DAVID COLE
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REPRESENTING: MYSELF

ACIP

Conflicts of Interest

Presented to the Health and Insurance Committee

4/15/2019

i. Written Statement

1) "Conflicts of Interest and Vaccine Development" Hearing before the Committee on Government Reform, June 15th 2000, pp.7-10
2) "Advisors on Vaccines Often Have Conflicts, Report Says" New York Times, Dec 17th 2009
3) "CDC's Ethics Program..." Office of Inspector General, HHS, Dec 17th 2009, pp.i-iii
4) Krahling and Wlochowski V. Merck & Co., filed 2012, case active 7 years
5) "Candidate to Lead FDA Has Close Ties to Big Pharma," Time, Feb 19th 2015
6) CDC Director quits over financial conflicts, NPR, Jan 31st 2018

i. Written Statement

Thank you, members of the committee for this opportunity to speak.

I am in firm opposition to HB 1312.

This Bill forces our State Board of Health to blindly enforce recommendations by ACIP (Advisory Committee on Immunization Practices), it behooves the committee to take a very close look at ACIP.

Submitted for your review are Six references spanning 18 years. In Ref. 1, a Hearing before the Committee on Government reform; to quote from Committee Chair Dan Burton:

> *"Families need to have confidence that the vaccines... their children take are safe, effective and very necessary... Has that trust been violated? How confident... would doctors and parents be if they learned the following:*
>
> *One, that members, including the chair of the FDA and CDC advisory committees... own stock in drug companies that make the vaccines.*
>
> *Two, that individuals on both advisory committees own patents for vaccines under consideration...*
>
> *Three, that three out of the five of the members of the FDA's advisory committee... for the rotavirus vaccine had conflicts of interest that were waived.*
>
> *Four, that 7 individuals... were not present at the meeting. Two others were excluded from the vote, and the remaining five were joined by five temporary voting members who all voted [YES] to license the product.* [Rotashield]
>
> *Five, that the CDC grants conflict of interest waivers to every member of their advisory committee a year at a time, and allows full participation in the discussions leading up to a vote by every member, whether they have a financial stake in the decision or not. So they're discussing it, influencing other members possibly, whether they have a financial stake or not.*
>
> *Sixth, that [ACIP] has no public members, no parents have a vote in whether or not a vaccine belongs on the childhood immunization schedule. The FDA's committee only has one public member.*
>
> *These are just a few of the problems we found."*

I implore the Committee to abandon party lines and responsibly OPPOSE this Bill. Thank you.

[House Hearing, 106 Congress]
[From the U.S. Government Printing Office]

FACA: CONFLICTS OF INTEREST AND VACCINE DEVELOPMENT--PRESERVING THE INTEGRITY OF THE PROCESS

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HEARING

before the

COMMITTEE ON
GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

SECOND SESSION

JUNE 15, 2000

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COMMITTEE ON GOVERNMENT REFORM

DAN BURTON, Indiana, Chairman

two important advisory committees. The Food and Drug Administration and the Centers for Disease Control and Prevention rely on these advisory committees to help them make vaccine policies that affect every child in America. We've looked very carefully at conflicts of interest. We've taken a good, hard look at whether the pharmaceutical industry has too much influence over these committees.

From the evidence we've found, we believe that they do. The first committee is the Food and Drug Administration's Vaccine and Related Biological Products Advisory Committee. This committee makes recommendations on whether new vaccines should be licensed.

The second committee is the CDC's Advisory Committee on Immunization Practices. This committee recommends which vaccines should be included in the childhood immunization schedule.

To make these issues easier to understand, we're going to focus on one issue handled by these two committees, the rotavirus vaccine. There are other vaccines that we may get into later, but today we're going to use this as the primary example.

It was approved for use by the FDA in August 1998. It was recommended for universal use by the CDC in March 1999. Serious problems cropped shortly after it was introduced. Children started developing serious bowel obstructions. The vaccine was pulled from the U.S. market in October 1999.

So the question is, was there evidence to indicate that the vaccine was not safe, and if so, why was it licensed in the first place? How good a job did the advisory committees do?

We reviewed the minutes of the meetings. At the FDA's committee, there were discussions about adverse events. They were aware of potential problems. Five children out of 10,000 developed bowel obstructions. There were also concerns about children failing to thrive and developing high fevers, which as we know from other vaccine hearings, can lead to brain injury. Even with all of these concerns, the committee voted unanimously to approve it.

At the CDC's committee, there was a lot of discussion about whether the benefits of the vaccine really justified the cost. Even though the cost benefit ratio was questioned, the committee voted unanimously to approve it.

Were they vigilant enough? Were they influenced by the pharmaceutical industry? Was there appropriate balance of expertise and perspective on vaccine issues?

We've been reviewing their financial disclosure statements. We've interviewed staff from the FDA and the CDC. The staff has prepared a staff report summarizing what we found. At the end of this statement, while I won't ask unanimous consent to enter this report in the record today, I've already agreed not to do that, we've identified a number of problems that need to be brought to light, and we will be discussing those.

Families need to have confidence that the vaccines that their children take are safe, effective and very necessary. Doctors need to feel confident that when the FDA licenses a drug, that it's really safe and that the pharmaceutical industry has not influenced the decisionmaking process. Doctors place trust in the FDA and assume that if the FDA has licensed

a drug, it's safe for use.

Has that trust been violated? How confident in the safety and need of specific vaccines would doctors and parents be if they learned the following: One, that members, including the chair of the FDA and CDC advisory committees who make these decisions own stock in drug companies that make the vaccines. Two, that individuals on both advisory committees own patents for vaccines under consideration, or affected by the decisions of the committees.

Three, that three out of the five of the members of the FDA's advisory committee who voted for the rotavirus vaccine had conflicts of interest that were waived. Four, that 7 individuals of the 15 member FDA advisory committee were not present at the meeting. Two others were excluded from the vote, and the remaining five were joined by five temporary voting members who all voted to license the product.

Five, that the CDC grants conflict of interest waivers to every member of their advisory committee a year at a time, and allows full participation in the discussions leading up to a vote by every member, whether they have a financial stake in the decision or not. So they're discussing it, influencing other members possibly, whether they have a financial stake or not.

Sixth, that the CDC's advisory committee has no public members, no parents have a vote in whether or not a vaccine belongs on the childhood immunization schedule. The FDA's committee only has one public member.

These are just a few of the problems we found. Specific examples of this include Dr. John Modlin. He served for 4 years on the CDC advisory committee and became the chair in February 1998. He participated in the FDA's committee as well. He owns stock in Merck, one of the largest manufacturers of the vaccine, valued at $26,000. He also serves on Merck's immunization advisory board.

Dr. Modlin was the chairman of the rotavirus working group. He voted yes on eight different matters pertaining to the ACIP's rotavirus statement, including recommending for routine use and for inclusions in the Vaccines for Children program. It was not until this past year that Dr. Modlin decided to divest himself of his vaccine manufacturer stock.

At our April 6th autism hearing, Dr. Paul Offit disclosed that he holds a patent on a rotavirus vaccine and receives grant money from Merck to develop this vaccine. He also disclosed that he is paid by the pharmaceutical industry to travel around the country and teach doctors that vaccines are safe. Dr. Offit is a member of the CDC's advisory committee and voted on three rotavirus issues, including making the recommendation of adding the rotavirus vaccine to the Vaccines for Children program.

Dr. Patricia Ferrieri, during her tenure as chair of the FDA's advisory committee, owned stock in Merck valued at about $20,000 and was granted a full waiver.

Dr. Neal Halsey, who serves as a liaison member to the CDC committee on behalf of the American Association of Pediatrics, and is a consultant to the FDA's committee, has extensive ties to the pharmaceutical industry, including having solicited and received startup funds from industry for his Vaccine Center. As

a liaison member to the CDC committee, Dr. Halsey is there to represent the opinions of the organizations he represents, but was found in the transcripts to be offering his personal opinion.

Dr. Harry Greenberg, who serves as chair of the FDA committee, owns $120,000 of stock in Aviron, a vaccine manufacturer. He also is a paid member of the board of advisors of Chiron, another vaccine manufacturer, and owns $40,000 of stock. This stock ownership was deemed not to be a conflict, and a waiver was granted. To the FDA's credit, he was excluded from the rotavirus discussion, because he holds the patent on the Rotashield vaccine.

How confident can we be in the process when we learned that most of the work of the CDC advisory committee is done in ``working groups'' that meet behind closed doors, out of the public eye? Members who can't vote in the full committee because of conflicts of interest are allowed to work on the same issues in working groups, and there is no public scrutiny. I was appalled to learn that at least 6 of the 10 individuals who participated in the working group for the rotavirus vaccine had financial ties to pharmaceutical companies developing rotavirus vaccines.

How confident can we be in the recommendations for the Food and Drug Administration when the chairman and other individuals on their advisory committee own stock in major manufacturers of vaccines?

How confident can we be in a system when the agency seems to feel that the number of experts is so few around the country that everyone has a conflict and thus waivers must be granted? It almost appears that there is an ``old boys network'' of vaccine advisors that rotate between the CDC and FDA, at times serving simultaneously. Some of these individuals served for more than 4 years. We found one instance where an individual served for 16 years continuously on the CDC committee. With over 700,000 physicians in this country, how can one person be so indispensable that they stay on a committee for 16 years?

It's important to determine if the Department of Health and Human Services has become complacent in their implementation of the legal requirements on conflicts of interest and committee management. If the law is too loose, we need to change it. if the agencies aren't doing their job, they need to be held accountable. That's the purpose of this hearing, to try to determine what needs to be done.

Why is this review necessary? Vaccines are the only substances that a government mandates a U.S. citizen receive. State governments have the authority to mandate vaccines be given to children prior to admission to day care centers and schools. State governments rely on the recommendations of the CDC and the FDA to determine the type and schedule of vaccines.

I am not alone in my concern about the increasing influence of industry on medicine. Last year, the New England Journal of Medicine learned that 18 individuals who wrote drug therapy review articles had financial ties to the manufacturer of the drugs they were discussing. The Journal, which has the most stringent conflict of interest disclosures of medical journals, had a recent editorial discussing the increasing level of academic research funded by the industry. The editor stated,

``What is at issue is not whether researchers can be `bought' in the sense of a quid pro quo, is that close and remunerative collaboration with a company naturally creates goodwill on the part of the researchers and the hope that the largesse will continue. This attitude can subtly influence scientific judgment.''

Can the FDA and the CDC really believe that scientists are more immune to self-interest than anybody else?

Maintaining the highest level of integrity over the entire spectrum of vaccine development and implementation is essential. The American people have to have trust in the system. The Department of Health and Human Services has a responsibility to the American public to ensure the integrity of this process by working diligently to appoint individuals that are totally without financial ties to the vaccine industry to serve on these and all vaccine-related panels.

No individual who stands to gain financially from the decisions regarding vaccines that may be mandated for use should be participating in the discussion or policymaking for vaccines. We have repeatedly heard in our hearings that vaccines are safe and needed to be protecting the public. If the panels that have made the decisions on all vaccines on the childhood immunization schedule had as many conflicts as we have found with rotavirus, then the entire process has been polluted and the public trust has been violated. I intend to find out if the individuals who have made these recommendations that affect every child in this country and around the world stood to gain financially and professionally from the decisions of the committees on which they served.

The hearing record will remain open until June 28th for those who would like to submit a statement for the record.

I now recognize the ranking minority member, Mr. Waxman, for his opening statement.

[The prepared statement of Hon. Dan Burton follows:]

[GRAPHIC] [TIFF OMITTED] T3042.001

[GRAPHIC] [TIFF OMITTED] T3042.002

[GRAPHIC] [TIFF OMITTED] T3042.003

[GRAPHIC] [TIFF OMITTED] T3042.004

[GRAPHIC] [TIFF OMITTED] T3042.005

[GRAPHIC] [TIFF OMITTED] T3042.006

Mr. Waxman. Thank you very much, Mr. Chairman.

This hearing is about conflicts of interest and vaccine decisionmaking. This is an issue I take very seriously. I have probably done more than any other member of this committee to identify and oppose genuine conflicts of interest in Federal decisionmaking.

In 1991, I held a hearing on conflicts of interest in Vice President Quayle's Council on Competitiveness. These hearings revealed that the executive director of the council owned 50 percent of a chemical plant subject to regulation under the Clean Air Act at the same time that he was chairing biweekly

Advisers on Vaccines Often Have Conflicts, Report Says

By GARDINER HARRIS

Published: December 17, 2009

PRINT

REPRINTS

SHARE

WASHINGTON — A new report finds that the Centers for Disease Control and Prevention did a poor job of screening medical experts for financial conflicts when it hired them to advise the agency on vaccine safety, officials said Thursday.

Most of the experts who served on advisory panels in 2007 to evaluate vaccines for flu and cervical cancer had potential conflicts that were never resolved, the report said. Some were legally barred from considering the issues but did so anyway.

Related

Document: CDC's Ethics Program for Special Government Employees on Federal Advisory Committees (pdf)

In the report, expected to be released Friday, Daniel R. Levinson, the inspector general of the Department of Health and Human Services, found that the centers failed nearly every time to ensure that the experts adequately filled out forms confirming they were not being paid by companies with an interest in their decisions.

The report found that 64 percent of the advisers had potential conflicts of interest that were never identified or were left unresolved by the centers. Thirteen percent failed to have an appropriate conflicts form on file at the agency at all, which should have barred their participation in the meetings entirely, Mr. Levinson found. And 3 percent voted on matters that ethics officers had already barred them from considering.

The inspector general recommended that the centers do a far better job of screening. In a reply, the agency's new director, Dr. Thomas R. Frieden, agreed.

"Since the period covered in this review, C.D.C. has strengthened the financial disclosures and conflict-of-interest process by instituting improved business processes and realigning responsibilities and oversight," Dr. Frieden wrote.

As numerous medicines have been pulled from the market in recent years, worries have grown that experts may be recommending medical products — even ones they know to be unsafe — in part because manufacturers are paying them.

As a result, government agencies, medical societies and medical journals have become increasingly insistent that experts disclose potential conflicts. And while the experts invariably insist that they have done so, government audits routinely find large gaps between these disclosures and the experts' actual income from consulting.

Congress tightened the rules on outside consulting after similar conflicts were found among members of advisory panels to the Food and Drug Administration. But little attention has been paid to the potential conflicts of advisers to the C.D.C., even though that agency's committees have significant influence over what vaccines are sold in the United States, what tests are performed to detect cancer and how coal miners are protected.

Most of the advisers identified by Mr. Levinson had either a job or a grant from a company or other entity whose interests were affected by the committees' discussions, and a considerable number also owned stock in such companies, the report said.

Representative Rosa DeLauro, a Connecticut Democrat who said she had long been a supporter of the C.D.C., said: "That is why I am so concerned about this report issued by the inspector general exposing serious ethics violations within the C.D.C. All members of the federal advisory committees, whose recommendations direct federal policy, should be without conflict of interest."

A version of this article appeared in print on December 18, 2009, on page A28 of the New York edition.

Washington, D.C. 20201

DEC 17 2009

TO: Thomas R. Frieden, M.D., M.P.H.
Director
Centers for Disease Control and Prevention

FROM: Daniel R. Levinson *Daniel R. Levinson*
Inspector General

SUBJECT: OIG Final Report: *CDC's Ethics Program for Special Government Employees on Federal Advisory Committees*, OEI-04-07-00260

Attached is our final report entitled *CDC's Ethics Program for Special Government Employees on Federal Advisory Committees*.

Please send us your final management decision, including any action plan, as appropriate, within 60 days. If you have any questions about this report, please do not hesitate to call me or one of your staff may contact Linda Abbott, Deputy Director, Evaluation Planning and Support Division, at (410) 786-4662 or through email [Linda.Abbott@oig.hhs.gov]. To facilitate identification, please refer to report number OEI-04-07-00260 in all correspondence.

Attachment

cc: Edgar Swindell
Designated Agency Ethics Official
Office of the General Counsel

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

CDC'S ETHICS PROGRAM FOR SPECIAL GOVERNMENT EMPLOYEES ON FEDERAL ADVISORY COMMITTEES

Daniel R. Levinson
Inspector General

December 2009
OEI-04-07-00260

Office of Inspector General

http://oig.hhs.gov

The mission of the Office of Inspector General (OIG), as mandated by Public Law 95-452, as amended, is to protect the integrity of the Department of Health and Human Services (HHS) programs, as well as the health and welfare of beneficiaries served by those programs. This statutory mission is carried out through a nationwide network of audits, investigations, and inspections conducted by the following operating components:

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EXECUTIVE SUMMARY

OBJECTIVE

To determine the extent to which the Centers for Disease Control and Prevention (CDC) and its special Government employees (SGE) on Federal advisory committees (committees) complied with ethics requirements.

BACKGROUND

Committees play an influential role in decisionmaking for the Federal Government. Committee members (i.e., SGEs) are typically involved in work outside the Federal Government in the same areas as their committees' work. To protect the committees' integrity and credibility, agencies must not permit SGEs with conflicts of interest to inappropriately influence their committees' work.

At CDC, committees address important public health topics. For example, in 2007, one committee recommended the routine vaccination of young females in the United States to prevent cervical cancer. In 2009, this same committee recommended that H1N1 influenza vaccination efforts focus on five target groups in the United States.

CDC must obtain from SGEs Confidential Financial Disclosure Reports, Office of Government Ethics (OGE) Forms 450, containing information such as the SGEs' assets, sources of income, and non-income-earning activities. Before permitting SGEs to participate in committee meetings, CDC must review these forms and certify them to indicate that they are complete and that it has identified and resolved all conflicts of interest. CDC must create ethics agreements (e.g., waivers) to resolve SGEs' conflicts of interest. CDC collaborates with the Department of Health and Human Services' (HHS) Office of the General Counsel to identify and resolve conflicts of interest.

CDC must also provide initial and annual ethics training to SGEs within required timeframes and obtain ethics training certificates from SGEs to document that they received the training. Finally, CDC must monitor SGEs' compliance with ethics requirements during committee meetings. That is, SGEs must not participate in committee work during committee meetings without current, certified OGE Forms 450 or participate in committee work related to particular matters if their waivers prohibit such participation.

We reviewed financial disclosure files (e.g., current, certified OGE Forms 450 and ethics agreements) for 246 SGEs on 17 CDC committees in

2007. We determined whether SGEs' OGE Forms 450 were complete after CDC certified them. Then, we determined whether CDC identified potential conflicts of interest that we identified. We also determined the extent to which CDC created ethics agreements and adequately documented them to resolve potential conflicts of interest. Further, we determined whether CDC ensured that SGEs' financial disclosure files contained ethics training certificates to document that SGEs received ethics training within required timeframes. Finally, we determined whether SGEs complied with ethics requirements during committee meetings.

