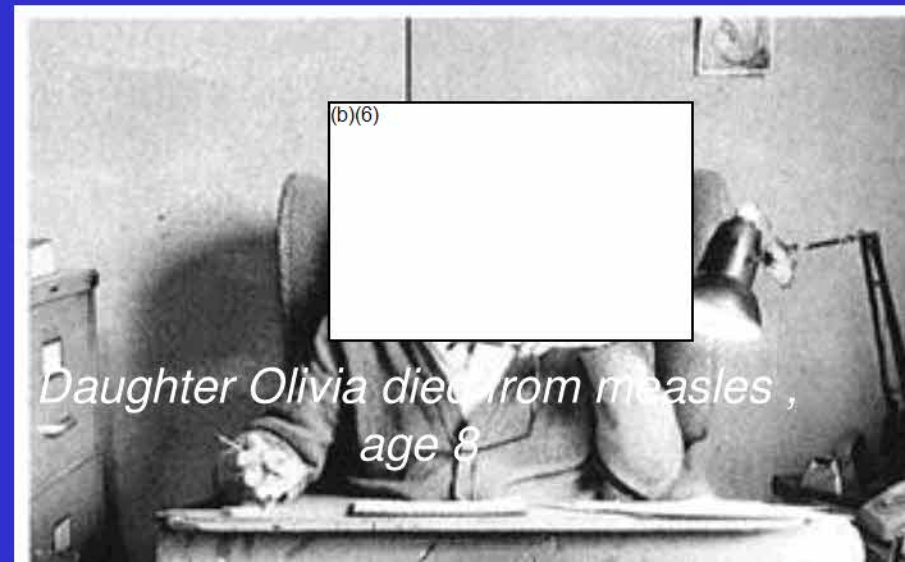
The saga of vaccine-induced autism

The science of vaccine safety

London, May 30 2019

Eric Fombonne
Professor of Psychiatry
OHSU, Department of Psychiatry
Director of Autism Research at IDD

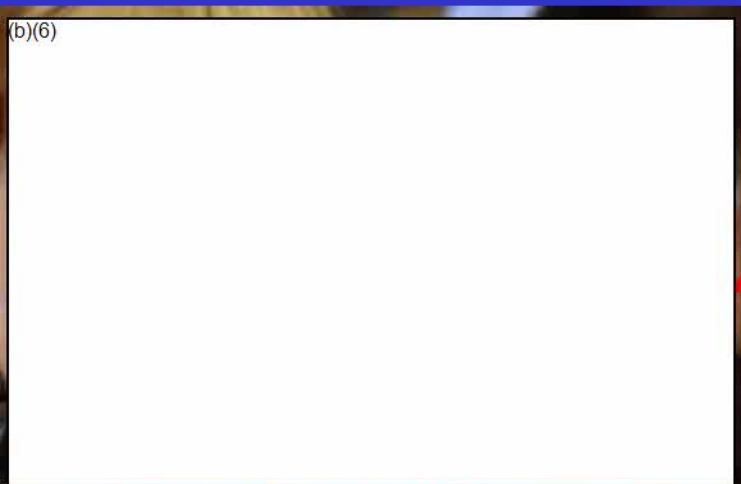
Roald Dahl



Outline

- Studies of ASD risk and vaccine exposure
 - epidemiological studies
 - search for a vulnerable autism subtype
- Autism specific context
 - epidemiology of ASD: rates, trends
 - developmental trajectories
 - etiology: genes, environment, both?
 - persistent beliefs
- Other issues
 - litigation
 - medias
 - publication bias, negative studies

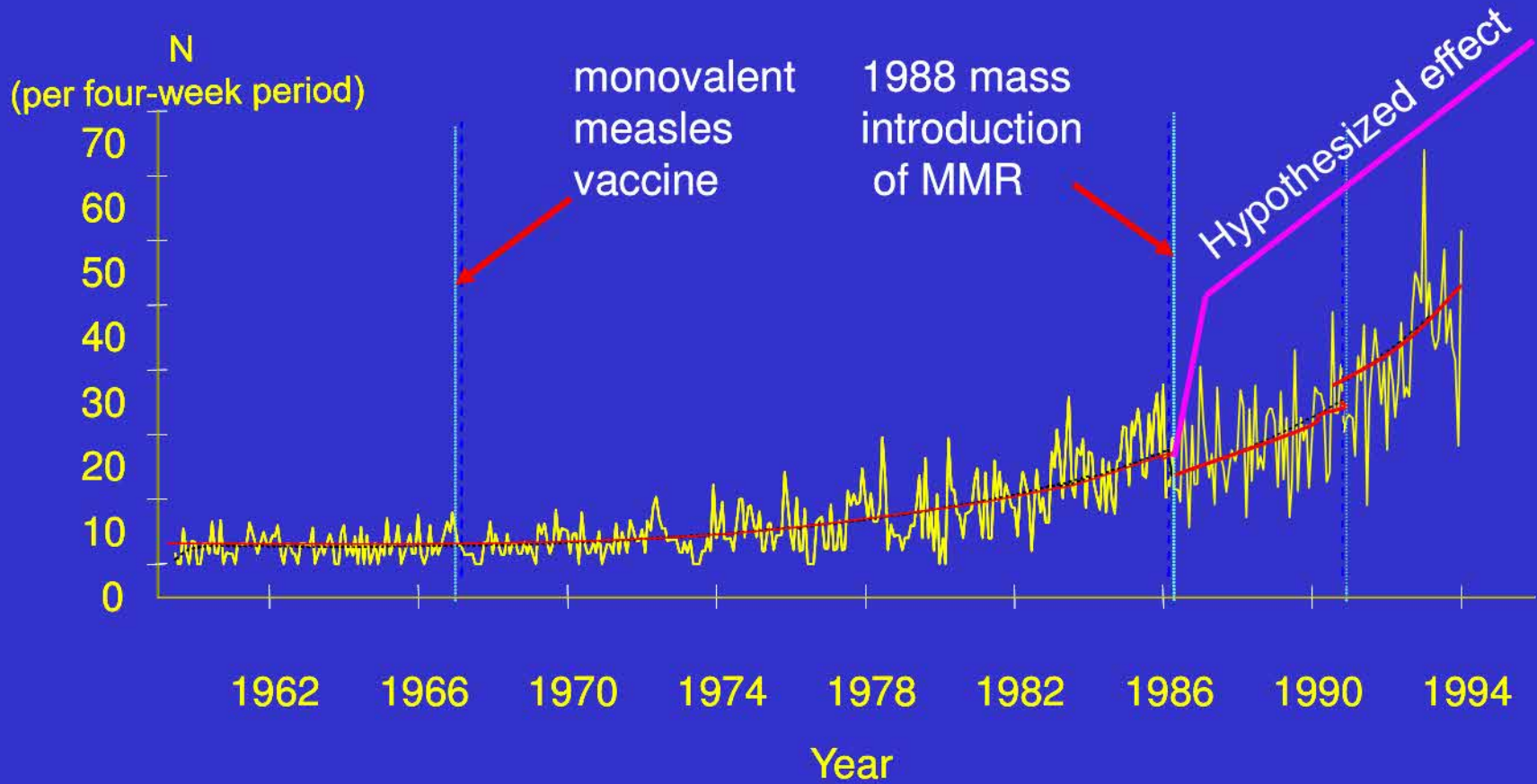
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autism?

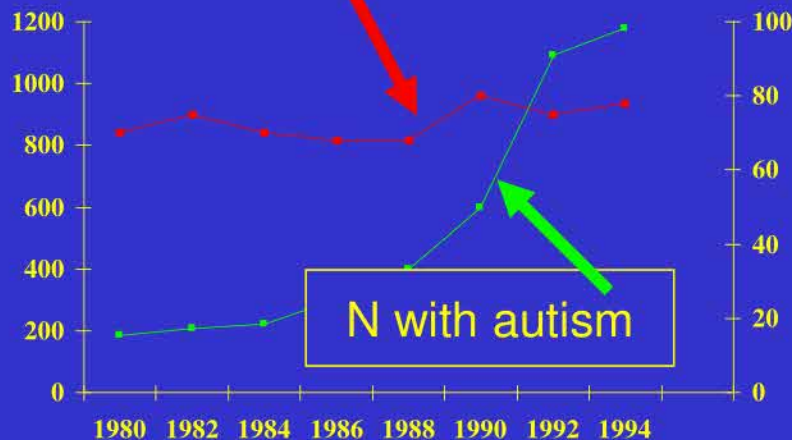
UK epidemiological survey

Autism Disorder count per 100,000 births



MMR: ecological studies

% MMR coverage by 24 months



Japan discontinuation study

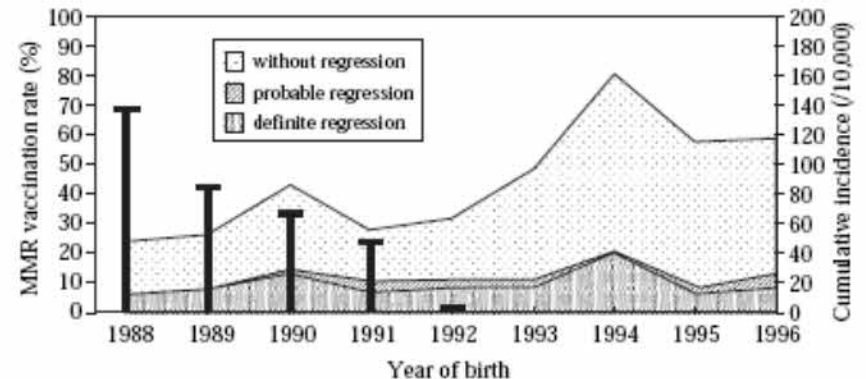


Figure 3 Yokohama City MMR vaccination rates by birth year (1988–1992), and annual trends in cumulative incidences of ASD with and without developmental regression up to seven years in the birth cohort in the catchment area

Dales et al. 2001; see also Fombonne et al., 2006; Chen & Fombonne, 2004; Taylor et al 2002

Case-control studies

MMR vaccination and pervasive developmental disorders: a case-control study

Liam Smeeth, Claire Cook, Eric Fombonne, Lisa Heavey, Laura C Rodrigues, Peter G Smith, Andrew J Hall

Summary

Background Concern that measles-mumps-rubella (MMR) vaccination might cause autism has led to a fall in vaccine coverage. We investigated whether MMR vaccination is associated with an increased risk of autism or other pervasive developmental disorders.

Methods We did a matched case-control study using the UK General Practice Research Database. Cases were people born in 1973 or later who had first recorded diagnosis of pervasive developmental disorder while registered with a contributing general practice between 1987 and 2001. Controls were matched on age, sex, and general practice.

Findings 1294 cases and 4469 controls were included. 1010 cases (78.1%) had MMR vaccination recorded before diagnosis, compared with 3671 controls (82.1%) before the age at which their matched case was diagnosed. After

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	p (for adjusted OR)
MMR vaccination before index date			
Autism only			
No MMR vaccination	(1.0)		
Vaccinated with MMR	0.77 (0.60–0.98)	0.88 (0.67–1.15)	0.35
Other PDDs only			
No MMR vaccination	(1.0)		
Vaccinated with MMR	0.60 (0.39–0.92)	0.75 (0.46–1.23)	0.25

Cohort Studies

Initial Danish register study

		Autism			ASD		
		N	RR _{adj}	95%CI	N	RR _{adj}	95%CI
<u>MMR</u>	<u>Person-Years</u>						
No	482,360	53	1.0		77	1.0	
Yes	1,647,504	263	0.92	.68-1.24	345	0.83	.65-1.07

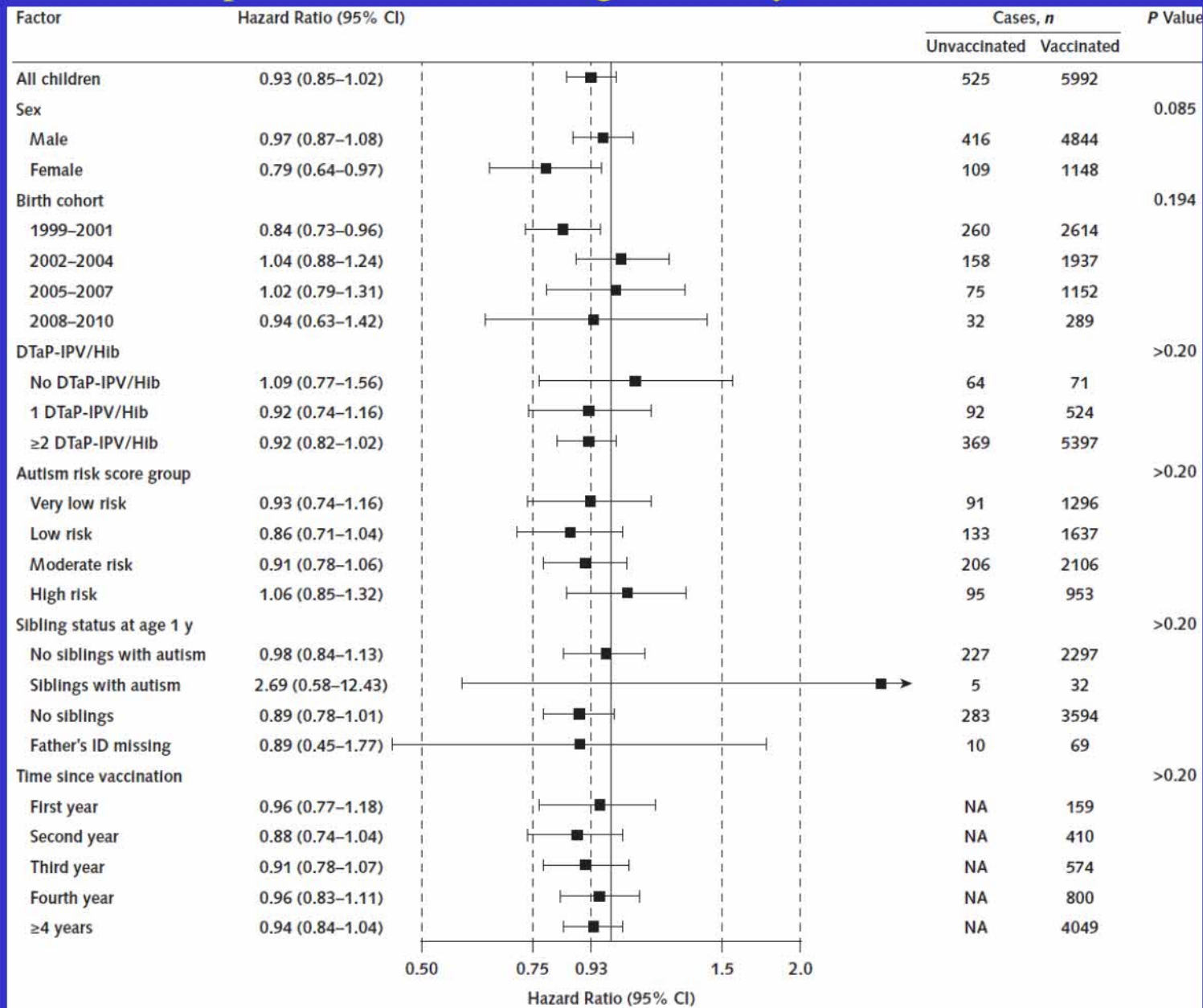
No association between risk of autism and age at vaccination, interval since vaccination and calendar period at the time of vaccination

Incidence rate ratios adjusted for age, calendar period, sex, birth weight, gestational age, mother's education and SES

Cohort Studies:

recent replication of Danish register study

- N=657,461 children, over 5M person-years
- Adjustment of multiple confounders (propensity scores)
- Tested clustering after MMR vaccination, and at risk siblings



