ADVISORY COMMISSION ON CHILDHOOD VACCINES
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ADVISORY COMMISSION ON CHILDHOOD VACCINES

Agenda

June 3, 2014

ADVISORY COMMISSION ON CHILDHOOD VACCINES (ACCV)

Teleconference and Adobe Connect

June 05, 2014
(10:00 am – 5:00 pm Eastern Daylight Time)
Dial: 1-877-917-4913
Passcode: ACCV

https://hrsa.connectsolutions.com/accv/

Thursday, June 05, 2014

Time	Agenda Item	Presenter
10:00 AM	Welcome and Chair Report	Mr. David King, Chair
10:10 AM	Public Comment on Agenda Items	
10:15 AM	Approval of March 2014 Minutes	Mr. David King, Chair
10:20 AM	Report from the Division of Vaccine Injury Compensation	Dr. A. Melissa Houston Acting Director, DVIC
10:50 AM	Clarification on Proposed Changes to the Vaccine Injury Table • Modify Category XIV on the Table from "Trivalent influenza vaccines" to "Seasonal influenza vaccines • Modify Category IX from Haemophilus influenzae type b polysaccharide conjugate vaccines to Haemophilus influenzae type b vaccines • Clarify definition of thrombocytopenic purpurain the Qualifications and Aids to Interpretation • Clarify exclusions to encephalopathy in the Qualifications and Aids to Interpretation • Clarify the definition of Shoulder Injury Related to Vaccine Administration (SIRVA) in the Qualifications and Aids to Interpretation	Dr. A. Melissa Houston Acting Director, DVIC
11:20 AM	Report from the Department of Justice	Mr. Vince Matanoski Deputy Director Torts Branch, DOJ
12:00 PM	Lunch	

Time	Agenda Item	Presenter
1:00 PM	Petition to Add Diabetes Mellitus as an Injury for the Measles, Mumps and Rubella Vaccine to the Vaccine Injury Table,	Dr. Mary Rubin Medical Officer, DVIC
2:00 PM	Report from the Process Workgroup	Ms. Luisita dela Rosa, ACCV Member
2:30 PM	Review of Vaccine Information Statements	Mr. Skip Wolfe, CDC
3:30 PM	Update on the National Institute of Allergy and Infectious diseases (NIAID), National Institutes of Health (NIH) Vaccine Activities	Ms. Barbara Mulach NIAID, NIH
3:45 PM	Update on the Center for Biologics, Evaluation and Research (CBER), Food and Drug Administration (FDA) Vaccine Activities	LT. Valerie Marshall CBER, FDA
4:00 PM	Update from the National Vaccine Program Office (NVPO)	Dr. Karin Bok NVPO
4:15 PM	Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC) Vaccine Activities	Dr. Tom Shimabukuro CDC
4:30 PM	Public Comment (follows the preceding topic and may commence earlier or later the 4:30 pm)	
4:45 PM	Future Agenda Items/New Business	Mr. David King, Chair
5:00 PM	Adjournment of the ACCV June Quarterly Meeting	Mr. David King, Chair

Charter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Resources and Services Administration

Rockville, MD 20857

CHARTER

ADVISORY COMMISSION ON CHILDHOOD VACCINES

Authority

42 U.S.C. 300aa-19, Section 2119 of the PHS Act. The Advisory Commission on Childhood Vaccines (hereinafter referred to as the "Commission") is governed by the provisions of Public Law 92-463 (5 U.S.C. App. 2), which sets forth standards for the formation of advisory committees.

Objectives and Scope of Activities

The Secretary of Health and Human Services is mandated under Section 2119 of the Public Health Service (PHS) Act to appoint an advisory commission to give advice regarding the National Vaccine Injury Compensation Program (the Program), which provides compensation for certain vaccine-related injuries or deaths.

Description of Duties

The Commission shall: (1) advise the Secretary on the implementation of the Program; (2) on its own initiative or as the result of the filing of a petition, recommend changes in the Vaccine Injury Table; (3) advise the Secretary in implementing the Secretary's responsibilities under Section 2127 of the PHS Act regarding the need for childhood vaccination products that result in fewer or no significant adverse reactions; (4) survey Federal, State, and local programs and activities relating to the gathering of information on injuries associated with the administration of childhood vaccines, including the adverse reaction reporting requirements of Section 2125(b), and advise the Secretary on means to obtain, compile, publish, and use credible data related to the frequency and severity of adverse reactions associated with childhood vaccines; (5) recommend to the Director of the National Vaccine Program research related to vaccine injuries which should be conducted to carry out the Program; and (6) consult regarding the development or revision of vaccine information materials as required by Section 2126 of the PHS Act.

Agency or Official to Whom the Commission Reports

The Commission on Childhood Vaccines shall advise and make recommendations to the Secretary on matters related to the Program responsibilities.

Support

Management and support services shall be provided by the Division of Vaccine Injury Compensation, Healthcare Systems Bureau, Health Resources and Services Administration.

Estimated Annual Operating Costs and Staff Years

Estimated annual cost for operating the Commission, including compensation and travel expenses for members, but excluding staff support, is approximately $84,685. The estimate of annual person-years of staff support required is 1.5 at an estimated annual cost of $257,582.

Designated Federal Officer

HRSA will select a full-time or permanent part-time Federal employee to serve as the Designated Federal Officer (DFO) to attend each Commission meeting and ensure that all procedures are within applicable, statutory, regulatory, and HHS General Administration Manual directives. The DFO will approve and prepare all meeting agendas, call all of the Commission or subcommittee meetings, adjourn any meeting when the DFO determines adjournment to be in the public interest, and chair meetings when directed to do so by the official to whom the Commission reports. The DFO or his/her designee shall be present at all meetings of the full Commission and subcommittees.

Estimated Number and Frequency of Meetings

The Commission shall meet no less than 4 times per year and at the call of the DFO. Meetings shall be open to the public except as determined otherwise by the Secretary or designee in accordance with the Government in the Sunshine Act 5 U.S.C. 552b(c) and the Federal Advisory Committee Act. Notice of all meetings shall be given to the public. Meetings shall be conducted, and records of the proceedings kept, as required by applicable laws and departmental regulations.

Duration

Continuing.

Termination

Unless renewed by appropriate action prior to its expiration, this charter will expire two years from the date the charter is filed.

Membership and Designation

The Secretary shall select members of the Commission. The members of the Commission shall select a Chair and Vice Chair from among the members. Appointed members of the Commission shall be appointed for a term of office of 3 years. Members may serve after the expiration of their term until their successors have taken office.

The Commission shall be composed of the following:

(1) Nine members appointed by the Secretary as follows:

(A) three members who are health professionals, who are not employees of the United States, and who have expertise in the health care of children, the epidemiology, etiology, and prevention of childhood diseases, and the adverse reactions associated with vaccines, of whom at least two shall be pediatricians;

(B) three members from the general public, of whom at least two shall be legal representatives of children who have suffered a vaccine-related injury or death; and

(C) three members who are attorneys, of whom at least one shall be an attorney whose specialty includes representation of persons who have suffered a vaccine-related injury or death and of whom one shall be an attorney whose specialty includes representation of vaccine manufacturers.

(2) The Director of the National Institutes of Health, the Assistant Secretary for Health, the Director of the Centers for Disease Control and Prevention, and the Commissioner of the Food and Drug Administration (or the designees of such officials), each of whom shall be a nonvoting ex officio member.

The nine members appointed by the Secretary shall serve as Special Government Employees. The ex officio members and the DFO shall be Regular Government Employees.

Subcommittees

Subcommittees may be established with the approval of the Secretary or designee. Subcommittee members may be members of the parent Commission. The subcommittee shall make recommendations to be deliberated by the parent Commission. The Department's Committee Management Officer will be notified upon the establishment of the each subcommittee and will be provided information on the subcommittee's name, membership, function, and estimated frequency of meetings.