FINDINGS

For almost all special Government employees, CDC did not ensure that financial disclosure forms were complete in 2007. CDC certified OGE Forms 450 with at least one omission in 2007 for 97 percent of SGEs. Most of the forms had more than one type of omission.

CDC did not identify or resolve potential conflicts of interest for 64 percent of special Government employees in 2007. Sixty-four percent of SGEs had potential conflicts of interest in 2007 that CDC did not identify and/or resolve before it certified their OGE Forms 450. Specifically, 58 percent of SGEs had potential conflicts of interest that CDC did not identify. In addition, 32 percent of SGEs had potential conflicts of interest that CDC identified but did not resolve. Twenty-six percent of SGEs had both CDC-unidentified and unresolved potential conflicts of interest.

CDC did not ensure that 41 percent of special Government employees received required ethics training in 2007. CDC did not ensure that 41 percent of SGEs had ethics training certificates on file to document that SGEs received initial or annual ethics training within required timeframes in 2007.

Fifteen percent of special Government employees did not comply with ethics requirements during committee meetings in 2007. Fifteen percent of SGEs did not comply with ethics requirements during committee meetings in 2007. Specifically, 13 percent of SGEs participated in committee meetings in 2007 without having current, certified OGE Forms 450 on file. In addition, 3 percent of SGEs voted on particular matters when their waivers prohibited such participation. Four SGEs both participated in committee meetings without current, certified OGE Forms 450 on file and voted on particular matters when their waivers prohibited such participation.

RECOMMENDATIONS

We found that CDC had a systemic lack of oversight of the ethics program for SGEs. That is, CDC and its SGEs did not comply with ethics requirements in 2007.

To address our findings, we recommend that CDC:

Ensure that special Government employees' Confidential Financial Disclosure Reports are complete before certifying them.

Require special Government employees to disclose their involvement in grants and other relevant interests that could pose conflicts but that are not disclosed on the Confidential Financial Disclosure Report.

Identify and resolve all conflicts of interest for special Government employees before permitting them to participate in committee meetings.

Increase collaboration among CDC officials and with the HHS Office of the General Counsel.

Ensure that special Government employees and CDC employees receive ethics training.

Monitor special Government employee compliance with ethics requirements during committee meetings.

Track special Government employee compliance with ethics requirements.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

CDC concurred with all seven of our recommendations. Since the time of our review, CDC indicated that it has begun or plans to implement improvements that coincide with our recommendations.

We made technical changes to the report based on CDC's comments.

(CDJ)

(12)

UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

United States of America *ex rel.*,	Civil Action No. 10-4374 (CDJ)
Stephen A. Krahling and Joan A. Wlochowski,	
Plaintiffs,	**AMENDED COMPLAINT FOR VIOLATIONS OF THE FEDERAL FALSE CLAIMS ACT**
v.	
Merck & Co., Inc.	**JURY TRIAL DEMANDED**
Defendant.	

Stephen Krahling and Joan Wlochowski bring this *qui tam* action as Relators on behalf of the United States against their former employer, Merck & Co., Inc. ("Merck"), under the False Claims Act, 31 U.S.C. §§ 3729-3733, and allege -- upon knowledge with respect to their own acts and those they personally witnessed, and upon information and belief with respect to all other matters -- as follows:

INTRODUCTION

1. This case is about Merck's efforts for more than a decade to defraud the United States through Merck's ongoing scheme to sell the government a mumps vaccine that is mislabeled, misbranded, adulterated and falsely certified as having an efficacy rate that is significantly higher than it actually is.

2. Specifically, in an effort to maintain its exclusive license to sell the vaccine and its monopoly of the U.S. market for mumps vaccine, Merck has fraudulently represented and continues to falsely represent in its labeling and elsewhere that its mumps vaccine has an

efficacy rate of 95 percent or higher. This is the efficacy rate on which Merck's original government approval for the vaccine was based more than forty years ago. In truth, Merck knows and has taken affirmative steps to conceal -- such as by using improper testing techniques, falsifying test data in a clinical trial, and violating multiple duties of government disclosure -- that the efficacy rate of Merck's mumps vaccine is, and has been since at least 1999, significantly lower than this 95 percent rate.

3. Relators Krahling and Wlochowski were employed as virologists in the Merck lab that performed this fraudulent efficacy testing. They witnessed firsthand the improper testing and data falsification in which Merck engaged to conceal what Merck knew about the vaccine's diminished efficacy. In fact, their Merck superiors and senior Merck management pressured them to participate in the fraud and subsequent cover-up when Relators objected to and tried to stop it.

4. As a result of Merck's fraudulent scheme, the United States has over the last decade paid Merck hundreds of millions of dollars for a vaccine that does not provide the efficacy Merck claims it provides and does not provide the public with adequate immunization. Had Merck complied with its multiple duties of disclosure and reported what it knew of the vaccine's diminished efficacy -- rather than engage in fraud and concealment -- that information would have affected (or surely had the potential to affect, which is all the law requires) the government's decision to purchase the vaccine. However, since the government was not fully informed, it did not have the opportunity to consider its options, including not purchasing the vaccine from Merck, paying less, requiring a labeling change, requiring additional testing, or prioritizing development and approval of a new vaccine from Merck or another manufacturer.

5. Merck's failure to disclose what it knew about the diminished efficacy of its mumps vaccine has caused the government to purchase mislabeled, misbranded, adulterated and falsely certified vaccines in violation of Merck's contract with the Centers for Disease Control ("CDC") and in violation of the law.

6. As the single largest purchaser of childhood vaccines (accounting for more than 50 percent of all vaccine purchases), the United States is by far the largest financial victim of Merck's fraud. But the ultimate victims here are the millions of children who every year are being injected with a mumps vaccine that is not providing them with an adequate level of protection against mumps. And while this is a disease the CDC targeted to eradicate by now, the failure in Merck's vaccine has allowed this disease to linger with significant outbreaks continuing to occur.

7. Relators bring this case on behalf of the United States to recover the funds that the government spent for this fraudulently mislabeled, misbranded, adulterated and falsely certified vaccine, and for all associated penalties. They also bring this case to stop Merck from continuing with its scheme to misrepresent the true efficacy of its mumps vaccine and require Merck to comply with its reporting, labeling and testing obligations under its contract with the CDC and under this country's vaccine regulatory regime.

PARTIES

8. Relator Stephen A. Krahling is a citizen of the United States and a resident of Pennsylvania. He was employed by Merck from 1999 to 2001 as a virologist in Merck's vaccine division located in West Point, Pennsylvania. During his employment at Merck, Krahling witnessed firsthand, and was asked to directly participate in, fraud in a clinical trial relating to

the efficacy of Merck's mumps vaccine.

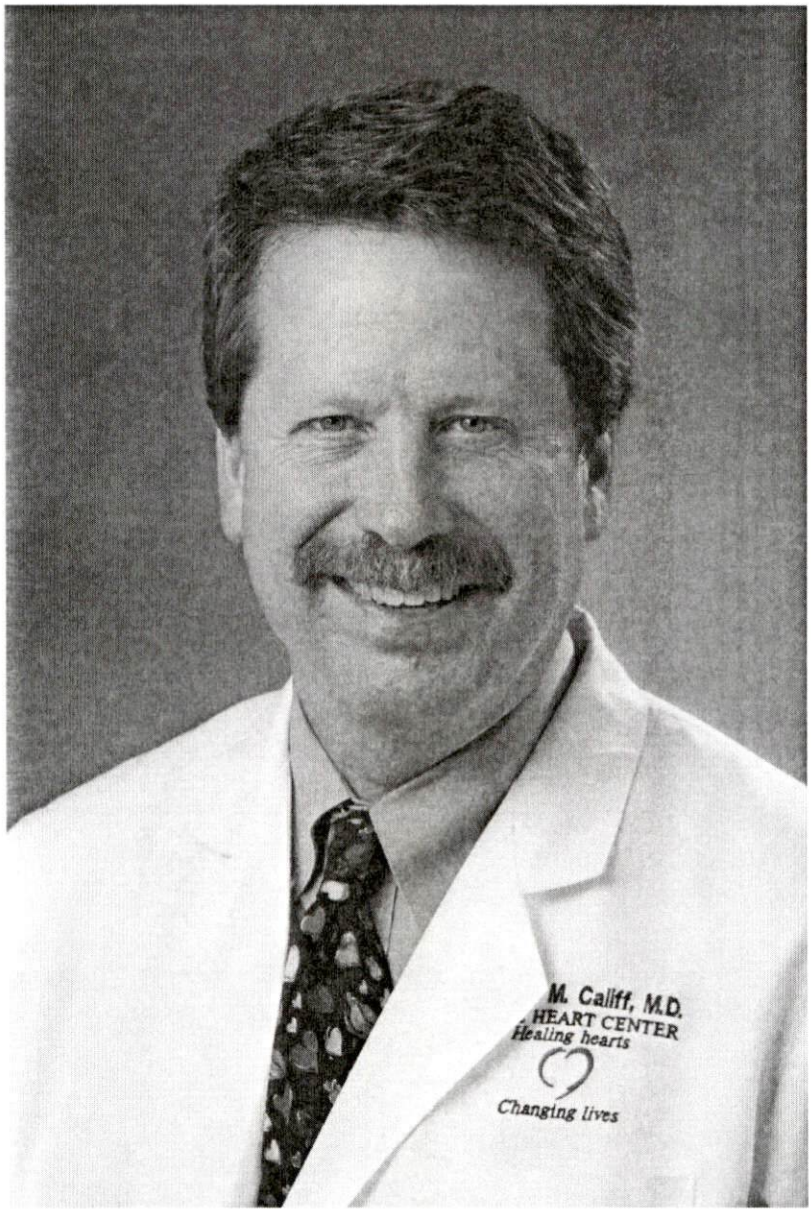
9. Relator Joan Wlochowski is a citizen of the United States and a resident of Connecticut. She was employed by Merck from January 2001 to August 2002 as a virologist in Merck's vaccine division in West Point, Pennsylvania. During her employment there, Wlochowski also witnessed firsthand, and was asked to directly participate in, fraud in a clinical trial relating to the efficacy of Merck's mumps vaccine.

10. Defendant Merck is headquartered in New Jersey with its vaccine division based in West Point, Pennsylvania. Merck is one of the largest pharmaceutical companies in the world with annual revenues exceeding $20 billion. Merck is also a leading seller of childhood vaccines and currently markets in the U.S. vaccines for 12 of the 17 diseases for which the CDC currently recommends vaccination.

11. Merck is the sole manufacturer licensed by the Food and Drug Administration ("FDA") to sell mumps vaccine in the United States. Merck's mumps vaccine, together with Merck's vaccines against measles and rubella are sold as MMRII. Merck annually sells more than 7.6 million doses of the vaccine in the U.S. for which it derives hundreds of millions of dollars of revenue. The U.S. purchases approximately 4 million of these doses annually. Merck also has a license in the U.S. to sell ProQuad, a quadravalent vaccine containing MMRII vaccine and chickenpox vaccine. Under a license from the European Medicines Agency ("EMA"), Merck also sells mumps vaccine in Europe as a part of the trivalent MMRVaxpro and the quadravelent ProQuad through Sanofi Pasteur MSD, a joint venture with the vaccine division of the Sanofi Aventis Group. ProQuad has been sold intermittently in the U.S. and Europe from its approval in 2005 until 2010.

TIME

Candidate to Lead FDA Has Close Ties to Big Pharma



Dr. Robert Califf Jared Lazarus—Duke Photography

BY MASSIMO CALABRESI FEBRUARY 19, 2015

Last May, Duke University's Vice Chancellor for clinical research, Dr. Robert Califf, told an audience of executives that the American system for developing drugs and medical devices was in crisis. Using slides [pdf] developed by Duke's business school, he said the system was too slow and too expensive, and required disruption and transformation. Towards the end of his talk, he put up a slide that identified a key barrier to change: regulation.

Such views are not uncommon in industry, academic research and on Capitol Hill, but they are noteworthy coming from Califf because he could soon be America's top regulator overseeing the safety and efficacy of the country's drugs and medical devices. Califf is already set to become deputy commissioner at the Food and Drug Administration (FDA) next month. Now sources familiar with the process tell TIME he is on President Barack Obama's short list to run the agency following this month's announcement that its long-serving commissioner, Margaret Hamburg, will step down in March.

The White House declined to comment on pending personnel decisions, but word that Califf is in contention for the top spot at the FDA comes at a key moment. The agency faces potentially dramatic changes this year as Congress prepares to rewrite many of the rules for how drugs and medical devices are reviewed and tested for safety and efficacy. Califf is widely respected in the public and private sectors, but his candidacy is seen by some as a threat to the independence and authority of the FDA, thanks to his views on the need to accelerate change and his deep financial and intellectual ties to the pharmaceutical and medical device industries.

Califf says his salary is contractually underwritten in part by several large pharmaceutical companies, including Merck, Bristol-Myers Squibb, Eli Lilly and Novartis. He also receives as much as $100,000 a year in consulting fees from some of those companies, and from others, according to his 2014 conflict of

interest disclosure [pdf]. In an interview with TIME, Califf estimates that less than half of his annual income comes from research money provided by the pharmaceutical industry, though he says he is not certain because he doesn't tend to distinguish between industry and government research funding. He says he is divesting his holdings in two privately-held pharmaceutical companies he helped get off the ground.

Califf says such collaboration, not just between industry and academia, but with government, too, is the way of the future. "The greatest progress almost certainly will be made by breaking out of insular knowledge bases and collaborating across the different sectors," Califf says. He says there is "a tension which cannot be avoided between regulating an industry and creating the conditions where the industry can thrive, and the FDA's got to do both." He says it would be "useful to have someone [leading the FDA] who understands how companies operate because you're interacting with them all the time."

Diana Zuckerman, President of the National Center for Health Research, which advocates for FDA regulatory authority, says such ties "should be of great concern." Dr. Califf is "a very accomplished, smart physician who's been an important name in the field," Zuckerman says, but his "interdependent relationships" raise questions about his "objectivity and distance." She cites several studies suggesting the medical products industry uses such ties to influence the behavior and decision making of doctors and researchers, even when the scientists don't realize it.

The tension over Califf's collaboration with industry gets to the heart of the future of the FDA at a pivotal moment. While FDA defenders see the collaboration as a threat to its independence, others see close relationships between government, industry and academia as the model for the future. Califf heads a successful and powerful clinical research program, the Duke

Translational Medicine Institute, which brings together industry drug researchers, academic scientists and federal regulators to speed drug development and approval. Califf estimates 50-60% of its $320 million in annual research funding comes from industry.

Capitol Hill is considering codifying parts of that collaborative model for the FDA. The powerful Energy and Commerce Committee in the U.S. House of Representatives recently introduced a draft bill called 21st Century Cures, which would loosen the drug approval and post-market oversight process. Califf says because the bill is still in draft it is too early to pass an overall judgment on it but he says, "I support a lot of the concepts in the bill."

In the Senate, the Health, Education, Labor and Pensions (HELP) committee has begun work on its own bill, with committee chairman Lamar Alexander declaring, "It takes too long and costs too much to develop medical products." In a report paving the way for his legislation, Alexander concluded the FDA has grown too large, has fallen behind scientific innovation and threatens American leadership in biomedical innovation. Reform efforts in the Senate may be aided by the support of liberals like Elizabeth Warren who back looser regulations on the medical device industry.

The FDA uses a model for drug testing and oversight largely developed in the early 1960s, with phased trials before drugs and devices are approved for sale to ensure they are safe and effective, and "post-market" studies afterwards to monitor them. Over time, the agency has come to rely on the medical product industry for more than 60% of its budget for post-market monitoring. Accused of regulatory capture by those who see undue industry influence, the FDA has faced attacks from both sides.

That means the FDA has few defenders and will rely heavily on its next

commissioner to stand up for it in public and on Capitol Hill. "This is a very dangerous time for the agency," says Zuckerman of the National Center for Health Research, "It's under fire in a way that is unprecedented in the last 20 years."

Califf's supporters point out that he is among the ten most cited medical authors in America, and that he has spent his career as a clinician helping patients. Regarding the danger of regulators being "captured" by their interactions with industry, Califf says, "The difference between capture and collaboration towards improving human health is a pretty big difference."

The White House has set no time frame for its decision on Hamburg's replacement. It has announced the acting commissioner will be Dr. Stephen Ostroff, a scientist and long-time official at the Health and Human Services department, when she steps down in March.

Contact us at editors@time.com.

PUBLIC HEALTH

CDC Director Resigns Because Of 'Complex' Financial Entanglements

January 31, 2018 · 10:18 AM ET

JOE NEEL

Brenda Fitzgerald, Georgia Department of Public Health commissioner, and Gov. Nathan Deal respond to questions

about Ebola victims at Emory University Hospital and efforts to screen for Ebola in 2014. A report in *Politico* revealed documents showing several new investments, including in a tobacco company, by Centers for Disease Control and Prevention Director Brenda Fitzgerald.

David Tulis/AP

Dr. Brenda Fitzgerald, director of the Centers for Disease Control and Prevention, resigned Wednesday following reports that she bought shares in a tobacco company, among other financial dealings that presented a conflict of interest.

"Dr. Fitzgerald owns certain complex financial interests that have imposed a broad recusal limiting her ability to complete all of her duties as the CDC Director," according to a statement issued by Matt Lloyd, a spokesman for the Department of Health and Human Services. "Due to the nature of these financial interests, Dr. Fitzgerald could not divest from them in a definitive time period."

SHOTS - HEALTH NEWS

How To Drive Down Smoking In Groups That Still Light Up

A report in *Politico* published Tuesday revealed documents showing several new investments, including in a tobacco company, that Fitzgerald made after she took over the agency's top job. The CDC is a lead federal agency in preventing smoking and tobacco-related diseases.

Fitzgerald had come under fire on Capitol Hill for not divesting financial interests in other companies that present potential conflicts of interest, including drugmaker Merck, health insurer Humana and US Food Holding Co.

HEALTH

Trump Administration Appoints Dr. Brenda Fitzgerald As New CDC Director

LISTEN · 2:36 QUEUE Download Transcript

The *Politico* report, relying on documents obtained under the Freedom of Information Act, shows that one day after Fitzgerald purchased stock in Japan Tobacco, she toured the CDC's Tobacco Laboratory, which studies tobacco's toxic effects. She sold the tobacco shares on Oct. 26 and all of her stock holdings above $1,000 by Nov. 21, well into her term as CDC director.

Fitzgerald previous served as the commissioner of the Georgia Division of Public Health.

conflict of interest cigarettes tobacco cdc

More Stories From NPR

Hello, my name is Brittany Dock and I am here to speak to you in opposition of HB 1312. I live in Douglas County, which is, according to USA today's most recent publication, the healthiest county in America!!! I find it interesting that one of the reasons for this bill is a low vaccination rate, yet we have some of the healthiest people in the nation.