MMR does not increase risk of ASD among siblings at risk

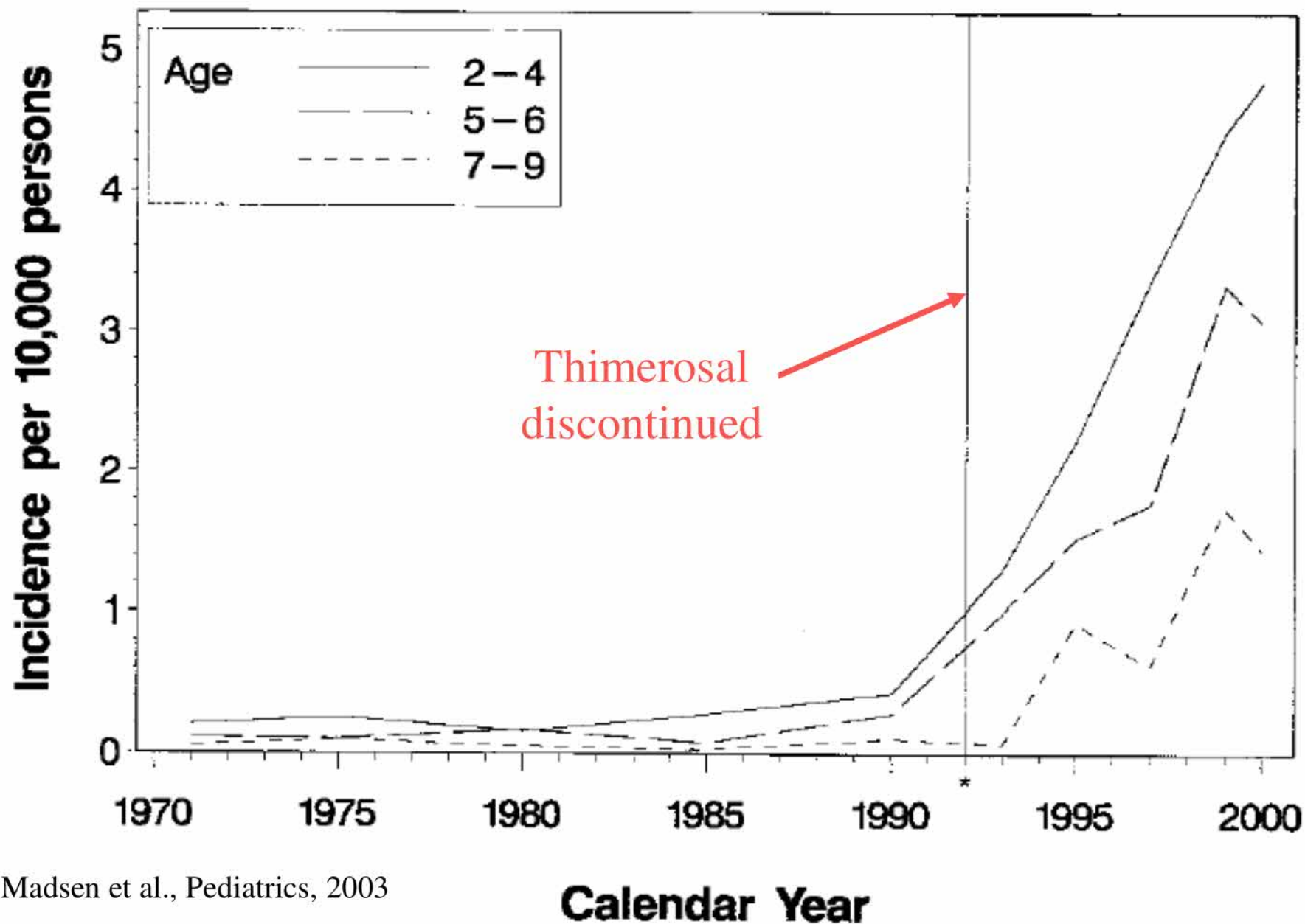
Optum Research Database, N=95,727 children with older siblings

- Prevalence ASD: - 6.9% with older sib with ASD, 0.9% without older sib with ASD
- MMR coverage: - Children without ASD sibs: 84% at age 2, 92% at age 5
- - Children with ASD sibs: 73% at age 2, 86% at age 5

Table 2. Unadjusted and Adjusted Relative Risk Estimates for MMR Vaccination and ASD at Ages 2 to 5 Years in Children With Older Siblings With and Without Diagnosed ASD

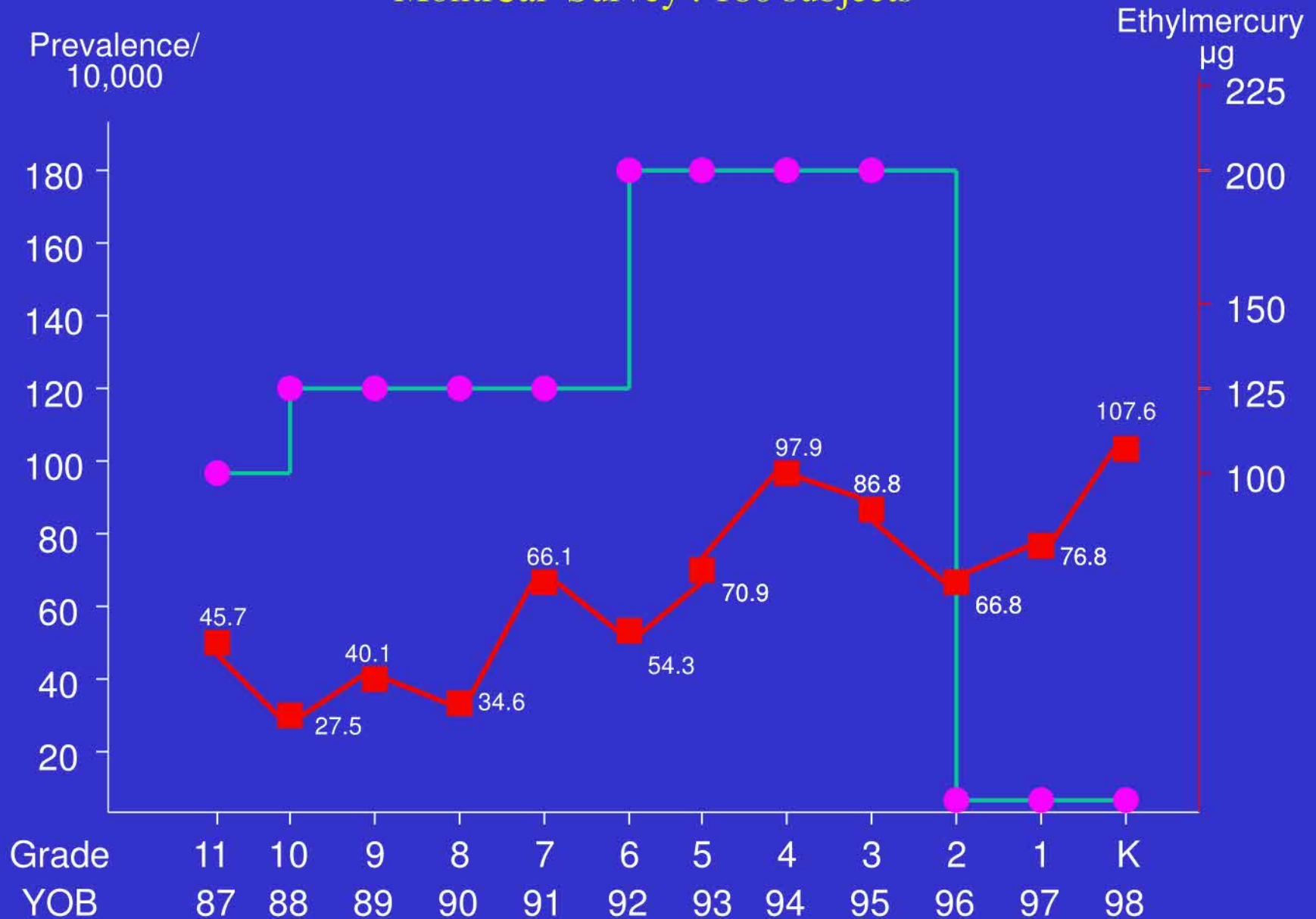
MMR Status	Older Sibling Without ASD (n = 93 798)					Older Sibling With ASD (n = 1929)				
	No. of ASD Cases/Total No. ^a	Unadjusted ^b		Adjusted ^c		No. of ASD Cases/Total No. ^a	Unadjusted ^b		Adjusted ^c	
		RR (95% CI)	P Value ^d	RR (95% CI)	P Value		RR (95% CI)	P Value ^d	RR (95% CI)	P Value
Age 2 y										
1 dose	53/77 822	0.80 (0.44-1.46)	.57	0.91 (0.68-1.20)	.50	7/1394	0.44 (0.15-1.29)	.22	0.76 (0.48-1.22)	.25
Unvaccinated	13/15 249	1 [Reference]		1 [Reference]		6/520	1 [Reference]		1 [Reference]	
Age 5 y										
2 doses	244/45 568	0.74 (0.55-0.99)	.049	1.09 (0.76-1.54)	.65	30/796	0.44 (0.26-0.75)	.003	0.56 (0.30-1.04)	.07
1 dose	339/40 495	1.16 (0.87-1.53)	.35	1.10 (0.79-1.53)	.59	51/864	0.69 (0.43-1.11)	.16	0.92 (0.56-1.50)	.74
Unvaccinated	56/7735	1 [Reference]		1 [Reference]		23/269	1 [Reference]		1 [Reference]	

Thimerosal Ecologic Studies



Birth cohort prevalence rates and EthylHg exposure

Montréal Survey : 180 subjects



Ecological Studies

US discontinuation quasi-experiment

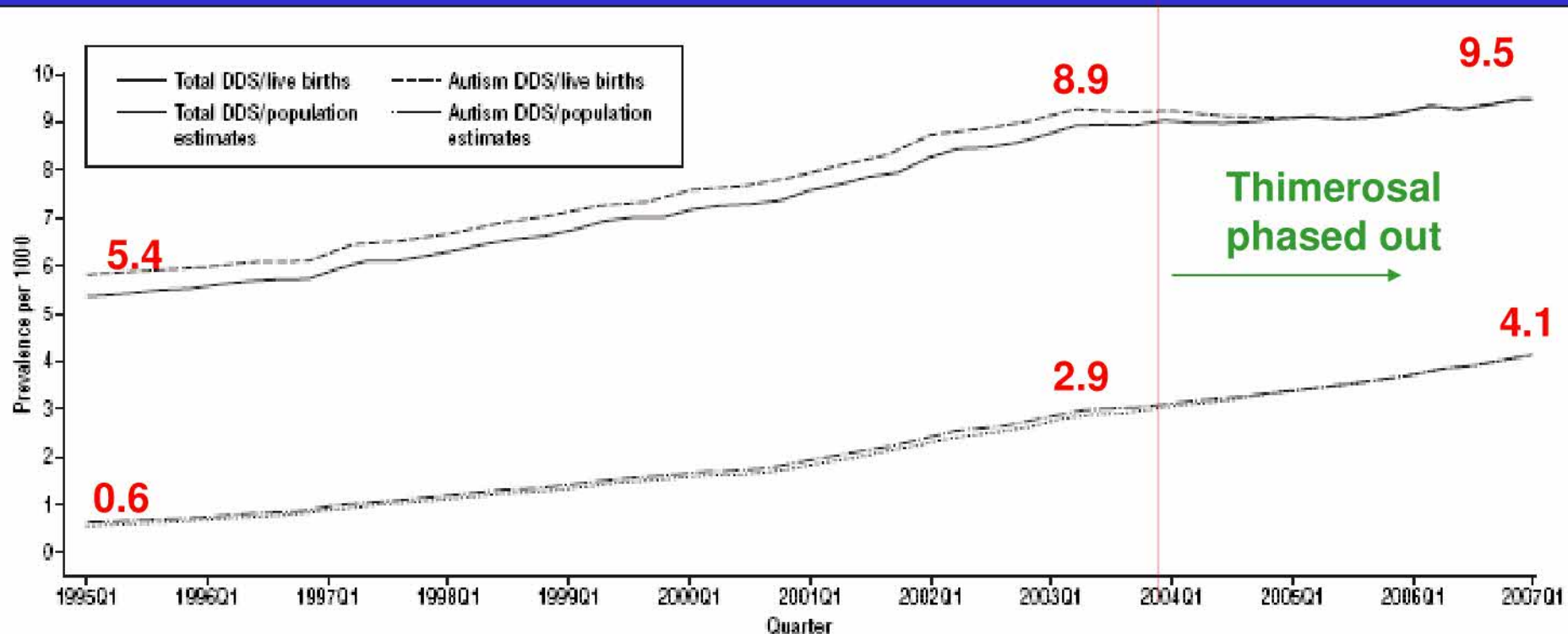


Figure 3. Prevalence of autism and total California Department of Developmental Services (DDS) client enrollment reported by the DDS for children aged 3 to 5 years by reporting quarter (Q), January 1, 1995, through March 31, 2007. Prevalence is estimated by dividing the number of active status children with autism²⁸ by the number of live births in California for each quarterly cohort from 1989 to 2003²⁶ (solid and dotted lines) and the number of children estimated to reside in California for each quarter from 1995 to 2004²⁷ (hashed lines).

