



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

March 2, 2020

SENT VIA EMAIL

Allison Lucas
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200 Park Ave
17th Floor
New York, NY 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 December 31, 2019, assigned #20-00379-FOIA, seeking:

- “1. Each and every email communication between January 1, 2017, and the present which includes Amanda Cohn 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.
2. Each and every email communication between January 1, 2017, and the present which includes Amanda Cohn or her email address on the “To”, “From”, “Cc” or “Bcc” line and also includes either of the terms “Advisory Committee on Immunization Practices” and/or “ACIP.”
3. Each and every email communication between January 1, 2017, and the present which includes Amanda Cohn or her email address on the “To”, “From”, “Cc” or “Bcc” line and also includes any of the following terms: “vaccine hesitancy”, “antivaccine”, “antivaccination”, “anti-vaxx”, “anti-vax”, “antivax” and/or “antivaxx.”

We located 410 pages of responsive records (307 pages released in full or part; 94 pages withheld in full) are retrievable by accessing the following link: [20-00379](#). Please be advised, the link will expire 30 days from the date of this letter. Further, some information you requested falls under the jurisdiction of the Department of Food and Drug Administration (9 pages). Should you have questions regarding the status of the referred records, you may contact:

[Food and Drug Administration \(FDA\)](#)
Freedom of Information Officer
5630 Fishers Lane, Room 1035
Rockville, MD 20857
Phone: 301-796-3900
FOIA Officer: Sarah Kotler

After a careful review of these pages, some information was withheld from release pursuant to 5 U.S.C. §552 Exemptions 4, 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 meeting minutes; policy discussion comments; draft page proofs of Chapter 73 in *Plotkin's Vaccines, ed 7*, and draft Mumps document.

Exemption 6 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 meeting dial in numbers and passcodes, conference identification numbers, and email addresses. We have determined that the individuals to whom this information pertains has a substantial privacy interest in withholding it.

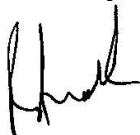
In accordance with the Department's implementing regulations, 45 CFR Part 5, no fees are due for processing your request #20-00379-FOIA.

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 Monday, June 1, 2020.

Sincerely,



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

From: Marin, Mona (CDC/OID/NCIRD)

Sent: 12 Jul 2017 16:45:11 -0400

To:

Kelly.Moore@tn.gov;RomeroJose@uams.edu;phunte@milwaukee.gov;Pellegrini, Cynthia;Rubin, Steven (FDA/CBER);Zucker, Jane R. (CDC health.nyc.gov);noltd@ohsu.edu;Baker, Carol (CDC bcm.edu);EvenS@health.missouri.edu;DeBolt, Chas (DOH);Groom, Amy V. (IHS/HQ);Seward, Jane (CDC/OID/NCIRD) (CTR);Quinlisk, Patricia (CDC idph.iowa.gov);McLean Phd, Huong Q;MLMartinez@salud.unm.edu;Shalini Desai;Stanley Plotkin

Cc: HoganTanyaG@UAMS.edu;Patel, Manisha M. (CDC/OID/NCIRD);Routh, Janell A. (CDC/OID/NCIRD);Clemmons, Nakia (CDC/OID/NCIRD);Ayers, Tracy (CDC/OID/NCIRD);Rota, Paul (CDC/OID/NCIRD);Hickman, Carole (CDC/OID/NCIRD);Wharton, Melinda (CDC/OID/NCIRD);Zhou, Fangjun (CDC/OID/NCIRD);Wodi, Akpobome (CDC/OID/NCEZID);Maiuri, Allison M. (CDC/OID/NCIRD);Mason, Karen A. (CDC/OID/NCIRD);Latner, Don (CDC/OID/NCIRD);Pallansch, Mark A. (CDC/OID/NCIRD);Cohn, Amanda (CDC/OID/NCIRD);Ortega-Sanchez, Ismael (CDC/OID/NCIRD);Marlow, Mariel Asbury (CDC/OID/NCIRD);Lee, Adria (CDC/OID/NCIRD) (CTR)

Subject: ACIP Mumps WG - conf call 7/13

Attachments: 1_Results 1st WG survey_WG call_July 13 2017.pptx, 2_Policy discussions overview_WG call_July 13 2017.pptx, Minutes June 8, 2017.docx, Patel_Mumps in a highly vaccinated population, NYC 2014_CID2017.pdf

Dear Mumps Work Group Members,

Welcome to the summer session of the WG! Hope everyone has enjoyed the 5 week break since the last call! Please find attached the materials for tomorrow and the minutes of the last call. Most of the slides in the 1st presentation are included as reference and will not be presented and the other updates are pretty short so that we will have ample time for discussion. Also attached is a recent publication describing an outbreak where a 3rd dose was not administered.

Dial In Number: (b)(6)

Participant passcode: (b)(6)

Agenda: Thursday, July 13, 2017, 3:30 pm ET

1. Roll call and administrative issues (Mona Marin/Kelly Moore)
2. Re-cap of mumps session at June ACIP meeting (Mona/Kelly)
3. Results of 1st WG survey (Mona)
4. Policy discussion overview: current guidance for mumps outbreak control, ACIP process, proposed framework for WG policy discussions (Mona)
5. WG discussion and interpretation of the scientific evidence
6. Other issues or questions/summer WG schedule (Mona/Kelly)

Next call: Thursday, July 27 @ 3:30 pm EST

- Topics
 - Continue WG discussion and interpretation of the scientific evidence

We look forward to speaking with you tomorrow.

Best regards,
Mona.



Feedback from June ACIP Meeting & Results of 1st WG Survey (June 15, 2017)

ACIP Mumps WG Conference Call July 13, 2017

June 2017 ACIP Meeting

- Presentations Update on mumps epidemiology in the US
Evidence reviewed by the WG on the 3rd dose
Immune response, published studies on use of MMR3 for mumps outbreak control, safety
IA vaccine effectiveness study
Questions & comments
Timing of WG policy considerations to ACIP (Oct 2017 vs. Feb 2018)
The role of the difference in circulating vs. vaccine mumps strain for current epi
Do we know how much asymptomatic infection there is among vaccinated persons
Are we seeing problems with mumps outbreaks in countries that use other mumps vaccines
Is there replication after the 3rd dose
IA vaccine effectiveness study
Timing of the intervention in relation to the peak of the outbreak
Suggestions for other ways to look at the data to increase our confidence in the results
Restrict the analysis to the period after 3rd dose intervention
Matched cohort analysis to account for the secular trends in the background rate (3 vs. 2 dosers)

WG Survey - Results

- Based on the evidence presented so far, the current 2-dose MMR vaccination schedule provides substantial long-term protection against mumps and its complications, but will not prevent all clinical disease I am satisfied that I have enough information to accept this statement: 14/14 (100%) Given the data the working group has been presented thus far, there may be circumstances where an additional dose beyond the current recommended schedule would be helpful in preventing additional disease or complications. The available data are sufficient to make this statement: 6/14 (43%) I believe the available data suggest this, need additional information: 6/14 (43%) I do not believe the available data support this. Additional information is needed: 2/14 (14%)

WG Survey - Results

- At this point, given the data provided to the working group thus far, I am inclined to agree most with the following:
No changes are justified to the current recommendations, either routine or outbreak: 4/14 (29%)
A change to the routine immunization schedule is justified to more effectively prevent clinical disease and complications (adding a dose at a particular age e.g., adolescent platform or at college matriculation): 0/14 (0%)
A third/an additional dose is justified as part of mumps outbreak control in outbreaks among groups with high 2-dose coverage: 10/14 (71%)
All outbreaks: 6/10 (60%)
In specific circumstances (e.g., timing, size, other circumstances to be determined and specified): 4/10 (40%)

WG Survey: Comment Categories

- Severity of mumps in MMR2 vaccinated
Factors associated with MMR2 vaccine failure
MMR3 vaccine effectiveness and effectiveness for outbreak control
MMR3 outbreak guidance
Cost/benefit MMR2 or MMR3 at admission to at risk/close-contact setting
Lab evidence
Other: Evidence from other countries, immunocompromised, exclusion policy

Severity of Mumps in MMR2 Vaccine Recipients (6)

- One WG member stated that the rate of complications appears greatly reduced compared with the rates seen in the pre-vaccine era; the rest of the comments inquired whether there are less complications in MMR2 vaccinated vs. unvaccinated (specifically orchitis)? Literature summary presented to WG (see slides 15-16) suggests vaccinated/cases in vaccine era have lower attack rate for orchitis and other complications than unvaccinated; Orchitis rates significantly lower in 2 dose vaccinees than unvaccinated in the 2009-10 Northeast outbreak; Data collected in WA outbreak supports higher orchitis attack rate in unvaccinated (not presented); Data collection on complications by vaccination status in outbreaks reported since 2016 in progress; There may not be enough unvaccinated during the recent outbreaks to compare vaccinated and unvaccinated in the US Lower rates/2-doses effective against all complications and hospitalizations among 2-dose vaccinees vs. unvaccinated in international studies (slide 16); For meningitis two studies suggested effectiveness but the confidence interval crossed zero

Factors Associated with MMR2 Vaccine Failure (5)

- Define factors associated with MMR2 vaccine failure Literature summary on risk factors for MMR2 vaccine failure presented (see slide 17); Factors reported in the literature included: time since MMR2/waning immunity; behavioral/intensity of exposure; ↑on campus vs. off campus residence (IA 2006); ↑off campus living vs. living in residence halls (reported by WG member); Evidence of decreased antibody titers in 2-dose vaccinees with time since vaccination (see slides 18-21) Role of antigenic difference vaccine strain vs. circulating strains not determined; evidence of lower antibody titers against non Jeryl Lynn strains than against Jeryl Lynn and decrease in antibody titers for JL and other wild type strains in MMR2 vaccinated overtime, with the difference in titers seen soon after vaccination maintained (see slides 22-23); Two dose VE evaluations done in a period when other wild type strains circulated predominantly Informative to have data on efficacy of vaccine strains other than Jeryl Lynn (is there an issue with the US mumps vaccine or across mumps vaccine strains)? We will hear a presentation on international mumps but most of the countries that reported outbreaks use the Jeryl Lynn strain; Uncommon for countries to use only a non-Jeryl Lynn vaccine

MMR3 VE and Effectiveness for Outbreak Control (12)

- 1. Can we conduct a study similar to or better than Iowa to support MMR3 use (MMR3 implemented before the outbreak peaks; other settings (non-university, military); more information on mumps among MMR3 vaccinees)? 2. Can we compare epi-curves of outbreaks with and without an outbreak dose campaign (size and duration)? 1-2: Additional MMR3 outbreak studies that could be presented before Oct ACIP meeting depend on occurrence and investigations of outbreaks by states; Outbreak data collection from states in progress and could provide descriptive statistics and identify outbreaks for further study; Difficult to anticipate which clusters/small outbreaks will turn into larger outbreaks and which will burn out on their own Can we model outbreaks by size and duration to see the effect of MMR3? Modeling of Iowa outbreak in early stages; plan presentation to WG in September

MMR3 Outbreak Guidance (15)

- 1. What are stakeholders' experiences and practices with MMR3? Timing, resources
 - 2. At what point in an outbreak should an MMR3 campaign be implemented to be effective?
 - 3. Would implementing an outbreak dose in all outbreaks prevent larger, more costly outbreaks by avoiding delays in implementing interventions? Also, easier to implement? Or over a certain designated size?
 - 4. Should MMR3 campaign be targeted intervention (narrower group, close contacts/social group/population)?
 - 5. Data to support a 3rd dose has some weaknesses/could not draw a definitive conclusion that a 3rd dose can end an outbreak sooner than no intervention
- 1-5: Outbreak data collection from states and a qualitative survey of state's experiences and practices in progress; Depending on state response and follow up time, preliminary results may be presented in September; We will try to answer some questions with modeling

Cost/benefit (9)

- What was the cost benefit of the Iowa campaign? Economic evaluation of the response during the IA outbreak completed, to be scheduled for WG presentation; Cost study at UW in progress1. What is the cost benefit of an MMR3 outbreak vs catch up vs no campaign (specifics mention: reduce number of cases, outbreak duration, complications)?2. Is it more cost beneficial to implement for all outbreaks vs outbreaks based on criteria?3. What is the experience of stakeholders for the feasibility of an MMR3 campaign?1-3: Outbreak data collection from states and a qualitative survey of state's experiences and practices in progress could be used to investigate these questions; Cost effectiveness analysis planned and will be presented to the WG after October

MMR2 or MMR3 at Admission to “at Risk Settings” (8)

- Would giving MMR2 at admission (vs at 4-6 years) provide better protection for close contact settings for young adults? Would giving an MMR3 booster at admission (or only for those with specified time since MMR2) provide protection for close contact settings/stop outbreaks? Could we study international students or military recruits who get their MMR2 at admission? 1-3: No studies compared MMR2 antibody titers overtime in persons vaccinated at 4-6 yrs vs 18-22 yrs (e.g. at admission); One study examined MMR2 vaccination at 4-6 yrs vs. 11-12 yrs and at age 17 yrs both groups had comparable antibody levels¹; Available data on changes in MMR2 and MMR3 antibody titers overtime presented, limited follow up for MMR3 vaccinees (see slides 18-22 and see slides 24-25) Without a correlate of protection, difficult to determine level of protection for MMR2 or MMR3 during extended close contact setting ***0/14 WG members agreed a change to the routine immunization schedule is justified 1. LeBaron et al. JID 2009

Lab Evidence (2)

- Is there lab evidence to support MMR3 effectiveness in Iowa outbreak? Serology not done during the Iowa investigation
Is there lab evidence to demonstrate difference in MMR2 vs MMR3 antibodies overtime to answer the question on whether there is greater degradation of effectiveness against strains other than A over time
The only data available after MMR3 is through 1 year after MMR3 and for Jeryl Lynn vaccine strain only; 5 year sera collected, plans for testing including antibodies to genotype G strain; Considering avidity testing on a subsample

Other Comments

- Evidence from other countries (3) Are there studies from other countries with a different schedule than US MMR2? Experience of other countries to be presented to the WG; most developed countries have pretty close schedule to the US schedule (3 W. European countries have 2nd dose at 9-12 yrs) What is the VE of vaccines from strains other than JL? Only 2 estimates (China and Moldova) of VE of other mumps vaccines, many limitations; presented during the 2-dose VE session (see slide 26) Immunocompromised (2) Can we estimate herd protection provided by MMR3 for immunocompromised populations in the college/university setting? No planned studies. Exclusion policy (1) Is there evidence to support that exclusion prevents mumps infection susceptible persons and reduces outbreak duration? Evidence on exclusion policy not presented to WG

Reference slides

Burden of Disease

- Vaccine failure can result in mumps illness despite full/2-dose vaccination Lower attack rates among 2 dose vaccine recipients (2.2%-7.7%, range 0-14.5%) than among unvaccinated persons (23%-52%, even 83% in one investigation) Mumps complications among 2 dose MMR recipients reduced compared with pre-vax era US: difficult to compare 0 vs. 1 vs. 2 doses during the vaccine era due to high 2-dose coverage (lower orchitis rate demonstrated) Lower rates in 2 dose vax than in unvax for selected complications and hospitalizations in studies in Netherlands, Israel, and UK**

**Sane et al, EID 2014; Zamir et al, HVI 2015; Yung et al, EID 2011 WG meetings 3/9, 6/8

Orchitis†	up to 30%	3-11
Mastitis†	up to 30%	≤1
Oophoritis‡	5	≤1
Hearing loss	4	≤1
Pancreatitis	4	≤0.1
Aseptic meningitis	1-15	0.2-0.5
Encephalitis	0.03-0.5	0-0.3
All complications§	19	5.7§
Hospitalizations	5.5	<1.2

*Mcleod et al, JMMWR 2013 & Rubin SA and Plotkin SA, Vaccines, 6th edition, 2013; †Data from US outbreak investigations 2006-2015; ‡Assessed in postpubertal male/female patients§Sane et al. EID 2014; vaccine era rates are for 2-dose vaccinees

2-Dose Mumps Vaccine Effectiveness Against Complications

Complication	Netherlands	UK	Israel	Attack Rates
Orchitis*	74 (57-85)	36 (-44 to 72)	77 (45-91)	unvax: 7.7-15.52 doses: 1.5-4.7
Meningitis	-	83 (-26 to 98)	44 (-82 to 82)	unvax: 0.5-0.82 doses: 0.1-0.5
All complications	76 (61-86)	-	63 (26-81)	unvax: 3.9-19.02 doses: 1.1-5.7
Hospitalization	82 (53-93)	55 (20-75)	44 (27-57)	unvax: 3.8-21.02 doses: 1.1-10.0
	Sane et al., EID 2014 Sept 2009- Aug 2012N=1,557 cases, 68% age 18 -25y	Yung et al., EID 2011April 2002-March 2006N=43,344 cases (15,524 with known vax status and enhanced clinical data)	Zamir et al., HVI 2015Sept 2009-Aug 2011N=3,130 cases, median age=13y	

Vaccine Effectiveness adjusted for age (age groups <18y, 18-25y and >25y) and sex, except orchitis which was adjusted only for age (Netherlands); adjusted for age only (UK and Israel)*Male-patients age >12y (Netherlands and Israel), ≥12 y (UK)

Summary Risk Factors for 2-Dose Mumps Vaccine Failure

- 2 studies reported VE by time the 2nd MMR dose and both found decreasing VE with time since 2nd dose. Several college investigations reported increased risk for mumps with longer time since vaccination (assessed as ≥ 10 years or ≥ 13 years since the 2nd dose) or increased odds of mumps by 10%-36% with every year increase in time since the 2nd dose. In populations with high 2-dose coverage, outbreaks occurred in settings with higher density of living/educational settings (crowding, behaviors that facilitate transmission). Outbreaks did not readily spread to older persons. Outbreaks due to a heterologous strain compared with the vaccine strain – significance? Mumps cases declined in the US by >98% in association with the use of genotype A Jeryl Lynn vaccine while various heterologous strains of wild-type mumps virus circulated. Mumps generally did not spread to the broader population/population outside the outbreak setting.



Mumps WG: Policy Discussions Overview

Mona Marin, MD Division of Viral Diseases, CDC

ACIP Mumps WG Conference Call July 13, 2017

Guidance for Mumps Outbreak Control

- In 2012 the MMR WG discussed the topic of a 3rd dose of MMR for mumps outbreak control among other updates for the ACIP MMR statement and concluded that the data were insufficient to recommend for or against the use of a 3rd dose. Presentations were made to the ACIP but topic not presented for an ACIP vote. The WG thought that it was important to provide CDC guidance since CDC was receiving many requests and a 3rd dose had been used in some situations.

Current CDC Guidance Mumps Outbreak Control

- Currently data are insufficient to recommend for or against the use of a 3rd dose of MMR vaccine for mumps outbreak control During mumps outbreaks, public health authorities may administer a 3rd dose of MMR vaccine for specifically identified target populations Criteria to consider prior to administering a third dose in a target population for mumps outbreak control include: High two-dose vaccination coverage (i.e., vaccination coverage >90%) Intense exposure settings likely to facilitate transmission (e.g., schools, colleges, correctional facilities, congregate living facilities) or healthcare settings High attack rates (i.e., >5 cases per 1,000 population); and evidence of on-going transmission for at least two weeks in the target population (i.e., population with the high attack rates)

Current CDC Guidance for Mumps Outbreak Control

- Additional data on the effectiveness and impact of a third dose of MMR vaccine for mumps outbreak control are needed to guide control strategies in future outbreaks. Authorities who decide to administer a third dose as part of mumps outbreak control are encouraged to collect data to evaluate the impact of the intervention. The following data should be collected: Incidence of mumps in target population (before and after the intervention, by vaccination status), Incidence of adverse events following vaccination with a third dose, and Costs associated with the intervention (vaccine, personnel). Catch-up vaccination efforts to ensure that populations at risk are up to date with the recommended number of vaccine doses, as well as reducing opportunities for close contact, remain the recommended strategies for mumps outbreak control.

Key Factors for Developing ACIP Recommendations

- Balance of benefits and harms
Assessed through review of the baseline risk for disease and the expected effects of vaccination on health outcomes
Type or quality of evidence
Values and preferences
Values can be described as the relative importance of outcomes related to benefits, harms and costs
Should reflect those of the people affected, including the general population, patients, clinicians and policy-makers
Health economic data

ACIP Recommendations

- Category A: Recommendation that applies to all persons in an age-or risk-based group
- Category B: Recommendation for individual clinical decision making
- No recommendation/unresolved issue (when additional information is needed)
- Considerations that may result in a Category B recommendation
 - Smaller net benefits (low baseline risk, small relative or absolute effects)
 - Lower confidence in the estimated effect of vaccination on health outcomes (lower evidence grade)
 - Variability in values attributed to benefits and harms
 - Lower cost-effectiveness or uncertainty about whether the net benefits are worth the costs (because of lack of data on input assumptions that substantially affect the results of economic models)

Mumps WG Policy Discussions – Proposed Steps

- Develop an analytical framework with elements important to evaluate when considering policy options (for mumps outbreak control)
Discuss each element of the framework
Discuss available evidence and reach a conclusion that reflects WG interpretation of the evidence
Assess the quality of the evidence for each element
Examine and synthesize the cumulative evidence presented across the entire framework
Formulate options for recommendations that the WG will present to the full ACIP

Proposed Analytic Framework for Mumps WG

1. Disease burden: overall and in high risk exposure groups
Immune response after 2-dose mumps vaccination, including duration of immune response
2-dose mumps vaccine effectiveness
Antigenic differences between vaccine and circulating mumps strains
3rd dose intervention: lab evidence, epi evidence, safety
Programmatic implications/Feasibility of implementing a new recommendation in the context of existing recommendations
Cost-effectiveness?

Additional elements indicated in other frameworks: acceptability, resource priorities, patient and social expectations, social considerations, ethical and legal considerations, equity, vaccine supply, political will/considerations

Proposed WG Assessment

Element of framework	WG interpretation of the evidence	Estimate the confidence in the interpretation (OR quality of evidence that supports the interpretation)*
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1. ...

*whenever possible; confidence in the estimated effect of vaccination on health outcomes (types of studies that provided the evidence)

WG Discussion: Proposed Steps and Analytic Framework

- Does the approach for policy discussions seem reasonable? Are there elements/scientific evidence that WG members would like to be added to the proposed framework or not considered important enough to be included?

WG Discussion: 1. Current Burden of Mumps

- Are we content with the current burden of mumps disease in the US? Overall/in the general population vs. specific settings/high risk exposure groups What are we striving for with the 2 dose program? Mumps elimination? Outbreak control? Reduce disease severity/complications? How confident are we in our assessment/quality of evidence that supports the interpretation?

WG Discussion: 2. Immune Response to Mumps Vaccination

- Is it possible to further reduce the current burden of mumps given our understanding of mumps immunology? Is the immune response to first encounter with the antigen robust enough? Is the duration of the mumps immune response after 2 doses of vaccine long enough to provide adequate protection? Can/should we make any inference regarding immune response after 2 doses of vaccine from what we know about the response to wild-type mumps virus? How confident are we in our assessment/quality of evidence that supports the interpretation?

WG Discussion: 3. 2-Dose Mumps Vaccine Effectiveness

- How good are our current vaccination recommendations at preventing mumps? Is there evidence of waning of 2 dose vaccine-induced protection? Under what conditions are fully vaccinated people more likely to become infected? Can we do better at controlling mumps if we achieve higher MMR coverage for both 1 and 2 doses? How confident are we in our assessment/quality of evidence that supports the interpretation?

WG Discussion: 4. Antigenic Differences between Vaccine and Circulating Mumps Strains

- Do antigenic differences between vaccine and circulating mumps strains contribute to the current burden of disease? How confident are we in our assessment/quality of evidence that supports the interpretation?

WG Discussion: 5. 3rd MMR Dose Intervention

- Is there a benefit to the 3rd dose administration? Epi evidence Lab evidence Safety of the 3rd dose Is there a benefit from a recent dose rather than a 3rd dose (recent immunization vs. number of doses)? How confident are we in our assessment/quality of evidence that supports the interpretation?

WG Discussion: 6. Programmatic Implications

- Programmatic implications for no change of current guidance
Feasibility of implementing a new recommendation in the context of existing recommendations
Acceptability
Cost
How confident are we in our assessment/quality of evidence that supports the interpretation?

Mumps Outbreak Among a Highly Vaccinated University Community—New York City, January–April 2014

Leena N. Patel,¹ Robert J. Arciuolo,^{2,3} Jie Fu,⁴ Francesca R. Giancotti,⁴ Jane R. Zucker,^{2,5} Jennifer L. Rakeman,⁴ and Jennifer B. Rosen²

¹Public Health/Preventive Medicine Residency Program, Division of Epidemiology, and ²Bureau of Immunization, New York City Department of Health and Mental Hygiene, Queens, New York;

³Council of State and Territorial Epidemiologists Applied Epidemiology Fellowship, Atlanta, Georgia; ⁴Public Health Laboratory, New York City Department of Health and Mental Hygiene, Queens, New York; and ⁵National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. On 14 January 2014, a vaccinated student presented with parotitis. Mumps immunoglobulin M (IgM) testing was negative and reverse-transcription polymerase chain reaction (RT-PCR) testing was not performed, resulting in a missed diagnosis and the start of an outbreak at a New York City (NYC) university.

Methods. Mumps case investigations included patient interviews, medical records review, and laboratory testing including mumps serology and RT-PCR. Case patients were considered linked to the outbreak if they attended or had epidemiologic linkage to the university. Epidemiologic, clinical, and laboratory data for outbreak cases residing in NYC were analyzed.

Results. Fifty-six NYC residents with mumps were identified with onset between 12 January and 30 April 2014. Fifty-three cases (95%) were university students, 1 (2%) was a staff member, and 2 (4%) had epidemiologic links to the university. The median age was 20 years (range 18–37 years). All cases had parotitis. Three cases were hospitalized, including 1 of 2 cases with orchitis. Fifty-four (96%) cases had received ≥ 1 mumps-containing vaccine, 1 (2%) was unvaccinated due to religious exemption, and 1 (2%) had unknown vaccination status. Two of the 44 (5%) cases tested by serology were mumps IgM positive, and 27 of the 40 (68%) tested by RT-PCR were positive.

Conclusions. Mumps outbreaks can occur in highly vaccinated populations. Mumps should be considered in patients with parotitis regardless of vaccination status. RT-PCR is the preferred testing method; providers should not rely on IgM testing alone. High vaccination coverage and control measures likely limited the extent of the outbreak.

Keywords. mumps; outbreak; parotitis; university; vaccination.

Mumps is an acute viral infection characterized by inflammation of the parotid and other salivary glands [1]. Parotitis is the most common clinical presentation; however, 20%–30% of people with mumps infection are asymptomatic [2, 3]. Although most people recover, complications of infection can include orchitis, oophoritis, aseptic meningitis, encephalitis, pancreatitis, and deafness [2]. The incubation period, or time from exposure to symptom onset, ranges from 12 to 25 days. People with mumps are most likely to be infectious up to 2 days before parotitis onset through 5 days after [4–6].

In the United States, mumps was a universal childhood disease prior to the introduction of the vaccine in 1967 [1]. Following the recommendation for routine use of mumps vaccine in 1977, incidence declined 98% in the United States by 1985 [1, 7]. A resurgence of mumps occurred in 1986–1987, largely due to cohorts of unvaccinated persons [8]. With the

recommendation of a 2-dose measles, mumps, and rubella (MMR) vaccination policy in 1989, mumps incidence further declined to 0.1 case per 100 000 annually by 2001 [9]. However, outbreaks continue to occur, particularly in communities with large, congregate settings [10–12]. In 2006, a large multistate outbreak occurred in the Midwestern United States with >6500 cases reported, primarily among young, vaccinated university students [11, 13, 14]. An outbreak involving >3500 cases followed in 2009–2010 in the Northeastern United States, among vaccinated religious communities [10].

On 19 February 2014, the student health center at a university in New York City (NYC) reported a cluster of students with suspected mumps infection to the NYC Department of Health and Mental Hygiene (DOHMH). We describe the epidemiology of the ensuing outbreak in a highly vaccinated student population.

METHODS

Case Identification and Investigation

Mumps is a reportable disease in NYC [15]. The outbreak case definition was acute parotitis or other salivary gland swelling, orchitis, or oophoritis in a person who had an epidemiologic link to the affected university between 12 January 2014 and 25 May 2014. Patients were classified according to the Council

Received 24 June 2016; editorial decision 28 October 2016; accepted 14 November 2016; published online December 4, 2016.

Correspondence: J. B. Rosen, Bureau of Immunization, New York City Department of Health and Mental Hygiene, 42-09 28th St, CN-21, Queens, NY 11101 (jrosen4@health.nyc.gov).

Clinical Infectious Diseases® 2017;64(4):408–12

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From: Stetz, Carrie L G. (ELS-STL)
Sent: 23 Feb 2017 14:47:20 +0000
To: Cohn, Amanda (CDC/OID/NCIRD)
Cc: stanley.plotkin@vaxconsult.com;kathryn.edwards@vanderbilt.edu
Subject: Chapter 73: "Plotkin's Vaccines," ed 7
Attachments: 73 Plotkin Reference Renumbering Export File.doc,
secured__Plotkin_7616_Chapter_73_main_LN.pdf
Importance: High

Greetings:

Attached are page proofs of Chapter 73 in *Plotkin's Vaccines*, ed 7. Please review the proofs at your earliest convenience and return them to my attention by **Monday, March 6**, copying the section editor, Dr. Edwards (kathryn.edwards@vanderbilt.edu), on your response. Please make your comments directly on the PDF and be sure to answer any author queries. Please note that this chapter is being proofread simultaneously with your review, so you may see a few typographical errors. *(Note: significant reference renumbering was necessary in this chapter; the attached Word file explains the changes.)*

IMPORTANT NOTES: Please mark up the file with the "Comment" tools. Do not use the "Edit PDF" or "Content Editing" toolbar options. If you are a Mac user, please do not use Apple's document reader software to mark up a PDF; it will cause your comments to display incorrectly. Please save the file to your computer, then use Adobe Acrobat (Reader or Professional) to view and mark up the file.

If you have any questions, feel free to contact me at any time. Thank you,

Carrie

Carrie Stetz
Senior Project Manager/Specialist
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+1 314-447-8020 fax
c.stetz@elsevier.com

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 27 Jul 2017 13:04:24 +0000
To: Stanley Plotkin
Cc: Patel, Manisha M. (CDC/OID/NCIRD)
Subject: FW: Mumps WG

Good Morning Dr. Plotkin,

Please see below for a recap of the discussion regarding your consultation work with vaccine manufacturers and your participation as a scientific consultant on the WG. The guidelines regarding conflicts of interest for work group participants are in place to ensure there is no appearance of conflict of interest. I am happy to discuss more with you, I know your contributions to the scientific discussion thus far has been invaluable for the WG and I appreciate your lending your expertise to the ACIP process.

Best,

Amanda

From: Marin, Mona (CDC/OID/NCIRD)
Sent: Friday, March 03, 2017 3:44 PM
To: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Cc: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

Hello Dr. Plotkin,

We are thrilled to invite you to participate in the mumps ACIP WG as an expert consultant to contribute to the scientific discussions. According to the call schedule we have to date, the first 4 calls will not include policy discussions.

Please note that the regular calls are on the 2nd Thursday of each month, 3:30-5:00 pm EST, with the first being next week, on March 9th. We may add extra calls depending on the need to address first in the WG topics that will be presented to the ACIP.

Regarding the conflict of interest form, we would still want to have a form for you but you can just indicate where your conflicts are, without being specific on the manufacturer/vaccine. Please let us know if you want us to resend the form.

Thanks and hope to talk with you soon,
Mona.

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]
Sent: Wednesday, February 15, 2017 4:34 PM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>
Cc: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

OK, let me know which is preferred. I would be willing to participate in the scientific discussions but not policy discussions if that's best.

Stanley

From: Marin, Mona (CDC/OID/NCIRD) [<mailto:zsn8@cdc.gov>]
Sent: Wednesday, February 15, 2017 4:26 PM
To: Stanley Plotkin
Cc: Cohn, Amanda (CDC/OID/NCIRD)
Subject: RE: Mumps WG

Dear Dr. Plotkin,

My understanding from Amanda's email was that she was aware of your potential conflict of interest and she indicated that you can participate in the scientific discussions, with withholding the participation in the policy discussions. We are going to have several calls initially to present mumps epi (in the US and we're working on a lit review on mumps internationally) and immune response to natural infection and vaccination that would probably not involve policy discussions and in which your perspectives and expertise would be very useful. There are also calls on examining epi and lab evidence for risk factors for 2nd dose failure and potential benefit of the 3rd dose that are focused on science.

So my opinion is that if you want to go through the process of completing the conflict of interest form, we can further confirm with ACIP that you can participate in the science discussions and that would be an important proportion of WG calls. Alternatively, we can invite you to participate as a consultant on the science calls (not being a WG member per se), not sure if COI is needed for that. We had presenters for specific topics but they did not participate in more than 1 or 2 calls.

Amanda, any suggestions?

Thanks,
Mona.

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]
Sent: Wednesday, February 15, 2017 10:12 AM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>
Subject: RE: Mumps WG

Dear Mona:

I have received the forms and unfortunately there is no way I could join in view of the insistence that I have nothing to do with vaccine manufacturers. In fact, I consult for practically all of them. That being said, the question that interests me most is whether or not a new vaccine strain should be developed that gives longer persistence of immunity. If the WG does discuss that question perhaps I could participate for some minutes as a guest. Of course, first the WG has to decide that the current situation is untenable.

Thanks for your welcome,
Stanley

From: Marin, Mona (CDC/OID/NCIRD) [<mailto:zsn8@cdc.gov>]
Sent: Tuesday, February 14, 2017 9:35 PM
To: 'stanley.plotkin@vaxconsult.com'
Subject: FW: Mumps WG

Dear Dr. Plotkin,

Thank you so much for your interest in the mumps WG! Your expertise will be of great value to the WG discussions and recommendations. The primary objective of the WG is to evaluate and formulate policy options to prevent or control mumps outbreaks in the United States. We will start the WG calls in March and the day/time of the calls most likely is going to be the second Thursday of the month, 3:30-5:00 pm EST.

We will email you tomorrow a short intake form that includes questions to complete the WG roster and assess potential conflicts of interest. The email may come from me or Adria Lee.

We look forward to working with you on this policy activity,
Mona.

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: Tuesday, February 14, 2017 10:49 AM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>; Patel, Manisha M. (CDC/OID/NCIRD) <dmn4@cdc.gov>
Subject: FW: Mumps WG

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]
Sent: Tuesday, February 14, 2017 10:44 AM
To: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

Dear Amanda:
Much thanks,
Stanley

From: Cohn, Amanda (CDC/OID/NCIRD) [<mailto:anc0@cdc.gov>]
Sent: Tuesday, February 14, 2017 10:37 AM
To: Stanley Plotkin
Cc: Marin, Mona (CDC/OID/NCIRD); Patel, Manisha M. (CDC/OID/NCIRD)
Subject: Mumps WG

Hi Dr. Plotkin,

I spoke to Mona Marin and Manisha Patel, the CDC leads for mumps, who would be thrilled if you could join the ACIP Mumps WG as an expert consultant, or in whatever capacity you are able to contribute to the discussions. Mona is working on the times of the calls with the ACIP voting members, and can send you some follow-up information.

The one issue we did not discuss is the conflict of interest disclosures. We do have some guidelines for WG participation that may limit your role in the policy discussions, depending on your current financial relationships. But, regardless you can participate as an expert during the science discussions.

Mona will follow-up with information. Thanks for considering participating!

Amanda

Amanda Cohn, MD
CDR, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices
NCIRD/CDC
Office: 404-639-6039
Cell: 404-451-6204
Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus
1600 Clifton Road MS A-87
Atlanta, GA 30329-4027

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 14 Feb 2017 15:36:48 +0000
To: Stanley Plotkin
Cc: Marin, Mona (CDC/OID/NCIRD); Patel, Manisha M. (CDC/OID/NCIRD)
Subject: Mumps WG

Hi Dr. Plotkin,

I spoke to Mona Marin and Manisha Patel, the CDC leads for mumps, who would be thrilled if you could join the ACIP Mumps WG as an expert consultant, or in whatever capacity you are able to contribute to the discussions. Mona is working on the times of the calls with the ACIP voting members, and can send you some follow-up information.

The one issue we did not discuss is the conflict of interest disclosures. We do have some guidelines for WG participation that may limit your role in the policy discussions, depending on your current financial relationships. But, regardless you can participate as an expert during the science discussions.

Mona will follow-up with information. Thanks for considering participating!

Amanda

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CDR, US Public Health Service
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Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus
1600 Clifton Road MS A-87
Atlanta, GA 30329-4027

From: Patsy Stinchfield
Sent: 13 Nov 2018 16:27:05 -0600
To: (b)(6); Cohn, Amanda (CDC/DDID/NCIRD/OD); Amy Pisani; 'Erica DeWald'; Ashley Shelby (b)(6); 'Dorit Reiss'; Karen Ernst (b)(6); Paul Offit; kirsten thistle; Deborah L. Wexler; Hinman, Alan (CDC taskforce.org); Stanley Plotkin
Subject: Re: [EXTERNAL] FW: Request time for public comment at next February ACIP meeting
Attachments: Patsy Stinchfield.vcf

Hi All;

I have added Amanda Cohn to this email regarding changes to public comment for everyone's situational awareness. I am glad to see that public response below to you Deborah from ACIP which should signal to all there will be changes.

I checked the "Inundate Feb 2019 CDC ACIP" Facebook page and they are aware and talking about changes to comment period (Tia Severino, their event organizer who brought her son to the last meeting is saying changes will be after the Feb meeting). There are 62 people who say they are attending, 141 who say they are interested and 53 shares and over 702 likes on their Facebook page.

Here are some of their comments, some are worrisome:

Someone points out there is not a guarantee of any verbal comment time. The group is still encouraging people to attend though they may not be able to comment, some are saying they are not willing to travel if they cannot speak and tell their story. Others are saying it would be good just to meet other Moms "on our crazy journey". Some are saying they want to bring their children "twins with autism from vaccines" and Tia is encouraging them to do so and just take them out if needed. Others are saying it is a long boring day for adults so would be hard for kids so bring a back up babysitter. They are encouraging more men to attend and one (Thomas Milcarek) responded "See you in 3 months Mr. Proffitt--I will have a different way of talking to this guy. I will not be, so to speak, so gentle with a guy who I think is killing and maiming children with his way of doing things...I almost died from Tdap vaccine which has left me suicidal for 2 years...I have personal perspective let alone a deep anger I have for all the beautiful children these policies are harming". Some are saying these public comment changes are "a way to silence us and censor everything." One suggested a "class action lawsuit against each ACIP voter personally and individually". One woman says if her tax returns come back early (sad) she may be able to attend which makes me question if they are being funded to attend. They have taken their planning off this public Facebook site and Tia Severino (the organizer) has set up a private group called "Speak Truth to Power" #SayitNow so they can plan travel together privately.

Amanda, in addition to the good list of interventions you are working on, I would make sure all of the voting and liaison members are aware in advance of the potential for drama (for lack of a better word) at the Feb meeting for their own informed decision-making. I would also post on your website that you discourage children from attending, though I doubt you could prohibit it. (Many conferences have language around this). There are many reasons why I don't think kids belong there including the stress to the kids seeing adults cry while they talk about their child who died and watching adults get upset and yell at other adults. It's too much for them.

Thanks for your efforts all.

fyi,
Patsy

Patricia (Patsy) Stinchfield, MS, RN, CPNP, CIC
Senior Director, Infection Prevention and Control, The Children's Immunization Project and Skin Integrity Program

~
Nurse Practitioner, Infectious Disease/Immunology

Children's Hospitals and Clinics of Minnesota
347 North Smith Avenue
Mailstop 70-504
Suite 504, Room 5075
St. Paul, MN 55102
office phone: (651) 220-6444
cell: (651) 245-7171
fax: (651) 220-7233
patsy.stinchfield@childrensMN.org

>>> "Deborah L. Wexler" <Deborah@immunize.org> 11/13/2018 2:31 PM >>>

I submitted a request to make a public comment (as a just-in-case placeholder) after we had our call yesterday.

I received a reply back (below) that they are planning to change how public comment submissions are handled and it will be announced in the federal register.

See below.

Deborah L. Wexler, MD
Executive Director
Immunization Action Coalition
Email: deborah@immunize.org

Subscribe to *IAC Express*, our free weekly email news service
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From: Advisory Committee on Immunization Practices (CDC) [<mailto:acip@cdc.gov>]
Sent: Tuesday, November 13, 2018 2:17 PM
To: Deborah L. Wexler
Subject: Re: Request time for public comment at next February ACIP meeting

Hi Deborah,

We are working on making several updates to our public comment process. The changes will be announced in the Federal Register notice and on the ACIP website in the coming weeks. We expect to have an online registration process for public comment in advance of the meeting, so please be on the look out for the instructions on how to register.

Thanks,
Jessica

From: Deborah L. Wexler <Deborah@immunize.org>
Sent: Monday, November 12, 2018 4:38 PM
To: Advisory Committee on Immunization Practices (CDC)
Subject: Request time for public comment at next February ACIP meeting

Hi Stephanie,
I am submitting this request to make a public comment at the February ACIP meeting on day 1.
Thank you!
Deborah

Deborah L. Wexler, MD
Executive Director
Immunization Action Coalition
2550 University Avenue West
Suite 415 North
Saint Paul, MN 55114
Phone: 651-647-0043 direct
Email: deborah@immunize.org
www.immunize.org
www.vaccineinformation.org

Subscribe to *IAC Express*, our free weekly email news service
www.immunize.org/subscribe

"Didn't get polio again today! SO LIT!" *Last Week Tonight with John Oliver* (6/25/17)
https://www.youtube.com/watch?v=7VG_s2PCH_c
Thanks, vaccines!

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From: Marin, Mona (CDC/OID/NCIRD)

Sent: 8 Mar 2017 17:19:45 -0500

To:

Kelly.Moore@tn.gov;RomeroJose@uams.edu;phunte@milwaukee.gov;Pellegrini, Cynthia;Rubin, Steven (FDA/CBER);Zucker, Jane R. (CDC health.nyc.gov);noltd@ohsu.edu;Baker, Carol (CDC bcm.edu);EvenS@health.missouri.edu;DeBolt, Chas (DOH);Groom, Amy V. (IHS/HQ);Seward, Jane (CDC/OID/NCIRD) (CTR);Quinlisk, Patricia (CDC idph.iowa.gov);McLean Phd, Huong Q;MLMartinez@salud.unm.edu;Shalini Desai;Stanley Plotkin

Cc: HoganTanyaG@UAMS.edu;Patel, Manisha M. (CDC/OID/NCIRD);Routh, Janell A. (CDC/OID/NCIRD);Clemmons, Nakia (CDC/OID/NCIRD);Ayers, Tracy (CDC/OID/NCIRD);Rota, Paul (CDC/OID/NCIRD);Hickman, Carole (CDC/OID/NCIRD);Wharton, Melinda (CDC/OID/NCIRD);Zhou, Fangjun (CDC/OID/NCIRD);Wodi, Akpobome (CDC/OID/NCEZID);Lee, Adria (CDC/OID/NCIRD) (CTR);Maiuri, Allison M. (CDC/OID/NCIRD);Mason, Karen A. (CDC/OID/NCIRD);Latner, Don (CDC/OID/NCIRD);Pallansch, Mark A. (CDC/OID/NCIRD);Smith, Jean Clare (CDC/OID/NCIRD);Cohn, Amanda (CDC/OID/NCIRD);Guo, Angela (CDC/OID/NCIRD) (CTR);Ortega-Sanchez, Ismael (CDC/OID/NCIRD)

Subject: RE: ACIP mumps WG - conf call 03/09/17

Attachments: 1_Mumps WG Intro_Moore_WG call_March 2017_pic.ppt, 2_Mumps Background_Marin_WG call_March 2017_pic.pptx, 3_AR Outbreak_Routh_WG call_March 2017_pic.pptx

Dear Mumps Work Group Members,

Please find attached the materials for the meeting tomorrow and below the agenda. Please be prepared to briefly introduce yourself during the roll call (no more than 1-3 sentences).

Dial in number: (b)(6)

Passcode: (b)(6)

Agenda: Thursday, March 9, 2017, 3:30-5:00 pm ET

1. Roll call (Mona Marin)
 - 2-3 sentence introduction of each member
2. Welcome and thank you (Kelly Moore)
3. Conflict of interest policy and confidentiality (Mona)
4. Mumps ACIP WG: introduction (Kelly)
 - Terms of reference with discussion
 - Proposed WG/ACIP timeline
5. Background on mumps: disease, transmission, diagnosis, ACIP recommendations, epidemiology in the United States (Mona)/Discussion
6. 2016 Arkansas mumps outbreak (Janell Routh)/Discussion
7. Other issues or questions (Mona)

We look forward to the call tomorrow!

Sincerely,
Mona.

Mona Marin-Nelson, MD
Medical Epidemiologist
Epidemiology Branch, Division of Viral Diseases
National Center for Immunization and Respiratory Diseases, CDC
1600 Clifton Rd, MS A-34
Atlanta, GA, 30333
Tel: 404-639-8791
e-mail: mmarin@cdc.gov

Advisory Committee on Immunization Practices (ACIP): Mumps Work Group

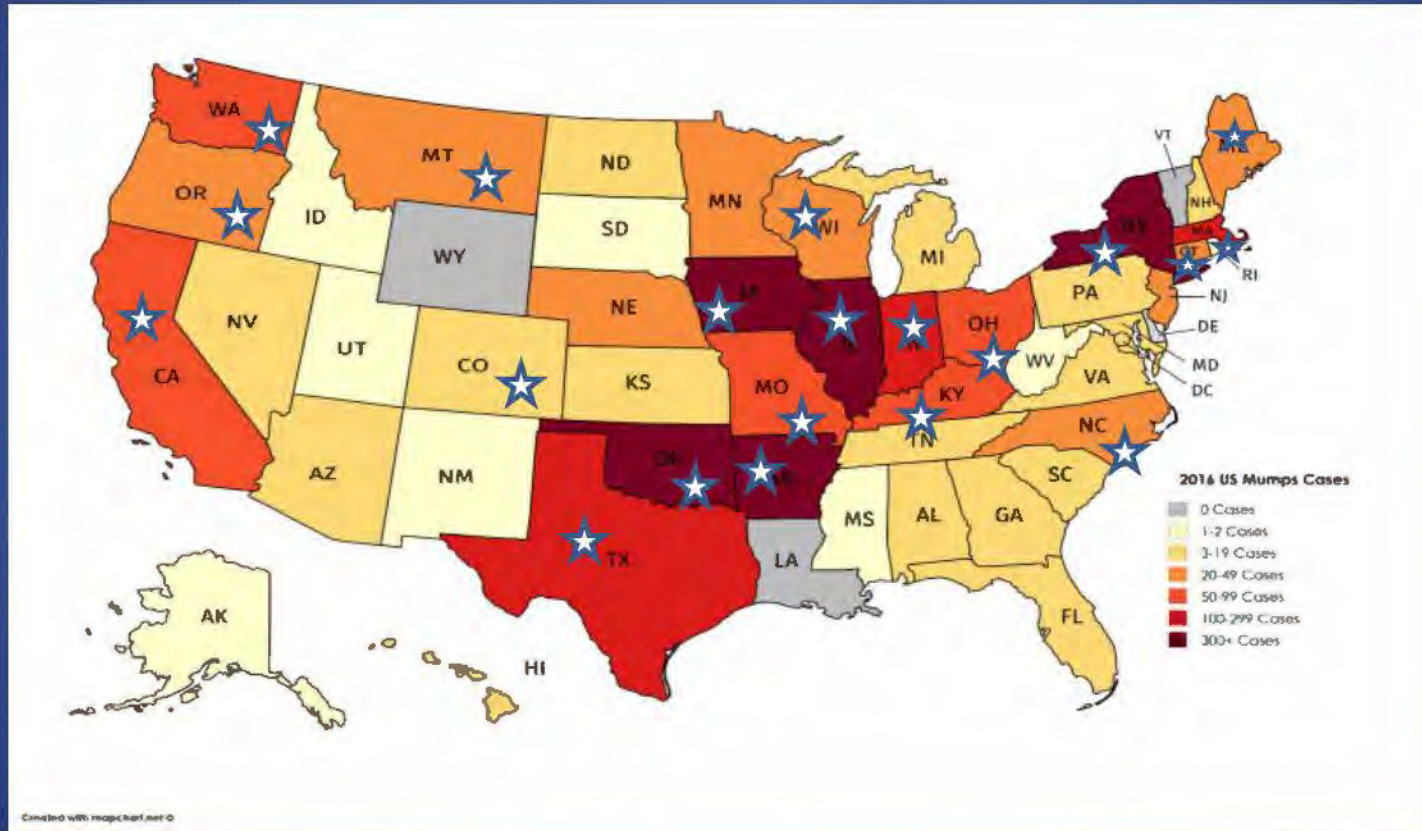
Kelly L. Moore MD, MPH
Director, Tennessee Immunization Program
Chair, Mumps ACIP Work Group

ACIP Mumps WG Conference Call
March 9, 2017

Mumps Work Group - Key Issues

- Numerous outbreaks have been reported in the United States since 2006, particularly among highly vaccinated college population
 - 2016: the second largest number of reported cases since 2006; widespread distribution of outbreaks
- Increasing interest from state/local health departments and universities to implement 3rd dose measles-mumps-rubella (MMR) vaccination campaigns to control these outbreaks
- Data on effect of a 3rd MMR dose for outbreak control are limited

Reported Mumps Cases and Outbreaks, United States, 2016 (n=5,642)



Stars indicate states that notified CDC of mumps outbreaks

Source: National Notifiable Diseases Surveillance System (cases, passive surveillance), preliminary (as of Feb 9, 2017); state reports to CDC (outbreaks) *

Mumps Work Group - Members

ACIP

Kelly Moore, Chair
Paul Hunter
Cynthia Pellegrini
Jose Romero

Consultants

Huong McLean
Patricia Quinlisk
Jane Seward
Stan Plotkin*

Ex Officio Members & Liaison Representatives

Carol Baker (IDSA)
Chas DeBolt (CSTE)
Shalini Desai (NACI)
Susan Even (ACHA)
Amy Groom (IHS)
Melissa Martinez (AAFP)
Dawn Nolt (AAP/COID)
Steven Rubin (FDA/CBER)
Jane Zucker (AIM)

CDC

Tracy Ayers
Nakia Clemmons
Carole Hickman
Mona Marin
Manisha Patel
Paul Rota
Janell Routh
Melinda Wharton
Patricia Wodi
Fangjun Zhou
Adria Lee

*expert consultant for scientific discussions

Mumps Work Group

Proposed Terms of Reference

Objective

- Evaluate and propose policy options to prevent or control mumps outbreaks in the United States

Activities

- Review epidemiology of mumps in the 2-dose vaccine era, including the international experience
- Review available evidence on duration of immunity for mumps after 2 doses of MMR and other risk factors for vaccine failure
- Review available evidence on benefit provided by a 3rd dose of MMR for mumps outbreak control
- Evaluate programmatic implications and cost of various policy options for a 3rd dose of MMR to prevent or control mumps outbreaks

Mumps Work Group - Proposed Timeline

- February 2017: ACIP meeting
 - Presented terms of reference and an overview of current mumps recommendations and epidemiology in the United States
- March-June 2017: Work Group conference calls
 - To cover: background on mumps, epidemiology in the US and international, immune response to vaccination, molecular epi, studies of 2 dose vaccine effectiveness and duration of protection/immunity, use of 3rd dose MMR for outbreak control, preliminary discussion on policy options
- June 2017: ACIP meeting
 - Present summary of studies discussed by the WG
- October 2017: Update ACIP on Work Group deliberations and policy options
- February 2018: Present Work Group recommendations to ACIP *



Current Mumps Vaccination Recommendations and Epidemiology in the United States

Mona Marin, MD

Division of Viral Diseases

National Center for Immunization and Respiratory Diseases, CDC

ACIP Mumps WG Conference Call

March 9, 2017

Outline

- Overview: mumps disease and transmission
- Mumps vaccine and vaccination recommendations in the United States
- Mumps epidemiology in the United States
- Summary epi data

Mumps

- Acute, viral illness that classically presents with parotitis (60%-70%)
 - Unilateral or bilateral
 - Lasts between 2-10 days
 - Fever
- Other presentations
 - Other salivary gland swelling (10%)
 - Non-specific respiratory symptoms/asymptomatic infection (30%)
 - Low grade fever
 - Malaise
 - Headache
 - Serious complications can occur in the absence of parotitis

Mumps Complications

Complications	Unvaccinated (%)*	Vaccine era (%)†
Orchitis‡	up to 30%	3-11
Mastitis‡	up to 30%	≤1
Oophoritis‡	5	≤1
Hearing loss	4	≤1
Pancreatitis	4	≤0.1
Aseptic meningitis	1-15	0.2-0.5
Encephalitis	0.03-0.5	0-0.3
Hospitalizations	5.5	<1-2

*McLean HQ et al. *MMWR* 2013 & Rubin SA and Plotkin SA. *Vaccines*, 6th edition, 2013;

†Data from US outbreak investigations 2006-2015; ‡Assessed in postpubertal male/female patients

Mumps Pathogenesis

- Droplet inoculation of upper respiratory mucosa → virus multiplication in epithelium of respiratory tract → spread to local lymph nodes → plasma & leukocyte (?T-cell) viremia → seeding of salivary glands (\pm gonads, other glandular tissue, e.g., pancreas...), central nervous system

Mumps Laboratory Diagnosis

- Buccal or oral swab specimen and blood specimen
- Molecular (RT-PCR) testing
 - Specimen ideally obtained within 0-3 days after parotitis onset (particularly for vaccinated patients)
 - The ability to detect mumps RNA among culture confirmed cases not associated with vax status
- Serologic testing: IgM and IgG
 - IgM: best timing for serum specimen collection is ≥ 3 days after parotitis onset
 - Most commercial assays work well in unvaccinated persons, much less sensitive in vaccinated
 - IgG: acute and convalescent serum specimens; not recommended for previously vaccinated persons
- Previously vaccinated or infected patients
 - Vaccinated patients may shed virus for a shorter period and may have low yield, IgM may be blunted or absent, 4-fold IgG rise rarely detected
 - Successful detection of virus by RT-PCR depends upon proper collection (parotid massage), timing of collection, and proper refrigeration and storage
 - In outbreaks among two-dose vaccine recipients, mumps virus RNA was detected in 30%–71% of case-patients if the samples were collected within 3 days after parotitis onset and IgM in 13%–50% of these cases¹