My greatest opposition to the bill is in regard to medial exemptions. Page___ Section___ My child, Kendetrick, who is here with me today, has faced forced vaccinations. After discovering that he was in liver failure and faced with a potential liver transplant, I was told that he was not eligible for a life-saving transplant, due to the fact he was "Under-immunized". I was FORCED, even with prior warning from his PCP and over four direct contraindications according to the vaccine manufacturers, to vaccinate Kendetrick because this was "hospital policy" and supposedly in his best interest. I fought it.

I voiced my opinion and provided facts, to many "health professionals" and was offered hospice for my son - MY ELEVEN YEAR OLD SON - if I did not comply. After allowing something I knew was wrong... I knew with every inch of my being was not right... being a stipulation to save his life, what I fully anticipated happening did. About 3 weeks following the Varivax vaccine, Kendetrick was hospitalized for what was found to be VACCINE INDUCED VARICELLA VIREMIA. Chicken pox. That hospital bill was a whopping 181 THOUSAND dollars - and was caused from vaccination.

If a child who is so medically fragile as mine, who is in organ failure and has over a few listed contraindications according to the manufacturer, can get a vaccine, according to ACIP and CDC guidelines, where does it end?

Who are those needed to be protected by the herd? The scope is so narrow. That he will not qualify for an exemption as this bill is currently written. Without a medical exemption, I will be forced to leave the state I love and the home I have built for my family. I fear for my other children, who are vaccine free and EXTREMELY healthy. I can not agree to signing any standardized form with verbiage I do not agree with and that often, tries to put guilt and blame on a parent for simply protecting their child.

Where there is risk THERE MUST BE CHOICE. Would you allow the government to mandate something on your child - a product on your child - that nobody stands behind? That nobody takes accountability for? I ask you to protect my children as well as our rights. Please vote no on HB 1312.

Please vote "YES" on HB 1213!

(Modernization of Immunization Requirements to Improve Vaccination Rates)

James K. Todd, MD 10 April 2019

1. **Vaccines have been shown to be safe and highly effective in Colorado, saving tens of thousands of hospitalizations and hundreds of millions of dollars annually.[1] [2]**

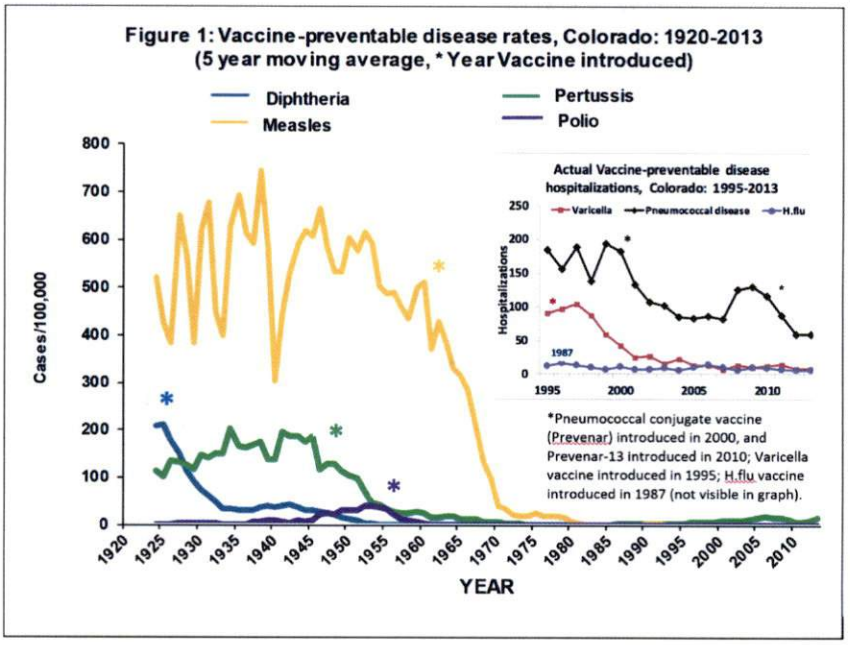


Table 2: Hospital cases and charges prevented among Colorado children due to vaccination, 2014

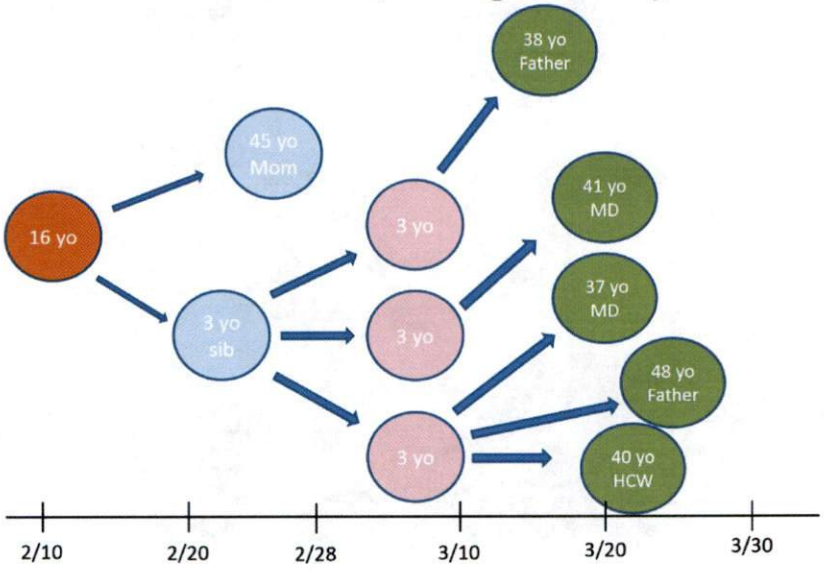
Disease	Index years[a]	Statewide pre-vaccination rate per 100,000[b]	Statewide rate per 100,000 2014[b]	Statewide reportable cases prevented: 2014[c]	Actual hospitalized cases: 2014[d]	Estimated hospitalized cases prevented: 2014[e]	Estimated hospital charges prevented: 2014[f]
Diphtheria	1920-1922	461	0.0	6,471	0	1,760	$75,359,651
H. influenzae	1984-1986	12.4	1.0	173	1	47	$2,051,743
Measles	1960-1962	784	0.0	11,004	2	2,993	$128,153,488
Mumps	1964-1966	408	0.0	5,736	0	1,560	$66,800,189
Pertussis	1945-1947	328	66.4	4,577	35	1,245	$68,223,045
Pneumococcal disease	1997-1999	14.8	2.6	159	48	148	$21,045,008
Polio	1952-1954	68	0.0	948	0	258	$11,040,083
Rubella	1966-1968	124	0.0	1,743	0	474	$20,301,335
Tetanus	1927-1929	1.1	0.0	15	0	4	$174,691
Varicella	1995-1997	8.7	22.6	113	9	114	$7,289,274
Total		**2,210**	**92.6**	**30,939**	**95**	**8,603**	**$400,438,507**

[1] https://www.childrenscolorado.org/globalassets/healthcare-professionals/vaccine-preventable-disease-2014.pdf

[2] https://www.childrenscolorado.org/globalassets/healthcare-professionals/vaccine-preventable-disease-2015.pdf

2. **Unvaccinated individuals put many others at risk at great cost to the community[3]**
    a. **Sick, unvaccinated individuals are highly contagious.**
    b. **Vaccinated individuals may still be at risk if heavily exposed.**
    c. **Immune compromised individuals are at special risk.**
    d. **Individual decisions impose public health costs on the community (tax payers).**

Measles Cluster 1, Orange County, 2014



Healthcare Workers with Measles Clinical and Epidemiologic Features, 2014

Age (y)	Measles Immunity Prior to Exposure	Exposure	Illness Onset	Fever	Cough	Coryza	Rash	Days Considered infectious while asymptomatic	Days working during active symptoms	Number of patients exposed
32	IgG+	3/3/2014	3/17/2014	Y	Y	N	3/18/14	3	0	0
36	IgG+	3/3/2014	3/14/2014	Y	N	N	3/18/14	0	4	850
41	2 MMR	3/7/2014	3/18/2014	Y	N	N	3/20/14	2	2	26
37	4 MMR IgG+	3/7/2014	3/16/2014	N	Y	N	3/20/14	0	4	72
40	Unknown vaccine history, IgG equivocal	3/7/2014	3/19/2014	Y	Y	Y	3/21/14	2	0	0

[3] Matt Zahn, MD; Medical Director Epidemiology and Assessment, Orange County Health Care Agency

Synergistic toxicity

[back] Vaccine Ingredients

[It isn't just vaccines, you have fluoride (found in water, cooking utensils, and drugs eg Antacids, SSRI), attaching to aluminium to enter the brain]

See: Fluoride increases lead uptake Glutathione Blood brain barrier

[2014 May] Fluoride combined with even trace amounts of aluminum in water can cause major brain damage

[2009 Oct] Aluminum in vaccines increases thimerosal's toxicity by Teresa Binstock

More on Thimerosal & things that synergistically increase the toxicity

Quotes

"And combination of substances in toxicology can be greater than the sum of its parts. "With lead and mercury, for instance, a toxicity rating of 1 for each mercury and lead equals not 2, but 60 when combined."---Hal Huggins

We now know that aluminum causes significant abnormalities in neurotubules, microscopic tubes in neurons essential to their function, and these abnormal neurotubules are strongly associated with Alzheimer's disease. Aluminum enters the brain by a number of mechanisms, for example by attaching to glutamate and fluoride. With the widespread use of the excitotoxin glutamate as a food additive and fluoride being added to drinking water supplies, aluminum absorption is common. In addition, injected aluminum can complex with fluoride within the body to produce a compound, fluoroaluminum, that has a number of harmful effects, including brain injury. There is some evidence that fluoride can trigger microglial activation and excitotoxicity, which in combination is particularly injurious to the brain. (Blaylock, RL. Fluoride 2004:37(4);301 -314.) Vaccine Safety Manual by Neil Z. Miller. (Preface)

A multitude of studies have shown that Aluminium, especially if combined with fluoride, is a powerful brain toxin and that it accumulates in the brain. How Vaccines Can Damage Your Brain: Vaccines, Depression and Neurodegeneration After Age 50: Another Reason to Avoid the Recommended Vaccines By Russell L. Blaylock, M.D.

"We have demonstrated the toxicity of thimerosal by using it to kill neurons in culture. At 50 nanomolar thimerosal the neuron killing capacity/rate is about **doubled with the addition of levels of aluminium** found in vaccines. The aluminium alone at this level is not demonstrated to be toxic, so it is enhancing the toxicity of the thimerosal. It likely does this by increasing the rate that thimerosal breaks down releasing ethylmercury which is the toxic material" -------Testimony Prof Boyd Haley, University of Kentucky, Chair and Head of Chemistry.....

Another important factor with regard to mercury on the mind, which officials at the CDC, FDA and the professors in the IOM do not consider, is synergistic toxicity - mercury's enhanced effect when other poisons are present. A small dose of mercury that kills 1 in 100 rats and a dose of aluminum that will kill 1 in 100 rats, when combined have a striking effect: all the rats die. Doses of mercury that have a 1 percent mortality will have a 100 percent mortality rate if some aluminum is there. Vaccines contain aluminum. Mercury on the Mind by Donald W. Miller, Jr., MD

"One publication showed that combining mercury and lead both at LD1 levels caused the killing rate to go to 100% or to an LD100 level (12). An LD1 level is where, due to the low concentrations, the mercury or the lead alone was not very toxic alone (i.e., killed less than 1% of rats exposed when metal were used alone). The 100% killing, when addition of 1% plus 1% we would expect 2%, represents synergistic toxicity. Therefore, mixing to non-lethal levels of mercury plus lead gave an extremely toxic mixture! **What this proves is that one cannot define a "safe level of mercury" unless you absolutely know what others toxicants the individual is being exposed to.** The combined toxicity of various materials, such as mercury, Thimerosal, lead, aluminum, formaldehyde, etc., is unknown. The effects various combinations of these toxicants would have is also not defined except that we know they would be much worse than any one of the toxicants alone. So how could the ADA take any exception, based on intellectual considerations, to my contention that combinations of Thimerosal and mercury could exacerbate the neurological conditions identified with autism and AD? Autism and AD have clinical and biological markers that correspond to those observed in patients with toxic mercury exposure. Why would the ADA take this position? I personally feel like I have been in a ten-year argument with the town drunk on this issue. Facts don't count and data is only valid if it meets the pro-amalgam agenda.....The synergistic effects of mercury with many of the toxicants commonly found in our environment make the danger unpredictable and possibly quite severe, especially any mixture containing elemental mercury, organic mercury and other heavy metal toxicants such as aluminum."--Boyd Haley http://www.whale.to/m/haley.html

"A single vaccine given to a six-pound newborn is the equivalent of giving a 180-pound adult 30 vaccinations on the same day. Include in this the toxic effects of high levels of aluminum and formaldehyde contained in some vaccines, and the synergist toxicity could be increased to unknown levels. Further, it is very well known that infants do not produce significant levels of bile or have adult renal capacity for several months after birth. Bilary transport is the major biochemical route by which mercury is removed from the body, and infants cannot do this very well. They also do not possess the renal (kidney) capacity to remove aluminum. Additionally, mercury is a well-known inhibitor of kidney function."--Boyd Haley Ph.D.

Antibiotics [**See**: Neomycin (MMR vaccine)]
"Studies on the toxicity of mercury to mammalian neurons in culture demonstrate that low nanomolar levels can have lethal effects. Experiments using this system have also demonstrated, in agreement with published literature, that many antibiotics, other heavy metals and chemicals increase the toxicity of mercury and thimerosal (ethyl mercury). Additionally, in this same system the female hormone estrogen decreases thimerosal's toxic effects. In contrast, the male hormone testosterone greatly increases the toxicity. This may explain the 4 to 1 ratio of boys to girls that become autistic and the observation that boys represent the vast majority of the severe cases of autism. "---Boyd Haley, Ph.D. (Testimony Before the House Government Reform Committee)

"Also, it's not only those children, but those who are on antibiotics are much more susceptible to all types of mercury toxicity, because antibiotics have been shown in experiments with rats to prevent the excretion of mercury. So, it builds up in the bodies of these children.....The same thing with diets: milk diets increase the retention of mercury in the bodies of children....the diet, the antibiotics and what we call synergistic toxicity of the exposure to other heavy metals, which is rampant in this country. Interview of Dr. Boyd E. Haley by Teri Small

Both ampicillin and tetracycline have been shown to enhance the neuron-killing effect of thimerosal, perhaps by enhancing its delivery to specific sites....Other heavy metals (Pb, Cd, Zn). Lead plus mercury has an effect 50 times that predicted from simply adding the individual effects. More on Thimerosal & things that synergistically increase the toxicity

Although ingredients like aluminum and mercury are toxic on their own, when they are included in vaccines they are rendered completely harmless. We do not understand how or why this is but it is undisputed fact.

Dr. Penny Proffet
Vaccine Marketing Specialist

Lies

2012 Final Pertussis Surveillance Report

Incidence of Reported Pertussis, By State

	Incidence (per 100,000)	No. of Cases
ALABAMA	4.4	212
ALASKA	48.3	353
ARIZONA	17.2	1130
ARKANSAS	8.4	248
CALIFORNIA	2.1	795
COLORADO	28.8	1494
CONNECTICUT	5.1	182
DELAWARE	6.2	57
D.C.	4.1	26
FLORIDA	2.3	575
GEORGIA	3.2	318
HAWAII	5.2	73
IDAHO	14.7	235
ILLINOIS	15.7	2026
INDIANA	6.8	441
IOWA	56.5	1736
KANSAS	30.7	887
KENTUCKY	15.2	666
LOUISIANA	1.6	72
MAINE	55.5	737
MARYLAND	6.3	369
MASSACHUSETTS	9.8	648
MICHIGAN	8.6	845
MINNESOTA	77.0	4142
MISSISSIPPI	2.6	77
MISSOURI	13.5	815
MONTANA	54.6	549
NEBRASKA	12.9	240
NEVADA	4.1	112
NEW HAMPSHIRE	20.4	269
NEW JERSEY	15.7	1395
NEW MEXICO	44.3	924
NEW YORK	24.2	2715
NEW YORK CITY	5.5	456
NORTH CAROLINA	6.3	612
NORTH DAKOTA	30.6	214
OHIO	7.7	893
OKLAHOMA	4.0	154
OREGON	23.2	906
PENNSYLVANIA	15.2	1945
RHODE ISLAND	10.8	113
SOUTH CAROLINA	4.7	224
SOUTH DAKOTA	8.4	70
TENNESSEE	4.7	305
TEXAS	8.5	2218
UTAH	55.7	1591
VERMONT	103.0	645
VIRGINIA	7.6	625
WASHINGTON	71.3	4916
WEST VIRGINIA	4.6	85
WISCONSIN	120.2	6880
WYOMING	10.8	62
TOTAL	**15.4**	**48,277**

Source: Meningitis and Vaccine Preventable Diseases Branch, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, at 404-639-3158

Weeks 1-52, 2012

Notice to Readers:
Final 2012 Reports of Notifiable Diseases

August 23, 2013 / 62(33)

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6233a6.htm?s_cid=mm6233a6_w

Reported Cases: 2011 and 2012

Weeks 1-52, 2011 18,719
Weeks 1-52, 2012 48,277

Reported Case Profiles, 2012 By Age, Weeks 1-52

Age	No. of Cases	%	Age Inc /100,000
< 1 yr	4994	10.3	126.7
1-6 yrs	8280	17.2	34.1
7-10 yrs	9532	19.8	58.5
11-19 yrs	14440	29.9	38.0
20+ yrs	10436	21.6	4.5
Unknown	595	(1.2)	N/A
Total	**48277**	**100.0**	**15.2***

*Total age incidence per 100,000 calculated from 47,682 cases with age reported.

2012 Reported Pertussis Deaths

Age	Deaths*†
Infants, aged < 3 months:	**15**
Infants, aged 3-11 months:	**1**
Children, 1-4 years:	**2**
Adults, aged 55+ years:	**2**
Total	**20**

*Deaths reported through NNDSS to CDC.
†11 of the 20 deaths were male.

DTaP Vaccination History of Pertussis Cases

Age	Unk	0 doses	1-2 doses	3+ doses	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No.
6-11 mo	320(26)	131(11)	230(19)	539(44)	1220
1-4 yrs	1613(28)	540(9)	233(4)	3404(59)	5790
5-6 yrs	630(25)	180(7)	60(3)	1620(65)	2490
Total*	**2563(27)**	**851(9)**	**523(5)**	**5563(59)**	**9500**

*Percent calculated from total cases aged 6 months to 6 years, n=9,500.