Cohort Studies

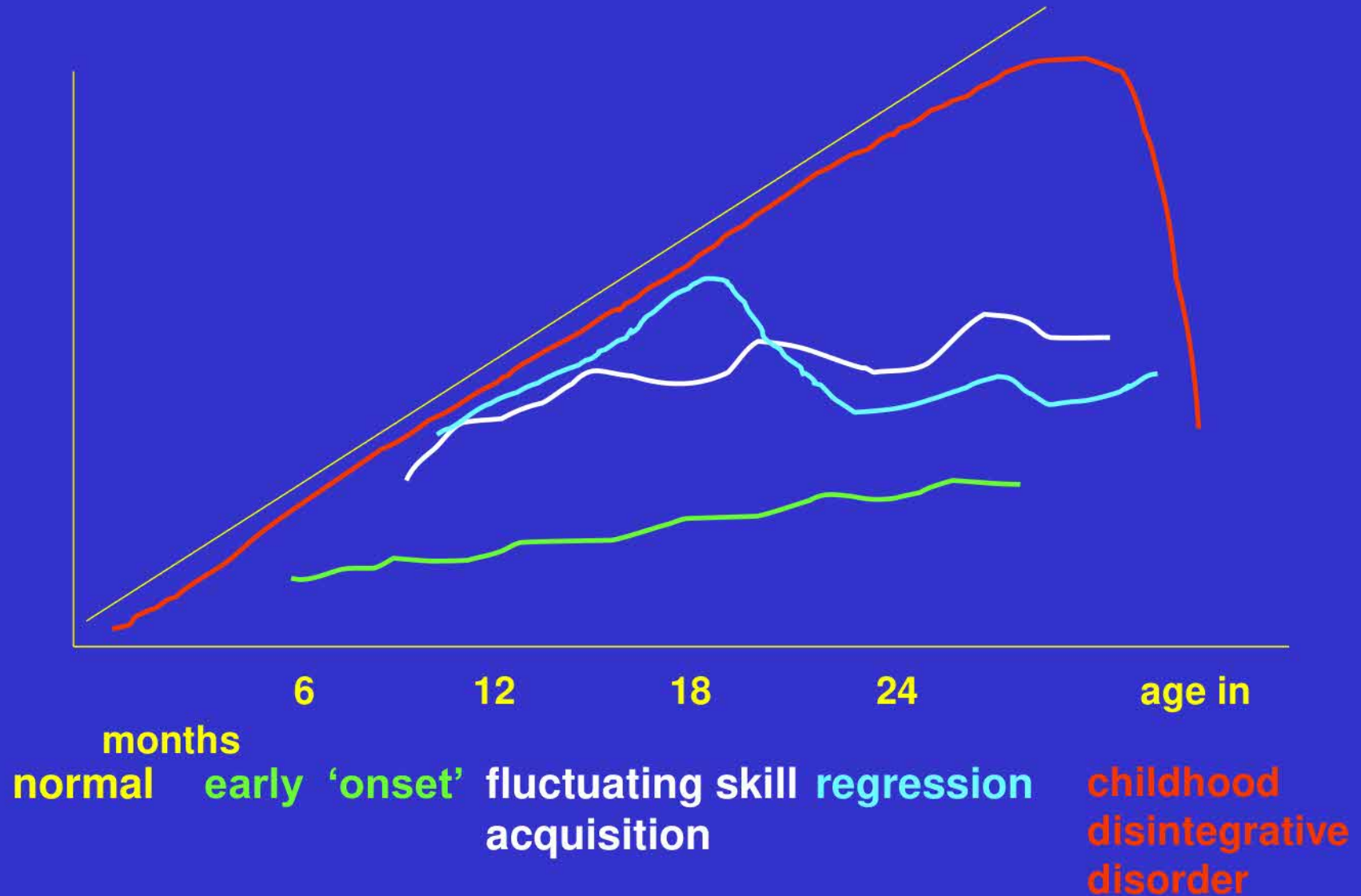
Thimerosal

	Person-Years at Risk	Autism			Other Autistic-Spectrum Disorders		
		No. of Cases	RR (95% CI)*	RR (95% CI)†	No. of Cases	RR (95% CI)*	RR (95% CI)†
Vaccinations							
All thimerosal-free	1 660 159	303	1.00	1.00	430	1.00	1.00
Any containing thimerosal	1 220 006	104	0.85 (0.60-1.20)	0.85 (0.60-1.20)	321	1.12 (0.88-1.43)	1.12 (0.88-1.43)
Doses of thimerosal-containing vaccine							
None	1 660 159	303	1.00	1.00	430	1.00	1.00
1 dose (25 µg eHg)	169 920	18	0.99 (0.59-1.68)	1.01 (0.60-1.71)	40	0.96 (0.67-1.39)	0.95 (0.66-1.37)
2 doses (75 µg eHg)	447 973	33	0.71 (0.46-1.09)	0.70 (0.46-1.09)	130	1.20 (0.92-1.56)	1.20 (0.92-1.56)
3 doses (125 µg eHg)	602 113	53	0.96 (0.63-1.46)	0.96 (0.63-1.47)	151	1.11 (0.83-1.48)	1.13 (0.84-1.51)
Trend (increase in RR per 25 µg eHg)			0.98 (0.90-1.06)	0.98 (0.90-1.06)		1.03 (0.97-1.09)	1.03 (0.98-1.09)

Search for vaccine-induced vulnerable subtype

- All epidemiological studies were negative
- Given this, could it be that the vaccine risk applies only to a (rare) subtype? If yes, what clues do we have to find it*?
 - Is the regressive subtype new? or has it increased in frequency since MMR was introduced?
 - Does autism develop after MMR vaccination?
 - Is autism associated with inflammatory bowel disorders?
 - Does measles virus persist abnormally in some children with autism?
- With respect to thimerosal, does mercury toxicity resemble autism?
- *: ASD caused by TS or FraX or other syndromes has distinctive phenotypic features

Developmental trajectories in ASD



‘Regressive autism’: not a new phenomenon

- **Case 3 : Richard, 2 yrs 10 months**

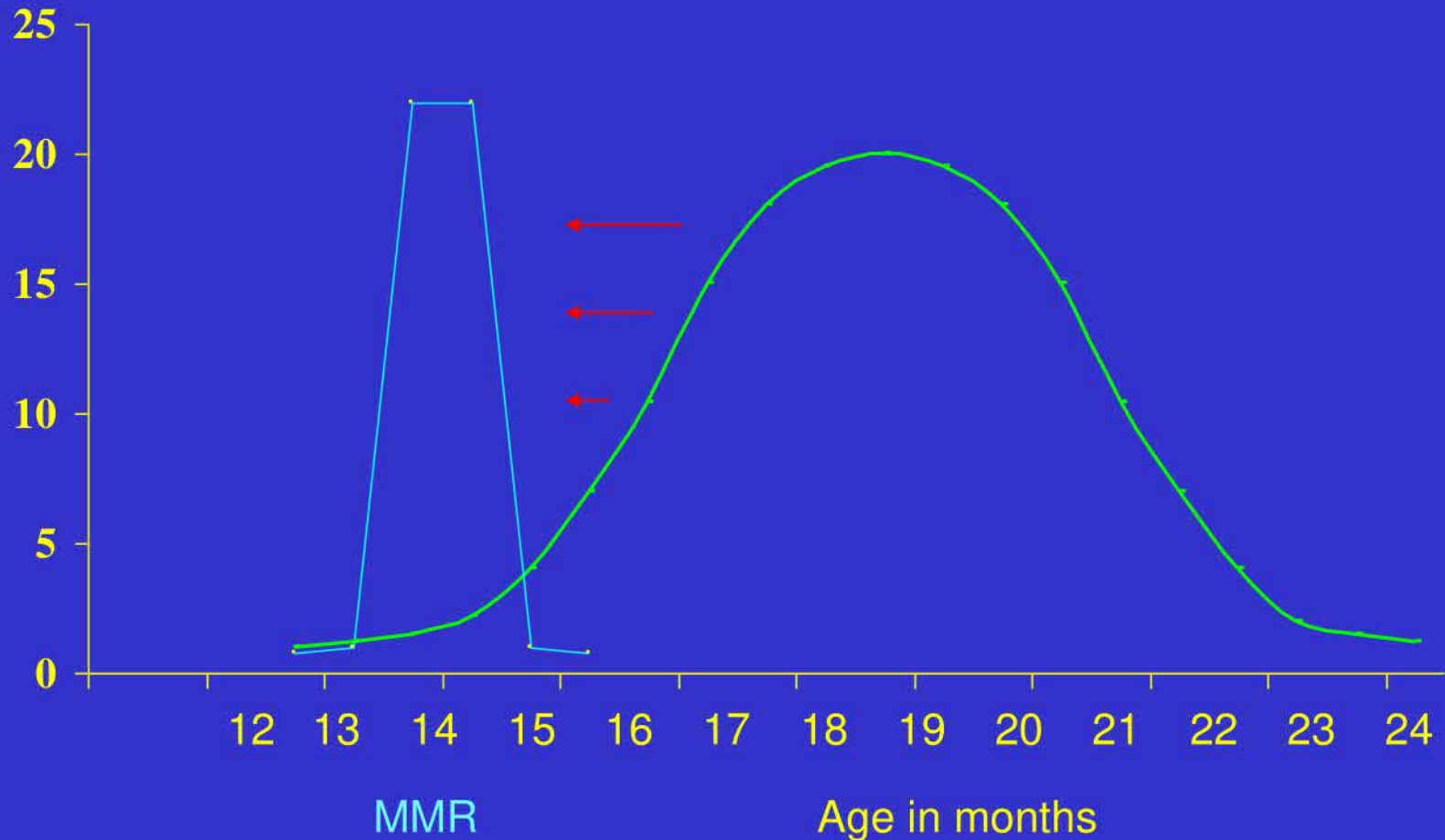
Following smallpox vaccination at 12 months, he had an attack of diarrhoea and fever, from which he recovered in somewhat less than a week. ...

“I can’t be sure just when he stopped the imitation of word sounds. It seems that he has gone backward mentally gradually for the last two years...

Now that he is making so many sounds, it is disconcerting because it is now evident that he can’t talk. Before, I thought he could if he only would. *He gave the impression of silent wisdom to me ...* (Mother’s notes) *Kanner, 1943*

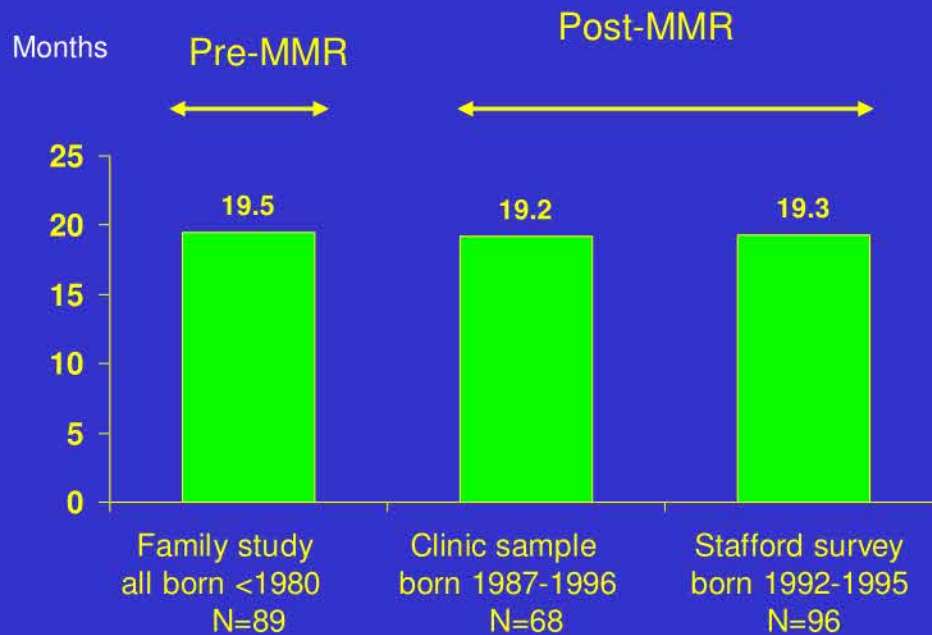
- Lotter 1966 (first epidemiological survey of autism)
31.3% with developmental “setback” that included speech loss
- Creak, 1963 (N=100 - clinical sample)
25% with a setback

Parental recognition of first autism symptoms

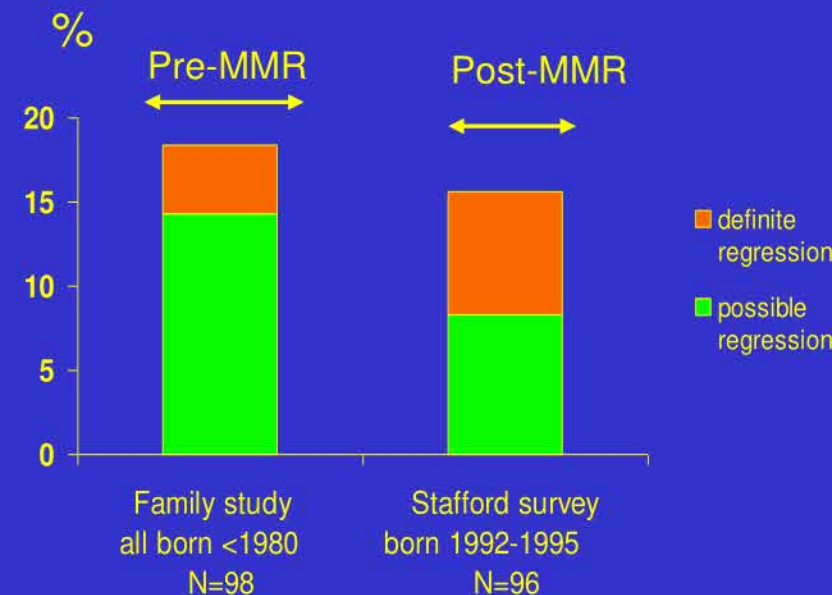


Parental 1st symptom recognition & Regression, pre- and post-MMR

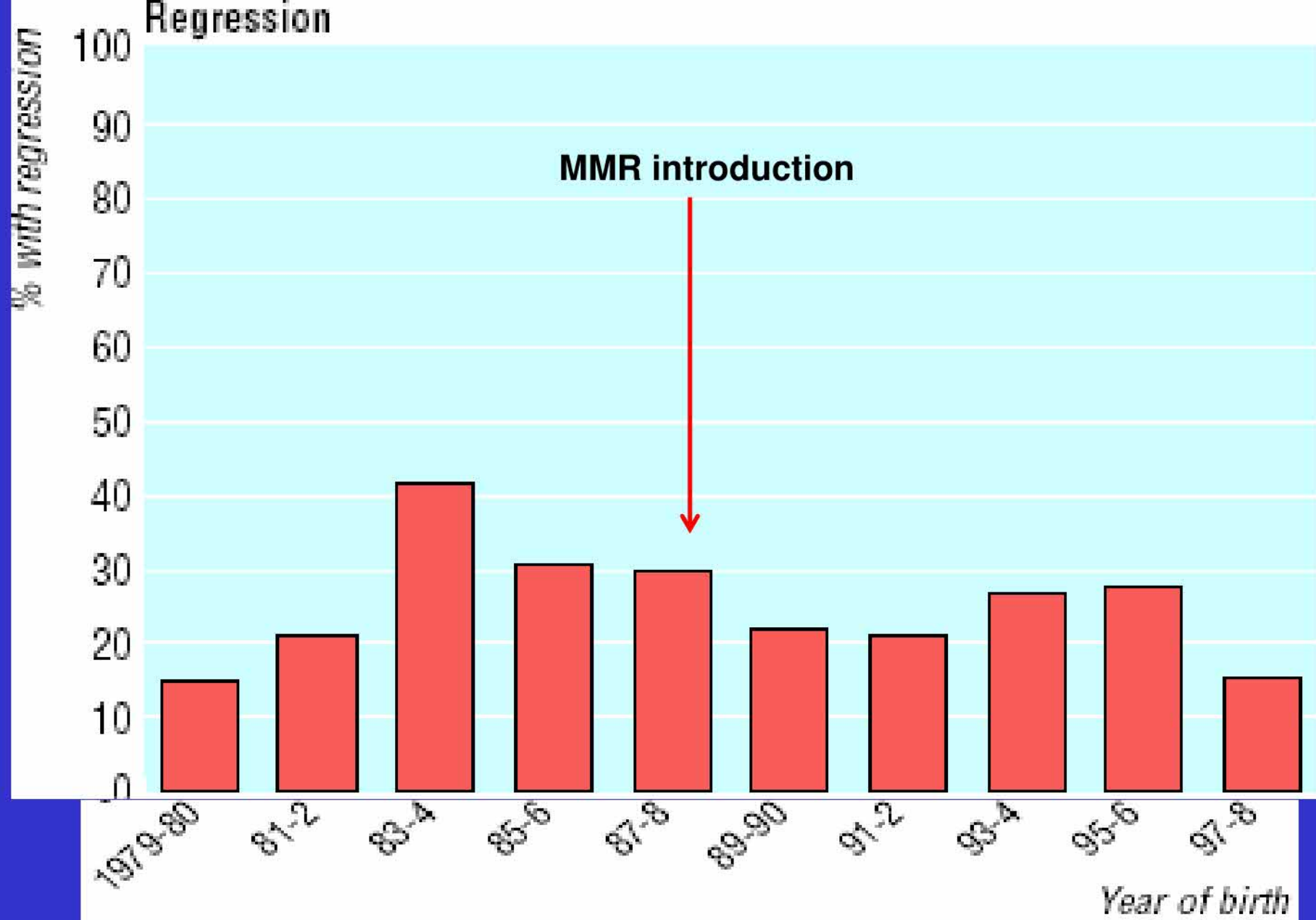
ADI-R data



$F_{2,250} = 0.02, NS$



Fisher exact test: $p = .70, NS$

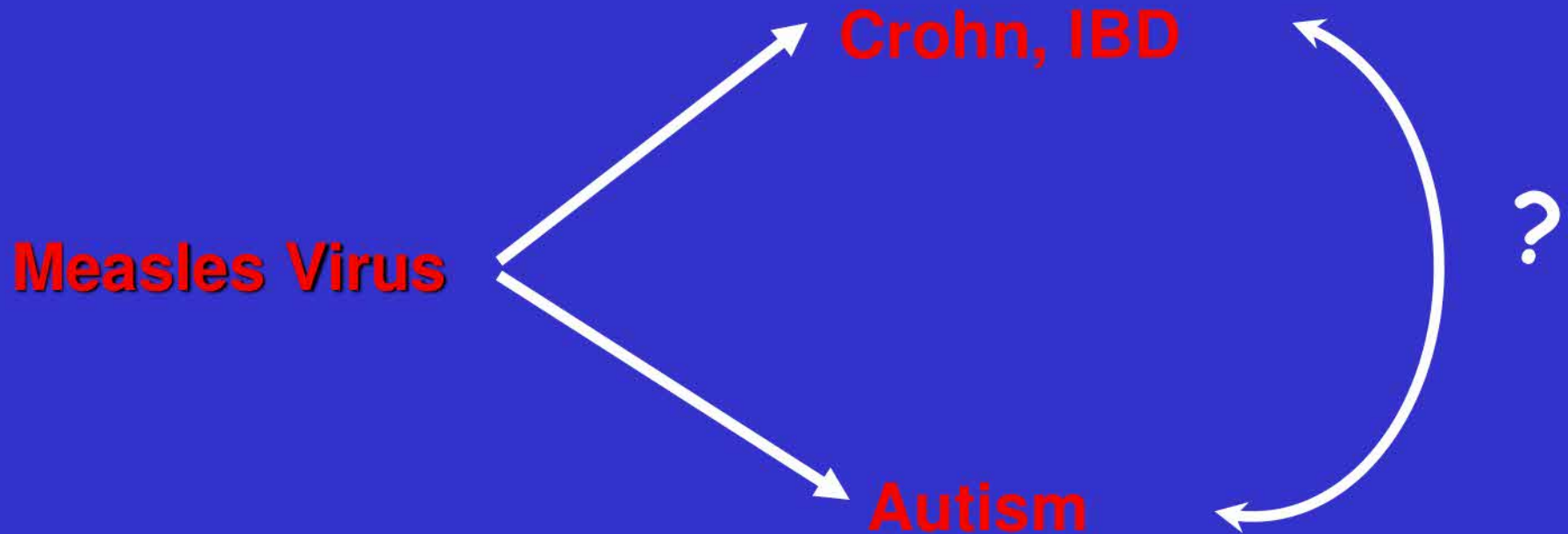


Do children who become autistic consult more often after MMR vaccination?