Recordkeeping

The records of the committee, formally and informally established subcommittees, or other subgroups of the committee, shall be handled in accordance with General Records Schedule 26, Item 2 or other approved agency records disposition schedule. These records shall be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

4 – ACCV Charter

Filing Date
July 21, 2012

Approved:

July 17, 2012
Date

for Jennifer Rizzle
Wendy Ponton
Director, Office of Management

Roster

ADVISORY COMMISSION ON CHILDHOOD VACCINES (ACCV) ROSTER
DIVISION OF VACCINE INJURY COMPENSATION (DVIC)
Parklawn Building, Room 11C-26
5600 Fishers Lane
Rockville, MD 20857

ACCV MEMBERS

David King, Chair ('14)
4 Briarcliff Lane
Holmdel, NJ 07733
(732)758-1111 (Direct)
e-mail: dking@salesmotion.com

Michelle Williams, J.D., Vice-Chair ('14)
Alston & Bird LLP
1201 West Peachtree Street
Atlanta, GA 30309
(404)881-7594 (Direct)
(404)253/8274 (Fax)
e-mail: michelle.williams@alston.com

Ann Linguiti Pron, DNP CPNP, R.N. ('14)
University of Pennsylvania
School of Nursing, 418 Curie Blvd
Philadelphia, PA 19104-4217;
Abington VNA, Community Services, Children's Health Center,
1421 Highland Avenue,
Abington, PA 19001
(215)635-3642 (Direct)
e-mail: aljjp@aol.com

Kristen A. Feemster, M.D., M.P.H., M.S.H.P. ('14)
Assistant Professor- UPenn School of Medicine, Division of Infectious Diseases
The Children's Hospital of Philadelphia
CHOP North- 3535 Market St, Rm 1511
Philadelphia, PA 19104
(267)426-0192 (Direct)
(215)590-2025 (Fax)
email: feemster@email.chop.edu

Jason Smith, J.D. ('14)
Assistant General Counsel
Pfizer Inc.
500 Arcola Road
Dock E – Office D 4214
Collegeville, PA 19426
(484)865-6196 (Direct)
(484)865-6419 (Fax)
e-mail: jason.smith@pfizer.com

Charlene Douglas, Ph.D., M.P.H., R.N. ('14)
Associate Professor, George Mason University
4400 University Drive, Mail Stop 3C4
Fairfax, VA 22030-4444
(703)993-1937 (Direct)
e-mail: cdouglas@gmu.edu

Sylvia Fernandez Villarreal, M.D., ('15)
Taos Clinic for Children & Youth
1393 Weimer Road
Taos, NM 87571
(515)758-8651(Direct)
e-mail: opus@taospeds.org

Edward Kraus, J.D., ('15)
Associate Professor of Clinical Practice
Chicago-Kent College of Law
565 West Adams, Suite 600
Chicago, IL 60661
(312)906-5072(Direct)
e-mail: ekraus@kentlaw.edu

Luisita dela Rosa, Ph.D. ('15)
22640 Lamplight Place
Santa Clarita, CA 91350
(515)708-0838 (Direct)
e-mail: luisitacdlr@earthlink.net

EX OFFICIO MEMBERS

Bruce Gellin, M.D.
Director, National Vaccine Program Office
200 Independence Ave, S.W. - Room 736E
Washington, D.C. 20201-0004
202/690-5566 (Direct)
202/690-7560 (Fax)
e-mail: bgellin@osophs.dhhs.gov

Marion Gruber, Ph.D.
Acting Director,
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
1451 Rockville Pike, Rm 3312
Rockville, MD 20852
301/796-2630
301/402-1290 (Fax)
e-mail: marion.gruber@hda.hhs.gov

Carole A. Heilman, Ph.D.
Director, Division of Microbiology
and Infectious Diseases,
NIAID, NIH
6700B Rockledge Drive - Room 3142,
MSC 7630 Bethesda, MD 20892-7630
For Federal Express Mailing:
(FED EX only: Bethesda, MD 20817)
301/496-1884 (Direct)
301/480-4528 (Fax)
e-mail: ch25v@nih.gov

Tom Shimabukuro, M.D., M.P.H., M.B.A
Immunization Safety Office
Centers for Disease Control and Prevention
1600 Clifton Road
Clifton Building, Mail Stop D-26
Atlanta, GA 30333
404/639-4848 (Direct)
404/639-8834 (Fax)
e-mail: tshimabukuro@cdc.gov

DVIC STAFF

A. Melissa Houston, M.D., M.P.H., F.A.A.P.
Acting Director, DVIC
Executive Secretary, ACCV
301/443-9350 (Direct)
301/443-0704 (Fax)
e-mail: ahouston@hrsa.gov

Andrea Herzog
Principal Staff Liaison, ACCV
301/443-6634 (Direct)
301/443-8196 (Fax)
e-mail: aherzog@hrsa.gov

OFFICE OF THE GENERAL COUNSEL

Andrea Davey, J.D.
Attorney
301/443-4500 (Direct)
301/443-2639 (Fax)
e-mail: Andrea.Davey@hhs.gov

2014 Meeting Dates

ADVISORY COMMISSION ON CHILDHOOD VACCINES

2014 MEETING DATES

June 5 , 2014
September 4 & 5, 2014
December 4 & 5, 2014

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Advisory Commission on Childhood Vaccines

March 6-7, 2014

91st Meeting

Meeting Day One – March 6, 2014

Members Present on March 6, 2014

David King, Chair ('14)
Charlene Douglas, Ph.D. ('14)
Edward Kraus, J.D. ('15)
Ann Linguiti Pron, DNP, CRNP, RN ('14)
Luisita dela Rosa, Ph.D. ('15)
Jason Smith, J.D. ('14)
Sylvia Fernandez Villareal, M.D. ('15) (via telephone)

Division of Vaccine Injury Compensation

Vito Caserta, M.D., Acting Director, DVIC
Andrea Herzog, Staff Liaison
Andrea Davey, J.D., Legal Counsel

Welcome, Report of the Chair and Approval of Minutes
Mr. David King, ACCV Chair

Noting a quorum present, Mr. King called the meeting to order and, after introductions, announced that Secretary Sebelius had responded to the Commission's request for comment on five recommendations submitted to the Secretary of the Department of Health and Human Service's (Secretary) office during the past year. She assured the Commissioners that each would receive careful review. The recommendations included the extension of the statute of limitations for filing injury and death claims; increasing benefit caps for pain and suffering and death; compensation for injuries sustained by a live-born infant whose mother received a vaccine while the infant was in utero; expanding coverage under the Vaccine Injury Compensation Program (VICP) to include vaccines that are recommended for routine administration in pregnant women but are not recommended for routine administration in children; and consideration of a health professional with expertise in obstetrics to serve as a member of the ACCV. A discussion will be scheduled as an agenda item in the future.

Mr. King commented that another item that should be considered for a future meeting is the succession plan for chair and vice-chair, since terms of office will certainly expire this year. He invited any member interested in serving in either capacity to indicate that interest.

Finally, Mr. King reminded the Commissioners of the purpose of the Vaccine Injury Compensation Program which is to support those who are injured as a result of receiving a

vaccine, and that the Commissioners should strive to put those individuals first in making recommendations and decisions with regard to the responsibilities of the Commission.

Public Comment on Agenda

Mr. King invited public comment specifically related to the agenda.

Theresa Wrangham, Executive Director of the National Vaccine Information Center, spoke to two agenda items -- Report from the Division of Vaccine Injury Compensation, and the Report from the Process Workgroup. Ms. Wrangham commented that the intention to provide more meaningful information on the web site has not been successful, partly based on the premise that the privacy of injured individuals may be compromised. She maintained that the regulations define the information that should be protected as name, address and telephone number. She stated that the information desired concerned the epidemiology of the injury – the vaccine, the most prevalent specific adverse events. She mentioned that she had sent to the Commission a description of the information desired.

Approval of December 2013 ACCV Meeting Minutes

Noting no further comment from the public, Mr. King invited approval of the minutes of the December 2013 meeting. On motion duly made and seconded, the minutes were unanimously approved.

Report from the Division of Vaccine Injury Compensation, Dr. Vito Caserta, Acting Director, DVIC

Dr. Caserta briefly reviewed the day's agenda, noting that the Commission would hear a report from the Department of Justice (Vince Matanoski), and an update from the ACCV Process Workgroup, and review two Vaccine Information Statements. There will also be a presentation on pneumococcal polysaccharide (Pneumovax 23) vaccine, a vaccine recommended for adults. Finally there will be updates from ACCV ex officio member agencies -- FDA, CDC, NIH and NVPO.

With regard to statistics, Dr. Caserta reported that 174 claims had been filed in the first five months of FY 2014. Extrapolating to the end of the fiscal year the number would be 417, in line with previous years. Similarly, the number of adjudicated compensable non-autism cases stood at 73 cases, 80% of which were settled, and that number slightly lags the rate for the previous years. The awards for the fiscal year to date are $66 million plus $7.5 million for attorney's fees. If extrapolated the total would be slightly less than last year. The Vaccine Injury Compensation Trust Fund (Trust Fund) balance is about $3.5 billion, with income of $63 million.

Dr. Caserta noted that there was a public hearing on January 13th for the rotavirus Notice of Proposed Rulemaking. However, since there may not have been sufficient public notice, an additional public hearing will be held in the near future, after which the Department of Health and Human Services (HHS or Department) will review public comments and publish a final rule.

The Vaccine Injury Table Notice of Proposed Rulemaking is being finalized and should be ready for the clearance process within the next two months. Dr. Caserta noted that he would be retiring and that Dr. Avril Melissa Houston would be taking on the duties of Executive Secretary for the Commission.

Finally, Dr. Caserta noted that the National Vaccine Advisory Committee (NVAC) met on February 11-12 and the Advisory Committee on Immunization Practices (ACIP) met on February 26-27, and there will be reports on both later in the meeting. Dr. Caserta provided Program contact information to the Commission. He concluded his presentation and asked if any of the Commission members had questions.

He was asked about the timeline for approval of the Vaccine Injury Table Notice of Proposed Rulemaking. Dr. Caserta explained that HHS would share the initial draft internally with other HHS agencies (i.e., CDC, FDA, NIH, CMS), incorporate responses from those agencies, and complete a final HHS clearance. HHS will forward the final draft to the Office of Management and Budget (the Executive Office of the White House), which would send the draft to other Federal departments to obtain their comments, consolidate the comments from those departments, and the final version would then be published in the Federal Register. There would be a six-month public comment period and a public hearing, and then the HHS would finalize the rule and it would become effective when published in the Federal Register.