Mumps Transmission

- Host: humans only
- Transmission: person-to-person direct contact with infected droplets or saliva or by inhalation of infectious respiratory droplets
 - Requires close contact for spread: infectiousness is less than measles and varicella¹
- Transmission can occur from persons with non-specific respiratory symptoms and asymptomatic infection
- Incubation period: 16-18 days (range 12-25 days)
- Virus detected in saliva 7 days before through 9/11-14 days after parotitis onset
 - Highest percentage of positive isolates and highest viral loads closest to parotitis onset and decreased rapidly after
- Infectious period: 2 days before to 5 days after parotitis onset (when viral load is highest)
- Infectiousness before symptoms, transmission from persons with asymptomatic/non-specific presentation contribute to prolongation of transmission/outbreaks

¹Hope Simpson RE. *The Lancet* 1952 (secondary attack rate in households among those age <15 years: measles-76%, varicella-61%, mumps 31%)

Mumps Vaccine in the United States

- Single antigen vaccine licensed in 1967
- Currently available as combination vaccines (Merck & Co., Inc.)
 - Measles, mumps, rubella (MMR) licensed in 1971 (for all persons aged ≥ 12 months)
 - Measles, mumps, rubella, varicella (MMRV) licensed in 2005 (for persons aged 12 months through 12 years)
- Composition
 - Live, attenuated mumps strain
 - Jeryl Lynn strain, Genotype A
- Effectiveness estimates (MMR)¹
 - 1 dose: $\sim 77\%$ (49%-91%)²
 - 2 doses: $\sim 88\%$ (66%-95%)²

¹ Schaffzin JK et al. *Pediatrics* 2007, Marin M et al. *Vaccine* 2008, Cohen C et al. *Emerg Infect Dis* 2007, Deeks SL et al. *CMAJ*. 2011, Dominguez A et al. *Vaccine* 2010, Sartorius B et al. *Euro Surveill* 2005, Harling R et al. *Vaccine* 2005

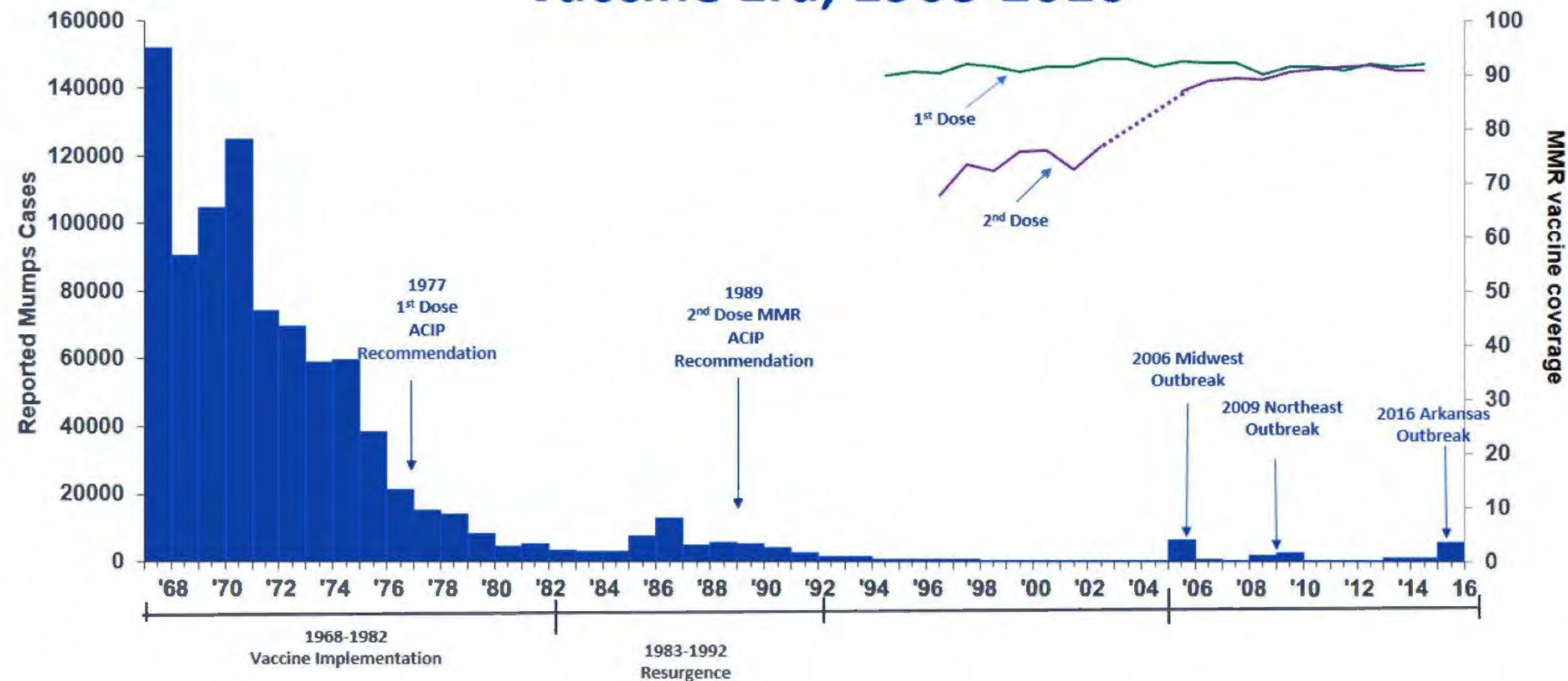
² Ranges indicate results of individual studies and not confidence intervals

Mumps Vaccination Recommendations in the United States

- 1977*: 1 dose recommended for all children at any age after 12 months¹
- 1989: a second dose of *measles* vaccine recommended for improved measles control²
 - Both doses of measles vaccine should be given as combined MMR, stating that “mumps revaccination is particularly important”
 - Effectively, this delivered a second dose of mumps vaccine
- 2006: formal recommendation for 2 doses of a live mumps virus-containing vaccine³
 - School-aged children (grades K-12)
 - Adults in high risk groups
 - Healthcare facility personnel
 - International travelers
 - Students at post-high school educational institutions
- Current schedule
 - 1st dose: 12-15 months of age
 - 2nd dose: 4-6 years of age

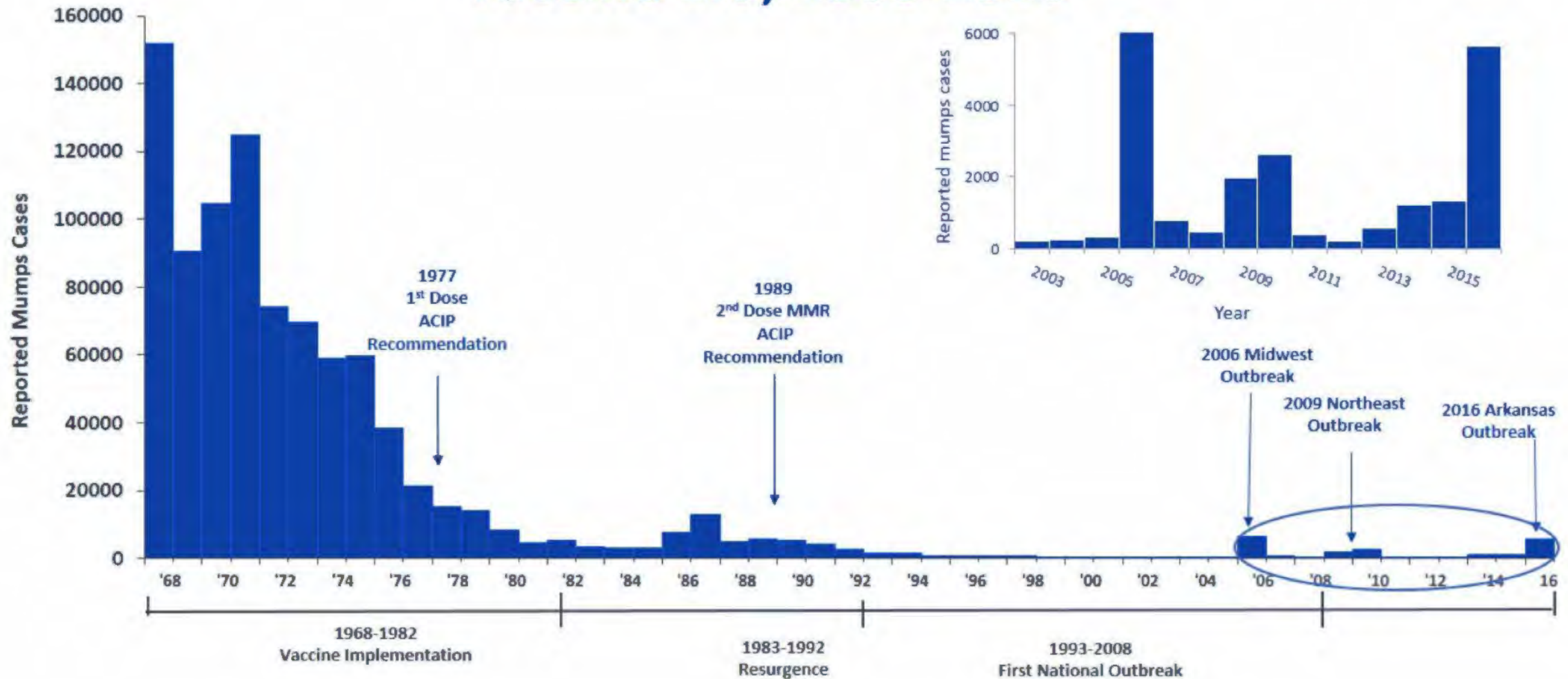
¹ACIP. *MMWR* 1977; 26:393-4; ²ACIP. *MMWR* 1989; 38(S-9):1-18; ³ACIP. *MMWR* 2006; 55(22):629-30

Reported Mumps Cases, United States, Vaccine Era, 1968-2016



Source: National Notifiable Diseases Surveillance System (cases, passive surveillance); National Immunization Survey (NIS) (1st dose coverage 19-35 year olds), National Health Interview Survey & NIS-Teen (2nd dose coverage); 2016 case data is preliminary (as of Feb 9, 2017) and subject to change

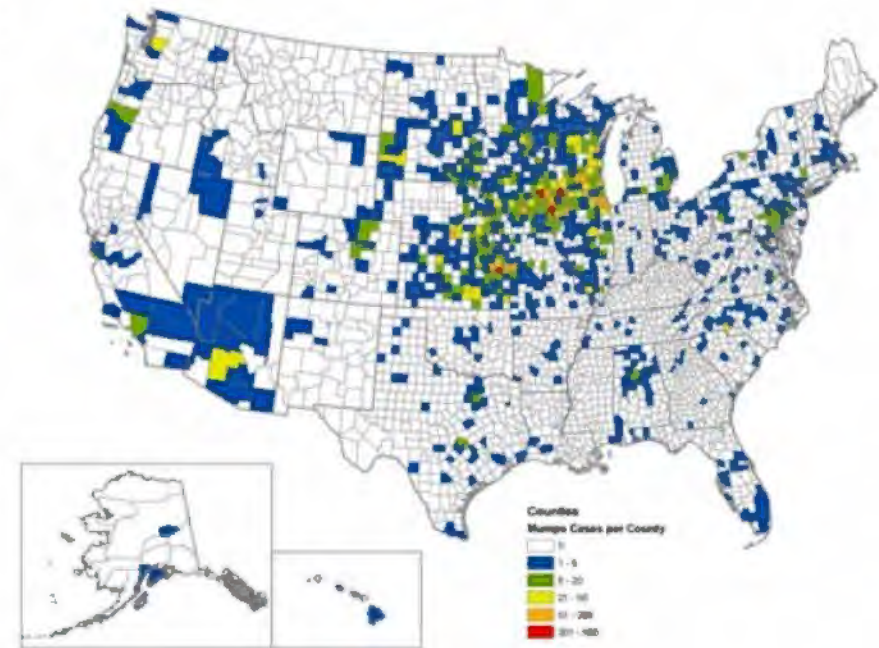
Reported Mumps Cases, United States, Vaccine Era, 1968-2016



Source: National Notifiable Diseases Surveillance System (passive surveillance); 2016 data is preliminary (as of Feb 9, 2017) and subject to change

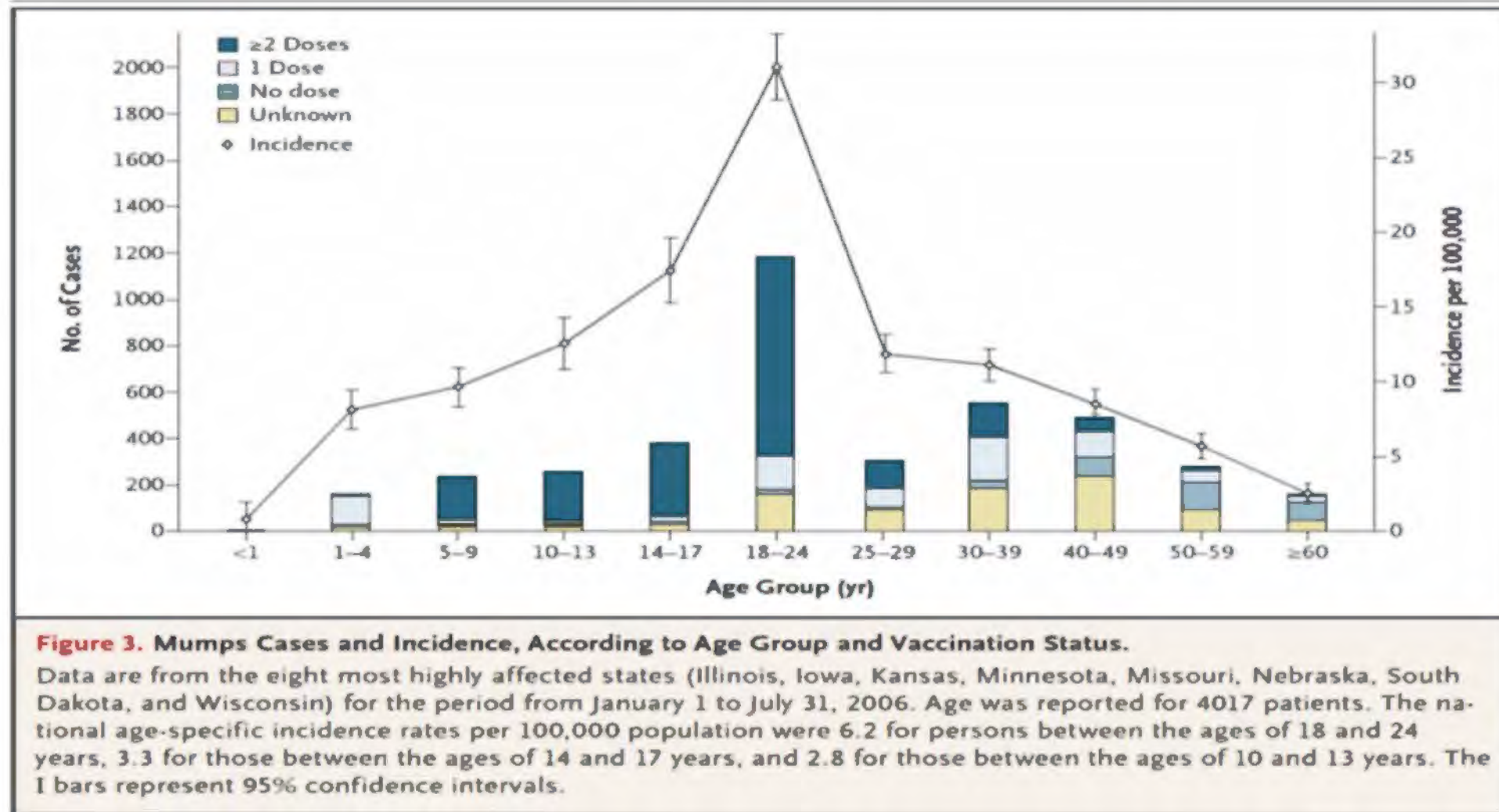
Midwest Outbreak - 2006

- 6,584 cases, geographically focused (85% in Midwest)¹
- First large outbreak attributable to 2-dose vaccine-failure
- Focal, peak incidence 18-24 years, majority (84%) 2 dose vaccinated
 - Most (83%) were college students (data from 4 states)
 - Investigations in IA and KS²
 - 2 dose MMR coverage in affected colleges: 90%-99%
 - Most students had received the second dose >10 years previously
 - Dormitory living, freshman class status, time since 2nd dose (≥ 10 years) were risk factors
 - 2 dose vaccine effectiveness: 79%-94%
 - NE: 94% IgG seroprevalence by EIA (median age 21 years)³
- Standard control measures (e.g., isolation and vaccine catch-up campaigns) for control



¹Dayan GH et al. *N Engl J Med* 2008; ²Cortese MM et al. *Clin Infect Dis* 2008; Marin M et al. *Vaccine* 2008; ³Date AA et al. *J Infect Dis* 2008

Midwest Outbreak - 2006



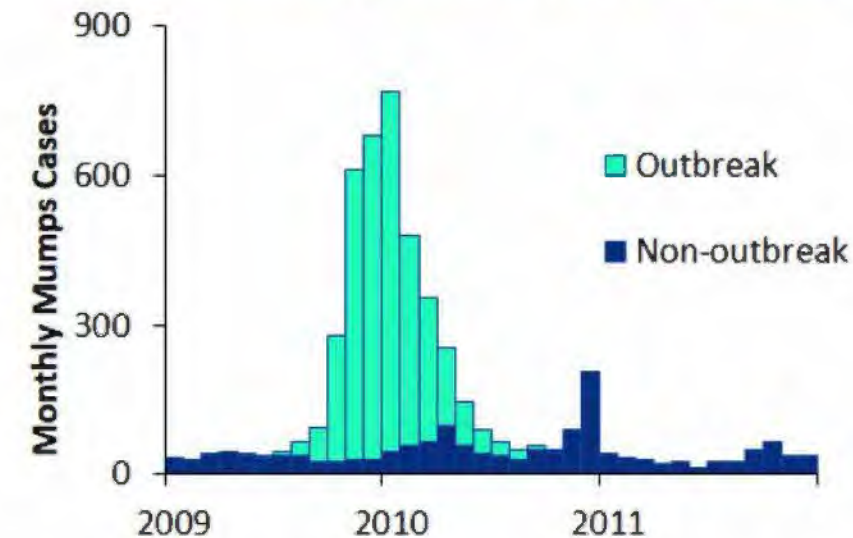
Midwest Outbreak – 2006

- What we learned
 - Resurgence was unexpected, abrupt and focal and not predicted by changing epidemiology over time
 - Colleges = high rate of transmission (contact rates, population density)
 - 2 dose vaccine effectiveness 79%-94% not sufficient to prevent all outbreaks
 - Waning of immunity from 2nd dose (likely contributing factor rather than the sole explanation)
 - Diagnostic challenges: ~30% of cases confirmed
- Concern: antigenic differences between vaccine and circulating mumps strains lead to suboptimal protection against circulating genotype (i.e., immune escape)?
 - Lab studies, VE data do not suggest this as a major factor
- Unanswered questions
 - Why did the resurgence occur in 2006? Why in the mid west?
 - What is the correlate of protection?
 - Does vaccine modify clinical presentation (spectrum of illness in vaccinated vs. unvaccinated) or disease severity?

Outbreaks in Northeast U.S. & Guam - 2009-2010

- Northeast: 3,502 cases¹
 - 97% of cases in Orthodox Jewish community
 - Adolescent (age 13-17 years) males the most affected group
 - 89% had 2 doses of MMR vaccine
 - Unique schools and large households; prolonged, intense exposures likely overcame protection afforded by the vaccine
- Guam: 505 cases²
 - Highest attack rate
 - School-aged children (aged 9-14 years), 96% two-dose vaccinated
 - Ethnic minorities with higher household densities
- Both outbreaks: highly dense living/educational conditions
- 3rd MMR vaccine dose was used for outbreak control
 - Interventions were late in the course of the outbreak and the declines observed being unrelated to the intervention could not be excluded

Reported Mumps Cases, US, 2009-2011



¹Barskey AE et al. *N Engl J Med* 2012; ²Nelson GE et al. *Pediatr Infect Dis J* 2013

Religious School (Yeshiva) in Northeast Outbreak

- Exposure may be intense
- Yeshivas are schools where Orthodox Jewish males 9th-12th grade intensively study religious texts
- School days typically last ≥ 12 h (9-15.5)
- Partner-style learning: one-on-one interaction with a partner where students sit opposite each other at tables with other pairs usually in a large study hall
 - ~7h face-to-face/day with 1-4 study partners



ACIP Statement Regarding a 3rd MMR Dose

- 2012: Data are *insufficient to recommend for or against* the use of a 3rd dose of MMR vaccine for mumps outbreak control
 - CDC issued guidance for consideration for use of a 3rd dose in specifically identified target populations along with criteria for public health departments to consider for decision making
 - Settings with >90% 2-dose vaccination coverage
 - Intense exposure settings such as schools and correctional facilities, and high attack rates (>5 per 1,000)
 - Ongoing transmission (>2 weeks)

Mumps Cases, United States, July 2010-December 2016

- Increase in the number of reported cases
 - Genotype G virus
- 2016: of 5,642 cases 2,287 (40%) were in Arkansas

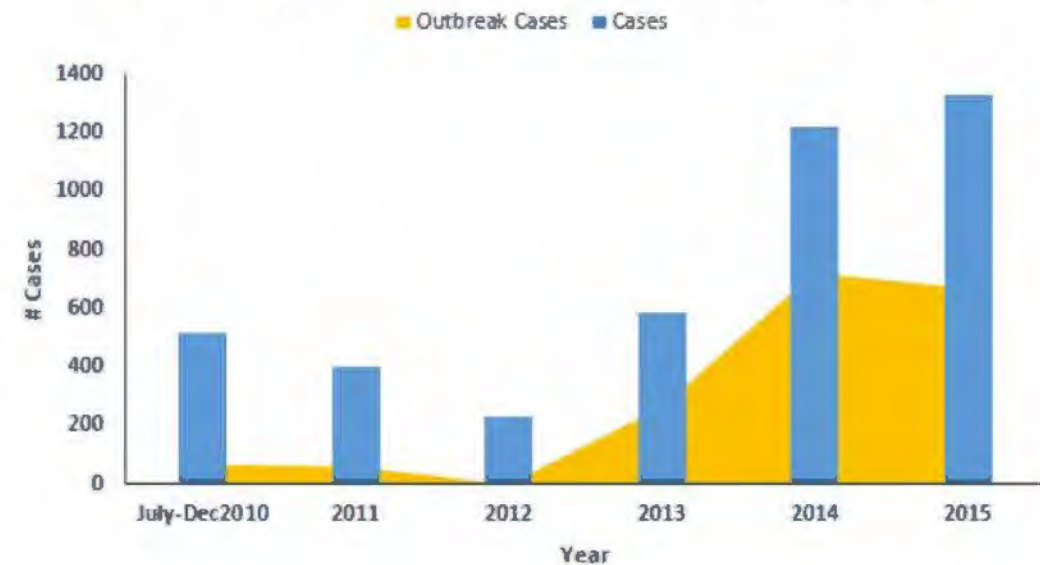
Mumps Cases and Incidence Rates by Year, 2010-2016



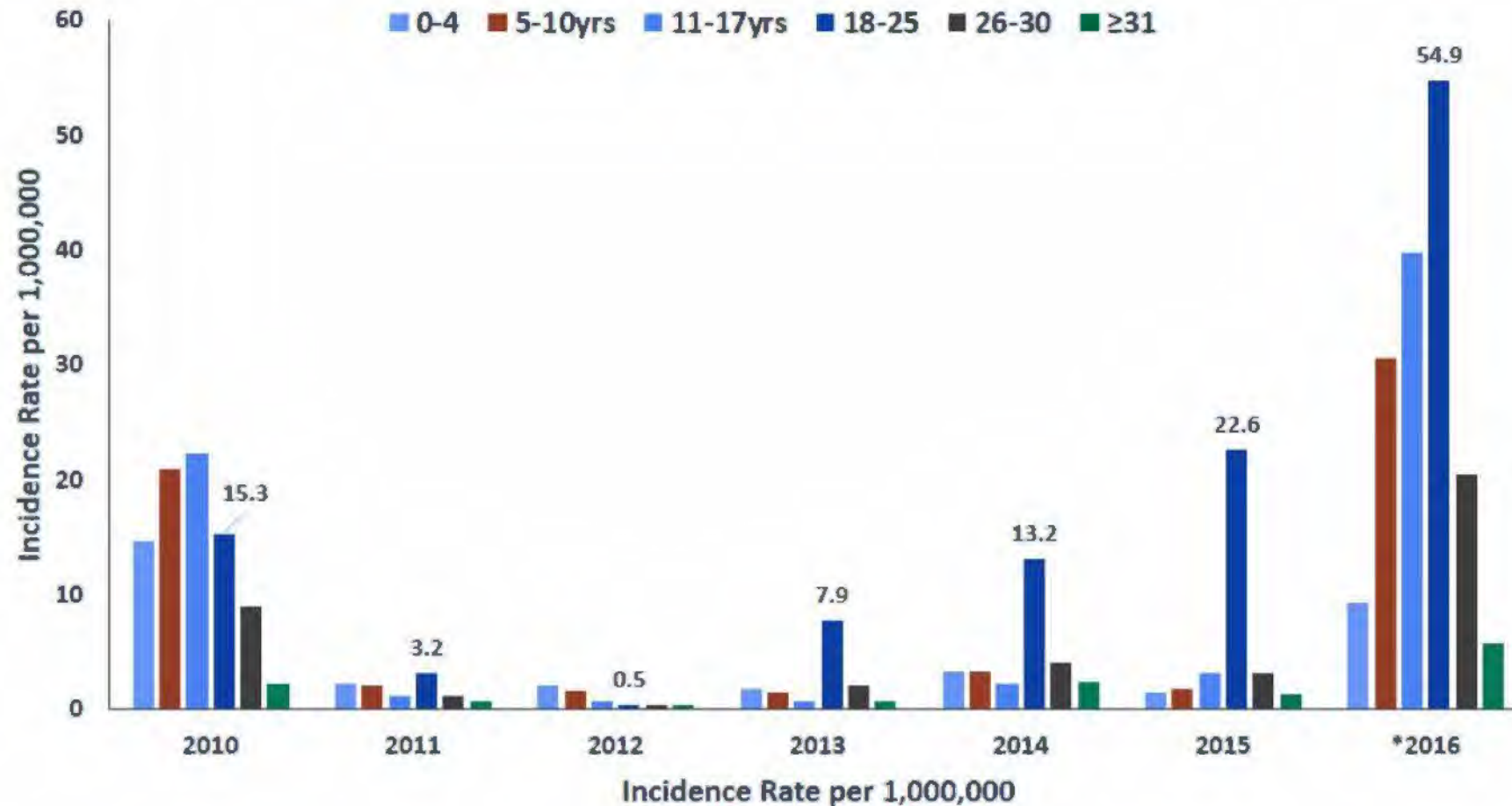
Mumps Outbreaks, United States, July 2010-December 2016

- 2010 through 2015: 23 outbreaks with ≥ 20 cases reported in 18 states
 - Median: 40 cases, range 20 to 485
 - 10 outbreaks (43%) consisted of ≥ 50 cases
 - 1,779 cases (41% of all reported cases)
 - 22 (96%) outbreaks occurred in close contact settings (18 [78%] in universities)
 - Highest incidence in the 18-25 years age group
 - Median age 19-23 years in 16 outbreaks
 - In half of university outbreaks $>85\%$ of case-patients had documented 2 MMR doses
 - Spread outside affected setting was minimal (3)
- 2016: >40 outbreaks (3+ cases): 19 in university settings, at least 5 in close-knit communities

Reported Mumps Cases and Outbreaks, U.S., July 2010-December 2015 (n=4,289)



Reported U.S. Mumps Incidence Rate by Year and Age Group, 2010-2016*



Source: National Notifiable Diseases Surveillance System (cases, passive surveillance); 2016 data is preliminary (Feb 9, 2017) and subject to change

Factors that May Contribute to the Increasing Number of Mumps Outbreaks (1)

- Vaccine effectiveness
 - 1 dose: ~77% (49%-91%)
 - 2 doses: ~88% (66%-95%)
- Waning of vaccine-induced immunity
 - Serologic studies suggest waning: seropositivity and neutralizing antibody titers decline over time¹⁻⁵,
 - No established correlates of protection, implications of declining titer uncertain³
 - Cellular immunity declines less than seropositivity over time (if at all)⁶
 - Epidemiologic studies suggest waning: decreased vaccine effectiveness⁷ and increased odds of disease with time since vaccination^{8,9}, evidence still limited
 - Waning of immunity does not explain the general geographical focal nature and that the oldest vaccinated cohorts not always most affected in the outbreak setting

¹Davidkin I et al. *J Infect Dis* 2008; ²LeBaron CW et al. *J Infect Dis* 2009; ³Rubin SA et al. *J Infect Dis* 2008; ⁴Date AA et al. *J Infect Dis* 2008;

⁵Kontio, *J Infect Dis* 2012; ⁶Jokinen S et al. *J Infect Dis* 2007; ⁷Cohen C et al. *Emerg Infect Dis* 2007; ⁸Cortese MM et al. *Clin Infect Dis* 2008;

⁹Vygen S et al. *Euro Surveill* 2016

Factors that May Contribute to the Increasing Number of Mumps Outbreaks (2)

- Force of infection
 - Outbreaks in settings with high population density and contact rates that facilitate transmission (e.g., college campuses, close knit communities)
- Vaccine-induced immunity less effective against other strains?
 - No evidence to date, sera from vaccinated children neutralized diverse mumps strains^{1,2}
 - Antigenic differences among mumps virus strains detected¹⁻³
 - Lower antibody levels against non-vaccine strains
 - Might become more important with increasing time since vaccination
- ?Mumps virus characteristics
 - Lower antibody levels after natural infection and vaccination (compared with measles and rubella)
 - Reinfection^{4,5}
 - Qualitative aspects: low avidity antibodies⁶, lower frequency of mumps-specific memory B cells⁷ -
→ suggest that mumps infection may not generate robust B-cell memory

¹Rubin SA et al. *J Infect Dis* 2008; ²Rubin SA et al. *J Virol* 2012; ³Orvell C et al. *J Gen Virol* 2002; ⁴Gut JP et al. *J Med Virol* 1995;

⁵Yoshida N et al. *J Med Virol* 2008; ⁶Kontio M et al. *J Infect Dis* 2012; ⁷Latner DR et al. *Clin Vaccine Immunol* 2011

Summary

- Use of the mumps vaccine reduced disease levels ~99% versus pre-vaccine era in the United States
- Since 2006, mumps outbreaks have occurred in highly 2-dose vaccinated populations
- Current 2-dose schedule is sufficient for mumps control in the general population, but outbreaks can occur in well vaccinated populations in specific settings
- Intense exposure settings and waning immunity appear to be risk factors for secondary vaccine failure
- The benefit of a 3rd MMR dose still needs to be assessed

Acknowledgements

Manisha Patel

Nakia Clemmons

Janell Routh

Paul Rota

Carole Hickman

Adria Lee

Rebecca McNall

Amy Parker Fiebelkorn

Albert Barskey

Susan Redd

Mark Pallansch

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1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Mumps Case Definition

- Suspect
 - Parotitis, acute salivary gland swelling, orchitis, or oophoritis unexplained by another more likely diagnosis OR
 - A positive lab result with no mumps clinical symptoms
- Probable
 - Acute parotitis or other salivary gland swelling lasting ≥ 2 days, or orchitis, or oophoritis unexplained by another more likely diagnosis, in:
 - A person with a positive test for serum IgM, OR
 - A person with an epi link to another probable or confirmed case or link to a group/community defined by public health during an outbreak of mumps
- Confirmed
 - A positive mumps lab confirmation for mumps virus with RT-PCR or culture in a patient with an acute illness characterized by any of the following:
 - Acute parotitis or other salivary gland swelling lasting ≥ 2 days, aseptic meningitis, encephalitis, hearing loss, orchitis, oophoritis, mastitis, pancreatitis

U.S. Mumps Cases, 2016

- Age range: <1 yr to 88 yrs old
 - Median age: 22 yrs
- Gender
 - Male = 51%
 - Female = 48%
- Race/Ethnicity
 - White = 53%
 - Asian = 41%
 - African American = 4%
 - Hispanic = 12%
- 79% (4,454) reported vaccination status
 - 85% (3,792) vaccinated
 - 69% (2,628) 2 or more doses
- Case Status
 - 54% confirmed
 - 46% probable
- >40 reported outbreaks
 - Majority in university settings
 - At least 5 in close-knit community settings

Mumps Outbreak among the Marshallese

Northwest Arkansas

Janell Routh, MD MHS

ACIP Workgroup

March 9, 2017

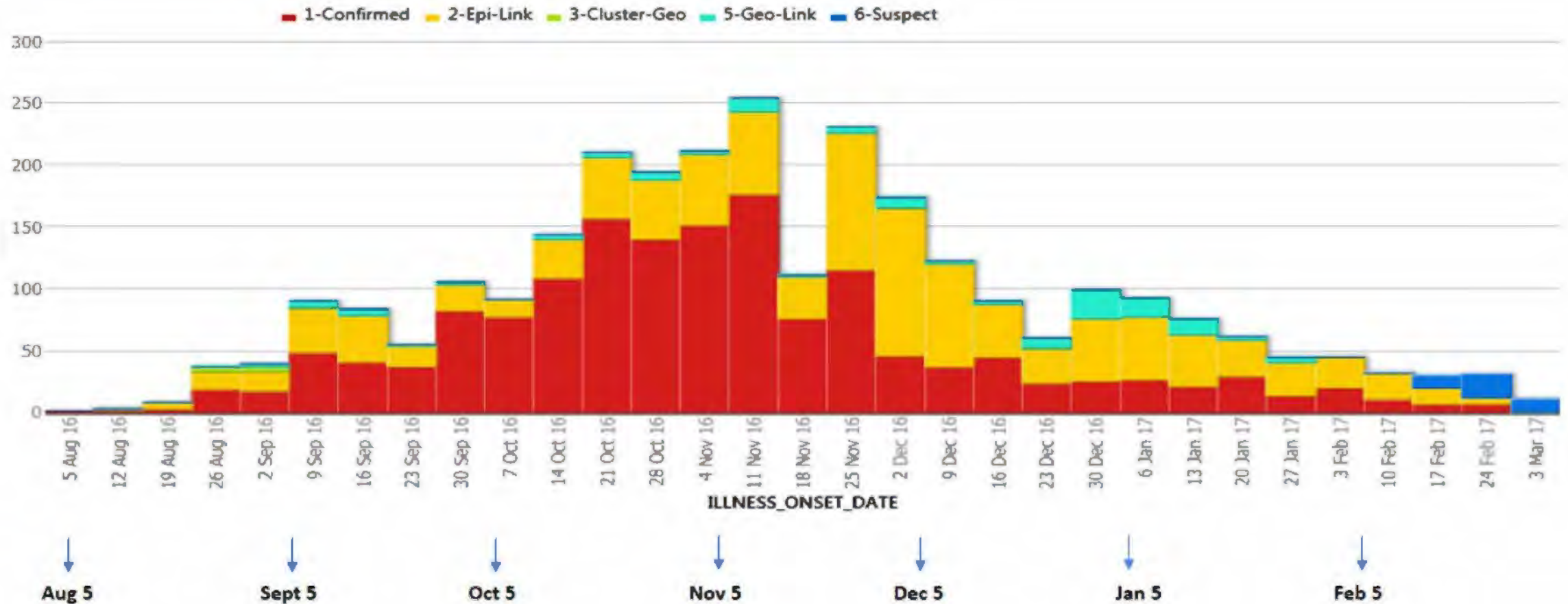
Background

- On August 5, 2016, a case of mumps was identified in the Marshallese community in Springdale, AR., the largest settlement in the U.S. (~6,000-12,000 persons)
- Republic of the Marshall Islands (RMI) citizens migrate to Springdale for jobs in the manufacturing plants (poultry, pet food and other large corporations)
- Close-knit community that depends on each other for social interactions
 - In churches, mens/womens groups, bible study
 - In pool-halls and Marshallese specific stores
 - For birthday parties, funerals and weddings
- Live in crowded conditions (12-25 Marshallese per home)
 - Living conditions dictated by custom, not for economic reasons
 - Each home has between 1-3 men who provide economic support
 - Children often sleep in different homes and change their names to match the adults in each home

Current Epidemiology



Number of cases by illness onset date and case status (as of 3/7/17, n=2,832)*



*Data provided by the Arkansas Department of Health

Average age of mumps cases increases as outbreak continues

November:

67.5% of all cases are among school-aged children (age 5-17)

January:

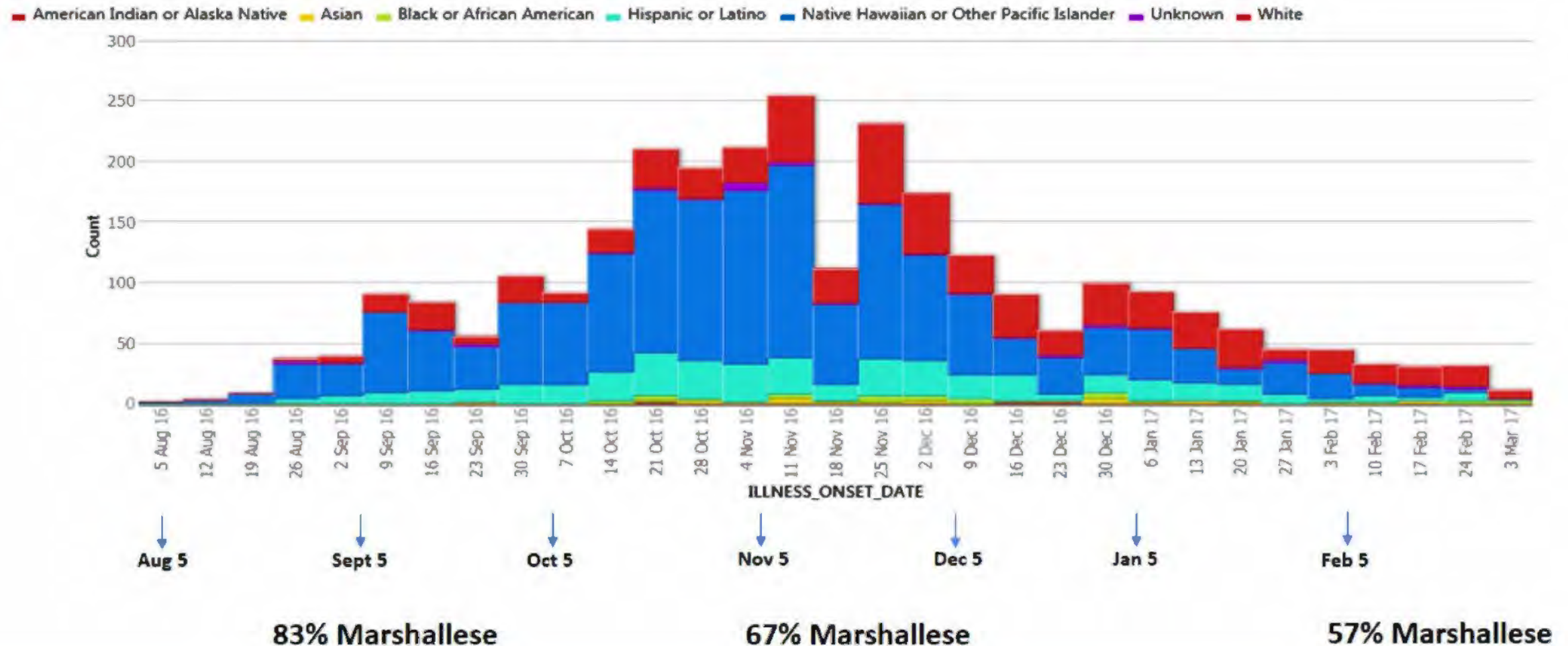
59% of all cases are among school-aged children (age 5-17)

March:

57% of all cases are among school-aged children (age 5-17)

Case Status by Age Group (as of 3/7/17)				
	Lab Confirmed	Probable	Suspect	TOTAL
Age 0-<1	1	7	2	10
Age 1-4	52	44	8	104
Age 5-10	365	335	13	713
Age 11-17	584	362	18	964
Age 18-30	355	240	9	604
Age 31-40	160	157	3	320
Age 41-50	71	75	3	149
Age 51-60	24	23	0	47
Age 61-70	2	15	1	18
Age 71-80	1	0	0	1
Age 81+	0	1	0	1
Missing	2	2	0	4
TOTAL	1617	1261	57	2935

Number of cases by illness onset date and race/ethnicity (as of 3/17/17, n=2,832)



89% of mumps cases with known vaccine status have two or more doses of MMR

Age Group	0-4	5-17	18+	Unknown	Total
1 MMR	38	48	139	0	216
2+ MMR	22	1523	287	0	1833
Unknown MMR	53	106	723	4	886
Total	113	1677	1149	4	2935

Outbreak Response

Challenges to outbreak response

- Majority of cases are in the Marshallese, an ethnic minority within Springdale
 - Difficult to gain access to this close-knit community for prevention efforts
 - Do not want to draw attention to the community in a negative way
- Marshallese believe that illness is a sign of weakness, and prefer not to be seen going to a doctor or clinic unless very necessary
- Community not opposed to vaccination, but also do not believe mumps is medically concerning
- Difficult to adhere to other forms of prevention, like isolation, when there is no paid sick leave and households depend on daily income
- Cultural beliefs require Marshallese to attend social functions-even when not feeling well. To do otherwise would be considered rude.

Places to get an outbreak dose of MMR

# doses	Number of MMR doses given at all mumps-related vaccine clinics as of 3/7/17	
3119	Schools	41%
268	Churches	3%
2,601	Worksites	34%
459	ADH Clinics	6%
1,122	WCHD Mass MMR Clinics	15%
85	Residence (Apts/Homes)	1%
18	Grocery store	0%
7,672	TOTAL	

Visit from RMI Ministry of Health

Outcomes

- Presented epidemiology of mumps outbreak to Marshallese community
- Held two community meetings with church pastors/wives
- Formed partnerships between the Marshallese community and ADH
 - Started a Marshallese Mumps Task Force composed of 8 influential pastors and their wives
- Promoted 3rd dose vaccination clinics
- Drafted and translated mumps education materials for use in community (churches and radio)



Current Situation

- Mumps cases are reduced but the Arkansas Department of Health is still reporting 25-40 suspected cases per week
- Limited spread beyond Marshallese community in Arkansas
- Seeded mumps outbreaks in at least 7 other states among Marshallese communities

Thank you!

Acknowledgments

ADH:

Dirk Haselow

Virgie Fields

Haytham Safi

Karen Fowler

CDC:

Angela Guo

Tracy Ayers

Mona Marin

Manisha Patel

RMI:

Mailyynn Konelios-Lang

Daisy Pedro

Herroko Neamon

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

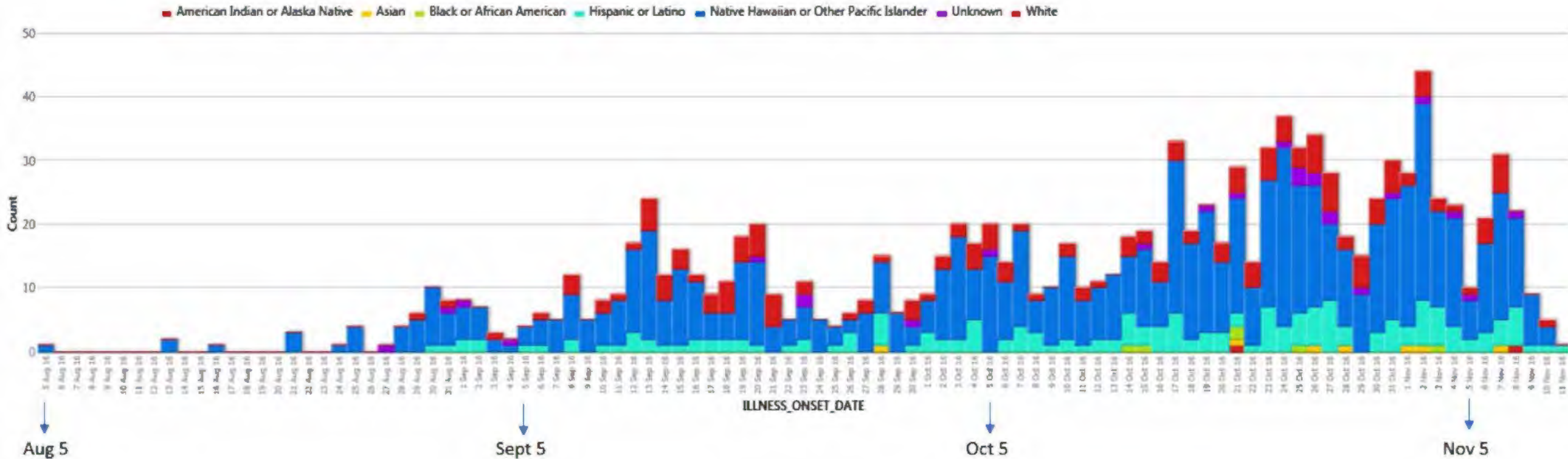
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All cases under investigation as of 3/7/17	Obs	Mean (sd)	Range	Median	75%
American Indian or Alaska Native	4	21 (16)	9-44	15.5	31
Asian	28	20 (15)	4-59	12	31
Black or African American	47	21 (12)	6-61	17	29
Hispanic or Latino	443	16 (12)	0-66	12	17
Native Hawaiian or Other Pacific Islander	1669	18 (11)	0-63	15	24
Unknown	53	25 (14)	5-65	22	37
White	687	22 (15)	0-82	16	33

Number of cases by illness onset date and race/ethnicity (as of 11/14/16, n=1,164)



Outcomes of RMI visit and next steps

- Formed partnerships between the Marshallese community and ADH
 - Between ACOM (Arkansas Coalition of the Marshallese) and ADH
 - Laid foundations for collaboration with UAMS (University of Arkansas Medical School)
 - Identified contacts within the Marshallese community for rapid access and information dissemination
 - Groundwork established for continued partnership between ADH and RMI Ministry of Health
 - Started a Marshallese Mumps Task Force composed of 8 influential pastors and their wives
- Promoted 3rd dose vaccination clinics
 - Churches are willing to host clinics during the week or on Sundays
 - Offered suggestions of stores or birthday celebrations as options for clinics
 - Large clinic to be held December 3, 2016 at the Jones Center, a community center where many parties are held
- Drafted and translated mumps education materials for use in community
 - Flyers circulated at all 30 Marshallese churches
 - Radio spots on the Marshallese radio station run hourly with messages to “stay home if sick” and “get vaccinated at one of the clinics to protect your community”

From: Lee, Adria (CDC/OID/NCIRD) (CTR)
Sent: 10 May 2017 15:32:34 -0400
To: Marin, Mona
(CDC/OID/NCIRD); Kelly.Moore@tn.gov; RomeroJose@uams.edu; phunte@milwaukee.gov; Pellegrini, Cynthia; Rubin, Steven (FDA/CBER); Zucker, Jane R. (CDC health.nyc.gov); noltd@ohsu.edu; Baker, Carol (CDC bcm.edu); EvenS@health.missouri.edu; DeBolt, Chas (DOH); Groom, Amy V. (IHS/HQ); Seward, Jane (CDC/OID/NCIRD) (CTR); Quinlisk, Patricia (CDC idph.iowa.gov); McLean Phd, Huong Q; MLMartinez@salud.unm.edu; Shalini Desai; Stanley Plotkin
Cc: HoganTanyaG@UAMS.edu; Patel, Manisha M. (CDC/OID/NCIRD); Routh, Janell A. (CDC/OID/NCIRD); Clemmons, Nakia (CDC/OID/NCIRD); Ayers, Tracy (CDC/OID/NCIRD); Rota, Paul (CDC/OID/NCIRD); Hickman, Carole (CDC/OID/NCIRD); Wharton, Melinda (CDC/OID/NCIRD); Zhou, Fangjun (CDC/OID/NCIRD); Wodi, Akpobome (CDC/OID/NCEZID); Maiuri, Allison M. (CDC/OID/NCIRD); Mason, Karen A. (CDC/OID/NCIRD); Latner, Don (CDC/OID/NCIRD); Pallansch, Mark A. (CDC/OID/NCIRD); Cohn, Amanda (CDC/OID/NCIRD); Ortega-Sanchez, Ismael (CDC/OID/NCIRD); Marlow, Mariel Asbury (CDC/OID/NCEZID); Cardemil, Cristina (CDC/OID/NCIRD)
Subject: RE: ACIP mumps WG - conf call 05/11/17
Attachments: 2_3-dose epi studies_Marin_WG call_May 11 2017.pptx, 3_MMR3 lab studies_McLean_Latner_WG call_May 11 2017.pptx, Barskey_Mumps resurgencies in the US_Vaccine 2009.pdf, Fiebelkorn_Mumps antibody response to a 3rd dose of MMR_OFID2014.pdf, Minutes April 27, 2017.docx

Dear Mumps Work Group Members,

Please find attached two of the presentations for the meeting tomorrow and the minutes from the last call. As previously indicated, the first presentation will be via webconference. We are also attaching two papers: Barskey et al that was referenced several times during last call and Parker Fiebelkorn et al that reports findings of the main 3rd dose lab study to date. Agenda for tomorrow is below.

Please also note the change in call in number for tomorrow (an updated calendar invite will follow):

CDC Participants: <https://webconf.cdc.gov/xd5/13M6Q0VM>

External Participants: <https://webconf.cdc.gov/xd5/13M6Q0VM?sl=1>

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Agenda: Thursday, May 11, 2017, 3:30 pm ET

1. Roll call and Administrative issues (Mona Marin/Kelly Moore)
2. Effectiveness of the 3rd dose of MMR vaccine in a mumps outbreak in a highly vaccinated university population, Iowa, 2015-2016 (Cristina Cardemil)

3. Published studies of the 3rd dose MMR for mumps outbreak control (Mona)
4. Laboratory studies of the 3rd dose MMR (Huong McLean/ Don Latner)
5. Other issues or questions (Mona/Kelly)

Next call: Thursday, May 25 @ 3:30 pm EST

- Topics
 - Safety of 3rd MMR dose
 - New York City experience with mumps outbreaks

Sincerely,

Adria Lee, MSPH
IHRC, Inc. Contractor
Epidemiologist
MMRHP/DVD/NCIRD
Centers for Disease Control and Prevention
Phone: 404-639-6247
Fax: 404-471-8070

From: Marin, Mona (CDC/OID/NCIRD)

Sent: Tuesday, May 09, 2017 2:08 PM

To: Kelly.Moore@tn.gov; RomeroJose@uams.edu; phunte@milwaukee.gov; Pellegrini, Cynthia <CPellegrini@marchofdimes.org>; Rubin, Steven (FDA/CBER) <Steven.Rubin@fda.hhs.gov>; Zucker, Jane R. (CDC health.nyc.gov) <JZucker@Health.nyc.gov>; noltd@ohsu.edu; Baker, Carol (CDC bcm.edu) <cbaker@bcm.edu>; EvenS@health.missouri.edu; DeBolt, Chas (DOH) <Chas.DeBolt@DOH.WA.GOV>; Groom, Amy V. (IHS/HQ) <Amy.Groom@ihs.gov>; Seward, Jane (CDC/OID/NCIRD) (CTR) <jfs2@cdc.gov>; Quinlisk, Patricia (CDC idph.iowa.gov) <patricia.quinlisk@idph.iowa.gov>; McLean Phd, Huong Q <mclean.huong@marshfieldclinic.org>; MLMartinez@salud.unm.edu; Shalini Desai <shalini.desai@phac-aspc.gc.ca>; Stanley Plotkin <stanley.plotkin@vaxconsult.com>

Cc: HoganTanyaG@UAMS.edu; Patel, Manisha M. (CDC/OID/NCIRD) <dnv4@cdc.gov>; Routh, Janell A. (CDC/OID/NCIRD) <iyp1@cdc.gov>; Clemmons, Nakia (CDC/OID/NCIRD) <xjb4@cdc.gov>; Ayers, Tracy (CDC/OID/NCIRD) <eyk6@cdc.gov>; Rota, Paul (CDC/OID/NCIRD) <par1@cdc.gov>; Hickman, Carole (CDC/OID/NCIRD) <cjh3@cdc.gov>; Wharton, Melinda (CDC/OID/NCIRD) <mew2@cdc.gov>; Zhou, Fangjun (CDC/OID/NCIRD) <faz1@cdc.gov>; Wodi, Akpobome (CDC/OID/NCEZID) <lgz1@cdc.gov>; Lee, Adria (CDC/OID/NCIRD) (CTR) <xda5@cdc.gov>; Maiuri, Allison M. (CDC/OID/NCIRD) <fpg3@cdc.gov>; Mason, Karen A. (CDC/OID/NCIRD) <bbx3@cdc.gov>; Latner, Don (CDC/OID/NCIRD) <grq2@cdc.gov>; Pallansch, Mark A. (CDC/OID/NCIRD) <map1@cdc.gov>; Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>; Ortega-Sanchez, Ismael (CDC/OID/NCIRD) <iao8@cdc.gov>; Marlow, Mariel Asbury (CDC/OID/NCEZID) <klt8@cdc.gov>; Cardemil, Cristina (CDC/OID/NCIRD) <iyk8@cdc.gov>

Subject: ACIP mumps WG - conf call 05/11/17

Dear Mumps Work Group Members,

I wanted to give you a heads-up that on Thursday the first presentation will be delivered via webconference and we will not distribute the slides. Therefore, to see the slides you'll need to be at a

computer at the time of the presentation. If you cannot be at the computer during the presentation, you will still be able to hear the presentation but will not be able to follow along with the slides. For the other 2 presentations we will send the slides ahead of time.

We will send tomorrow the call in info and the materials.

Regards,
Mona.