Table 1. Consultation patterns of study cases and control group.

	Cases (n = 71)			Control (n = 284)			Paired difference (case-control)		
	Total consultations	Mean	Standard error	Total consultations	Mean	Standard error	Mean	95% CI	Wilcoxon rank sum test
Consultations within 2 months of MMR									
60 days before	81	1.14	0.17	335	1.18	0.09			
60 days after	78	1.04	0.19	321	1.13	0.08			
Difference	-7	-0.10	0.21	-14	-0.05	0.10	-0.05	-0.54-0.44	P = 0.45
Consultations within 6 months of MMR									
180 days before	295	4.16	0.44	1146	4.04	0.23			
180 days after	246	3.47	0.45	939	3.31	0.18			
Difference	-49	-0.69	0.34	-207	-0.73	0.20	0.04	-0.75-0.83	P = 0.59
Consultations in months prior to autism diagnosis									
60 days before	127	1.79	0.30	225	0.79	0.07	1.00	0.38-1.61	P = 0.007
180 days before	317	4.47	0.55	727	2.56	0.17	1.90	0.81-2.99	P = 0.009

Are inflammatory bowel disorders associated with autism?



Inflammatory bowel disease and autism

Eric Fombonne

A recent report has raised concerns about measles, mumps, and rubella (MMR) vaccine, inflammatory bowel disease (IBD), and autism in children.¹ No association between Crohn's disease and autism has been reported previously. We looked for such an association in two large datasets.

The Child and Adolescent Psychiatric Services of the Maudsley Hospital, a teaching hospital in south London, UK, provides services for a local catchment area, and receives referrals from the Greater London area and other regions in

children. These results are also consistent with a recent review of epidemiological surveys of autism where IBD did not appear in the list of medical conditions reported in 11 samples, including 836 people with autism.⁵ Finally, it is noteworthy that, in the UK sample, the incidence of IBD remained nil amongst 201 autistic children likely to have been exposed to the MMR vaccine, suggesting no particular association between Crohn's disease and autism among children immunised with MMR.

	Autism / PDD		Controls		p of IBD	95%
	IBD +	IBD -	IBD +	IBD -	(/100,000)	CI
• Maudsley Series	0	762	2	8125	22.5	3.9-90.7
• French survey	0	174	2	5924	32.8	5.7-132.2

Lancet 1998

No Evidence of Persisting Measles Virus in Peripheral Blood Mononuclear Cells From Children With Autism Spectrum Disorder

Yasmin D'Souza, MSc^a, Eric Fombonne, MD^b, Brian J. Ward, MDCM^a

^aDivision of Infectious Diseases, McGill University Health Center, Montreal, Quebec, Canada; ^bDepartment of Psychiatry, McGill University, Montreal Children's Hospital, Montreal, Quebec, Canada

- 54 children (48 males, mean age: 4.0 years) with ASD (ADI-R, ADOS-G, expert clinician)
- 34 pediatric controls (26 boys, mean age: 4.0 years), screened negative for ASD
- All children normally vaccinated with MMR
- All manipulations blinded to study group
- Uhlmann and Takishawa primers lead to false positives
- In-house probes for the F gene of MV show no persistence of MV in PDD children and controls
- No difference across groups in measles antibodies levels

Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study

Mady Hornig^{1*}, Thomas Brieese¹, Timothy Buie², Margaret L. Bauman³, Gregory Lauwers⁴, Ulrike Siemetzki¹, Kimberly Hummel⁵, Paul A. Rota⁵, William J. Bellini⁵, John J. O'Leary⁶, Orla Sheils⁶, Errol Alden⁷, Larry Pickering⁸, W. Ian Lipkin^{1*}

Background: The presence of measles virus (MV) RNA in bowel tissue from children with autism spectrum disorders (ASD) and gastrointestinal (GI) disturbances was reported in 1998. Subsequent investigations found no associations between MV exposure and ASD but did not test for the presence of MV RNA in bowel or focus on children with ASD and GI disturbances. Failure to replicate the original study design may contribute to continued public concern with respect to the safety of the measles, mumps, and rubella (MMR) vaccine.

Methodology/Principal Findings: The objective of this case-control study was to determine whether children with GI disturbances and autism are more likely than children with GI disturbances alone to have MV RNA and/or inflammation in bowel tissues and if autism and/or GI episode onset relate temporally to receipt of MMR. The sample was an age-matched group of US children undergoing clinically-indicated ileocolonoscopy. Ileal and cecal tissues from 25 children with autism and GI disturbances and 13 children with GI disturbances alone (controls) were evaluated by real-time reverse transcription (RT)-PCR for presence of MV RNA in three laboratories blinded to diagnosis, including one wherein the original findings suggesting a link between MV and ASD were reported. The temporal order of onset of GI episodes and autism relative to timing of MMR administration was examined. We found no differences between case and control groups in the presence of MV RNA in ileum and cecum. Results were consistent across the three laboratory sites. GI symptom and autism onset were unrelated to MMR timing. Eighty-eight percent of ASD cases had behavioral regression.

Conclusions/Significance: This study provides strong evidence against association of autism with persistent MV RNA in the GI tract or MMR exposure. Autism with GI disturbances is associated with elevated rates of regression in language or other skills and may represent an endophenotype distinct from other ASD.

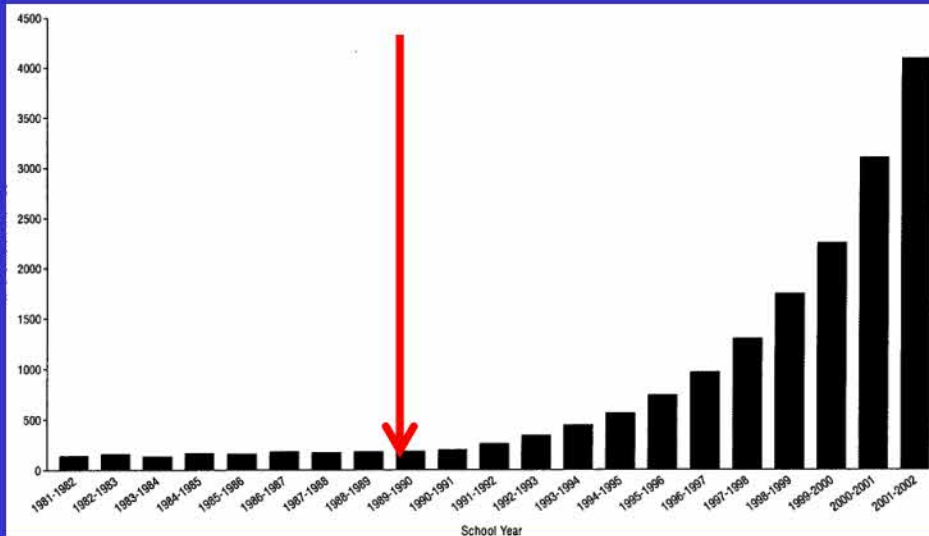
Autism and mercury poisoning

	<u>Autism</u>	<u>Mercurism</u>
Motor	Stereotypies	Ataxia, dysarthria
Vision	----	Constricted visual fields
Speech	Delay, echolalia	Dysarthria
Sensory	Hyperresponsiveness	Peripheral neuropathy
Psychiatric	Aloof, ritualistic	Toxic psychosis, non specific mild ss
Head size	Macrocephaly	Microcephaly
Medical	Epilepsy	Skin eruption, hypertension, thrombocytopenia

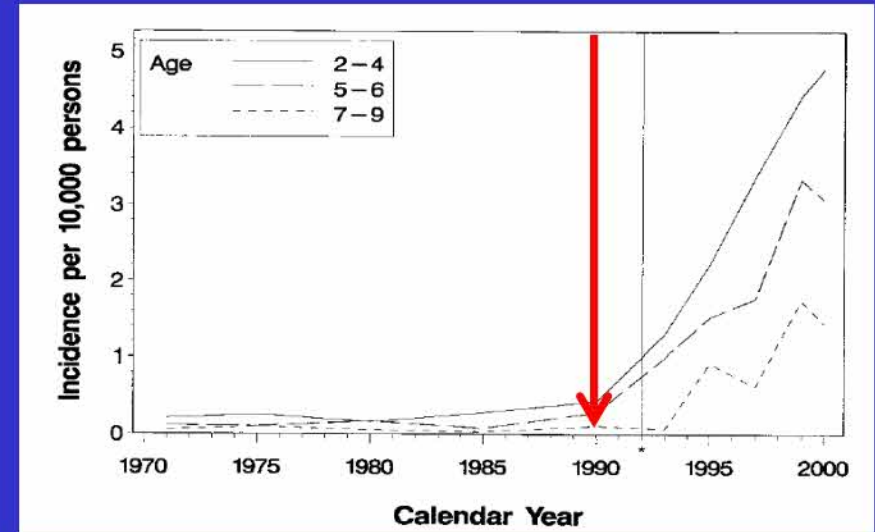
Outline

- *Studies of ASD risk and vaccine exposure*
 - *epidemiological studies*
 - *search for a vulnerable autism subtype*
- **Autism specific context**
 - epidemiology of ASD: rates, trends
 - developmental trajectories
 - etiology: genes, environment, both?
 - persistent beliefs
- *Other issues*
 - *litigation*
 - *medias*
 - *publication bias, negative studies*