Mr. King asked about the best approach for realizing the Commission's goal to improve communications with the Secretary's office. Dr. Caserta suggested that a first step might be to identify the goals and objectives of the Secretary that, in terms of vaccines, comes under the aegis of the Office of the Assistant Secretary for Health (OASH). That office typically communicates with the National Vaccine Advisory Committee with regard to vaccine goals and objectives and it might be possible for ACCV to be included in that information loop.

Dr. Caserta suggested that the Commissioners should become familiar with the National Vaccine Plan and seek to develop a relationship with the NVAC and OASH to achieve that end. He added that staffing for ACCV is relatively limited, mainly to support the regular meetings that Ms. Herzog handles. To expand support for ACCV, such as developing the liaison with OASH and NVAC, might require additional staffing and requisite funding. Asked whether the Trust Fund could be such a source of funding, Dr. Caserta explained that the Trust Fund pays for compensable claims, the legal fees involved in those cases, some budget requirements related to the VICP for the Court, the Department of Justice and HHS. Ultimate budget decisions are made by the Office of Management and Budget.

Mr. King took exception to the practice of the NVAC to fund travel for all meetings, while the ACCV is not able to receive the same kind of meeting support. Dr. Caserta explained that the budget decisions are made by different departments, which may have different priorities and requirements. Mr. Kraus suggested that, rather than trying to resolve the issue at the meeting, it might be more appropriate if the Commission would draft a statement or recommendation describing its position with regard to the importance of face-to-face meetings, and the addition of sufficient staff support to provide the liaison with OASH and NVAC and to prepare appropriate reports as discussed earlier with regard to the National Vaccine Plan

priorities, the important issues related to the vaccine program as a whole, and how the ACCV plays a role in the process. Dr. Caserta endorsed that proposal. Dr. Pron added that the support might also serve to expedite the distribution of the meeting minutes to the Commissioners, and Ms. Herzog commented that she would work on expediting that process. Mr. King suggested, rather than a detailed set of minutes, perhaps a short summary of the main discussion points could be created immediately after the meeting.

Report from the Department of Justice, Vince Matanoski, Deputy Director, Torts Branch

Mr. Matanoski referenced the Department of Justice PowerPoint materials (DOJ PP), dated March 6, 2014, as part of his presentation. He commented that the DOJ's statistics reflect the period between ACCV meetings, whereas HHS reports statistics based on the fiscal year. As a result, there may be a slight difference in the numbers reported by Dr. Caserta and DOJ. During the three month reporting quarter, 128 cases were filed, which is a significant increase in the filing rate over similar historical periods (DOJ PP at 2), but a slight decrease from last quarter's numbers. The average annual filing rate for the preceding five years was approximately 400 cases; this year it is projected to be about 500, a 25% increase. Mr. Matanoski observed that the filing rate increased during the summer of 2013, and that higher filing rate continues. If the filing rate continues to increase, it may pose a challenge to the DOJ's ability to process cases as funding has not been increased. The rise in adult petitioner filings continues an upward trend. Of the 128 cases filed this quarter, 80% of the claims involved adult injuries compared with 75% for the two preceding reporting periods. In response to a question, Mr. Matanoski explained that a minor is considered anyone under the age of 18.

Mr. Matanoski reported that 113 cases were adjudicated since the last report, slightly down from last quarter, which may be attributable to fallout from the government shutdown. (DOJ PP at 3). While the number of adjudicated cases was slightly down from last quarter and less than the number of newly filed cases, Mr. Matanoski did not consider this to be a trend. He added that the Office of Special Masters now has a full complement of special masters, which may affect case adjudication levels.

Turning to appellate proceedings, petitioners filed a *writ of certiorari* in the U.S. Supreme Court in *Tembenis v. Sebelius*. (DOJ PP at 5), asking the Supreme Court to hear the case involving future damages available to the estate of a child who suffered an alleged vaccine related injury and death. The special master held that the child's estate could recover lost future damages based on the expected lifetime earnings of the child. The U.S. Court of Federal Claims (CFC) affirmed. On appeal by the government, the U.S. Court of Appeals for the Federal Circuit (CAFC) reversed, finding that the estate was limited to damages calculated up to the date of death. (DOJ PP at 5). Turning to the CAFC, in *Carson v. HHS*, the CAFC denied petitioners' request for a rehearing *en banc* after a three-judge panel dismissed the case as untimely. (DOJ PP at 6). In *Snyder/Harris v. HHS*, on appeal by respondent, the CAFC reversed the CFC and reinstated the special master's decision denying compensation in both cases finding that the genetic mutation, SCN1A caused the alleged injuries. This is consistent with other SCN1A cases affirming the special master's denials of compensation. There were two new cases filed by petitioners at the CAFC. (DOJ PP at 7). *Koehn v. HHS* was originally part of the Omnibus Autism Proceeding, and was dismissed by the special master. One year later, the petitioner, now *pro se*, moved for relief from judgment at the CFC claiming that the

vaccination date was erroneous. The CFC denied the appeal. *Price v. HHS,* involved a denial of entitlement.

Turning to the CFC, five cases were decided. Four of which involved entitlement and one involved jurisdiction. (DOJ PP at 8). Mr. Matanoski also discussed two new appeals filed by petitioners. (DOJ PP at 9). In *Contreras v. HHS*, petitioner appealed a decision on remand by the special master again denying compensation finding that the timing of onset of petitioner's injury was too soon for the type of injury alleged, and that the evidence did not support a short time frame. In *Chuisano v. HHS*, petitioner appealed the special master's denial of $45,000 in attorneys' fees sought by two different attorneys/firms because the claim lacked a reasonable basis. There was some discussion about the precedential value, if any, of this decision. Mr. King questioned whether a decision might prejudice an attorney's willingness to file claims. Mr. Matanoski observed that there has not been a decline in the number of filings or attorneys new to the Program filing cases. The statute requires that a petition be filed with complete evidentiary records, and that it is the responsibility of petitioner and his/her counsel to do that. In *Chuisano*, the special master focused on whether or not counsel should be compensated if the claim had no reasonable basis to begin with. The court typically looks at the circumstances at a given time in the case in determining whether there was a reasonable basis for the claim. A case filed without evidence because the statute of limitations was about to expire may be deemed to have a reasonable basis initially, but the Court may deem that reasonable basis would end if counsel continued to pursue a claim without developing evidence of causation, or if the claim was filed without evidence when no imminent deadline existed. Mr. Kraus added that the concern is attorney access, and very rarely do courts find that a case was filed without reasonable basis. Oral argument in *Flores v. HHS* took place on February 25, 2014 (DOJ PP at 10).

Turning to the slides entitled Adjudicated Settlements (DOJ PP at 11-14), Mr. Matanoski noted that 40 cases were settled during the current reporting period. Of those, it appeared that 33 were for adults and 7 for minors. Twenty-eight cases involved the flu vaccine or flu vaccine in combination with other vaccines. The average time to reach settlement for all cases in this quarter was two years, four months, up slightly from the past. Nevertheless, the overall percentages remained consistent. Of the 40 cases, 28% settled within one year, 63% within two years, and 80% within three years. The length of time to resolve the outlier cases went down to four years. Responding to questions about the overall time it takes to process cases, Mr. Matanoski explained that sometimes petitioners face challenges compiling medical records and obtaining expert reports. Mr. Kraus agreed that petitioners faced those challenges, and added that the Office of Special Masters had not been staffed to its full complement until recently. There was also discussion about the extent to which Court and DOJ resources may be strained if the upward filing trend continues. Mr. King asked that those issues continue to be monitored. Mr. Matanoski offered that some implemented efficiencies include a "fast-track" settlement process and shorter stipulation processing.

Finally, Mr. Matanoski noted a change in the DOJ presentation with the glossary of terms and diagrams illustrating case processing being moved to an Appendix at the end of the presentation. (DOJ PP at 15-21

Report from the Process Workgroup, Dr. Luisita dela Rosa, Chair

Dr. dela Rosa noted that the workgroup had only one opportunity to meet since the last meeting. She stated that the workgroup discussed the recommendations already submitted to the

Secretary. The first general area -- consideration of a third Commission membership category who could be a member of the general public who is a vaccine-injured adult (or his or her representative), a member of the medical community, perhaps from the maternal workgroup area; and an attorney who has experience with the vaccine injury compensation program. The second recommendation was to extend the statute of limitations for filing; and the third was to increase the cap on awards for death and pain and suffering.

Dr. dela Rosa reported that the workgroup agreed that one way to support the Secretary with regard to the membership recommendation would be to develop a list of potential candidates, perhaps by recommending three specific candidates in each of the three areas recommended. With regard to the other recommendations, the ACCV should invite comment from the Secretary on the feasibility of changing the statute of limitations and increasing the award cap. That feedback could help the Commission develop a strategy to achieve the objectives.

The Commission could also invite comment from other interested stakeholders, such as the Office of the Special Masters and vaccine manufacturers, as well as parents of vaccine-injured children, and others interested in the VICP. There was also a suggestion that parents be encouraged to take advantage of the opportunity to offer public comments during the regular ACCV meetings.