3rd Dose MMR for Mumps Outbreak Control – Published Studies

Mona Marin, MD Division of Viral Diseases, CDC

ACIP Mumps WG Conference Call May 11, 2017

Literature Reports of 3rd/Additional Dose of MMR for Mumps Outbreak Control

- Orange County, NY: schools, 2009-2010Guam: schools, 2009-2010CA: college, 2011IL: college, 2015-2016UK: school, 2013

Orange County, NY – Outbreak and 3rd MMR Dose Study

- 790 (23%) of 3,502 mumps cases during the 2009-2010 Northeast outbreak72% of cases among adolescents age 11-17 years; two dose MMR coverage - 92% → school based 3rd dose vaccination for 6th-12th–grade studentsCases concentrated in one village; 3 of 4 schools eligible to participate (ongoing transmission in the 2 weeks before intervention and high 2-dose coverage); 94% 2-dose MMR coverageMumps case ascertainment*: surveys – baseline (before intervention) and 2 months after intervention; Orange County health department records 2-dose vaccination: documented from school vaccination records or student's physician 1,755 (81%) 2-dose vaccinees received a 3rd doseAge-specific attack rates compared before and after vaccination among students in the participating schools and among residents of the village (population: 20,363, median age 10.6 years)

*2008 Council of State and Territorial Epidemiologists (CSTE) definition: acute onset of unilateral or bilateral tender, self-limited swelling of the parotid and or other salivary gland(s), lasting at least 2 days, and without other apparent cause Ogbuanu IU et al. Pediatrics 2012

Orange County, NY - 3rd MMR Dose Study

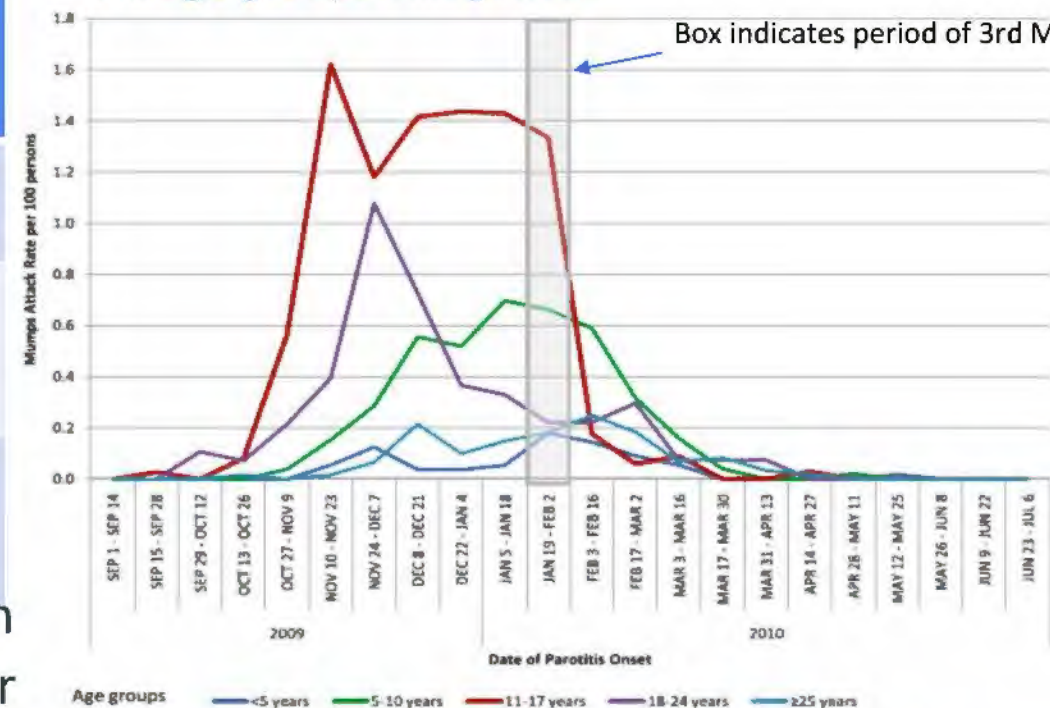
Schools	21 days Prevax	1st 21 days Postvax-P1	2 nd 21 days Postvax-P2	Relative RiskP2 vs. P1	Relative Risk3- vs. 2- doses
All 6-12 gr students	113 (4.93)	35 (1.55)	3 (0.13)	0.06; p<.001	
2 MMR(n=4 20)		7 (1.67)	2 (0.48)	0.3 (0.06- 1.40);P=.18	
3 MMR(n=1 751)		28 (1.60)	1 (0.06)	0.04 (0.005- 0.27); p<.001	0.12 (0.01- 1.32); p=.097

Conclusions 81% of eligible students received a 3rd MMR

dose After intervention, reduction in cases in all age groups in community Decline highest and more rapid among 11-17 year olds (targeted by 3rd dose vaccination) 2nd highest decline in 5-10 year-olds, the other age group that attended the same schools as the vaccinated children In schools lower attack rates after MMR3 than MMR2 but not statistically significant The intervention occurred immediately after the peak of the outbreak Could not exclude the possibility that the decline in

Orbach et al Pediatrics 2012

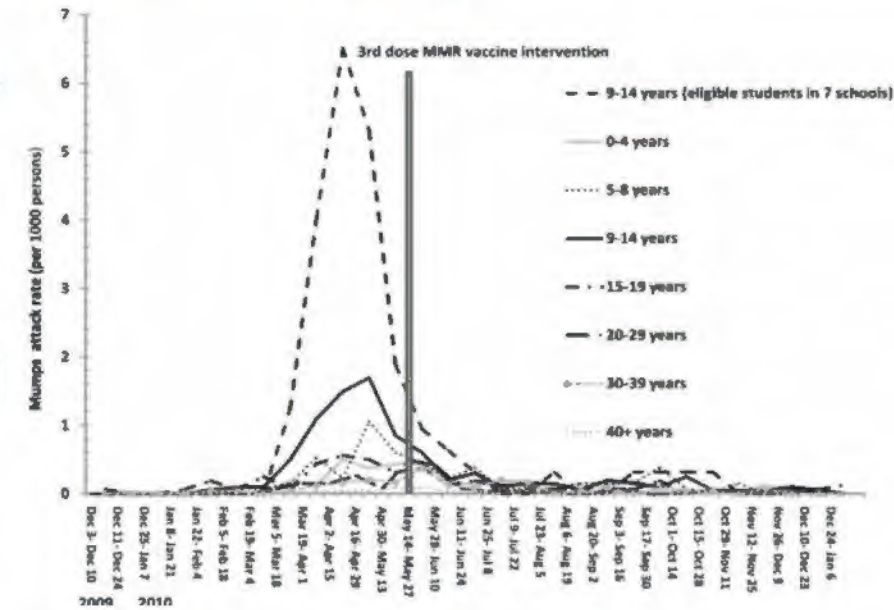
All age groups villagewide



Attack rates fell among all age groups (P2 vs. prevax) All: 76% <5: 27%; 5-10: 73%*; 11-17: 96%*; 18-24: 53%; ≥25: 11% (*significant decline)

Guam – Outbreak and 3rd MMR Dose Study

- Dec 1, 2009-Dec 31, 2010: 505 cases
Highest attack rate: 9-14 year olds; two dose MMR coverage - 96%; 7 schools had attack rate >5% → 3rd dose (highest attack rate schools in the most affected group (grades 4-8)) Mumps case ascertainment*: surveys – baseline (before intervention) and ~4 months after intervention; Guam public health records



- 2-dose vaccination: documented from immunization cards, health department or school records, healthcare providers 1,068 (33%) of 2-dose vaccinees received a 3rd dose
Attack rates compared between 2-dose and 3 dose vaccinees aged 9-14 years >1 incubation period after intervention

*2008 CSTE definition Nelson GE et al. Pediatr Infect Dis J 2013

Guam - 3rd MMR Dose Study

	>1 Incubation Period After 3rd Dose Cases (Attack Rate)	Attack Rate 3- vs. 2- dose
≤2 MMR* (n=2, 171)	5(2.3)	
3 MMR (n=1, 068) * 2-dose MMR coverage 99%-100%	1(0.9)	0.4 (0.05-3.5); p=.67

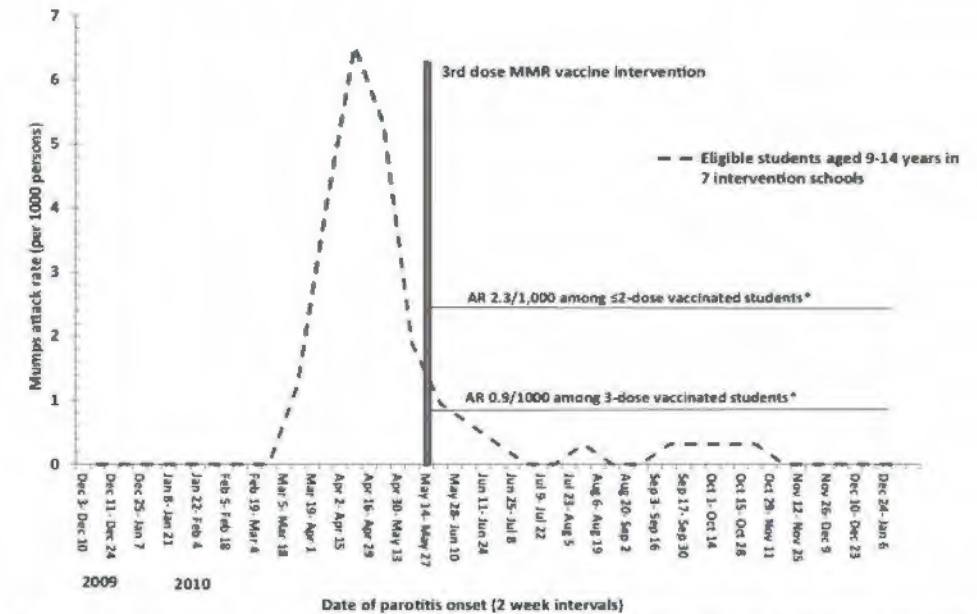


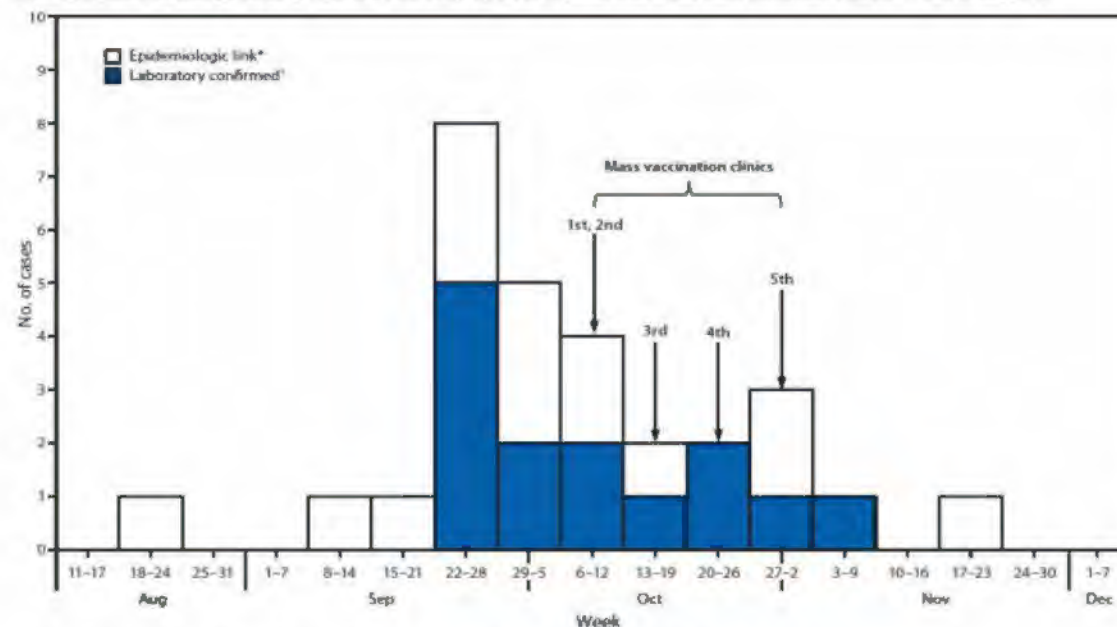
FIGURE 4. Comparison of mumps attack rates (cases/1000) postintervention among eligible students who received the third MMR vaccine dose compared with those who did not receive the third dose, Guam, December 1, 2009, to December 31, 2010. *More than 1 incubation period postintervention.

- Conclusions 33% of eligible students received a 3rd dose. Attack rate in 3 dose vaccinees lower than in students with ≤2 doses but statistical significance not established perhaps due to the small number of cases postintervention. The possibility of the declines being unrelated to the intervention could not be excluded.

California Outbreak, 2011

- University: 36,000 students enrolled29 cases; 22 (76%) among students with 2 doses of MMRAn additional dose of MMR vaccine recommended irrespective of previous MMR vaccination status5 vaccination clinics over 4 weeks, 3,631 persons received a dose of MMR

FIGURE. Number of mumps cases (n = 29) at a university, by week of illness onset, and mass vaccination clinics — California, 2011



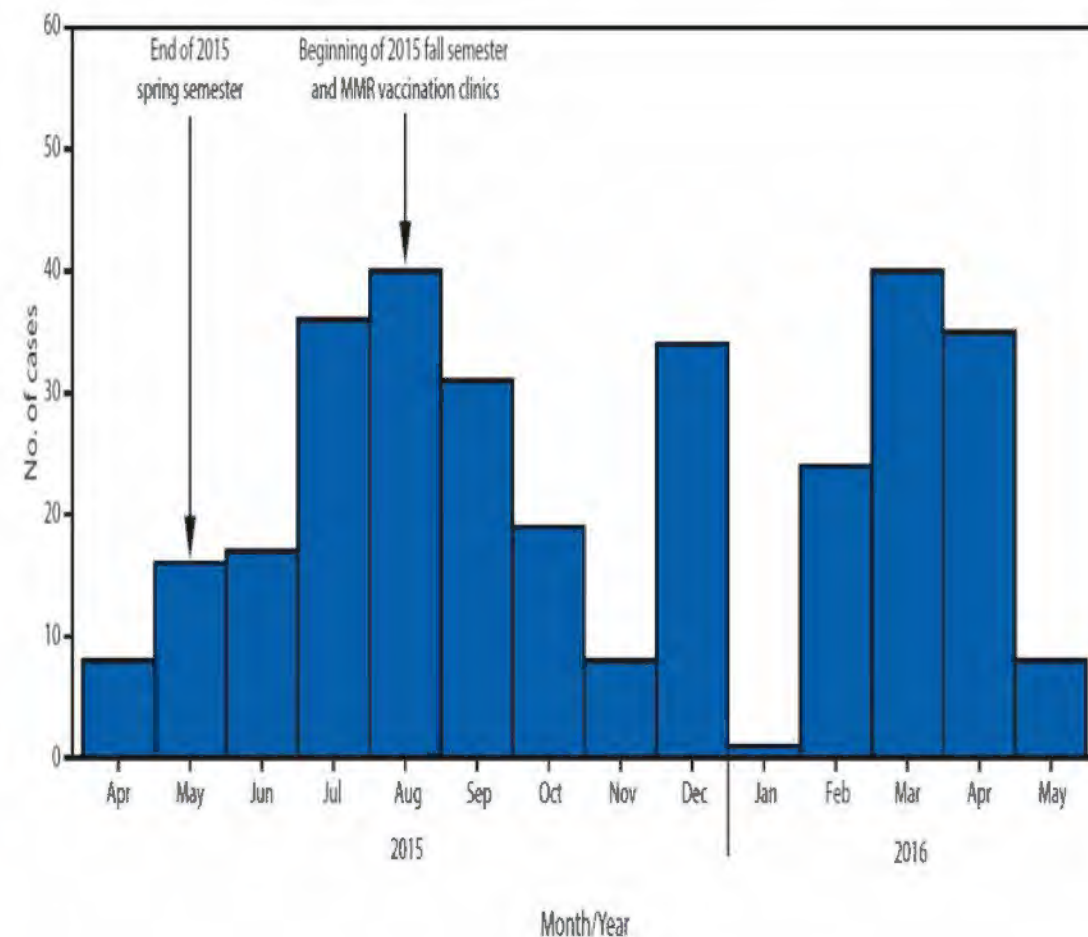
* Defined as a patient associated with the university and with signs and symptoms consistent with mumps.

† Defined as detection of virus by polymerase chain reaction or by the presence of serum mumps immunoglobulin M.

Illinois Outbreak, 2015-2016

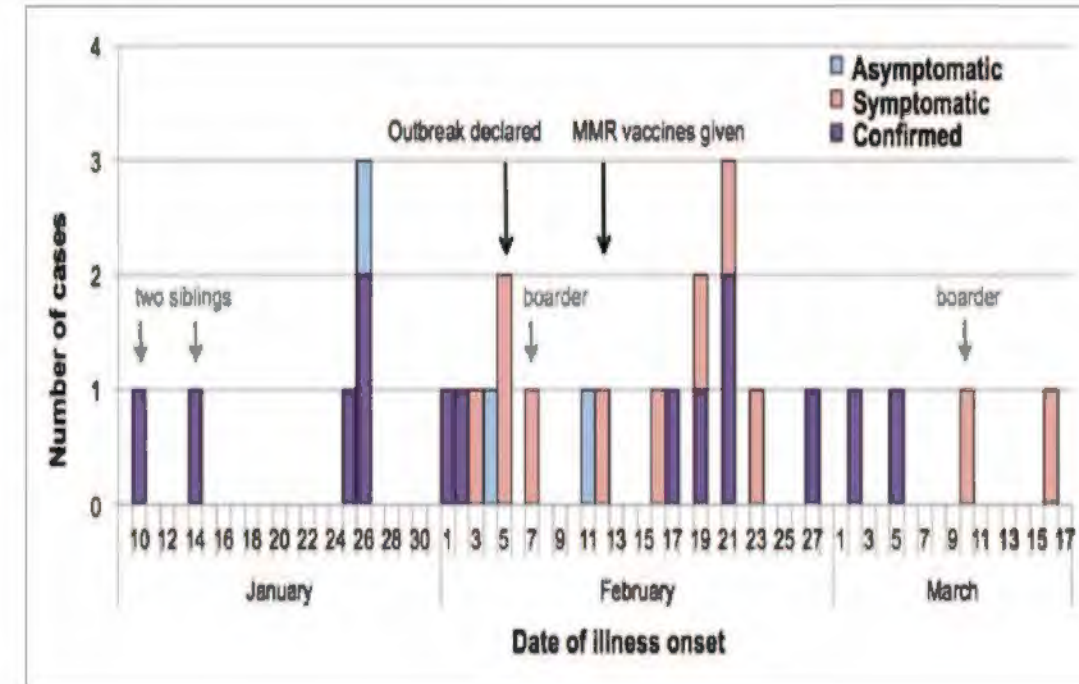
- University: ~50,000 students and staff 97% 2-dose MMR coverage among students 317 cases (278 in students, 3 in staff, 36 non-univ but epi-linked): 3 MMR-50; 2 MMR-232, 1 MMR-12, unvax-73 MMR: 5 vaccinated before outbreak; 27 >4 weeks after receiving the 3rd dose An additional dose of MMR vaccine recommended for all students and staff 5 vaccination clinics over 3 weeks in August, 8,200 doses of MMR administered Unknown number of doses to those living off-campus during summer from a health care provider or pharmacy; 3,300 doses during the fall and spring semesters A decline in cases in the months following the campaign, followed by a second peak before the outbreak was over

FIGURE. Number of confirmed and probable cases of mumps (N = 317) on the University of Illinois at Urbana-Champaign campus, by month of onset — Illinois, April 2015–May 2016



UK Outbreak, 2013

- School: 540 students (age 11-19 years) and 170 staff
28 cases (24 students and 4 staff)
2 MMR-21 (84%); 1 MMR-2 (8%), unvax-2 (8%), unkn-3
An additional dose of MMR vaccine recommended
103 students received vaccine, 76 (74%) were third doses
Effectiveness of intervention could not be assessed reliably
Intervention acceptable to parents and feasible to organize and administer in a timely manner



Laboratory Studies of 3rd Dose MMR

**Huong McLean, PhD, MPH Marsfield Clinic Research
Institute, WI Don Latner, PhD Division of Viral Diseases,
CDC**

ACIP Mumps WG Conference Call May 11, 2017

Outline

- **Antibody response to a third dose of MMR vaccine (MMR3) Nebraska study (Date, JID 2008) Marshfield, WI study (Parker Fiebelkorn, OFID 2014) Comparison of hemagglutinin (HN) and nucleoprotein (NP) ELISAs with neutralizing antibody (PRN) among MMR3-recipients (Latner)**

Long-Term Persistence of Mumps Antibody after Receipt of 2 Measles-Mumps-Rubella (MMR) Vaccinations and Antibody Response after a Third MMR Vaccination among a University Population

Anand A. Date,^{1,6} Moe H. Kyaw,^{2,a} Alison M. Rue,² Julie Klahn,³ LeAnn Obrecht,³ Terry Krohn,⁴ Josh Rowland,⁵ Steve Rubin,⁷ Thomas J. Safraneck,⁶ William J. Bellini,² and Gustavo H. Dayan^{2,a}

¹Epidemic Intelligence Service and ²Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; ³University of Nebraska at Kearney and ⁴Two Rivers Public Health Department, Kearney, ⁵Nebraska Public Health Laboratory, University of Nebraska Medical Center, Omaha, and ⁶Nebraska Health and Human Services System, Lincoln, Nebraska; ⁷Food and Drug Administration, Bethesda, Maryland

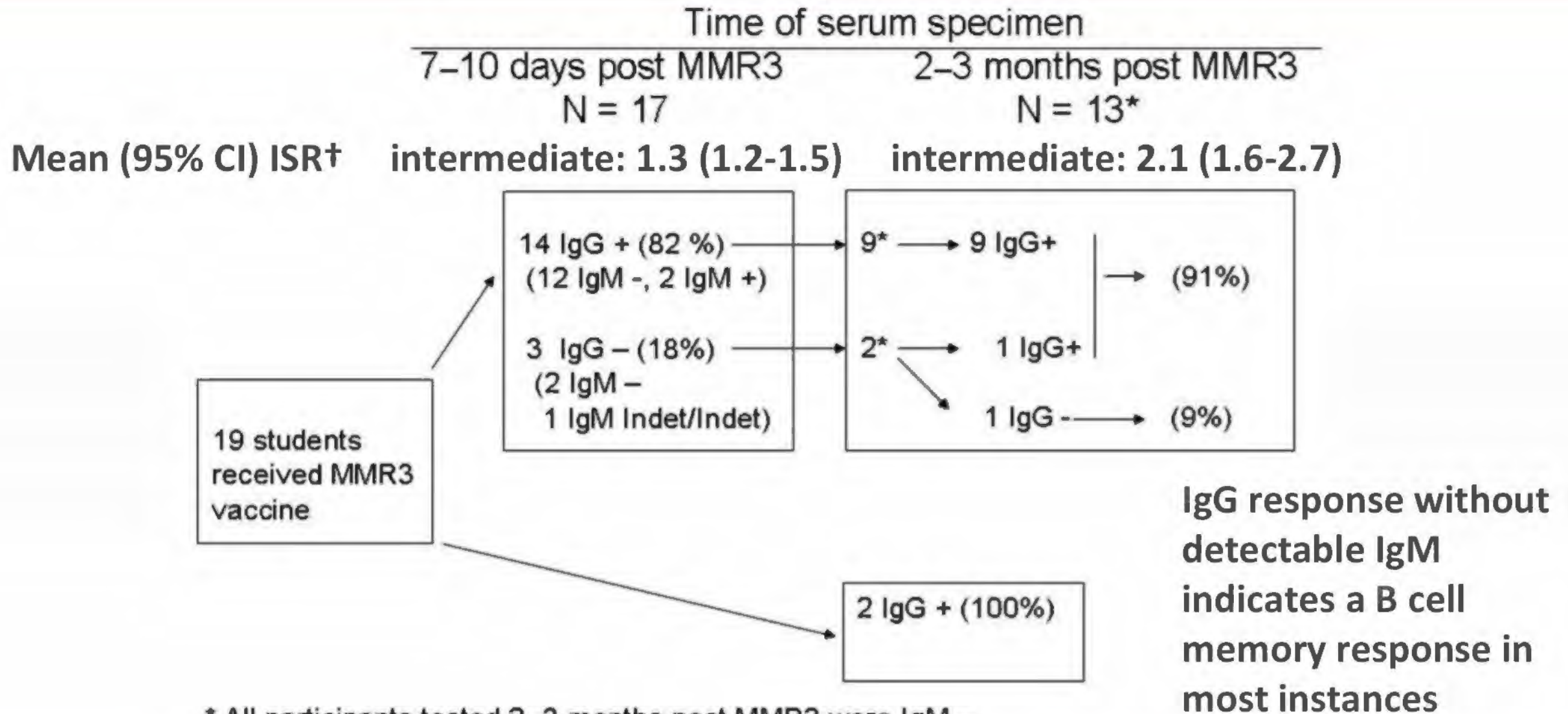
The Journal of
Infectious Diseases

2008;197:1662-8.

Study Setting, Population, and Design

- A Nebraska university with no reported cases during 2006 outbreak
Convenience sample of university students and staff aged 19-30 years with documented receipt of 2 doses of MMR vaccine
Participants without evidence of mumps antibody by EIA were offered another dose (MMR3)
Serum sample obtained 7-10 days and 2-3 months after vaccination

Antibody Response after MMR3



* All participants tested 2–3 months post MMR3 were IgM –

† Index standard ratio values among participants with paired specimens

Mumps Antibody Response in Young Adults After a Third Dose of Measles-Mumps-Rubella Vaccine

Amy Parker Fiebelkorn,¹ Laura A. Coleman,^{2a} Edward A. Belongia,² Sandra K. Freeman,² Daphne York,² Daoling Bi,¹ Cheryl Zhang,^{3,b} Laurie Ngo,³ and Steven Rubin³

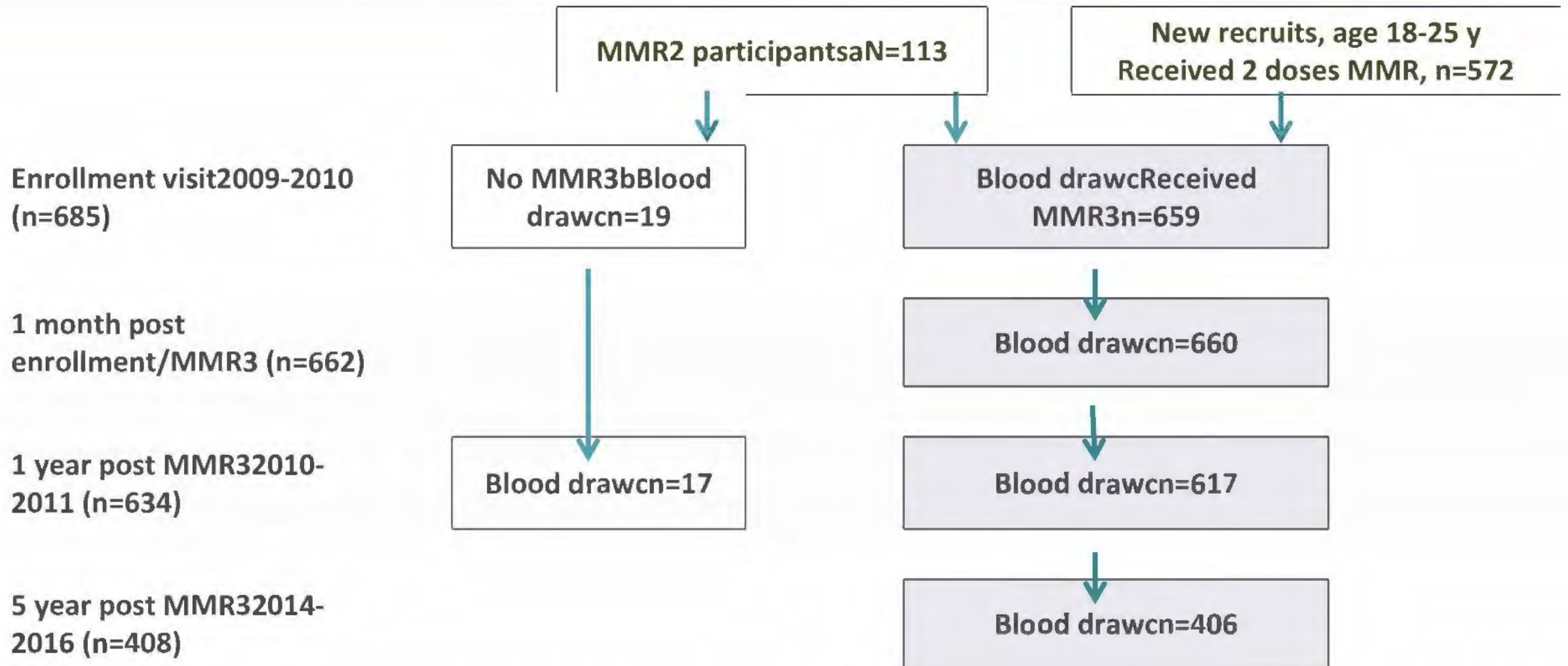
¹National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; ²Marshfield Clinic Research Foundation, Wisconsin; and ³Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland

Open Forum Infectious Diseases 2014;1:ofu094.

Objective of the Marshfield MMR3 study

To examine the short- and long-term immunogenicity and adverse events associated with a third dose of MMR vaccine (MMR3)

Study Population and Design



a Adults who previously participated in the longitudinal MMR2 study at Marshfield Clinic from 1994-2007 (aged 18-31 years); b Participants with documented high titers to all 3 antigens during MMR2 follow-up period; c Participants with sera for mumps titer analysis

Characteristics of the Study Population

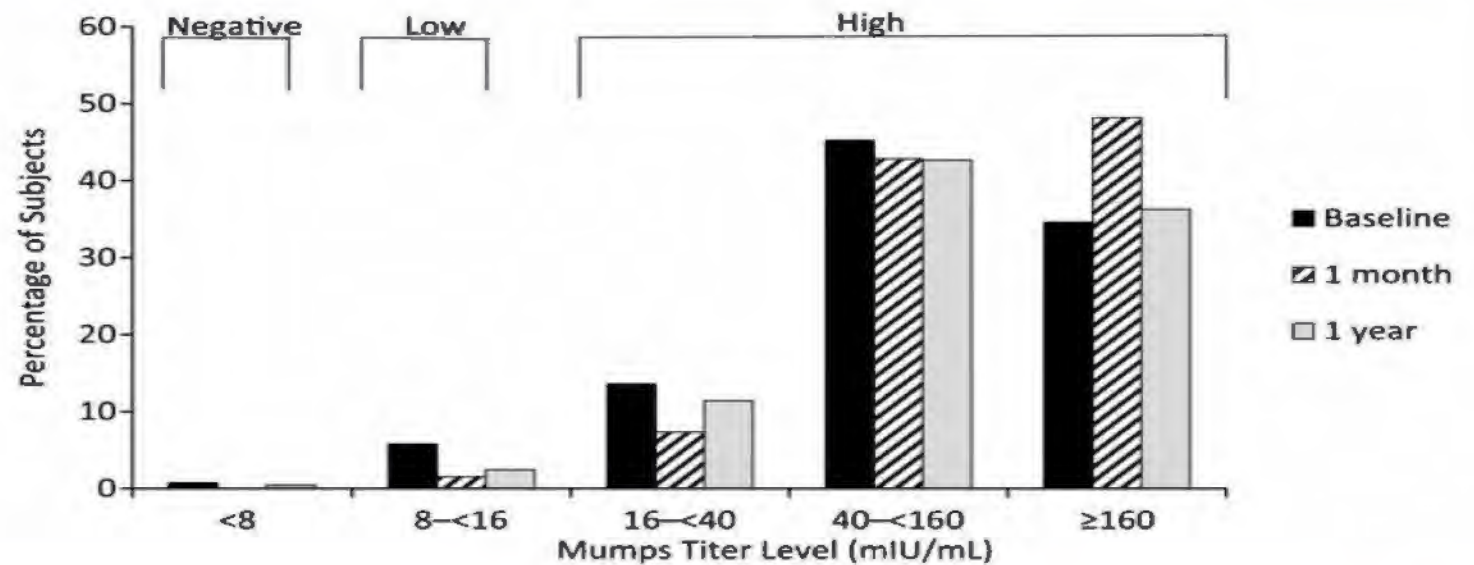
	MMR2 Participants, n=90	New Recruits, n=566
Median age at MMR3, years (range)	20.3 (19.2-28.5)	21.2 (18-25)
Male	45 (50)	321 (57)
White, non-Hispanic	88 (98)	556 (98)
Age at MMR1		
12-14 months	49 (55)	367 (65)
≥15 months (up to 92)	40 (45)	199 (35)
Age at MMR2		
1-3 years	0	4 (1)
4-6 years	74 (82)	548 (97)
7-14 years	16 (18)	14 (2)
Mean years since MMR2 (95% CI)	15.1 (14.9-15.3)	15.8 (15.7-16.0)
Low or negative ^a mumps titers at baseline	7(8) ^b	36 (6)

^a Neutralizing antibody titers <16, ^b 24 were seronegative with mumps titer ≤10 at ≥1 MMR2 follow-up visit

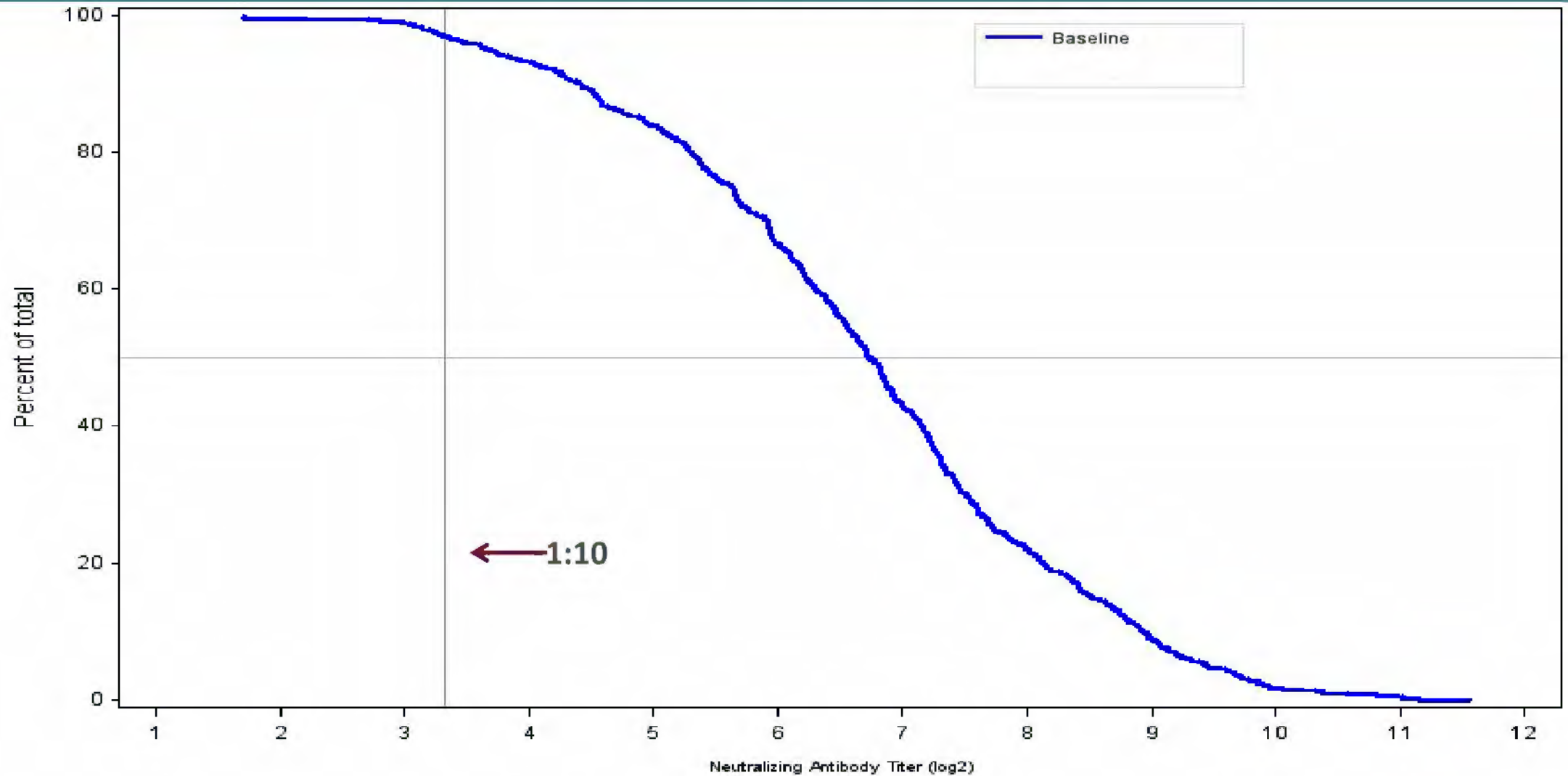
Mumps Antibody^a Before and After Vaccination

	Baseline	1-month post MMR3	1-year post MMR3
N	656	655	612
GMT (95% CI)	104 (95, 114)	159 (147, 172) ^b	126 (115, 137) ^c
≥4-fold increase from baseline, n (%)	--	40 (6)	--
Mean fold increase (95% CI)	--	1.8 (1.7, 2.0)	--
Negative or low titers ^d , n (%)	43 (7)	10 (2)	19 (3)

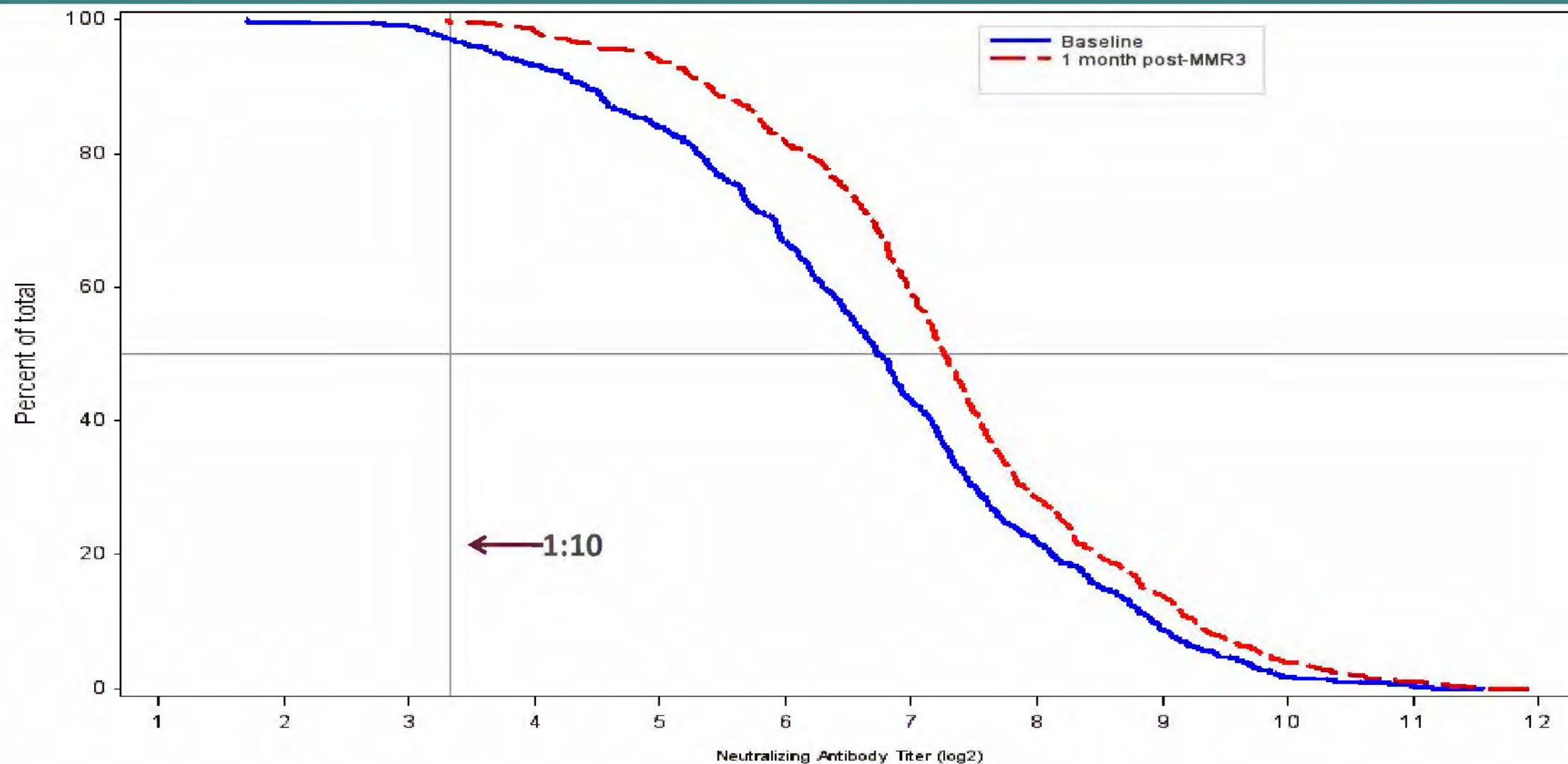
^a Neutralizing antibody against Jeryl Lynn vaccine virus ^b $p < 0.0001$ for comparison with baseline ^c $p < 0.01$ for comparison with baseline ^d titers < 16



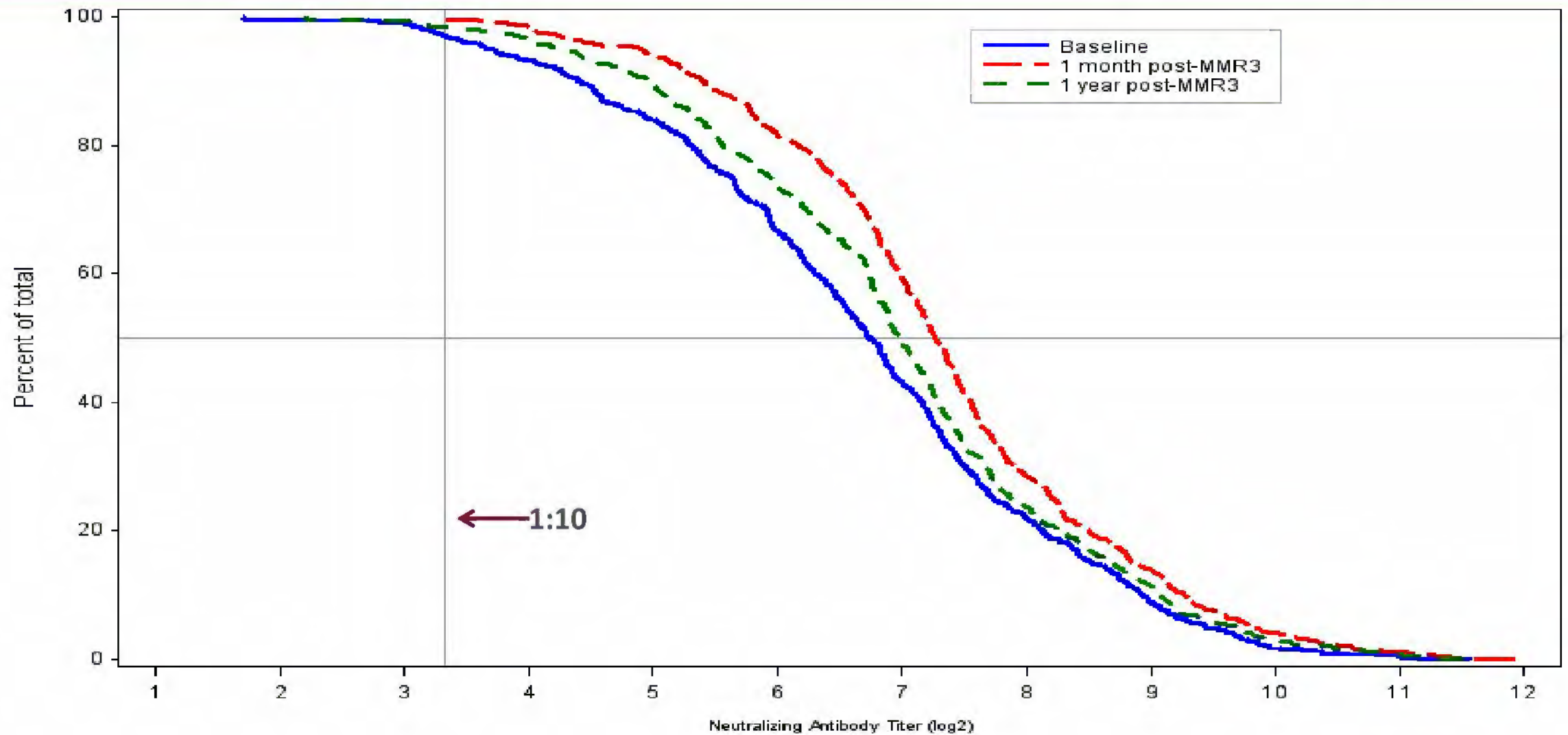
Distribution of Mumps Titer: Baseline



Distribution of Mumps Titer: 1 Month Post MMR3

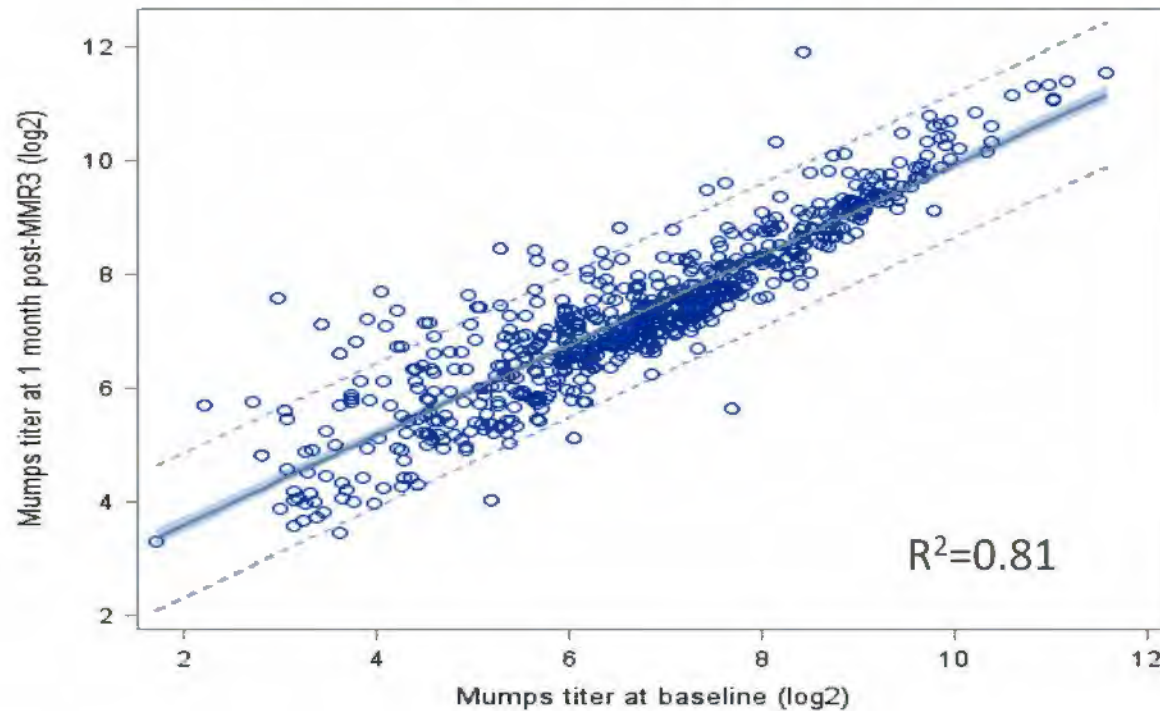


Distribution of Mumps Titers: 1 Year Post MMR3

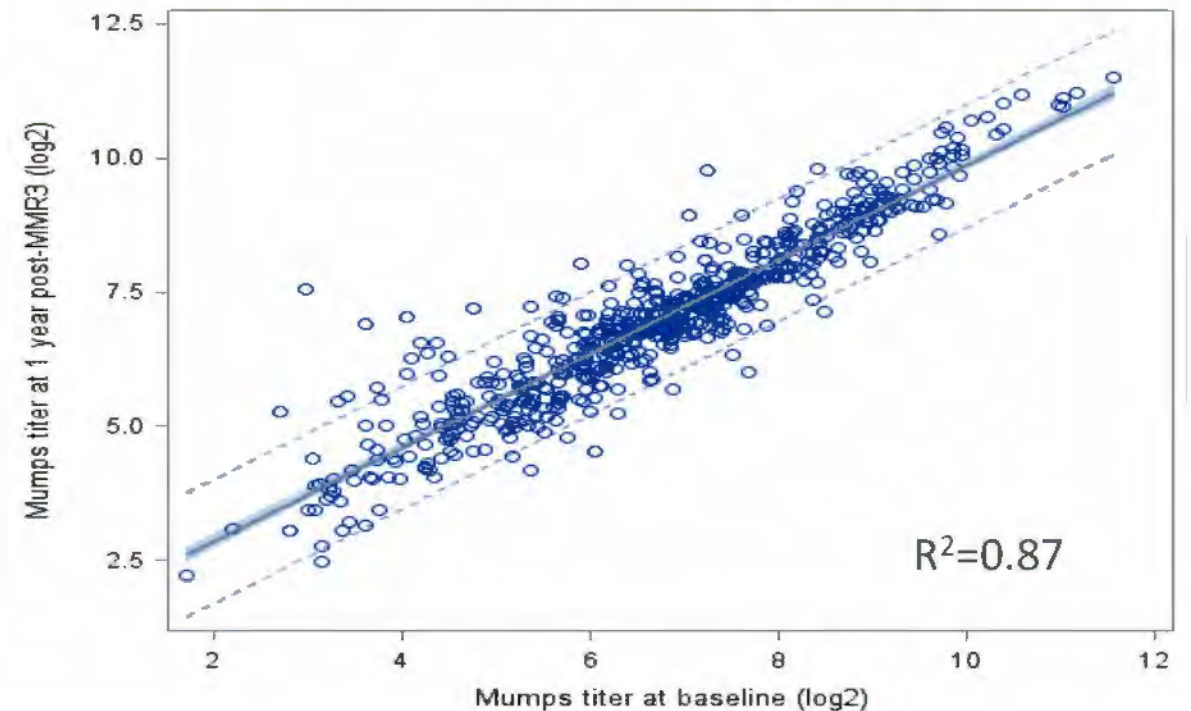


Post Vaccination Titer Highly Correlated with Baseline Titer

1 Month post-MMR3 (n=655)



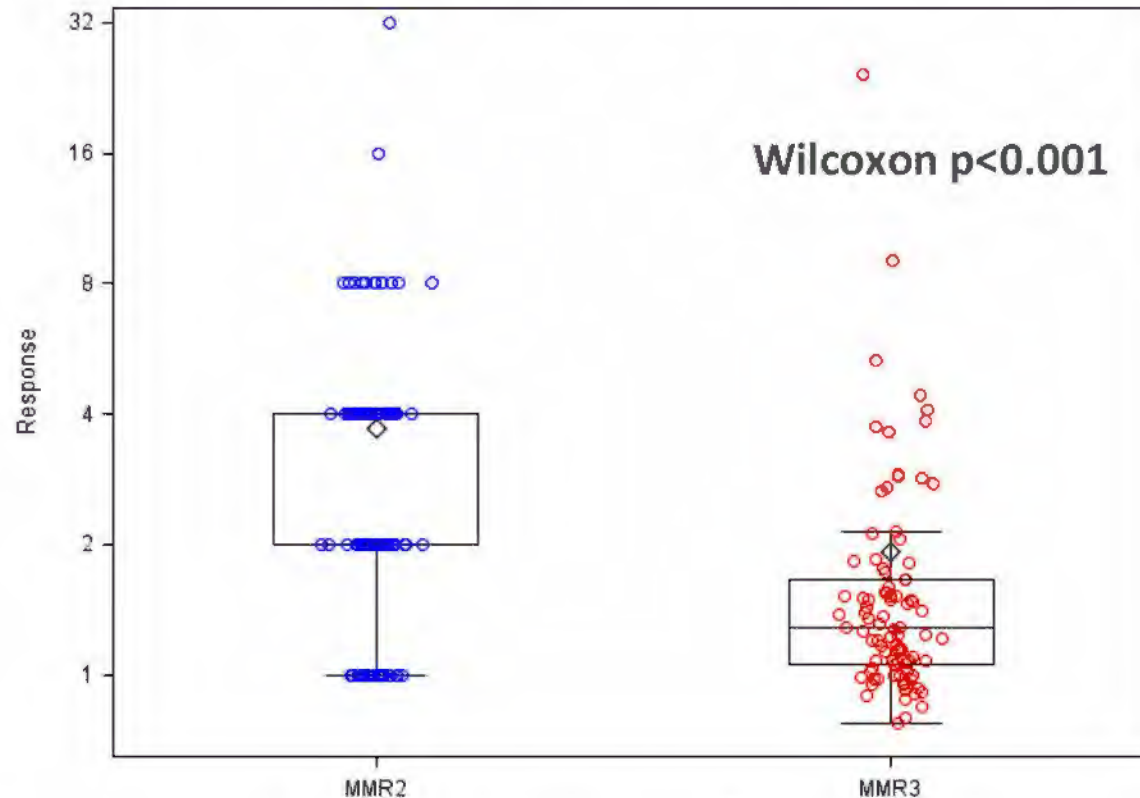
1 Year post-MMR3 (n=612)



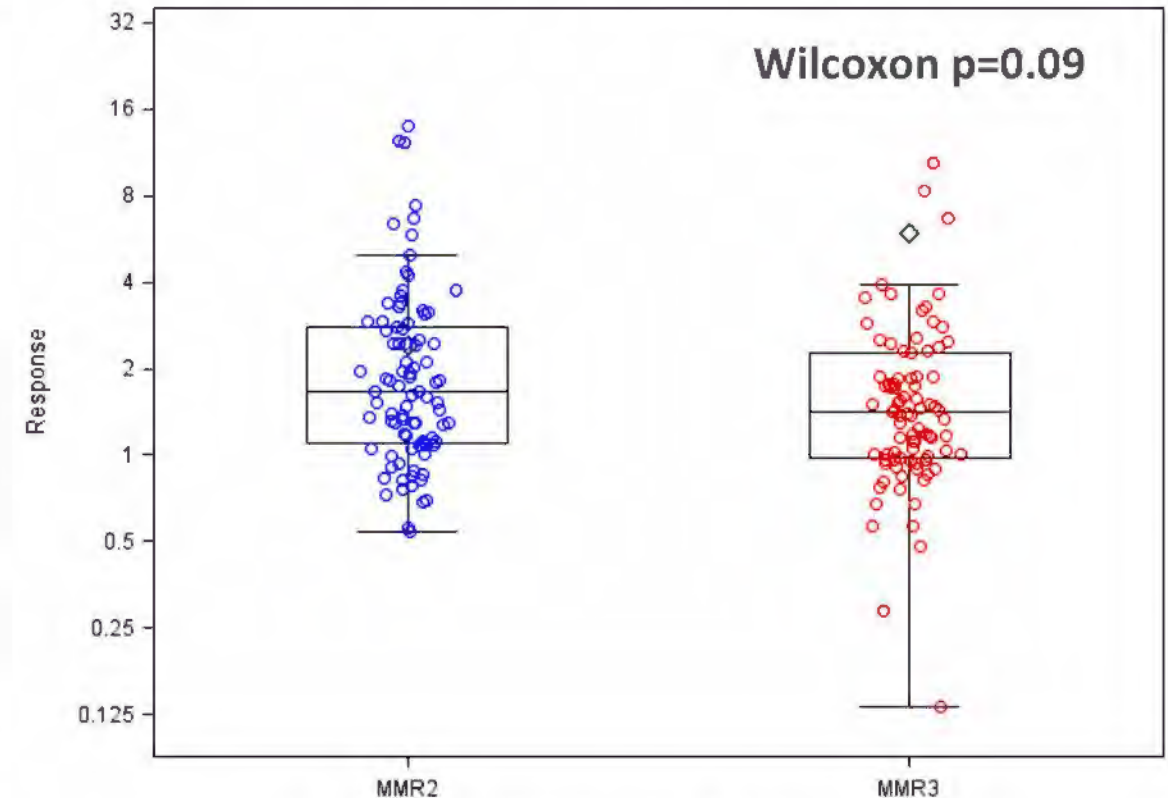
— Fit ■ 95% Confidence Limits - - - 95% Prediction Limits