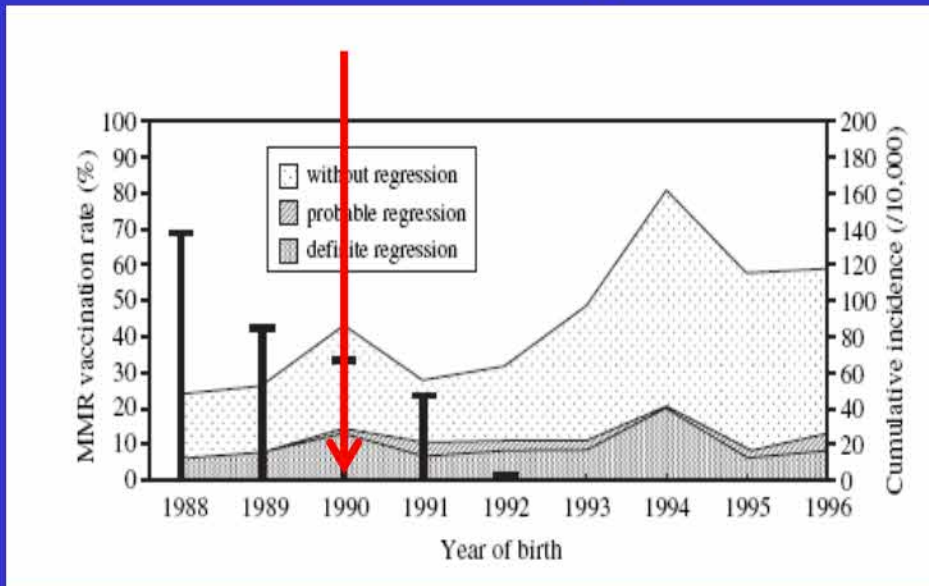
The 1990's



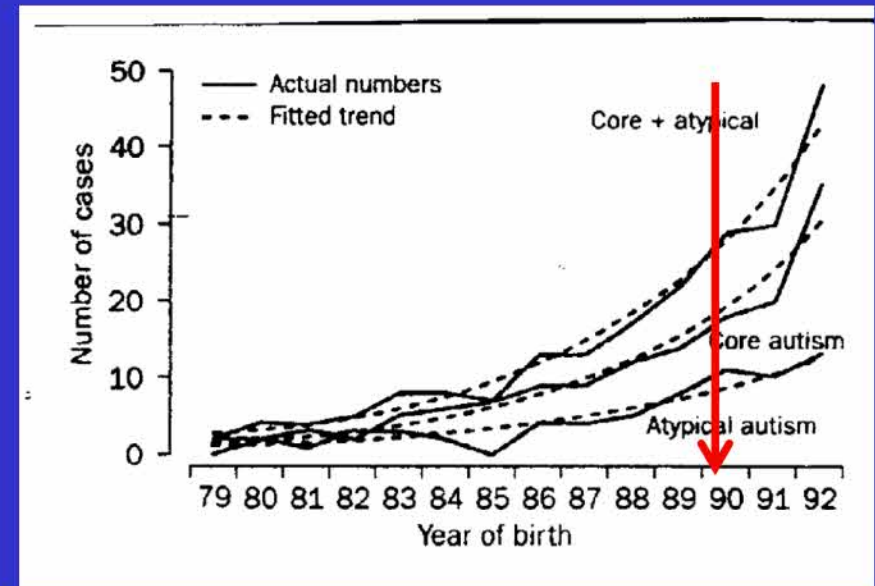
Minnesota, USA – Gurney et al., 2003



Denmark – Madsen et al., 2003

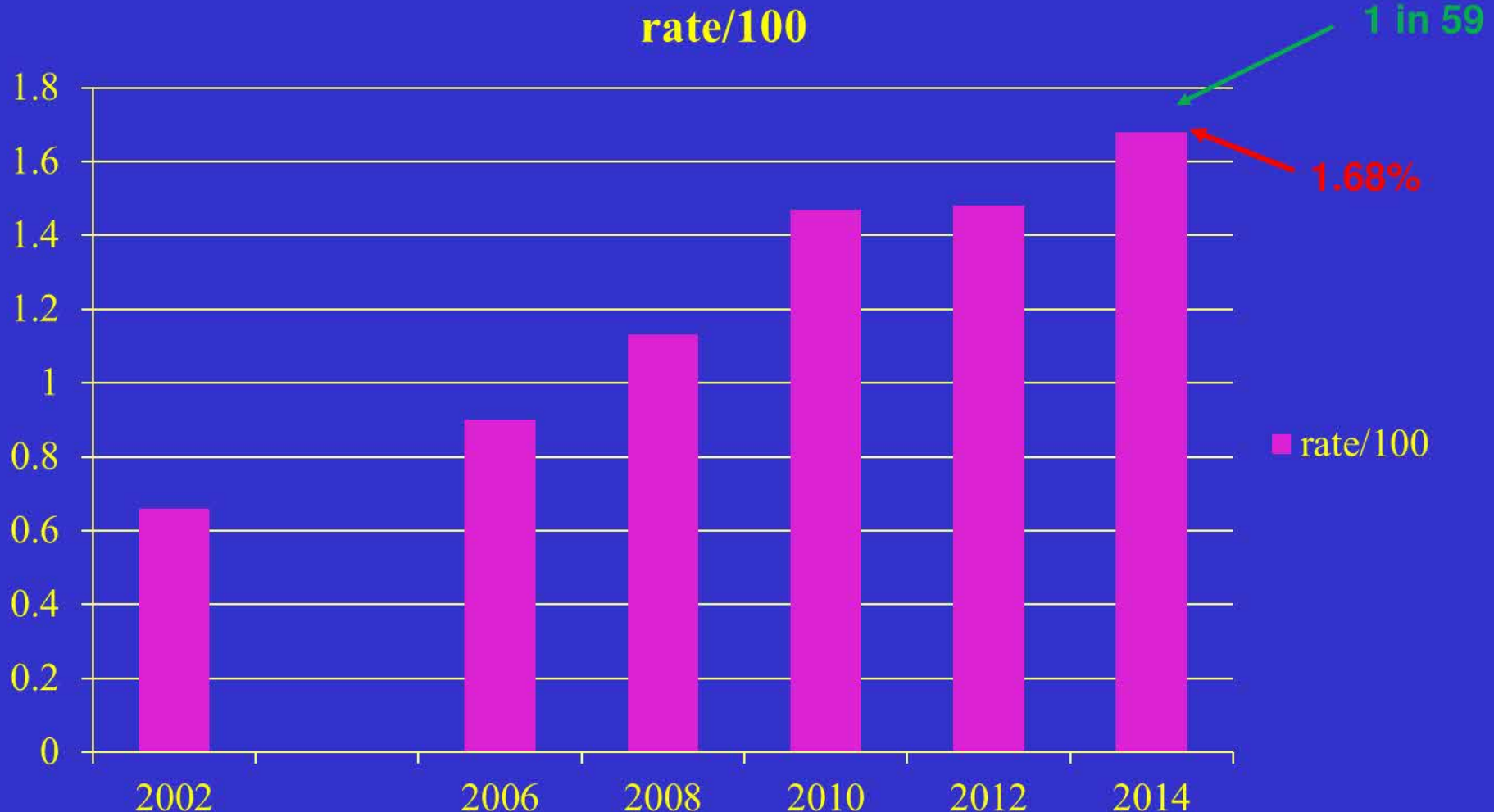


Japan – Honda et al, 2005



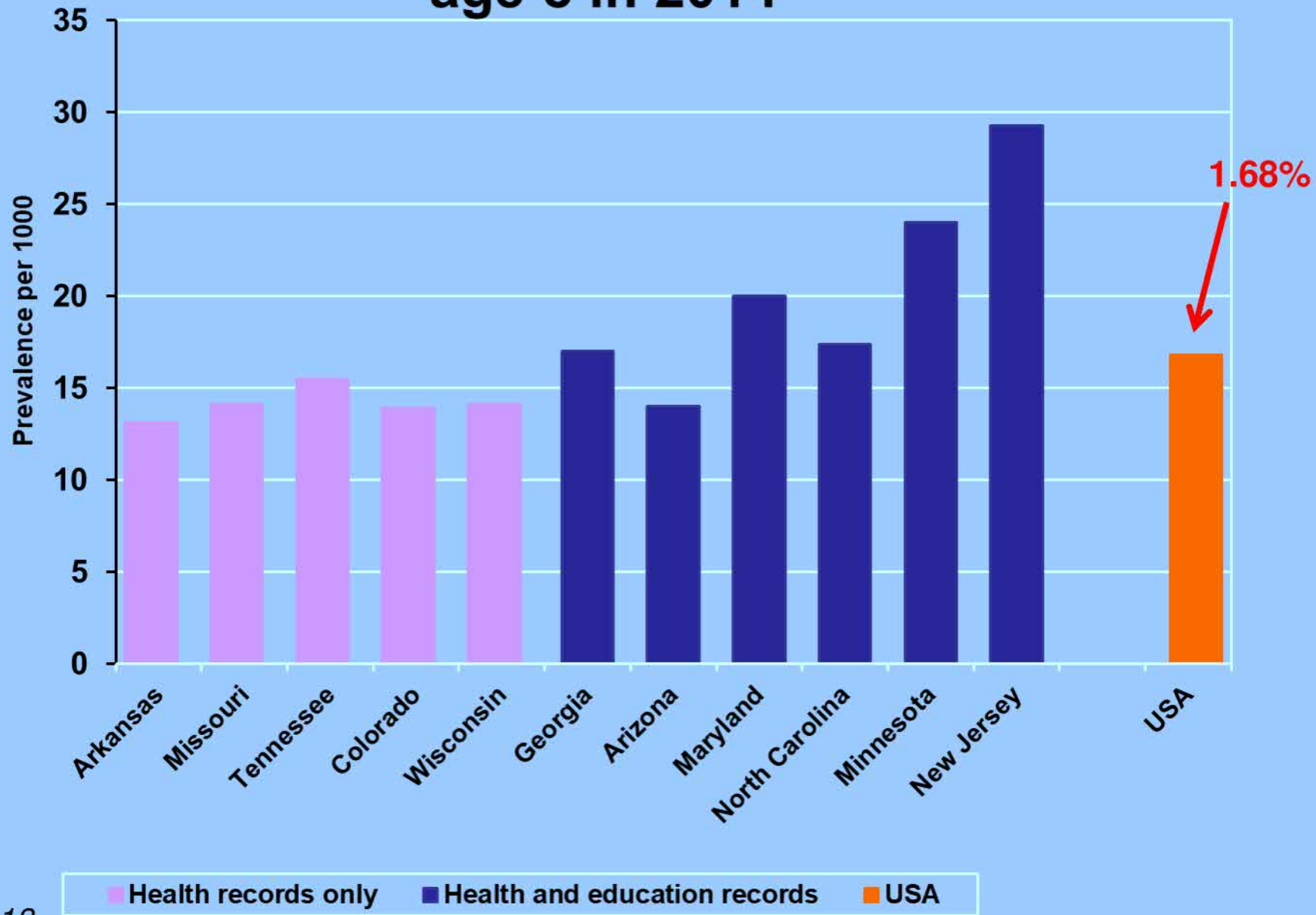
United Kingdom – Taylor et al, 1999

CDC surveys: birth cohorts 1994 to 2006

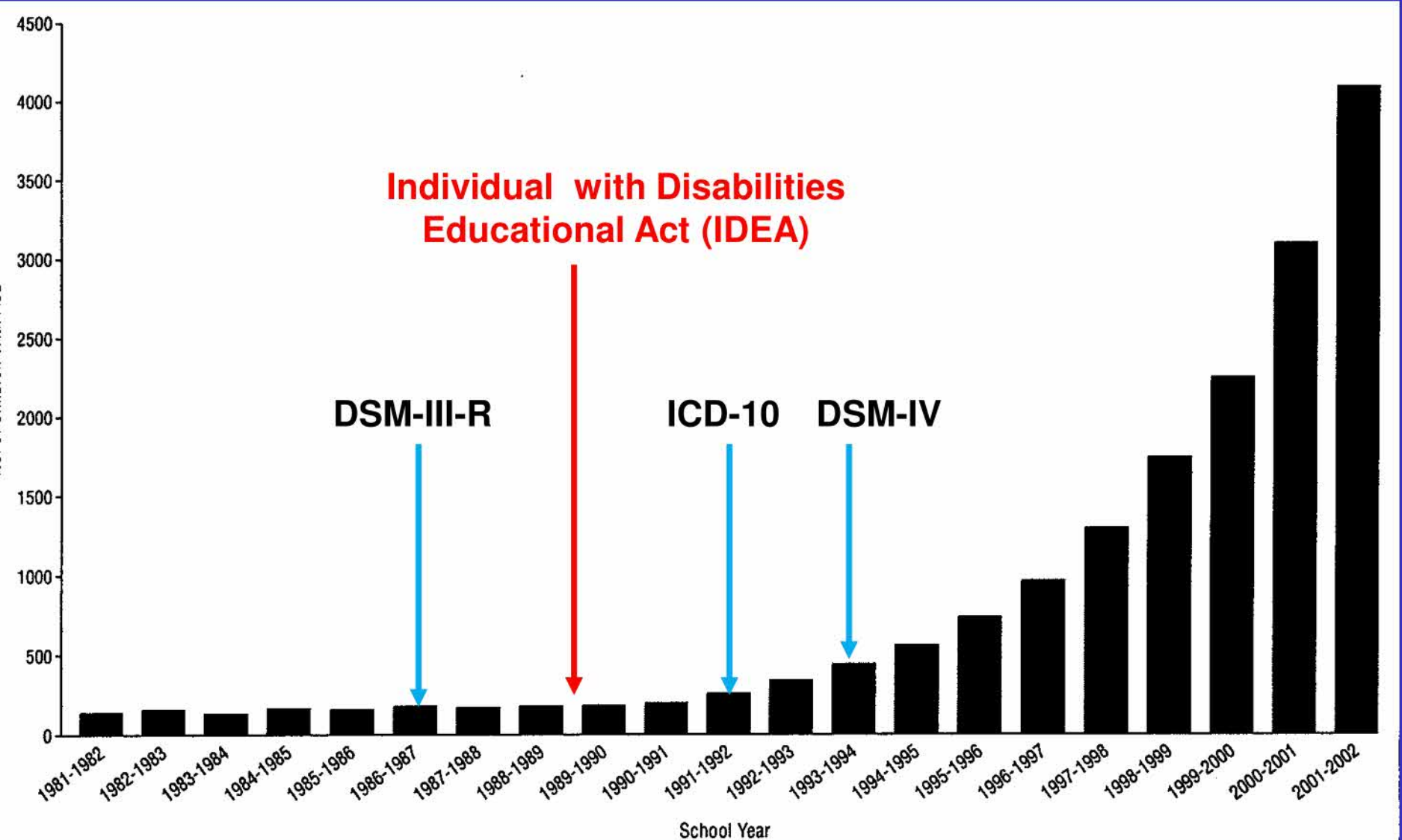


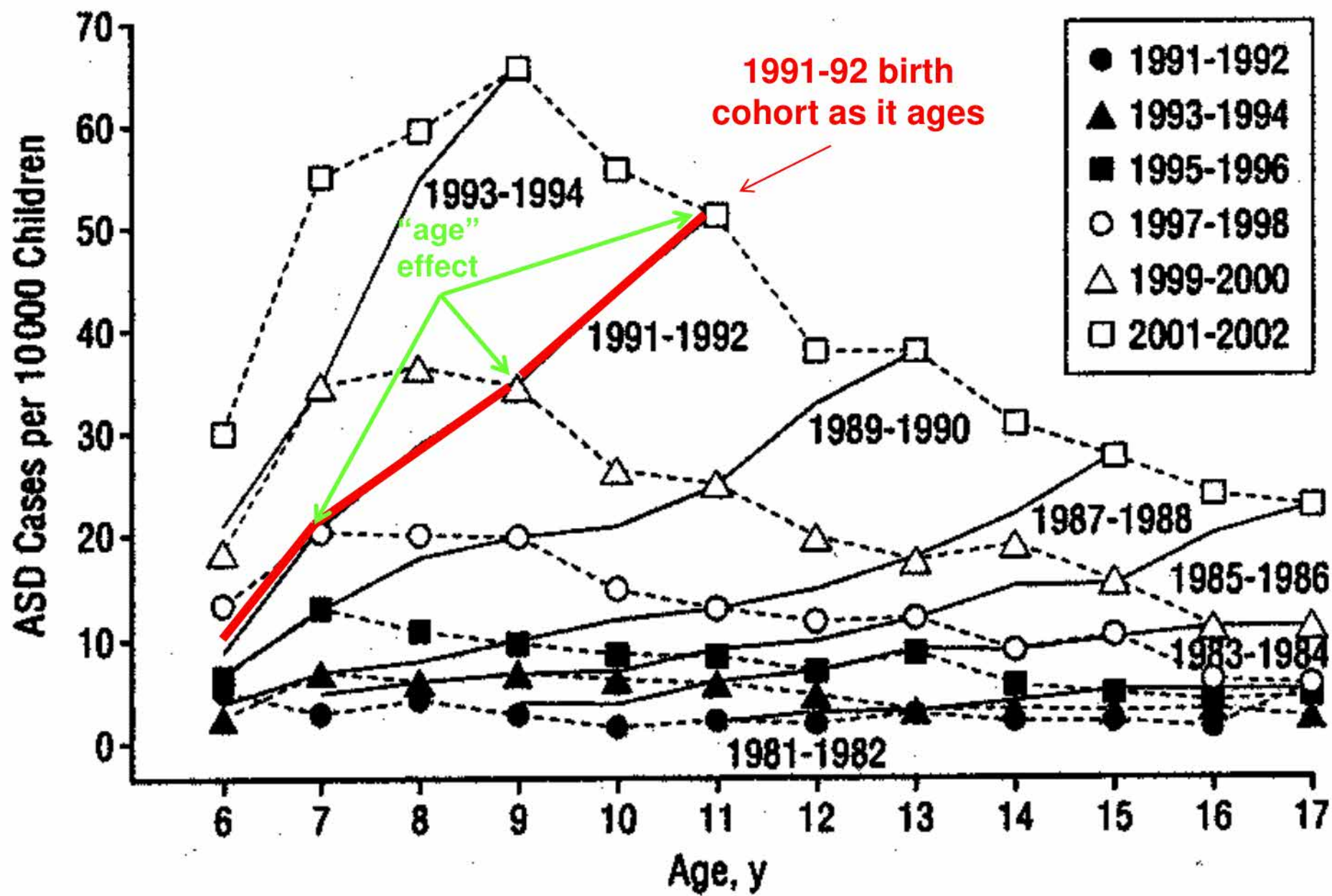
Note: most of the increase occurred in the high-functioning subjects