Dr. dela Rosa commented that there was discussion about data mining, and Mr. King commented that a proposed future science group would be concerned with data mining of reports of vaccine compensation settlements and awards. He noted that, as Ms. Wrangham mentioned in her public comment, there is some information available that could be sent to the Commission members for consideration at a future ACCV meeting. Mr. Kraus suggested that the information should be vetted by the Process Workgroup before the next meeting, perhaps inviting Ms. Wrangham to contribute her comments, and the Workgroup could develop the detailed agenda item for the next ACCV meeting.

Mr. King observed that some of the ideas and discussion that originated in the Process Workgroup would be appropriate for a more complete discussion at the Commission level. These ideas and issues could be articulated by testimony from stakeholders, including parents, special masters, attorneys, the DOJ, injured individuals, and the Commissioners, themselves. Dr. Douglas commented that recommendations to the Secretary may be promptly acknowledged as received, but before the recommendation actually reaches the Secretary it is processed through what can be a lengthy review process. Mr. Kraus suggested that the process does not preclude an occasional reminder that the Commission is interested in a response. Mr. King suggested that the reminder should consider a rationale for providing the response.

Concerning the Process Workgroup's recommendation to invite outside comment from stakeholders, Mr. King invited comments by the Commissioners. There was an observation that the Commission should have a mechanism to vet community input, and assess the value of testimony that the Commission had not heard in other ways, although that would require resources that might not be available to the Commission. For example, there was a suggestion that a presentation from the former Chief Special Master Golkiewicz might be enlightening in

terms of what the court must address. Since there is no clear national constituency for vaccine-injured individuals, there was also a suggestion that the Commission might benefit from hearing from Ms. Wrangham in her role asEexecutive Director of the National Vaccine Information Center, rather than a participant in the public comment section of the agenda. That would allow a more interactive discussion of the issues she might raise.

Jason Smith suggested there could be an agenda item for the June meeting that would address the statute of limitations in much greater depth than any earlier discussion, perhaps even inviting some testimony from appropriate advocates. An important question to address is why vaccine-injured people allow the deadline to pass? After consensus for the idea of the in-depth discussion was expressed by the members present, Mr. King asked how to implement the idea. Dr. Caserta suggested that a small group from the Commission develop a list of appropriate witnesses, after which staff could make the arrangements. Mr. Kraus suggested that the Process Workgroup might be the appropriate group to develop the witness list, adding that a face-to-face meeting might be more effective than a teleconference (in which case the target meeting would be in September).

Mr. King noted the consensus for the Process Workgroup to take on the responsibility for developing the proposal for the agenda item to be scheduled for the September meeting. He closed the discussion and invited public comment under the last agenda item for the day.

Public Comment

Ms. Theresa Wrangham, Executive Director of the National Vaccine Information Center, expressed appreciation for the Commission support of developing a spreadsheet of data related to settlement of vaccine injury claims. She also commented on the proposal to recommend to the Secretary an extension of the statute of limitations, mentioning her own experience of being unaware of the benefits of the VICP in part because of her family's absence from the country after her child was injured. She commented that people may be unaware of the program for various reasons, or may encounter discouragement in reporting injuries because a health professional suggests that the injury is not related to a vaccine. She also felt the research gaps identified in the IOM report may be responsible for physicians being unaware of some adverse events that are, in fact, caused by vaccines.

Adjournment

There being no further requests for public comment, Mr. King announced that the meeting would be recessed until 9:00 a.m. the following morning, March 7, 2014.

Meeting Day Two – March 7, 2014

Members Present on March 7, 2014

David King, Chair ('14)
Charlene Douglas, Ph.D. ('14)
Edward Kraus, J.D. ('15)
Ann Linguiti Pron, DNP, CRNP, RN ('14)
Luisita dela Rosa, Ph.D. ('15)
Jason Smith, J.D. ('14)(via telephone)
Sylvia Fernandez Villareal, M.D. ('15) (via telephone)

Division of Vaccine Injury Compensation

Vito Caserta, MD., Acting Director, DVIC
Andrea Herzog, Staff Liaison
Andrea Davey, JD, Legal Counsel

Federal Government Representatives

Steve Bende, M.D., NVPO, HHS
Theresa Finn, Office of Vaccines, FDA
Claire Schuster, NIAID, NIH
Tom Shimabukuro, M.D., Immunization Safety Office, CDC

Welcome and Introductions and Unfinished Business from Day One

Mr. King called the meeting to order and welcomed those present in person and on the phone. After introductions, he invited discussion of any item of business unfinished from the day before. Dr. Douglas asked for clarification on the extension requested for the statute of limitations, and Mr. Kraus confirmed that the recommendation to the Secretary was to extend the statute of limitation to at least six years, and preferably eight years. Ms. Herzog confirmed that the recommendation was for eight years, with no mention in the recommendation of an alternative six years.

Dr. Shimabukuro supported the recommendation made the day before by Dr. Caserta that the Commission obtain some supporting data that would indicate examples of individuals who missed the filing deadline and the reasons why they missed it, includingperhaps some data to indicate the extent to which individuals fail to file a claim in a timely way. Dr. Houston added that when any recommendation is put forward that both the positive and negative aspects, if any, be discussed, and in particular how the negative aspects could be ameliorated.

Dr. Pron commended the staff for preparing the table of statistics that is on the ACCV website under "Statistics Reports – February 3, 2014." It was referred to during the meeting on Day One as a "spreadsheet." Dr. Caserta added that, in cooperation with CDC, the statistics are updated monthly with regard to adverse events and annually with regard to doses distributed.

Dr. Villarreal commented that the terms of service for six of the current ACCV members would expire in 2014 and she requested a discussion about the succession and about which remaining members would fill required categorical positions. Mr. King agreed that the issue could be addressed during the "Future Agenda Items/New Business" agenda item at the end of the meeting.

Review of Vaccine Information Statements, Skip Wolfe, CDC

Mr. Wolfe announced that the Commission would review two VIS's, one for hepatitis A and one for hepatitis B. He commented that earlier in the year there was a meeting of the parents and professional consultants group (hereafter "consultants"), which reviewed VIS's unrelated to the two under consideration, but the consultants made some general observations that could be helpful to the Commission's review process. Those observations would be mentioned at the appropriate time during the discussion to follow.

Beginning with the hepatitis A VIS, under Section 1, Dr. Caserta suggested removing "dark urine" from "Hepatitis A can cause" because it could occur in the absence of jaundice. Mr. Wolfe commented that, concerning disease burden, the consultants felt that using actual numbers rather than percentages to describe reduction in disease burden was more effective. Barring providing both figures, there was agreement that, considering health literacy, numbers might be easier for the general population to understand. Particularly if the denominator was one – e.g., one person in 500. Mr. Wolfe commented that the CDC legal counsel, referring to a recent article in Pediatrics, suggested that the way risks are currently described may actually exacerbate public concern about adverse events. Although no alternative was suggested, Mr. Wolfe felt the issue could be considered in the future. Mr. Wolfe also stated that vaccine effectiveness is not explicitly addressed in the VIS, relying on the wording "vaccines *can* prevent," rather than stating that the vaccine is not 100% effective.

As a matter of process, Mr. Kraus asked about the original purpose of the VIS, and Dr. Caserta explained that the VIS is required by the National Childhood Vaccine Injury Act of 1986, as amended, (Act)to provide information to the public about the purpose of the Act, provide information about the risks and benefits of vaccines, and to provide an incentive for doctors to discuss vaccine issues since it was the feeling on the part of parents that doctors avoided the subject. Asked whether the VIS was intended to increase public acceptance of vaccines, Mr. Wolfe said that the purpose was rather to inform objectively about the benefits and risks and to provide information about the VICP. Dr. Pron noted that, for the physician informing a patient in a limited time frame, the VIS is useful as a supplemental information piece.

Mr. Wolfe commented that, by the nature of the format, the discussion of risks is longer than the discussion of benefits because of the need to discuss the numbers. Dr. Pron commented that the hepatitis A disease could affect an adult's ability to work. The risk section should be expanded to be more specific, perhaps mentioning specific occupations such as food handlers. Concerning the final notice about the VICP, Mr. King agreed with an earlier suggestion that the actual statute of limitation be specified on the VIS. Mr. Wolfe commented that the consultants

also made that suggestion. Dr. Caserta commented that the statute on death claims is different from injury claims, but Mr. Wolfe indicated that that issue could be resolved, perhaps with a general statement that there is a limited time to file.

In Section 2, Dr. Pron was concerned that the phrase "two doses are needed for lasting protection" could be confusing – lasting for years, a lifetime? Mr. Wolfe said that he would investigate the anticipated period of protection. Dr. Shimabukuro suggested that the wording be simplified to recommend two doses, rather than imply that one dose could be sufficient for protection. There was a brief discussion about high risk populations, such as Native Americans, although Mr. Wolfe pointed out that the risk in that population has been significantly reduced mainly because of vaccination programs. Dr. Villarreal suggested that adding the CDC web site link to travel recommendations under the heading "Others who should be vaccinated." Mr. Wolfe agreed that the reference should be added to Section 7, "How can I learn more?" Dr. Villarreal also suggested revision of the category "Men who have sex with men," to indicate unprotected sex.