2013 Final Pertussis Surveillance Report

Incidence of Reported Pertussis, By State

	Incidence (per 100,000)	No. of Cases
ALABAMA	4.1	200
ALASKA	43.1	317
ARIZONA	21.7	1440
ARKANSAS	15.8	466
CALIFORNIA	5.3	2011
COLORADO	26.9	1418
CONNECTICUT	1.7	61
DELAWARE	6.2	57
D.C.	6.5	42
FLORIDA	3.7	732
GEORGIA	3.2	317
HAWAII	3.6	50
IDAHO	14.7	237
ILLINOIS	6.1	785
INDIANA	9.4	616
IOWA	10.0	308
KANSAS	14.0	405
KENTUCKY	8.7	383
LOUISIANA	4.6	214
MAINE	25.0	332
MARYLAND	3.6	213
MASSACHUSETTS	5.2	349
MICHIGAN	10.0	988
MINNESOTA	16.0	865
MISSISSIPPI	2.0	59
MISSOURI	9.3	559
MONTANA	65.3	663
NEBRASKA	12.4	232
NEVADA	6.5	181
NEW HAMPSHIRE	9.9	131
NEW JERSEY	4.6	406
NEW MEXICO	29.4	613
NEW YORK	6.4	722
NEW YORK CITY	1.7	142
NORTH CAROLINA	5.9	583
NORTH DAKOTA	12.0	87
OHIO	12.7	1464
OKLAHOMA	6.6	255
OREGON	12.4	486
PENNSYLVANIA	5.0	633
RHODE ISLAND	15.2	160
SOUTH CAROLINA	4.6	218
SOUTH DAKOTA	7.9	67
TENNESSEE	3.8	247
TEXAS	15.1	3985
UTAH	45.1	1308
VERMONT	18.2	114
VIRGINIA	5.1	418
WASHINGTON	10.7	748
WEST VIRGINIA	1.0	19
WISCONSIN	21.9	1258
WYOMING	12.9	75
TOTAL	9.1	28,639

Source: Meningitis and Vaccine Preventable Diseases Branch, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, at 404-639-3158

Weeks 1-52, 2013 CDC/NCIRD/DBD/MVPDB

Notice to Readers:
Final 2013 Reports of Notifiable Diseases

August 15, 2014 / 63(32)
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a6.htm?s_cid=mm6332a6_w

Reported Cases: 2012 and 2013

Weeks 1-52, 2012: 48,277 Weeks 1-52, 2013: 28,639

Reported Case Profiles, By Age

Age	No. of Cases	%	Age Inc /100,000
< 6 mos	3,159	(11.0)	160.3
6-11 mos	892	(3.1)	45.3
1-6 yrs	5,343	(18.7)	22.1
7-10 yrs	5,014	(17.5)	30.6
11-19 yrs	8,026	(28.0)	21.3
20+ yrs	6,110	(21.3)	2.6
Unknown	95	(0.4)	N/A
Total	**28,639**	**(100.0)**	**9.0***

*Total age incidence per 100,000 calculated from 28,544 cases with age reported.

Reported Pertussis Deaths

Age	Deaths*†
Infants, aged < 3 mos	12
Infants, aged 3-11 mos	0
Children, aged 1-4 yrs	1
Adults, aged 55+ yrs	0
Total	**13**

*Deaths reported through NNDSS to CDC.
†7 of the13 deaths were female.

DTaP Vaccination History of Pertussis Cases

Age	Unknown	0 doses	1-2 doses	3+ doses	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No.
6-11 mos	276 (31)	95 (11)	179 (20)	342 (38)	892
1-4 yrs	1,317 (34)	445 (12)	189 (5)	1,874 (49)	3,825
5-6 yrs	478 (32)	170 (11)	48 (3)	822 (54)	1,518
Total*	**2,071 (33)**	**710 (11)**	**416 (7)**	**3,038 (49)**	**6,235**

*Percent calculated from total cases aged 6 months to 6 years, n=6,235.

2014 Final Pertussis Surveillance Report

Incidence of Reported Pertussis, By State

	Incidence (per 100,000)	No. of Cases
ALABAMA	5.9	285
ALASKA	23.0	169
ARIZONA	7.8	517
ARKANSAS	9.7	286
CALIFORNIA	22.8	8,723
COLORADO	24.3	1,282
CONNECTICUT	2.8	100
DELAWARE	22.1	205
D.C.	3.4	22
FLORIDA	3.7	719
GEORGIA	4.1	408
HAWAII	2.7	38
IDAHO	22.8	367
ILLINOIS	5.9	764
INDIANA	7.5	492
IOWA	7.2	222
KANSAS	14.9	431
KENTUCKY	6.8	300
LOUISIANA	2.0	90
MAINE	41.9	557
MARYLAND	3.4	203
MASSACHUSETTS	4.6	308
MICHIGAN	14.4	1424
MINNESOTA	17.5	950
MISSISSIPPI	2.3	68
MISSOURI	9.2	558
MONTANA	48.7	494
NEBRASKA	19.6	366
NEVADA	5.2	144
NEW HAMPSHIRE	6.4	84
NEW JERSEY	4.4	387
NEW MEXICO	17.7	370
NEW YORK	8.0	901
NEW YORK CITY	1.4	122
NORTH CAROLINA	7.6	752
NORTH DAKOTA	7.2	52
OHIO	12.6	1,463
OKLAHOMA	3.7	142
OREGON	10.6	416
PENNSYLVANIA	6.4	813
RHODE ISLAND	10.3	108
SOUTH CAROLINA	3.6	170
SOUTH DAKOTA	13.0	110
TENNESSEE	5.1	330
TEXAS	9.7	2,576
UTAH	32.4	940
VERMONT	6.7	42
VIRGINIA	6.1	505
WASHINGTON	8.6	601
WEST VIRGINIA	1.0	18
WISCONSIN	26.4	1,515
WYOMING	10.6	62
TOTAL	10.3	32,971

Source: Meningitis and Vaccine Preventable Diseases Branch, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, at 404-639-3158

Weeks 1-53, 2014 CDC/NCIRD/DBD/MVPDB

Notice to Readers:
Final 2014 Reports of Notifiable Diseases

September 18, 2015 / 64(36)
www.cdc.gov/mmwr/preview/mmwrhtml/mm6436a8.htm?s_cid=mm6436a8_w

Reported Cases: 2013 and 2014

Weeks 1-52, 2013: 28,639 Weeks 1-53, 2014: 32,971

Reported Case Profiles, By Age

Age	No. of Cases	%	Age Inc /100,000
< 6 mos	3,330	(10.1)	169.0
6-11 mos	875	(2.7)	44.4
1-6 yrs	6,082	(18.5)	25.1
7-10 yrs	5,576	(16.9)	34.0
11-19 yrs	11,159	(33.8)	29.6
20+ yrs	5,839	(17.7)	2.2
Unknown	110	(0.3)	N/A
Total	**32,971**	**(100.0)**	**10.3***

*Total age incidence per 100,000 calculated from 32,861 cases with age reported.

Reported Pertussis Deaths

Age	Deaths*†
Infants, aged < 3 mos	8
Infants, aged 3-11 mos	1
Children, aged 1-4 yrs	2
Adults, aged 55+ yrs	2
Total	**13**

*Deaths reported through NNDSS to CDC.
†9 of the 13 deaths were male.

DTaP Vaccination History of Pertussis Cases

Age	Unknown	0 doses	1-2 doses	3+ doses	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No.
6-11 mos	282(32)	76(9)	190(22)	327(37)	875
1-4 yrs	2,099(48)	341(8)	153(3)	1,810(41)	4,403
5-6 yrs	691(41)	139(8)	36(2)	813(49)	1,679
Total*	**3,072(44)**	**556(8)**	**379(6)**	**2,950(42)**	**6,957**

*Percent calculated from total cases aged 6 months to 6 years, n=6,957.

National Center for Immunization and Respiratory Diseases
Division of Bacterial Diseases

2015 Final Pertussis Surveillance Report

Incidence of Reported Pertussis, By State

	Incidence (per 100,000)	No. of Cases
ALABAMA	3.3	160
ALASKA	14.2	105
ARIZONA	8.5	580
ARKANSAS	2.0	59
CALIFORNIA	9.2	3597
COLORADO	16.7	913
CONNECTICUT	2.1	74
DELAWARE	2.1	20
D.C.	1.6	11
FLORIDA	1.7	339
GEORGIA	2.4	244
HAWAII	3.3	47
IDAHO	11.7	194
ILLINOIS	5.6	718
INDIANA	3.4	223
IOWA	5.5	173
KANSAS	14.5	421
KENTUCKY	4.2	184
LOUISIANA	1.2	55
MAINE	21.1	281
MARYLAND	2.2	134
MASSACHUSETTS	3.7	251
MICHIGAN	4.8	475
MINNESOTA	10.9	598
MISSISSIPPI	0.4	12
MISSOURI	4.4	266
MONTANA	22.3	230
NEBRASKA	27.2	515
NEVADA	3.9	112
NEW HAMPSHIRE	3.1	41
NEW JERSEY	5.5	491
NEW MEXICO	11.6	242
NEW YORK	5.5	616
NEW YORK CITY	5.1	436
NORTH CAROLINA	4.4	443
NORTH DAKOTA	5.7	43
OHIO	7.1	827
OKLAHOMA	2.3	88
OREGON	14.6	589
PENNSYLVANIA	6.9	888
RHODE ISLAND	2.6	27
SOUTH CAROLINA	3.5	171
SOUTH DAKOTA	1.2	17
TENNESSEE	2.8	186
TEXAS	5.5	1504
UTAH	16.6	498
VERMONT	7.8	49
VIRGINIA	4.4	369
WASHINGTON	19.3	1382
WEST VIRGINIA	4.3	80
WISCONSIN	13.1	755
WYOMING	5.0	29
TOTAL	6.5	20762

Source: Meningitis and Vaccine Preventable Diseases Branch, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, at 404-639-3158

Weeks 1-52, 2015 CDC/NCIRD-DBD-MVPDB

Notice to Readers:
Final 2015 Reports of Notifiable Diseases

November 25, 2016 / 65(46)
https://www.cdc.gov/mmwr/volumes/65/wr/mm6546a9.htm?s_cid=mm6546a9

Reported Cases: 2014 and 2015

Weeks 1-53, 2014: 32,971 Weeks 1-52, 2015: 20,762

Reported Case Profiles, By Age

Age	No. of Cases	%	Age Inc /100,000
< 6 mos	1,970	(9.5)	99.0
6-11 mos	739	(3.6)	37.2
1-6 yrs	3,739	(18.0)	15.6
7-10 yrs	2,892	(13.9)	17.5
11-19 yrs	6,734	(32.4)	17.9
20+ yrs	4,650	(22.4)	1.9
Unknown	38	(0.2)	N/A
Total	**20,762**	**(100.0)**	**6.5***

*Total age incidence per 100,000 calculated from 20,724 cases with age reported.

Reported Pertussis Deaths

Age	Deaths*†
Infants, aged < 1 yr:	3
Persons, aged ≥ 1 yr:	3
Total	**6**

†4 of the 6 deaths were female.

DTaP Vaccination History of Pertussis Cases

Age	Unknown	0 doses	1-2 doses	3+ doses	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No.
6-11 mos	317(43)	60(8)	120(16)	242(33)	739
1-4 yrs	1,083(39)	269(10)	112(4)	1,321(47)	2,785
5-6 yrs	374(39)	78(8)	27(3)	475(50)	954
Total*	**1,774(40)**	**407(9)**	**259(6)**	**2,038(45)**	**4,478**

*Percent calculated from total cases aged 6 months to 6 years, n=4,478.

2016 Final Pertussis Surveillance Report

Reported Pertussis Incidence and Cases

STATES	Incidence (per 100,000)	No. of Cases
ALABAMA	3.62	176
ALASKA	21.30	158
ARIZONA	4.14	287
ARKANSAS	2.31	69
CALIFORNIA	3.84	1509
COLORADO	12.92	716
CONNECTICUT	2.68	96
DELAWARE	1.58	15
D.C.	1.61	11
FLORIDA	1.62	334
GEORGIA	1.84	190
HAWAII	3.85	55
IDAHO	4.93	83
ILLINOIS	8.08	1034
INDIANA	2.68	178
IOWA	5.14	161
KANSAS	5.54	161
KENTUCKY	10.44	463
LOUISIANA	1.39	65
MAINE	19.45	259
MARYLAND	2.24	135
MASSACHUSETTS	2.97	202
MICHIGAN	4.19	416
MINNESOTA	18.39	1015
MISSISSIPPI	0.20	6
MISSOURI	5.86	357
MONTANA	2.01	21
NEBRASKA	7.97	152
NEVADA	1.22	36
NEW HAMPSHIRE	4.50	60
NEW JERSEY	6.33	566
NEW MEXICO	7.69	160
NEW YORK	5.92	663
NEW YORK CITY	3.56	304
NORTH CAROLINA	2.92	296
NORTH DAKOTA	5.81	44
OHIO	8.62	1001
OKLAHOMA	4.69	184
OREGON	4.69	192
PENNSYLVANIA	12.45	1591
RHODE ISLAND	8.61	91
SOUTH CAROLINA	2.66	132
SOUTH DAKOTA	1.62	14
TENNESSEE	2.10	140
TEXAS	4.62	1286
UTAH	8.69	265
VERMONT	46.43	290
VIRGINIA	2.67	225
WASHINGTON	8.48	618
WEST VIRGINIA	1.42	26
WISCONSIN	24.97	1443
WYOMING	3.59	21
TOTAL	**5.54**	**17,972**

Source: NCHS Bridged Race Intercensal Population Estimate for 2016

Weeks 1-52, 2016 CDC/NCIRD/DBD/MVPDB

Notice to Readers:
Final 2016 Reports of Notifiable Diseases

January 5, 2018 / 66 (52)
https://www.cdc.gov/mmwr/volumes/66/wr/mm6652md.htm?s_cid=mm6652md_w

Reported Pertussis Cases

2015: **20,762** 2016: **17,972**

Reported Pertussis Cases and Percent Hospitalization by Age Group

Age	No. of Cases (% of total)	Age Inc /100,000	% Hospitalized by age**
< 6 mos	1407 (7.8)	70.9	44.3
6-11 mos	634 (3.5)	31.9	11.7
1-6 yrs	3279 (18.3)	13.7	2.7
7-10 yrs	2450 (13.7)	14.8	1.5
11-19 yrs	6135 (34.1)	16.3	0.9
20+ yrs	4046 (22.5)	1.7	7.8
Unknown Age	21 (0.1)	N/A	N/A
Total	**17,972 (100)**	**5.6***	**6.7**

*Total age incidence per 100,000 calculated from 17,951 cases with age reported.
**Age-specific proportion of cases that were hospitalized, calculated from those with a known hospitalization status.

Reported Pertussis Deaths

Age	Deaths*
Cases, aged < 1 yr	6
Cases, aged ≥ 1 yr	1
Total	**7**

*4 of the 7 deaths were female.

Reported DTaP Vaccine Status of Children with Pertussis, Ages 6 months through 6 years

Age	Vaccine History Unknown	Unvaccinated	Unvaccinated (1-2 doses)	Completed Primary DTaP Series (3+ doses)	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No.
6-11 mo	259 (41)	52 (8)	91 (14)	232 (37)	634
1-4 yrs	1003 (41)	226 (9)	103 (4)	1003 (41)	2436
5-6 yrs	286 (34)	61(7)	24 (3)	472 (56)	843
Total*	**1548 (40)**	**339 (9)**	**218 (5)**	**1808 (46)**	**3913**

*Percent calculated from total cases aged 6 months to 6 years, n=3,913

Footnote: This table reflects reported vaccination history of pertussis cases aged 6 months through 6 years. CDC recommends all children receive at least 3 doses of DTaP by age 6 months. DTaP coverage in the United States is very high. Over 95% of all children 19-35 months of age have received at least 3 doses of DTaP. This table illustrates a similar trend among the pertussis cases reported during 2016—the majority have received at least 3 doses of DTaP. Because protection from DTaP wanes over time, even children who are up to date with their pertussis vaccines may contract pertussis. Unvaccinated children are more likely to contract pertussis and have more severe disease than those who are fully vaccinated (see references). Note: surveillance data have limitations and are often incomplete; more than a third of pertussis cases in this table have unknown pertussis vaccination history. You cannot use these data to interpret vaccine effectiveness or to assess risk, as the data are incomplete and there is no healthy comparison group.

National Center for Immunization and Respiratory Diseases
Division of Bacterial Diseases

2017 Final Pertussis Surveillance Report

Reported Pertussis Incidence and Cases

STATES	Incidence (per 100,000)	No. of Cases
ALABAMA	4.74	231
ALASKA	7.98	59
ARIZONA	5.99	420
ARKANSAS	7.49	225
CALIFORNIA	6.52	2576
COLORADO	11.97	671
CONNECTICUT	2.12	76
DELAWARE	0.94	9
D.C.	3.17	22
FLORIDA	1.71	358
GEORGIA	2.24	234
HAWAII	2.73	39
IDAHO	5.18	89
ILLINOIS	5.38	689
INDIANA	5.73	382
IOWA	5.12	161
KANSAS	6.97	203
KENTUCKY	10.08	449
LOUISIANA	1.86	87
MAINE	30.69	410
MARYLAND	1.77	107
MASSACHUSETTS	5.95	408
MICHIGAN	7.47	744
MINNESOTA	13.09	730
MISSISSIPPI	1.17	35
MISSOURI	6.74	412
MONTANA	10.09	106
NEBRASKA	5.10	98
NEVADA	3.07	92
NEW HAMPSHIRE	5.59	75
NEW JERSEY	5.16	465
NEW MEXICO	9.43	197
NEW YORK	4.84	543
NEW YORK CITY	1.72	148
NORTH CAROLINA	4.16	427
NORTH DAKOTA	6.62	50
OHIO	7.42	865
OKLAHOMA	5.27	207
OREGON	5.91	245
PENNSYLVANIA	7.69	985
RHODE ISLAND	7.93	84
SOUTH CAROLINA	3.80	191
SOUTH DAKOTA	1.03	9
TENNESSEE	3.31	222
TEXAS	6.24	1765
UTAH	14.38	446
VERMONT	17.32	108
VIRGINIA	3.49	296
WASHINGTON	9.99	740
WEST VIRGINIA	0.72	13
WISCONSIN	13.01	754
WYOMING	3.11	18
TOTAL	**5.83**	**18,975**

Source: NCHS Bridged Race Intercensal Population Estimate for 2017

Weeks 1-52, 2017 CDC/NCIRD/DBD/MVPDB

Notice to Readers:
Final 2017 Reports of Notifiable Diseases

https://wonder.cdc.gov/nndss/nndss_annual_tables_menu.asp

Reported Pertussis Cases

2016: **17,972** 2017: **18,975**

Reported Pertussis Cases and Percent Hospitalization by Age Group

Age	No. of Cases (% of total)	Age Inc /100,000	% Hospitalized by age**
< 6 mos	1545 (8.1)	78.4	43.3
6-11 mos	731 (3.9)	37.1	10.8
1-6 yrs	3646 (19.2)	15.2	3.4
7-10 yrs	2597 (13.7)	15.8	1.1
11-19 yrs	6348 (33.4)	16.8	1.0
20+ yrs	4080 (21.5)	1.7	8.8
Unknown Age	28 (0.2)	N/A	N/A
Total	**18,975 (100)**	**5.8***	**6.9**

*Total age incidence per 100,000 calculated from 18,947 cases with age reported.
**Age-specific proportion of cases that were hospitalized, calculated from those with a known hospitalization status.