Prevalence of ASDs, 11 sites, USA - children age 8 in 2014

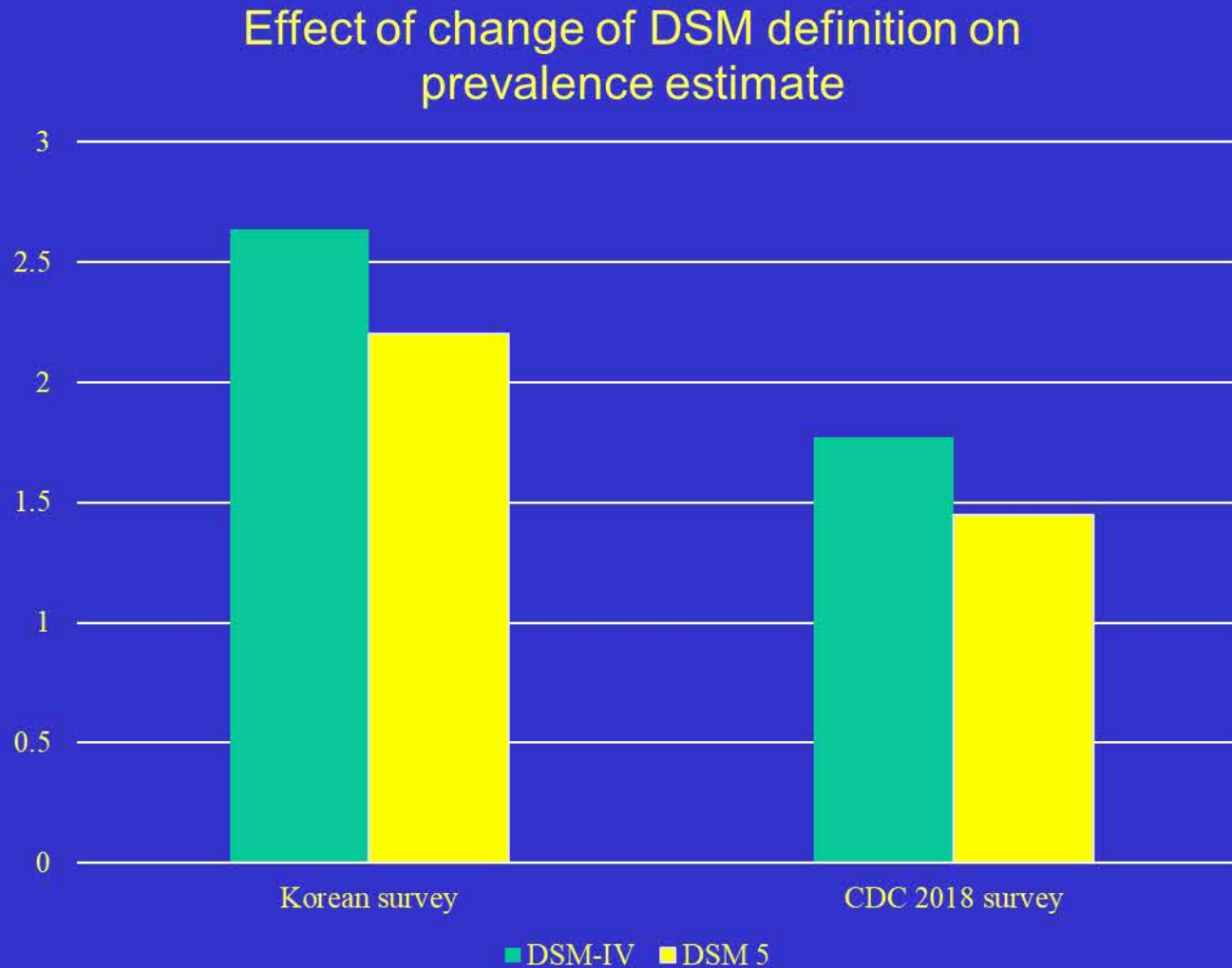


Service use data: Special Ed 'PDD' (Minnesota)





Same survey data, different diagnostic algorithms



Sources: Kim et al., 2013; Fombonne, 2018

“Onset”, recognition & diagnosis of ASD

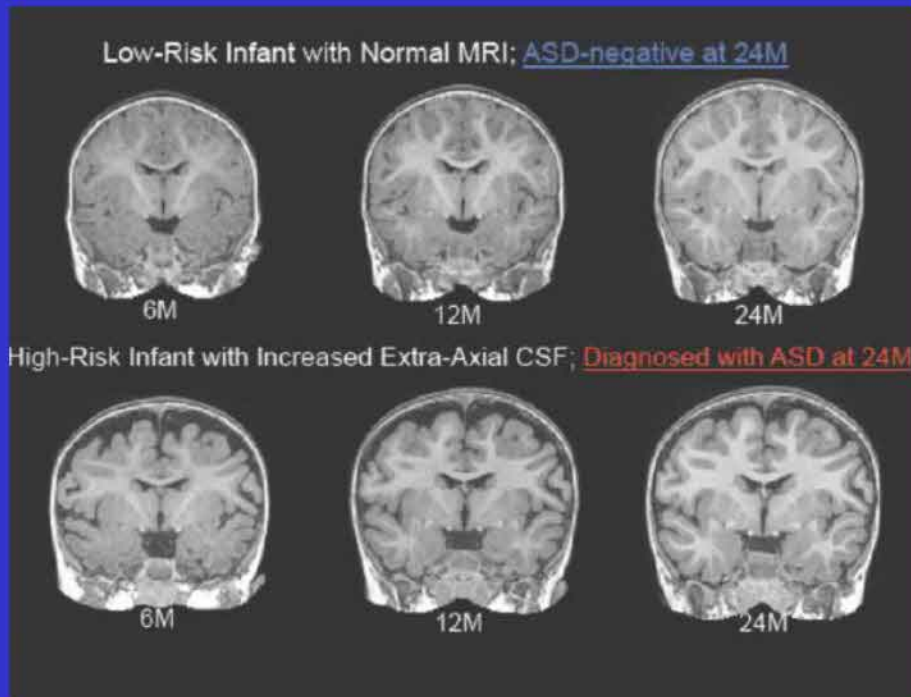
- Average age at diagnosis: \approx 4 years (US)
- Average age at parental recognition of first symptoms: 18 months. Recognition is earlier when child is also delayed and/or parents have had children already (DeGiacomo & Fombonne, 1998).
- Symptoms do not occur over night, they cannot be dated; rather, it is the cumulative observation of mild deviations from normalcy that progressively result on parental state of alert.
- With hindsight, parents recognize first abnormalities in first 12 months in about 50% of cases.
- About 20%-25% of children show loss of skills, a regressive pattern, usually between 15 to 24 months. Although they may be described as ‘normal’ before the regression, up to 70% of children who regress had prior developmental delays/abnormalities (CPEA, 2006).
- Regression is a marker of more severe outcome.

Early markers (12-24 months) of ASD: Reduced levels of social attention and social communication

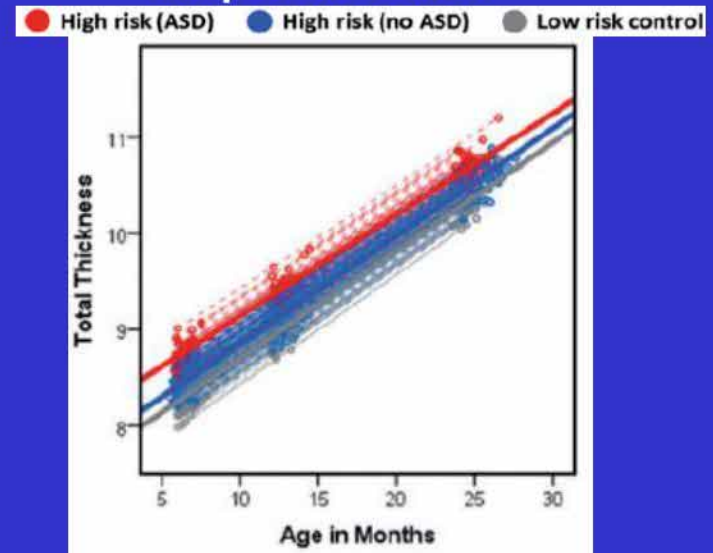
- Reduced orienting to name
 - Frequent 1st parental concern
 - Specific to ASD (differentiation with other DDs)
- Reduced visual attention to social stimuli
 - Eye-tracking: reduced attention to social scenes, preference for geometric shapes
- Reduced Joint Attention (JA) behaviors
 - Pointing, showing, coordinating looks, head turns, gaze shifts
 - Integration of utterances + gestures + eye gaze
 - Initiation and Response to JA are impaired
 - Lower frequency of gestures
- Repetitive behavior with objects
 - Spinning, lining up, rotating, visual fixation
- Atypical body movement and motor development (*less robust*)
 - Atypical posturing, hand flapping, finger flicking
 - Gross/fine motor delays, poor motor control
- Unusual temperamental profile
 - Reduced positive affect, low sensitivity to social reward cues, emotional dysregulation
 - Reduced attentional flexibility

Very early biological markers of autism

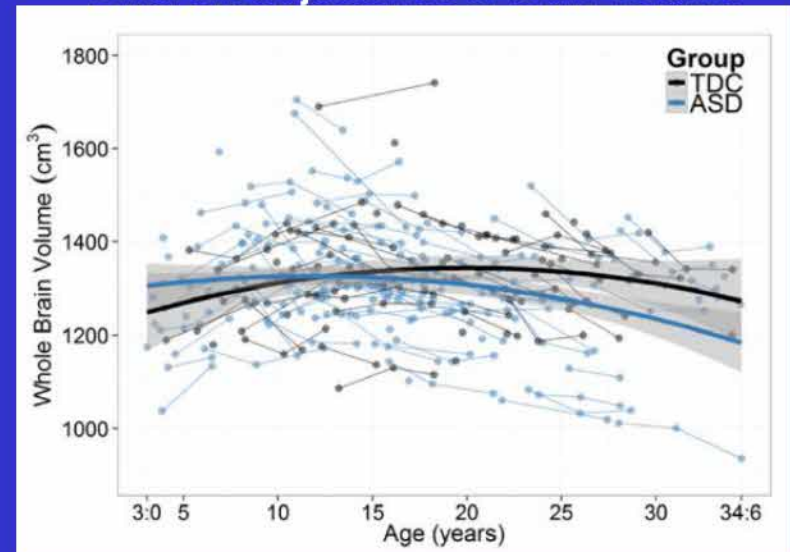
Extra cerebral fluid



Corpus callosum



Different trajectories of brain volume



Eye tracking studies

198 BIOL PSYCHIATRY K. Chawarska *et al.*

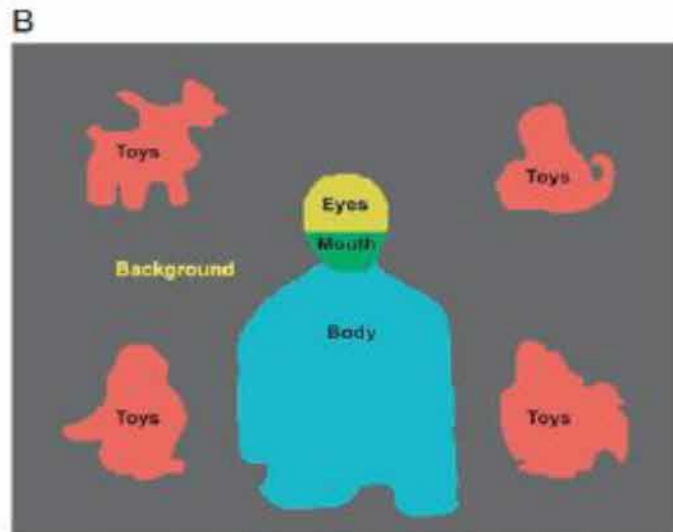
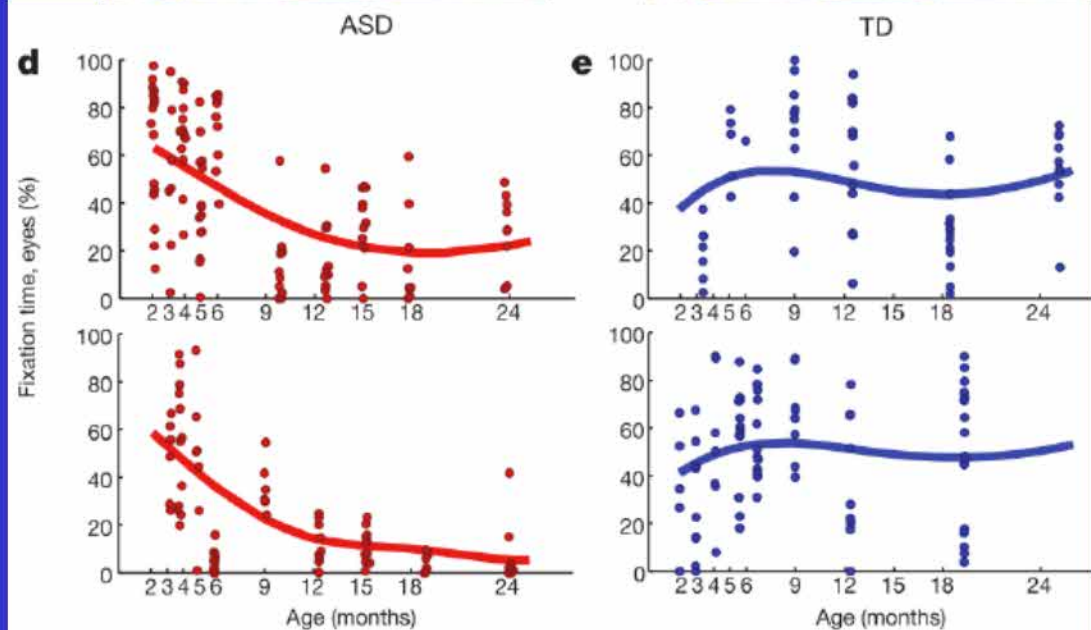
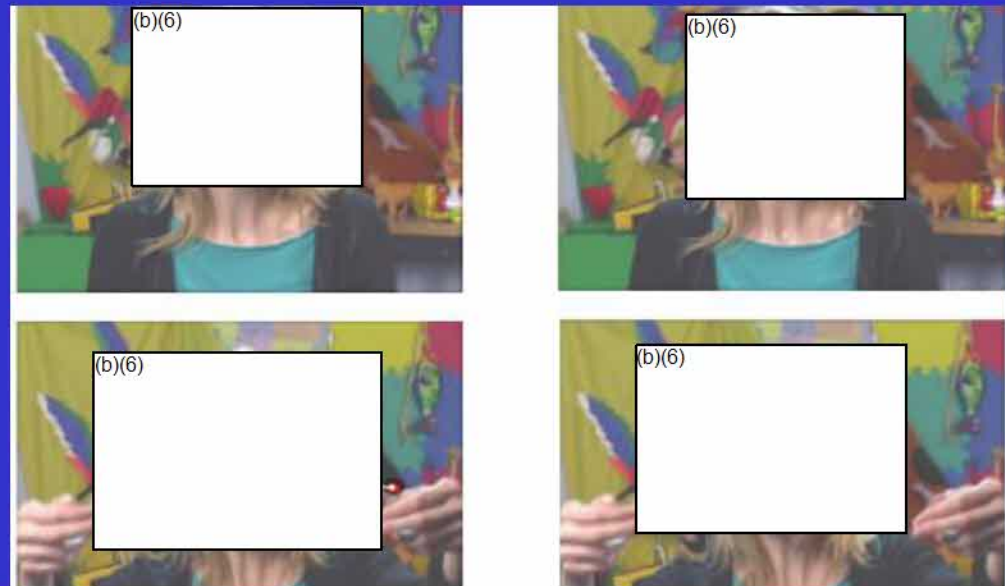
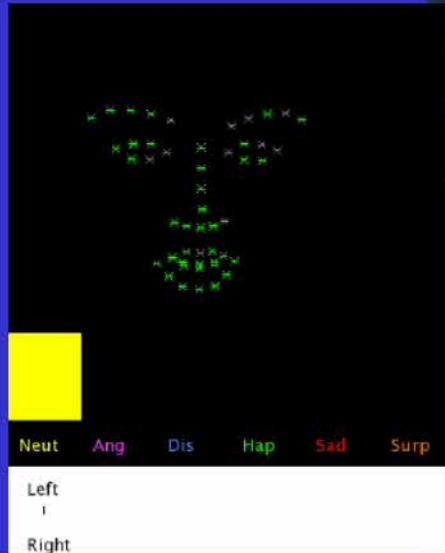
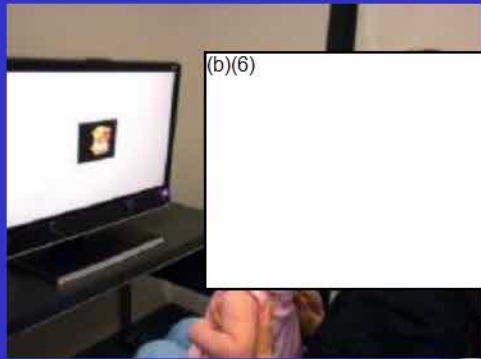


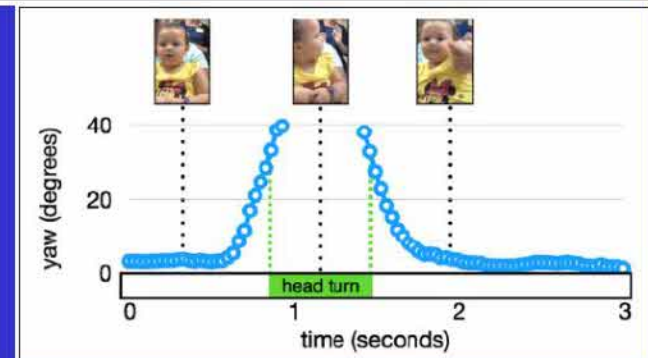
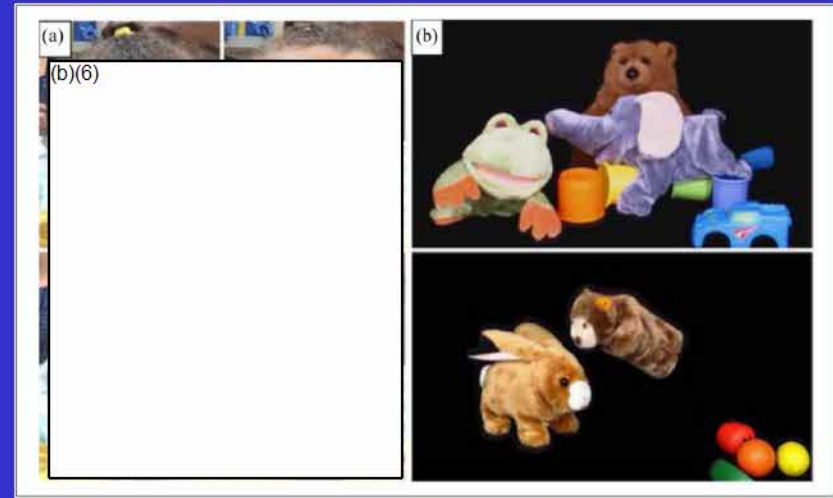
Figure 1. (A) Frame from video stimulus with (B) regions of interest used in analysis. The regions of interest: scene (face [eyes + mouth] person + toys + background), person (face + body), toys, eyes, and mouth.