Comparison of Response after MMR2 and MMR3

89 participants with titer data pre and post MMR2 and MMR3



mumps*

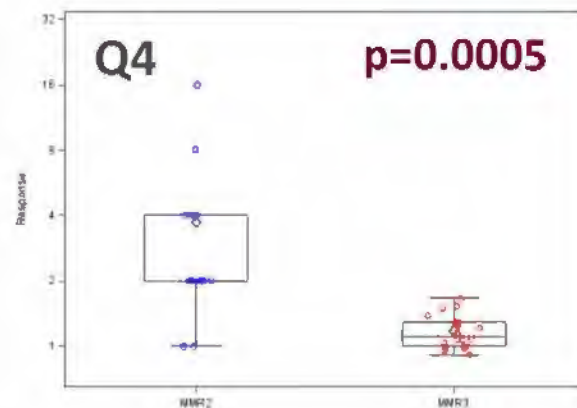
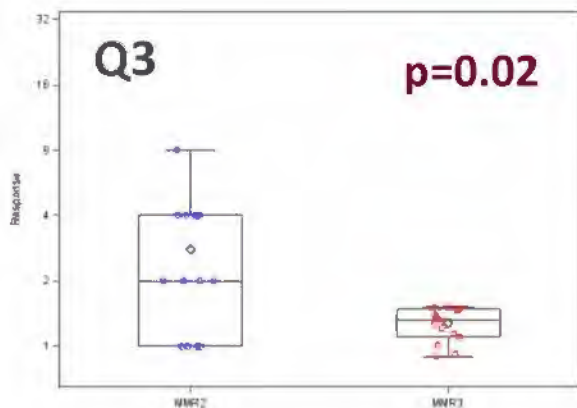
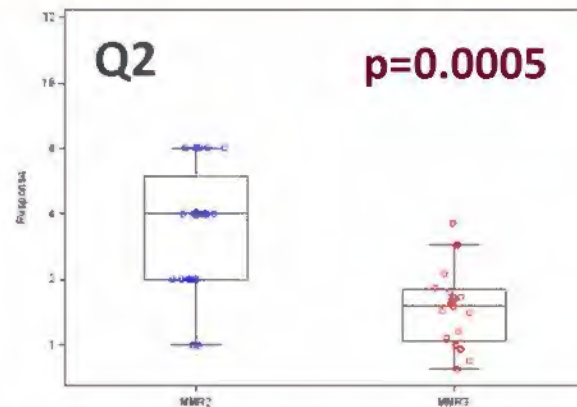
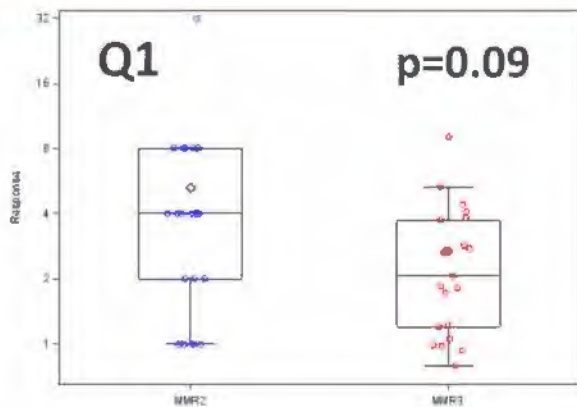


measles

unpublished data

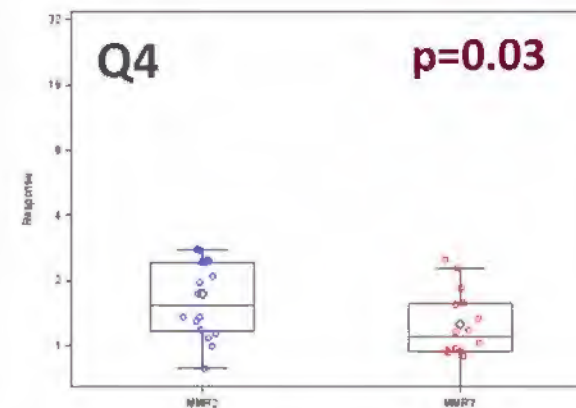
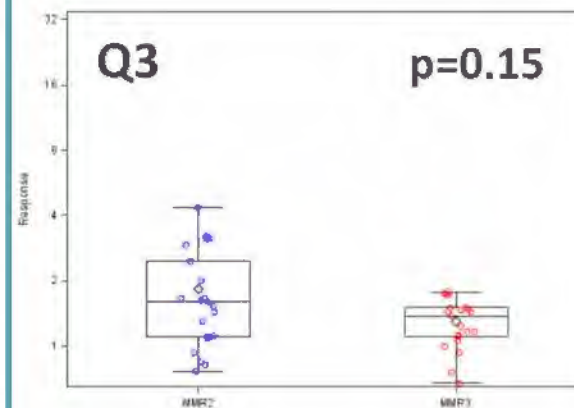
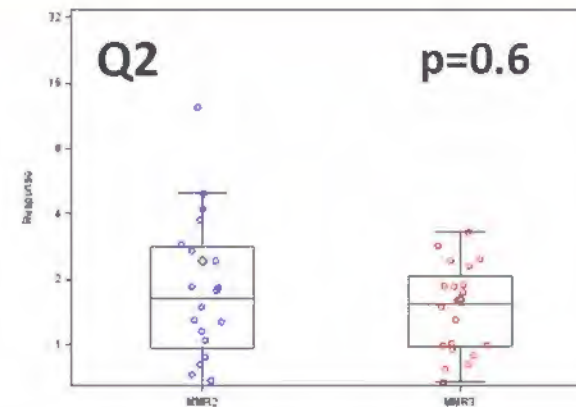
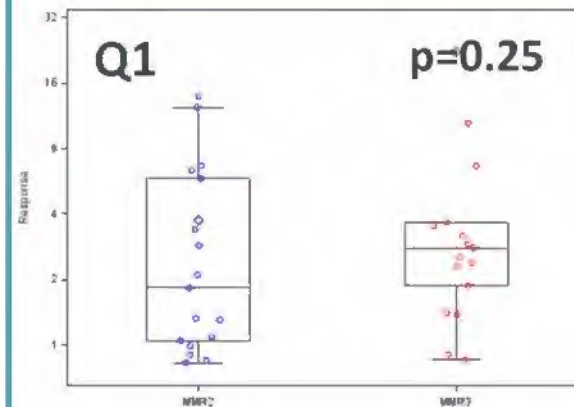
Response=Post vaccination/Pre vaccination
titers*mumps testing differed between the 2
studies

Response by Quartile of Baseline Titer



mumps

unpublished data

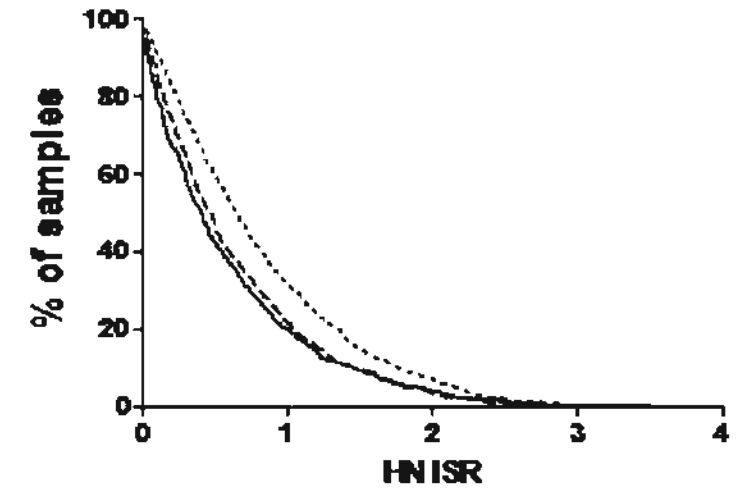
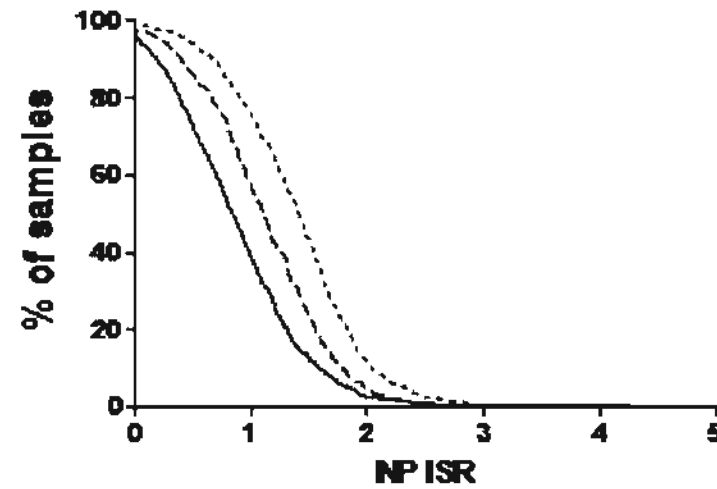
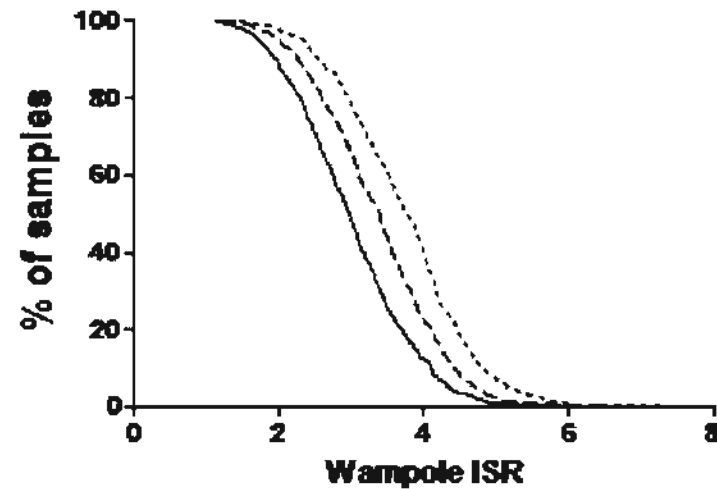
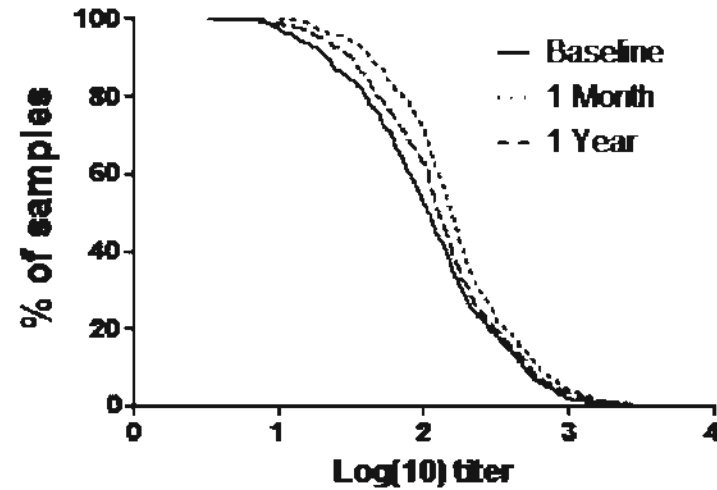


measles

Summary

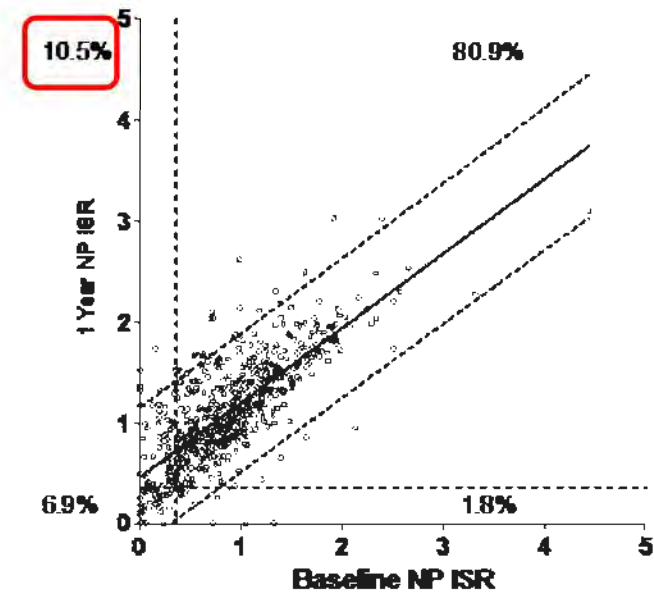
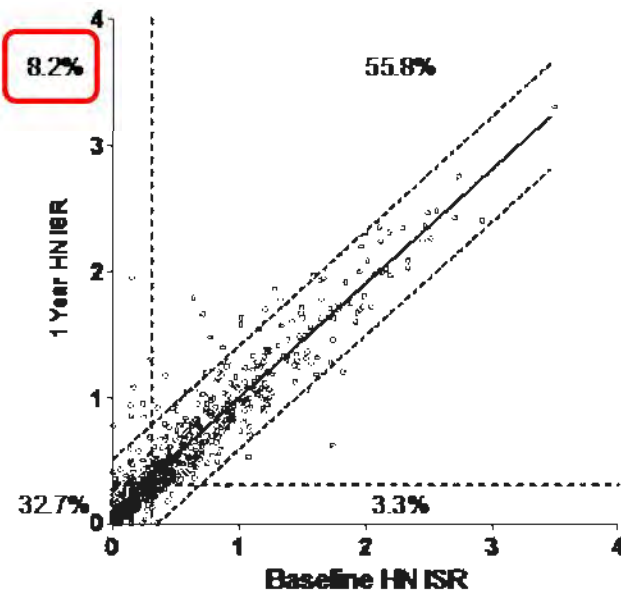
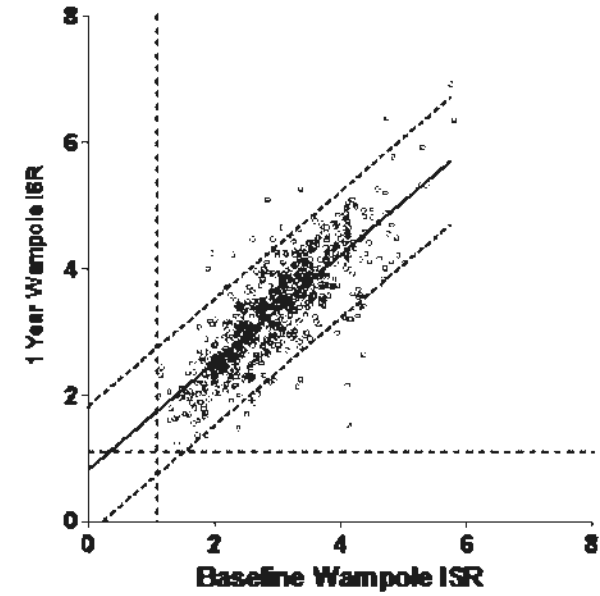
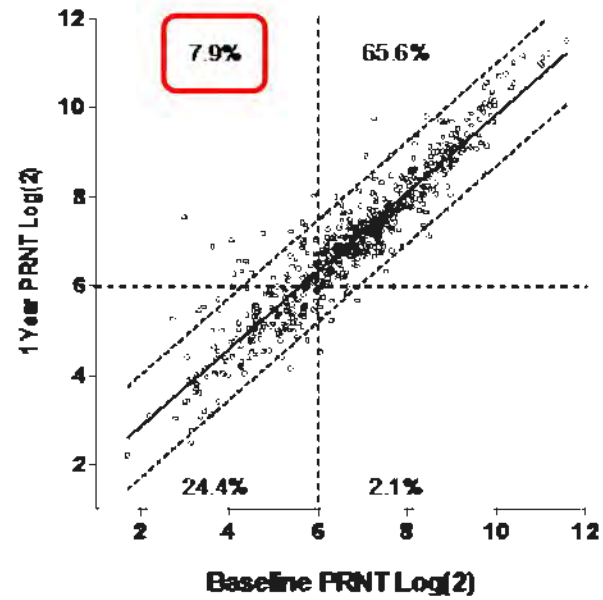
- **93% retention at 1 year post-MMR3**Very few subjects had low or negative antibody levels at baseline (7%) and post-MMR3 (<3%)**Modest** (mean <2-fold), but significant increase 1 month post-MMR3**Titers** returned to near-baseline levels 1 year post-MMR3**Post-vaccination titers** highly correlated with baseline titers; may be an inherent trajectory for mumps titer**Mumps antibody response to MMR3** may be lower than response to MMR2**Limitations** include study population from rural WI, predominately non-Hispanic white, no comparison group, selection bias (MMR2 participants only offered MMR3 if low/negative titers to a MMR antigen), different testing method for mumps

Fiebelkorn, A.P., et al., *Mumps antibody response in young adults after a third dose of measles-mumps-rubella vaccine*. Open Forum Infect Dis, 2014. 1(3): p. ofu094.



Mumps IgG by ELISA following MMR3
Commercial ELISA (whole virus; Enders strain – genotype A)
Antigen-Specific ELISA (recombinant NP and HN; Jeryl Lynn – genotype A)
 Latner, D.R., et al., *Clin Vaccine Immunol*, 2014. 21(3): p. 286-97.
Statistically significant increases for each method
Trend toward baseline by 1 year post-MMR3

Baseline vs. 1 Year post-MMR3 antibody measurements: Individual set points with modest overall increases



ELISA by Baseline Neutralization Quartile

Sample	Quartile	Means			
		PRNT	Wampole	HN	NP
Baseline	4	554.1	3.442	1.278	1.247
	3	152.8	3.111	0.626	0.949
	2	75.6	2.811	0.340	0.779
	1	26.3	2.620	0.119	0.577

Quartile	% of samples	
	HN+	NP+
4	93.9	93.9
3	79.3	89.0
2	49.4	81.7
1	9.8	62.8
total	58.1	81.9

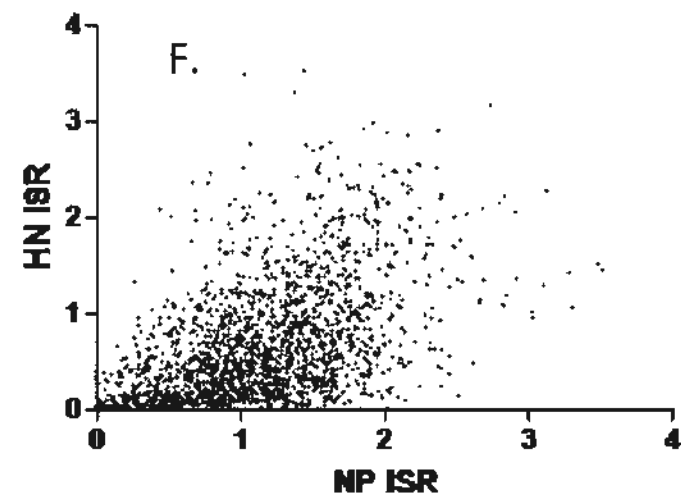
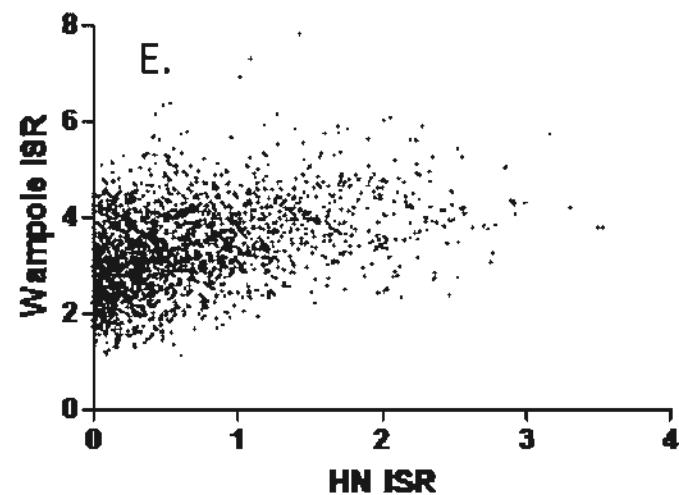
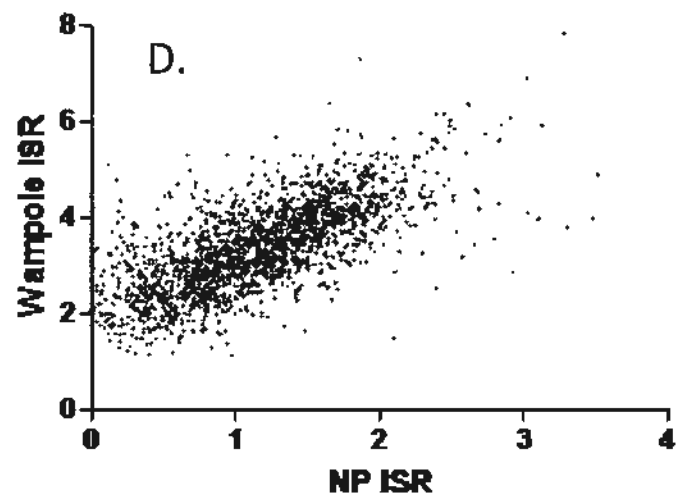
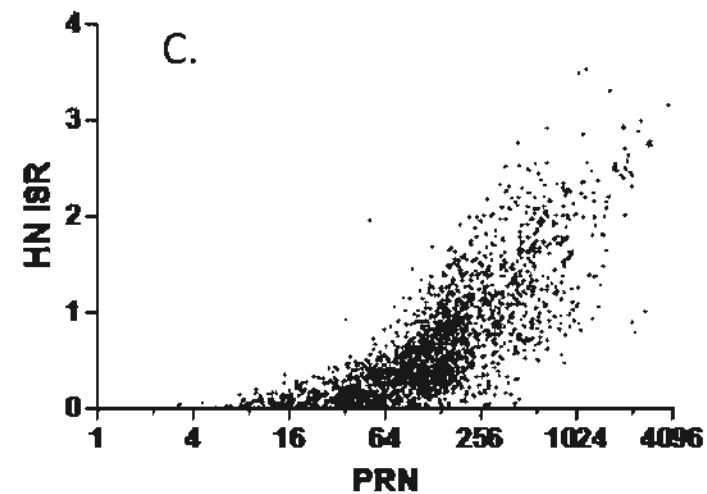
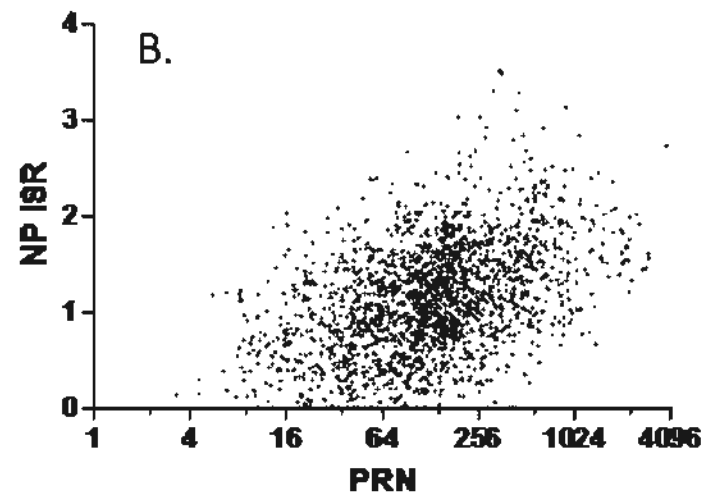
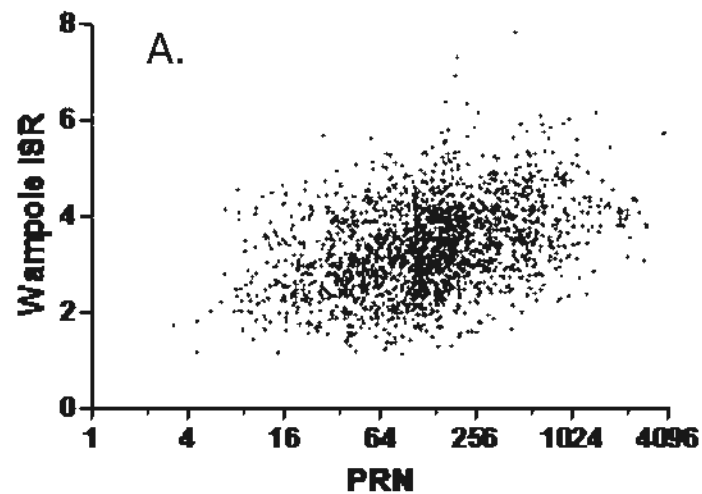
1 Month	4	714.5	4.087	1.516	1.671
	3	199.0	3.696	0.827	1.335
	2	128.9	3.626	0.591	1.344
	1	66.1	3.531	0.304	1.206

4	97.5	98.8
3	88.4	97.6
2	72.0	95.1
1	37.8	94.5
total	73.9	96.5

1 Year	4	607.3	3.688	1.270	1.365
	3	172.1	3.376	0.652	1.122
	2	100.4	3.272	0.415	1.061
	1	42.2	3.099	0.173	0.899

4	94.2	96.8
3	84.6	93.6
2	59.3	91.3
1	16.6	83.4
total	64.0	91.3

Poor correlation among test methods



Summary According to IgG ELISAs specific for mumps HN, NP, and whole virus, MMR3 resulted in modest overall elevation in individual antibody levels at 1 month and 1 year post-MMR3 as compared to baseline. The correlation between antibody measurements at baseline and subsequent time points indicates there is a set point for individual antibody levels that is minimally affected by MMR3. Poor correlation among tests – unable to predict PRNT from ELISA data. Is there a protective role for non-neutralizing antibody? Need for tests to measure antibody to other components (fusion protein).



Mumps resurgences in the United States: A historical perspective on unexpected elements[☆]

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ABSTRACT

In 2006 the United States experienced the largest nationwide mumps epidemic in 20 years, primarily affecting college dormitory residents. Unexpected elements of the outbreak included very abrupt time course (75% of cases occurred within 90 days), geographic focality (85% of cases occurred in eight rural Midwestern states), rapid upward and downward shift in peak age-specific attack rate (5–9-year olds to 18–24-year olds, then back), and two-dose vaccine failure (63% of case-patients had received two doses).

To construct a historical context in which to understand the recent outbreak, we reviewed US mumps surveillance data, vaccination coverage estimates, and relevant peer-reviewed literature for the period 1917–2008.

Many of the unexpected features of the 2006 mumps outbreak had been reported several times previously in the US, e.g., the 1986–1987 mumps resurgence had extremely abrupt onset, rural geographic focality, and an upward-then-downward age shift. Evidence suggested recurrent mumps outbreak patterns were attributable to accumulation of susceptibles in dispersed situations where the risk of endemic disease exposure was low and were triggered when this susceptible population was brought together in crowded living conditions. The 2006 epidemic followed this pattern, with two unique variations: it was preceded by a period of very high vaccination rates and very low disease incidence and was characterized by two-dose failure rates among adults vaccinated in childhood.

Data from the past 80 years suggest that preventing future mumps epidemics will depend on innovative measures to detect and eliminate build-up of susceptibles among highly vaccinated populations.

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1. Introduction

Mumps is an infectious viral disease, classically manifested by inflammation of salivary glands and fever [1]. Mortality is rare, but aseptic meningitis can affect 10% of case-patients [2]. Mumps is an important cause of pediatric deafness, and up to 37% of post-pubertal males develop orchitis, 13% of whom have impaired fertility [1]. In the absence of vaccination, most persons have been infected by young adulthood [2]. In 1967 a live, attenuated mumps virus vaccine was licensed in the United States, and by 2005 high two-dose childhood vaccination coverage reduced disease rates by >99% [3,4].

In 2006 the US experienced a multi-state outbreak involving 6584 reported cases, with the highest attack rate among persons

18–24 years of age, many of whom were college students [4]. In affected colleges, most case-patients had received a second dose of the measles–mumps–rubella vaccine (MMR) ≥ 10 years previously [5,6]. This was the first large-scale US mumps outbreak among two-dose vaccinees.

Waning immunity appeared to play a role in facilitating this outbreak, consistent with effectiveness data from the United Kingdom [7] and serological data from Finland [8]. However, certain epidemiologic features were unexpected. The onset was sudden – a >50-fold rise in case counts within a 30-day period, followed by a sudden decrease, so that three-quarters of the epidemic's total cases occurred within 3 months [4]. After a decade in which the geographical distribution of mumps cases had been proportional to population, 85% of case-patients during the 2006 epidemic came from eight rural states located in the central US, followed by a return to an unremarkable geographic pattern [4]. In parallel, the peak age-specific attack rate shifted suddenly from primary school children to the college age group, then began moving back toward primary school children [4,9].

Previous resurgences of vaccine-preventable diseases in the United States had not shown these characteristics. The 1989–1991

[☆] The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, US Department of Health and Human Services.

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measles resurgence had been preceded in the mid-1980s by a rising tide of incidence and increasing mean age of disease acquisition [10]. Lasting for 3 years, the measles resurgence saw outbreaks distributed widely across the US, but incidence was most intense in urban, rather than rural, areas [10]. The pertussis resurgence of the 1990s differed markedly from measles in many respects, but it too was widely distributed across the US, without any clear rural focality, and showed a slowly progressive pattern, both in terms of incidence and changing age-distribution [11].

We reviewed the history of mumps disease reports in the US to assess whether the 2006 resurgence patterns should have been unexpected – or whether they reflected recurrent phenomena that might shed light on the behavior of the mumps virus in the population, thereby helping us to anticipate and prevent future epidemics.

2. Methods

2.1. Surveillance data

2.1.1. Data sources

National notification of mumps cases was begun in 1922, discontinued in 1950 (though some states continued to report voluntarily), then restored in 1968 [12]. Where incidence was unavailable (1922–1967), we used the method of Siström and Mergo to scan graphic data four times, recorded the average value, and then used a cubic spline to interpolate missing values [12,13]. In 1968, printed monthly case counts by state were available. Beginning in 1977, case-patients' age group was increasingly included. In 1990 computerized case reporting was initiated, and more variables were progressively included, though completeness ranged 22–99%.

2.1.2. Inclusion criteria

Reporting criteria (including clinical case definition and case status classification) evolved over time. Because sufficient data were not available to allow application of the current definitions (Council of State and Territorial Epidemiologists, Position Statement 07-ID-02, accessed 12/1/08, <http://www.cste.org/PS/2007ps/2007psfinal/ID/07-ID-02.pdf>) to the whole period under examination (1917–2008), we included all reports of confirmed and probable mumps cases according to the case definition in use at the time.

2.1.3. Peak/trough analysis

We measured incidence amplitude by calculating a peak/trough ratio, obtained by dividing a peak incidence by the previous nadir incidence.

2.2. Population data

We calculated mumps incidence (overall, state-specific, and age group-specific), using annual US population estimates (Census Bureau, Population Estimates, accessed 12/1/08, <http://www.census.gov/popest/datasets.html>).

2.3. Vaccination coverage

One- and two-dose mumps-containing vaccine coverage was assessed from three national surveys whose methods have been described in detail elsewhere:

- (1) US Immunization Survey (USIS): vaccination-card-verified, one-dose coverage of 24-month-old children, 1979–1985 [14].
- (2) National Health Interview Survey (NHIS): vaccination-card-verified, two-dose coverage for 13–15-year-old adolescents, 1997–2003 [15].

- (3) National Immunization Survey (NIS): (Centers for Disease Control and Prevention, Immunization Coverage in the US, accessed 12/1/08, <http://www.cdc.gov/vaccines/stats-survey/imz-coverage.htm#nis>).

- (a) Provider-verified, one-dose coverage for 19–35-month-old children, 1995–2008.
- (b) Provider-verified, two-dose coverage for 13–17-year-old adolescents, 2006–2008.

2.4. Mumps in the military

We obtained mumps case counts and population denominators for 1998–2007 (Armed Forces Health Surveillance Center, Defense Medical Epidemiology Database, accessed 12/1/08, <http://www.afhsc.mil/dmed/overview.asp>). Policy memoranda supplied by the Military Vaccine Agency provided a history of military vaccination practices.

2.5. Literature review

We reviewed available peer-reviewed literature concerning mumps outbreaks and epidemic patterns, particularly for the years where original reporting data were not available.

2.6. Analytic periods

We defined four time periods:

- (1) Pre-vaccine 1917–1967.
- (2) Vaccination Program Implementation 1968–1982.
- (3) First Resurgence 1983–1992.
- (4) Second Resurgence 1993–2008.

We chose to end the Period of Vaccination Implementation when a steady baseline incidence appeared to have been reached. We ended the Period of the First Resurgence when the annual incidence had returned to the level observed at the beginning of this period.

2.7. Modeling

To evaluate the multi-annual periodicity of mumps in the pre-vaccine era, we performed Fourier decomposition, identifying a single cycle with a 3-year period. As the annual rates also increased from early to mid-century and decreased thereafter, our harmonic regression model also includes terms for non-cyclic secular variation. We estimated its coefficients via least squares.

3. Results

3.1. Pre-vaccine Period: 1917–1967

Irregular epidemic cycles of relatively moderate amplitude (mean peak/trough 1.6, range 1.1–2.5) had a periodicity of approximately 3 years, and a superimposed secular trend peaked during World War II (Fig. 1A). By age 14 years, approximately 90% of urban children had been infected, with peak incidence at age 5–9 years [12,16], suggesting that millions of cases occurred each year, but reported incidence was much lower (50–251/100,000). Cases were reported throughout the year, with highest incidence during winter and spring [12,17]. No geographic patterns were reported, but in the early years of this period, disease acquisition may have been delayed among rural children, as explosive outbreaks occurred when young military recruits, particularly those from rural areas, were crowded into barracks [18,19]. A report from World War

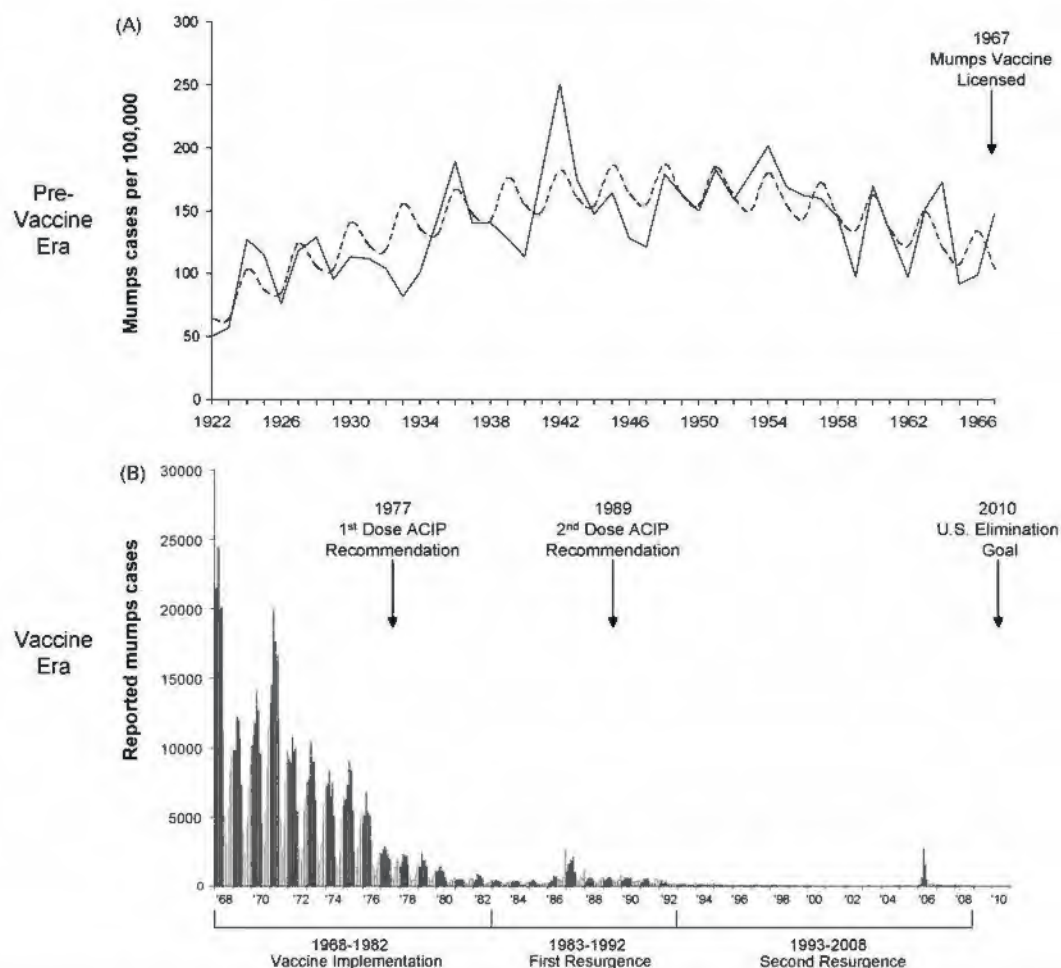


Fig. 1. Mumps Activity in the US, 1922–2008. (A) Pre-vaccine era mumps incidence, 1922–1967. Reported incidence (solid line); 3-year epidemic cycle with secular trend (broken line). (B) Vaccine era monthly mumps cases, 1968–2008. Cases of mumps reported to the Centers for Disease Control and Prevention (CDC) by month of onset date are shown in bars: cases that occurred January to June (dark bars) and cases that occurred July to December (white bars).

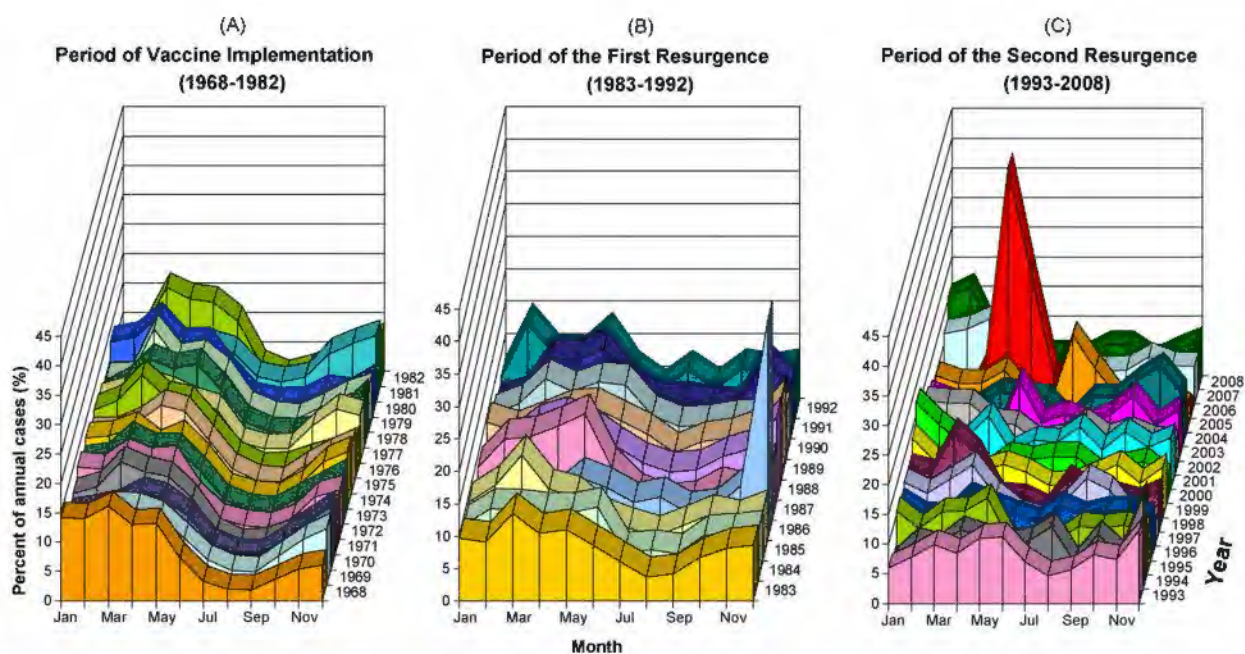


Fig. 2. Mumps Seasonality, 1968–2008. For each graph, percent of annual cases is plotted on the z-axis, with months on the x-axis and years on the y-axis.

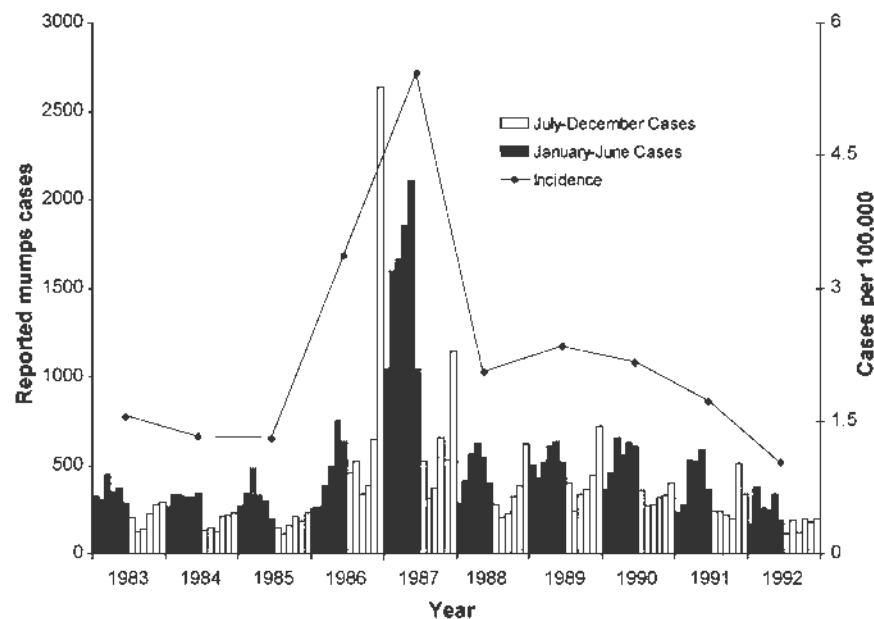


Fig. 3. Period of the First Resurgence, 1983–1992. Monthly mumps cases (bars): cases of mumps reported to CDC by month of onset date are shown in bars: cases that occurred January to June (dark bars) and cases that occurred July to December (white bars). Annual mumps incidence (solid line): number of annual cases reported to CDC per 100,000 US population.

I stated: "...mumps has appeared most frequently among rural rather than urban troops. Our percentage has been 85 per cent rural and 15 per cent urban." [18] Another World War I report attributed this rural preponderance to lack of prior exposure: "They had not been accustomed, like their urban cousins, to epidemics of any sort and therefore, from their lack of immunity, geographically furnished good soil for the virus" [20].

3.2. Period of Vaccination Implementation: 1968–1982

Progress toward universal childhood vaccination was gradual. In 1967, after mumps vaccine licensure, the Advisory Committee on Immunization Practices (ACIP) stated the "vaccine may be considered for use in children approaching puberty, in adolescents, and in adults, especially males," but "the vaccine is not recommended for routine use" [3]. In 1968, this was modified to indicate "that consideration be given to immunizing all susceptible children over 1 year of age" [21]. Finally, in 1977,

ACIP recommended mumps vaccination "for all children at any age after 12 months" [22]. Annual mumps coverage rates for 24-month olds ranged 70–80% according to a national survey conducted 1979–1985 [14]. Enactment of school mumps vaccination requirements was gradual: by 1982 twenty states still lacked such laws [23]. However, because combined MMR was used in school-based measles elimination efforts, 95% of school enterers had been vaccinated for mumps according to a 1982 survey, though state-specific rates were as low as 69% [23]. The number of reported mumps cases decreased by 97% compared to the Pre-Vaccine Era: 152,209 (incidence 88/100,000) in 1968 to 5270 (incidence 2.5/100,000) in 1982. Winter-spring seasonality persisted (Fig. 2A), but the 3-year cycles were gradually eliminated (Fig. 1B). Although incidence declined across all age groups, reduction was greatest in the primary school ages targeted for immunization, producing a relative up-shift in the age of case-patients [23]. However, the peak attack rate remained age 5–14 years [23].

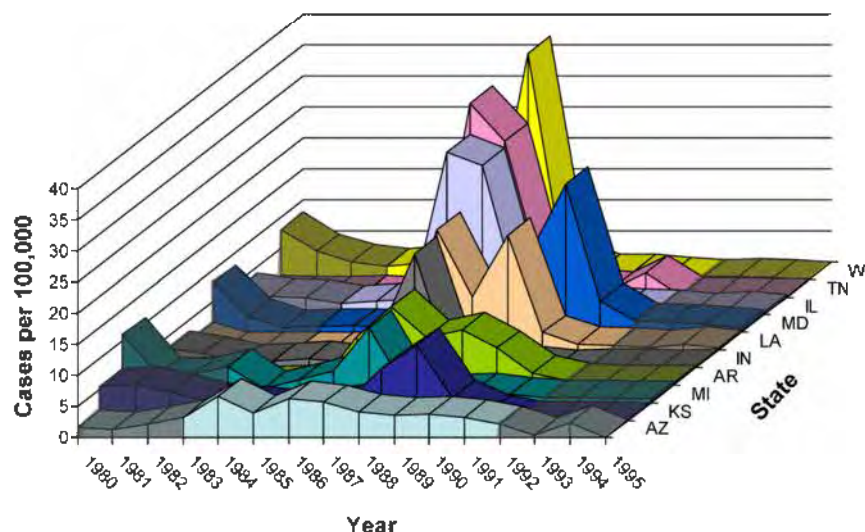


Fig. 4. Highest incidence states in the Period of the First Resurgence, 1983–1992. The ten states shown along the y-axis had the highest aggregate incidence reported to CDC during 1983–1992. Annual incidence for each state is shown on the z-axis. Bracketing years 1980–1982 and 1993–1995 are shown in shaded colors.

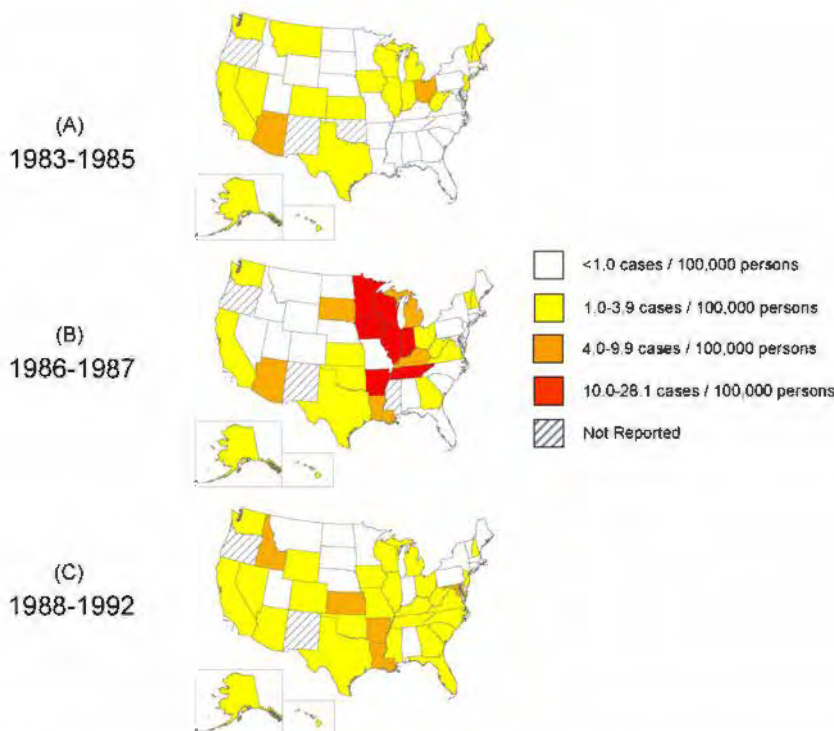


Fig. 5. Geography of the Period of the First Resurgence, 1983–1992. For each map, the state's aggregate incidence reported to CDC over the given time period is shown.

3.3. Period of First Resurgence: 1983–1992 (Fig. 3)

After 17 years of marked decline in mumps incidence, a historical nadir of 2982 cases (incidence 1.3/100,000) was reached in 1985. Abruptly in December 1986 a resurgence began, with the single-month case count (2633) nearly equaling the previ-

ous year's total. The outbreak peaked in 1987 with 12,848 annual cases (incidence 5.4/100,000). Of the 10 states with the highest incidence for 1983–1992 (Fig. 4), 9 showed an explosive pattern (mean peak/trough 64, range 2–419). Compared to a diffuse geographic incidence before and after, the 1986–1987 resurgence was highly focal: the eight states with highest incidence were contigu-

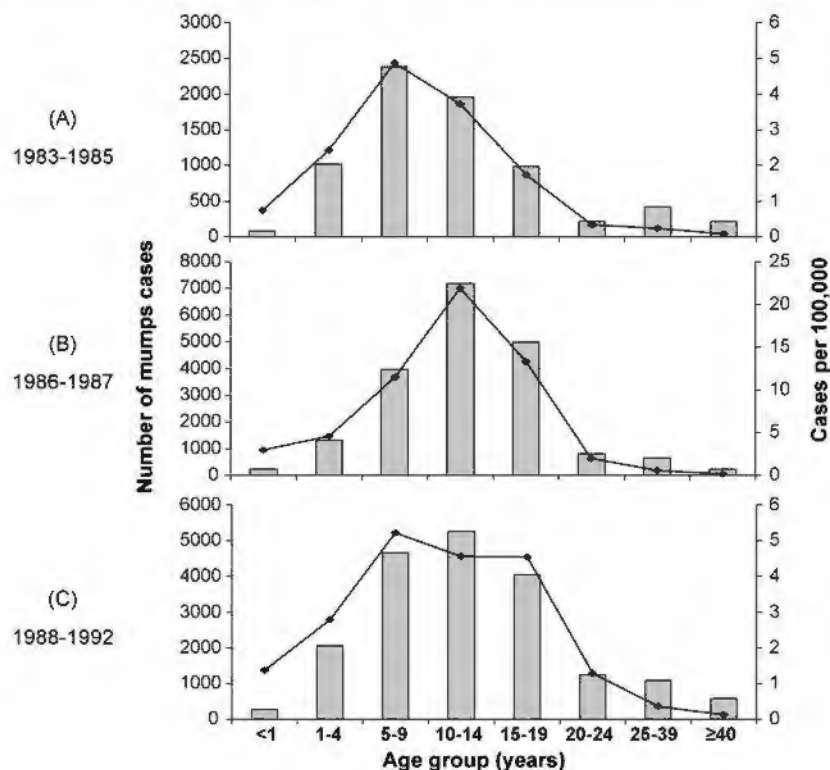


Fig. 6. Age-specific incidence and case numbers, Period of the First Resurgence, 1983–1992. For each graph, bars represent total cases of mumps reported to CDC, and the solid line represents aggregate incidence. Note that y-axes are on a different scale for each graph.

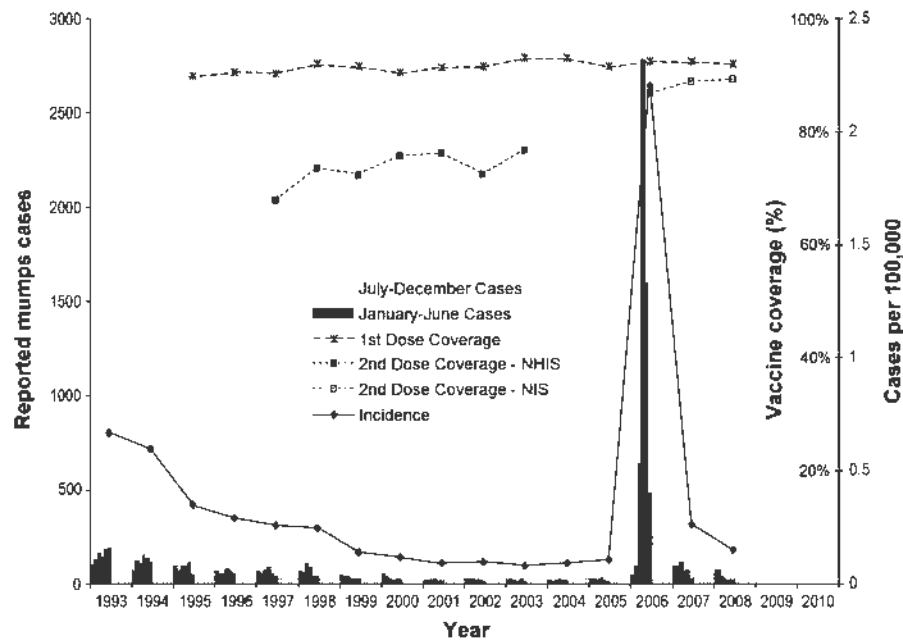


Fig. 7. Period of the Second Resurgence, 1993–2008. Monthly mumps cases (bars): cases of mumps reported to CDC by month of onset date are shown in bars: cases that occurred January to June (dark bars) and cases that occurred July to December (white bars). Annual mumps incidence (solid line): number of annual cases reported to NNDSS per 100,000 US population. First dose coverage (broken line): Single dose coverage with the measles–mumps–rubella vaccine (MMR) among 19–35-month olds measured by the National Immunization Survey and verified by provider records. Second dose coverage – NHIS (dotted line with solid square markers): second dose coverage with MMR among 13–15-year olds measured by the National Health Interview Survey and verified by vaccination cards [15]. Second dose coverage – NIS (dotted line with hollow square markers): Second dose coverage with MMR among 13–17-year olds measured by the National Immunization Survey and verified by provider records.

ously located in the central, rural US, and two states accounted for 57% of the nation's cases in 1986 (Fig. 5). Outbreaks were often reported from high schools and colleges serving rural populations [24,25]. During 1986–1987, incidence increased for all age groups, but the peak shifted from the 5–9-year age group into 10–19-year olds where 63% of cases occurred (Fig. 6). Vaccination status of case-patients was not quantified nationally, but the resurgence was

attributed to an increase in susceptibility among older cohorts of children who had not been vaccinated but who had been spared previous disease exposure by declining mumps incidence [26]. During the post-resurgence years (1988–1992), outbreaks associated with one-dose vaccine failure were first reported [27–29]. In December 1989, ACIP, for improved measles control, recommended a second dose of measles vaccine, but suggested it be administered

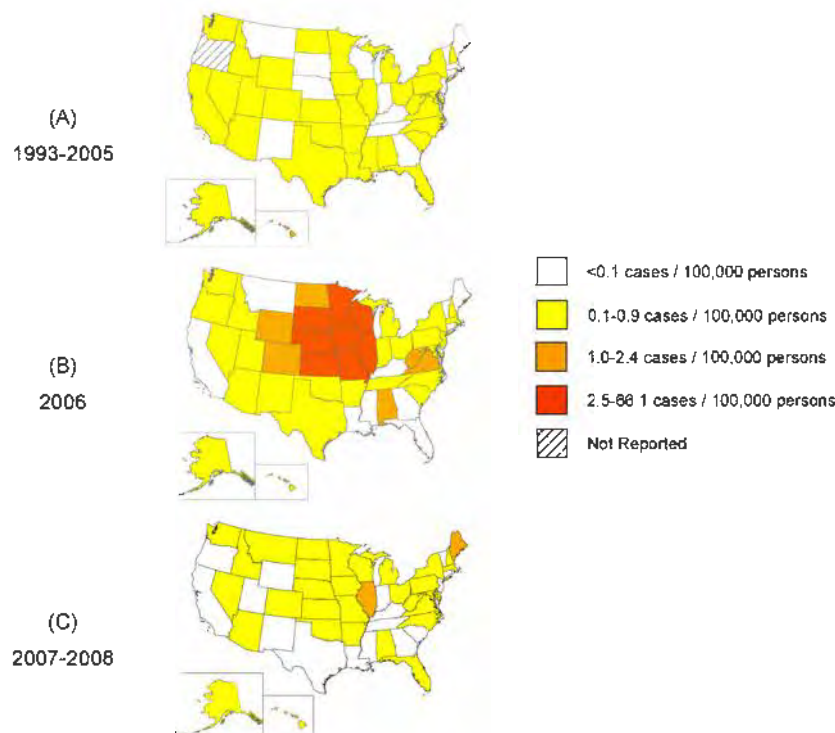


Fig. 8. Geography of the Period of the Second Resurgence, 1993–2008. For each map, the state's aggregate incidence reported to CDC over the given time period is shown.