In Section 3, about informing the health care provider, Dr. Pron suggested that the wording be expanded to include a health care provider other than the doctor. The doctor may not be available at the time. She emphasized that it is important to encourage communication. Mr. Wolfe commented that the change is a complicated issue since there are so many individuals who could be consulted – perhaps "health care provider" might suffice. Dr. Shimabukuro stated that health care professional would be more specific and exclude providers who are insurance companies and so on. Mr. Kraus suggested "tell your doctor (or the person giving the vaccine)."

Under Section 4, there was a discussion about placement in the VIS of the severe allergic reactions warning, and there was agreement to move the severe adverse reactions to the beginning of the section. Mr. Wolfe mentioned that the consultants had suggested dealing with unknown risks, but Dr. Shimabukuro commented that such a statement in the VIS could place the provider in the difficult position of trying to explain unknowns. Dr. Pron agreed that there are so many unknown risks, not only in vaccines but in foods, other medicines and so on, that trying to deal with unknowns could be a significantly complicating factor. Mr. Wolfe also commented that the term "death" is no longer used in VIS discussions, except in reference to disease outcome. Dr. Shimabukuro noted that there is almost no data on deaths from vaccines, which would impact the discussion of how to deal with death information in a VIS. Mr. Kraus suggested that if death is mentioned in a VIS it should be clearly explained that the risk is extremely low. Dr. Bende commented that, regardless of the remote possibility of a fatal outcome, the mere mention of the risk will have an effect on an individual's consideration about accepting a vaccination. Dr. Pron agreed, adding that a parent would probably be even less rational about a decision involving an infant. Mr. Wolfe also agreed, adding that if the decision is to include mention of death as a rare outcome, the wording must be very carefully crafted. He and Dr. Shimabukuro agreed to confer about the issue after the meeting.

Mr. Wolfe stated that the remaining sections are the same in all VIS's and have been extensively reviewed over the past years. Dr. Caserta suggested that the admonition to report severe allergic reactions should be generalized to apply to any adverse reaction. Dr.

Shimabukuro recommended depersonalizing the sentence about "they" Vaccine Adverse Event Reporting System (VAERS) do not give medical advice.

Hepatitis B VIS

Turning to Section 1 of the hepatitis B VIS, it was noted that data from 2009 appears to be dated. Mr. Wolfe felt it would be better to choose an average number that would apply to the last several years, and specify that the number applies to U.S. cases. There was also a suggestion that providing a statistic from the period before the vaccine became available would be helpful.

Dr. Villareal commented that most of the risks under paragraph 2 do not apply to children. She felt that the sentence stating that a baby whose mother is infected could be infected at birth is the most important warning for mothers. She commented that if there is no infection within a family there can be resistance to allowing vaccination in a child. There is also the issue of a person being positive but undetected, which would argue for a birth dose of the vaccine. Mr. Krause suggested that there should be a specific separate section for babies. Dr. Caserta observed that infection at birth is more likely to result in chronic hepatitis B, which has a higher risk for developing cancer.

There was a suggestion to include the CDC web site URL for travel vaccinations at some location in the VIS. Finally, sections 3 through 7 are standard in most VIS's. There was a suggestion that a timeframe would be useful in some of the adverse events, such as the caveat in the hepatitis A VIS that "If these problems occur they usually last 1 or 2 days."

Update on the Immunization Safety Office, CDC, Tom Shimabukuro, M.D.

Dr. Shimabukuro stated that he would provide an overview of the recent ACIP February 2014 meeting, an update on the serogroup B meningococcal vaccine programs that are ongoing, and review some selected publications. The influenza session included safety updates for live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) for children and individuals less than 18 years of age, and the safety of LAIV vs. IIV in healthy children (Grading of Recommendations Assessment, Development and Evaluation - GRADE). The presentations were provided to ACIP to inform discussions around a possible preferential recommendation for LAIV in young children. This season the new quadrivalent LAIV was used exclusively (in previous seasons it was a trivalent LAIV). Both IIV3 and IIV4 are being used this influenza season. The interim results indicate that the safety profiles of quadrivalent vaccines (both LAIV an IIV) are comparable to the trivalent formulations. In the GRADE analysis the safety data for LAIV vs. IIV were reassuring.

Data on Tdap vaccination in pregnant women in both VAERS and Vaccine Safety Datalink (VSD) data is reassuring. However, currently there is limited data on repeated Tdap in pregnant women. Dr. Shimabukuro stated that he would provide additional information in an update at the next ACCV meeting.

Dr. Shimabukuro commented on the outbreaks of serogroup b meningococcal disease at Princeton University and University of California (UC) at Santa Barbara. CDC is currently

working with these institutions, public health agencies and the FDA to coordinate vaccination programs with serogroup B meningococcal vaccine. The vaccine (Bexsero) is not licensed in the US and is being given under an Expanded Access to Investigational New Drug (IND) protocol approved by FDA. The vaccine is licensed in Europe and Australia. The vaccine is a two-dose regimen and the program was recently completed at Princeton and is under way at UC Santa Barbara.

Regarding recent publications of interest, Dr. Shimabukuro cited the Stockwell et al., study "Risk of Fever after Pediatric Trivalent Inactivated Influenza Vaccine and13-Valent Pneumococcal Conjugate Vaccine." JAMA Pediatr. 2014 Jan 6. [Epub ahead of print]. The authors found that simultaneous trivalent inactivated influenza vaccine (TIV) and 13-valent pneumococcal conjugate vaccine (PCV13) in young children was associated with higher transient increased fever risk than administration of either vaccine without the other product.

Moro et al., in the study "Reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women." Am J Obstet Gynecol. 2013 Dec 27. [Epub ahead of print], looked at reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women. In their review, they did not identify any concerning pattern of adverse events in pregnant women or their infants following maternal Hep A or Hep AB immunizations during pregnancy.

Vellozzi et al., in the review "Guillain-Barre Syndrome, Influenza, and Influenza Vaccination: The Epidemiologic Evidence." Clin Infect Dis. 2014 Feb 5. [Epub ahead of print], descried evidence of a small increased risk of Guillain-Barré syndrome (GBS) that has been observed following influenza vaccines but 10-fold less than that observed following the1976 swine-influenza vaccine. The authors note that the risk of GBS following influenza is much greater than the small risk following vaccination.

In a study by Hibbs et al., "Notes from the field: rotavirus vaccine administration errors - United States, 2006-2013." MMWR (Morbidity and Mortality Weekly Report). 2014 Jan 31;63(4):81, CDC identified 39 reports of rotavirus vaccine administration by injection in VAERS and 27 reports of eye splashes. Administration errors are largely preventable with proper education and training. During discussion, Dr. Villarreal noted that the product itself is delivered for use in a syringe, albeit one that should be used as a spray – but a needle could be attached for injection. She suggested that the manufacturer should be made aware of the errors, since they could have resulted from confusing packaging.

Lastly, a study by Vellozi et al., "Cumulative Risk of Guillain-Barré Syndrome Among Vaccinated and Unvaccinated Populations During the 2009 H1N1 Influenza Pandemic." Am J Public Health. 2014 Feb 13. [Epub ahead of print], found that cumulative GBS risk was less among the pH1N1vaccinated than the unvaccinated population, suggesting the benefit of vaccination as it relates to GBS. The observed potential protective effect on GBS attributed to vaccination warrants further study.

Update on National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Activities, Ms. Claire Schuster, NIAID

Ms. Schuster cited two studies with regard to immune response to vaccines. In Haralembeiva et al, which assessed immune response to rubella vaccine, subjects of African descent demonstrated higher antibody response than individuals of European descent and/or Hispanic ethnicity. In Furman et al, a study examining the immune response of 53 women and 34 men to seasonal influenza vaccine, the women produced antibodies that more effectively neutralized influenza virus. In the men, testosterone appeared to suppress immune response by altering the expression of specific genes. This study helps explain differences in male and female responses to vaccines, but more research is needed.

In a recent issue of the publication Vaccine, the World Health Organization and NIAID put out a call to accelerate vaccine research for sexually transmitted infections, particularly in the areas of herpes simplex virus, chlamydia, gonorrhea, trichomoniasis and syphilis.

Ms. Schuster then provided links to several NIH web resources including the NIAID Showcase that provides information on HIV, malaria, dengue, RSV and universal flu vaccine; NIAID's Antibacterial Resistance Program: Current Status and Future Directions; and the Accelerating Medicine Partnership, a collaboration between NIH, industry and nonprofits, an effort to increase new diagnostics and therapies. Finally, Ms. Schuster mentioned the Global Vaccine and Immunization Research Forum (March 4-6) sponsored by NIAID, WHO and the Bill and Melinda Gates Foundation.