Reported Pertussis Deaths

Age	Deaths*
Cases, aged < 1 yr	9
Cases, aged ≥ 1 yr	4
Total	**13**

*Deaths reported through NNDSS to CDC. Confirmation of non-infant deaths is ongoing and may result in changes to the final pertussis-related death count for 2017
†6 of the 13 deaths were female

Reported DTaP Vaccine Status of Children with Pertussis, Ages 6 months through 6 years

Age	Vaccine History Unknown	Unvaccinated	Undervaccinated (1-2 doses)	Completed Primary DTaP Series (3+ doses)	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No.
6-11 mo	290 (40)	67 (9)	119 (16)	255 (35)	731
1-4 yrs	1137 (41)	281 (10)	122 (4)	1228 (44)	2768
5-6 yrs	306 (35)	82 (9)	24 (3)	466 (53)	878
Total*	**1733 (40)**	**430 (10)**	**265 (6)**	**1949 (44)**	**4377**

†Percent calculated from total cases aged 6 months to 6 years, n=4,377.

Footnote: This table reflects reported vaccination history of pertussis cases aged 6 months through 6 years. CDC recommends all children receive at least 3 doses of DTaP by age 6 months. DTaP coverage in the United States is very high. Over 95% of all children 19-35 months of age have received at least 3 doses of DTaP. This table illustrates a similar trend among the pertussis cases reported during 2017—the majority have received at least 3 doses of DTaP. Because protection from DTaP wanes over time, even children who are up to date with their pertussis vaccines may contract pertussis. Unvaccinated children are more likely to contract pertussis and have more severe disease than those who are fully vaccinated (see references). Note: surveillance data have limitations and are often incomplete; more than a third of pertussis cases in this table have unknown pertussis vaccination history. You cannot use these data to interpret vaccine effectiveness or to assess risk, as the data are incomplete and there is no healthy comparison group.

National Center for Immunization and Respiratory Diseases
Division of Bacterial Diseases

2018 Provisional Pertussis Surveillance Report

Reported Pertussis Incidence and Cases

STATES	Incidence (per 100,000)	No. of Cases
ALABAMA	4.02	196
ALASKA	12.30	91
ARIZONA	3.25	228
ARKANSAS	2.30	69
CALIFORNIA	4.14	1638
COLORADO	10.65	597
CONNECTICUT	1.14	41
DELAWARE	16.01	154
D.C.	1.44	10
FLORIDA	1.60	336
GEORGIA	1.28	134
HAWAII	2.10	30
IDAHO	22.66	389
ILLINOIS	2.48	318
INDIANA	2.59	173
IOWA	4.32	136
KANSAS	4.19	122
KENTUCKY	4.33	193
LOUISIANA	2.56	120
MAINE	33.16	443
MARYLAND	1.93	117
MASSACHUSETTS	3.47	238
MICHIGAN	4.29	427
MINNESOTA	4.16	232
MISSISSIPPI	1.34	40
MISSOURI	2.75	168
MONTANA	13.52	142
NEBRASKA	8.12	156
NEVADA	1.23	37
NEW HAMPSHIRE	9.98	134
NEW JERSEY	2.25	203
NEW MEXICO	10.78	225
NEW YORK	3.07	345
NEW YORK CITY	1.82	157
NORTH CAROLINA	3.31	340
NORTH DAKOTA	6.35	48
OHIO	5.33	621
OKLAHOMA	2.04	80
OREGON	11.47	475
PENNSYLVANIA	3.37	431
RHODE ISLAND	2.93	31
SOUTH CAROLINA	3.82	192
SOUTH DAKOTA	13.68	119
TENNESSEE	1.61	108
TEXAS	3.64	1030
UTAH	8.77	272
VERMONT	5.45	34
VIRGINIA	2.60	220
WASHINGTON	6.98	517
WEST VIRGINIA	1.32	24
WISCONSIN	14.58	845
WYOMING	2.24	13
TOTAL	**4.13**	**13,439**

Source: NCHS Bridged Race Intercensal Population Estimate for 2017; 2018 estimates were not available at the time of publication.

Weeks 1-52, 2018 CDC/NCIRD/DBD/MVPDB

Notice to Readers:
Provisional 2018 Reports of Notifiable Diseases

https://wonder.cdc.gov/nndss/static/2018/52/2018-52-table2M.html

Reported Pertussis Cases

2017: **18,975** 2018: **13,439**

Reported Pertussis Cases and Percent Hospitalization by Age Group

Age	No. of Cases (% of total)	Age Inc /100,000	% Hospitalized by age**
< 6 mos	1127 (8.4)	57.2	42.9
6-11 mos	556 (4.1)	28.2	12.5
1-6 yrs	2671 (19.9)	11.1	2.8
7-10 yrs	1596 (11.9)	9.7	1.3
11-19 yrs	4214 (31.4)	11.2	0.9
20+ yrs	3039 (22.6)	1.2	7.4
Unknown Age	236 (1.8)	N/A	N/A
Total	**13,439 (100)**	**4.1***	**6.9**

*Total age incidence per 100,000 calculated from 13,203 cases with age reported.
**Age-specific proportion of cases that were hospitalized, calculated from those with a known hospitalization status.

Reported Pertussis Deaths

Age	Deaths*
Cases, aged < 1 yr	4
Cases, aged ≥ 1 yr	6
Total	**10**

*Deaths reported through NNDSS to CDC. Confirmation of non-infant deaths is ongoing and may result in changes to the final pertussis-related death count for 2018
†4 of the 10 deaths were female.

Reported DTaP Vaccine Status of Children with Pertussis, Ages 6 months through 6 years

Age	Vaccine History Unknown	Unvaccinated	Undervaccinated (1-2 doses)	Completed Primary DTaP Series (3+ doses)	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No.
6-11 mo	237 (43)	61 (11)	91 (16)	167 (30)	556
1-4 yrs	901 (45)	202 (10)	70 (4)	826 (41)	1999
5-6 yrs	265 (39)	67 (10)	15 (2)	325 (48)	672
Total*	**1403 (43)**	**330 (10)**	**176 (5)**	**1318 (41)**	**3227**

†Percent calculated from total cases aged 6 months to 6 years, n=3,227.

Footnote: This table reflects reported vaccination history of pertussis cases aged 6 months through 6 years. CDC recommends all children receive at least 3 doses of DTaP by age 6 months. DTaP coverage in the United States is very high. Over 95% of all children 19-35 months of age have received at least 3 doses of DTaP. This table illustrates a similar trend among the pertussis cases reported during 2017—the majority have received at least 3 doses of DTaP. Because protection from DTaP wanes over time, even children who are up to date with their pertussis vaccines may contract pertussis. Unvaccinated children are more likely to contract pertussis and have more severe disease than those who are fully vaccinated (see references). Note: surveillance data have limitations and are often incomplete; more than a third of pertussis cases in this table have unknown pertussis vaccination history. You cannot use these data to interpret vaccine effectiveness or to assess risk, as the data are incomplete and there is no healthy comparison group.

National Center for Immunization and Respiratory Diseases
Division of Bacterial Diseases

Madam Chair and House representatives,

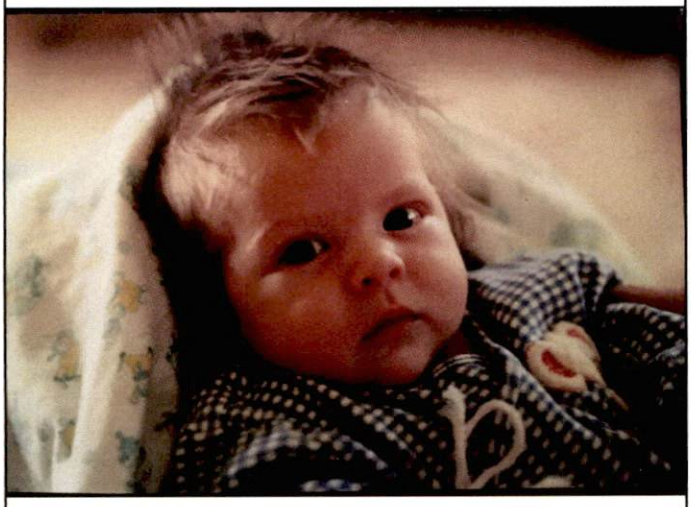
My name is Susanne Senk and I **oppose** HB 1312.

Please refer to Page 5, lines 4 through 9.
*Requires CDPHE to develop educational materials regarding **only the benefits** of immunizations and update those annually.*

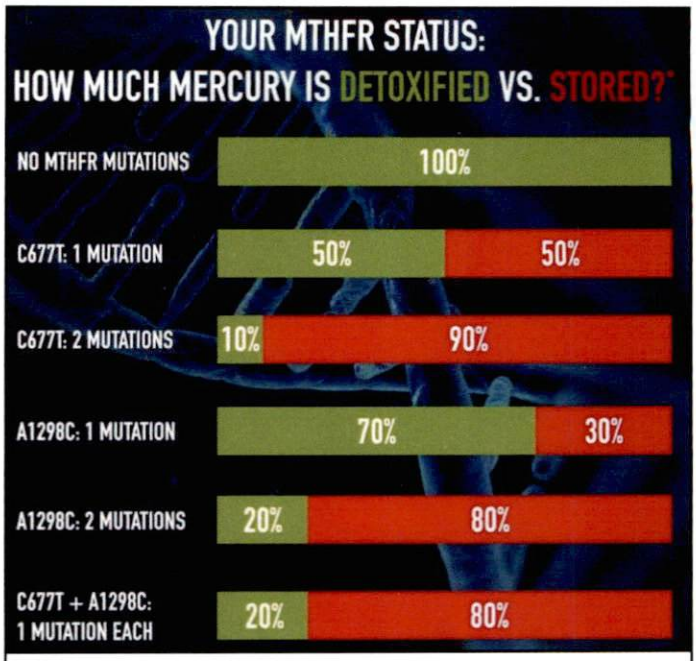
Parents must be informed of **adverse vaccine effects.** As a case in point, my 28-year-old son is **permanently mentally disabled**! He was diagnosed with **schizophrenia** at age 20. Like all parents I wanted my child to be protected and so he was fully vaccinated.
However, his body has extremely toxic levels of Mercury, Lead, and Tin, which are neurotoxins found in vaccines. In 2014, laboratory tests revealed this, and, that he was born with two (2) MTHFR/ **M**ETHYLENE**T**ETRA**H**YDRO**F**OLATE**R**EDUCTASE gene mutations. Specifically, **MTHFR C677T** and **A1298C** which impair his body of detoxification and creates a vulnerability to disease processes. His body is less tolerant of toxins such as heavy metals. This phenomenon has been termed **"epigenetics"** 40% of the world population has at least one MTHFR gene mutation. Moreover, 90% of Autistic children have it.

Please refer to Page 3, lines 4 and 5.
Save **$9.9 billion** in direct health care costs.

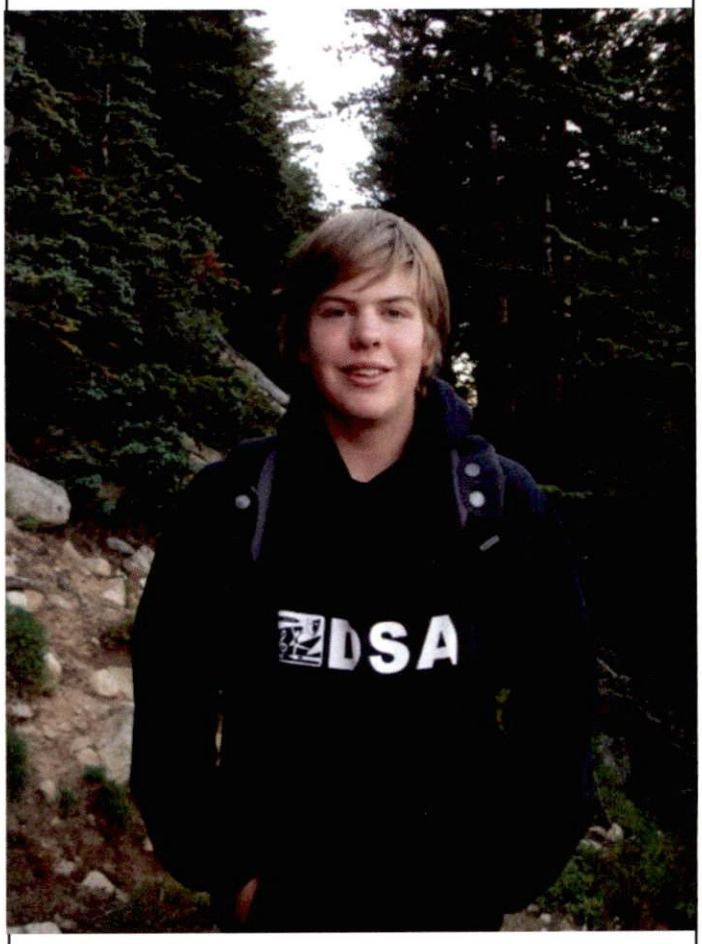
My son's care must cost in the hundreds of thousands if not **millions** of dollars. He receives help from me, Social Security and Medicaid. He lives in a Federally funded assisted living home for mentally ill adults. MHCD provides psychiatry, therapy and resources. His hospital stays between 2010 and 2016 were over 100 days and transportation was by ambulance.



My son in 1990: 6 weeks old– smart, happy and healthy development, breast fed, easy baby, slept through the night.



Neurotoxins like Mercury can penetrate the blood-brain barrier and trigger brain inflammation which can lead to Schizophrenia, Autism, Type 1 diabetes, Asthma, and a whole host of other debilitating auto-immune diseases.



My son in 2006: 16 years old–a sweetheart. Sometime after this photo was taken his behavior changed and cognitive decline presented.

2018

COMPLETE

VAERS DATA

443* (44,300) Reported Deaths

1,267* (126,700) Permanent Disabilities

619* (61,900) Life Threatening Reactions

4,414 (441,400) Hospitalizations

***Harvard Pilgrim Health Care, Inc. study showed that "Adverse events from drugs and vaccines are common, but underreported. Although 25% of ambulatory patients experience an adverse drug event, less than 0.3% of all adverse drug events and 1-13% of serious events are reported to the Food and Drug Administration (FDA)."**

The Vaccine Adverse Event Reporting System (VAERS) Results

Event Category	Events Reported	Percent (of 55,827)
Death	443	0.79%
Life Threatening	619	1.11%
Permanent Disability	1,267	2.27%
Congenital Anomaly / Birth Defect *	29	0.05%
Hospitalized	4,414	7.91%
Existing Hospitalization Prolonged	94	0.17%
Emergency Room / Office Visit **	921	1.65%
Emergency Room *	4,469	8.01%
Office Visit *	13,521	24.22%
None of the above	34,767	62.28%
Total	**60,544**	**108.45%**

Note: Submitting a report to VAERS does not mean that healthcare personnel or the vaccine caused or contributed to the adverse event (possible side effect).

*** These values are only available from VAERS 2.0 Report Form, active 06/30/2017 to present.**

**** These value are only available from VAERS-1 Report Form, active 07/01/1990 to 06/29/2017.**

Notes:

Grant Final Report

Grant ID: R18 HS 017045

Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP:VAERS)

Inclusive dates: 12/01/07 - 09/30/10

Principal Investigator:
Lazarus, Ross, MBBS, MPH, MMed, GDCompSci

Team members:
Michael Klompas, MD, MPH

Performing Organization:
Harvard Pilgrim Health Care, Inc.

Project Officer:
Steve Bernstein

Submitted to:
The Agency for Healthcare Research and Quality (AHRQ)
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Abstract

Purpose: To develop and disseminate HIT evidence and evidence-based tools to improve healthcare decision making through the use of integrated data and knowledge management.

Scope: To create a generalizable system to facilitate detection and clinician reporting of vaccine adverse events, in order to improve the safety of national vaccination programs.

Methods: Electronic medical records available from all ambulatory care encounters in a large multi-specialty practice were used. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions were evaluated for values suggestive of an adverse event.

Results: Restructuring at CDC and consequent delays in terms of decision making have made it challenging despite best efforts to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial and comparison of ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. However, Preliminary data were collected and analyzed and this initiative has been presented at a number of national symposia.

Key Words: electronic health records, vaccinations, adverse event reporting

Final Report

Purpose

This research project was funded to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS), via the following aims:

Aim 1. Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration.

Aim 2. Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS).

Aim 3. Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.

Aim 4. Distribute documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems.

Scope

Public and professional confidence in vaccination depends on reliable postmarketing surveillance systems to ensure that rare and unexpected adverse effects are rapidly identified. The goal of this project is to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS). This project is serving as an extension of the Electronic Support for Public Health (ESP) project, an automated system using electronic health record (EHR) data to detect and securely report cases of certain diseases to a local public health authority. ESP provides a ready-made platform for automatically converting clinical, laboratory, prescription, and demographic data from almost any EHR system into database tables on a completely independent server, physically located and secured by the same logical and physical security as the EHR data itself. The ESP:VAERS project developed criteria and algorithms to identify important adverse events related to vaccinations in ambulatory care EHR data, and made attempts at formatting and securely sending electronic VAERS reports directly to the Centers for Disease Control and Prevention (CDC).

Patient data were available from Epic System's Certification Commission for Health Information Technology-certified EpicCare system at all ambulatory care encounters within Atrius Health, a large multispecialty group practice with over 35 facilities. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions are evaluated for values

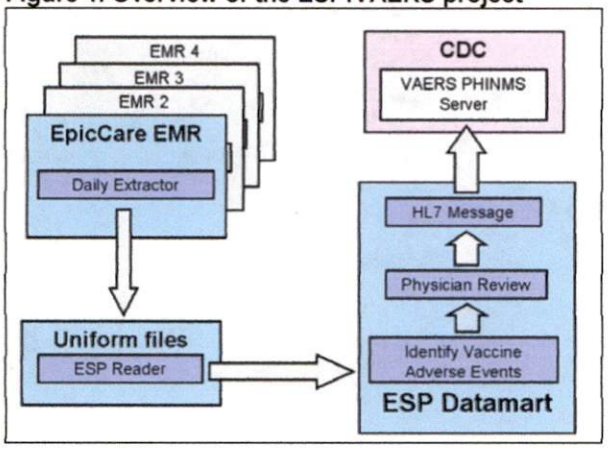
suggestive of an adverse vaccine event. When a possible adverse event was detected, it was recorded, and the appropriate clinician was to be notified electronically.