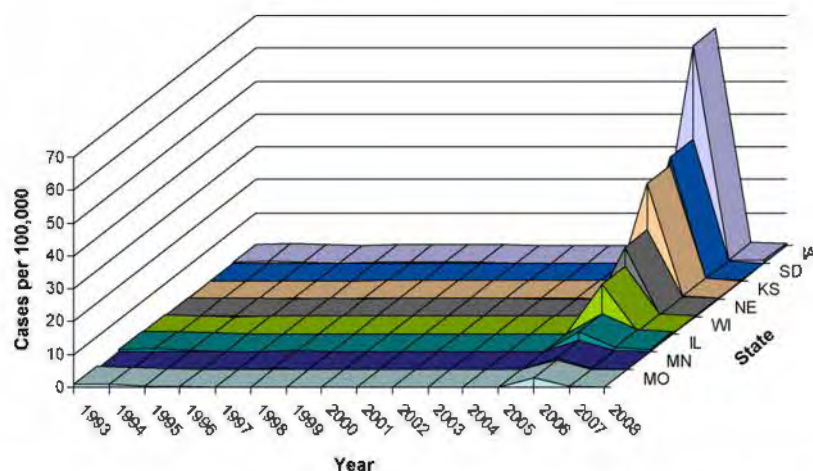


Fig. 9. Highest Incidence States in the Period of the Second Resurgence, 1993–2008. The eight states shown along the y-axis had the highest aggregate incidence reported to CDC during 1993–2008. Annual incidence for each state is shown on the z-axis.

as MMR, stating “Mumps revaccination is particularly important” [30]. By 1992, mumps incidence finally returned to pre-resurgence levels at 1.0/100,000.

3.4. Period of Second Resurgence: 1993–2008 (Fig. 7)

3.4.1. Coverage

Annual national immunization coverage surveys resumed in 1995 with NIS: for every year through 2008, first dose preschool mumps vaccination coverage was $\geq 90\%$, with a slow upward trend. Second dose coverage among adolescents was measured by two different surveys. The first showed coverage rose from 68% in 1997 to 77% in 2003 [15], and the second (NIS) showed a rise from 87% in 2006 to 89% in 2008.

3.4.2. Pre-resurgence (1993–2005)

Reported annual mumps cases continuously declined from 1989 through 2001, then plateaued through 2005, averaging 268 (aver-

age incidence 0.1/100,000) with a historical nadir of 231 in 2003. Of case-patients, 72% were vaccinated, 37% with two doses. Peak incidence remained primarily in the 5–9-year age range. Seasonal patterns were no longer recognizable (Fig. 2C). The eight Midwestern states most affected in the subsequent resurgence (representing 13% of the US population) accounted for 10% of total cases (Fig. 8A). Compared to these eight states, cumulative mumps incidence in the rest of the country was 41% higher (0.24 vs. 0.17/100,000).

3.4.3. Resurgence (2006)

Abruptly the number of cases rose from 13 in December 2005 (the third lowest month in US history) to 2786 in April 2006 (the highest month in 29 years) with an annual total of 6584 (incidence 2.2/100,000). Eight states contiguously located in the central US (13% of US population) accounted for 85% of 2006 cases (Fig. 8B). These states tended to have a lower population density than the rest of the country (56.2 persons vs. 96.9 persons per square mile,

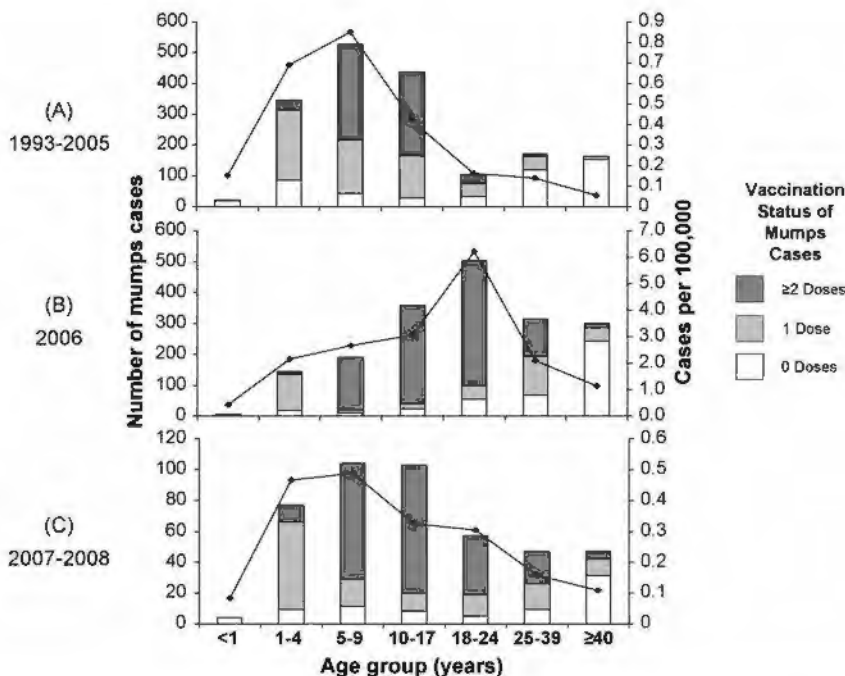


Fig. 10. Age-specific incidence and case numbers by vaccination status. Period of the Second Resurgence, 1993–2008. For each graph, bars represent total cases of mumps reported to CDC by vaccination status, and the solid line represents aggregate incidence. Note that y-axes are on a different scale for each graph.

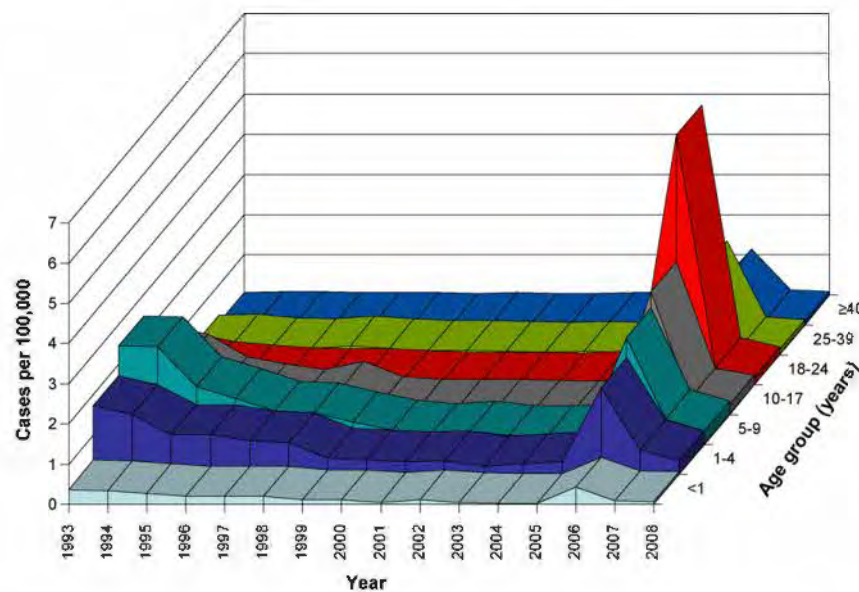


Fig. 11. Annual incidence by age group, 1993–2008. Year is plotted along the x-axis, and age group in years is plotted along the y-axis. Mumps incidence for each year and age group, as reported to CDC, is plotted along the z-axis.

$P=0.08$). For each of the preceding 11 years, each of these states had $\geq 86\%$ first dose mumps vaccination coverage according to NIS and near-zero mumps incidence. Each experienced explosive epidemic onsets (mean peak/trough 165, range 13–350, excluding one infinite value) and almost equally abrupt decreases (Fig. 9). Peak incidence shifted abruptly to 18–24-year olds (Figs. 10 and 11). Of case-patients, 76% were vaccinated, 57% with two doses. However, for the most highly affected 18–24-year age group, 80% had received two doses (Fig. 10B). Studies suggested 83% of case-patients in this age group were college students, mainly in rural states, 89–99% of whom had received two doses of vaccine, most ≥ 10 years before [4–6].

3.4.4. Post-resurgence (2007–2008)

Case counts declined rapidly toward pre-resurgence levels. Of case-patients, 82% were vaccinated, 53% with two doses. Peak incidence progressively shifted back toward the 5–9-year age group, and the geographic pattern was unremarkable.

3.4.5. Military

Military recruits were apparently spared involvement in the resurgence, despite belonging to the same age group and residing in barracks across the US. During the years for which data are available (1998–2007), the number of first-occurrence mumps cases in an ambulatory setting averaged 30 annually (range 16–53) in a total military population that averaged 1.38 million (range 1.36–1.41 million) for an aggregate incidence of 2.2/100,000. During the 2006 nationwide resurgence, 53 cases but no outbreaks were reported. In 1991, the military had begun routine administration of MMR to recruits without regard to prior vaccination status. In 1995 this was changed to provide measles and rubella vaccination regardless of prior history and mumps vaccination (either as MMR or as single antigen) to those without written proof of prior vaccination or mumps disease. In 2006 this policy was updated again to provide MMR to those without documentation of vaccination or serologic evidence of immunity against measles and rubella. Under these policies, an unknown proportion of recruits may have received a third dose of a mumps-containing vaccine [31,32].

4. Discussion

Many of the unexpected features of the 2006 mumps resurgence had occurred before in the history of mumps activity in the United States. Both the 1986–1987 and 2006 resurgences were immediately preceded by historic low points in disease activity. Both resurgences had extremely abrupt onsets, with incidence rising 10- to >100 -fold over baseline within a month. In both resurgences, a few states contiguously located in the central US contributed most cases. In both the 1986–1987 and 2006 resurgences, there was a sudden upward shift in peak attack rate from children 5–9 years old to teenagers/young adults, followed by a return to the 5–9-year age group after the resurgence had subsided.

However, in two important respects, the 2006 resurgence appears to have been unique. First was the apparent near-elimination of viral transmission in the preceding decade: vaccination levels higher than the estimated herd immunity threshold (88–92%) [33], disease incidence rate <1 case per million, loss of seasonality, and absence of any foci of ongoing transmission.

Second was the preponderance of cases among two-dose vaccinees. Though outbreaks attributable to one-dose vaccine failure were first reported in the late 1980s, and sporadic cases of two-dose failure were common after the early 1990s, large-scale outbreaks attributable to two-dose failure had not been reported in the US or elsewhere, to our knowledge, prior to 2006. After the US reported the 2006 resurgence, however, other nations have begun reporting mumps outbreaks attributed to two-dose failure. The Czech Republic, which had implemented a routine two-dose mumps vaccination policy just 2 years prior to the US, experienced a large outbreak in 2006 with characteristics similar to that of the US: 70% of cases had received two doses, and among these, the median age was 15 years [34]. In 2008–2009, North Wales experienced an outbreak in which 87% of case-patients had received two doses of MMR, and the median age was also 15–16 years [35].

These apparently novel outbreak characteristics may have historical precedents, however. The 1986–1987 resurgence has been explained as resulting from the growth of a population who had missed vaccination as children but who had been spared previous disease exposure, so that when they entered into high school and college environments where transmission was facilitated, a resurgence resulted [26]. Though the 2006 resurgence involved

a highly vaccinated, rather than an unvaccinated population, one can speculate that the conditions which gave rise to it may not have been so different from the 1986–1987 resurgence. In rural sections of Midwestern states, where population density was very low and vaccination coverage high, natural boosting attributable to importations or endemic disease may have been rare, allowing vaccine-induced immunity to wane. Although susceptibles accumulated, mumps is much less infectious than measles [36], and the force of infection in sparsely populated areas was insufficient to cause outbreaks until young adults entered concentrated living conditions in colleges [5,6]. Such an outbreak pattern has been reported as far back as World War I, in which outbreaks occurred among rural populations placed in barracks conditions [17–20].

In support of this hypothesis is the fact that these eight Midwestern states had an aggregate population density almost half of the rest of the United States and a much lower cumulative mumps incidence in the period preceding the resurgence. Compared to other rural areas in the country (e.g., the Southeast or Mountain West), they also had higher rates of college attendance (National Center for Education Statistics, Total fall enrollment in degree-granting institutions, by state or jurisdiction: Selected years, 1970 through 2005, accessed 6/25/09, http://nces.ed.gov/programs/digest/d06/tables/dt06_193.asp). Studies in the eight Midwestern states during the resurgence suggested that among 18–24-year olds (the most affected group) 83% of cases were college-associated, with the highest attack rate among first-year students living in dormitories [4–6]. Thus it is possible that these Midwestern states may have been at increased risk because of the relatively larger numbers of well-vaccinated young adults leaving home in rural areas to live together in dormitory conditions. While lower preceding disease incidence, lower population density, and greater rates of college attendance may have contributed to higher attack rates in the Midwest, the extreme focality of the 2006 mumps resurgence – which contrasts dramatically with the geographic patterns of the measles and pertussis resurgences of the 1990s – suggests that other factors, not accounted for in this analysis, may also have played a role.

Regardless of hypothetical mechanisms, the patterns of mumps outbreaks, both in 2006 and in the past, have implications for mumps surveillance and vaccination programs. First, given the explosive characteristics of mumps outbreaks in the past, historically low disease rates may not be proof that the risk of epidemic disease is remote. Thus, the usual indicators of an impending epidemic (e.g., gradually rising numbers or increasing spread rates) may not occur. Similarly, if epidemics arise specifically from lack of wild disease boosting, the search for foci of ongoing transmission may not be helpful in identifying locations at risk. Coverage surveys to identify pockets of under-vaccination will not be fruitful when outbreaks occur among highly vaccinated populations. And when mumps does occur among highly vaccinated populations, data suggest clinical manifestations may be atypical, the proportion of asymptomatic case-patients may be greater than the previous estimate of 30%, and the usual laboratory tests (e.g., IgM) may have lowered yield [6]. Thus silent or unrecognized transmission can contribute to difficulties in identifying and containing disease introductions, problems in recognizing outbreaks, and diminished effectiveness of isolation/quarantine measures.

This may be particularly important since mumps disease patterns in 2007 and 2008 appeared to be returning to those existing in the period leading up to the 2006 resurgence. Provisional data from the first 6 months of 2009 seem to confirm this trend (CDC, unpublished data).

Novel strategies are needed for identifying disease and detecting and eliminating build-up of susceptible individuals. Neutralizing antibodies may be protective against mumps disease [37], and their titers have been shown to decline over time [38]. If the 2006

resurgence occurred because the protective value of a second dose waned in a proportion of vaccinated cohorts, particularly in rural populations who had been spared disease exposure, then serologic monitoring of antibody levels may be needed in addition to monitoring vaccination and disease rates. Studies to better characterize the protective level of mumps antibody would be particularly useful in interpreting such surveys. Improved laboratory methods for diagnosing mumps in vaccinated populations would also be valuable. Evidence suggests the 2006 US resurgence was preceded and possibly seeded by mumps epidemics in nations such as the United Kingdom and Canada with which the US has substantial contact [7,39]. Expanding and improving global surveillance for mumps, particularly in developed countries with vaccination programs, will assist in evaluating the potential risk of mumps activity in the US. The relative absence of mumps activity in the military during the 2006 resurgence raises the possibility that a third dose could be effective in preventing or controlling future epidemics. The immunogenicity, long-term efficacy, and adverse events associated with a third dose of mumps vaccine in young adults need to be studied so that data will be available to guide vaccination response in future resurgences.

There are several limitations to this study. The data analyzed were obtained from a passive surveillance system, with much missing data. For the pre-vaccine era, we relied on data summaries, sometimes drawing on a limited number of individual studies to make inferences about population-based conditions. Viral strain differences may affect the level of antibodies needed to neutralize mumps virus [40,41], but too few viral specimens were available to examine the potential role of virus strains in mumps epidemiology (1917–2008).

Nonetheless, we believe our findings demonstrate many aspects of the 2006 resurgence were consistent with patterns of mumps epidemiology for the preceding 80 years. Following periods of low disease, explosive outbreaks occurred when young adults from rural areas were brought into close contact. These recurrent patterns help provide insight into how to anticipate and prevent future mumps epidemics. As in the past, this will depend on detecting and eliminating build-up of susceptible individuals – now among highly vaccinated populations.

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Mumps Antibody Response in Young Adults After a Third Dose of Measles-Mumps-Rubella Vaccine

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Background. Mumps outbreaks in populations with high 2-dose measles-mumps-rubella (MMR) vaccine coverage raise the question whether a third dose of MMR vaccine (MMR3) is needed. However, data on the immunogenicity of MMR3 are limited. We assessed mumps virus neutralizing antibody levels pre- and post-MMR3 in a nonoutbreak setting.

Methods. Mumps antibody titers were assessed at baseline, 1 month, and 1 year after MMR3 in subjects aged 18–28 years.

Results. At baseline, 5 of 656 (0.8%) subjects had seronegative mumps neutralizing antibody titers and 38 (5.8%) had low titers. One year post-MMR3, these numbers declined to 3 (0.5%) and 16 (2.4%), respectively. Subjects with low baseline titers were more likely to have low 1-month and 1-year titers ($R^2 = 0.81$ – 0.87 , $P < .0001$). Compared to baseline, geometric mean titers were significantly higher at 1 month ($P < .0001$) and 1 year ($P < .01$) post-MMR3; however, reverse cumulative distribution curves showed only minimal shifts in mumps titers from baseline to 1 month and 1 year.

Conclusions. Very few subjects had negative or low baseline mumps titers. Nonetheless, mumps titers had modest but significant increases when measured 1 month and 1 year post-MMR3. This temporary increase in titers could decrease susceptibility to disease during outbreaks, but may have limited value for routine use in vaccinated populations.

Keywords. mumps; third-dose measles-mumps-rubella (MMR) vaccine; mumps immunogenicity; vaccine-preventable disease; immunization.

Mumps is an acute viral disease that classically presents with parotitis. Serious complications include orchitis, deafness, and encephalitis [1]. A monovalent mumps vaccine was licensed in 1967, and in 1977, the Advisory Committee on Immunization Practices (ACIP) recommended universal childhood vaccination with 1 dose [2]. In 1989, the ACIP recommended that school-aged

children receive 2 doses of measles-mumps-rubella (MMR) vaccine for improved measles control, with the first dose at age 15 months (high-risk areas) or 12 months (non-high-risk areas) and the second dose at age 4–6 years [3]. Vaccine coverage against mumps increased, which was associated with a >99% decline in disease incidence compared with the prevaccine era [4]. Following this success, the Healthy People 2010 goal of mumps elimination was established [5]. However, unlike measles [6] and rubella [7], mumps elimination in the United States was never documented. The current Healthy People 2020 mumps goal is to reduce the number of US-acquired cases, rather than elimination [8].

Between 2006 and 2013, several large mumps outbreaks occurred in the United States and abroad, primarily among 2-dosed vaccinated school-aged children and

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young adults in high-contact settings [9–16]. Although current MMR vaccination recommendations are for the first dose at age 12–15 months and the second dose at 4–6 years [17], a third dose of MMR vaccine (MMR3) was offered at school-based immunization clinics during 2 of these outbreaks as part of a public health response [10, 11]. However, serologic response was not measured. Although attack rates declined after administering MMR3 in both school-based studies, in one study, statistical significance could not be established due to the small number of cases, and in both studies, the possibility of the declines being unrelated to the intervention could not be excluded [10, 11].

A third dose of mumps-containing vaccine is also administered in some nonoutbreak settings. Healthcare personnel, military recruits, international travelers, and college students who may have been vaccinated as children but who lack documentation are routinely given an additional dose, which is often the third dose [17–19]. Pregnant women with a negative rubella titer are revaccinated after delivery even if they have had 2 previous MMR doses [20].

Despite mumps outbreaks occurring in communities with high 2-dose MMR vaccine coverage and third doses being routinely administered in some settings, data on the immunogenicity of MMR3 are limited [21, 22]. The objective of this study was to assess the magnitude and duration of aggregate mumps virus neutralizing antibody responses after MMR3 in a healthy, young adult population.

METHODS

Setting

The source population comprised patients who received care from the Marshfield Clinic, a large multispecialty group practice with 54 locations in rural central, western, and northern Wisconsin. The clinic developed and maintains an electronic vaccination registry (www.recin.org) for all immunizations administered by Marshfield Clinic providers, in addition to those given by many local public health agencies and immunization providers.

Subjects

Two cohorts comprising 685 subjects were enrolled over a 1-year period. Cohort 1 comprised 113 young adult subjects who participated in a 12-year longitudinal study at the Marshfield Clinic examining immunogenicity and adverse events following the second dose of MMR vaccine, hereafter called the “longitudinal study” [23, 24]. To achieve adequate sample size, cohort 2 was recruited. Cohort 2 comprised 572 young adults identified using Marshfield’s vaccination registry who had 2 documented doses of MMR vaccine but did not participate in the longitudinal study. Invitation letters were mailed to both cohorts, and follow-up phone calls were made.

Although only 25 (22.1%) cohort 1 subjects had low or negative mumps titers at any point during the longitudinal study, all 93 cohort 1 subjects with at least 1 low or negative titer to any of the 3 antigens during the longitudinal study (defined as <121 mIU/mL for measles [25], ≤ 10 mIU/mL for mumps [23], or ≤ 10 mIU/mL for rubella [26]) and all cohort 2 subjects were offered a third dose of MMR vaccine (M-M-R II, Merck & Co) in this study. We combined cohorts 1 and 2 for analysis purposes as there were no statistically significant differences between the 2 cohorts in terms of sex, race/ethnicity, age, geometric mean titers (GMTs) at baseline or 1 year post-MMR3, or percentage with negative or low baseline mumps titers (Supplementary Table 1). Serum was collected from these study subjects immediately before, and 1 month and 1 year after MMR3.

Study Design

At each visit, subjects were questioned concerning mumps disease, exposures, vaccinations, and other health events. MMR vaccine was administered during the initial visit according to a standard protocol. Adverse events were evaluated and will be reported elsewhere. Informed consent was obtained by all subjects. The study was approved by the institutional review boards of the Marshfield Clinic Research Foundation and the Centers for Disease Control and Prevention (CDC).

The analysis of data for all 3 antigens was taken into consideration when determining sample size. To detect a decrease in the proportion of subjects who had low or negative titers from the last draw of the longitudinal study compared with 1 year post-MMR3, we based our sample size on a decrease from approximately 20% with low or negative titers at the last draw of the longitudinal study in 2006–2007 to 10% 1 year post-MMR3 for mumps, 5% to 1% for measles, and 50% to 30% for rubella, with 90% power and 95% confidence intervals. The target sample size of 375 was increased to 685 to account for the fact that more than one-third of the 312 subjects from the longitudinal study were ineligible to receive a third dose based on high titers for all 3 antigens throughout the longitudinal study and 53% attrition during the longitudinal study [23, 25, 26].

Exclusion Criteria

Subjects were excluded if they had a history of measles, mumps, or rubella disease, lived in the same household with anyone who had these diseases during the subject’s lifetime, previously received a third MMR vaccine dose, received any vaccinations within 30 days of enrollment, had any contraindications to MMR vaccination, or had any condition likely to impair immune response, as specified in the ACIP recommendations [27].

Laboratory Methods

Although there is no established correlate of immunity for mumps, neutralizing antibody is likely essential for protection against mumps and is considered the gold standard for

mumps serology. Thus, plaque reduction neutralization (PRN) assay was used to determine virus neutralizing antibody titer in sera as described previously [28, 29]. Heat-inactivated sera were serially diluted 2-fold from 1:4 to 1:128 and mixed with an equal volume of the Jeryl Lynn vaccine virus diluted to contain approximately 80 plaque-forming units (PFU), resulting in a final serum dilution range of 1:8 to 1:256. Virus control wells were incubated with the virus preparation and an equal volume of minimal essential media (MEM) containing 5% fetal bovine serum (FBS). Reference serum “Lot 3” was included in each assay run. Following a 1-hour incubation period, half of each of the virus/serum mixtures (containing approximately 40 PFU of virus) was transferred to each of 2 wells in 24-well plates containing Vero cell monolayers and overlaid with 2% carboxymethylcellulose (Sigma) in MEM supplemented with 10% FBS. After 5 days of incubation at 37°C, wells were stained with neutral red (Sigma), and plaques were counted the following day. The mean plaque number was determined for duplicate wells at each serum dilution. The neutralizing antibody titer was calculated as the serum dilution capable of reducing the mean number of virus plaques by $\geq 50\%$ compared to the mean number of plaques in virus control wells using the Kärber formula [30]. Sera not reaching a 50% endpoint were retested in assays using a higher dilution series.

No established PRN mumps titer correlates with mumps immunity [31]. Therefore, the cutoffs used in this study for seronegative, low-positive, and high-positive were chosen based on a previous study [29]. Mumps virus neutralizing antibody titers $<1:8$ (limit of assay detection) were considered seronegative. For analysis purposes, we considered titers between 1:8 and $<1:16$ (ie, within a single dilution factor of the limit of detection) to be low-seropositive and titers $\geq 1:16$ to be high-seropositive.

Data were pooled across assay runs that met the following 2 validity criteria: (1) the mean plaque number in the negative serum control wells was between 20 and 60 (a range validated in the laboratory to not influence measured neutralizing antibody titers), and (2) the neutralizing antibody titer for reference mumps serum Lot 3 was required to be within 2 standard deviations (SD) of its GMT based on historic data. Assays not meeting these poolability requirements were retested. Serum samples from individual subjects were tested in the same assay run. Other than each subject's unique identifier code and serum collection dates, laboratories were blinded to study information.

Data Analysis

Mantel-Haenszel χ^2 and Fisher exact tests were run to assess categorical variables. Wilcoxon rank-sum tests were used for continuous variables. Variables that were considered potential risk factors for low or negative mumps titers (defined as <16 mIU/mL in this study) included age at first MMR dose, time since second MMR dose (we used <15 years vs ≥ 15 years prior based on the average age of subjects at enrollment minus the age

when the second dose was recommended), sex, race/ethnicity, military member, post-secondary school attendance, number of household members, current illnesses, current medications, and (for post-MMR3 serum samples) the binary variable of whether the subject had low or negative baseline mumps titers. In multivariate logistic regression, a forward stepwise selection approach that used P values $<.4$ for inclusion and $<.05$ for retention identified whether any factors were independently associated with negative or low mumps antibody titer levels at baseline, 1 month and 1 year post-MMR3. GMTs were calculated from base 2 log-transformed data. Statistical significance was assigned for P values $<.05$. Data were analyzed with SAS software, version 9.3. Reverse cumulative distribution curves were created by SigmaPlot 12 (Systat Software, Inc) and were used to compare the shift in the curves from baseline, 1 month, and 1 year.

RESULTS

Enrollment

From the longitudinal study, we successfully contacted 194 of 200 persons attempted. Of those, 113 (58%) were enrolled, 45 (23%) refused, and 36 (19%) were ineligible (15 due to prior receipt of MMR3 and 21 for other reasons). To achieve adequate sample size, we attempted to contact an additional 1795 persons and successfully reached 1379 (77%). Of those, 572 (41%) were enrolled, 664 (48%) refused, and 143 (10%) were ineligible (4 due to prior MMR3 receipt and 139 for other reasons).

Baseline serum samples were obtained from 678 of 685 subjects enrolled from the combined group of longitudinal study participants and new recruits; 656 (95.8%) received MMR3 and completed at least 1 follow-up draw. There were 655 (99.5%) subjects who completed the 1-month draw and 612 (93.3%) who completed the 1-year draw. We excluded 20 (2.9%) subjects who were not given MMR3, because the group was too small to be considered a comparison group. An additional 2 (0.3%) were excluded because they only had baseline data. We analyzed data from 656 subjects (Figure 1); 290 (44.2%) were male and 644 (98.2%) were self-declared non-Hispanic white. Subjects ranged in age from 18 to 28 years, (mean, 20.8 [SD, 2.1] years).

Mumps Titers Pre- and Post-MMR3

At baseline, 5 (0.8%) subjects were seronegative, 38 (5.8%) were low-seropositive, and 613 (93.4%) were high-seropositive (Figure 2A). Of the 613 subjects with high-seropositive baseline titers, 612 had sera drawn at 1 month and 572 had sera drawn at 1 year; all remained high-seropositive. Of the 5 subjects who were seronegative at baseline, 1 became low-seropositive and 4 became high-seropositive 1 month after MMR3. One year post-MMR3, the low-seropositive subject returned to seronegative status, while 2 high-seropositive subjects at 1 month

Figure 1. Flow chart for enrollment, analysis, and vaccination of subjects with a third dose of measles-mumps-rubella (MMR) vaccine.

Overall, at 1 month post-MMR3, 0 of 655 subjects had negative mumps titers, 10 (1.5%) had low-seropositive titers, and 645 (98.5%) had high-seropositive titers. One year post-MMR3, 3 of 612 (0.5%) subjects had negative mumps titers, 16 (2.6%) had low-seropositive titers, and 593 (96.9%) had high-seropositive titers. A majority of subjects with high-seropositive titers were in the upper end of the titer distribution at baseline, 1 month, and 1 year (Figure 2B).

GMT's were statistically different between baseline and 1 month post-MMR3 (104.1 vs 159.2; $P < .0001$), as well as between baseline and 1 year post-MMR3 (104.1 vs 125.9; $P < .01$). However, as shown in the reverse cumulative distribution curves (Figure 3), the shift in mumps titers from baseline to 1 month to 1 year was minimal. The shape and distribution of

Forty of 655 (6.1%) subjects had 4-fold rises from baseline to 1 month post-MMR3, of whom 4 had negative baseline titers, 11 had low baseline titers, and 25 had positive baseline titers. Thirteen of 612 (2.1%) subjects had 4-fold rises from baseline to 1 year post-MMR3, of whom 2 had negative baseline titers, 3 had low baseline titers, and 8 had positive baseline titers. There were no subjects with a 4-fold rise in titer from 1 month to 1 year.

By χ^2 analysis, sex, race/ethnicity, military member, post-secondary school attendance, number of household members, current illnesses, and current medications were not associated with negative or low-seropositive mumps titers at baseline, 1 month, or 1 year post-MMR3 (Table 1).

Significant risk factors for negative or low baseline mumps titers by χ^2 analysis were age at first MMR dose (odds ratio [OR] = 2.58; 95% confidence interval [CI], 1.08–6.13; $P = .03$).

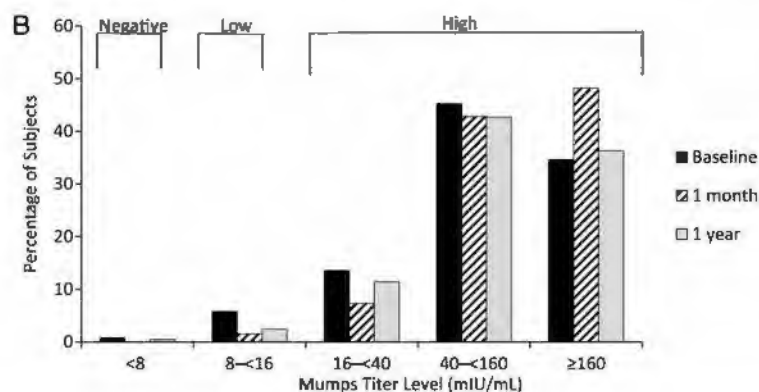
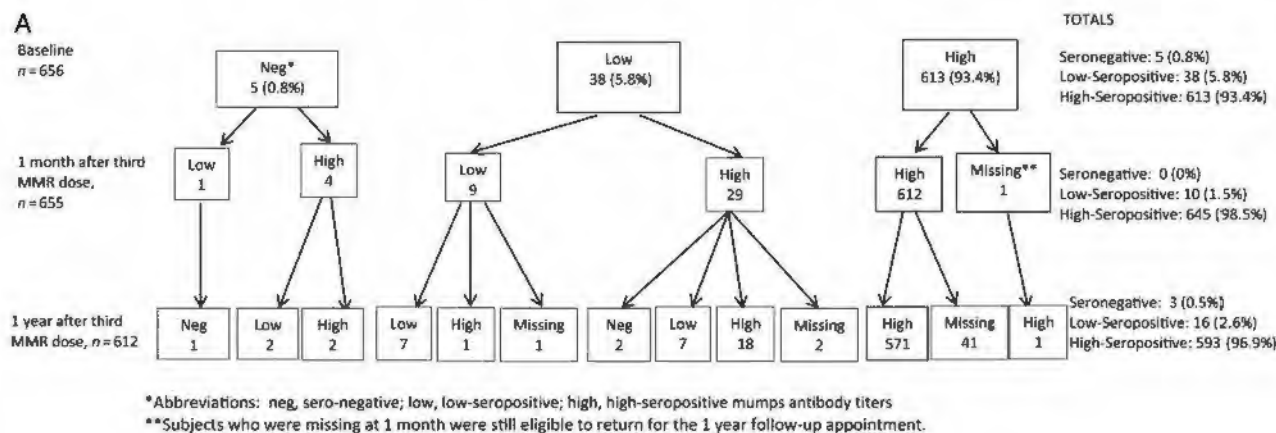


Figure 2. A, Flow chart of mumps antibody titer levels at baseline, 1 month, and 1 year. B, Percentage of subjects who had negative, low-seropositive, and high-seropositive mumps antibody titer levels at baseline, and 1 month and 1 year following a third dose of measles-mumps-rubella (MMR) vaccine.

and time since second MMR dose (OR = 0.38; 95% CI, 0.16–0.92; $P = .03$). Of the 50 (7.6%) subjects who received their first dose at age 12 to <15 months, 7 (14%) had negative or

low baseline mumps titers, compared with 36 of 606 (5.9%) subjects who were vaccinated with their first dose at age ≥15 months. Of the 189 (28.8%) subjects who received their second dose <15 years prior, 6 (3.2%) had negative or low titers, whereas, of the 467 (71.2%) subjects who received their second dose ≥15 years prior, 37 (7.9%) had negative or low titers.

By χ^2 analysis, a significant risk factor for negative or low mumps titers 1 month post-MMR3 was whether a subject had low or negative baseline mumps titers (OR, 384.0; 95% CI, 22.0–6692.9; $P < .0001$). Significant risk factors for negative or low mumps titers 1 year post-MMR3 were whether a subject had low or negative baseline mumps titers (OR, 1038.5; 95% CI, 60.7–17 773.6; $P < .0001$) and the time since the second MMR dose (OR, 0.38; 95% CI, 0.16–0.92, $P = .02$). When mumps titer levels were assessed as a continuous variable, baseline MMR3 titers were significantly associated with individual log-transformed mumps titer levels at 1 month and 1 year. Subjects with lower baseline titers were more likely to have lower titers at 1 month and 1 year, whereas subjects with higher baseline titers were more likely to have higher titers at 1 month and 1 year ($R^2 = 0.81$ – 0.87 ; $P < .0001$; Figure 4).

A logistic regression model showed that age at first MMR dose and time since second MMR dose remained independently

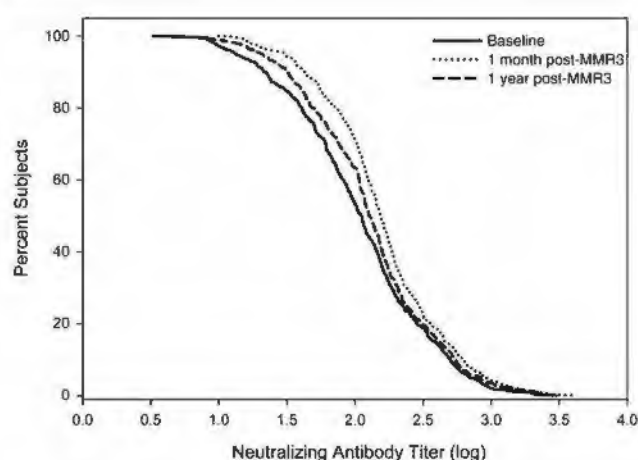


Figure 3. Reverse cumulative distribution curve using log-transformed titers by percent of subjects who had neutralizing mumps antibody titers at baseline and 1 month and 1 year following a third dose of measles-mumps-rubella (MMR3) vaccine.

Table 1. Risk Factors for Negative or Low Mumps Titers at Baseline and 1 Month and 1 Year After Receiving the Third Measles-Mumps-Rubella Vaccine Dose

Risk Factor	Baseline (n = 656)		Adjusted Baseline (n = 656)		1 Month Post-MMR3 (n = 655)		1 Year Post-MMR3 (n = 612)	
	Unadjusted OR (95% CI)	P Value*	Adjusted OR (95% CI) ^a	Adjusted P Value	Unadjusted OR (95% CI)	P Value	Unadjusted OR (95% CI)	P Value
Sex								
Female	0.82 (0.44–1.52)	.53	0.79 (0.23–2.76)	.71	1.04 (0.41–2.62)	.94
Male	Reference							
Race/ethnicity								
White, non-Hispanic	1.81 (0.11–31.05)	.35	0.41 (0.02–7.47)	.66	0.77 (0.04–13.54)	.55
All other races	Reference							
Military member								
Yes	1.27 (0.07–23.38)	.55	5.55 (0.29–106.86)	.78	4.33 (0.22–86.66)	.76
No	Reference							
Post-secondary school attendance								
Yes	0.71 (0.38–1.32)	.27	0.61 (0.17–2.17)	.44	0.41 (0.15–1.09)	.06
No	Reference							
No. of other persons in household								
≥1 person	0.49 (0.20–1.22)	.12	0.76 (0.09–6.09)	.79	1.59 (0.21–12.13)	.65
None	Reference							
Current medical conditions								
≥1 condition	0.31 (0.04–2.29)	.22	0.63 (0.04–10.90)	.39	0.75 (0.10–5.74)	.78
None	Reference							
Current medications								
≥1 medication	0.80 (0.43–1.50)	.49	0.58 (0.17–2.03)	.39	1.21 (0.45–3.22)	.71
None	Reference							
Age at 1st MMR dose								
12 to <15 mo	2.58 (1.08–6.13)	.03*	2.85 (1.18–6.85)	.02*	3.11 (0.64–15.05)	.14	2.34 (0.66–8.34)	.18
≥15 mo	Reference							
Time since 2nd MMR dose								
<15 y	0.38 (0.16–0.92)	.03*	0.36 (0.15–0.87)	.02*	0.27 (0.03–2.15)	.19	0.13 (0.02–0.98)	.02*
≥15 y	Reference							
Baseline titers								
<16 mIU/mL	384.0 (22.0–6692.9)	<.0001*	1038.5 (60.7–17 773.6)	<.0001*
≥16 mIU/mL	Reference			

Abbreviations: CI, confidence interval; MMR, measles-mumps-rubella vaccine; MMR3, third dose of measles-mumps-rubella vaccine; OR, odds ratio.

^a Adjusted ORs are not reported for 1 month post-MMR3 and 1 year post-MMR3 because the models that included the significant variables from χ^2 analysis were poor fits. When the variable "baseline titers" was excluded from the 1 month and 1 year models, no significant results were found.

* Statistical significance at $P < .05$.

associated with a subject's baseline mumps titer levels (OR, 2.85; CI, 1.18–6.85 [$P = .02$] and OR, 0.36; CI, 0.15–0.87 [$P = .02$], respectively) (Table 1). No factors were independently associated with a subject's mumps titers 1 month or 1 year post-MMR3. The 1 month and 1 year post-MMR3 models that included the significant variables from χ^2 analysis were poor-fitting models. Even when the significant variable "baseline titers" was excluded from the 1-month and 1-year models because of its instability due to a zero-cell in bivariate analysis, and other variables were included, no significant results were found.

DISCUSSION

Almost all subjects were mumps virus seropositive prior to receiving MMR3. Virus neutralizing antibody titers had a modest but significant increase following MMR3 when measured 1 month after vaccination. Of 43 subjects with low or negative baseline titers, 33 (76.7%) increased to high titers 1 month after receiving a third MMR dose. This increase in neutralizing titers could facilitate outbreak control by temporarily boosting mumps titers, particularly for those on the cusp of protection.

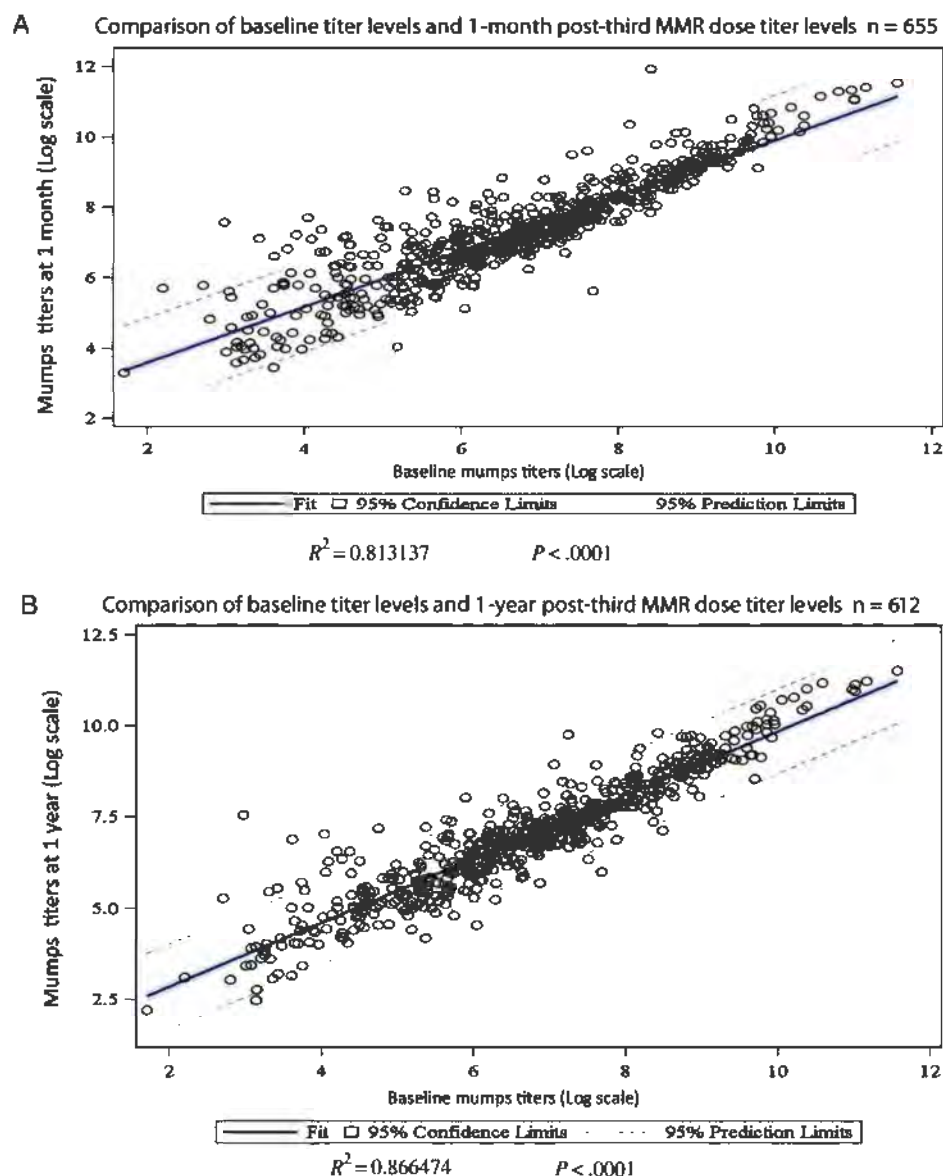


Figure 4. A, Comparison of individual mumps titer levels at baseline and 1 month following a third dose of measles-mumps-rubella (MMR) vaccine. Circles represent individual titer levels. The dark solid line represents the linear regression of the best-fit of the comparison. The light shading around the line represents the 95% confidence interval. The dotted lines represent the 95% confidence limit. B, Comparison of individual mumps titer levels at baseline and 1 year following a third dose of MMR vaccine. Circles represent individual titer levels. The dark solid line represents the linear regression of the best fit of the comparison. The light shading around the line represents the 95% confidence interval. The dotted lines represent the 95% confidence limit.

However, only 52.5% of subjects with low or negative baseline titers sustained high titers 1 year post-MMR3. Overall, titers returned to near-baseline levels 1 year later, which does not support routine administration of a third MMR dose.

Even though the mumps component of the MMR vaccine is the least effective of the 3 antigens, with a 1-dose and 2-dose vaccine effectiveness ranging from 49% to 91% [32–36] and 66% to 95% [34, 35, 37], respectively, 2 MMR doses are generally sufficient to prevent large-scale transmission. During 2006–2012, a median of 454 cases was reported in the United States annually; when outbreaks occurred, they were primarily

contained to the affected group (eg, school-aged children, college students, insulated religious communities, inmates), with minimal spread to the broader community.

Although timing of the administration of the first and second doses of MMR vaccine significantly affected mumps titer levels later in life, these findings represented only a small proportion of the population. Nonetheless, individuals who received their first MMR dose at the earlier end of the recommended age range spectrum (12 to <15 months) had nearly 3 times the odds of low or negative baseline mumps titers compared with those who had their first dose at ≥ 15 months. However, unpublished

data from previous outbreaks in New York and Guam did not find that those who received their first MMR dose at age 12 to <15 months vs ≥ 15 months were more likely to become infected with mumps (CDC, unpublished data). We found that subjects who received their second dose more recently had a protective effect. Research shows conflicting findings regarding an association between vaccine failure and increasing time since vaccination, with a positive correlation found in some studies [32, 37] and no association found in others [36, 38].

Subjects with high baseline antibody levels tended to stay high over time, and those with lower levels tended to stay lower. This finding suggests there may be an inherent trajectory for mumps antibody production based on an individual's baseline titers (ie, some individuals may be predisposed to lower mumps titers or higher mumps titers, irrespective of the number of additional doses of mumps-containing vaccine they receive).

Although the antibody threshold that provides protection against mumps disease has not been established [31], a prospective study published in 1969 found that clinical mumps during an outbreak did not occur in individuals with titers ≥ 8 mIU/mL; however, even lower titers offered protection to some individuals [29]. In a recent outbreak-related study conducted among MMR vaccinees, significantly higher neutralizing antibody titers appeared to be associated with protection, although no antibody titer unambiguously discriminated cases from non-cases [31]. Without a correlate of immunity, we cannot assume that the presence of antibodies below the arbitrary cutoff is insufficient to offer protection, nor can we postulate that the presence of antibodies at or above the cutoff necessarily provides protection from mumps infection.

Similar to results previously reported in the longitudinal study [23], <1% of subjects in the current study had negative baseline titers. In contrast, whereas 20% of subjects in the longitudinal study had low neutralizing baseline antibody titers, only 5.8% of subjects in the current study possessed low neutralizing baseline titers. This likely reflects that in the longitudinal study, subjects at baseline had previously received 1 MMR dose, whereas, in our current study, subjects at baseline had previously received 2 MMR doses. This also likely explains why only 2.1% of subjects in the present study vs 50% in the longitudinal study demonstrated a 4-fold rise in titer from baseline to 1 year postvaccination [23]. Also, numerous studies have found mumps virus neutralizing antibody titers to be dependent on the challenge virus strain used in the assay [31, 39]. Whereas the Barnes challenge virus strain was used in the neutralization assay during the longitudinal study, the Jeryl Lynn strain was used during the current study.

Our study has limitations. Subjects resided in predominantly rural areas and self-declared as non-Hispanic white. Thus, they are not representative of the US population. Selection bias may have been present in cohort 1, because MMR3 was only offered to those who had a low or negative measles, mumps, or rubella

titer during the longitudinal study. The number of subjects not receiving MMR3 was small, which prevented us from having an adequate comparison group. Although the refusal rate among subjects was high, participation bias based on baseline titer category was unlikely, because individuals were unaware of their baseline titer levels.

Overall, mumps virus neutralizing antibody titers initially increased in response to MMR3 but declined to near-baseline levels 1 year later. Nonetheless, the temporary boosting at 1 month might be sufficient to help control outbreaks if the appropriate population is targeted. Although these quantitative findings show limited application of a third dose of MMR vaccine for routine use, future studies on qualitative aspects of the mumps immune response (eg, antibody avidity, B-cell memory, or cellular-mediated immune responses) are necessary to determine whether MMR3 might be beneficial in nonoutbreak settings.

Supplementary Material

Supplementary material is available online at *Open Forum Infectious Diseases* (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

Notes

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Potential conflicts of interest. Dr Coleman is an employee of Abbott Nutrition. However, at the time of the study, she was employed by the Marshfield Clinic Research Foundation. All other authors report no conflicts of interest.

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From: Stanley Plotkin
Sent: 4 Dec 2019 12:13:27 -0500
To: Cohn, Amanda (CDC/DDID/NCIRD/OD)
Subject: RE: ACIP
Attachments: London mss Oct 21.docx, London ideas final.pdf

Dear Amanda:

Delighted to hear that Mina may speak at ACIP. I did speak to Redfield about increasing CDC efforts in the field of vaccine safety. I am attaching two documents I discussed with him, one of which is in press in Vaccine. I hope you are withstanding well the pressures at ACIP.

Regards,

Stanley

From: Cohn, Amanda (CDC/DDID/NCIRD/OD) [mailto:anc0@cdc.gov]
Sent: Tuesday, December 03, 2019 10:48 PM
To: Stanley Plotkin
Subject: Re: ACIP

Hi Dr. Plotkin,

I have had the pleasure of meeting Dr. Mina and we are definitely considering inviting him to speak as part of an ACIP session. We are working on ways of updating our communications materials as well to incorporate this new data into our messaging around measles in particular.

I heard you are speaking to Dr. Redfield soon to give him an update on the Vaccine Safety meeting, I am very excited he will have the opportunity to hear from you. I would love to hear more about the outcome of the vaccine safety meeting if you have a chance. You may also be at the WHO meeting this week on safety?

Hope you are doing well!

Amanda

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Sent: Tuesday, November 12, 2019 3:46:41 PM
To: Cohn, Amanda (CDC/DDID/NCIRD/OD) <anc0@cdc.gov>
Subject: ACIP

Dear Amanda:

In the November 1 issue of Science Michael Mina and colleagues report that measles wipes out antibodies to other pathogens the patient might have seen previously, so that he or she again becomes susceptible. MMR does not do that. I suggest that you invite Mina to present his data to ACIP, preferably just before Public Comment. I think the vaccine opponents should hear it.

I would be glad to talk to Mina if the idea is acceptable to you.

Best wishes,

Stanley

The Science of Vaccine Safety: Summary of Meeting at Wellcome Trust

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<p>Jason Glanz, PhD Senior Investigator, Kaiser Permanente Colorado, Institute for Health Research Clinical Associate Professor, Colorado School of Public Health, Department of Epidemiology</p>

The Science of Vaccine Safety

Vaccines are everywhere hugely successful but are also under attack. The reason for the latter is the perception by some people that vaccines are unsafe. However that may be, vaccine safety, like any other scientific subject, must be constantly studied. It was from this point of view that a meeting was organized at the Wellcome Trust in London in May 2019 to assess some aspects of vaccine safety as subjects for scientific study. The objective of the meeting was to assess what is known beyond reasonable doubt and conversely what areas need additional studies. Although the meeting could not cover all aspects of vaccine safety science, many of the most important issues were addressed by a group of about 30 experts to determine what is already known and what additional studies are merited to assess the safety of the vaccines currently in use. The meeting began with reviews of the current situation in different parts of the world, followed by reviews of specific controversial areas, including the incidence of certain conditions after vaccination and the safety of certain vaccine components. Lastly, information about the human papillomavirus vaccine was considered because its safety has been particularly challenged by vaccine opponents. The following is a summary of the meeting findings. In addition to this summary, the meeting organizers will explore opportunities to perform studies that would enlarge knowledge of vaccine safety.