Increased use of technologies for screening and management



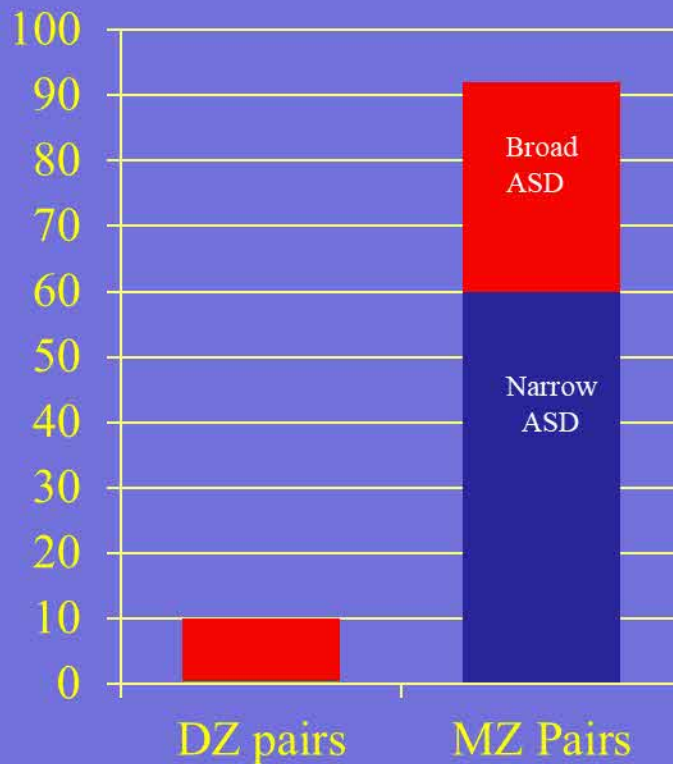
Apple ResearchKit



Less frequent social orientation, increased latency

Heritability of ASD in UK twin studies

Colvert et al., JAMA Psych. 2015



Bailey et al., 1995

Table 1. MZ and DZ Probandwise Concordance Rates Across MZ and DZ Affected Twins^a

Measure	MZ Twin Pairs		DZ Twin Pairs	
	No. of Discordant/Concordant Pairs	Probandwise Concordance Rate	No. of Discordant/Concordant Pairs	Probandwise Concordance Rate
ASD^b				
DAWBA	12/15	0.71	74/2	0.05
ADI-R	15/12	0.62	80/8	0.17
ADOS	8/12	0.75	57/9	0.40
Best-estimate diagnosis	8/17	0.87	77/11	0.22
ASD and Broad-Spectrum Disorder^c				
DAWBA	16/24	0.75	118/5	0.08
ADI-R	4/24	0.92	54/43	0.61
ADOS	7/16	0.82	56/18	0.39
Best-estimate diagnosis	3/24	0.94	70/30	0.46

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; DAWBA, Development and Well-being Assessment; DZ, dizygotic; MZ, monozygotic.

^a Includes same-sex and opposite-sex twin pairs.

^b Rates reflect twins included in category 2 (ASD) only.

^c Rates reflect pairs in which a child was included in category 1 (broad-spectrum disorder) or 2.

Recurrence risk estimates: baby sib consortium

- Old recurrence estimates: 3-10%
- Prospective study of 664 at risk infants followed up to age 3
- 18.7% of siblings had ASD at age 3
- If the family is multiplex, there is a 3-fold increase in males and a 2-fold increase in females
- Risk is not associated with gender or level of functioning of the older sibling
- Implications for genetic counselling

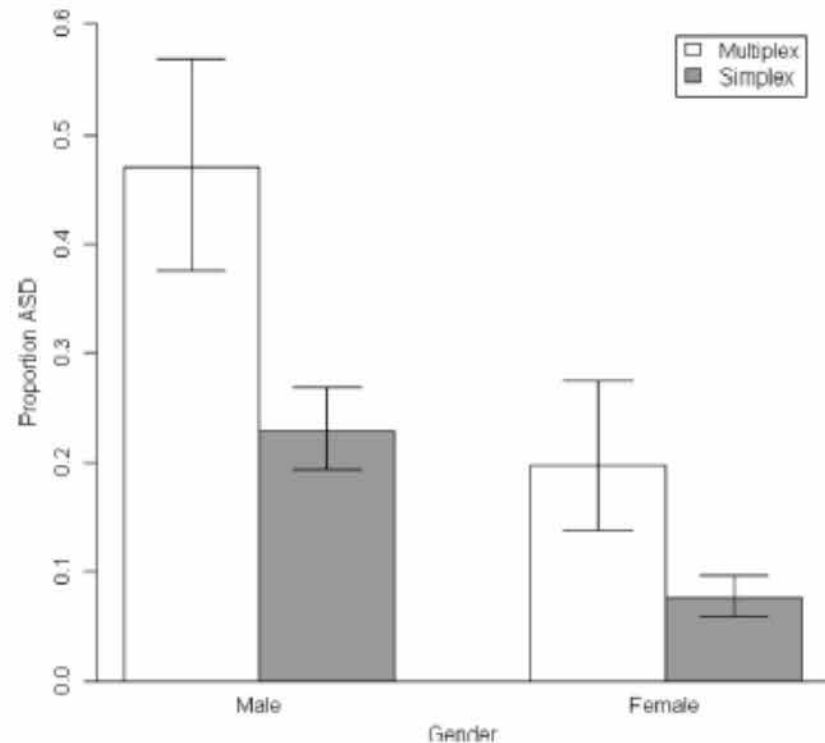


FIGURE 2
Proportion of ASD outcome according to infant gender and family multiplex status.

The SPARK Gene List

The SPARK gene list contains 141 single genes (blue) and 19 copy number variants (orange) that are known to be associated with autism. More information about each autism-linked gene or CNV, along with its associated symptoms, is available [here](#).

Copy Number Variants	Single Genes				
1q21.1	ACTB	CIC	KRAS	PHF21A	SMARCC2
2p16.3	ADNP	CNOT3	KMT2A	PHIP	SON
3q29	ADSL	CREBBP	KMT2C	POGZ	SOS1
5q35	AFF2	CTNNB1	LZTR1	POMGNT1	SOS2
7q11.23	AHDC1	CUL3	MAGEL2	PPP1CB	SPAST
8p23.1	ALDH5A1	DDX3X	MAP2K1	PPP2R5D	SRCAP
15q11.2 BP1-BP2 deletion	ANK2	DHCR7	MAP2K2	PSMD12	STXBP1
15q11.2-q13.1	ANK3	DMPK	MBD5	PTCHD1	KMT5B (SUV420H1)
15q13.3	ANKRD11	DNMT3A	MBOAT7	PTPN11	SYNGAP1
15q15	ARHGEF9	DSCAM	MECP2	PTEN	TBCK
16p11.2	ARID1B	DYRK1A	MED13	RAF1	TBR1
16p12.1	ARX	EBF3	MED13L	RAI1	TCF20
16p13.3	ASH1L	EHMT1	MEIS2	RELN	TCF4
17p11.2	ASXL3	EP300	MYT1L	RERE	TLK2
17q11.2	ATRX	FMR1	NAA15	RIMS1	TRIO
17q12	AUTS2	FOXG1	NBEA	RIT1	TRIP12
17q21.3	BAZ2B	FOXP1	NCKAP1	SCN1A	TSC1
22q11.2	BCKDK	GIGYF1	NF1	SCN2A	TSC2
22q13.3	BCL11A	GIGYF2	NIPBL	SCN8A	TSHZ3
	BRAF	GRIN2B	NLGN2	SETBP1	UBE3A
	BRSK2	HIVEP2	NLGN3	SETD2	UPF3B
	CACNA1C	HNRNPH2	NRAS	SETD5	VPS13B
	CASK	HNRNPU	NR4A2	SHANK2	WAC
	CDKL5	HRAS	NRXN1	SHANK3	WDFY3
	CHAMP1	IQSEC2	NRXN2	SHOC2	ZBTB20
	CHD2	KANSL1	NRXN3	SIN3A	ZNF462
	CHD3	KCNB1	NSD1	SLC6A1	
	CHD7	KDM6B	PACS1	SLC9A6 (NHE6)	
	CHD8	KIAA2022	PCDH19		

Currently, from 20% to 30% of cases of ASD can be ascribed to a specific genetic cause

Each mutation affects only a small (<0.5%) proportion of families

Ongoing work on somatic mutations, mutations in non coding regions of genome, epigenetic changes

Environmental risk: paternal age, valproic acid et al.

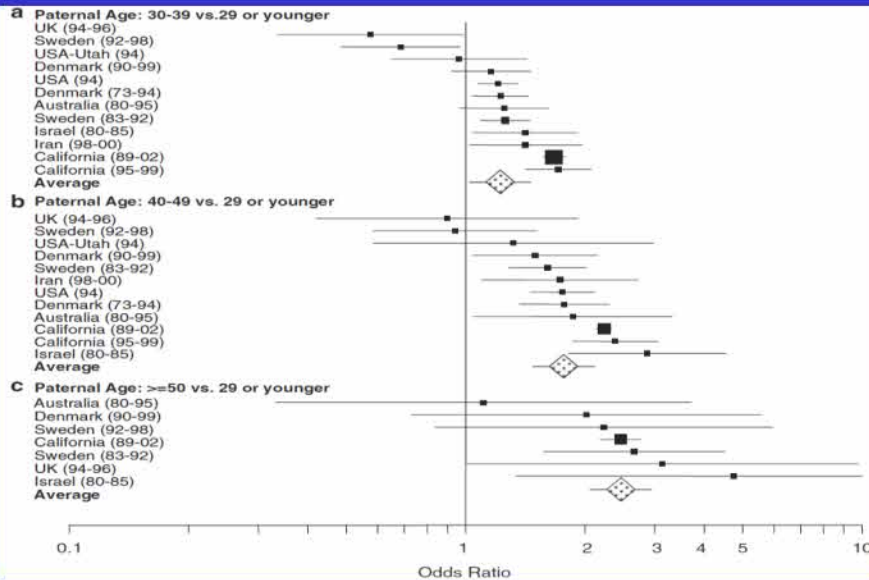
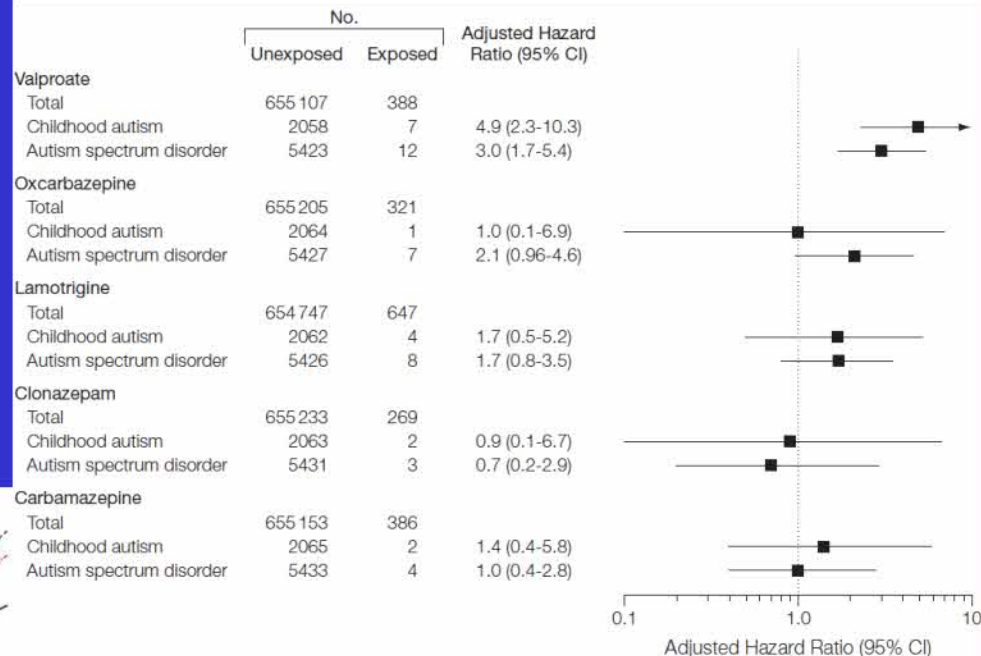


Figure 2. Autism Spectrum Disorder and Childhood Autism in Offspring of Mothers Who Used Antiepileptic Drugs as Monotherapy During Pregnancy Compared With Offspring of Women Who Did Not Use the Individual Antiepileptic Drug

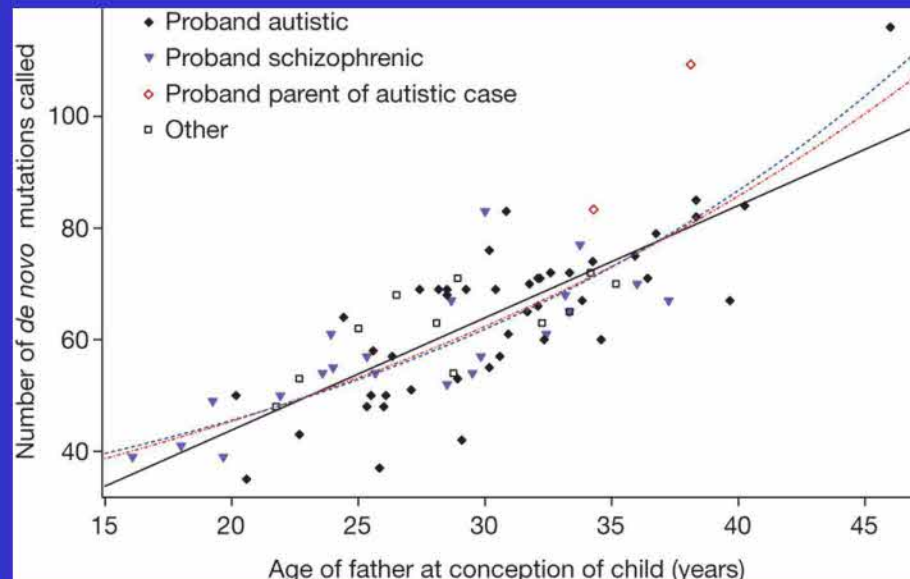


Christensen et al. 2014

. Other exposures; IP interval, folic acid insufficiency, maternal diabetes and autoimmune disorders, pesticides, pollution, prenatal infections, ...