Clinicians in-basket messaging was designed to provide a preview a pre-populated report with information from the EHR about the patient, including vaccine type, lot number, and possible adverse effect, to inform their clinical judgment regarding whether they wish to send a report to VAERS. Clinicians would then have the option of adding free-text comments to pre-populated VAERS reports or to document their decision not to send a report. The CDC's Public Health Information Network Messaging System (PHIN-MS) software was installed within the facilities so that the approved reports could be securely transferred to VAERS as electronic messages in an interoperable health data exchange format using Health Level 7 (HL7).

Methods

The goal of Aim 1: *Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration*, and Aim 2: *Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS)*, was to construct the below flow of data in order to support the first two Aims:

Figure 1. Overview of the ESP:VAERS project



Existing and functioning ESP components are shown on the left, and Aims 1 and 2 on the right. ESP:VAERS flags every vaccinated patient, and prospectively accumulate that patient's diagnostic codes, laboratory tests, allergy lists, vital signs, and medication prescriptions. A main component of Aim 1 was to *Develop AE criteria to assess these parameters for new or abnormal values that might be suggestive of an adverse effect.* A reporting protocol & corresponding algorithms were developed to detect potential adverse event cases using diagnostic codes, and methods were tested to identify prescriptions or abnormal laboratory values that might be suggestive of an adverse effect. These algorithms were designed to seek both expected and unexpected adverse effects.

This reporting protocol was approved by both internal & external partners. We initially prepared a draft document describing the elements, algorithms, interval of interest after vaccination, and actions for broad classes of post-vaccination events, including those to be reported immediately without delay (such as acute anaphylactic reaction following vaccination), those never to be reported (such as routine check-ups following vaccination) and those to be reported at the discretion and with additional information from the attending physician through a feedback mechanism. The draft was then widely circulated as an initial / working draft for comment by relevant staff in the CDC and among our clinical colleagues at Atrius. In addition to review by the internal CDC Brighton Collaboration liaison, this protocol has also received review & comment via the CDC's Clinical Immunization Safety Assessment (CISA) Network.

The goal of Aim 2 was the *Development of HL7 messages code for ESP:VAERS to ensure secure transmission to CDC via PHIN-MS.* The HL7 specification describing the elements for an electronic message to be submitted to Constella, the consultants engaged by CDC for this project was implemented. Synthetic and real test data was been generated and transmitted between Harvard and Constella. However, real data transmissions of non-physician approved reports to the CDC was unable to commence, as by the end of this project, the CDC had yet to respond to multiple requests to partner for this activity.

The goal of Aim 3 was to *Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.*

We had initially planned to evaluate the system by comparing adverse event findings to those in the Vaccine Safety Datalink project—a collaborative effort between CDC's Immunization Safety Office and eight large managed care organizations. Through a randomized trial, we would also test the hypothesis that the combination of secure, computer-assisted, clinician-approved, adverse event detection, and automated electronic reporting will substantially increase the number, completeness, validity, and timeliness of physician-approved case reports to VAERS compared to the existing spontaneous reporting system; however, due to restructuring at CDC and consequent delays in terms of decision making, it became impossible to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial, and compare ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. Therefore, the components under this particular Aim were not achieved.

Aim 4 *Distribution of documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems* has been successfully completed. Functioning source code is available to share under an approved open source license. ESP:VAERS source code is available as part of the ESP source code distribution. It is licensed under the LGPL, an open source license compatible with commercial use. We have added the ESP:VAERS code, HL7 and other specifications and documentation to the existing ESP web documentation and distribution resource center http://esphealth.org, specifically, the Subversion repository available at:
http://esphealth.org/trac/ESP/wiki/ESPVAERS.

Results

Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions (2.6 percent of vaccinations) were identified. This is an average of 890 possible events, an average of 1.3 events per clinician, per month. These data were presented at the 2009 AMIA conference.

In addition, ESP:VAERS investigators participated on a panel to explore the perspective of clinicians, electronic health record (EHR) vendors, the pharmaceutical industry, and the FDA towards systems that use proactive, automated adverse event reporting.

Adverse events from drugs and vaccines are common, but underreported. Although 25% of ambulatory patients experience an adverse drug event, less than 0.3% of all adverse drug events and 1-13% of serious events are reported to the Food and Drug Administration (FDA). Likewise, fewer than 1% of vaccine adverse events are reported. Low reporting rates preclude or slow the identification of "problem" drugs and vaccines that endanger public health. New surveillance methods for drug and vaccine adverse effects are needed. Barriers to reporting include a lack of clinician awareness, uncertainty about when and what to report, as well as the burdens of reporting: reporting is not part of clinicians' usual workflow, takes time, and is duplicative. Proactive, spontaneous, automated adverse event reporting imbedded within EHRs and other information systems has the potential to speed the identification of problems with new drugs and more careful quantification of the risks of older drugs.

Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed with testing and evaluation.

Inclusion of AHRQ Priority Populations

The focus of our project was the Atrius Health (formerly HealthOne) provider & patient community. This community serves several AHRQ inclusion populations, specifically low-income and minority populations in primarily urban settings.

Atruis currently employs approximately 700 physicians to serve 500,000 patients at more than 18 office sites spread throughout the greater Metropolitan Boston area. The majority of Atruis physicians are primary care internal medicine physicians or pediatricians but the network also includes physicians from every major specialty.

The entire adult and pediatric population served by Atruis was included in our adverse event surveillance system (ESP:VAERS). Atruis serves a full spectrum of patients that reflects the broad diversity of Eastern Massachusetts. A recent analysis suggests that the population served by Atruis is 56% female, 16.6% African American, 4% Hispanic. The prevalence of type 2 diabetes in the adult population is 5.7%. About a quarter of the Atruis population is under age 18.

List of Publications and Products

ESP:VAERS [source code available as part of the ESP source code distribution]. Licensed under the GNU Lesser General Public License (LGPL), an open source license compatible with commercial use. Freely available under an approved open source license at: http://esphealth.org.

Lazarus, R, Klompas M, Hou X, Campion FX, Dunn J, Platt R. Automated Electronic Detection & Reporting of Adverse Events Following Vaccination: ESP:VAERS. The CDC Vaccine Safety Datalink (VSD) Annual Meeting. Atlanta, GA; April, 2008.

Lazarus R, Klompas M Automated vaccine adverse event detection and reporting from electronic medical records. CDC Public Health Informatics Network (PHIN) Conference August 27, 2008.

Klompas M, Lazarus R ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 17th.

Lazarus R, Klompas M, Kruskal B, Platt R Temporal patterns of fever following immunization in ambulatory care data identified by ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

Linder J, Klompas M, Cass B, et al. Spontaneous Electronic Adverse Event Reporting: Perspectives from Clinicians, EHR Vendors, Biopharma, and the FDA. Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

3.1.6.2 USA

The first measles vaccines, both an inactivated and a live attenuated vaccine (Edmonston B strain), were licensed in 1963. The inactivated vaccine was withdrawn in 1967. The original Edmonston B vaccine was withdrawn in 1975. The live, further attenuated Schwarz strain was first introduced in 1965 but also is no longer used. Another live, further attenuated strain vaccine (Edmonston-Enders strain) was licensed in 1968 (CDC 2015, p. 217).

The average death rate from measles was 10.02 per 100,000 inhabitants in the 1900–1904 period. It reached its peak in the 1916–1918 period, when it was 12.1. Before the introduction of vaccination (1958–1963), the average death rate dropped to 0.24. This means that there was a **97.6% decline** in mortality from measles in the population compared to the initial period and a **98.01% decline** in mortality compared to the peak period. The mortality was reduced **by 42 times** before the introduction of vaccination. It is thus clear that **vaccination cannot take any credit at all** for the reduction of measles deaths. To claim otherwise is to **deliberately lie**.

Source of the data: Federal Security Agency, 1947; U.S. Department of Health, editions 1964–2002. For more detailed information see *Graph 10* and *Appendix 2: Table 38*.

Table 7: Measles – number of deaths per 100,000 persons in a specific category – USA

Measles – number of deaths per 100,000 persons in a specific category – USA						
	under 1 year of age		1–4 years of age		under 5 years of age	
year	a	b	a	b	a	b
1850	86.11	**97.43%**	55.68	**97.55%**	30.63	**94.99%**
1860	81.39	**97.28%**	52.53	**97.40%**	58.1	**97.35%**
1870	170.02	**98.70%**	104.07	**98.69%**	117.23	**98.69%**
1880	138.33	**98.40%**	63.4	**97.85%**	79.09	**98.06%**
1890	128.04	**98.27%**	61.34	**97.77%**	74.03	**97.92%**
1900	156.79	**98.59%**	75.02	**98.18%**	92.12	**98.33%**
1958 – 1962	*2.20*	*	*1.36*	*	*1.53*	*

Source of the data: United States Census (1855 : 17-20, 35); U.S. Department of the Interior (1866 : xxxvi, 48-55), (1872 : 18-21, 560-574), (1882 : 43-53, 548), (1894 : 15-23), (1897 : 2-5), (1902 : 228-235), Federal Security Agency, 1947; U.S. Department of Health, editions 1964-2002. The first measles vaccines, both an inactivated and a live attenuated vaccine (Edmonston B strain), were licensed in 1963 (CDC, 2015 : 217).

deaths" (UNICEF, December 2014, p. 2).

Measles – number of deaths per 100,000 persons in a specific category – USA								
	5–9 years of age		10–14 years of age		under 15 years		population	
year	a	b	a	b	a	b	a	b
1850							12.86	**98.11%**
1860							12.41	**98.04%**
1870	19.86	**97.82%**	9.36	**99.05%**	52.06	**98.60%**	23.96	**98.98%**
1880	12.08	**96.42%**	6.0	**98.53%**	34.51	**97.89%**	16.09	**98.49%**
1890	11.51	**96.24%**	6.03	**98.54%**	32.36	**97.75%**	14.78	**98.36%**
1900	12.49	**96.54%**	6.81	**98.70%**	38.69	**98.12%**	16.86	**98.56%**
1958 – 1962	*0.43*	*	*0.08*	*	*0.72*	*	*0.24*	*

Source of the data: United States Census (1855 : 17-20, 35); U.S. Department of the Interior (1866 : xxxvi, 48-55), (1872 : 18-21, 560-574), (1882 : 548), (1885 : 43-53), (1894 : 15-23), (1897 : 2-5), (1902 : 228-235), Federal Security Agency, 1947; U.S. Department of Health, editions 1964-2002. The first measles vaccines, both an inactivated and a live attenuated vaccine (Edmonston B strain), were licensed in 1963 (CDC, 2015 : 217).

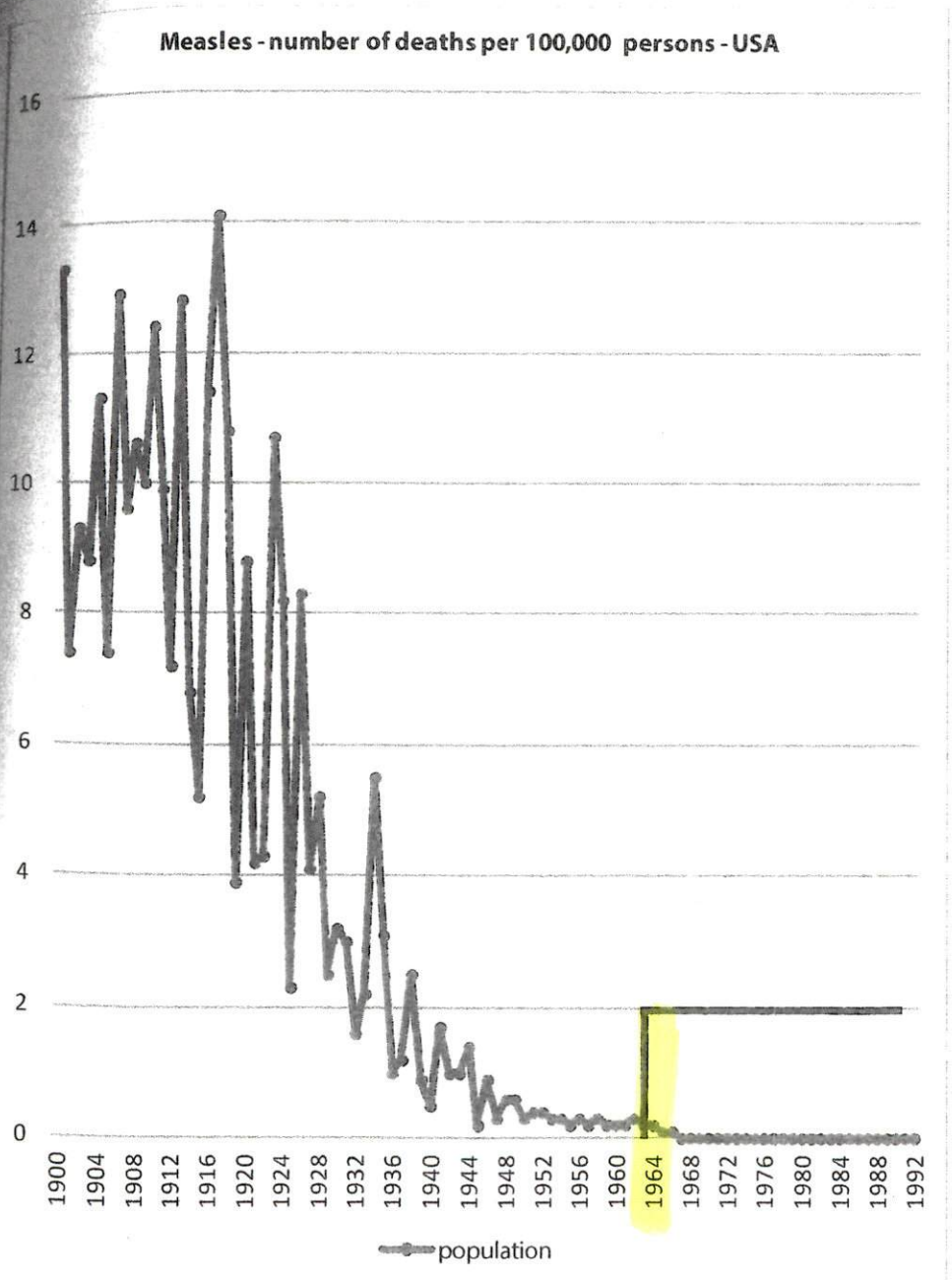
a … death rate – number of deaths per 100,000 persons
b … reduction of mortality; comparison between the death rate in the chosen period and the death rate in the 5-year period before routine/mass vaccination (1958–1962)

From the end of the 19th century to the period before the measles vaccination (1958–1963), mortality in all age-categories dropped by **96%–99%** (in most cases by more than **98%**). It is crystal clear that **measles vaccination played no role whatsoever** in the decline of mortality. It is sickening how institutions and authorities **continue to lie** about this, despite the available historical data.

3.1.6.3 Australia

Situation in Australia is the same as in the UK and in the USA. Measles mortality declined by about **98%** since the last quarter of the 19th century and before the introduction of vaccination (1964–1968). Mortality rates were reduced **by 16–67 times**. In the case of measles there is absolutely no question and no doubt that **vaccination didn't play any role** in the reduction of measles mortality. To claim that vaccination played an important role (or any role at all, for that matter) is unfounded, false, and misleading. In other words, it is **a deliberate lie**.

Graph 10: Measles – number of deaths per 100,000 persons – USA



The first measles vaccines, both an inactivated and a live attenuated vaccine (Edmonston B strain), were licensed in 1963. The inactivated vaccine was withdrawn in 1967. The original Edmonston B vaccine was withdrawn in 1975. The live, further attenuated Schwarz strain was first introduced in 1965 but also is no longer used. Another live, further attenuated strain vaccine (Edmonston-Enders strain) was licensed in 1968 (CDC, 2015 : 217). The source of the data in the graph: Federal Security Agency, 1947; Department of Health, editions 1964-2002.

Physicians for Informed Consent Finds MMR Vaccine Causes Seizures in 5,700 U.S. Children Annually

ON DECEMBER 20, 2017 • (LEAVE A COMMENT)

FOR IMMEDIATE RELEASE: December 20, 2017
Contact: pr@picphysicians.org (mailto:pr@picphysicians.org)

PHYSICIANS FOR INFORMED CONSENT (https://physiciansforinformedconsent.org/news/physicians-informed-consent-finds-mmr-vaccine-causes-seizures-5700-u-s-children-annually/)

Los Angeles, Calif. — The California-based nonprofit organization, Physicians for Informed Consent (PIC), recently reported in *The BMJ* (http://www.bmj.com/content/359/bmj.j5104/rr-13) that every year about 5,700 U.S. children suffer seizures from the measles, mumps and rubella (MMR) vaccine.

This finding is derived from results of the most statistically powered safety study ever to measure the association between MMR vaccination and febrile seizures. More than half a million children were evaluated, both vaccinated and unvaccinated, from a Danish population that is relied upon globally to examine vaccine safety. The results showed that seizures from the MMR vaccine occur in about 1 in 640 children up to two weeks following MMR vaccination. Applying this risk of seizures to the 3.64 million U.S. children vaccinated with a first dose of MMR every year results in about 5,700 annual MMR-vaccine seizures.

> "To make accurate and ethical public health decisions, the risks of a vaccine must be compared to the risks of the disease one is trying to prevent," said Dr. Shira Miller, PIC president and founder. "When considering the MMR vaccine to prevent measles, the risks of the MMR vaccine need to be compared to the risks of measles."

There is a five-fold higher risk of seizures from the MMR vaccine than seizures from measles, and a significant portion of MMR-vaccine seizures cause permanent harm. For example, 5% of febrile seizures result in epilepsy, a chronic brain disorder that leads to recurring seizures. Annually, about 300 MMR-vaccine seizures (5% of 5,700) will lead to epilepsy.

Furthermore, the Vaccine Adverse Event Reporting System (VAERS), designed to be a warning system for identifying vaccine side effects, receives only about 90 annual reports of MMR-vaccine seizures following the first dose—only 1.6% of the 5,700 MMR-vaccine seizures that actually occur. Thus, other serious vaccine adverse events from MMR, including permanent neurological harm and death, may similarly be underreported.