General Remarks [Offit]

Any medical product that has a positive effect can have a negative effect. Vaccines are no different. Serious adverse events following vaccination have been reported since the first vaccine (smallpox) was developed. Historically, real vaccine safety issues include eczema vaccinatum, progressive vaccinia, congenital vaccinia, myopericarditis, encephalopathy, and encephalitis caused by the smallpox vaccine[1] as well as seizures, paralysis, and coma caused by nervous tissue-based rabies vaccines contaminated with myelin basic protein.[2]

Two historical tragedies were also noted. In 1929, a laboratory error in Lubeck, Germany, resulted in the inadvertent inoculation of 250, 10-day old children with *Mycobacterium tuberculosis* instead of attenuated *Mycobacterium bovis* (BCG). Seventy-two infants died as a result of the mistake.[3] Also, in 1955, Cutter Laboratories failed to fully inactivate a poliovirus vaccine. As a consequence, about 120,000 children were inoculated with live, fully virulent poliovirus. When the dust settled on this man-made polio epidemic, 70,000 people developed abortive, short-lived polio, 164 people were paralyzed, and 10 were killed. This was arguably one of the worst biological disasters in American history.[4]

More recently, the oral polio vaccine was shown to be a rare cause of paralysis, affecting about 1 person per 2.4 million doses.[5] Measles-containing vaccine was found to be a rare cause of transient thrombocytopenia, affected about 1 of every 25,000 recipients.[6] Gelatin, which is used as a stabilizer in the MMR, MMRV, and Zostavax vaccines has been shown to cause a severe, immediate, type 1 hypersensitivity reaction in about 1.3 per million vaccine recipients.[7] Rotavirus vaccines were found to be a rare cause of intussusception, which,

depending on the currently licensed product, affects between 1.5 to 5 children per 100,000 vaccinated.[8] Yellow fever vaccine can itself cause yellow fever, affecting about 1 per million recipients primarily greater than 65 years of age.[9] Influenza vaccine is a rare cause of Guillain-Barré Syndrome, affecting about 1 per million recipients.[10] Pandemrix, an influenza vaccine with a novel adjuvant was used in Europe during the 2009 influenza pandemic, and was found to cause narcolepsy, a permanent disorder of wakefulness, in between 1 in 16,000 to 1 in 55,000 recipients.[11] Finally, dengue vaccine (Dengvaxia) has been shown to enhance hemorrhagic-shock syndrome upon exposure to wild-type virus in seronegative, vaccinated children.[12]

All of these issues have been instructive. It is an uncomfortable truth that science evolves. We learn as we go. And sometimes that learning process comes with a human cost.

The role of vaccine safety monitoring in maintaining vaccine confidence [DeStefano]

The existence of a comprehensive robust vaccine safety monitoring system can bolster public confidence in the safety of vaccines. Pre-licensure activities, from the initial development of a vaccine through the various phases of pre-licensure clinical trials, form the foundation of vaccine safety. Pre-licensure trials, however, may not be large enough to detect rare adverse events following immunization (AEFI), they may not last long enough to detect adverse events with delayed onset, and they may not include certain population groups (e.g., pregnant women). Thus, post-licensure monitoring is crucial to assure the safety of vaccines after they begin to be used on a large scale in the general population.

In the United States, several government agencies, vaccine manufacturers and other entities are involved in evaluating and monitoring the safety of vaccines. The core of the U.S. vaccine safety post-licensure monitoring enterprise consists of four systems operated by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA): 1) the Vaccine Adverse Event Reporting System (VAERS); 2) the Vaccine Safety Datalink (VSD); 3) the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program; and 4) the Clinical Immunization Safety Assessment (CISA) project. VAERS is co-managed by CDC and FDA. [13] It is a national surveillance system intended to rapidly detect potential safety problems or signals. It is a voluntary (i.e., passive) reporting system that accepts reports from anyone, including physicians, manufacturers, patients and parents. VAERS is subject to a number of limitations, including incomplete reporting and lack of an unvaccinated comparison group, and generally cannot be used to assess causality. VSD is a large linked database system that is operated by CDC in collaboration with several large integrated health care systems that cover over 10 million people. [14] It can be used for active surveillance and epidemiologic research by linking computerized vaccination records with computerized databases of hospital, emergency department and outpatient clinic encounters, as well as other databases and medical records. PRISM is a post-licensure safety surveillance network run by FDA to actively monitor the safety of vaccines.[15] It comprises a distributed data network that utilizes claims data from 4 national health insurance companies and vaccine data from 8 immunization registries. CISA is operated by CDC and involves the participation of 7 medical research centers. It conducts clinical research and provides expert consultation to U.S. healthcare providers with complex vaccine safety cases.[16]

Outside of the United States, vaccine safety monitoring capabilities tend to be limited. A few efforts are underway to establish multi-country distributed vaccine data networks in Europe and more globally. These could offer several advantages, such as: 1) providing local data that may be more persuasive in fostering confidence in vaccines at the country level; and 2) the possibility of combining data from several countries to quickly detect extremely rare adverse events (e.g., in a pandemic mass vaccination situation).

Vaccine Safety Concerns in Europe [Larson]

In 2016 and 2018, global studies on public confidence in vaccines showed that the lowest levels of confidence were specific to vaccine safety, with the European region being the least confident in vaccine safety globally.[17-19] Similar findings have emerged in other studies with safety consistently being reported as the biggest reason for vaccine reluctance or refusal.[20,21]

Contributing to these safety anxieties are a variety of tactics by vaccine-critical groups, including billboards instilling doubt with headlines such as “Vaccines are not Safe: Know the Risks” and “If an apple contained: Aluminium, Mercury, Formaldehyde, Polysorbate 80, MSG, Animal & Fetal Cells, would you eat it?” While billboards and similar social media sentiments spread ungrounded fears and heighten risk perceptions, these images and messages also reveal key issues and questions that are on the minds of the public and are important clues to inform where safety research is needed, or where already available safety research needs to be made more accessible to the public.

The European Medicines Agency(EMA) conducted a study monitoring online and social media in all European Union (EU) member states, in order to listen for concerns related to the human papillomavirus(HPV) vaccine. In response to a series of adverse events following immunization, particularly in Denmark, the EMA was asked to conduct a review of the safety of the HPV vaccine[22], and the media monitoring preceded the launch of the EMA safety review and helped to prepare the EMA officials to anticipate questions around the launch of the final report, which confirmed the HPV vaccine's safety.[23-25]

Vaccine safety concerns vary across countries, with aluminium a more prominent concern than thimerosal, and France home to an organized movement against aluminium and formaldehyde in vaccines. France also has historic concerns about multiple sclerosis following hepatitis B vaccination, a risk perception which has also transferred to HPV vaccination along with anxieties about auto-immune disease following HPV vaccination. While we have considerable evidence for the safety of HPV vaccine, what is needed is more evidence for the safety of the ingredients in the HPV as well as other vaccines.

Vaccine Hesitancy in Lower Middle-Income Countries [Arora]

In 2013, the pentavalent vaccination program was suspended in Vietnam, Sri-Lanka and Bhutan and was the subject of public controversy in other Lower Middle Income Countries (LMICs) due to unverified reports of serious vaccine side-effects, including deaths.[26] More recently, the Measles Rubella (MR) campaign was disrupted in parts of India in 2018-2019 due to negative social media messaging.[27]. In Karachi, Pakistan entrenched socio-cultural norms

regarding decision making informed pregnant women's intention to reject pertussis vaccination [28].

Common concerns regarding vaccination in LMICs include fear of adverse events, lack of trust in medical community or public health program, health system related issues such as quality of service delivery, cost and access to vaccines and may even be politically motivated.[29]. The above reasons accounted for nearly 80% of the responses for missing vaccinations from care givers of under-vaccinated children during the Mission Indradhanush (MI) campaign in India. Ethnicity and faith based perceptions towards vaccination, reinforced by local social, economic and community connections have also been identified as factors driving hesitancy during the Pulse Polio (2006) and the MI campaigns (2018) in India. [30,31]. In Brazil, nearly one in five parents with children under the age of five surveyed were vaccine hesitant with concerns about vaccine safety and effectiveness being the most commonly cited reasons for hesitancy.[32] A pre-existing environment of mistrust towards local governments and politically motivated resistance to public health interventions have also been identified as factors contributing to lack of vaccine acceptability in a study investigating the Oral Cholera Vaccine in Mozambique.[33]

The past decade has seen a dramatic transformation of the communication and information exchange landscape; the spread and reach of vaccine associated misinformation, exacerbated by nearly universalized access to internet has derailed on-going immunization campaigns against polio and measles rubella in several Asian countries.[27,31] The current

systems for pharmacovigilance are not mature enough to address emerging concerns by rapidly and systematically investigating safety signals.

Diagnosis of vaccine hesitancy requires a multi-dimensional diagnostic approach particularly in traditional societies and emerging economies with aspirations for better health and civic services. It is necessary to take comprehensive approaches to delineate local socio-cultural and economic contexts, historical and anthropological factors, the effect of geo-political events and specific programmatic determinants of vaccine hesitancy to inform strategies for addressing this complex interdisciplinary challenge. Adopting a human centered approach with proactive engagement of the local communities is essential for diagnosing and finding solutions. Findings from proposed studies might be country and context specific but the lessons learnt shall have the potential to support initiatives with similar contexts elsewhere and strengthen global efforts to maintain public trust in immunization program.

Vaccine safety concerns as seen by the World Health Organization [Zuber]

Safety of vaccines utilized in global public health programs is a paramount concern for the World Health Organization (WHO). In the past 20 years, WHO has paid increasing attention to vaccine safety and developed a program dedicated to managing those issues. The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to respond promptly, efficiently and with scientific rigor to vaccine safety issues of potential global importance.[34] GACVS has examined the robustness of vaccine safety concerns to assist risk/benefits-based vaccine safety policies development. On occasions GACVS has proposed contra-indications to

vaccine utilization (BCG in HIV infected persons,[35] Dengvaxia in dengue-naïve individuals).[36] Beyond those examples, the most important role of the committee is in assessing the robustness of scientific evidence and to advise on how to enhance monitoring and hypothesis-testing. This work is documented on a dedicated website and is a proven global scientific reference.[37] Table 1, adapted from Asturias et al [37a] displays the range of issues examined by the committee over 20 years. Those are related to vaccine components, specific vaccine products including all novel products that became available during that period, methods of vaccine pharmacovigilance and systems building.

Spectacular progress with global immunization programs (better coverage, new and geographically-indicated vaccines), warranted additional investments into capacity-building for vaccine safety monitoring. The goal is to ensure that any concern, anywhere in the world, could be detected, reported and documented through a competent network and corrective action promptly taken. The Global Vaccine Safety Initiative (GVSII) was established by WHO in 2012 to implement a vaccine safety strategy that aims to ensure minimal capacity for vaccine safety monitoring everywhere, enhanced capacity (for surveillance of specific safety concerns) where newer products are deployed, and the establishment of a global network with adequate expertise and geographical proximity.[38]

Enhanced capacity to monitor novel vaccines, many of which dedicated to parts of the world where adequate safety systems are not available, requires concerted efforts. A global network, with adequate expertise, cultural and geographical proximity is progressively being established through the GVSII.[39] Beyond broader capacity for general vaccine pharmacovigilance through the GVSII, the GACVS is on the forefront of safety concerns of global

relevance. Occasional acute safety issues are addressed. Those include early post-licensure deviations from quality and safety profiles as well as novel safety signals. The GACVS-ALERT system allows timely reviews of emerging safety concerns as illustrated with the detection of porcine circovirus DNA in rotavirus vaccines.[40]

Methodologies for vaccine safety require agile epidemiological designs, such as the use of case-based studies where time intervals are the preferred measurement unit which allows dissecting rare effects.[41] Novel vaccines are being developed for pregnant women. Monitoring their benefits and risks in resource-poor countries, will require enhanced collaborations with harmonized methodologies (distributed data networks) that take full advantage of current information technologies.[42] Evidence-based policy-making is currently driven by the gold standard of randomized trials. Assessing rare events, so critically important for the monitoring of preventive interventions, cannot meet that standard. Yet, powerful data analytic systems are available that allow testing numerous hypotheses. Novel approaches to qualify available evidence in pharmacovigilance are therefore urgently needed.

Autism [Fombonne]

In the late 1990s, claims that childhood vaccines increased the risk of autism were made and widely publicized despite weak, if any, empirical evidence to support them. The claims entailed two purported separate mechanisms. The first one incriminated the measles component of the triple MMR vaccine, arguing that in children previously developing normally, a regression and loss of skills occurred 5 to 6 days after vaccination, leading to autism

associated with gastrointestinal symptoms and inflammatory pathology. The second 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 exceeded safety thresholds.

Several epidemiological investigations tested both claims. Ecological studies showed in various countries that underlying trends in rates of autism (equivalent to PDD: Pervasive Developmental Disorders, and to ASD: Autism Spectrum Disorders) were not correlated to trends in MMR coverage,[41] to the introduction or discontinuation of monovalent measles vaccines and later introduction of MMR,[42] to increased use, and to discontinuation of inclusion of the preservative thimerosal in most vaccine preparations.[41] Controlled observational studies (case-control and cohort studies) equally failed to show that past exposure to MMR vaccination was higher in children with autism compared to controls[43]; similarly, infants and toddlers exposed to MMR or to thimerosal-containing vaccines in various doses, when followed up several years later, were not an increased risk of developing autism, findings that extended to their siblings.[44,45] Remarkably, no well-designed study ever supported a risk association of autism with vaccines, and the convergence of negative findings across investigators, study designs, samples and countries has been impressive. Several meta-analyses of these questions confirmed the lack of association between exposure to MMR and thimerosal containing vaccines and autism.[46,47]

Further claims were 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 gastro-intestinal symptoms, and purported persistence of the

measles virus in the gut and other biological specimens). A systematic search for this hypothetical phenotype failed to validate its existence.[48] Regression/loss of skills had been described since the 1940s in up to 30% of children with ASD, and there was evidence that this regressive phenotype had not increased recently or in post-MMR years. 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; furthermore, parents of vaccinated children compared to those of unvaccinated children were not more likely to express earlier concerns about their child's development, or at a time clustering around the immunization date, or more often seek health care provider advice after the MMR immunization. Moreover, studies of peripheral blood mononuclear cells, measles antibodies titers,[49] and measles RNA in gut specimen[50] all failed to document the presumed persistence of the measles virus in biological compartments of children with autism exposed to MMR. In addition, studies investigating possibly higher exposure to methylmercury in autism showed no increased levels in hair or blood samples, no toxicity levels, and no evidence that well known signs of mercury toxicity were part of the autism phenotype.[51,52] Moreover, new data indicated that ethylmercury used in vaccines had a much shorter half-life than methylmercury[53] ruling out that the cumulative use of thimerosal in vaccines from birth to age 2 could surpass already conservative safety thresholds and lead to toxicity.

Quite separately, research on autism has established through twin and family studies the strong role of genetic factors in autism etiology. Current sequencing techniques can identify up to 25% of inherited or de novo genetic variants in subjects with autism, and the ever-growing list of high-risk genes now contains 141 genes and 19 additional copy number variants

(<https://www.sfari.org>). Studies examining the early developmental trajectories of children at risk of autism identified, in research experiments, abnormal social development in the first 6 months of life as well as biological markers (increased brain volume, eye-tracking abnormalities, etc.) that point to a prenatal onset of atypical brain development in autism. Research on environmental risk factors has provided new insights on factors that may operate, alone or in conjunction with genes, during prenatal life although most remain to be confirmed (with the exception of advanced paternal age, and the rare prenatal exposure to valproic acid). [53a,53b] Yet, reliable diagnosis assessment cannot be reached before age 15 months, at best. The middle of the second year of life remains the period when parents commonly become first aware of the atypical development in their child while the average age at diagnosis remains around age 4 in the US. This developmental trajectory creates conditions for parental causal attributions in the etiologic role of environmental factors (e.g. MMR immunization) to develop, contemporaneously of first ASD symptoms emergence. This temporal correlation supports the persistence of beliefs that something happening in the second year of life could be the 'cause' of autism in their child despite all scientific findings pointing at genetic, peri-conceptual and prenatal etiologies.

Neurologic Adverse Events Following Immunizations [Sejvar]

Neurologic adverse events following immunizations (NeuroAEFI) are fortunately infrequent, but are among the most devastating of the AEFIs; there are few 'benign' neurologic conditions. As such, there is a very low threshold for tolerance of these adverse events. There are various potential mechanisms for the etiology of NeuroAEFI depending on whether the

vaccine is a live vaccine, an inactivated vaccine, or a toxoid / protein vaccine. NeuroAEFI, which causally related to vaccination or not, can basically be broken down into two large categories – ‘Neurotropic’ illness, and ‘Autoimmune / Post-immunization’ illness. Neurotropic illness can happen when vaccine (usually live vaccine) gains access to the nervous system, producing an infection within the nervous system. By nature, neurotropic illnesses involve the Central Nervous System (CNS); autoimmune illnesses may affect either the CNS or the peripheral nervous system (PNS). When we refer to the neurotropic illnesses, we are referring to (aseptic) meningitis, encephalitis, and anterior (polio)myelitis. The autoimmune illnesses are constituted by acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome (GBS), and less common ones such as transverse myelitis, brachial neuritis, optic neuritis, and others. Again, they may or may not be caused by vaccination.

NeuroAEFI neurotropic disease may be seen with live vaccines.[54,55] These illnesses are characterized by an incubation period of around 2 – 10 days (roughly) after the immunization. They are associated with evidence of CNS inflammation, including a cerebrospinal fluid (CSF) pleocytosis (elevation of CSF inflammatory white blood cells) and protein elevation, and evidence of brain parenchymal changes / abnormalities on neuroimaging, usually magnetic resonance imaging (MRI). NeuroAEFI may be substantiated by finding evidence of vaccine viral invasion of the intrathecal space.

Autoimmune NeuroAEFI may consist of an immune response to the antigenic stimulus provided by a vaccination; this results in the formation of cross-reactive antibodies and/or autoreactive T-cells that are stimulated by vaccine epitopes to react with self-neural proteins. Alternatively, the antigenic stimulus of the vaccine may lead to perturbation of

immunoregulatory mechanisms by vaccine proteins resulting in a loss of self-tolerance. The association with the vaccine is generally temporal only; this is because vaccine virus or vaccine-specific IgM antibodies may not be present, peripheral serology is not useful since one would expect an antibody response to the vaccine, and often there is a limited search for alternative antecedent events that may lead to the reaction. Thus, 'temporal association' does not equate to 'causality'.

Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the CNS.[58] Two-thirds of persons with ADEM will report an antecedent infectious-like illness or vaccination in the days and weeks prior to onset of neurologic signs. It is more common in childhood; it is estimated that ADEM may represent up to 10-15% of childhood encephalitides. It is characterized by clinical signs / symptoms of encephalitis approximately 3-20 days following the antecedent event; patients will present with altered mental status, cranial nerve palsies, focal weakness, ataxia, and other neurologic signs. It is by definition a monophasic illness, with progression followed by a plateau of symptoms, or more frequently, recovery. Neuroimaging will demonstrate characteristic scattered or confluent multifocal white matter lesions in the subcortical white matter or deep gray structures. CSF shows pleocytosis and protein elevation. The diagnosis rests upon the clinical features and the characteristic MRI findings, along with report of an antecedent illness or immunization.

Guillain-Barré syndrome (GBS) is a post-infectious / post-immunization autoimmune disease of the peripheral nerves. Autoantibodies or T-cells lead to damage to the peripheral nerves / nerve roots to produce limb weakness and sensory abnormalities.[57] Incidence in North America and Europe is estimated to be 1.2 – 1.6 / 100,000 population / year; this

incidence increases with age, particularly after age 50. Incidence also tends to be higher in Asia and South America, presumably due to increased exposure to infectious agents. This is because, similar to ADEM, 2/3 of persons with GBS will report an antecedent viral – like illness or immunization. There are several subtypes of GBS; the most common one in North America and Europe being the demyelinating form, while the axonal form predominates in Asia and South America. Clinically, GBS is characterized by an acute or subacute onset of weakness that evolves over days to weeks; onset is generally between 1-4 weeks after the antecedent event, and most persons experience maximal weakness ('clinical nadir') within 2 weeks. Weakness tends to be ascending, e.g. beginning in the legs and spreading to the arms and then cranial nerve-innervated muscles. CSF is characterized by 'cytoalbuminologic dissociation' – an elevation in CSF protein levels, but with an absence of pleocytosis. Electrodiagnostics – nerve conduction studies and electromyography – may be very useful in confirming the diagnosis and differentiating the various subtypes of GBS.

Although the 1976 formulation of the H1N1 swine-origin influenza vaccine was associated with a slightly increased risk of developing GBS – to the amount of approximately 1 excess case of GBS per 100,000 vaccinees – subsequent formulations of the seasonal influenza vaccine have demonstrated either no increased risk or a very mild increased risk, to the amount of 1-3 excess GBS cases per million vaccinees, and nothing like the magnitude of that seen with the 1976 formulation. These studies, however, may be underpowered, and the 2009 formulation of the H1N1 pandemic influenza vaccine was associated with a mild increased risk (1 excess case/million vaccinees). Nonetheless, the Centers for Disease Control and Prevention has stated that it is 'prudent' for persons who developed GBS following influenza vaccine to

avoid subsequent influenza immunizations; of course, this would depend on an individual's particular risk profile for developing influenza illness. Current evidence suggests that there is no increased risk of relapse of multiple sclerosis following immunizations, and in fact the infectious illnesses that immunizations prevent may present a more significant antigenic challenge, leading to risk of relapse of multiple sclerosis demyelinating events. It would appear that the risks of immunizations for MS relapse are greatly outweighed by the benefits of prevention of infectious illnesses.

Future investigations into vaccine-associated GBS will benefit from exploration of epitopes in vaccines and how they may lead to cross-reactions with peripheral nerve neural substrates. In addition, host factors are likely to play a role in vaccine-associated GBS, and should be explored.

Vaccination and Autoimmunity [Lambert]

There are an increasing number of allegations suggesting the occurrence of autoimmune manifestations following vaccination, listed in Table 2 The scientific basis of these allegations is usually lacking. This situation is largely the result of coincidental events linked with the increasing administration of vaccines in adolescents and young adults at an age known to be associated with autoimmune diseases. It is also reflecting a trend to call autoimmune a variety of vague clinical manifestations of unknown origin (e.g. the ASIA syndrome)(‘ Everything is autoimmune until proven otherwise“. [58] Serious epidemiological studies did not confirm an association of autoimmune diseases with HBV, HPV nor with seasonal influenza vaccination.

[59,60]

However some older vaccines were occasionally associated with autoimmune manifestations. This was the case for the Semple rabies vaccine [61] and the 1976 swine influenza vaccine.

Present immunological concepts allow the understanding of the relative risk of post-vaccination autoimmunity. Cross-reacting autoantibodies can occasionally be generated by some vaccines. The risk is limited by the basic level of tolerance for self B-cell epitopes. It can be assessed at pre-clinical or early clinical stages of development. A higher risk exists (i) for vaccines against infections known to be associated with autoimmunity, e.g. Group A Streptococci, (ii) when a vaccine antigen has a B cell epitope that cross-reacts with a host antigen. This usually requires extensive sequence homology, e.g. >35% identity in >50-80 aa peptidic sequences (conformation!) and a linkage of the cross-reacting B-cell epitope to a dominant T helper epitope (foreign). It is facilitated by a strong concomitant activation of innate immunity (danger signal!).[62]

Although T-cell epitope mimicry is common, cell-mediated autoimmune manifestations are particularly rare. This reflects the potent regulatory mechanisms which limit the activation of self-reacting T-cells.[63] When exceptionally occurring, it likely reflects a particular host susceptibility related to multiple factors, e.g. genetics, failure of thymic negative selection for relevant self-peptides, or failure of peripheral regulatory mechanisms.[64] These should also be combined with a strong activation of innate immunity and is difficult to predict at pre-clinical or early clinical trial stages. Existing adjuvanted vaccines do not appear to exacerbate autoimmune

diseases.[65,66] Post-licensure studies in autoimmune patients may be useful for novel adjuvants.

An example of the complexity of this issue is the observation of an increased incidence of narcolepsy after vaccination with AS03-pH1N1 influenza in Nordic European countries[67] which was assumed to be due to a vaccine-induced autoimmune response to hypocretin producing neurons. However, there is still scarce evidence for an autoimmune process in this situation whereas there is a growing evidence for a role of the influenza viral infection in the disease. Indeed, a peak of narcolepsy was seen in China [68] and Taiwan following the 2009 pH1N1 outbreak. In Nordic European countries, the pandemic peak overlapped or immediately preceded the vaccination.[69] Experimental data also indicate that most Influenza A viruses can infect olfactory receptor neurons, that some of these viruses (H1N1, H5N1) can move to the olfactory bulb (OB) within a few days [70-72] and that exceptionally, some Influenza A viruses can slowly move from olfactory bulb to other CNS sites (H5N1>H1N1>>H3N2), including lateral hypothalamus and hypocretin-producing neurons.[73]. In transgenic mice expressing H1N1-HA in Hypocretin-producing neurons, anti-H1N1 HA CD8 T-cells were shown to eliminate HA-expressing Hcrt-neurons.[74] AS03-pH1N1 vaccine-associated narcolepsy may represent an example of vaccine-enhanced viral immunopathology rather than a vaccine-induced autoimmune event. Timing of vaccination in relation to the outbreak may be critical.

Thiomersal and Mercury [Hviid]

Thiomersal has been used as a vaccine preservative since the 1930s primarily in multidose vials. Thiomersal contains ethylmercury and concerns about expanding childhood

vaccination schedules with increasing cumulative mercury exposure in infants led to the withdrawal of thiomersal-containing vaccines in many high income countries throughout the 1990s. Mercury compounds including ethylmercury are neurotoxic at sufficiently large doses.[75] Accidental poisoning episodes involving ethylmercury at much larger doses than those found in vaccines have been reported to cause neurotoxicity. Ethylmercury has been compared to methylmercury, another organic mercury compound. Adverse effects on neurodevelopment are well-established for methylmercury exposure through primarily maternal fish consumption. However, ethylmercury has a shorter half-life in the body.[76]

The majority of large observational studies of thiomersal exposure have focused on autism. There have been no support for an association in key analytical studies from Denmark, the United Kingdom and the United States comprising more than 690,000 children.[77-80] Similarly, studies looking at a wide range of neurodevelopmental outcomes including both diagnostic outcomes and questionnaire information on early life behavior, cognition and motor skills have been reassuring.[79-84] Some of these studies do test a large number of possible statistical associations and as expected purely by chance report a small number of both beneficial and adverse effects which should be carefully interpreted in the context of multiple testing. Tics have been associated with thiomersal exposure in several studies.[79,80,84] The ascertainment of tics differ in all of these studies, and the clinical relevance of this finding is unclear.

The available observational evidence do have some noteworthy limitations. First, a common feature of many of the available observational studies is the lack of a large group of thiomersal-unexposed children. The majority of studies compare children with varying degrees

of thiomersal exposure at pre-defined ages. Second, while some studies do include subgroups such as low birth weight infants and do try to take other mercury sources into account, low statistical power limits the interpretability. Third and final, there is little evidence available on fetal exposure throughout pregnancy primarily from maternal vaccination.

In conclusion, the available evidence is reassuring; thiomersal-containing vaccines do not increase the risk of autism or the risk of many other neurodevelopmental outcomes.

Formaldehyde and Aluminum [Halsey]

Formaldehyde is a natural component of cell metabolism in all mammalian cells, many plants, and some foods.[85] In humans, metabolism is very rapid with a half-life only 1-2 minutes. Normal human blood levels are 2-3 mcg/mL. Most people are exposed to formaldehyde every day from wood products, automobile exhaust, cigarette smoke, paints and varnishes, carpets permanent press fabrics, and some food products. Prolonged exposure via inhalation can rarely cause nasopharyngeal cancer(adenomas) and repeated contact with highly concentrated solutions can cause irritation, cell changes, and squamous cell carcinoma.[86] Advocates for removal of formaldehyde exposures from vaccines want to eliminate exposure to any potentially carcinogenic substance, but this is not feasible or necessary. The very small amounts of residual formaldehyde in vaccines following removal after inactivation of the target organisms are not additive to the amounts produced from the body's natural metabolism, are below the levels deemed acceptable by regulatory authorities, and are not harmful.[87]

Aluminum is used in the manufacture of many household products. People are exposed to aluminum from cookware, water, drinking containers, and foods including breast milk, infant formulas, flour, baking powders, coloring agents, anticaking agents, seafood, and other products. An average adult consumes 7–9 mg of aluminum per day, but only 0.1% - 0.3% is absorbed.[88] The brain normally contains about 1% of the total body aluminum stores. Intravenous exposure through parenteral nutrition and renal dialysis has resulted in encephalopathy. Guidelines for maximum intake from food vary from 1 mg/kg body weight per week (European Food Safety Authority) to 1 mg/kg/day in the United States (Agency for Toxic Substances and Disease Registry).

Aluminum adjuvants do rarely induce delayed type hypersensitivity reactions manifested as injection site urticarial papules, nodules, and sterile abscesses[89]. Completing recommended immunization series for these patients is problematic due to the lack of the recommended vaccines without aluminum adjuvants. The amount of aluminum in vaccines with aluminum adjuvants varies from 0.125 mg per dose for Prevnar 13, to 1.5 mg in DT; most vaccines contain 0.5 mg per dose or less (<http://www.vaccinesafety.edu>). After injection, aluminum adjuvants are dissolved by alpha-hydroxycarboxylic acids, absorbed into the blood, distributed to tissues, and slowly excreted in the urine[90]. Some remains in tissues with most storage in bone.[91] Aluminum taken up by macrophages can be detected by injection site biopsy for at least 12 months.[92] Although there have been allegations that aluminum adjuvants cause persistent myalgia, fatigue, autoimmune diseases, encephalopathy and other conditions based on poor science, expert reviews have concluded that the scientific evidence does not support these claims. The detection of aluminum at injection sites many months after

vaccination "... represent(s) a simple marker of vaccination with long-term persistence of aluminum at the injection site and local inflammatory response to it, without other symptoms or consequences." [93] Similarly, the U.S. FDA has concluded "...episodic exposures to vaccines that contain aluminum adjuvant continue to be extremely low risk to infants and that the benefits of using vaccines containing aluminum adjuvant outweigh any theoretical concerns." [94]

New adjuvants in vaccines [Garçon]

For a vaccine to induce protection, it must be able to stimulate the immune system efficiently. Nature has designed a way for humans to mount such an immune response, by designing what is known as pathogen associated molecular patterns that are recognized by the first line of defense, the innate immune response, and initiate the cascade of events leading to the generation of a protective immune response.

Through the continuous evolution of vaccines, from the pathogen itself to fractions of it, pathogen-associated molecules have been lost, decreasing or losing the ability to launch the response. Adjuvants augment the responses to those molecules. [96,97]

Within a vaccine, the antigen brings the specificity of the response against the pathogen while the adjuvant enhances and modulates the immune response to the vaccine antigen. Therefore the quality of the immune response will depend on the potential of the antigen to be protective, and the adjuvant to optimize its potential. Both efficacy and safety are therefore

considered in the context of each adjuvanted vaccines individually following the current guidelines defined by regulatory agencies.

In general, adjuvants can induce some local reactogenicity such as redness, heat, swelling, the 3 markers of a local immune response (as seen during a local infection) as well as some systemic effect (flu-like symptoms, fever in particular). Their intensity can vary depending on the age, status (naïve versus primed) of the individual vaccinated, and all individuals do not respond in the same way.

Over the past 20 years and through the evolution of knowledge and available technologies, it has been possible to assess the mode (what the adjuvant does) and the mechanism of action (how the adjuvant acts). Those studies have shown for current licensed adjuvanted vaccines, that they act locally (effect limited to the site of administration and the draining lymph nodes, with an effect limited in time (days), supporting the safety observed in animal models and humans.[97-99] Knowledge of the mechanism and defining the pathway triggered during the response, have allowed us to establish more finely their safety profile, and to evaluate hypothetical risks of adverse events. For example, the knowledge of cell populations that can be activated or not allows closer study of hypothetical risks associated with vaccination.

As their mode of action is limited in space and time, no adjuvants currently present in vaccines have been shown to induce de novo rare events such as autoimmune diseases.

[100-101]

Residual Cell-Substrate DNA in Vaccines [Peden]

The production of viral vaccines in eukaryotic cell substrates inevitably means that they contain some cell-substrate DNA. When mammalian cell lines were considered for vaccine production, concerns were raised that the residual DNA could induce cancer or contain infectious agents. These concerns were heightened with regard to tumorigenic cells or cells derived from human cancers. The issue of whether cellular DNA could be a risk to vaccine recipients has been debated for more than 50 years without resolution.[102,103]

DNA can have two activities that could be of concern.[102,104] DNA could have an infectivity activity, *i.e.*, the mammalian genome contains the genome of a DNA virus or of a retroviral provirus, or it could have an oncogenic activity, either through the introduction of a dominant activated oncogene or by inducing an oncogenic event through insertion into the host genome. To address whether DNA can induce an infectious event and with what efficiency, we have established a transfection/co-culture system to quantify HIV DNA infectivity. In dose-response studies, we showed that 1 pg of HIV DNA and 2 µg of the cellular DNA isolated from HIV-infected cells can be infectious. We have used this system to quantify the reduction in infectivity afforded by various treatments used in vaccine manufacture, such as nuclease digestion, beta-propiolactone treatment and binary ethylenimine treatment. We have shown that these treatments can reduce infectivity by $\geq 10^5$ -fold and combined with reducing the amount of DNA to 10 ng (the WHO recommended amount of residual DNA per vaccine dose), safety margins of $\geq 10^7$ can be achieved.[105]

With respect to DNA oncogenicity, we generated expression plasmids for activated human *H-ras* and murine *c-myc*; these genes are driven by a long-terminal repeat [106]. When inoculated into mice, we found that tumors were induced but with low efficiency. To increase

the efficiency, we combined the two oncogenes on the same plasmid, and used it to evaluate the efficiency of various rodents to tumor induction.[107] With certain newborn rodents, DNA amounts of ≤ 1 ng induced tumors. However, even with such sensitive animal models, no cellular DNA from tumorigenic cells or from tumors induced by the ras/myc plasmid has ever scored positive. Also, not all dominant oncogenes are active in these *in vivo* systems. As a consequence, regulators have considered the best approach to dealing with DNA is to reduce both the amount of DNA and its size. Such considerations have recently permitted the introduction of vaccines produced in tumorigenic cell substrates.

Non-specific effects of vaccines [Pollard]

Non-specific or off target effects of vaccines refer to the responses induced by an immune stimulus to a vaccine (or infection) which alter the immune response to a subsequent heterologous infection.[108]. That such effects occur is without doubt as it is embedded in current and long-standing understanding of the innate and adaptive immune system, that the initiation of immune responses are non-specific, and can result in alterations in resistance to infection through production of mediators. For example, production of interferon-alpha during viral infection reduces susceptibility of cells to subsequent heterologous viral challenge. More recent evidence indicates that there is a profound activation of the transcriptome during infection or vaccination with the vast majority of the genes that are being expressed being non-specific innate responses.[109] Indeed, adjuvants are utilized to capture these nonspecific components of the immune response and enhance the focused adaptive response to the vaccine with which it is formulated. The extent to which alterations in innate immune

responses occur following vaccination in human infants has been little studied, and the effects of these responses on resistance or susceptibility to subsequent infection is unknown. We attempted to systematically analyze the literature in 2016 with a focus on EPI vaccines and concluded that there was “some evidence that in some study designs, with some vaccines, administered in some settings, where samples are taken at some time-points, and some in vitro assays are undertaken that non-specific immunological effects may be detected in response to some in vitro stimuli but it is difficult to identify consistent findings”.[110] We noted that measles and BCG vaccines were associated with increased interferon-gamma responsiveness during later in vitro stimulation. A recent study by Blok et al in 75 adults indicated that there were changes in responsiveness to various in vitro stimuli measurable at one and 4 days after vaccination with either BCG or BCG+DTaP, and they have proposed that such changes that are observed are likely to be driven by changes in the epigenome following an immune trigger[111].

While the immunological phenomenology is fascinating and further exploration of the characteristics, magnitude and persistence of these effects is warranted in understanding of the immune system, the clinical significance of the measurable changes is unknown, and there is currently no rationale for attempting to deliberately enhance or reduce any of these effects for clinical benefit.

However, a large number of animal studies have provided compelling evidence that infection with one organism or exposure to an antigen can confer some resistance to another heterologous infection. For example, live candida administration in mice can provide up to 70% protection against lethal infection with *Staphylococcus aureus*[112]; BCG vaccination protects

mice against malaria infection[113]; and rabies vaccine protects young dogs against fatal sepsis[114].

While there is great interest in the phenomenon, the scientific community has become very polarised in views about the importance of non-specific clinical effects in humans. A systematic review[115] concluded that BCG and measles-containing vaccines reduced all cause mortality, though the relative risks, when restricted to the highest quality RCTs showed that these findings were non-significant. Recent studies have found that there was a non-significant reduction in mortality with early vs late BCG in premature infants in Guinea Bissau, which was significant in a sub-population censored for oral polio vaccine. By contrast there was no difference in hospitalisation rates for infants randomised to receive BCG in Denmark up to 15 months of age.[116] A high quality study in low birthweight infants (<200g) in India found that there was no difference in mortality with early BCG-Russia.[117] While the data are inconclusive for the magnitude or clinical importance of these effects with BCG and measles, some investigators now claim that all live vaccines have substantial beneficial effects, which is supported by the current WHO position paper, despite the uncertainty that is presented by evaluating the data.

The systematic review also evaluated studies of non-specific effects of DTP containing vaccines but found no high-quality studies. However, observational studies resulted in a positive relative risk, indicating increased mortality following vaccination, especially in girls, but without statistical significance. Despite the high risk of bias in these low-quality studies, which did not provide statistically robust relative risks, some investigators have seized on these data and claim that all non-live vaccines might be harmful.

Recent studies have investigated how bias could influence the observations described above, and further increase the uncertainty about the clinical importance of the claims.[118,119]

While it seems that immunological non-specific effects occur, we don't know enough about them to predict when or for how long they might last and have no understanding of their clinical relevance. The animal studies show that there are intriguing effects, whether underpinned by the above immunological observations or not, which can be induced in these controlled settings and can have a profound impact on survival. The animal studies, provide a strong case for improved understanding of the biology that might one day be translated into benefits for humans. The human data, with clinical endpoints, indicate that there are intriguing signals which warrant investigation, but trials to provide a definitive answer will be challenging to realize as global childhood mortality continues to fall. Today we do not have definitive evidence of non-specific effects of vaccines that should lead to a change in immunization policy.

HPV vaccines [Markowitz]

Available human papillomavirus (HPV) vaccines are virus-like particle (VLP) vaccines, made from the L1 major capsid viral protein. Three HPV vaccines have been licensed: bivalent (2vHPV), quadrivalent (4vHPV) and 9-valent vaccines (9vHPV). The adjuvant in 2vHPV is ASO4, which contains aluminum hydroxide and monophosphoryl lipid A, while the adjuvant in 4vHPV and 9vHPV is alum. The first vaccine was licensed in 2006; by the end of 2018, vaccination

programs had been introduced in over 80 countries. Despite reassuring safety data from HPV vaccine clinical trials and post-licensure monitoring studies, listed in Table 3, safety concerns continue to be raised. Several countries have had challenges with their programs due to safety concerns, including Japan (chronic regional pain syndrome [CRPS]), Denmark (postural orthostatic tachycardia syndrome [POTS]), and Ireland and Colombia (a variety of different concerns).

The World Health Organization's (WHO) Global Advisory Committee on Vaccine Safety (GACVS) reviewed safety of HPV vaccines seven times since 2007; in 2017 GACVS conducted a comprehensive assessment and systematic review focusing on serious events after 2vHPV and 4vHPV.[120] In this systematic review, 26 randomized controlled trials and six good quality post-licensure cohort studies were included.[120-122] Among the cohort studies: four looked at autoimmune diseases, two venous thromboembolic disease and one multiple sclerosis and other demyelinating conditions. Results from both clinical trial evidence and cohort studies were consistent in finding no relationship between serious adverse events and HPV vaccination. POTS and CRPS were not considered in the systematic review, as WHO used a report by the European Medicines Agency (EMA) to inform about these events.[123] While EMA did not find a relationship between HPV vaccination and POTS or CRPS, they felt that further monitoring should be conducted given public concern.

Since the GACVS systematic review, numerous additional large post-licensure safety studies have been published for 4vHPV and 2vHPV from several countries.[124-130] At least ten evaluated autoimmune disease, including six that evaluated multiple autoimmune diseases,

three Guillain Barré Syndrome only [128-130] and one type 1 diabetes only.[127] In addition, since the 2017 review, there have been systematic reviews examining autoimmune disease.[131,132] Aside from these outcomes, studies specifically investigated primary ovarian insufficiency[133] and chronic fatigue[134] finding no consistent evidence of safety concerns. A study using a new methodology, the self-controlled tree-temporal scan statistical method, scanned hundreds of diagnoses among 1.9 million 4vHPV recipients and found no new associations.[135] At least five post-licensure studies of inadvertent HPV vaccination in pregnancy, such as one examining data from Denmark's nationwide registers [136], have been published since 2017, showing no association with adverse outcomes of pregnancy.

To date, the only post-licensure safety data for 9vHPV are from the United States. During a period of time when 29 million doses were distributed, VAERS identified no concerning signals.[137] A rapid cycle analysis in the Vaccine Safety Datalink raised no safety concerns.[138]

Too Many Vaccines? (Glanz)

Many parents have concerns that children are receiving too many vaccines in too short of a time, with specific concerns that vaccines are overloading the child's immune system and vaccine ingredients are toxic. To minimize vaccine exposure, an estimated 10-15% of parents are choosing alternative vaccination schedules for their children.[139] The Institute of Medicine (IOM) responded by publishing a report in 2013 that recommended additional research on the safety of the recommended childhood immunization schedule.[46] The report emphasized that

the studies should be observational, focused on the schedule as a whole rather than individual vaccines, and be designed to evaluate chronic and long-term outcomes occurring months to years after vaccination. The report also concluded that the Vaccine Safety Datalink (VSD) represents an ideal research environment to conduct such studies.

The Centers for Disease Control and Prevention has made the safety of the recommended schedule a research priority and commissioned a white paper on how the VSD could be used to address the safety gaps presented in the IOM report.[140] Through subject matter expert engagement, the white paper identified important methodological challenges to studying the schedule and generated a list of 20 outcomes prioritized by public health significance and public concern. The methodological challenges with studying the safety of the recommended schedule included unmeasured confounding, inadequate statistical power, and misclassification of exposures and outcomes. The prioritized outcomes included both acute and chronic conditions, such as asthma, anaphylaxis, type 1 diabetes mellitus, epilepsy, juvenile rheumatoid arthritis, seizures, all-cause mortality, all-cause morbidity (non-targeted infection), and chronic urticarial

Guided by the white paper, the VSD has developed analytic metrics for measuring adherence to the recommended schedule, including cumulative vaccine antigen exposure, cumulative vaccine aluminum exposure, and a summary measure called the average days under-vaccinated. Thus far, these metrics have been used to study all-cause mortality and non-targeted infection, both of which produced null results.[141,142] Studies examining asthma and type 1 diabetes mellitus are currently underway.

While progress is being made, there remain substantial challenges to studying the safety of the schedule, including the potential for uncontrolled bias and inadequate sample sizes to study the rarer outcomes on the white paper priority list. This points to a need for independent data sources in which both positive and negative safety signals can be replicated and validated, and for continued research to develop methodological approaches to minimize biases that may affect safety studies of the recommended childhood immunization schedule.

Summary

As stated in the introduction, this review of major safety issues related to vaccination has identified gaps in the scientific evidence and the need for new studies so as to add new knowledge to a controversial field. Although vaccination remains a highly positive procedure to maintain the health of populations, science requires that careful study continues to add to our knowledge and to maintain public confidence in the vaccine enterprise.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The findings and conclusions in this report are those of the authors and have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination of policy.

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Table Vaccine safety issues addressed by the Global Advisory Committee for Vaccine Safety by year, type of review and decision 1999–2019
(Adapted with permission from Asturias et al. Vaccine 2016)

Vaccine / Year	'99	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	'19
BCG					RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS
Dengue					RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS
DPT				RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS
DTwP-HBV-Hib																					
DTaP-HBV-Hib-IPV						RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS
Ebola virus																	RS				
Hepatitis A																					
Hepatitis B				RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS
Hepatitis E																					
HPV																					
Influenza				RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS	RS
Japanese encephalitis																					
Malaria																					
Measles																					
Meningococcal																					
MMR																					
Mumps																					
Pneumococcal																					
Rotavirus																					
Smallpox																					
Typhoid conjugate																					
Varicella zoster																					
Yellow Fever																					
Other safety issue																					
Adjuvants																					
Aluminium																					
Communication																					
Formulations																					
Immune overload																					
Immunisation stress response																					
Immunocompromised																					
Nonspecific effects vaccines																					
Oculo-respiratory syndrome																					
Pregnancy																					
Thiomersal																					
Transmissible spongiform encephalitis																					
Vaccine information sheets																					
Vaccine Safety Systems																					

RS Review safety Evidence gathering Policy recommendation

GA: GACVS evaluation; PI: Performance indicators; W: Websites assessment; UMC: Uppsala Monitoring Centre; 3S: Project 3S; MCC: Multi-country collaborations; VSN: Vaccine Safety Net; EVI: Essential Vaccine Information; IRR: Inter-rater reliability; GVS: Global Vaccine Safety Initiative; VICP: Vaccine injury compensation programmes; DDN: Distributed data networks; VS: Vaccine safety; VDN: Vaccine safety detection networks; PV: Pharmacovigilance; VSM: Vaccine safety monitoring; CA: Causality assessment; GVSP: Global vaccine safety plan

Table 1

Table 2. Autoimmune or Immune-mediated diseases reported following vaccination		
Autoimmune/ immune-mediated disease	Type of vaccine	Confirmed association
encephalitis	Rabies	YES
Multiple sclerosis	HBV	NO
Rheumatoid arthritis	HBV, tetanus, typhoid, MMR	NO
Systemic lupus erythematosus	HBV, tetanus, anthrax	NO
Reactive arthritis	BCG, typhoid, MMR, influenza, Ebola	YES
Guillain-Barré syndrome	Swine Influenza,	YES
Idiopathic thrombocytopenia	MMR	POSSIBLE
Diabetes mellitus-type I	HIB	NO
Hashimoto thyroiditis	HBV	NO
Polymyositis/ dermatomyositis	BCG, smallpox, diphtheria, DPT	POSSIBLE
Polyarteritis nodosa	Influenza, pertussis, HBV	NO
Narcolepsy	Pandemic influenza (p2009)	YES
Myocarditis	Smallpox	POSSIBLE
ASIA syndrome	Adjuvanted vaccines	NO

Table 3*

Outcomes studied in post-licensure human papillomavirus vaccine safety evaluations and selected references^a

Outcome	Selected References	Vaccine
Autoimmune and neurologic diseases ^b	Chao C. J Intern Med 2012	4vHPV
	Arnheim-Dahlstrom L. BMJ 2013	4vHPV
	Grimaldi-Bensouda L. J Intern Med 2014	4vHPV
	Langer-Gould A. JAMA Neurol 2014	4vHPV
	Baxter R. Clin Infect Dis 2016	4vHPV
	Grimaldi-Bensouda L. J Autoimmun 2017	4vHPV
	Sridhar G. Hum Vaccin Immunother 2017	4vHPV
	Miranda S. Vaccine 2017	4vHPV
	Hviid A. J Intern Med 2018	4vHPV
	Frisch M. Int J Epidemiol 2018	4vHPV
	Liu EY. CMAJ 2018	4vHPV
Guillain-Barré syndrome only	Andrews NJ. Vaccine 2017	2vHPV and 4vHPV
	Gee J. Vaccine 2017	4vHPV
	Deceuninck G. Expert Rev Vaccines 2018	4vHPV
Type-1 diabetes only	Klein NP. Vaccine 2019	4vHPV
Thromboembolism ^c	Arnheim-Dahlstrom L. BMJ 2013	4vHPV
	Scheller NM. JAMA 2014	4vHPV
	Naleway AL. Vaccine 2016	4vHPV
	Yih WK. Vaccine 2016	4vHPV
	Frisch M. Int J Epidemiol 2018	4vHPV
Multiple outcomes ^d	Gee J. Vaccine 2011	4vHPV
	Klein NP. Arch Pediatr Adolesc Med. 2012	4vHPV
	Yih WK. AJE 2018	4vHPV
	Skufca J. Vaccine 2018	2vHPV
	Donahue JG. Pediatrics (in press)	9vHPV

Primary ovarian insufficiency	Naleway AL. Pediatrics 2018	4vHPV
Chronic fatigue	Feiring B. Vaccine 2017	4vHPV
	Schurink-Van't Klooster TM. Vaccine 2018	2HPV
Death	McCarthy NL. Pediatrics 2016	4vHPV

2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, 9-valent HPV vaccine

^acase series, case reports and reports from passive reporting systems not included

^bStudies focused on autoimmune outcomes, demyelinating or other neurologic conditions (most included many different outcomes including Guillain-Barré syndrome)

^cNaleway and Scheller studied only thromboembolism; other studies included many outcomes ^dStudies not limited to autoimmune or neurologic outcomes

*Acknowledgement: Thanks to Julianne Gee for assistance with the table data.

SUMMARY OF IDEAS FOR FUTURE STUDIES OF VACCINE SAFETY PROPOSED BY ATTENDEES AT THE WELLCOME TRUST LONDON VACCINE SAFETY MEETING (MAY 30-31, 2019)

The following is a brief summary of ideas for scientifically motivated vaccine safety studies proposed by experts after discussion at a meeting on the science of vaccine safety

Study of Specific Reactions

Badly needed is a controlled study in adolescents of Postural Orthostatic Tachycardia Syndrome (POTS) and Complex Regional Pain Syndrome (CRPS) and whether or not vaccination with HPV vaccine increases the risk.

Denmark provides an excellent country in which to do comparative studies in view of specimen availability and investigator interest. Dried blood spots have been collected since 1982. These samples have already been used successfully for a GWAS of febrile seizures after MMR vaccination. Examples of other phenomena which could be studied given enough financial support include idiopathic thrombocytic purpura (ITP) after MMR vaccine and granulomas after aluminum adjuvanted vaccines. Study of ITP would require collaboration with other countries, but sufficient numbers are available for GWAS of granuloma cases.

Narcolepsy was associated with influenza vaccination in certain countries. Together with increased studies of narcolepsy in the canine model, more study of the genetics of narcolepsy in relation to vaccination is needed, which could be done in Nordic countries where narcolepsy is more common.

Maternal Immunization

Immunization in pregnancy is now a widespread recommended vaccination strategy. Therefore, it is important to study outcomes in infants born to vaccinated mothers. Large cohorts will be needed in which infants of vaccinated and unvaccinated mothers are followed for at least several years with regard to health phenomena. Among the outcomes studied in infants would be

neurological development and abnormalities in relation to time of vaccination in the mother, and time of first vaccine in the child.

Adjuvants and Preservatives

Again, advantage could be taken of the Danish population to study granulomas following the use of aluminum adjuvants, as granulomas appear to have a familial tendency. Predisposing factors, including genetics through GWAS, could be studied, as well as rates of autism in relation to quantity of aluminum received. Critical would be biopsy studies both in individuals complaining of fasciitis after alum-containing vaccines in comparison to control biopsies taken from cadavers of individuals in whom vaccination was done.

Another study that could be done in Denmark involves a follow up of vaccinees to determine if tics are associated with mercury content received. A CDC study raised questions about this, although parents did not report noticing more tics. Anti-vaccinationists nevertheless raise this question.

Advantage could be taken of the fact that there is twice as much of aluminum adjuvant in the 9-valent HPV vaccine as the 4-valent HPV vaccine (500 vs 250 mcg), although the adjuvants were not of the exact same composition. Long term health phenomena could be compared.

The new zoster vaccine and one influenza vaccine both have strong adjuvants. No study has looked at patients who receive both simultaneously.

Although there would be difficulties in analyzing equivalent populations, the fact that certain adjuvants are used in Europe but not the US might serve as a basis for a comparative study.

Genetics

Aside from the studies mentioned above, a registry of reactions to vaccines in patients with mitochondrial or metabolic diseases would help determine contra-indications if any.

Moreover, a registry of genetic samples from patients with severe reactions to vaccines would permit attempts to correlate adverse reactions and genetic predisposition.

Other

Create a DNA biobank of samples from vaccinees with adverse reactions. Admittedly this might be difficult owing to concerns about storage, privacy, etc, however some countries already have such biobanks, which could serve for research.

If possible, compare reactions in children given vaccines individually or in combination.

More publications are needed on the subject of vaccine safety. For example, using US data to calculate the rate of reactions with regard to the number of doses given, and publishing safety reviews concerning individual vaccines, particularly HPV vaccines.

The CISA network is in operation but is not sufficiently used. Appeals could be made to medical specialists to report patients for study at CISA. In addition, a repository for information on vaccination in patients with specific conditions, including mitochondrial disorders, inborn errors of metabolism, and receipt of immunosuppressive drugs would contribute new knowledge.

A phenomenon that has arisen in particular with dengue vaccine, but which may apply to other partly protective vaccines, is enhancement of disease in those not protected. That phenomenon should be searched for with prospective studies when new vaccines are licensed.

Funding Vaccine Safety Studies

A frequent recommendation was that the US tax on vaccines be used to finance safety studies. This would require congressional action. Moreover, a vaccine safety agenda using such monies was proposed by NVAC in the late 1990s, but nothing has happened. Although this recommendation is out of the scope of scientific studies, backing could be sought from interested organizations to seek congressional action. Outside of the US, funding could be sought from European organizations, and foundations that support vaccine purchase could be asked to support pharmacovigilance.

TABULAR SUMMARY

IDEAS FOR FUTURE STUDIES PROPOSED BY ATTENDEES AT THE WELLCOME TRUST LONDON VACCINE SAFETY MEETING

based upon Version 4, Sept 2/19)

Need for basic research	Need for Clinical Studies	Need for Observational Studies
Evaluation of the two-hit hypothesis for narcolepsy risk following vaccine in ferret or in other animal models	POTS and CRPS need further definition of criteria for diagnosis. Need for clinical studies to evaluate risk following vaccines.	Long term studies of maternal immunization impact on infants. Large cohorts will be needed in which infants of vaccinated and unvaccinated mothers are followed for at least several years to study neurological development and abnormalities in relation to time of vaccination in the mother, and time of first vaccine in the child.
Create a DNA biobank for individuals with vaccine reactions to assess genomic risk factors.	The new zoster vaccine and one influenza vaccine both have strong adjuvants. No study has looked at patients who receive both simultaneously.	Evaluation as to whether tics are associated with the level of mercury exposure in vaccines.
Need for genetic studies of the risk factors for narcolepsy following influenza vaccine and disease	A registry of reactions to vaccines in patients with mitochondrial or metabolic diseases would help determine contra-indications if any.	Evaluate the risk factors granulomas following the use of aluminum including genomics. Critical would be biopsy studies both in individuals complaining of fasciitis and perhaps comparison with biopsies taken from cadavers where vaccination was done
Genetic studies of ITP after MMR vaccine and granulomas after aluminum adjuvanted	A phenomenon that has arisen in particular with dengue vaccine, but which may apply to other partly protective vaccines, is enhancement	Advantage could be taken of the fact that there is twice as much of aluminum adjuvant in the 9-valent HPV vaccine as the 4-valent HPV vaccine (500 vs 250 mcg), although the adjuvants were

vaccines.	of disease in those not protected. That phenomenon should be searched for with prospective studies when new vaccines are licensed.	not of the exact same composition. Long term health phenomena could be compared.
	Compare reactogenicity of vaccines given together or separately.	Although there would be difficulties in analyzing equivalent populations, the fact that certain adjuvants are used in Europe but not the US might serve as a basis for a study.
		Comparative studies of adjuvants used in Europe versus the US.