Update on the Center for Biologics Evaluation and Research (CBER) Vaccine Activities Theresa Finn, Ph.D., CBER

Dr. Finn commented that at the last meeting the Commission had heard about four vaccines approved for H1N1 influenza. These vaccines are manufactured by CSL Limited, MedImmune, Novartis and Sanofi Pasteur. On November 10 the FDA approved an additional H1N1 vaccine for use in adults 18 years of age and over. This vaccine is manufactured by IDBiomedical (distributed by GlaxoSmithKline), the manufacturing process is the same as the Flulaval manufacturing process. On the same date the FDA approved Afluria, a seasonal flu vaccine manufactured by CSL, for use in children 6 months of age through 17 years of age (it had previously been approved for use in persons 18 and over). This approval also expands use of the H1N1 vaccine manufactured by CSL for use in children 6 months of age and older. Another seasonal flu vaccine, Agriflu, manufactured by Novartis, was approved for use in adults on November 27. Finally, on October 19, FDA approved the seasonal influenza vaccine Fluarix for use in children three years of age and older (also previously approved for adult use).

Dr. Finn reported that FDA had approved Cervarix on October 16 for use in females 10 through 25 years of age. It is a HPV vaccine manufactured by GlaxoSmithKline for prevention of cervical cancer. On the same day the FDA approved Gardasil for use in males 9 through 26 years of age for the prevention of genital warts caused by HPV 6 and 11.

Dr. Finn reported that a number of other vaccines are currently under review, including a meningococcal conjugate vaccine for prevention of disease caused by *Neisseria meningitides,* and a seasonal influenza vaccine. She noted that the VRBPAC meeting in November had discussed and made recommendations on the safety and effectiveness of Prevnar 13, a pneumococcal conjugate vaccine for use in infants and FluBlok, a recombinant seasonal influenza vaccine made in insect cells and manufactured by Protein Sciences.

Update from the National Vaccine Program Office, Dr. Steve Bende, NVPO

Dr. Bende reported on the NVAC meeting in February. The annual report of the NVPO described the contributions of the federal partners to achieve the National Vaccine Plan, which is approaching its mid-course review, which NVPO will coordinate. During the meeting the CDC provided an update on state immunization programs and an analysis of funding in those programs. There was a presentation on the Institute of Medicine's Strategic Multi-Attribute Ranking Tool (SMART) that allows a ranking of vaccines to assist policy makers in prioritizing vaccines for development. IOM will release a report in November on its utility and future use based on current testing with potential users.

NIAID sponsored the Global Vaccine and Immunization Research Forum, a venue to track progress on the vaccine R&D agenda. BARDA also presented opportunities on the R&D continuum in terms of emergency preparedness based on threat assessments, and identifying areas in the "valley of death" where opportunities exist but where product development success is hampered by lack of funding and other limitations.

CDC provided a historical overview of supply management, including the pediatric stockpile that was established in 1983 to prevent interruptions in supply. The current management of the stockpile relies on vendor-managed inventories, but CDC remains the distributor for some vaccines. The stockpile has been successful for managing short-term shortages.

An ongoing issue is adult immunization, and the NVAC heard a presentation on adult immunization coverage data. The NVAC Standards for Adult Immunization Practices lay out a list of actions for organizations involved in adult immunization to insure that everyone is assessed for immunizations at every health care encounter. The NVAC discussed plans to implement the standards. NVPO discussed its intention to present a national adult immunization plan, including drafting the National Adult Immunization Plan expected in August.

NVPO announced it was collaborating with others within the OASHto administer a grant, Mobilization for Health: National Prevention Partnership Awards, to increase community awareness and action on community health services, including immunizations.

The Vaccine Hesitancy Working Group is developing metrics to measure vaccine attitudes, and assessing methods of communications to encourage such acceptance. The Maternal Immunization Working Group will release an early draft report of its activities within a week or so. There was a report from the President's Cancer Panel on human papillomavirus

vaccine, in which there was an assertion that increased acceptance of HPV vaccine could be a very important opportunity to prevent cancer. The recommendations in the report include reducing missed clinical opportunities; increase acceptance of HPV by parents, caregivers and adolescents; and maximize access to the vaccine. The NVAC Working Group also presented a report in its activities. Finally there was a session on vaccine storage and handling practices.

During discussion, Mr. Kraus requested a future briefing on the FDA PRISM surveillance program.

Public Comment

Ms. Wrangham, who introduced herself earlier in the meeting, stated that the National Vaccine Information Center (NVIC) supports the extension of the statute of limitations, but noted that the original intent of the Act would allow alternative recourse to pursue damages for vaccine injuries. The NVIC does not support the extension of the statute of limitation if the result is that the VICP becomes the sole recourse for damages. The NVIC recommends that the ACCV also recommend additional strategies to reduce the number of dismissals.

Ms. Wrangham noted that the VIS is shorter today and that information is limited and that the risk of death is not optional information and should appear on the VIS. Consumers should have complete information even if the information results in the consumer declining vaccination. The NVIC supports a recommendation that came from a parent consultation held by CDC that the VIS should be distributed well in advance of the vaccination, and not in the moments just prior to vaccination. There should also be information that there are other sources of vaccine safety information available.

The NVIC recommends that all VIS's introduce a different message than "Why get vaccinated?" That appears to be a policy statement. There must be an acknowledgment that vaccines do not always work. The risk statement should reflect the injuries in the Vaccine Injury Table. There should also be a clear description of the disease for which the vaccine is recommended.

Regarding the legal requirement to report adverse events to VAERS, it should be supplemented by information that helps individuals report adverse events beyond the minimum legal requirements. The VIS should identify the existence of the manufacturer's product insert, which should be mentioned in section 7. It should also clearly provide the information about how to file an injury claim and the length of time available to do so.

New Agenda Items/New Business

Mr. King noted that a discussion of replacement members was not appropriate since the Commission does not nominate or approve new Commission members. Dr. Caserta noted that the list of nominations has not been finalized, but there are several names being considered. Concerning the chair and vice chair, Mr. Kraus made a motion that the current leadership remain in place through the next two meetings. The motion was unanimously approved.

Adjournment

Mr. King called for a motion to adjourn. On motion duly made and seconded, the Commission approved adjournment.

3

Vaccine Injury Compensation Trust Fund

Balance as of March 31, 2014

$3,475,302,680.15

Figures for October 1, 2013 – March 31, 2014

Excise Tax Revenue: $95,277,401
Interest on Investments: $30,317,260
Net Income: $125,594,662
Interest as a Percentage of Net Income: 24%

Source: U.S. Treasury, Bureau of Public Debt
May 6, 2014

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4.1

NATIONAL VACCINE INJURY COMPENSATION PROGRAM [1]

PROGRAM STATISTICS REPORT

As of Tuesday, May 06, 2014

I. PETITIONS FILED

Fiscal Year	Totals
FY 1988	24
FY 1989	148
FY 1990	1,492
FY 1991	2,718
FY 1992	189
FY 1993	140
FY 1994	107
FY 1995	180
FY 1996	84
FY 1997	104
FY 1998	120
FY 1999	411
FY 2000	164
FY 2001	216
FY 2002	957
FY 2003	2,592
FY 2004	1,214
FY 2005	735
FY 2006	325
FY 2007	410
FY 2008	417
FY 2009	397
FY 2010	449
FY 2011	386
FY 2012	400
FY 2013	503
FY 2014	311
Totals:	**15,193**

NATIONAL VACCINE INJURY COMPENSATION PROGRAM [1]

PROGRAM STATISTICS REPORT

As of Tuesday, May 06, 2014

II. ADJUDICATIONS [2]

Fiscal Year	Compensable	Dismissed	Totals
FY 1989	9	12	21
FY 1990	100	33	133
FY 1991	141	447	588
FY 1992	166	487	653
FY 1993	125	588	713
FY 1994	162	446	608
FY 1995	160	575	735
FY 1996	162	408	570
FY 1997	189	198	387
FY 1998	144	181	325
FY 1999	98	139	237
FY 2000	125	104	229
FY 2001	86	87	173
FY 2002	104	103	207
FY 2003	56	99	155
FY 2004	62	233	295
FY 2005	60	121	181
FY 2006	69	191	260
FY 2007	83	120	203
FY 2008	147	134	281
FY 2009	134	231	365
FY 2010	181	292	473
FY 2011	261	1,370	1,631
FY 2012	259	2,439	2,698
FY 2013	365	627	992
FY 2014	148	98	246
Totals:	**3,596**	**9,763**	**13,359**

NATIONAL VACCINE INJURY COMPENSATION PROGRAM [1]