"In the United States, measles is generally a benign, short-term viral infection; 99.99% of measles cases fully recover," said Dr. Miller. "As it has not been proven that the MMR vaccine is safer than measles, there is insufficient evidence to demonstrate that mandatory measles mass vaccination results in a net public health benefit in the United States."

Physicians for Informed Consent is an independent 501(c)(3) nonprofit educational organization dedicated to safeguarding informed consent in vaccination. To learn more about vaccine risks vs. disease risks, read PIC's Letter to the Editor in *The BMJ*

(http://www.bmj.com/content/359/bmj.j5104/rr-13), and PIC's Measles Disease Information Statement (DIS) and Vaccine Risk Statement (VRS) at physiciansforinformedconsent.org/measles (http://physiciansforinformedconsent.org/measles).

###

SOURCE: https://physiciansforinformedconsent.org/news/physicians-informed-consent-finds-mmr-vaccine-causes-seizures-5700-u-s-children-annually/ (https://physiciansforinformedconsent.org/news/physicians-informed-consent-finds-mmr-vaccine-causes-seizures-5700-u-s children-annually/)

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NIHMSID: NIHMS107979
PMID: 18454680

Genetic Basis for Adverse Events Following Smallpox Vaccination

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INTRODUCTION

Although reactions following inoculation with vaccinia virus were common in the recent population-wide vaccination programs [1], the biological basis for these adverse events (AEs) is not well understood. The performance of two independent clinical studies of a single vaccinia vaccine at our study site afforded us the unique opportunity to assess genetic factors that might predict systemic AEs. All of the vaccinia-naïve subjects enrolled developed pock formation at the vaccination site, and a subset experienced systemic reactions including fever, rash or regional lymphadenopathy. Since poxviruses have evolved multiple mechanisms to evade host immune responses, such as targeting of primary innate immunity and manipulating intracellular signal transduction pathways [2], we questioned whether subjects encountering AEs exhibited unique genetic polymorphisms in these pathways that made them more susceptible to these reactions.

In earlier studies, we characterized humoral and cellular immune responses and outlined patterns of systemic cytokine expression following smallpox vaccination [3–8]. In the current report, we utilized data collected during two independent studies to identify stable genetic factors associated with AEs. Since many genetic association studies fail to replicate during subsequent studies, we sought to repeat the assessment on an additional study group [9,10]. Independent replication of the results of our first study with the second strengthens the plausibility of these genetic associations. An identical panel of candidate single-nucleotide polymorphisms (SNPs) was evaluated in each of the studies. Subjects with systemic AEs including fever, lymphadenopathy, or generalized acneiform rash, were compared with those who did not experience these reactions. For both studies, the data were genotypes at 1442 SNPs across at least 386 candidate genes. This investigation provides important preliminary findings in two independent data sets addressing the contribution of common genetic variants to a complex clinical phenotype, which also bears substantial importance with respect to public health.

METHODS

Study Subjects

Vaccines, study subjects, and study design for both of the clinical trials have been described previously in detail. Both trials were conducted at Vanderbilt University in the NIH-funded Vaccine and Treatment Evaluation Unit (VTEU) [4,8,11]. The first study [7] enrolled 85 healthy vaccinia-naïve adults in genotyping studies and the second study [11] also enrolled 46 healthy vaccinia-naïve adults. In both studies, individuals were asked to self-identify ethnic background. Both studies complied with the Internal Review Board policies of Vanderbilt and the NIH, and written consent was obtained for all individuals.

Clinical Assessments

For both studies, the same team of trained physicians and nurses used the same forms to obtain medical history and to record local and systemic AEs after vaccination. Subjects were examined at regular intervals (days 3–5, 6–8, 9–11, 12–15, and 26–30 after vaccination). Local and systemic AEs were recorded. Subjects with an oral temperature of greater than 38.3 °C anytime during the study, generalized skin eruptions on non-contiguous areas to the site of vaccination [11], or enlarged or tender regional lymph nodes associated with vaccination were defined as those experiencing systemic AEs.

Identification of Genetic Polymorphisms

We used a previously described custom SNP panel based on the NCI SNP500 Cancer project [12]; specifically, this panel targets investigation of soluble factor mediators and signaling pathways, many of which have known immunological significance [13]. There is a heavy weighting towards non-synonymous SNPs in this panel (*i.e.*, those that result in an amino acid substitution). Genotyping for single nucleotide polymorphisms (SNPs) was performed using DNA amplified directly from EBV-transformed B cells generated from peripheral blood samples collected from each subject. Genotyping was performed at the Core Genotyping Facility of the National Cancer Institute (NCI) in Gaithersburg, MD. Genotypes were generated using the Illumina™ GoldenGate assay technology. Of the 1536 SNPs assayed, a total of 1442 genotypes passed quality control filters for both the first and second sample sets. A complete list of the SNPs examined in this study is found in Supplemental Table 1.

Statistical Analysis

Demographic characteristics including age, gender, and race were compared between the first and second study using Student's t-test (for age) and two-sample tests of proportions (for AE status, gender, and race). Allele frequencies were estimated from the total number of copies of individual alleles divided by the number of all alleles in the sample, and compared between the two studies using a two-sample test of proportions. Deviations in the fitness for Hardy-Weinberg proportion were evaluated using the exact test described in Wigginton *et al* [14].

We chose a two-stage design for identifying and replicating genetic associations in the independent clinical trials. This study design was selected with the goal of minimizing Type I errors (false positives). For comparison, we also performed the genetic association analysis in a single pooled sample. In the first study, potential associations were tested between each of the 1442 SNPs passing quality control filters and the occurrence of AEs using logistic regression. For each SNP in the first sample set, we recorded the odds ratio estimate and p-value of the likelihood ratio test for a univariate logistic model. No correction for multiple comparisons was made in our first set, because we reserved the second study sample set for determination of probable true positives. In the second sample set, we

tested only those SNPs having an AE-associated p-value ≤ 0.05 in the first study. We considered a significant SNP association in the first study to have replicated if it met the following criteria in the second study: an odds ratio that consistently associated AE risk with the same genotypes and a p-value ≤ 0.05. To obtain an empirical probability of meeting our replication criteria purely by chance, we generated 1,000 simulated data sets from both study sample sets by permuting case-control labels. An additional association with p-value 0.06 is discussed below because of its high biologic plausibility.

Patterns of linkage disequilibrium (LD) between replicated SNPs on the same chromosome were assessed using Haploview [15]. Haplotypes were inferred for SNPs in high LD using the iterative approach described in Lake *et al* [16]. The resulting haplotypes were tested for association with AEs using univariate logistic models. Statistical analyses and simulations were performed using R version 2.5.1, Stata version 9 (Stata Corp, College Station, TX), and Haploview version 3.32 [15,17,18].

RESULTS

Demographic Characteristics of Subjects Included in Genetic Analysis

In both studies, all participants were invited to donate genetic samples. In the first study, of the 148 vaccinia-naïve participants enrolled in the clinical trial, a total of 96 individuals gave consent for the genetic substudy. Of those 96 subjects with genetic data, 16 experienced *systemic* AEs following immunization. An additional 11 genotyped subjects who reported only a localized rash near the inoculation site were removed from the analysis to focus only on systemic AEs. The other 69 reporting no AEs were used as controls. Thus the first study included analysis of 85 subjects. In the second study, which included 48 vaccinia-naïve healthy adults, 46 gave consent for genotyping and were enrolled. Of the 46 individuals, 24 experienced systemic AEs.

Table 1 summarizes age, race, gender, and AE status decompositions of both studies. Table 1 also describes the results of the demographic comparisons between the first and second studies. As the table indicates, there was no statistical difference in age, gender, or race between the two study populations. In the first study, 40 (47%) individuals were male, 84 (99%) were white and 1 (1%) was Asian. In the second study, 27 (59%) individuals were male, 44 (96%) were white, 1 (2%) was black, and 1 (2%) was Asian.

Table 1

Summary of AE status, age, gender, and race for both studies.

Dataset	AE/nonAE	Age[a]	Gender (M/F)	Race (W/B/A)[b]
First study ($N = 85$)	16/69	23.2 (3.9)	40/45	84/0/1
Second study ($N = 46$)	24/22	24.2 (3.8)	27/19	44/1/1
[c] P-value of difference	< 0.01	0.15	0.20	0.25

[a]Mean (standard deviation)
[b]W = white, B = black, A = Asian
[c]Two-sided p-value for t-test (age) or two-sample test of proportions (AE/nonAE, gender, race)

Genetic Associations with Adverse Events

A total of 36 SNPs (within 26 genes) that showed significant associations in the first study were tested for potential associations in the second study. Three variant genotypes were confirmed to be associated with AEs in the second study. These included one SNP in *MTHFR* ($p < 0.01$) and two SNPs in *IRF1* ($p = 0.03$). The strong significance of the association in the replication study suggested a high level of plausibility that the gene products were involved in the pathogenesis of the AEs. The results of our simulation study indicated that the probability of meeting our replication criteria (an odds ratio that consistently associated AE risk with the same genotypes and a p-value ≤ 0.05) entirely by chance was $p < 0.001$. It is important to note that we also reanalyzed the data as a single pooled sample and found the same pattern of statistically significant associations. The statistical results that replicated in the second study are shown alongside those from the first study in Table 2.

Table 2

Genetic polymorphisms associated with AEs in both studies.

Gene	SNP (rs#)	SNP Location (Base pair) [a]	Chromosomal Location	First Study		Second Study	
				Odds Ratio[b]	p-value (X^2)[b]	Odds Ratio[b]	p-value (X^2)[c]
MTHFR	1801133	6393745	1p36.3	2.3 (1.1–5.2)	0.04	4.1 (1.4–11.4)	< 0.01
IRF1	9282763	34237146	5q31.1	3.2 (1.1–9.8)	0.03	3.0 (1.1–8.3)	0.03
	839	34234139	5q31.1	3.2 (1.1–9.8)	0.03	3.0 (1.1–8.3)	0.03

[a]Base pair according to dbSNP (NCBI Human Genome Build 36.1).
[b]Estimated odds ratio (95% confidence interval)
[c]Likelihood ratio chi-square (X^2) test with one degree of freedom

Three SNPs in a third gene, *IL4*, had p-values equal to 0.06 in the second study. While not significant using a strict requirement for $p \leq 0.05$, we thought this association of great interest because of the prior biologic studies showing a central role for this cytokine in poxvirus biology [19–21]. Considering the reduced size of the second sample and the fact that the AE risk associated with variant genotypes was consistent across studies, these *IL4* SNPs warrant further study, because additional variants in linkage disequilibrium could also be associated with AE outcomes (Table 3).

Table 3

Distribution of genotypes at SNPs in *MTHFR*, *IRF1*, and *IL4*.

Gene	SNP (rs #)	SNP Location (Base Pair)	Genotype	First Study Count (Percent)	Second Study Count (Percent)
MTHFR	1801133	6393745	CC	36 (42)	18 (39)
			CT	39 (46)	21 (46)
			TT	10 (12)	7 (15)
IRF1	9282763	34237146	AA	39 (46)	17 (37)
			AG	43 (51)	24 (52)
			GG	3 (4)	5 (11)
	839	34234139	GG	39 (46)	17 (37)
			AA	43 (51)	24 (52)
			AG	3 (4)	5 (11)
IL4	2070874	34424723	CC	52 (62)	34 (74)
			CT	28 (33)	12 (26)
			TT	4 (5)	0 (0)
	2243268	34428976	AA	52 (62)	34 (74)
			AC	27 (32)	12 (26)
			CC	5 (6)	0 (0)
	2243290	34433182	CC	53 (62)	34 (74)
			AA	26 (31)	12 (26)
			AC	6 (7)	0 (0)

Open in a separate window

The SNPs located in *IRF1* and *IL4* are located in the same chromosomal region (5q31.1), suggesting an indirect association with one or more functional variants in that region. Because of the close physical proximity of the associated variants in the two genes, Haploview [15] software was used to examine the patterns of LD among those variants in each sample. Figure 1 shows that the LD plots for SNPs in the two genes follow the same pattern in each study sample. While there is strong LD between SNPs within the two genes, there is little evidence for LD between the two genes, indicating that the associations for each gene are statistically separate signals.

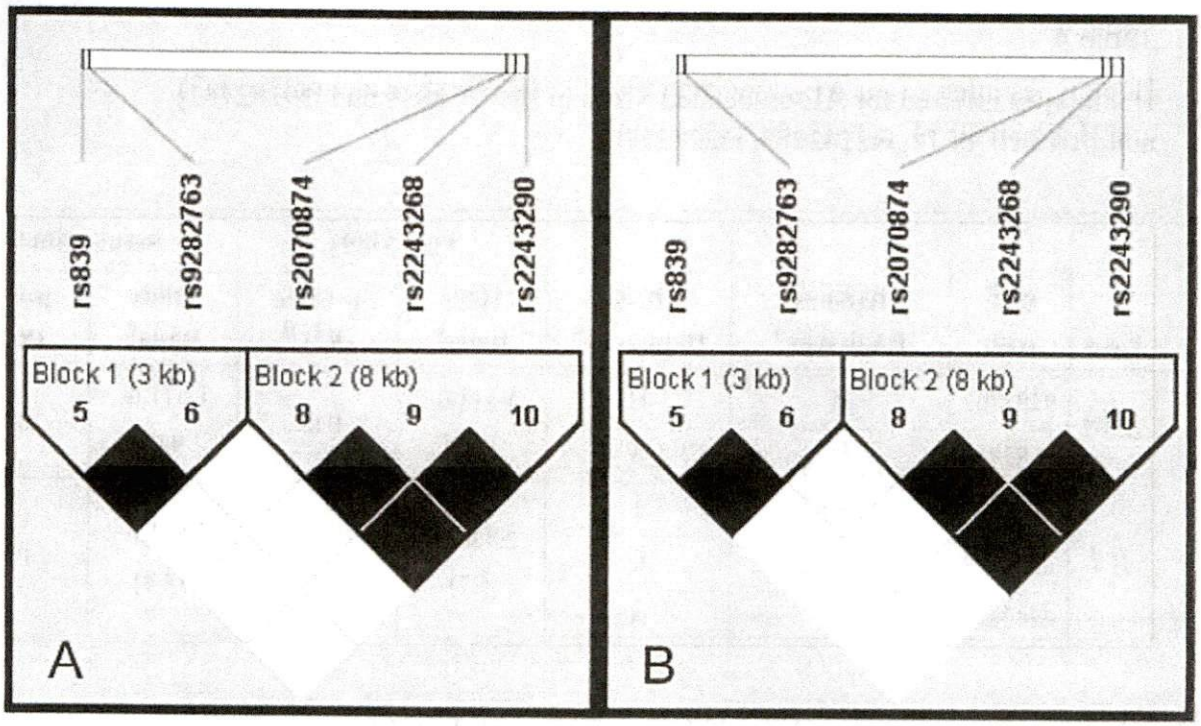

Figure 1

Haploview plot of SNPs at chromosome 5q31.1

Panel A =first study; panel B =second study. Squares are shaded to indicate strength of evidence for LD between the pairwise markers. Dark = strong evidence ($r^2 > 0.90$), light gray = weak evidence ($r^2 < 0.10$), white = no evidence ($r^2 < 0.0$). The same two LD blocks are apparent in both studies, encompassing SNPs in *IRF1* (rs839 and rs9282763) or *IL4* (rs2070874, rs2243268, and rs2243290).

This region of chromosome 5q31 contains discrete haplotype blocks [22]. Accordingly, haplotypes were inferred for AE-associated SNPs in *IRF1* (rs839 and rs9282763) and *IL4* (rs2070874, rs2243268, rs2243290). In both studies, two *IRF1* haplotypes accounted for all subjects. The common *IRF1*haplotype listed in Table 4 represented 71% of the first sample set and 63% of the second sample set. The rare *IRF1* haplotype was significantly associated with AEs in both studies ($p = 0.03$). Across both studies, two different three-SNP haplotypes in *IL4* accounted for 99% of subjects. The common *IL4*haplotype listed in Table 4 represented 78% of the first set and 87% of the second set. The rare *IL4*haplotype was significantly associated with risk of AEs in the first study ($p = 0.05$); the association was similar in the second study ($p = 0.06$).

Table 4

Haplotypes inferred for AE-associated SNPs in *IRF1* (rs839 and rs9282763) and *IL4*(rs2070874, rs2243268, rs2243290).

Gene	SNP (rs#)	Baseline Haplotype[a]	Risk Haplotype[b]	First Study		Second Study	
				Odds Ratio[c]	p-value (X^2) [d]	Odds Ratio[c]	p-value (X^2) [d]
IRF1	9282763	A	G	3.2 (1.0–10.2)	0.03	3.0 (1.0–9.0)	0.03
	839	G	A				
IL4	2070874	C	T	2.4 (1.0–5.7)	0.05	3.8 (1.0–14.4)	0.06
	2243268	A	C				
	2243290	C	A				

[a]Most common haplotype considering 2 SNPs in *IRF1* or 3 SNPs in *IL4*
[b]Rare (variant) haplotype considering 2 SNPs in *IRF1* or 3 SNPs in *IL4*
[c]Estimated odds ratio comparing risk haplotype to baseline haplotype (95% confidence interval)
[d]Likelihood ratio chi-square (X^2) test with one degree of freedom

DISCUSSION

The candidate genes identified with the strongest association with AEs in both studies include a metabolism gene previously associated with adverse reactions to a variety of pharmacologic agents (*MTHFR*) and an immunological transcription factor (*IRF1*). The statistical results from these studies have strong biological plausibility and are in agreement with previous work on the immune response to poxviruses.

MTHFR

A SNP in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene (rs1801133) was associated strongly with AE risk in both studies. This non-synonymous SNP in exon 5 causes an amino acid change from alanine to valine, and functional characterization of this SNP demonstrated that it is thermolabile and affects both the quantity and activity of the MTHFR enzyme [23]. The enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is a co-substrate for homocysteine remethylation to methionine. *MTHFR* function provides pools of methyl groups that are crucial for the control of DNA synthesis and repair mechanisms [24]. *MTHFR* is a key enzyme in homocysteine metabolism, which plays a major role in regulating endothelial function. It may be of interest in the future to examine the association of genetic variation in this gene with the rare cardiac events that occur after vaccination.

Genetic variation of *MTHFR* has been associated with a range of clinical outcomes, including altered cardiovascular function, organ transplantation, toxicity of immunosuppressive drugs, and systemic inflammation [25–28]. Elevated plasma homocysteine levels stimulate endothelial inflammatory responses, which could contribute to systemic AEs. Alternatively, since vaccination elicits immune responses involving the rapid proliferation of cells, demand for DNA synthesis metabolites would be elevated, and alterations in the level or activity of *MTHFR* enzyme may exert significant influence over this process.