From: Edwards, Kathryn
Sent: 26 Feb 2017 21:56:02 +0000
To: Stetz, Carrie L G. (ELS-STL);Cohn, Amanda (CDC/OID/NCIRD)
Cc: stanley.plotkin@vaxconsult.com
Subject: RE: Chapter 73: "Plotkin's Vaccines," ed 7
Attachments: Plotkin_7616_Chapter_73_main_LNkeESke.pdf

Amanda

I checked and made sure that you cross referenced the correct chapters and you did. Also add a few edits or questions. Really nice job. Thanks so much. k

From: Stetz, Carrie L G. (ELS-STL) [C.Stetz@Elsevier.com]
Sent: Thursday, February 23, 2017 8:47 AM
To: acohn@cdc.gov
Cc: stanley.plotkin@vaxconsult.com; Edwards, Kathryn
Subject: Chapter 73: "Plotkin's Vaccines," ed 7

Greetings:

Attached are page proofs of Chapter 73 in *Plotkin's Vaccines*, ed 7. Please review the proofs at your earliest convenience and return them to my attention by **Monday, March 6**, copying the section editor, Dr. Edwards (kathryn.edwards@vanderbilt.edu), on your response. Please make your comments directly on the PDF and be sure to answer any author queries. Please note that this chapter is being proofread simultaneously with your review, so you may see a few typographical errors. (*Note: significant reference renumbering was necessary in this chapter; the attached Ward file explains the changes.*)

IMPORTANT NOTES: Please mark up the file with the "Comment" tools. Do not use the "Edit PDF" or "Content Editing" toolbar options. If you are a Mac user, please do not use Apple's document reader software to mark up a PDF; it will cause your comments to display incorrectly. Please save the file to your computer, then use Adobe Acrobat (Reader or Professional) to view and mark up the file.

If you have any questions, feel free to contact me at any time. Thank you,

Carrie

Carrie Stetz
Senior Project Manager/Specialist
ELSEVIER | Global Book Production
+1 314-447-8925  office
+1 314-447-8020  fax
c.stetz@elsevier.com

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 16 Mar 2017 15:08:15 +0000
To: 'Edwards, Kathryn'; Stetz, Carrie L G. (ELS-STL)
Cc: stanley.plotkin@vaxconsult.com
Subject: RE: Chapter 73: "Plotkin's Vaccines," ed 7
Attachments: Plotkin_7616_Chapter_73_main_LNkeESke_AC.pdf

Hi Carrie,

Attached are edits to the proof for the chapter, all of the comments have been addressed except for the following. I am still working on replacing figures 73.1 and 73.2 with the 2017 schedule. Can I just send you the powerpoints like I did originally with the updated schedules?

I am also still working on Table 73.5, making sure the footnotes and numbers are correct. I can have this done by tomorrow.

Let me know if you have any questions!

Amanda

From: Edwards, Kathryn [mailto:kathryn.edwards@Vanderbilt.Edu]
Sent: Sunday, February 26, 2017 4:56 PM
To: Stetz, Carrie L G. (ELS-STL) <C.Stetz@Elsevier.com>; Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Cc: stanley.plotkin@vaxconsult.com
Subject: RE: Chapter 73: "Plotkin's Vaccines," ed 7

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If you have any questions, feel free to contact me at any time. Thank you,


Carrie

Carrie Stetz

Senior Project Manager/Specialist

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+1 314-447-8020  fax

c.stetz@elsevier.com

From: Stanley Plotkin
Sent: 29 Jul 2017 12:12:37 -0400
To: Cohn, Amanda (CDC/OID/NCIRD)
Cc: Patel, Manisha M. (CDC/OID/NCIRD); Marin, Mona (CDC/OID/NCIRD)
Subject: RE: Mumps WG

I understand, at least formally, why I cannot participate in the policy discussions, but I wish to propose development of new mumps vaccines as one of the policy proposals. If that is a possible recommendation by the Working Group I would submit it in written form.

Stanley

From: Cohn, Amanda (CDC/OID/NCIRD) [mailto:anc0@cdc.gov]
Sent: Thursday, July 27, 2017 9:04 AM
To: Stanley Plotkin
Cc: Patel, Manisha M. (CDC/OID/NCIRD)
Subject: FW: Mumps WG

Good Morning Dr. Plotkin,

Please see below for a recap of the discussion regarding your consultation work with vaccine manufacturers and your participation as a scientific consultant on the WG. The guidelines regarding conflicts of interest for work group participants are in place to ensure there is no appearance of conflict of interest. I am happy to discuss more with you, I know your contributions to the scientific discussion thus far has been invaluable for the WG and I appreciate your lending your expertise to the ACIP process.

Best,

Amanda

From: Marin, Mona (CDC/OID/NCIRD)
Sent: Friday, March 03, 2017 3:44 PM
To: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Cc: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

Hello Dr. Plotkin,

We are thrilled to invite you to participate in the mumps ACIP WG as an expert consultant to contribute to the scientific discussions. According to the call schedule we have to date, the first 4 calls will not include policy discussions.

Please note that the regular calls are on the 2nd Thursday of each month, 3:30-5:00 pm EST, with the first being next week, on March 9th. We may add extra calls depending on the need to address first in the WG topics that will be presented to the ACIP.

Regarding the conflict of interest form, we would still want to have a form for you but you can just indicate where your conflicts are, without being specific on the manufacturer/vaccine. Please let us know if you want us to resend the form.

Thanks and hope to talk with you soon,
Mona.

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]
Sent: Wednesday, February 15, 2017 4:34 PM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>
Cc: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

OK, let me know which is preferred. I would be willing to participate in the scientific discussions but not policy discussions if that's best.
Stanley

From: Marin, Mona (CDC/OID/NCIRD) [<mailto:zsn8@cdc.gov>]
Sent: Wednesday, February 15, 2017 4:26 PM
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Cc: Cohn, Amanda (CDC/OID/NCIRD)
Subject: RE: Mumps WG

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Amanda, any suggestions?

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Mona.

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Thanks for your welcome,

Stanley

From: Marin, Mona (CDC/OID/NCIRD) [<mailto:zsn8@cdc.gov>]

Sent: Tuesday, February 14, 2017 9:35 PM

To: 'stanley.plotkin@vaxconsult.com'

Subject: FW: Mumps WG

Dear Dr. Plotkin,

Thank you so much for your interest in the mumps WG! Your expertise will be of great value to the WG discussions and recommendations. The primary objective of the WG is to evaluate and formulate policy options to prevent or control mumps outbreaks in the United States. We will start the WG calls in March and the day/time of the calls most likely is going to be the second Thursday of the month, 3:30-5:00 pm EST.

We will email you tomorrow a short intake form that includes questions to complete the WG roster and assess potential conflicts of interest. The email may come from me or Adria Lee.

We look forward to working with you on this policy activity,
Mona.

From: Cohn, Amanda (CDC/OID/NCIRD)

Sent: Tuesday, February 14, 2017 10:49 AM

To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>; Patel, Manisha M. (CDC/OID/NCIRD) <dmn4@cdc.gov>

Subject: FW: Mumps WG

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Sent: Tuesday, February 14, 2017 10:44 AM

To: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>

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Mona will follow-up with information. Thanks for considering participating!

Amanda

Amanda Cohn, MD
CDR, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices
NCIRD/CDC
Office: 404-639-6039
Cell: 404-451-6204
Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus
1600 Clifton Road MS A-87
Atlanta, GA 30329-4027

From: Stanley Plotkin
Sent: 1 Aug 2017 12:19:18 -0400
To: Cohn, Amanda (CDC/OID/NCIRD)
Cc: Patel, Manisha M. (CDC/OID/NCIRD); Marin, Mona (CDC/OID/NCIRD)
Subject: RE: Mumps WG
Attachments: MUMPS.docx, Mumps References.docx

Dear Amanda, Manisha and Mona:

I decided to send you a brief outline of my proposal with several references. Ideally, the proposal could be discussed by the Working Group, with me present or absent. If the proposal for a new vaccine is considered out of the scope of the Working Group please let me know and I will go elsewhere.

Thanks,
Stanley

From: Stanley Plotkin [mailto:stanley.plotkin@vaxconsult.com]
Sent: Saturday, July 29, 2017 12:13 PM
To: 'Cohn, Amanda (CDC/OID/NCIRD)'
Cc: 'Patel, Manisha M. (CDC/OID/NCIRD)'; 'Marin, Mona (CDC/OID/NCIRD)'
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Amanda Cohn, MD
CDR, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices
NCIRD/CDC
Office: 404-639-6039
Cell: 404-451-6204
Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus
1600 Clifton Road MS A-87
Atlanta, GA 30329-4027

Mumps References

Gouma, S., M. P. Koopmans and R. S. van Binnendijk (2016). "Mumps virus pathogenesis: Insights and knowledge gaps." Hum Vaccin Immunother **12**(12): 3110-3112.

Gouma, S., H. I. Ten Hulscher, T. M. Schurink-van 't Klooster, H. E. de Melker, G. J. Bolland, P. Kaaijk, C. A. van Els, M. P. Koopmans and R. S. van Binnendijk (2016). "Mumps-specific cross-neutralization by MMR vaccine-induced antibodies predicts protection against mumps virus infection." Vaccine **34**(35): 4166-4171.

Vermeire, T., Gouma, S., et al (2016). "Differences among mumps virus surface proteins between genotype G and other genotypes and their potential effect on mumps virus immunity and pathogenesis." Journal of Clin Virology **82**5: S1-S142.

Zengel, J., S. I. Phan, A. Pickar, P. Xu and B. He (2017). "Immunogenicity of mumps virus vaccine candidates matching circulating genotypes in the United States and China." Vaccine **35**(32): 3988-3994.

From: Marin, Mona (CDC/OID/NCIRD)
Sent: 3 Mar 2017 15:44:01 -0500
To: Stanley Plotkin
Cc: Cohn, Amanda (CDC/OID/NCIRD)
Subject: RE: Mumps WG

Hello Dr. Plotkin,

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Thanks and hope to talk with you soon,
Mona.

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Sent: Wednesday, February 15, 2017 4:34 PM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>
Cc: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

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Stanley

From: Marin, Mona (CDC/OID/NCIRD) [mailto:zsn8@cdc.gov]
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To: Stanley Plotkin
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From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: Tuesday, February 14, 2017 10:49 AM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>; Patel, Manisha M. (CDC/OID/NCIRD) <dv4@cdc.gov>
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Amanda

Amanda Cohn, MD
CDR, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices
NCIRD/CDC
Office: 404-639-6039
Cell: 404-451-6204
Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus
1600 Clifton Road MS A-87
Atlanta, GA 30329-4027

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 11 Aug 2017 13:19:06 +0000
To: 'Stanley Plotkin'
Cc: Patel, Manisha M. (CDC/OID/NCIRD); Marin, Mona (CDC/OID/NCIRD)
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Dear Amanda, Manisha and Mona:

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To: 'Cohn, Amanda (CDC/OID/NCIRD)'
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From: Marin, Mona (CDC/OID/NCIRD)
Sent: Friday, March 03, 2017 3:44 PM
To: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Cc: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
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Dr. Plotkin,

We would be honored for you to make a statement at the October meeting, and thank you for letting us know it will be your last meeting, we will miss you but i am so happy you will be able participate by watching on webcast.

Best,
Amanda

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Date: August 11, 2017 at 9:56:34 AM EDT
To: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Cc: Marin, Mona (CDC/OID/NCIRD) <zs8@cdc.gov>, Patel, Manisha M. (CDC/OID/NCIRD) <dv4@cdc.gov>
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Dear Amanda:

I will take your advice about contacting NVAC, where I have spoken before but not about mumps. However, I would also like to take advantage of your offer to make a statement at the October ACIP. I have a second reason for doing the latter, as I have decided that because of age it is time for me to stop traveling to ACIP and rather watch on the Web. So I will take that opportunity to say goodbye.

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To: Stanley Plotkin
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kimt@kidrisk.org

Here you go. Let me know what else I can do to help!

Amanda

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]
Sent: Friday, August 11, 2017 10:02 AM
To: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

Please send me Thompson's email

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Sent: Saturday, July 29, 2017 12:13 PM
To: 'Cohn, Amanda (CDC/OID/NCIRD)'
Cc: 'Patel, Manisha M. (CDC/OID/NCIRD)'; 'Marin, Mona (CDC/OID/NCIRD)'
Subject: RE: Mumps WG

I understand, at least formally, why I cannot participate in the policy discussions, but I wish to propose development of new mumps vaccines as one of the policy proposals. If that is a possible recommendation by the Working Group I would submit it in written form.
Stanley

From: Cohn, Amanda (CDC/OID/NCIRD) [<mailto:anc0@cdc.gov>]
Sent: Thursday, July 27, 2017 9:04 AM
To: Stanley Plotkin
Cc: Patel, Manisha M. (CDC/OID/NCIRD)
Subject: FW: Mumps WG

Good Morning Dr. Plotkin,

Please see below for a recap of the discussion regarding your consultation work with vaccine manufacturers and your participation as a scientific consultant on the WG. The guidelines regarding conflicts of interest for work group participants are in place to ensure there is no appearance of conflict of interest. I am happy to discuss more with you, I know your contributions to the scientific discussion thus far has been invaluable for the WG and I appreciate your lending your expertise to the ACIP process.

Best,

Amanda

From: Marin, Mona (CDC/OID/NCIRD)
Sent: Friday, March 03, 2017 3:44 PM
To: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Cc: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

Hello Dr. Plotkin,

We are thrilled to invite you to participate in the mumps ACIP WG as an expert consultant to contribute to the scientific discussions. According to the call schedule we have to date, the first 4 calls will not include policy discussions.

Please note that the regular calls are on the 2nd Thursday of each month, 3:30-5:00 pm EST, with the first being next week, on March 9th. We may add extra calls depending on the need to address first in the WG topics that will be presented to the ACIP.

Regarding the conflict of interest form, we would still want to have a form for you but you can just indicate where your conflicts are, without being specific on the manufacturer/vaccine. Please let us know if you want us to resend the form.

Thanks and hope to talk with you soon,
Mona.

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]
Sent: Wednesday, February 15, 2017 4:34 PM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>
Cc: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

OK, let me know which is preferred. I would be willing to participate in the scientific discussions but not policy discussions if that's best.
Stanley

From: Marin, Mona (CDC/OID/NCIRD) [<mailto:zsn8@cdc.gov>]
Sent: Wednesday, February 15, 2017 4:26 PM
To: Stanley Plotkin
Cc: Cohn, Amanda (CDC/OID/NCIRD)
Subject: RE: Mumps WG

Dear Dr. Plotkin,

My understanding from Amanda's email was that she was aware of your potential conflict of interest and she indicated that you can participate in the scientific discussions, with withholding the participation in the policy discussions. We are going to have several calls initially to present mumps epi (in the US and we're working on a lit review on mumps internationally) and immune response to natural infection and vaccination that would probably not involve policy discussions and in which your perspectives and expertise would be very useful. There are also calls on examining epi and lab evidence for risk factors for 2nd dose failure and potential benefit of the 3rd dose that are focused on science.

So my opinion is that if you want to go through the process of completing the conflict of interest form, we can further confirm with ACIP that you can participate in the science discussions and that would be an important proportion of WG calls. Alternatively, we can invite you to participate as a consultant on the science calls (not being a WG member per se), not sure if COI is needed for that. We had presenters for specific topics but they did not participate in more than 1 or 2 calls.

Amanda, any suggestions?

Thanks,
Mona.

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]
Sent: Wednesday, February 15, 2017 10:12 AM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>
Subject: RE: Mumps WG

Dear Mona:

I have received the forms and unfortunately there is no way I could join in view of the insistence that I have nothing to do with vaccine manufacturers. In fact, I consult for practically all of them. That being said, the question that interests me most is whether or not a new vaccine strain should be developed that gives longer persistence of immunity. If the WG does discuss that question perhaps I could participate for some minutes as a guest. Of course, first the WG has to decide that the current situation is untenable.

Thanks for your welcome,
Stanley

From: Marin, Mona (CDC/OID/NCIRD) [<mailto:zsn8@cdc.gov>]
Sent: Tuesday, February 14, 2017 9:35 PM
To: 'stanley.plotkin@vaxconsult.com'
Subject: FW: Mumps WG

Dear Dr. Plotkin,

Thank you so much for your interest in the mumps WG! Your expertise will be of great value to the WG discussions and recommendations. The primary objective of the WG is to evaluate and formulate policy options to prevent or control mumps outbreaks in the United States. We will start the WG calls in March and the day/time of the calls most likely is going to be the second Thursday of the month, 3:30-5:00 pm EST.

We will email you tomorrow a short intake form that includes questions to complete the WG roster and assess potential conflicts of interest. The email may come from me or Adria Lee.

We look forward to working with you on this policy activity,
Mona.

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: Tuesday, February 14, 2017 10:49 AM
To: Marin, Mona (CDC/OID/NCIRD) <zsn8@cdc.gov>; Patel, Manisha M. (CDC/OID/NCIRD) <dmn4@cdc.gov>
Subject: FW: Mumps WG

From: Stanley Plotkin [<mailto:stanley.plotkin@vaxconsult.com>]
Sent: Tuesday, February 14, 2017 10:44 AM
To: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Mumps WG

Dear Amanda:

Much thanks,

Stanley

From: Cohn, Amanda (CDC/OID/NCIRD) [<mailto:anc0@cdc.gov>]
Sent: Tuesday, February 14, 2017 10:37 AM
To: Stanley Plotkin
Cc: Marin, Mona (CDC/OID/NCIRD); Patel, Manisha M. (CDC/OID/NCIRD)
Subject: Mumps WG

Hi Dr. Plotkin,

I spoke to Mona Marin and Manisha Patel, the CDC leads for mumps, who would be thrilled if you could join the ACIP Mumps WG as an expert consultant, or in whatever capacity you are able to contribute to the discussions. Mona is working on the times of the calls with the ACIP voting members, and can send you some follow-up information.

The one issue we did not discuss is the conflict of interest disclosures. We do have some guidelines for WG participation that may limit your role in the policy discussions, depending on your current financial relationships. But, regardless you can participate as an expert during the science discussions.

Mona will follow-up with information. Thanks for considering participating!

Amanda

Amanda Cohn, MD
CDR, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices
NCIRD/CDC
Office: 404-639-6039
Cell: 404-451-6204
Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus
1600 Clifton Road MS A-87
Atlanta, GA 30329-4027

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 21 Aug 2017 13:55:14 +0000
To: Baker, Carol (CDC bcm.edu); Weber, David
Cc: Charles E Rupprecht; Advisory Committee on Immunization Practices (CDC); Schaffner, William (CDC vanderbilt.edu); dkimberlin@peds.uab.edu; Hahn, Christine G. <ID> (CDC dhw.idaho.gov); Duchin, Jeff (CDC kingcounty.gov); gregory@mayo.edu; Stanley Plotkin
Subject: RE: New ACIP Rabies Consultation?

Thanks all. We will review your request and get back to you with an official response shortly..

Best,

Amanda

Amanda Cohn, MD
CAPT, US Public Health Service
Executive Secretary, Advisory Committee on Immunization Practices
National Center for Immunization and Respiratory Diseases
Phone: (404) 639-6039
Email: acohn@cdc.gov

-----Original Message-----

From: Baker, Carol (CDC bcm.edu)
Sent: Monday, August 21, 2017 9:52 AM
To: Weber, David <David.Weber@unchealth.unc.edu>
Cc: Charles E Rupprecht <charleserupprechtii@gmail.com>; Advisory Committee on Immunization Practices (CDC) <acip@cdc.gov>; Schaffner, William (CDC vanderbilt.edu) <William.schaffner@vanderbilt.edu>; dkimberlin@peds.uab.edu; Hahn, Christine G. <ID> (CDC dhw.idaho.gov) <hahnc@dhw.idaho.gov>; Duchin, Jeff (CDC kingcounty.gov) <jeff.duchin@kingcounty.gov>; gregory@mayo.edu; Stanley Plotkin <stanley.plotkin@vaxconsult.com>; Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: Re: New ACIP Rabies Consultation?

Dear Dr Weber,

My current role at ACIP is as a liaison member representing the IDSA, but I agree with your comments. Since CDC designates work groups I am copying Dr Amanda Cohn, Executive Secretary to ACIP, for an official response.

Regards

Carol

> On Aug 20, 2017, at 12:50 PM, Weber, David <David.Weber@unchealth.unc.edu> wrote:

>

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

>

> I have had a long standing interest in zoonotic diseases (see attached paper) I think that an ACIP working group to re-evaluated our pre- and post-exposure rabies prevention would be an excellent idea

>

> David

>
> David Jay Weber, MD, MPH, FIDSA, FSHEA Professor of Medicine,
> Pediatrics and Epidemiology School of Medicine and Gillings School of
> Global Public Health University of North Carolina, Chapel Hill, NC,
> 27599-7030
>
> Associate Chief Medical Officer, UNC Hospitals Medical Director,
> Hospital Epidemiology, UNC Hospitals Medical Director, Occupational
> Health Service, UNC Hospitals Medical Director, North Carolina
> Statewide Program in Infection Control and Epidemiology Co-Chair,
> Biomedical IRB University of North Carolina at Chapel Hill
> From: Charles E Rupprecht [mailto:(b)(6)]
> Sent: Sunday, August 20, 2017 12:20 PM
> To: acip@cdc.gov
> Cc: william.schaffner@vanderbilt.edu; dkimberlin@peds.uab.edu;
> hahnc@dhw.idaho.gov; cbaker@bcm.edu; jeff.duchin@kingcounty.gov;
> Weber, David; gregory@mayo.edu; Stanley Plotkin
> Subject: New ACIP Rabies Consultation?
>
> Dear Madam/Sir:
>
> Hello.
>
> Rabies is a neglected zoonotic disease of major global significance and still a concern within north
America because of diverse wildlife reservoirs.
>
> Would you be so kind as to please let me know if and when you may consider formation of a new
advisory committee on rabies?
>
> It has been more than 7 years since the last major consultation on the revision of the human rabies
vaccine schedules.
>
> Since that time, there has been a major discussion at WHO with a new expert consultation regarding
harmonization of the basic definition of an antibody response needed for a booster; suggestions of a
shortened 1 week course for pre-exposure and post-exposure prophylaxis; and formation of a SAGE
working group for expansion of the concept of human sub-populations at risk, including pediatric patients
in enzootic regions.
>
> In addition, a new human rabies immune globulin product is slated to come on the national market,
produced by Kamada. Similarly, the U.S. FDA has held a major meeting on human anti-rabies monoclonal
antibodies and at least one such product has been licensed in India. Moreover, novel lyssaviruses have been
detected with less than ideal cross reactivity to licensed human and veterinary vaccines.
>
> Such developments suggest that it may be time for consideration of a thorough review by the ACIP and
subject matter experts, before any new global recommendations take effect.
>
> I look forward to your reply.
>
> Best regards. CER
>
> CE Rupprecht VMD, MS, PhD
> WHO Expert Technical Advisor on Rabies
> ----- Confidentiality Notice -----
> The information contained in (or attached to) this electronic message may be legally privileged and/or
confidential information. If you have received this communication in error, please notify the sender
immediately and delete the message.

> <20170820134806.pdf>

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 22 Aug 2017 17:26:55 +0000
To: Baker, Carol (CDC bcm.edu); Weber, David
Cc: Charles E Rupprecht; Advisory Committee on Immunization Practices (CDC); Schaffner, William (CDC vanderbilt.edu); dkimberlin@peds.uab.edu; Hahn, Christine G. <ID> (CDC dhw.idaho.gov); Duchin, Jeff (CDC kingcounty.gov); gregory@mayo.edu; Stanley Plotkin
Subject: RE: New ACIP Rabies Consultation?

Hello Everyone,

As part of the regular cycle of reviewing ACIP statements, the Rabies group has been planning to activate the ACIP Rabies WG and is doing background work on it. We are trying to balance a high number of WGs right now so we have not decided exactly when it will be started, but it will be in the next several months.

Best,

Amanda

Amanda Cohn, MD
CAPT, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices
NCIRD/CDC
Office: 404-639-6039
Cell: 404-451-6204
Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus
1600 Clifton Road MS A-87
Atlanta, GA 30329-4027

-----Original Message-----

From: Baker, Carol (CDC bcm.edu)
Sent: Monday, August 21, 2017 9:52 AM
To: Weber, David <David.Weber@unchealth.unc.edu>
Cc: Charles E Rupprecht <charleserupprechtii@gmail.com>; Advisory Committee on Immunization Practices (CDC) <acip@cdc.gov>; Schaffner, William (CDC vanderbilt.edu) <William.schaffner@vanderbilt.edu>; dkimberlin@peds.uab.edu; Hahn, Christine G. <ID> (CDC dhw.idaho.gov) <hahnc@dhw.idaho.gov>; Duchin, Jeff (CDC kingcounty.gov) <jeff.duchin@kingcounty.gov>; gregory@mayo.edu; Stanley Plotkin <stanley.plotkin@vaxconsult.com>; Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: Re: New ACIP Rabies Consultation?

Dear Dr Weber,

My current role at ACIP is as a liaison member representing the IDSA, but I agree with your comments. Since CDC designates work groups I am copying Dr Amanda Cohn, Executive Secretary to ACIP, for an official response.

Regards
Carol

> On Aug 20, 2017, at 12:50 PM, Weber, David <David.Weber@unchealth.unc.edu> wrote:

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> I have had a long standing interest in zoonotic diseases (see attached paper) I think that an ACIP working group to re-evaluated our pre- and post-exposure rabies prevention would be an excellent idea

>

> David

>

> David Jay Weber, MD, MPH, FIDSA, FSHEA Professor of Medicine, Pediatrics and Epidemiology School of Medicine and Gillings School of Global Public Health University of North Carolina, Chapel Hill, NC, 27599-7030

>

> Associate Chief Medical Officer, UNC Hospitals Medical Director, Hospital Epidemiology, UNC Hospitals Medical Director, Occupational Health Service, UNC Hospitals Medical Director, North Carolina Statewide Program in Infection Control and Epidemiology Co-Chair, Biomedical IRB University of North Carolina at Chapel Hill

> From: Charles E Rupprecht [mailto:(b)(6)]

> Sent: Sunday, August 20, 2017 12:20 PM

> To: acip@cdc.gov

> Cc: william.schaffner@vanderbilt.edu; dkimberlin@peds.uab.edu;

> hahnc@dhw.idaho.gov; cbaker@bcm.edu; jeff.duchin@kingcounty.gov;

> Weber, David; gregory@mayo.edu; Stanley Plotkin

> Subject: New ACIP Rabies Consultation?

>

> Dear Madam/Sir:

>

> Hello.

>

> Rabies is a neglected zoonotic disease of major global significance and still a concern within north America because of diverse wildlife reservoirs.

>

> Would you be so kind as to please let me know if and when you may consider formation of a new advisory committee on rabies?

>

> It has been more than 7 years since the last major consultation on the revision of the human rabies vaccine schedules.

>

> Since that time, there has been a major discussion at WHO with a new expert consultation regarding harmonization of the basic definition of an antibody response needed for a booster; suggestions of a shortened 1 week course for pre-exposure and post-exposure prophylaxis; and formation of a SAGE working group for expansion of the concept of human sub-populations at risk, including pediatric patients in enzootic regions.

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>

> Such developments suggest that it may be time for consideration of a thorough review by the ACIP and subject matter experts, before any new global recommendations take effect.

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> I look forward to your reply.
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> Best regards. CER
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> CE Rupprecht VMD, MS, PhD
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> <20170820134806.pdf>

From: Stanley Plotkin
Sent: 29 Mar 2017 10:31:15 -0400
To: Cohn, Amanda (CDC/OID/NCIRD)
Subject: RE: Response to your YF comments
Attachments: Cohn Bennett 2017.pdf

Please see attached.
Stanley

From: Cohn, Amanda (CDC/OID/NCIRD) [mailto:anc0@cdc.gov]
Sent: Thursday, March 23, 2017 11:58 AM
To: stanley.plotkin@vaxconsult.com
Cc: Advisory Committee on Immunization Practices (CDC); Dr. Chip Walter (walte002@mc.duke.edu)
Subject: Response to your YF comments

Dear Dr. Plotkin,

Attached is a letter from Dr. Bennett responding to the concerns you raised regarding discontinuing the use of YF vaccine booster doses for most travelers. I apologize for the delay and appreciate your patience!

The YF workgroup reviewed your concerns and references during a workgroup meeting and the letter details what was done and provides specific comments on each reference. Two additional documents are included as Appendices: the final GRADE tables and the final policy note. Finally, I am also attaching e-mail communications from the Brazil MOH regarding the potential error in the publication by Camara et al.

I speak on behalf of all ACIP members when I say we are so grateful for your comments, questions, and insight you provide around vaccine policy issues.

Best Regards,

Amanda

Amanda Cohn, MD
CDR, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices
NCIRD/CDC
Office: 404-639-6039
Cell: 404-451-6204
Email: acohn@cdc.gov

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Atlanta, GA 30329-4027

STANLEY A PLOTKIN, MD
Consultant in Vaccinology

Professor Emeritus of Pediatrics, University of Pennsylvania
Professor Emeritus, Wistar Institute, Philadelphia
Adjunct Professor, Johns Hopkins University, Baltimore

215-297-9321 (tel)
215-297-9323 (fax)
215-262-3665 (cell)
stanley.plotkin@vaxconsult.com

March 29, 2017

Dr. Nancy Bennett
Dr. Amanda Cohn
CDC

Dear Nancy and Amanda:

Let me express my sincere appreciation to the Yellow Fever Working Group for all the work that went into its response to my concerns. I am genuinely impressed that my objection resulted in so much thorough work and I completely understand the Working Group's conclusions, which may well be correct.

I do have to observe that a lot depends on the inferences regarding the validity of the Camara article and also that there is no mention of a long article by Campi-Azevedo and a list of 41 Brazilians studying immune responses to YF vaccination that expressly concludes with a recommendation for boosters. (Campi-Azevedo AC et al, "Booster dose after 10 years is recommended following 17DD-YF primary vaccination." Human Vaccines, 12:491-502, 2016). This suggests to me that Brazilian opinion is at least divided.

So there is no misunderstanding, I do not expect the Working Group to reconsider its conclusion, but I would appreciate it if this letter is circulated to its members.

Thank you.

(b)(6)

Stanley A. Plotkin, M.D.

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 3 Apr 2017 17:26:19 +0000
To: Stanley Plotkin
Subject: RE: Response to your YF comments

Thank you so much! I have forwarded this to Dr. Bennett and the Flavivirus Work Group.

We hope to see you in June,

Amanda

From: Stanley Plotkin [mailto:stanley.plotkin@vaxconsult.com]
Sent: Wednesday, March 29, 2017 10:31 AM
To: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: RE: Response to your YF comments

Please see attached.
Stanley

From: Cohn, Amanda (CDC/OID/NCIRD) [mailto:anc0@cdc.gov]
Sent: Thursday, March 23, 2017 11:58 AM
To: stanley.plotkin@vaxconsult.com
Cc: Advisory Committee on Immunization Practices (CDC); Dr. Chip Walter (walte002@mc.duke.edu)
Subject: Response to your YF comments

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The YF workgroup reviewed your concerns and references during a workgroup meeting and the letter details what was done and provides specific comments on each reference. Two additional documents are included as Appendices: the final GRADE tables and the final policy note. Finally, I am also attaching e-mail communications from the Brazil MOH regarding the potential error in the publication by Camara et al.

I speak on behalf of all ACIP members when I say we are so grateful for your comments, questions, and insight you provide around vaccine policy issues.

Best Regards,

Amanda

Amanda Cohn, MD
CDR, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices

NCIRD/CDC

Office: 404-639-6039

Cell: 404-451-6204

Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus

1600 Clifton Road MS A-87

Atlanta, GA 30329-4027

From: Cohn, Amanda (CDC/DDID/NCIRD/OD)
Sent: 10 Jul 2019 23:08:07 +0000
To: Stanley Plotkin
Cc: Messonnier, Nancy (CDC/DDID/NCIRD/OD); 'Tom Monath'; 'Mark Slifka'
Subject: RE: yellow fever boosters

Dr. Plotkin,

Thank you so much for reaching out, I always appreciate your raising important issues that need to be on ACIP's radar. I reached out to the yellow fever SMEs, they have been reviewing the findings in the new study and thinking through the implications.

In the setting of the current shortage of yellow fever vaccine and with multiple new vaccines on the horizon for ACIP to consider, readdressing the current US recommendations for yellow fever vaccine is not in our short-term (6 month) work plan. CDC and ACIP are constantly reviewing new evidence on safety, impact, and effectiveness of vaccines that may inform changes to immunization recommendations. I can assure you that this question will remain on the list of issues for ACIP to address in the near future, especially once there is adequate supply to support and potential changes to a recommendation.

I'm happy to have a call to discuss this issue further as well as some of your other concerns related to ACIP meeting procedures if you are interested.

Best,

Amanda

Amanda Cohn, MD
CAPT, US Public Health Service
Executive Secretary
Advisory Committee on Immunization Practices
NCIRD/CDC
Office: 404-639-6039
Cell: 404-271-0909
Email: acohn@cdc.gov

Centers for Disease Control and Prevention (CDC) Roybal Campus
1600 Clifton Road MS A-87
Atlanta, GA 30329-4027

From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Sent: Wednesday, July 10, 2019 11:09 AM
To: Cohn, Amanda (CDC/DDID/NCIRD/OD) <anc0@cdc.gov>
Cc: Messonnier, Nancy (CDC/DDID/NCIRD/OD) <nar5@cdc.gov>; 'Tom Monath'

<tom.monath@crozetbiopharma.com>; 'Mark Slifka' <slifkam@ohsu.edu>

Subject: yellow fever boosters

Dear Amanda:

You may recall that a couple of years ago the ACIP recommended against routine boosters of yellow fever vaccine except in individuals with immune deficits. You may also recall that I spoke against that change based on the available data but the committee went on to make the recommendation anyway.

I return to the subject because of a new publication (the last on the attached list) that shows considerable loss of titer in normal individuals in Brazil. Of those who received a single dose 31% were seronegative, although among those with defined times since vaccination 15% were seronegative. The authors of the study conclude that despite issues regarding test sensitivity and the possible protective effect of CD8+ T cells, that booster doses are indicated. At the very least the Yellow Fever Working Group should review that article as well as my commentary on a previous article. Although this may sound like "I told you so" all I want is an unprejudiced look at the data. I am aware that there is a shortage of yellow fever vaccine so there is no urgency to add boosters but in the interests of scientific accuracy the data should be fairly evaluated.

Best wishes,

Stanley

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 3 Nov 2017 13:16:39 +0000
To: Stanley Plotkin
Subject: RE: yesterday
Attachments: Cohn Bennett Welcome Oct 2017_final.pptx

Hi Dr. Plotkin,

I apologize for the delayed response, I don't look at emails during ACIP and this got lost in the many I am wading through. We are so happy we were able to honor you in person, your presence all these years has been so impactful to the meeting deliberations. Please always continue to email any comments or issues if you would like for us to include them in the meetings. Specifically, I can give you a small heads up that in June we are going to be talking early about Lyme vaccines, which I know you will be excited about!

Of course I will send you the slides! They are attached here, towards the end of the presentation. I can also send you Larry's comments if you would like.

And here are the emails below:

Nana Bennett:
Nancy_Bennett@URMC.Rochester.edu

Kelly Moore:
Kelly.Moore@tn.gov

Look forward to seeing you soon,

Amanda

From: Stanley Plotkin [mailto:stanley.plotkin@vaxconsult.com]
Sent: Sunday, October 29, 2017 10:33 AM
To: Cohn, Amanda (CDC/OID/NCIRD) <anc0@cdc.gov>
Subject: FW: yesterday

Dear Amanda:

I was very moved by the presentation of the gavel and the kindness of everybody, and am more than grateful. Would it be possible to send me the slides that Larry showed? Also, could you send me the emails of Drs. Bennett and Moore?

I am really sorry to be absent in the future, but I will be watching!

Kind regards,
Stanley

Advisory Committee on Immunization Practices (ACIP)

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES Centers for I

Advisory Committee on Immunization Practices (ACIP)

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ACIP

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Get Email Updates

Updated Guidance for Yellow Fever Vaccine

To avoid a lapse in yellow fever vaccine availability in the United States, the manufacturer, Sanofi Pasteur, has received approval from FDA to import Stamaril yellow fever vaccine. Stamaril is produced by Sanofi Pasteur in France and has comparable safety and efficacy to YF-Vax. See the MMWR [Addressing a Yellow Fever Vaccine Shortage — United States, 2016–2017](#) for further information for providers regarding yellow fever vaccine.

Register for upcoming October ACIP meeting

October 25-26, 2017

Deadline for registration:

Non-US Citizens: September 25, 2017

US Citizens: October 5, 2017

Registration is NOT required to watch the live meeting webcast or to listen via telephone.

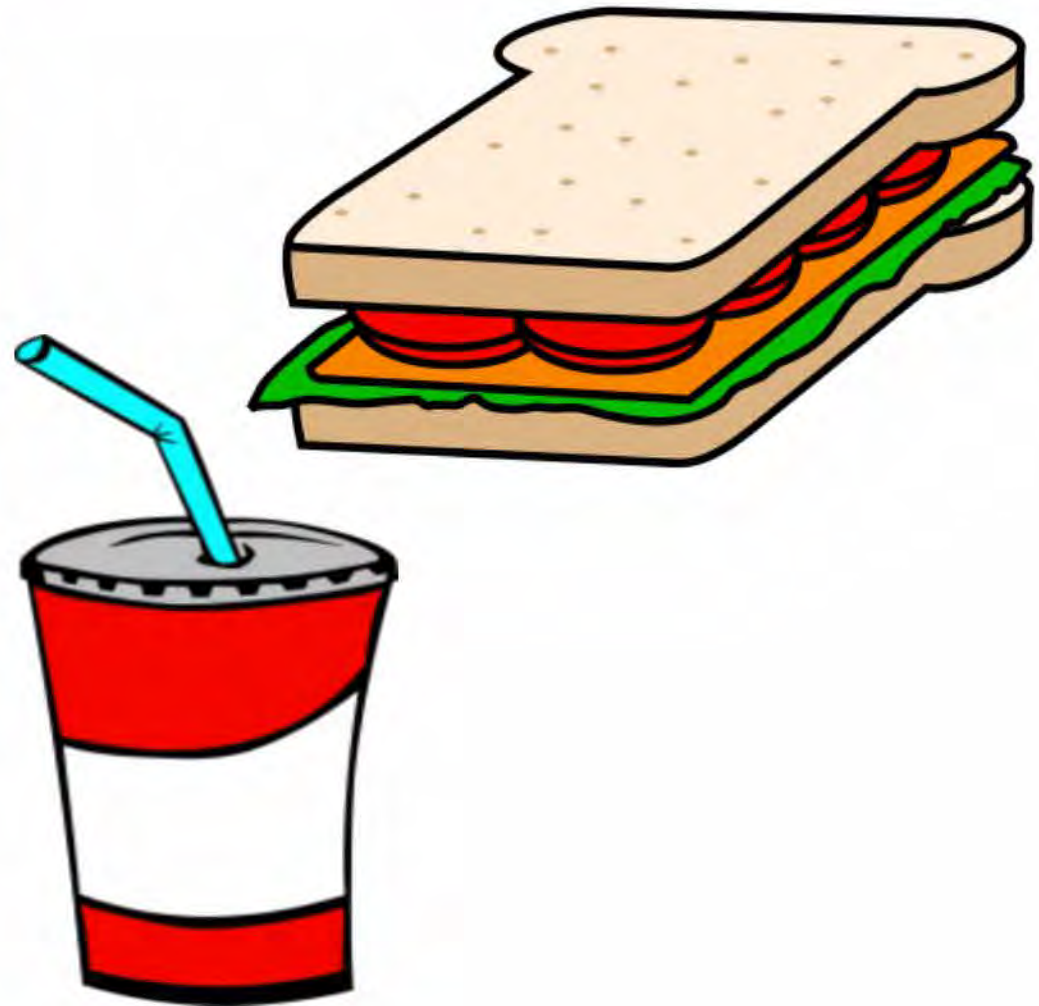
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ACIP Meetings

- **Meeting Information** Recent ACIP meeting agendas, detailed meeting minutes, live meetings, and presentation slides.
- **Upcoming Meetings** List of scheduled ACIP meeting

Very Important Information!



New Deputy ACIP Executive Secretary



Jessica MacNeil, MPH

Advisory Committee on Immunization Practices (ACIP)

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ACIP Meeting Information



The ACIP holds three meetings each year at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia to review scientific data and vote on vaccine recommendations. Meetings are open to the public and available online via live webcast. During committee meetings, members present findings and discuss vaccine research and scientific data related to vaccine effectiveness and safety, clinical trial results, and manufacturer's labeling or package insert information. Outbreaks of vaccine-preventable disease or changes in vaccine supply also are reviewed during these meetings. Vaccine recommendations include the age(s) when the vaccine should be given, number of doses needed, dosing interval, and precautions and contraindications to administration of vaccines.

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Meeting Minutes

February 21-22, 2018 Meeting

Registration Opens October 27, 2017

- Registration online at www.cdc.gov/acip For non-US citizens, registration deadline: January 24, 2018 For US citizens, registration deadline: February 5, 2018

Guest Attendee at this Meeting

Hope Peisley Director – Immunisation Policy Section
Immunisation
Branch
Office of Health Protection
Australian Government Department
of Health

Member Substitutions for this Meeting

Liaison Representatives Dr. Scott Cyrus, AOADr. Susan Lett,
CSTEDr. Bonnie Maldonado, AAPDr. Corey Robertson,
PhRMAAmy Walker, BIODr. Victoria Statler, APTR Ex-officio
MembersDr. Barbara Mulach, NIHDr. Melinda Wharton, NVPO

Update on ACIP Membership

- Drs. Arthur Reingold, Ms. Cindy Pelligrini, and Dr. Allison Kempe have been extended through December 31, 2017. Nominations for membership beginning July 1, 2018 are under review. Applications for membership beginning July 1, 2019 will open in January 2018. Any questions: acip@cdc.gov

Process for Public Comment

- Public comment period is scheduled immediately preceding each ACIP vote and at end of meeting day
Individuals should limit public comments to 3 minutes in total
Registration for public comments is solicited in advance of the meeting
Comments not presented at meeting may be submitted for inclusion in the minutes

Disclosure of Conflicts of Interest

- Members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure on the committee. CDC has issued limited conflict of interest waivers as follows: Members who conduct vaccine clinical trials or serve on data safety monitoring boards are prohibited from participating in committee votes related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions, with the provision that he/she abstains on all votes related to the vaccines of that company. At the beginning of each meeting, ACIP members state any conflicts of interest.

Surprise #1: Electronic.....



Surprise #1: Electronic Voting

- ACIP members will vote simultaneouslyResults will be displayed on the screen when voting is closedWe will then verbally verify votes around the table and ACIP members can add a comment if they choose

Surprise #2: Special Presentation





Stanley A.
Plotkin



Introducing....



Please Turn off Your Cell Phones....



Advisory Committee on Immunization Practices (ACIP)

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES Centers for

From: Cohn, Amanda (CDC/OID/NCIRD)
Sent: 23 Mar 2017 15:57:50 +0000
To: stanley.plotkin@vaxconsult.com
Cc: Advisory Committee on Immunization Practices (CDC); Dr. Chip Walter (walte002@mc.duke.edu)
Subject: Response to your YF comments
Attachments: Plotkin Letter_March 2017.pdf, Appendix 2_YF vaccine booster dose immunity GRADE.pdf, Appendix 3_YF vaccine booster policy note MMWR.pdf, FW_ Brazil YF data.msg

Dear Dr. Plotkin,

Attached is a letter from Dr. Bennett responding to the concerns you raised regarding discontinuing the use of YF vaccine booster doses for most travelers. I apologize for the delay and appreciate your patience!

The YF workgroup reviewed your concerns and references during a workgroup meeting and the letter details what was done and provides specific comments on each reference. Two additional documents are included as Appendices: the final GRADE tables and the final policy note. Finally, I am also attaching e-mail communications from the Brazil MOH regarding the potential error in the publication by Camara et al.

I speak on behalf of all ACIP members when I say we are so grateful for your comments, questions, and insight you provide around vaccine policy issues.

Best Regards,

Amanda

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta, GA 30341-3724

March 8, 2017

Dear Dr. Plotkin,

We wanted to thank you for raising your concerns at the last ACIP meeting and through your subsequent letter about the potential continued need for booster doses following yellow fever (YF) vaccination. We have shared your concerns and reference list with the ACIP Flavivirus Vaccines Workgroup. They have reviewed the references as well as their previous GRADE analysis, and their findings are noted below.

Members of the workgroup, including the ACIP members, reviewed the references you cited, searched PubMed for additional relevant articles, and formally discussed the additional references and concerns you raised. Of the nine references provided, six were published before ACIP recommended removing YF vaccine booster dose recommendations for most travelers (**Appendix 1**). All but one of the previously published references were included in the GRADE analysis which is attached for your reference (**Appendix 2**). Of the three articles published since ACIP recommended removing the booster dose recommendation, one was a review, one had data that had already been partially included in the GRADE analysis, and the last reported the immunologic response to vaccination in a type I interferon knockout mouse. From the PubMed search, the workgroup identified one additional article that looked at differences in the immunologic response to the vaccine by population. They also provided specific input on each of the articles as they relate to the GRADE policy question and analysis (**Appendix 1**).

In reviewing the information, the workgroup did not think there was sufficient new evidence to revise the current ACIP recommendations: that a single primary dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers (**Appendix 3**). The work group also did not think the new evidence would: 1) change the current groups for whom revaccination is recommended or considered based on either a suboptimal immune response to the vaccine or an increased risk of disease; or 2) suggest that further study is needed to determine if revaccination or booster doses should be considered. However, the workgroup will continue to review new data as they become available, particularly for groups where there are fewer data available on their longer-term immunologic response to YF vaccine, such as children.

Thank you again for voicing your concern to ensure that people are adequately protected against YF. We are so appreciative of your input and concerns.

Respectfully,

(b)(6)

Nancy M. Bennett, MD, MS
Chair, Advisory Committee on Immunization Practices
Professor of Medicine and Public Health Sciences
Director, Center for Community Health
University of Rochester School of Medicine and Dentistry

Appendix 1. References and ACIP Flavivirus Vaccines Workgroup notes

Below is a list of references provided by Dr. Plotkin and work group notes regarding the applicability of the reference to address the policy question of “Should booster doses of YF vaccine every 10 years continue to be recommended for healthy travelers and laboratory workers?”

1. **Gotuzzo, E., Yactayo, S., & Cordova, E. (2013). *Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. Am J Trop Med Hyg, 89(3), 434-444. doi: 10.4269/ajtmh.13-0264***
Review article performed by a WHO consultant for consideration by SAGE regarding the decision to retain or remove booster dose recommendations of yellow fever vaccine. This article was reviewed as part of the GRADE process and is cited in the GRADE document.
2. **Amanna, I. J., & Slifka, M. K. (2016). *Questions regarding the safety and duration of immunity following live yellow fever vaccination. Expert Rev Vaccines, 1-15. doi: 10.1080/14760584.2016.1198259***
Review article published following the approval of the booster dose recommendations by ACIP. The article emphasizes the number of vaccine failures in Brazil (published by Camara et al.) as one of the primary reasons for why they recommend continuing booster doses. The workgroup had concerns with the data published by Camara et al. and contacted the Brazil Ministry of Health during the GRADE process to verify the data. The Brazil Ministry of Health noted issues with the analysis by Camara and provided unpublished data on vaccine failures that was included in Table 2 in the GRADE analysis document.
3. **Watson, A. M., Lam, L. K., Klimstra, W. B., & Ryman, K. D. (2016). *The 17D-204 Vaccine Strain-Induced Protection against Virulent Yellow Fever Virus Is Mediated by Humoral Immunity and CD4+ but not CD8+ T Cells. PLoS Pathog, 12(7), e1005786. doi: 10.1371/journal.ppat.1005786***
Includes information on the immunologic response in a mouse model that is deficient in a Type I interferon receptor. Although the data suggest less of a role of CD8 T cells it is unclear how representative this mouse model is for the immunologic response in humans to yellow fever vaccine or the implications for recommendations for use of a booster dose.

4. ***A randomised double-blind clinical trial of two yellow fever vaccines prepared with substrains 17DD and 17D-213/77 in children nine-23 months old. (2015). Mem Inst Oswaldo Cruz, 110(6), 771-780. doi: 10.1590/0074-02760150176***

These data were published after the GRADE analysis was performed and presented to ACIP. However, the immunologic response to yellow fever vaccine of many of the children in this paper was previously published in a study by Nascimento et al where YF vaccine was given together with MMR vaccine or 30 days apart from MMR. The data from Nascimento has similar seroconversion rates as this study and were included in Table 9 of the GRADE analysis. The pediatric seroconversion data, including the Nascimento study, were reviewed by the AAP Committee on Infectious Diseases prior to the ACIP meeting and it was concluded the immunologic response in children was not different enough from adults to warrant a different recommendation in children for booster doses but they did recommend that additional follow-up studies be conducted.

5. ***Camara, F. P., de Carvalho, L. M., & Gomes, A. L. (2013). Demographic profile of sylvatic yellow fever in Brazil from 1973 to 2008. Trans R Soc Trop Med Hyg, 107(5), 324-327. doi: 10.1093/trstmh/trt014***

Per direct communication from the Brazil Ministry of Health, data presented in the paper were not correct (i.e., the authors misinterpreted the database provided by the Brazil MOH) and the Ministry of Health provided to the workgroup the number of vaccine failures that the MOH had recorded during this time frame and these data are presented in Table 2 of the GRADE document.

6. ***Niedrig, M., Lademann, M., Emmerich, P., & Lafrenz, M. (1999). Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA. Trop Med Int Health, 4(12), 867-871.***

Data included in Table 3 of the GRADE document.

7. ***Poland, J. D., Calisher, C. H., Monath, T. P., Downs, W. G., & Murphy, K. (1981). Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ, 59(6), 895-900.***

Data included in Table 3 of the GRADE document.

8. ***Coulange Bodilis, H., Benabdelmoumen, G., Gergely, A., Goujon, C., Pelicot, M., Poujol, P., & Consigny, P. H. (2011). [Long term persistence of yellow fever neutralising antibodies in elderly persons]. Bull Soc Pathol Exot, 104(4), 260-265. doi: 10.1007/s13149-011-0135-7***

Data included in Table 3 of the GRADE document.

9. ***Hepburn, M. J., Kortepeter, M. G., Pittman, P. R., Boudreau, E. F., Mangiafico, J. A., Buck, P. A., . . . Anderson, E. L. (2006). Neutralizing antibody response to booster vaccination with the 17d yellow fever vaccine. Vaccine, 24(15), 2843-2849. doi: 10.1016/j.vaccine.2005.12.055***

Data were reviewed but not included in the GRADE document as this paper detailed the immunologic response among laboratory workers at USAMRIID to a booster dose

of the vaccine (e.g., had been previously vaccinated). There were three groups of individuals based on their pre-booster dose titer (10, 20–40, and >40). The number of vaccine doses and the time from the last vaccine dose were not known or not included in the paper so determining the duration of an immunologic response was not possible. The data presented noted that African American individuals had a lower post vaccination titer than white individuals in response to the booster dose. They also found that antibody decay rates varied based on the pre-booster dose titer and fell below a titer of 40 using a PRNT₈₀ (what they called titer failures) within a few years of the booster dose. The work group used a detectable titer to represent protective immunity and WHO considers a PRNT₅₀ titer of 10 as satisfactory evidence of immunogenicity for new virus master and working seeds.¹

10. Muyanja E, et al. Immune activation alters cellular and humoral responses to yellow fever 17D vaccine. *J Clin Invest* 2014; 124: 3147–3158.

This article was not included among the reference but was identified by the workgroup through a PubMed search as having potential data relevant to the difference in the immunologic response to YF vaccination between different populations (endemic African population versus traveler population from Europe). The study included 50 persons from Entebbe, Uganda and 50 from Lusarne, Switzerland. Each location had persons who had previously received YF vaccine and those that reported never receiving the vaccine. The authors found the persons living in endemic areas had a less vigorous antibody response to the vaccine correlating this with higher background reactivity in CD8+ T cell and B cell in the endemic cohort that blunted vaccine viral replication and lead to decreased antibody levels. Although these populations were likely of different races, it is unclear if race had a role compared to the differences in the environment (e.g., chronic or acute inflammatory conditions) that would affect baseline immune activity and subsequent immunologic response to the vaccine.

¹ World Health Organization. Recommendations to Assure the Quality, Safety and Efficacy of Live Attenuated Yellow Fever Vaccines. Geneva, Switzerland: WHO, 2010.

Grading of recommendations, assessment, development, and evaluation (GRADE) for yellow fever vaccine booster doses

Background

Yellow fever (YF) is a mosquito-borne viral disease that is endemic to sub-Saharan Africa and tropical South America. YF virus causes an estimated 200,000 cases of clinical disease and 30,000 deaths annually [WHO 1992]. Clinical disease ranges from a mild, undifferentiated febrile illness to severe disease with jaundice and hemorrhage. The case-fatality ratio for severe YF is 20%-50% [Monath 2013]. Because no specific treatment exists for YF, prevention is critical to reduce disease risk. One of the most effective prevention measures against YF is vaccination with the live, attenuated YF 17D substrain virus vaccine.

YF vaccine is recommended for persons aged ≥ 9 months who are traveling to or living in areas with risk for YF virus transmission [CDC 2010]. In addition, International Health Regulations allow countries to require proof of YF vaccination from travelers entering their country [WHO 2005]. These requirements are intended to minimize the potential importation and spread of YF virus. Proof of YF vaccination is recorded on the International Certificate of Vaccination or Prophylaxis (i.e., yellow card). International Health Regulations specify that the International Certificate of Vaccination or Prophylaxis is valid for 10 years. Therefore, if 10 or more years have elapsed since the last vaccination, people planning travel to a country with a YF vaccination entry requirement need to receive a booster dose of the vaccine.