PROGRAM STATISTICS REPORT

As of Tuesday, May 06, 2014

III. AWARDS PAID [3]

	Compensated			Dismissed		Interim Fees		
Fiscal Year	No. of Awards	Petitioners' Award Amounts	Attorneys' Fees/Costs Payments	No. of Payments to Attorneys	Attorneys' Fees/Costs Payments	No. of Payments	Attorneys' Fees/Costs Payments	Total Outlays
FY 1989	6	$1,317,654.78	$54,107.14	0	$0.00	0	$0.00	$1,371,761.92
FY 1990	88	$53,252,510.46	$1,379,005.79	4	$57,699.48	0	$0.00	$54,689,215.73
FY 1991	114	$95,980,493.16	$2,364,758.91	30	$496,809.21	0	$0.00	$98,842,061.28
FY 1992	130	$94,538,071.30	$3,001,927.97	118	$1,212,677.14	0	$0.00	$98,752,676.41
FY 1993	162	$119,693,267.87	$3,262,453.06	272	$2,447,273.05	0	$0.00	$125,402,993.98
FY 1994	158	$98,151,900.08	$3,571,179.67	335	$3,166,527.38	0	$0.00	$104,889,607.13
FY 1995	169	$104,085,265.72	$3,662,770.57	221	$2,276,136.32	0	$0.00	$110,014,172.61
FY 1996	163	$100,425,325.22	$3,096,231.96	216	$2,364,122.71	0	$0.00	$105,885,679.89
FY 1997	179	$113,620,171.68	$3,998,284.77	142	$1,879,418.14	0	$0.00	$119,397,874.59
FY 1998	165	$127,546,009.19	$4,002,278.55	121	$1,936,065.50	0	$0.00	$133,484,353.24
FY 1999	96	$95,917,680.51	$2,799,910.85	117	$2,306,957.40	0	$0.00	$101,024,548.76
FY 2000	136	$125,945,195.64	$4,112,369.02	80	$1,724,451.08	0	$0.00	$131,782,015.74
FY 2001	97	$106,678,632.57	$3,373,865.88	57	$2,066,224.67	0	$0.00	$111,318,723.12
FY 2002	80	$59,798,604.39	$2,653,598.69	50	$656,244.79	0	$0.00	$63,108,448.07
FY 2003	65	$82,816,240.07	$3,147,755.12	69	$1,545,654.87	0	$0.00	$87,509,650.06
FY 2004	57	$61,933,764.20	$3,079,326.55	69	$1,198,615.96	0	$0.00	$66,211,708.71
FY 2005	64	$55,065,797.01	$2,694,664.03	71	$1,790,587.29	0	$0.00	$59,551,048.33
FY 2006	68	$48,746,162.74	$2,441,199.02	64	$1,353,632.61	0	$0.00	$52,540,994.37
FY 2007	82	$91,449,433.89	$4,034,164.37	61	$1,692,020.25	0	$0.00	$97,175,608.51
FY 2008	141	$75,716,552.06	$5,270,237.04	72	$2,432,847.05	2	$117,265.31	$83,536,901.46
FY 2009	131	$74,142,490.58	$5,404,711.98	36	$1,567,139.53	28	$4,241,362.55	$85,345,704.64
FY 2010	173	$179,387,341.30	$5,961,744.40	56	$1,686,239.95	22	$1,978,803.88	$189,214,129.53
FY 2011	251	$216,319,428.47	$9,736,216.67	402	$5,425,243.19	28	$2,001,770.91	$233,482,659.44
FY 2012	260	$163,511,998.82	$9,104,488.60	1,017	$8,621,182.32	37	$5,420,257.99	$186,657,927.73
FY 2013	375	$254,666,326.70	$13,333,179.53	703	$6,970,278.84	50	$1,454,851.74	$276,424,636.81
FY 2014	193	$128,193,096.13	$5,953,839.72	428	$5,002,188.12	26	$1,872,127.80	$141,021,231.77
Totals:	3,593	$2,726,100,414.54	$111,384,262.26	4,801	$62,066,216.85	193	$17,086,440.18	$2,918,637,333.83

1. Fiscal year statistics for petitions/claims alleging injuries or deaths resulting from vaccines administered on or after 10/1/1988.

2. Generally, petitions/claims are not adjudicated in the same fiscal year as filed. On average, it takes 2-3 years to adjudicate a petition/claim after it is filed.

3. "Compensated" are claims that have been paid as a result of a settlement between parties or a decision made by the U.S. Court of Federal Claims (Court). The # of awards is the number of petitioner awards paid, including the attorneys' fees/costs payments, if made during a fiscal year. However, petitioners' awards and attorneys' fees/costs are not necessarily paid in the same fiscal year as when the petitions/claims are determined compensable. "Dismissed" includes the # of payments to attorneys and the total amount of payments for attorneys' fees/costs per fiscal year. The VICP will pay attorneys' fees/costs related to the claim, whether or not the petition/claim is awarded compensation by the Court, if certain minimal requirements are met. "Total Outlays" are the total amount of funds expended for compensation and attorneys' fees/costs from the Vaccine Injury Compensation Trust Fund by fiscal year.

4.2

National Vaccine Injury Compensation Program (VICP) Adjudication Categories by Vaccine for Claims Filed Calendar Year 2006 to Present (as of May 6, 2014)[1]

		Compensable			Compensable Total	Dismissed/Non-Compensable Total	Grand Total
Vaccine Alleged by Petitioner[2]	No. of Doses Distributed US CY 2006 - CY 2012 (Source: CDC)[3]	Concession	Court Decision	Settlement			
DT	592,707	1	0	3	4	3	7
DTaP	68,113,573	10	17	72	99	64	163
DTaP-Hep B-IPV	38,347,667	4	6	18	28	33	61
DTaP-HIB	1,135,474	0	0	0	0	1	1
DTaP-IPV-HIB	46,633,881	0	0	5	5	8	13
DTP	0[4]	0	1	2	2	2	5
Hep A-Hep B	10,405,325	0	0	8	8	0	8
Hep B-HIB	4,621,999	1	1	1	3	1	4
Hepatitis A (Hep A)	110,596,300	1	5	17	23	17	40
Hepatitis B (Hep B)	116,853,062	2	10	35	47	32	79
HIB	70,755,674	0	1	4	5	4	9
HPV	55,168,454	10	0	59	69	73	142
Influenza[5]	809,000,000	27	67	650	744	143	887
IPV	52,439,162	0	0	3	3	2	5
Measles	135,660	0	0	1	1	0	1
Meningococcal	51,173,032	1	1	21	23	3	26
MMR	65,864,745	15	13	52	80	67	147
MMR-Varicella	8,073,618	7	0	7	14	8	22

[1] The date range for this table was selected to reflect the status of the current Program since the inclusion of influenza in July 2005, which now constitutes the majority of all VICP claims.

[2] This is the first vaccine listed by the petitioner in the claim, and other vaccines may be alleged or may form the basis of compensation.

[3] Vaccine doses are self-reported distribution data provided by US-licensed vaccine manufacturers. The data provide an estimate of the annual national distribution and do not represent vaccine administration. In order to maintain confidentiality of an individual manufacturer or brand, the data are presented in an aggregate format by vaccine type.

[4] Whole cell pertussis vaccines were not distributed during this time period.

[5] Flu doses are derived from CDC's FluFinder tracking system, which includes data provided to CDC by US-licensed influenza vaccine manufacturers as well as their first line distributors.

Nonqualified[6]	N/A	0	0	0	0	21	21
OPV	0	1	0	0	1	3	4
Pneumococcal Conjugate	123,606,306	0	1	5	6	13	19
Rotavirus	61,336,583	0	3	14	18	5	23
Rubella	422,548	0	1	0	1	0	1
Td	53,009,015	4	5	48	57	15	72
Tdap	133,744,203	9	6	62	77	9	86
TETANUS	3,836,052	3	0	14	17	10	27
Unspecified[7]	N/A	1	0	2	3	539	542
Varicella	82,534,257	3	5	18	26	10	36
Grand Total	**1,968,399,297**	**101**	**143**	**1,121**	**1,365**	**1,086**	**2,451**

DEFINITIONS:

1. Compensable – The injured person who filed a claim was paid money by the VICP. Compensation can be achieved through a concession by the Department of Health and Human Services (HHS), a decision on the merits of the claim by a special master or a judge of the United States Court of Federal Claims (Court), or a settlement between the parties.
    a. Concession: HHS concludes that a petition should be compensated based on a thorough review and analysis of the evidence, including medical records and the scientific and medical literature. The HHS review concludes that the petitioner is entitled to compensation, including a determination either that it is more likely than not that the vaccine caused the injury or the evidence supports fulfillment of the criteria of the Vaccine Injury Table. The Court also determines that the petition should be compensated.
    b. Court Decision: A special master or the court, within the United States Court of Federal Claims, issues a legal decision after weighing the evidence presented by both sides. HHS abides by the ultimate Court decision even if it maintains its position that the petitioner was not entitled to compensation (e.g., that the injury was not caused by the vaccine).
        i. For injury claims, compensable court decisions are based in part on one of the following determinations by the court:
            1. The evidence is legally sufficient to show that the vaccine more likely than not caused (or significantly aggravated) the injury; or

[6] Claims filed for vaccines which are not covered under the VICP.

[7] Insufficient information submitted by petitioner to make an initial determination. The concession was for multiple unidentified vaccines that caused abscess formation at the vaccination site(s), and the settlements were for multiple vaccines later identified in the Special Master's Decisions.

2. The injury is listed on, and meets all of the requirements of, the Vaccine Injury Table, and HHS has not proven that a factor unrelated to the vaccine more likely than not caused or significantly aggravated the injury. An injury listed on the Table and meeting all Table requirements is given the legal presumption of causation. It should be noted that conditions are placed on the Table for both scientific and policy reasons.

c. Settlement: The petition is resolved via a negotiated settlement between the parties. This settlement is not an admission by the United States or the Secretary of Health and Human Services that the vaccine caused the petitioner's alleged injuries, and, in settled cases, the Court does not determine that the vaccine caused the injury. A settlement therefore cannot be characterized as a decision by HHS or by the Court that the vaccine caused an injury. Claims may be resolved by settlement for many reasons, including consideration of prior court decisions; a recognition by both parties that there is a risk of loss in proceeding to a decision by the Court making the certainty of settlement more desirable; a desire by both parties to minimize the time and expense associated with litigating a case to conclusion; and a desire by both parties to resolve a case quickly and efficiently.