Interferon regulatory factor-1

The interferon regulatory factor-1 (*IRF1*) gene is part of the immunological gene cluster on chromosome 5q31. We found two SNPs in *IRF1* that are significantly associated with AEs in both study samples. The *IRF1* gene encodes an important member of the interferon regulatory transcription factor (IRF) family. The IRF family regulates interferons and interferon-inducible genes. *IRF1* activates transcription of the Type I interferons α and β as well as genes induced by the Type II interferon γ [29]. Many viruses target IRFs to evade host immune responses by binding to cellular IRFs and blocking transcriptional activation of IRF targets [30].

Polymorphisms in the gene coding for a transcription factor with such far-reaching effects as *IRF1* could have profound effects on the proper immune response and clearance of vaccinia virus. Mice deficient in interferon receptors are especially susceptible to vaccinia virus infection, suggesting an important role for these molecules in controlling vaccinia infection [31]. Vaccinia dedicates several host modifying genes to counteracting interferons. For example, the viral gene B18R encodes a protein that serves as a viral IFN-α/β binding protein that binds interferons from several species [32]. This protein also can bind to the cell surface after secretion, thus preventing host interferon from binding to cellular interferon receptors [33]. Although the SNPs identified in *IRF1* and *IL4* do not change amino acids in the encoded proteins, recent evidence suggests that synonymous SNPs, such as rs839, can alter regulation of mRNA or splice junctions [34,35]. It is also plausible that one or both SNPs are in LD with the causal variant not tested in this study.

Interleukin-4

Genetic polymorphisms in this major cytokine gene involved in adaptive immunity to viruses also may be associated with AEs, however with a p-value of 0.06 in our relatively small replication study. We found three SNPs in *IL4* that may be associated with AEs in both studies. There was high intragenic LD ($r^2 > 0.9$) between the tested SNPs within each gene, *IRF1* and *IL4*, and haplotypes inferred separately for each of these genes mirrored the significant risk patterns of the SNPs observed individually. Thus, the fact that multiple SNPs in high LD were identified in regions of *IRF1* and *IL4* strongly suggest that there are additional markers in LD, several of which could functionally contribute to the risk for AEs.

The *IL4* gene encodes a pleiotropic cytokine produced by a variety of immune cells, especially activated T cells. *IL4* controls humoral immune responses, isotype switching, and suppression of cytotoxic T cell function and expansion. Thus, genetic polymorphisms related to inappropriate regulation of *IL4* expression and/or activity of IL-4 cytokine could be associated with over-stimulated inflammatory responses leading to the development of clinical AEs. Previous studies on the role of *IL4* in poxvirus pathogenesis have shown it to have a central role in altering the adaptive immune response. *IL4* over-expression during infection with recombinant poxviruses encoding *IL4* suppresses

the induction of cytotoxic T cell activity by inhibiting CD8+ T cell proliferation, which increased the pathogenicity of such recombinant viruses even in previously immunized animals [36]. *IL4* also plays a role in preventing optimum innate immune responses to poxviruses. IL-4 secretion during vaccinia virus infection of individuals with atopic dermatitis alters the cytokine milieu, resulting in a block of production of the antimicrobial peptide LL-37, accounting in part for the increased risk of vaccinia virus infection in subjects with atopic dermatitis [37].

Model of pathogenesis

Since the outcome of interest here was the aggregation of specific AEs, it is logical that more than one gene may be involved. The genes with variants for which we discovered an association with AEs are all potentially involved in pathways that are in line with our previously hypothesized mechanism of AEs involving excess stimulation of inflammatory pathways and the imbalance of tissue damage repair pathways. This model was developed from studies of circulating cytokines and relevant immunological effector cells [3–5]. For subjects experiencing AEs, vaccination appears to trigger an acute inflammatory response that is excessive. Antigen presentation to T cells in the dermis leads to the release of T-cell cytokines that trigger a cascade of cytokines and chemokines whose release enhances the inflammatory response by promoting the migration of monocytes into the lesion and their maturation into macrophages and by further attracting T cells [38,39]. Taken together, these previous findings suggest that systemic AEs following smallpox vaccination may be consistent with low-grade macrophage activation syndrome caused by virus replication and vigorous tissue injury and repair.

There are limitations to this study. The subject numbers are small for a genetic association study of low-penetrance high-frequency alleles. The association of the *IL4* variations with AEs was weaker than that of the other genes. Nevertheless, findings of the same variants in two independent clinical trials, the high biologic plausibility of these associations in light of what is known about poxvirus biology, and the potential public health significance suggest the findings are of interest.

Conclusions and Future Directions

These data present the rare opportunity to study two independent cohorts of smallpox vaccinees relating common genetic variation to the occurrence of post-vaccination AEs. Statistical analysis of the first study revealed potentially significant associations between SNPs in biologically interesting candidate genes. Of the AE-associated genes identified in the first study, two replicated in an independent study, with one additional candidate gene just beyond our statistical significance cut-off but with a high level of biologic plausibility. It is possible that our findings could be due to chance, but we avoided multiple testing issues by testing only the most promising results in the validation sample. While all SNPs were tested in the first study, only those SNPs significantly associated with AEs were tested in the second study, and our empirically derived probability of replication by chance alone was less than 0.1%. The association of SNPs in three genes across both studies and their biologically plausible connection with AEs lends credence to the reproducibility of these associations.

As with any statistical association, follow-up studies are needed to identify the particular genetic susceptibility variants and examine the functional consequences of polymorphisms in the AE-associated genes. Since we found multiple AE-associated SNPs in regions of *IRF1* and *IL4*, focused studies should be undertaken to characterize the genetic variability in these candidate regions. Indeed, haplotypes in *IRF* and *IL4* displayed altered susceptibility to a specific systemic AE (fever) after smallpox vaccination [40]. While the association of AEs with a non-synonymous polymorphism in the

gene for *MTHFR* points toward functional significance of this SNP, fine mapping of this locus should determine whether this is indeed the case. For all three candidate genes, both follow-up replication and functional studies are needed to establish the plausibility of the association of common genetic polymorphisms with the hypothesized etiological pathways.

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Footnotes

CONFLICT OF INTEREST STATEMENT:

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SHALL INFORM THE PARENT, LEGAL GUARDIAN, OR STUDENT, AS DESCRIBED IN SUBSECTION (2)(b)(I) OF THIS SECTION, OF THE OPTION TO EXCLUDE THE STUDENT'S IMMUNIZATION INFORMATION FROM THE IMMUNIZATION TRACKING SYSTEM CREATED IN SECTION 25-4-2403. THE DEPARTMENT OF PUBLIC HEALTH AND ENVIRONMENT OR THE APPLICABLE COUNTY, DISTRICT, OR MUNICIPAL HEALTH AGENCY MUST SUBMIT THE RELIGIOUS OR PERSONAL BELIEF EXEMPTION DATA TO THE IMMUNIZATION TRACKING SYSTEM.

(3) The state board of health ~~may provide, by regulation, for further exemptions to immunization based upon sound medical practice~~ SHALL ADOPT BY RULE THE MEDICAL EXEMPTION RECOMMENDATIONS BASED ON CONTRAINDICATIONS FOR VACCINATIONS AS DESCRIBED BY THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION IN THE FEDERAL DEPARTMENT OF HEALTH AND HUMAN SERVICES, OR ANY SUCCESSOR ENTITY.

(6) THE DEPARTMENT OF PUBLIC HEALTH AND ENVIRONMENT SHALL INCLUDE IMMUNIZATION EXEMPTION INFORMATION AS PART OF ITS ANNUAL PRESENTATION TO THE GENERAL ASSEMBLY PURSUANT TO THE "STATE MEASUREMENT FOR ACCOUNTABLE, RESPONSIVE, AND TRANSPARENT (SMART) GOVERNMENT ACT", PART 2 OF ARTICLE 7 OF TITLE 2. THE IMMUNIZATION EXEMPTION INFORMATION PRESENTATION MUST INCLUDE, BUT IS NOT LIMITED TO:

(a) STATISTICS DEMONSTRATING RATES OF IMMUNIZATION, MEDICAL EXEMPTIONS, AND RELIGIOUS OR PERSONAL BELIEF EXEMPTIONS COMPARED TO PREVIOUS YEARS;

(b) STATISTICS DEMONSTRATING RATES OF IMMUNIZATION, MEDICAL EXEMPTIONS, AND RELIGIOUS OR PERSONAL BELIEF EXEMPTIONS

General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)

Printer friendly version [18 pages]

Updates

Major changes to the best practice guidance in this section include 1) enhancement of the definition of a "precaution" to include any condition that might confuse diagnostic accuracy and 2) recommendation to vaccinate during a hospitalization if a patient is not acutely moderately or severely ill.

General Principles

Contraindications (conditions in a recipient that increases the risk for a serious adverse reaction) and precautions to vaccination are conditions under which vaccines should not be administered. Because the majority of contraindications and precautions are temporary, vaccinations often can be administered later when the condition leading to a contraindication or precaution no longer exists. A vaccine should not be administered when a contraindication is present; for example, MMR vaccine should not be administered to severely immunocompromised persons (1). However, certain conditions are commonly misperceived as contraindications (i.e., are not valid reasons to defer vaccination).

National standards for pediatric vaccination practices have been established and include descriptions of valid contraindications and precautions to vaccination (2). Persons who administer vaccines should screen patients for contraindications and precautions to the vaccine before each dose of vaccine is administered (Table 4-1). Screening is facilitated by consistent use of screening questionnaires, which are available from certain state vaccination programs and other sources (e.g., the Immunization Action Coalition (http://www.immunize.org)).

Severely immunocompromised persons generally should not receive live vaccines (3). Because of the theoretical risk to the fetus, women known to be pregnant generally should not receive live, attenuated virus vaccines (4). Persons who experienced encephalopathy within 7 days after administration of a previous dose of pertussis-containing vaccine not attributable to another identifiable cause should not receive additional doses of a vaccine that contains pertussis (4, 5). Severe Combined Immunodeficiency (SCID) disease and a history of intussusception are both contraindications to the receipt of rotavirus vaccines (6).

A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction, might cause diagnostic confusion, or might compromise the ability of the vaccine to produce immunity (e.g., administering measles vaccine to a person with passive immunity to measles from a blood transfusion administered up to 7 months prior) (7). A person might experience a more severe reaction to the vaccine than would have otherwise been expected; however, the risk for this happening is less than the risk expected with a contraindication. In general, vaccinations should be deferred when a precaution is present. However, a vaccination might be indicated in the presence of a precaution if the benefit of protection from the vaccine outweighs the risk for an adverse reaction.

The presence of a moderate or severe acute illness with or without a fever is a precaution to administration of all vaccines (Table 4-1). The decision to administer or delay vaccination because of a current or recent acute illness depends on the severity of symptoms and etiology of the condition. The safety and efficacy of vaccinating persons who have mild illnesses

have been documented (8-11). Vaccination should be deferred for persons with a moderate or severe acute illness. This precaution avoids causing diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination or superimposing adverse effects of the vaccine on the underlying illness. After they are screened for contraindications, persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved. Studies indicate that failure to vaccinate children with minor illnesses can impede vaccination efforts (12–14). Among persons whose compliance with medical care cannot be ensured, use of every opportunity to administer appropriate vaccines is critical.

Hospitalization should be used as an opportunity to provide recommended vaccinations. Health-care facilities are held to standards of offering influenza vaccine for hospitalized patients, so providers are incentivized to vaccinate these patients at some point during hospitalization (15). Likewise, patients admitted for elective procedures will not be acutely ill during all times during their hospitalization. Most studies that have explored the effect of surgery or anesthesia on the immune system were observational, included only infants and children, and were small and indirect, in that they did not look at the immune effect on the response to vaccination specifically (16-35). They do not provide convincing evidence that recent anesthesia or surgery significantly affect response to vaccines. Current, recent, or upcoming anesthesia/surgery/hospitalization is not a contraindication to vaccination (16-35). Efforts should be made to ensure vaccine administration during the hospitalization or at discharge. For patients who are deemed moderately or severely ill throughout the hospitalization, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients' clinical symptoms have improved.

A personal or family history of seizures is a precaution for MMRV vaccination; this is because a recent study found an increased risk for febrile seizures in children 12-23 months who receive MMRV compared with MMR and varicella vaccine (36).

Clinicians or other health-care providers might misperceive certain conditions or circumstances as valid contraindications or precautions to vaccination when they actually do not preclude vaccination (2) (Table 4-2). These misperceptions result in missed opportunities to administer recommended vaccines (37).

Routine physical examinations and procedures (e.g., measuring temperatures) are not prerequisites for vaccinating persons who appear to be healthy. The provider should ask the parent or guardian if the child is ill. If the child has a moderate or severe illness, the vaccination should be postponed.

TABLE 4-1. Contraindications and precautions[a] to commonly used vaccines

DT, Td	(4)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	GBS <6 weeks after previous dose of tetanus-toxoid–containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine Moderate or severe acute illness with or without fever
DTaP	(38)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP	Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized GBS <6 weeks after previous dose of tetanus-toxoid–containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine Moderate or severe acute illness with or without fever
Hepatitis A	(39)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
Hepatitis B	(40)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Hypersensitivity to yeast	Moderate or severe acute illness with or without fever
Hib	(41)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Age <6 weeks	Moderate or severe acute illness with or without fever

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Abbreviations: DT = diphtheria and tetanus toxoids; DTaP = diphtheria and tetanus toxoids and acellular pertussis; DTP = diphtheria toxoid, tetanus toxoid, and pertussis; GBS = Guillain-Barré syndrome; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; HPV = human papillomavirus; IIV = inactivated influenza vaccine; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MenACWY = quadrivalent meningococcal conjugate vaccine; MMR = measles, mumps, and rubella; MPSV4

= quadrivalent meningococcal polysaccharide vaccine; PCV13 = pneumococcal conjugate vaccine; PPSV23= pneumococcal polysaccharide vaccine; SCID = severe combined immunodeficiency; RIV=recombinant influenza vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

(a) Events or conditions listed as precautions should be reviewed carefully. Benefits of and risks for administering a specific vaccine to a person under these circumstances should be considered. If the risk from the vaccine is believed to outweigh the benefit, the vaccine should not be administered. If the benefit of vaccination is believed to outweigh the risk, the vaccine should be administered. Whether and when to administer DTaP to children with proven or suspected underlying neurologic disorders should be decided on a case-by-case basis.

(b) In addition, ACIP recommends LAIV not be used for pregnant women, immunosuppressed persons, persons with egg allergy, and children aged 2-4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health-care provider stated that they had wheezing or asthma within the last 12 months. LAIV should not be administered to persons who have taken influenza antiviral medications within the previous 48 hours. Persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV, or should avoid contact with such persons for 7 days after receipt.

(c) **Source:** (52).

(d) HIV-infected children may receive varicella vaccine if CD4+ T-lymphocyte count is ≥15% and should receive MMR vaccine if they are aged ≥12 months and do not have evidence of current severe immunosuppression (i.e., individuals aged ≤5 years must have CD4+T lymphocyte [CD4] percentages ≥15% for ≥6 months; and individuals aged >5 years must have CD4+percentages ≥15% and CD4+≥200 lymphocytes/mm^3 for ≥6 months) or other current evidence of measles, rubella, and mumps immunity. In cases when only CD4+cell counts or only CD4+percentages are available for those older than age 5 years, the assessment of severe immunosuppression can be based on the CD4+values (count or percentage) that are available. In cases when CD4+percentages are not available for those aged ≤5 years, the assessment of severe immunosuppression can be based on age-specific CD4+counts at the time CD4+counts were measured; i.e., absence of severe immunosuppression is defined as ≥6 months above age-specific CD4+count criteria: CD4+count >750 lymphocytes/mm^3 while aged ≤12 months and CD4+count ≥500 lymphocytes/mm^3 while aged 1 through 5 years. **Sources:** (1, 50).

(e) MMR and varicella-containing vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

(f) A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent.

(g) family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings), unless the immune competence of the potential vaccine recipient has been substantiated clinically or verified by a laboratory.

(h) If active tuberculosis is suspected, MMR should be delayed. Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin or IGRA testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for ≥4 weeks after the vaccination. If an urgent need exists to skin test or IGRA, do so with the understanding that reactivity might be reduced by the vaccine.

(i) For details, see (55).

(j)No adverse events associated with the use of aspirin or aspirin-containing products after varicella vaccination have been reported; however, the vaccine manufacturer recommends that vaccine recipients avoid using aspirin or aspirin-containing products for 6 weeks after receiving varicella vaccines because of the association between aspirin use and Reye syndrome after varicella. Vaccination with subsequent close monitoring should be considered for children who have rheumatoid arthritis or other conditions requiring therapeutic aspirin. The risk for serious complications associated with aspirin is likely to be greater in children in whom natural varicella develops than it is in children who receive the vaccine containing attenuated VZV. No association has been documented between Reye syndrome and analgesics or antipyretics that do not contain aspirin."

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TABLE 4-2. Conditions incorrectly perceived as contraindications or precautions to vaccination (i.e., vaccines may be given under these conditions)

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Abbreviations: DT = diphtheria and tetanus toxoids; DTP = diphtheria toxoid, tetanus toxoid, and pertussis; DTaP = diphtheria and tetanus toxoids and acellular pertussis; GBS = Guillain-Barré syndrome; HBsAg = hepatitis B surface antigen; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; HPV = human papillomavirus; IIV = inactivated influenza vaccine; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MenACWY = quadrivalent meningococcal conjugate vaccine; MMR = measles, mumps, and rubella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine; PPSV23= pneumococcal polysaccharide vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

(a) Antibacterial drugs might interfere with Ty21a oral typhoid vaccine, and certain antiviral drugs might interfere with varicella-containing vaccines and LAIV4.

(b) Hepatitis B vaccination should be deferred for infants weighing <2,000 g if the mother is documented to be HBsAg negative. Vaccination should commence at chronological age 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 hours after birth, regardless of weight.

(c) An exception is Guillain-Barré syndrome within 6 weeks of a dose of influenza vaccine or tetanus-toxoid–containing vaccine, which are precautions for influenza vaccines and tetanus-toxoid containing vaccines, respectively.

(d) MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

(e) HIV-infected children should receive immune globulin after exposure to measles. HIV-infected children can receive varicella and measles vaccine if CD4+ T-lymphocyte count is >15%. (*54*).

(f) Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin or IGRA testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for at least 4 weeks after the vaccination. If an urgent need exists to skin test or IGRA, do so with the understanding that reactivity might be reduced by the vaccine.

(g) If a vaccinee experiences a presumed vaccine-related rash 7-25 days after vaccination, the person should avoid direct contact with immunocompromised persons for the duration of the rash.

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