The Strategic Advisory Group of Experts on Immunization (SAGE), the principal advisory group to the World Health Organization (WHO) for vaccines and immunization, concluded in April 2013 that a single dose of YF vaccine is sufficient to confer sustained immunity and lifelong protection against YF disease, and a booster dose of the vaccine is not needed [WHO 2013]. This conclusion was based on a systematic review of published studies on the duration of immunity following a single dose of YF vaccine, and on data that suggest vaccine failures are extremely rare and do not increase in frequency with time since vaccination [Gotuzzo 2013]. SAGE noted that future studies and surveillance data should be used to identify specific risk groups, such as infants or persons infected with human immunodeficiency virus (HIV), who could benefit from a booster dose. In May 2014, the World Health Assembly adopted the recommendation to remove the 10 year booster dose requirement from the International Health Regulations by June 2016 [WHO 2014].

In the United States, the current ACIP YF vaccine recommendations note that “[International Health Regulations] require revaccination at intervals of 10 years to boost antibody titer. Evidence from multiple studies demonstrates that YF vaccine immunity persists for many decades and might provide life-long protection” [CDC 2010]. The ACIP Japanese Encephalitis Vaccine Work Group was reformed to include YF vaccine in October 2013 to discuss the need for booster doses of YF vaccine.

Policy questions

The primary policy question was “Should booster doses of YF vaccine every 10 years continue to be recommended for healthy travelers and laboratory workers?”

Population: Healthy travelers and laboratory workers

Intervention: Remove current recommendation for booster doses of YF vaccine

Current option: Continue current recommendation for booster doses of YF vaccine

An additional policy question was created for special populations for whom their initial immunologic response to the vaccine might be suboptimal: “Should booster doses of YF vaccine every 10 years continue to be recommended for travelers or laboratory workers who had a precaution to vaccination that might have negatively impacted their immune response to their primary dose of YF vaccine (e.g., age 6–8 months, asymptomatic HIV infection with moderate immune suppression, pregnancy, or age ≥ 60 years)?”

Population: Travelers or laboratory workers who have a precaution to vaccination that might negatively impact their immune response to their primary dose of YF vaccine (e.g., age 6–8 months, HIV infection, pregnancy, and age ≥ 60 years)

Intervention: Remove current recommendation for booster doses of YF vaccine for these populations

Current option: Continue current recommendation for booster doses of YF vaccine for these populations

The Work Group also discussed and examined data on booster doses for travelers and laboratory workers in high-risk settings for exposure to YF virus. Data for these populations and those with conditions that might negatively impact their response to a primary dose of YF vaccine were reviewed and summarized but a further evaluation of the potential benefits and harms of booster doses could not be performed given the limited amount of data that existed.

Identify and rank relative importance of outcome measures

For the GRADE evaluation of YF vaccine booster doses, the benefits considered as critical outcomes included vaccine efficacy, effectiveness (i.e., lack of vaccine failures), and seroprotection. However, there are no vaccine efficacy data or long-term seroprotection data for YF vaccine. Given this, seropositivity was used as a surrogate for seroprotection (**Table 1**). The harms considered critical outcomes were any vaccine-related serious adverse event, vaccine associated-viscerotropic disease, and vaccine associated-neurologic disease. Evidence type for each critical outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations (i.e., publication bias, strength of association, dose response, or direction of all plausible confounding would reduce the effect) [Ahmed 2011].

Evidence retrieval

To identify published literature that contained relevant evidence, we conducted PubMed and Embase searches of papers in any language published as of May 19, 2014. We used the keyword “yellow fever vaccine” and then used additional keywords to identify articles that pertained to the critical outcomes. For benefits related to vaccine immunity, the following keywords were used: “immunogenicity”, “immunity”, or “long-term”. For harms related to adverse events, the following keywords were used: “adverse events”, “safety”, or “side effects”. The titles of the articles were first reviewed to identify potentially relevant articles and then the abstracts were reviewed of any article with a relevant title. If no abstract was provided, the paper itself was reviewed. In addition, reference lists of relevant articles were reviewed to identify any additional articles that might be of relevance but were not obtained through searching PubMed or Embase.

Articles that presented data on YF vaccine were included if they met the following criteria: 1) involved human subjects; 2) reported primary data; and 3) included data relevant to the outcome measures being assessed. Publications that met the above criteria but represented case reports of adverse events were excluded.

Of 1,166 articles in PubMed identified using the terminology “yellow fever vaccine”, 560 articles included keywords related to the critical outcomes. Of these, 263 articles included keywords related to benefits and 412 article related to harms. Following the removal of articles that did not meet the inclusion criteria, 30 articles were included in the GRADE evaluation. The Embase search identified 1,719 articles related to YF vaccine but no additional studies meeting the selection criteria were found. From the reference lists of relevant articles, two additional articles were identified and included in the GRADE evaluation. This search was repeated on February 2, 2015 to identify any literature that was recently published; no additional articles were identified.

Unpublished data were also considered, including data from studies conducted by the Brazilian Ministry of Health on duration of immunity and vaccine safety, CDC data on antibody titers in vaccine recipients, and VAERS data on vaccine safety.

Summarize relevant evidence for critical outcomes

Vaccine effectiveness

The evidence used to evaluate vaccine effectiveness was derived from eight published studies and one unpublished study that documented YF disease in persons who reported receiving YF vaccine. Of the eight published studies, four were from Brazil and likely contained individuals who were included in more than one of the studies. In response to an inquiry regarding the potential overlap between studies, the Brazilian Ministry of Health provided national level data that covered both the populations and the time period of the four studies; these data were used in place of the four published studies from Brazil (**Table 2**).

A total of 23 vaccine failures were identified following the administration of >540 million doses of YF vaccine [WHO 2013]. Of the 23 cases, five occurred <10 days after vaccination and were excluded as most persons are not expected to develop protective titers before 10 days after vaccination [Monath 2013]. Of the remaining 18 cases, 16 (89%) occurred in individuals who reported receiving a dose of the vaccine within the previous 10 years. Two vaccine failures occurred ≥ 10 years after the last dose of YF vaccine, including one at 20 years and one at 27 years post vaccination. Eleven cases (61%) lacked any YF laboratory testing. For seven cases, there was laboratory confirmation of YF virus infection; however, for some cases the only laboratory evidence of infection was detection of anti-YF virus IgM antibodies [Brazil 2014]. Since YF IgM antibodies can persist for several years following YF vaccination [Gibney 2012], these cases lacked definitive evidence of a recent infection with wild-type YF virus.

Seropositivity

The evidence used to evaluate seropositivity at ≥ 10 years following YF vaccination was derived from 12 published studies and one unpublished study (**Table 3**). The studies were published over a 60 year period (1952–2014) and included data for several different vaccines, some of which are no longer manufactured, and results from tests that are no longer used.

Of the 13 observational studies, immunogenicity data were available on 1,137 persons vaccinated ≥ 10 years previously. Of these, 1,002 (88%) were seropositive for YF virus neutralizing antibodies. Of 164 persons who reported receiving YF vaccine ≥ 20 years previously, 132 (80%) had detectable levels of neutralizing antibodies (i.e., seropositive). When study size differences and variability between studies was accounted for using a random effects model, the estimate of seropositivity for persons vaccinated ≥ 10 years previously was 92% (95% confidence interval [CI] 85%–96%) and those vaccinated ≥ 20 years previously was 80% (95% CI 74%–

86%).

Serious adverse events (SAE)

The evidence used to evaluate SAE following YF vaccine was derived from eight published and one unpublished observational studies. These studies included surveillance data from national authorities as well as data from vaccine manufacturers for approximately 333 million doses of distributed vaccine. There were 1,255 subjects reported to have a SAE following YF vaccination (**Table 4**). For the majority (84%) of subjects, it was unknown if the SAE occurred following a primary or booster dose of the vaccine. Furthermore, it was not known how many of the 333 million doses of vaccine were administered as a primary or booster dose. Of the 201 subjects with a SAE where dose type was known, 14 (7%) occurred following a booster dose of vaccine.

Viscerotropic disease

The evidence used to evaluate YF vaccine-associated viscerotropic disease (YEL-AVD) was derived from eight observational studies. These studies included surveillance data from national authorities as well as data from vaccine manufacturers for approximately 437 million doses of distributed vaccine. There were 72 subjects reported as having YEL-AVD (**Table 5**). Most of these YEL-AVD cases likely also were reported as SAE. For 41 (57%) subjects, it was unknown if YEL-AVD occurred following a primary or booster dose of the vaccine. Furthermore, it was not known how many of the 437 million doses of vaccine were administered as a primary or booster dose. Of the 31 subjects where dose type was known, 1 (3%) subject had YEL-AVD after receiving a booster dose of the vaccine; no laboratory testing was performed for that case.

Neurologic disease

The evidence used to evaluate YF vaccine-associated neurologic disease (YEL-AND) was derived from eight observational studies. These studies included surveillance data from national authorities as well as data from vaccine manufacturers for approximately 462 million doses of distributed vaccine. There were 218 subjects reported as having YEL-AND (**Table 6**). For 108 (50%) subjects, it was unknown if YEL-AND occurred following a primary or booster dose of the vaccine. Furthermore, it was not known for most of the 462 million doses of vaccine how many were administered as a primary or booster dose. Of the 110 subjects where dose type was known, 3 (3%) subjects reported YEL-AND after receiving a booster dose of the vaccine. All three of these YEL-AND cases were reported as an autoimmune-mediated event rather than direct vaccine viral invasion of the central nervous system. With autoimmune neurologic events seen following YF vaccination, there is no specific laboratory testing that is available to assess vaccine causality.

Summary of quality of evidence across outcomes

For the benefits considered critical outcomes, there were very few vaccine failures documented and most [92% (95% CI 85%–96%)] primary vaccine recipients were seropositive at ≥ 10 years post vaccination. However, evidence type is 4 for both vaccine effectiveness and seropositivity as there were only observational studies available that were downgraded because of the risk of bias (i.e., incomplete case capture, no comparison group, and bias in those tested for long-term seropositivity) and indirectness (i.e., different populations of interest, unknown how many persons had received a booster dose, and indirect measure of efficacy and seroprotection) (**Table 7**). For harms considered critical outcomes, very few safety concerns were reported after booster

doses. The evidence type is 4 for observational studies that were downgraded due to indirectness (i.e., unknown how many of the doses were administered as booster doses versus primary doses and thus the rates of adverse events for booster doses specifically could not be calculated). The overall quality of evidence is type 4 (**Table 8**).

Summary of other relevant evidence

In addition to the critical outcomes, data were reviewed on certain populations who had a condition that might have compromised their immune response to YF vaccine, including pregnant women, hematopoietic stem cell transplant recipients, HIV-infected individuals, and young children.

Pregnant women: The proportion of women who develop YF virus antibodies is variable and might be related to the trimester in which they received the vaccine. Of 83 pregnant women receiving YF vaccine predominantly in their third trimester, 32 (39%) had evidence of seroconversion to YF virus at 2–4 weeks post vaccination compared to 94% (89/95) in the general population [Nasidi 1993]. Of 433 women vaccinated predominantly in the first trimester (mean gestational age 5.7 weeks; 95% CI 5.2–6.2), 425 (98%) developed YF virus-specific neutralizing antibodies at 6 weeks post vaccination [Suzano 2006].

Hematopoietic stem cell transplant recipients: There are limited safety and immunogenicity data (i.e., a few case reports) for YF vaccination of hematopoietic stem cell transplant recipients [Yax 2009, Gowda 2004, Ljungman 2005]. However, data for other live virus vaccines suggest most recipients become seronegative following transplantation [Ljungman 1994]. Infectious Diseases Society of America guidelines recommend re-administering live viral vaccines, such as measles, mumps, and rubella (MMR) vaccine and varicella vaccine, to hematopoietic stem cell transplant recipients if they are seronegative and no longer immunosuppressed [Rubin 2014].

HIV-infected individuals: Published studies on the immunogenicity of YF vaccines in HIV-infected persons are limited. One retrospective cohort study found 65 (83%) of 78 HIV-infected persons had specific antibodies against YF virus in the first year after vaccination; however this was significantly lower than vaccinated persons without HIV infection (97%, 64/66) ($P=0.01$) [Veit 2009]. The rate of detectable YF virus-specific antibodies was also lower among HIV-infected persons at 1 to 10 years post vaccination (77%, 54/70) compared to uninfected controls (88%, 81/92) but this difference was not significant ($P=0.07$) [Veit 2009]. One additional study noted that only 3 (17%) of 18 HIV-infected infants in Cote d'Ivoire developed YF virus-specific neutralizing antibodies following vaccination compared to 42 (74%) of 57 HIV-uninfected controls matched for age and nutritional status ($P<0.01$) [Sibailly 1997]. The mechanisms for the diminished immune response in HIV-infected persons are uncertain but appear to be correlated with HIV RNA levels and inversely correlated with CD4+ cell counts [Veit 2010].

Young children: Twelve studies were identified that provided data on the initial immune response to YF vaccine in children aged 4 months to 10 years (**Table 9**). All the studies included children who resided in endemic areas and 10 (83%) studies included children who received at least one other vaccine co-administered with YF vaccine. Of the 4,675 children, 4,101 (88%) seroconverted 1–2 months following their primary YF vaccination. When study size differences and variability between studies were accounted for using a random effects model, the estimate of seroconversion rate was 93% (95% CI 88%–96%). Furthermore, when the random effects model was used to compare seroconversion rates between children aged <9 months and those aged ≥9 months, there was no difference. For children aged <9 months, data from four studies provided an estimated seroconversion rate of 95% (95% CI 91%–98%). In children aged ≥9 months, data

from 11 studies provided an estimated seroconversion rate of 92% (95% CI 86%–96%). There are limited data on the persistence of YF antibodies in children; with no data available on seropositivity by the time since last YF vaccination.

The data for seroconversion rates in children following YF vaccination were presented to the American Academy of Pediatrics Committee on Infectious Diseases (COID) in November 2014. Upon review of these data and comparing them to seroconversion rates in adults, COID members agreed that the response to YF vaccine in children did not appear to be different than adults. Given this, they concluded that children can be included with adults regarding their need for YF vaccine booster doses. However, they noted the need for long-term immunogenicity data from persons vaccinated as children to ensure the antibody decay kinetics are similar compared to persons vaccinated initially as an adult.

Higher-risk exposures: Finally, the Work Group considered persons who might be in a higher-risk setting for YF virus exposure based on season, location, activities, and duration of their travel. Limited epidemiologic data suggest that West Africa has the highest risk of disease with 90% of all YF disease cases over the preceding 20 years being reported from countries in West Africa [Monath 2013]. Furthermore, the Work Group considered persons traveling to an area with an ongoing outbreak, persons traveling for a prolonged period of time in an endemic area, and persons who routinely handle wild-type YF virus in the laboratory to be at higher-risk for YF virus exposure than other persons for whom YF vaccine is recommended.

Assess the values related to management options and outcomes

From 1970–2014, nine cases of YF were reported in unvaccinated travelers from the United States (n=3) and Europe (n=6) who traveled to West Africa or South America [McFarland 1997; Digoutte 1981; Rodhain 1979; CDC 1999; Colebunders 2002; CDC 2002; Teichmann 1999; WHO 1998; WHO 2000]. Eight of these nine travelers died. Only one case of YF has been documented in a vaccinated traveler from Spain who received the vaccine 5 years before traveling to several West African countries and being diagnosed with YF; the traveler survived [Nolla-Salas 1989]. YF vaccine has been available since the 1930s, including in the United States, and it is not known how many cases have been prevented due to vaccination or how many cases are not diagnosed or reported. Reports from U.S. travel clinics or international airports have documented that 91%–93% of travelers for whom YF vaccine was recommended received the vaccine [Jentes 2013; Lown 2014; Toovey 2004]. In one study of 3,207 travelers who received YF vaccine at a travel clinic visit in the United States, only 149 (5%) had reportedly received a previous dose of YF vaccine ≥ 10 years previously [Jentes 2013].

A traveler's risk of acquiring YF is determined by multiple factors, including immunization status, use of personal protection measures against mosquito bites, location of travel, duration of exposure, occupational and recreational activities while traveling, and local rate of virus transmission at the time of travel. In both West Africa and South America, YF virus transmission typically is seasonal and is associated with the mid-to-late rainy season [Monath 2002]. However, YF virus can be transmitted by *Aedes aegypti* even during the dry season in both rural and densely settled urban areas [Beeuwkes 1933]. Although the number of reported cases of human disease often is used to estimate the crude level of endemic transmission, cases might not be reported because of a low level of transmission, a high level of immunity in the local population, or cases not being detected by local surveillance systems. Therefore, a lack of human disease cases in an area does not equate to absence of risk for transmission.

The risk of acquiring YF is difficult to predict because of variations in ecologic determinants of virus transmission. For a 2-week stay, the estimated risks for illness and death attributed to YF for an unvaccinated traveler traveling to an area of West Africa where the disease is endemic are 50 and 10 per 100,000 population, respectively; for South America, the risks for illness and death are five cases and one case per 100,000 population, respectively [Monath 2002]. These crude estimates for unvaccinated travelers are based on risk to indigenous populations, often during peak transmission season. Thus, these risk estimates might not reflect accurately the actual risk to travelers, who might have a different immunity profile, take precautions against getting bitten by mosquitoes, and have less outdoor exposure. Furthermore, it is unknown how the potential risk of the disease differs in persons who have received at least one dose of YF vaccine ≥ 10 years previously.

Recommendations regarding the use of YF vaccine booster doses for travelers must weigh the overall risk for travel-associated YF disease in persons who have previously received a dose of the vaccine, the lack of treatment, high mortality (80%) in travel-related cases, the low probability of serious adverse events following revaccination, and the cost of the vaccine (Table 10). High value is placed on preventing this life-threatening disease. A survey performed in the United States in 2001 found that both parents and community members were willing to pay a median of \$500 to reduce the risk of bacterial meningitis from 21 per 100,000 to 6 per 100,000 [Prosser 2004]. Although the disease presentation and population used in the survey are different than what would be expected for YF among travelers, they establish a willingness to pay to prevent a serious outcome.

Review health economic data

There are no studies of the potential cost-effectiveness of vaccinating travelers or laboratory workers against YF either with primary or booster doses of the vaccine. However, given the large numbers of travelers to endemic areas (~3 million annually of which an estimated 150,000 could need a booster dose of vaccine), the risk for YF disease for unvaccinated travelers (5–50 case per 100,000 unvaccinated travelers), and the cost of YF vaccine (\$150–\$350) [Monath 2002; Costheller 2014], providing a booster dose of YF vaccine to all travelers going to endemic areas would not be cost-effective. In addition, for some travelers with lower risk itineraries, even a very low probability of vaccine-related serious adverse events might be higher than the risk for disease. Therefore, YF vaccine booster doses should be targeted to travelers who, on the basis of their planned travel itinerary and activities, are at increased risk for disease.

Travel vaccines, such as YF vaccine, are usually paid for by the travelers themselves; they are not covered under the Vaccines for Children (VFC) program or by most private insurance plans. As a result, we decided not to perform a cost-effectiveness study of removing booster doses of YF vaccine for U.S. travelers or laboratory workers. Furthermore, none of the Work Group members consider cost-effectiveness study critical to make recommendations regarding YF vaccine booster doses for healthy travelers and laboratory workers.

Assess the balance of risks and benefits

A primary dose of YF vaccine is effective with very few vaccine failures documented and most (92%) of vaccine recipients maintaining seropositive levels of neutralizing antibodies at ≥ 10 years post vaccination. However, the number of persons from whom the seropositivity data are derived is limited and over half (59%) of the data come from persons living in YF endemic areas. The data also suggest that 20% (95%CI 14%–26%) of persons who received YF vaccine ≥ 20

years previously do not have detectable levels of neutralizing antibodies. For previously vaccinated persons without evidence of circulating neutralizing antibodies, it is not known if other immunologic measures (e.g., cell-mediated immunity or memory B cell response) would provide adequate protection against YF.

Very few serious adverse events, including vaccine-related viscerotropic and neurologic disease, have been reported following booster doses of the vaccine. However, for most of the adverse event data, it is unknown whether the patients had received a primary or booster dose prior to their reported event, and how many of the total doses of vaccine were given as primary or booster doses.

In general, there is high value placed on prevention of a serious disease with no treatment and substantial mortality. The overall disease risk in persons who have already received a dose of the vaccine is likely quite low and vaccine cost is high.

Formulate recommendations and determine the category

Current ACIP recommendations for YF vaccine were approved in 2009 and contain the following wording in regards to the use of booster doses. “[International Health Regulations] require revaccination at intervals of 10 years to boost antibody titer. Evidence from multiple studies demonstrates that YF vaccine immunity persists for many decades and might provide life-long protection. To minimize the occurrence of adverse events and optimize the immune response, efforts should be taken to observe a 10-year interval between YF vaccine doses.” [CDC 2010].

The GRADE evaluation found that there are very few vaccine failures documented following primary doses of YF vaccine, most (92%) primary vaccine recipients maintain detectable levels of neutralizing antibodies ≥ 10 years post vaccination, and very few serious adverse events have been reported following booster doses of YF vaccine (Evidence type 4). However, additional data suggest that certain populations (e.g., pregnant women or HIV-infected person) might not have as robust or sustained immune response to YF vaccine compared to “healthy” persons. Furthermore, certain groups were felt to be at increased risk of the disease either due to their location and duration of travel or due to more consistent exposure to virulent virus (e.g., laboratory workers).

Upon reviewing the available data, the majority of the Work Group felt that booster doses of YF vaccine should not be recommended for most travelers or laboratory workers. However, based on limited data, YF vaccine should be recommended in certain populations at increased risk of YF disease either due to an increased risk of exposure to YF virus or due to suboptimal immune response to a dose of YF vaccine. The Work Group recommends the following language regarding booster doses of YF vaccine:

- A single dose of YF vaccine provides long-lasting protection and is adequate for most travelers. (Recommendation Category A)
- Additional doses of YF vaccine are recommended for certain travelers, including*:
 - Women who were pregnant when they received their initial dose of YF vaccine should receive one additional dose of YF vaccine prior to their next travel that puts them at risk for YF virus infection.
 - Persons who received a hematopoietic stem cell transplant after receiving a dose of YF vaccine and who are sufficiently immunocompetent to be safely vaccinated should be revaccinated prior to their next travel that puts them at risk for YF virus infection.

- Persons who were HIV-infected when they received their last dose of YF vaccine should receive a dose every 10 years if they continue to be at risk for YF virus infection.

*Persons being considered for additional doses of YF vaccine should be assessed for contraindications or precautions. (Recommendation Category A)

- A booster dose may be given to travelers who received their last dose of YF vaccine at least 10 years previously and who will be in a higher-risk setting based on season, location, activities, and duration of their travel. This would include travelers who plan to spend a prolonged period in endemic areas or those traveling to highly endemic areas such as rural West Africa during peak transmission season or an area with an ongoing outbreak. (Recommendation Category B)
- Laboratory workers who routinely handle wild-type YF virus should have YF virus-specific neutralizing antibody titers measured at least every 10 years to determine if they should receive additional doses of the vaccine. For laboratory workers who are unable to have neutralizing antibody titers measured, YF vaccine should be given every 10 years as long as they remain at risk. (Recommendation Category A)

Further study

The Work Group members prioritize the following areas of study to address gaps in our current knowledge regarding the need for YF vaccine booster doses in U.S. travelers and laboratory workers:

1. Assessing neutralizing antibody levels ≥ 10 years post initial vaccination in non-endemic populations (e.g., travelers)
2. Evaluating anamnestic immune response to revaccination in persons from non-endemic YF locations who fail to have detectable levels of neutralizing antibodies years ≥ 10 years following their initial YF vaccination
3. Determining seroprotective level of antibodies using a plaque reduction neutralization test (PRNT) by correlating to established level of seroprotective neutralizing antibodies by \log_{10} neutralization index (LNI) ($LNI \geq 0.7$)
4. Assessing long-term neutralizing antibody levels among certain populations, such as infants or HIV-infected persons, to obtain more information on the need for additional doses of YF vaccine
5. Establishing the role of cell-mediated immunity in long-term protection against YF disease in non-endemic populations

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Table 1. Summary of outcome measure ranking and inclusion for yellow fever (YF) vaccine booster doses

Outcome	Importance	Include in evidence profile	Data available
<u>Benefits</u>			
Vaccine efficacy	Critical	Yes	No
Vaccine effectiveness ¹	Critical	Yes	Yes
Seroprotection ²	Critical	Yes	No
Seropositivity	Critical	Yes	Yes
<u>Harms</u>			
Serious adverse events ³	Critical	Yes	Yes
Viscerotropic disease	Critical	Yes	Yes
Neurologic disease	Critical	Yes	Yes
Anaphylaxis	Important	No	--
Systemic adverse events	Important	No	--

¹Vaccine effectiveness was assessed as vaccine failures

²There are no long-term immunogenicity data using log₁₀ neutralization index (LNI), the only test for which a seroprotective titer has been established (i.e., LNI ≥ 0.7). Given this, it was decided that seropositivity (i.e., having detectable YF virus-specific antibodies) would be used as a surrogate for seroprotection and included in the evidence profile even though seropositivity was originally rated as important not critical.

³Serious adverse event is an event that is plausibly related to YF vaccination and was considered to be life-threatening or required hospitalization.

Table 2. Vaccine effectiveness measured by vaccine failures reported following yellow fever (YF) vaccination

Study	Population	Type	Age Group	No.	Lab confirmed	Timing post vaccination	Outcome
Elliot 1944	Non-endemic	Obs	Adult	3	0	15 mo, 16 mo, 16 mo	Died (2), Survived (1)
Ross 1953	Non-endemic	Obs	Adult	1	0	4 yr	Died
Nolla Salas 1989	Non-endemic	Obs	Adult	1	0	5 yr	Survived
Akoua-Koffi 2001	Endemic	Obs	Unknown	6	0	Unknown	Survived (6)
Brazil 2014 ¹	Endemic	Obs	Unknown	7 ²	7 ³	10 dy-10 yr (5), 20 yr (1), 27 yr (1)	Unknown
All	Non-endemic/ Endemic	Obs (5)	Adult or Unknown	18	7	10 dy – 27 yr	Died (3), Unknown (7), Survived (8)

Obs = observational study; dy = days; mo = months; yr = years

¹Data were provided by the Brazilian Ministry of Health to resolve overlap and errors in four published studies regarding vaccine failures in Brazil (Tuboi 2007, de Filippis 2004, Saraiva 2013, and Camara 2013).

²A total of 12 vaccine failures were identified but five occurred <10 days after vaccination and were excluded.

³Laboratory confirmation defined in the study as 1) detection of YF virus-specific IgM antibodies, 2) isolation of YF virus, 3) YF-compatible pathological changes in liver tissue, 4) detection of YF virus antigen by immunohistochemistry, or 5) four-fold or greater rise in YF virus-specific IgG antibody titers. The specific laboratory criteria used to confirm the seven cases was not noted. Due to the persistence of IgM antibodies that can occur following vaccination [Gibney 2012], these cases lacked definitive evidence of a recent infection with wild-type YF virus.

Table 3. Seropositivity at ≥ 10 years following yellow fever (YF) vaccination

Study	Population	Type	Seropositivity criteria ¹	Years post vaccination	Seropositive No.	(%)
Dick 1952	Endemic	Obs	Mouse protection	10	156/202	(77)
de Melo 2011	Endemic	Obs	PRNT ₅₀ ≥ 20	10	20/20	(100)
Reinhardt 1998	Non-endemic	Obs	PRNT ₉₀ ≥ 10	≥ 10	5/5	(100)
Machado 2013	Endemic	Obs	PRNT ₈₀ ≥ 10	≥ 10	19/19	(100)
CG YF vaccines 2014 ²	Endemic	Obs	PRNT ₅₀ ≥ 10	10-18	307/329	(93)
Rosenzweig 1963	Non-endemic	Obs	Mouse protection	10-15	24/24 ³	(100)
Courtois 1954	Endemic	Obs	Mouse protection	12	76/79	(96)
Groot 1962	Non-endemic	Obs	Mouse protection	17	105/108	(97)
Gomez 2008	Endemic	Obs	PRNT ₇₅ ≥ 10	10-24	13/19 ³	(68)
Niedrig 1999	Non-endemic	Obs	PRNT ₉₀ > 10	11-38	38/51	(75)
Coulangue Bodilis 2011	Non-endemic	Obs	PRNT ₈₀ ≥ 10	10-60	80/84	(95) ⁴
CDC 2014	Non-endemic	Obs	PRNT ₉₀ ≥ 10	10-69	68/81	(84) ⁵
Poland 1981	Non-endemic	Obs	PRNT ₉₀ ≥ 2	30-35	91/116	(78)
All	Non-endemic/Endemic	Obs (13)	Multiple	10-60	1,002/1,137	(88)

Obs = observational study; PRNT = plaque reduction neutralization test

¹For mouse protection assays, vaccine recipient serum for which ≥ 3 of 6 mice survived are included as seropositive. PRNTx% is the reciprocal of the highest serum dilution at which x% of YF virus is inhibited.

²CG YF vaccines = Collaborative group for studies on yellow fever vaccines (Brazil).

³Numbers are estimated as some cases included in the data received their vaccination < 10 years previously.

⁴88% (15/17) of subjects who received YF vaccine ≥ 20 years previously were seropositive [Coulangue Bodilis 2011]

⁵84% (26/31) of subjects who received YF vaccine ≥ 20 years previously were seropositive [CDC 2014]

Table 4. Serious adverse events reported following yellow fever (YF) vaccination by dose type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
CDC 2015	Non-endemic	2007-2013	Obs	3,631,535	96	11 ¹	0
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000 ²	-- ³	--	805
Schumacher 2010	Non-endemic	1991-2001	Obs	272,727	--	--	7
Lindsey 2008	Non-endemic	2003-2006 ⁴	Obs	902,500	54	1 ⁵	0
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	13	2 ⁶	32
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	24	--	9
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	164
Fernandes 2007	Endemic	1999-2005	Obs	499,714	--	--	24
Fitzner 2004	Endemic	2001	Obs	2,600,000	--	--	13 ⁷
All	Non-endemic/Endemic	1990-2013	Obs (9)	333,455,887	187	14	1054

Obs = observational study

¹All 11 serious adverse event cases were reported in adults who were hospitalized following their second (n=10) or third (n=1) dose of YF vaccine. The cases included: 1) Guillain-Barré syndrome (GBS) 16 days post vaccination; 2) GBS 7 days post vaccination; 3) encephalitis 4 days post vaccination; 4) bilateral optic neuritis 2 days post vaccination; 5) anaphylaxis with angioedema on the day of vaccination; 6) lower extremity cellulitis 7 days post vaccination; 7) acute appendicitis requiring surgery 2 days post vaccination; 8) fever and right lower quadrant pain 5 days post vaccination; 9) fever and syncope 1 day post vaccination; 10) myalgia and upper extremity weakness 3 days post vaccination; and 11) lymphadenitis 26 days post vaccination, subsequently diagnosed as Hodgkin's lymphoma.

²Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

³Indicates that cases are not reported for the specific dose type.

⁴The published study includes data from 2000–2006 but 2000–2002 removed to prevent overlap with data from Khromova 2005.

⁵One case of appendicitis requiring surgery at 1 day post vaccination.

⁶One case reporting numbness and weakness at 12 days post vaccination and one case with abdominal pain and yellow stools requiring hospitalization at 7 days post vaccination.

⁷Cases not explicitly defined as having serious adverse events but 13 out of 87 adverse events required hospitalization and were considered to be serious.

Table 5. Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) by dose type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000 ¹	4	1 ²	7
Lindsey 2008	Non-endemic	2003-2006 ³	Obs	902,500	6	-- ⁴	--
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	8	--	--
Kitchner 2004	Non-endemic	1991-2003	Obs	3,046,007	--	--	4
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	12	--	--
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	5
Martins 2010	Endemic	1999-2009	Obs	107,649,393	--	--	20
Whittembury 2009	Endemic	2007	Obs	42,742	--	--	5
All	Non-endemic/Endemic	1990-2010	Obs (8)	437,190,053	30	1	41

Obs = observational study

¹Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

²One suspect case in a 55-year-old male who had illness onset 2 days following a booster dose of yellow fever (YF) vaccine. He presented with polyarthralgia, and liver cytolysis; no YF specific-testing was performed. He was reported as recovering from his illness.

³The published study includes data from 2000–2006 but 2000–2002 removed to prevent overlap with data from Khromova 2005.

⁴Indicates that cases are not reported for the specific dose type.

Table 6. Yellow fever vaccine-associated neurologic disease (YEL-AND) by dose type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000 ¹	10	1 ²	13
Lindsey 2008	Non-endemic	2003-2006 ³	Obs	902,500	6	-- ⁴	--
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	10	--	--
Kitchner 2004	Non-endemic	1991-2003	Obs	3,046,007	--	--	4
Martins 2014	Endemic	2009-2012 ⁵	Obs	30,745,743 ⁶	59	2 ⁷	--
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	12	--	--
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	6
Martins 2010	Endemic	2000-2008	Obs	101,564,083	--	--	85
All	Non-endemic/Endemic	1990-2010	Obs (8)	461,807,744	107	3	108

Obs = observational study

¹Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

²One suspected case in a 45-year-old female who had illness onset 13 days following a booster dose of the vaccine. Her clinical features were listed as a suspected "multiple sclerosis syndrome"; no yellow fever (YF) specific-testing performed. She had "favorable outcome with corticosteroids".

³The published study includes data from 2000–2006 but 2000–2002 removed to prevent overlap with data from Khromova 2005.

⁴Indicates that cases are not reported for the specific dose type.

⁵The study includes data from 2007–2012 but 2007–2008 removed to prevent overlap with Martins 2010.

⁶Approximately 13 million doses were administered as booster doses. Total number of booster doses was derived by dividing the total number of booster doses administered by the number of years and assumed roughly the same number of doses delivered each year.

⁷One probable case in a 62-year-old female who was diagnosed with Guillain Barre syndrome at an unknown time post vaccination; one probable case in a 20-year-old male who became symptomatic 14 days post vaccination and was diagnosed with acute disseminating encephalomyelitis.

Table 7. Evidence type for benefits and harms for yellow fever (YF) vaccine booster doses in healthy travelers and laboratory workers

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other ¹	Evidence type ²
<u>Benefits</u>							
Vaccine effectiveness	Obs (5)	Yes ³	No serious	Yes ⁴	No serious	None	4
Seropositivity	Obs (13)	Yes ⁵	No serious	Yes ⁶	No serious	None	4
<u>Harms</u>							
Serious adverse events	Obs (9)	No serious	No serious	Yes ⁷	No serious	None	4
Viscerotropic disease	Obs (8)	No serious	No serious	Yes ⁷	No serious	None	4
Neurologic disease	Obs (8)	No serious	No serious	Yes ⁷	No serious	None	4

Obs = observational study

¹Publication bias, strength of association, dose response, or direction of all plausible confounding would reduce the effect.²Evidence type:

1 = Randomized control trials (RCTs) or overwhelming evidence from observational studies

2 = RCTs with important limitations, or exceptionally strong evidence from observational studies

3 = Observational studies, or RCTs with notable limitations

4 = Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

³Risk of bias because of incomplete case capture and no comparison group.⁴Indirectness due to different population (majority of data are from endemic areas) and it is unknown how many persons at risk of YF would not receive a booster dose of the vaccine.⁵Risk of bias among those tested for long-term seropositivity.⁶Indirectness due to different population (majority of data are from endemic areas). No efficacy data are available, no correlate of protection established for the assays used to assess long-term immunity, and different assays and antibody levels were used to assess either seropositivity or “seroprotection”.⁷Indirectness as it is not known for all but one study the number of doses that were administered as booster doses versus primary doses and thus rates for the adverse events could not be calculated.

Table 8. Overall quality of evidence for yellow fever (YF) vaccine booster doses in healthy travelers and laboratory workers

Outcome	Study design (# studies)	Finding	Evidence type¹	Overall quality of evidence
Vaccine effectiveness	Obs (5)	Very few vaccine failures documented	4	4
Seropositivity	Obs (13)	Most (92%) seropositive at ≥ 10 years post vaccination	4	
Serious adverse events	Obs (9)	Very few events reported after booster doses	4	
Viscerotropic disease	Obs (8)	Very few events reported after booster doses	4	
Neurologic disease	Obs (8)	Very few events reported after booster doses	4	

Obs = observational study

¹Evidence type:

1 = Randomized control trials (RCTs) or overwhelming evidence from observational studies

2 = RCTs with important limitations, or exceptionally strong evidence from observational studies

3 = Observational studies, or RCTs with notable limitations

4 = Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

Table 9. Seroconversion rates following a primary dose of yellow fever (YF) vaccine in young children

Study	Population	YF Vaccine	Other vaccine(s) ¹	Age	Assay used	Seroconverted ² No. (%)
Belmusto-Worn 2005	Endemic	17D-204	None	9 mo-10 yo	LNI	917/981 (93)
Nascimento 2011 ³	Endemic	17DD/17D-213	None MMR	12-23 mo	PRNT ₅₀	718/819 (88) 552/792 (70)
Yvonnet 1986	Endemic	17D-204	BCG, DTP, HepB, M, Polio	9-36 mo	PRNT ₉₀	170/183 (93)
Coursaget 1995	Endemic	17D-204	HepB, M	9 mo	PRNT ₉₀	165/172 (96)
Lhuillier 1989	Endemic	17D-204	M	6-9 mo	HIA	122/135 (90)
Mouchon 1990	Endemic	17D-204	M	6-10 mo	PRNT ₈₀	131/139 (94)
Stefano 1999	Endemic	17DD	M	9 mo	PRNT ₅₀	228/294 (78)
Adu 1996	Endemic	17D-204	M	6-12 mo	ELISA	379/400 (95)
Soula 1991	Endemic	17D-204	M	4-24 mo	PRNT	158/167 (95)
Ruben 1973	Endemic	17D-204	M, DPT, S	6-24 mo	PRNT ₉₀	158/165 (96)
Gateff 1973	Endemic	17D-204	BCG, M, S, T	1-5 yo	HIA	119/139 (86)
Osei-Kwasi 2001	Endemic	17D-204	None	6-9 mo	PRNT	284/289 (98)

BCG = Bacillus Calmette-Guerin vaccine; DTP = diphtheria, tetanus, and pertussis combined vaccine; ELISA = enzyme-linked immunosorbent assay; HepB = hepatitis B vaccine; HIA = hemagglutination inhibition assay; LNI = log₁₀ neutralization index; M = measles vaccine; MMR = measles, mumps, and rubella combined vaccines; mo = months old; PRNT = plaque reduction neutralization test; S = Smallpox; T = tetanus; yo = years old

¹Except for Nascimento, seroconversion rates following concurrent administration of YF vaccine with other vaccines compared to administration alone was not significantly different so the proportion are for all children who received YF vaccine. For Nascimento, a significant difference was seen between seroconversion rates when YF vaccine was co-administered with MMR vaccine versus given 30 days post MMR vaccine; these data are presented individually.

²Measured 30–90 days post YF vaccination.

³Percent seroconversion is for per protocol population; numerator and denominator data estimated from total numbers in each cohort.

Table 10. Considerations for formulating recommendations for use of yellow fever (YF) vaccine booster doses in healthy travelers and laboratory workers at increased risk of exposure to YF virus

Key factors	Comments
Evidence type for benefits and harms	<ul style="list-style-type: none"> • Overall evidence type 4 for vaccine effectiveness, seroprotection, and serious adverse events • Downgraded due to risk of bias (incomplete case capture, those tested for long-term seropositivity), and indirectness (data from endemic populations, no efficacy data, and unknown rates of adverse events with booster doses)
Balance between benefits and harms	<ul style="list-style-type: none"> • Very few vaccine failures identified following YF vaccine • Most (92%) of primary vaccine recipients are seropositive at ≥ 10 years post vaccination • Serious adverse events are uncommon following booster doses of the vaccine
Value	<ul style="list-style-type: none"> • Prevent a serious disease with no treatment and poor outcomes • Inform decisions about YF vaccination based on a traveler's planned itinerary
Cost-effectiveness	<ul style="list-style-type: none"> • Not evaluated • Likely low risk of disease in persons receiving a dose of YF vaccine • High vaccine cost for vaccines that is usually paid for by the travelers themselves; YF vaccine is not covered under the Vaccines for Children program or most insurance plans.

Yellow Fever Vaccine Booster Doses: Recommendations of the Advisory Committee on Immunization Practices, 2015

J. Erin Staples, MD¹; Joseph A. Bocchini Jr., MD^{2,3}; Lorry Rubin, MD^{2,4}; Marc Fischer, MD¹ (Author affiliations at end of text)

On February 26, 2015, the Advisory Committee on Immunization Practices (ACIP) voted that a single primary dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers (1). ACIP also approved recommendations for at-risk laboratory personnel and certain travelers to receive additional doses of yellow fever vaccine (Box). The ACIP Japanese Encephalitis and Yellow Fever Vaccines Workgroup evaluated published and unpublished data on yellow fever vaccine immunogenicity and safety. The evidence for benefits and risks associated with yellow fever vaccine booster doses was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (2,3). This report summarizes the evidence considered by ACIP and provides the updated recommendations for yellow fever vaccine booster doses.

Yellow Fever Epidemiology and Risk for Disease in Travelers

Yellow fever is a mosquito-borne viral disease that is endemic to sub-Saharan Africa and tropical South America. Worldwide, yellow fever virus causes an estimated 200,000 cases of clinical disease and 30,000 deaths annually (4). Clinical disease ranges

from a mild, nonspecific febrile illness to severe disease with jaundice and hemorrhage. The case-fatality ratio for severe yellow fever is 20%–50% (5). Because no specific treatment exists, prevention through vaccination is critical to reduce morbidity and mortality from yellow fever virus infection.

The risk of a traveler acquiring yellow fever varies based on season, location, activities, and duration of their travel. For a 2-week stay, the estimated risk for illness attributed to yellow fever for an unvaccinated traveler to West Africa is 50 cases per 100,000 population; for South America, the risk for illness is five cases per 100,000 population (6).

Yellow Fever Vaccine Recommendations and International Health Regulations Requirements

Yellow fever vaccine is recommended for persons aged ≥9 months who are traveling to or living in areas with risk for yellow fever virus transmission (7). International Health Regulations allow countries to require proof of yellow fever vaccination from travelers entering their country (8). These requirements are intended to minimize the potential importation and spread of yellow fever virus. Currently, International Health Regulations specify that a dose of yellow fever vaccine is valid for 10 years. Therefore, at present, travelers to countries with a yellow fever vaccination entry requirement must have received a dose of yellow fever vaccine within the past 10 years.

Recent changes to yellow fever vaccine recommendations. In April 2013, the World Health Organization Strategic Advisory Group of Experts on Immunization concluded that a single primary dose of yellow fever vaccine is sufficient to confer sustained immunity and lifelong protection against yellow fever disease, and that a booster dose is not needed (9). This conclusion was based on a systematic review of published studies on the duration of immunity after a single dose of yellow fever vaccine, and on data that suggest vaccine failures are extremely rare and do not increase in frequency with time since vaccination (10). The advisory group noted that future studies and surveillance data should be used to identify specific risk groups, such as persons infected with human immunodeficiency virus (HIV) or infants, who might benefit from a booster dose. In May 2014, the World Health Assembly adopted the recommendation to remove the 10-year booster dose requirement from the International Health Regulations by June 2016 (11).

Recommendations for routine use of vaccines in children, adolescents, and adults are developed by the Advisory Committee on Immunization Practices (ACIP). ACIP is chartered as a federal advisory committee to provide expert external advice and guidance to the Director of the Centers for Disease Control and Prevention (CDC) on use of vaccines and related agents for the control of vaccine-preventable diseases in the civilian population of the United States. Recommendations for routine use of vaccines in children and adolescents are harmonized to the greatest extent possible with recommendations made by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetricians and Gynecologists (ACOG). Recommendations for routine use of vaccines in adults are harmonized with recommendations of AAFP, ACOG, and the American College of Physicians (ACP). ACIP recommendations approved by the CDC Director become agency guidelines on the date published in the Morbidity and Mortality Weekly Report (MMWR). Additional information regarding ACIP is available at <http://www.cdc.gov/vaccines/acip>.

Yellow Fever Vaccine Long-term Immunogenicity Data

No data are available on vaccine efficacy or protective antibody titers (i.e., seroprotection) related to long-term immunogenicity after yellow fever vaccination. Benefits considered critical in assessing the need for booster doses of yellow fever vaccine for U.S. travelers or laboratory workers included vaccine effectiveness (i.e., a lack of vaccine failures) and evidence of seropositivity (i.e., yellow fever virus-specific antibodies detected in a blood sample) (3).

Vaccine effectiveness. A total of 23 vaccine failures were identified after the administration of >540 million doses of yellow fever vaccine (3). Of the 23 cases, five occurred <10 days after vaccination and were excluded because most persons are not expected to develop protective titers in that timeframe (5). Of the remaining 18 cases, 16 (89%) occurred in persons who reported receiving a dose of the vaccine within the previous 10 years (3). One vaccine failure occurred at 20 years and one at 27 years post-vaccination.

Seropositivity. Thirteen observational studies provided immunogenicity data on 1,137 persons vaccinated ≥ 10 years previously (3). Using a random effects model, the estimated seropositivity rate for persons vaccinated ≥ 10 years previously was 92% (95% confidence interval [CI] = 85%–96%). Of the 164 persons vaccinated ≥ 20 years previously, the estimated seropositivity rate was 80% (CI = 74%–86%).

Yellow Fever Vaccine Booster Dose Safety Data

Serious adverse events, yellow fever vaccine–associated viscerotropic disease (a severe illness similar to wild-type disease), and yellow fever vaccine–associated neurologic disease were considered critical risks to assess the need for yellow fever vaccine booster doses (7).

Serious adverse events. Nine observational studies provided data on serious adverse events for 333 million distributed doses of yellow fever vaccine (3). Overall, 1,255 persons were reported to have a serious adverse event after yellow fever vaccination. For most (84%) persons, it was unknown if the adverse event occurred after a primary or booster dose of the vaccine. Of the 201 persons with a serious adverse event where dose type was known, 14 (7%) of the adverse events occurred after a booster dose of vaccine.

Viscerotropic disease. Eight observational studies provided data on viscerotropic disease for 437 million distributed doses of yellow fever vaccine (3). A total of 72 persons had yellow fever vaccine–associated viscerotropic disease. Of the 31 persons where dose type was known, one (3%) had viscerotropic disease after receiving a booster dose of the vaccine; no

BOX. Recommendations for use of yellow fever vaccine booster doses*

- A single primary dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers [Category A].
- Additional doses of yellow fever vaccine are recommended for certain travelers:
 - Women who were pregnant (regardless of trimester) when they received their initial dose of yellow fever vaccine should receive 1 additional dose of yellow fever vaccine before their next travel that puts them at risk for yellow fever virus infection [Category A];
 - Persons who received a hematopoietic stem cell transplant after receiving a dose of yellow fever vaccine and who are sufficiently immunocompetent to be safely vaccinated should be revaccinated before their next travel that puts them at risk for yellow fever virus infection [Category A];
 - Persons who were infected with human immunodeficiency virus when they received their last dose of yellow fever vaccine should receive a dose every 10 years if they continue to be at risk for yellow fever virus infection [Category A].
- A booster dose may be given to travelers who received their last dose of yellow fever vaccine at least 10 years previously and who will be in a higher-risk setting based on season, location, activities, and duration of their travel [Category B]. This would include travelers who plan to spend a prolonged period in endemic areas or those traveling to highly endemic areas such as rural West Africa during peak transmission season or an area with an ongoing outbreak.
- Laboratory workers who routinely handle wild-type yellow fever virus should have yellow fever virus–specific neutralizing antibody titers measured at least every 10 years to determine if they should receive additional doses of the vaccine. For laboratory workers who are unable to have neutralizing antibody titers measured, yellow fever vaccine should be given every 10 years as long as they remain at risk [Category A].

* Persons being considered for additional doses of yellow fever vaccine should be assessed for contraindications or precautions in accordance with the current yellow fever vaccine ACIP recommendations (7).

laboratory testing to assess vaccine causality was performed for that case.

Neurologic disease. Eight observational studies provided neurologic disease data for approximately 462 million

distributed doses of yellow fever vaccine (3). A total of 218 persons had yellow fever vaccine–associated neurologic disease. Of the 110 persons where dose type was known, three (3%) persons reported neurologic disease after receiving a booster dose of the vaccine.

Other relevant evidence

Pregnant women. The proportion of women who develop yellow fever virus antibodies is variable and might be related to the trimester in which they received the vaccine. Among pregnant women who received yellow fever vaccine primarily in their third trimester, 39% (32 of 83) had evidence of seroconversion to yellow fever virus at 2–4 weeks post-vaccination, compared with 94% (89 of 95) in the general population (12). Of 433 women vaccinated primarily in the first trimester (mean gestational age = 5.7 weeks; CI = 5.2–6.2), 425 (98%) developed yellow fever virus–specific neutralizing antibodies at 6 weeks post-vaccination (13).

Hematopoietic stem cell transplant recipients. Data are limited on safety and immunogenicity for yellow fever vaccine in hematopoietic stem cell transplant recipients. However, data suggest most recipients become seronegative to live viral vaccine antigens after transplantation (14). Infectious Diseases Society of America guidelines recommend re-administering live viral vaccines, such as measles, mumps, and rubella vaccine and varicella vaccine, to post-transplant patients if the recipient is seronegative and is no longer immunosuppressed (15).

HIV-infected persons. Two published studies provide immunogenicity data for yellow fever vaccines in HIV-infected persons (16,17). Both studies found lower rates of yellow fever virus–specific neutralizing antibodies among HIV-infected persons compared with uninfected controls at 10 to 12 months post-vaccination. Although the mechanisms for the diminished immune response in HIV-infected persons are uncertain, an inverse correlation exists between immune response and HIV RNA levels and a positive correlation with CD4+ cell counts (18).

Young children. Twelve studies provided data on the initial immune response to yellow fever vaccine in children aged 4 months–10 years (3). All studies included children who resided in endemic areas, and 10 studies included children who received at least one other vaccine at the same time as yellow fever vaccine. Based on a random effects model, the estimated seroconversion rate in 4,675 children was 93% (CI = 88%–96%). No difference was observed in the seroconversion rates between children aged <9 months and those aged ≥9 months (3).

Other higher-risk groups. Over the preceding 20 years, 90% of all yellow fever cases were reported from countries in West Africa, and epidemiologic data suggest that travelers to West Africa are at the highest risk for travel-associated yellow

Summary

What is currently recommended?

In 2009, the Advisory Committee on Immunization Practices (ACIP) approved yellow fever vaccine recommendations that noted International Health Regulations require revaccination at intervals of 10 years to boost antibody titer. Evidence from multiple studies demonstrates that yellow fever vaccine immunity persists for many decades and might provide life-long protection.

Why are the recommendations being modified now?

The World Health Organization Strategic Advisory Group of Experts in Immunization concluded in April 2013 that a single primary dose of yellow fever vaccine is sufficient to confer sustained immunity and lifelong protection against yellow fever disease, and a booster dose of the vaccine is not needed. In May 2014, the World Health Assembly adopted the recommendation to remove the 10-year booster dose requirement from the International Health Regulations by June 2016. Once the International Health Regulations are updated, the current statement in the ACIP recommendation will no longer be relevant.

What are the new recommendations?

A single primary dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers. The recommendations also provide considerations and recommendations for at-risk laboratory personnel and certain travelers to receive additional doses of yellow fever vaccine.

fever (5). Persons traveling to an area with an ongoing outbreak, persons traveling for a prolonged period in an endemic area, and laboratory workers who routinely handle wild-type yellow fever virus are also considered to be at higher risk for yellow fever virus exposure and disease than other persons for whom yellow fever vaccine is recommended.

Rationale for Yellow Fever Vaccine Booster Dose Recommendations

The GRADE evaluation found that there are few vaccine failures documented after a primary dose of yellow fever vaccine, most (92%) primary vaccine recipients maintain detectable levels of neutralizing antibodies ≥10 years post-vaccination, and few serious adverse events have been reported after a booster dose of yellow fever vaccine (3). Based on the available data, ACIP voted to no longer recommend booster dose of yellow fever vaccine for most travelers, because a single dose of yellow fever vaccine provides long-lasting protection (Box). However, additional doses of yellow fever vaccine are recommended for certain populations (i.e., pregnant women, hematopoietic stem cell transplant recipients, and HIV-infected persons) who might not have as robust or sustained immune response to yellow fever vaccine compared with other recipients. Furthermore,

additional doses may be given to certain groups believed to be at increased risk for yellow fever disease either because of their location and duration of travel or because of more consistent exposure to virulent virus (i.e., laboratory workers). ACIP meeting minutes are available at <http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html>.

Acknowledgments

Members of the Advisory Committee on Immunization Practices (ACIP). ACIP Japanese Encephalitis and Yellow Fever Vaccines Workgroup. Bradley Biggerstaff, National Center for Emerging and Zoonotic Diseases, CDC. ACIP member roster for July 2014–June 2015 available at <http://www.cdc.gov/vaccines/acip/committee/members.html>.

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From: Stanley Plotkin
Sent: 10 Jul 2019 11:08:46 -0400
To: Cohn, Amanda (CDC/DDID/NCIRD/OD)
Cc: Messonnier, Nancy (CDC/DDID/NCIRD/OD); 'Tom Monath'; 'Mark Slifka'
Subject: yellow fever boosters
Attachments: Yellow Fever ReferencesJuly 10.docx

Dear Amanda:

You may recall that a couple of years ago the ACIP recommended against routine boosters of yellow fever vaccine except in individuals with immune deficits. You may also recall that I spoke against that change based on the available data but the committee went on to make the recommendation anyway.

I return to the subject because of a new publication (the last on the attached list) that shows considerable loss of titer in normal individuals in Brazil. Of those who received a single dose 31% were seronegative, although among those with defined times since vaccination 15% were seronegative. The authors of the study conclude that despite issues regarding test sensitivity and the possible protective effect of CD8+ T cells, that booster doses are indicated. At the very least the Yellow Fever Working Group should review that article as well as my commentary on a previous article. Although this may sound like "I told you so" all I want is an unprejudiced look at the data. I am aware that there is a shortage of yellow fever vaccine so there is no urgency to add boosters but in the interests of scientific accuracy the data should be fairly evaluated.

Best wishes,
Stanley

Yellow Fever References

July 10, 2019

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