evidence is preliminary and often weak

Hultman et al 2011; Kong et al. Nature (2012)



SPARK cohort (Simons Foundation; 2016-)



150,000 participants
70,000 subjects with ASD
35,000 'trios'

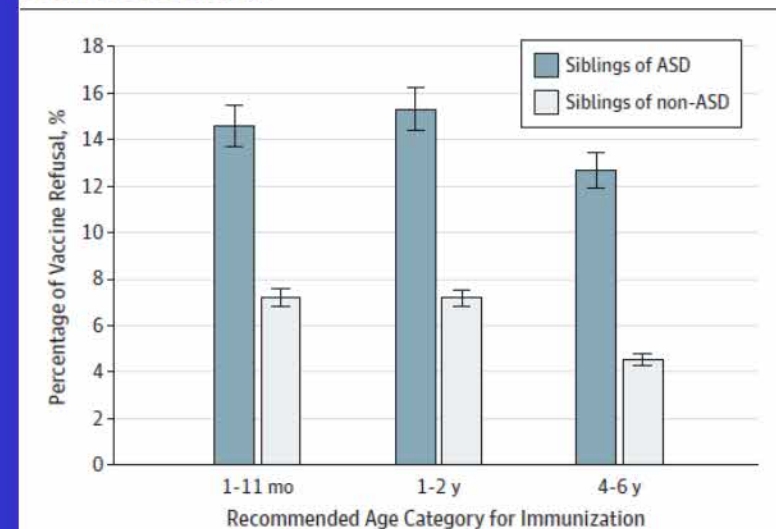
What is your opinion as to what may have caused child/dependent 's ASD?	% of 20,128 respondents
Genetic cause	60.0
Environmental exposures	22.3
Immunizations	16.7
Birth or delivery complication	16.4
Problems during pregnancy	16.1
Other medical conditions	8.3

Siblings are undervaccinated

Table 3. On-Time Vaccination Rates and Adjusted RRs Comparing Vaccination Among Younger Siblings of Children With ASD vs Younger Siblings of Children Without ASD by Age Group^a

Vaccine	Recommended Vaccine Doses	No. (%)		Adjusted RR (95% CI)
		Siblings of ASD	Siblings of non-ASD	
Ages 1-11 mo				
Sibling status, No.	NA	881	189 144	NA
DTaP	≥3	745 (84.6)	175 414 (92.7)	0.91 (0.88-0.94)
HBV ^b	≥2	751 (85.2)	182 907 (96.7)	0.88 (0.86-0.91)
Hib	≥2	791 (89.8)	182 807 (96.6)	0.93 (0.91-0.95)
IPV	≥3	708 (80.4)	172 878 (91.4)	0.88 (0.85-0.91)
PCV	≥3	NA	NA	NA
Rotavirus	≥2 ^c	741 (84.1)	173 680 (91.8)	0.91 (0.89-0.94)
Fully vaccinated	All of the above	645 (73.2)	160 773 (85.0)	0.86 (0.82-0.89)

Figure. Parental Vaccine Refusal of Any Vaccine Dose for Younger Siblings by Age Category and by Child Autism Spectrum Disorder (ASD) Status of Older Siblings



Outline

- *Studies of ASD risk and vaccine exposure*
 - *epidemiological studies*
 - *search for a vulnerable autism subtype*
- *Autism specific context*
 - *epidemiology of ASD: rates, trends*
 - *developmental trajectories*
 - *etiology: genes, environment, both?*
 - *persistent beliefs*
- Other issues
 - litigation
 - medias
 - publication bias, negative studies

Class action (>5,000 families), 2003-2011

US Court of Federal Claims

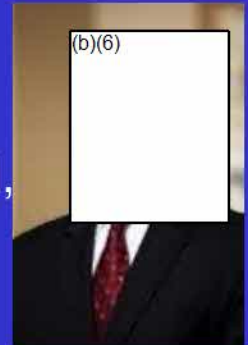


In 2010, the Special Masters of the Court render their opinion and reject the claims of the class action



Michelle C.
1st test case on MMR, 2007

6 other individual
cases on thimerosal,
2008



Supreme Court rejects vaccine lawsuit
Feb. 2011



★ NATIONAL AFFAIRS ★

DEADLY IMMUNITY

When a study revealed that mercury in childhood vaccines may have caused autism in thousands of kids, the government rushed to conceal the data – and to prevent parents from suing drug companies for their role in the epidemic

★ *By Robert F. Kennedy Jr.* ★ -

IN JUNE 2000, A GROUP OF TOP GOVERNMENT SCIENTISTS and health officials gathered for a meeting at the isolated Simpsonwood conference center in Norcross, Georgia. Convened by the Centers for Disease Control and Prevention, the meeting was held at this Methodist retreat center, nestled in wooded farmland next to the Chattahoochee River, to ensure complete secrecy. The agency had issued no public announcement of the session – only private invitations to fifty-two attendees. There were high-level officials from the CDC and the Food and Drug Administration, the top vaccine specialist from the World Health Organization in Geneva and representatives from major vaccine manufacturers.

two days discussing how to cover up the damaging data. According to transcripts obtained under the Freedom of Information Act, many at the meeting were concerned about how the damaging revelations about thimerosal would affect the vaccine industry's bottom line. "We are in a bad position from the standpoint of defending any lawsuits," said Dr. Robert Brent, a pediatrician at the Alfred I. duPont Hospital for Children in Delaware. "This will be a resource to our very busy plaintiff attorneys in this country." Dr. Bob Chen, head of vaccine safety for the CDC, expressed relief that "given the information

Junk science and the medical press

- *Lancet* paper 1998:
 - No control group
 - No blind assessment
 - No expertise in autism in authorship (and no peer review)
- Wakefield kept shifting his hypothesis to a new work that refutes his ‘theory’.
- Is it fair to spend enormous public money on something that does not exist, and how far should we go?

MMR vaccination and pervasive developmental disorders: a case-control study

Liam Smeeth, Claire Cook, Eric Fombonne, Lisa Heavey, Laura C Rodrigues, Peter G Smith, Andrew J Hall

Summary

Background Concern that measles-mumps-rubella (MMR) vaccination might cause autism has led to a fall in vaccine coverage. We investigated whether MMR vaccination is associated with an increased risk of autism or other pervasive developmental disorders.

Methods We did a matched case-control study using the UK General Practice Research Database. Cases were people born in 1973 or later who had first recorded diagnosis of pervasive developmental disorder while registered with a contributing general practice between 1987 and 2001. Controls were matched on age, sex, and general practice.

Findings 1294 cases and 4469 controls were included. 1010 cases (78.1%) had MMR vaccination recorded before diagnosis, compared with 3671 controls (82.1%) before the age at which their matched case was diagnosed. After adjustment for age at joining the database, the odds ratio for association between MMR and pervasive developmental disorder was 0.86 (95% CI 0.68–1.09). Findings were similar when restricted to children with a diagnosis of autism, to those vaccinated with MMR before the third birthday, or to the period before media coverage of the hypothesis linking MMR with autism.

Interpretation Our findings suggest that MMR vaccination is not associated with an increased risk of pervasive developmental disorders.

Inflammatory bowel disease and autism

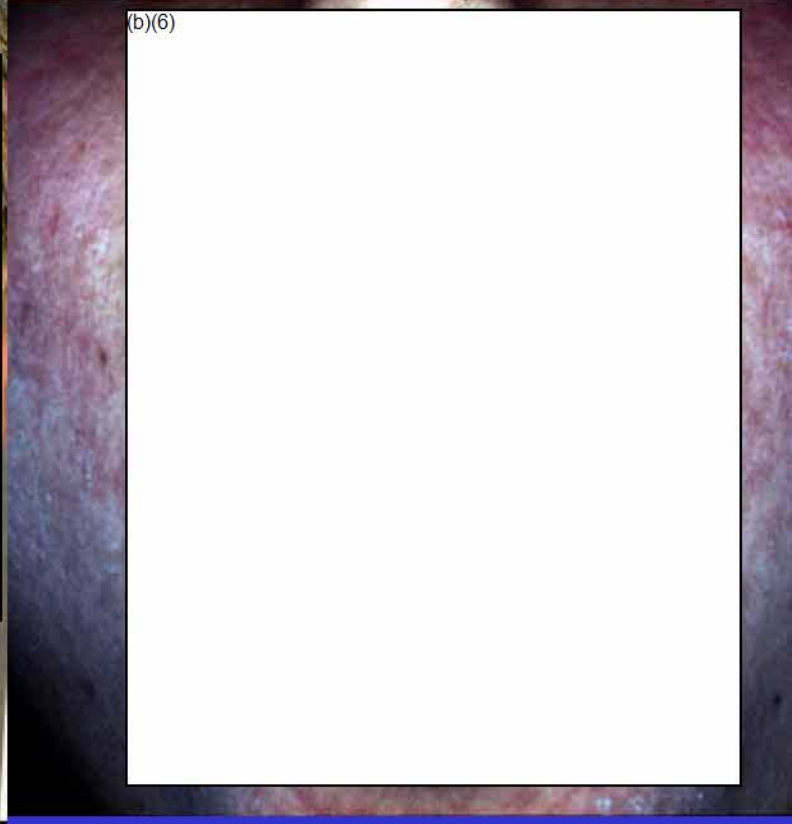
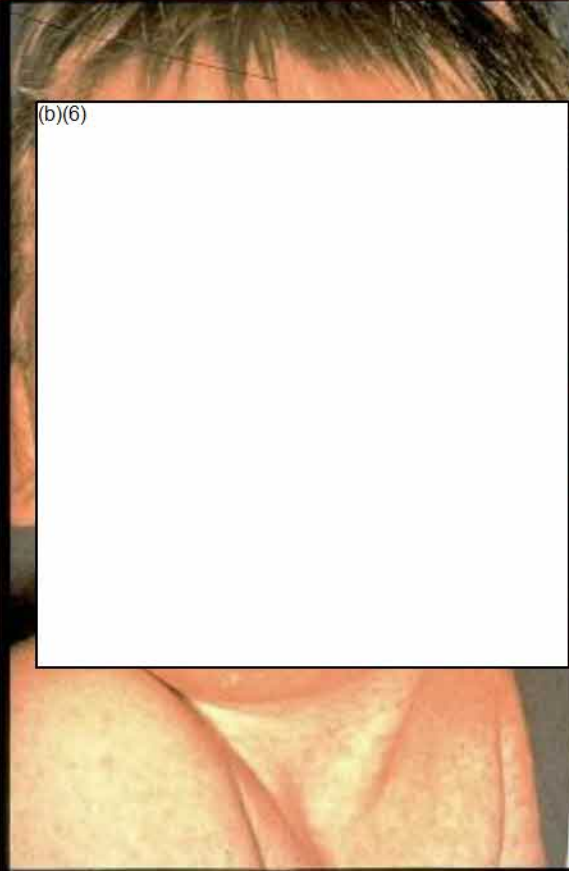
Eric Fombonne

A recent report has raised concerns about measles, mumps, and rubella (MMR) vaccine, inflammatory bowel disease (IBD), and autism in children.¹ No association between Crohn's disease and autism has been reported previously. We looked for such an association in two large datasets.

The Child and Adolescent Psychiatric Services of the Maudsley Hospital, a teaching hospital in south London, UK, provides services for a local catchment area, and receives referrals from the Greater London area and other regions in

children. These results are also consistent with a recent review of epidemiological surveys of autism where IBD did not appear in the list of medical conditions reported in 11 samples, including 836 people with autism.² Finally, it is noteworthy that, in the UK sample, the incidence of IBD remained nil amongst 201 autistic children likely to have been exposed to the MMR vaccine, suggesting no particular association between Crohn's disease and autism among children immunised with MMR.

- Definition of autism in the study



Roald Dahl's account – 24 years later

Olivia, my eldest daughter, caught measles when she was seven years old.

As the illness took its usual course I can remember reading to her often in bed and not feeling particularly alarmed about it. Then one morning, when she was well on the road to recovery, I was sitting on her bed showing her how to fashion little animals out of coloured pipe-cleaners, and when it came to her turn to make one herself, I noticed that her fingers and her mind were not working together and she couldn't do anything.

“Are you feeling all right?” I asked her.

“I feel all sleepy, ” she said.

In an hour, she was unconscious. In twelve hours she was dead.

The measles had turned into a terrible thing called measles encephalitis and there was nothing the doctors could do to save her.

That was twenty-four years ago in 1962, but even now, if a child with measles happens to develop the same deadly reaction from measles as Olivia did, there would still be nothing the doctors could do to help her. On the other hand, there is today something that parents can do to make sure that this sort of tragedy does not happen to a child of theirs. They can insist that their child is immunized against measles. I was unable to do that for Olivia in 1962 because in those days a reliable measles vaccine had not been discovered. Today a good and safe vaccine is available to every family and all you have to do is to ask your doctor to administer it.

From: GARCON Nathalie
Sent: 12 Dec 2019 21:32:13 +0000
To: Admin;nkarora@incentrust.org;fombonne@ohsu.edu;jason.m.glanz@kp.org;nhalsey@jhsph.edu;All@ssi.dk;paul.lambert@unige.ch;'Heidi Larson';Markowitz, Lauri (CDC/DDID/NCIRD/DVD);offit@email.chop.edu;Peden, Keith (FDA/CBER);'Andrew Pollard';Sejvar, James (CDC/DDID/NCEZID/DHCPP);Zuber, Patrick (CDC who.int);Destefano, Frank (CDC/DDID/NCEZID/DHQP);kathryn.edwards@vumc.org;jim.buttery@monash.edu;(b)(6);ulrich.heininger@ukbb.ch;dsalmon1@jhu.edu;m.c.j.sturkenboom@umcutrecht.nl;priya.bahri@ema.europa.eu;(b)(6);bodenstabh@email.chop.edu;(b)(6);hotez@bcm.edu;liz.miller@hpa.org.uk;h.petousis-harris@auckland.ac.nz
Cc: 'Stanley Plotkin'
Subject: RE: London Vaccines Meeting - Funding

Thanks for the heads up
Cheers
nathalie

From: Admin <admin@vaxconsult.com>
Sent: Thursday, December 12, 2019 3:16 PM
To: nkarora@incentrust.org; fombonne@ohsu.edu; GARCON Nathalie <Nathalie.GARCON@bioaster.org>; jason.m.glanz@kp.org; nhalsey@jhsph.edu; All@ssi.dk; paul.lambert@unige.ch; 'Heidi Larson' <Heidi.Larson@LSHTM.ac.uk>; lem2@cdc.gov; offit@email.chop.edu; keith.peden@fda.hhs.gov; 'Andrew Pollard' <andrew.pollard@paediatrics.ox.ac.uk>; zea3@cdc.gov; zuberp@who.int; fxd1@cdc.gov; kathryn.edwards@vumc.org; jim.buttery@monash.edu; (b)(6); ulrich.heininger@ukbb.ch; dsalmon1@jhu.edu; m.c.j.sturkenboom@umcutrecht.nl; priya.bahri@ema.europa.eu; (b)(6); bodenstabh@email.chop.edu; (b)(6); hotez@bcm.edu; liz.miller@hpa.org.uk; h.petousis-harris@auckland.ac.nz
Cc: 'Stanley Plotkin' <stanley.plotkin@vaxconsult.com>
Subject: London Vaccines Meeting - Funding

Dear All:

As promised I have been using the results of the London meeting to seek funding for vaccine safety studies. The response of the Wellcome Trust is that they would consider only studies by a UK investigator or by one associated with a UK investigator. The Gates Foundation is considering our proposals and it looks as if they may fund studies of HPV vaccine, and maybe maternal immunization. I will keep you posted.

Stanley

Sent on Behalf of Dr. Stanley Plotkin

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