2. Non-compensable/Dismissed – The injured person who filed a claim was ultimately not paid money.

a. Non-compensable Court decisions include the following:

i. The Court determines that the person who filed the claim did not demonstrate that the injury was caused (or significantly aggravated) by a covered vaccine or meet the requirements of the Table (for injuries listed on the Table).

ii. The claim was dismissed for not meeting other statutory requirements (such as not meeting the filing deadline, not receiving a covered vaccine, and not meeting the statute's severity requirement).

iii. The injured person voluntarily withdrew his or her claim.

5

5.1

HPV (Human Papillomavirus) Vaccine: What You Need to Know Gardasil®

Many Vaccine Information Statements are available in Spanish and other languages. See www.immunize.org/vis.
Hojas de Información Sobre Vacunas están disponibles en español y en muchos otros idiomas. Visite http://www.immunize.org/vis

1. Why get vaccinated?

The vaccine you are getting (Gardasil) prevents cancer caused by human papillomavirus (HPV) infection.

Gardasil prevents

- **cervical cancer** in women,
- **vaginal and vulvar cancers** in women, and
- **anal cancer** in women and men.

In addition to these cancers, Gardasil also prevents **genital warts** in both women and men.

In the U.S., about 12,000 women get cervical cancer every year, and about 4,000 women die from it. Gardasil can prevent 70% of these cancers.

HPV infection usually comes from sexual contact, and most people will become infected at some point in their life. About 14 million Americans get infected every year. Many infections will go away and not lead to serious problems. But thousands of women and men get cancer and diseases from HPV.

2. HPV vaccine

Gardasil is one of two HPV vaccines. It is recommended for both males and females. It is routinely given at 11 or 12 years of age, but it may be given through age 26 years for females and through age 21 years for males who did not get the vaccine earlier.

Vaccination is not a substitute for cervical cancer screening. Women should still get regular Pap tests.

3. Some people should not get this vaccine

- Anyone who has had a severe (life-threatening) allergic reaction to a dose of HPV vaccine should not get another dose.

  Anyone who has a severe (life threatening) allergy to any component of HPV vaccine should not get the vaccine.

  Tell your doctor if you have any severe allergies that you know of, including a severe allergy to yeast.

- HPV vaccine is not recommended for pregnant women. But if you learn that you were pregnant when you were vaccinated it is not a reason to consider ending the pregnancy. Women who are breastfeeding may be vaccinated.

- If you have a mild illness you can probably get the vaccine today. If you are moderately or severely ill, you should probably wait until you recover. Your doctor can advise you.

4. Risks of a vaccine reaction

With a vaccine, like any medicine, there is a chance of side effects. These are usually mild and go away on their own.

Serious side effects are also possible, but are very rare.

Mild or moderate problems after HPV vaccine

- Reactions in the arm where the shot was given:
  - Pain (about 8 people in 10)
  - Redness or swelling (about 1 person in 4)
- Fever:
  - Mild (100°F) (about 1 person in 10)
  - Moderate (102°F) (about 1 person in 65)
- Other problems:
  - Headache (about 1 person in 3)

No serious problems have been associated with HPV vaccine.

Problems that could happen after any vaccine

- Brief fainting spells can happen after any medical procedure, including vaccination. Sitting or lying down for about 15 minutes can help prevent fainting, and injuries caused by a fall. Tell your doctor if you feel dizzy, have vision changes, or ringing in the ears.

- Severe shoulder pain and reduced range of motion in the arm where a shot was given can happen, very rarely, after a vaccination.

- Severe allergic reactions from a vaccine are very rare, estimated at less than 1 in a million doses. If one were to occur, it would usually be within a few minutes to a few hours after the vaccination.

5. What if there is a serious reaction?

What should I look for?

- Look for anything that concerns you, such as signs of a severe allergic reaction, very high fever, or behavior changes.

  Signs of a **severe allergic reaction** can include hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, and weakness. These would usually start a few minutes to a few hours after the vaccination.

What should I do?

- If you think it is a **severe allergic reaction** or other emergency that can't wait, call 9-1-1 or get to the nearest hospital. Otherwise, call your doctor.

- Afterward, the reaction should be reported to the "Vaccine Adverse Event Reporting System" (VAERS). Your doctor should file this report, or you can do it yourself through the VAERS web site at www.vaers.hhs.gov, or by calling 1-800-822-7967.

VAERS does not give medical advice.

6. The National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP) is a federal program that was created to compensate people who may have been injured by certain vaccines.

Persons who believe they may have been injured by a vaccine can learn about the program and about filing a claim by calling 1-800-338-2382 or visiting the VICP website at www.hrsa.gov/vaccinecompensation. There is a time limit to file a claim for compensation.

7. How can I learn more?

- Ask your doctor.

- Call your local or state health department.

- Contact the Centers for Disease Control and Prevention (CDC):
  - Call **1-800-232-4636 (1-800-CDC-INFO)** or
  - Visit CDC's website at **www.cdc.gov/hpv**

5.2

HPV (Human Papillomavirus) Vaccine: What You Need to Know Cervarix®

Many Vaccine Information Statements are available in Spanish and other languages. See www.immunize.org/vis.
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1. Why get vaccinated?

The vaccine you are getting (Cervarix) prevents **cervical cancer** caused by human papillomavirus (HPV) infection.

In the U.S., about 12,000 women get cervical cancer every year, and about 4,000 women die from it. Cervarix can prevent 70% of these cancers.

HPV infection usually comes from sexual contact, and most people will become infected at some point in their life. About 14 million Americans get infected every year. Many of these infections will go away and not lead to serious problems. But thousands of women get cancer and diseases from HPV.

2. HPV vaccine

Cervarix is one of two HPV vaccines. It is recommended only for females. It is routinely given at 11 or 12 years of age. But it may be given through age 26 years for females who did not get it earlier.

Vaccination is not a substitute for cervical cancer screening. Women should still get regular Pap tests.

3. Some women should not get this vaccine

- Anyone who has had a severe (life-threatening) allergic reaction to a dose of HPV vaccine should not get another dose.

  Anyone who has a severe (life threatening) allergy to any component of HPV vaccine should not get the vaccine. *Tell your doctor if you have any severe allergies that you know of.*

- HPV vaccine is not recommended for pregnant women. But if you find that you were pregnant when you were vaccinated it is not a reason to consider ending the pregnancy. Women who are breastfeeding may be vaccinated.

- If you have a mild illness you can probably get the vaccine today. If you are moderately or severely ill, you should probably wait until you recover. Your doctor can advise you.

4. Risks of a vaccine reaction

With a vaccine, like any medicine, there is a chance of side effects. These are usually mild and go away on their own.

Serious side effects are also possible, but are very rare.

Mild or moderate problems after HPV vaccine

- Reactions in the arm where the shot was given:
  - Pain (about 9 people in 10)
  - Redness or swelling (about 1 person in 2)

- Mild fever (99.5°F) (about 1 person in 8)

- Headache or fatigue (about 1 person in 2)

- Nausea, vomiting, diarrhea, or abdominal pain (about 1 person in 4)

- Muscle or joint pain (up to 1 person in 2)

No serious problems have been associated with HPV vaccine.

Problems that could happen after any vaccine

- Brief fainting spells can happen after any medical procedure, including vaccination. Sitting or lying down for about 15 minutes can help prevent fainting, and injuries caused by a fall. Tell your doctor if you feel dizzy, have vision changes or ringing in the ears.

- Severe shoulder pain and reduced range of motion in the arm where a shot was given can happen, very rarely, after a vaccination.

- Severe allergic reactions from a vaccine are very rare, estimated at less than 1 in a million doses. If one were to occur, it would be within a few minutes to a few hours after the vaccination.

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What should I do?

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- Call your local or state health department.
- Contact the Centers for Disease Control and Prevention (CDC):
  - Call **1-800-232-4636 (1-800-CDC-INFO)** or
  - Visit CDC's website at **www.cdc.gov/hpv**

5.3

Vaccine Information Statement

Your Baby's First Vaccines: What you need to know

Many Vaccine Information Statements are available in Spanish and other languages. See www.immunize.org/vis.
Hojas de Información Sobre Vacunas están disponibles en español y en muchos otros idiomas. Visite http://www.immunize.org/vis

Your baby will get these vaccines today:
[ ] DTaP [ ] Hib [ ] Hepatitis B [ ] Polio [ ] PCV13 [ ] Rotavirus
(Provider: Check appropriate boxes)

Why get vaccinated?

Vaccines can protect your baby from these 8 childhood diseases:

1. Diphtheria
Signs and symptoms include a thick covering in the back of the throat that can make it hard to breathe.
Diphtheria can lead to breathing problems, paralysis and heart failure.
- About 15,000 people died each year in the U.S. from diphtheria before there was a vaccine.

2. Tetanus (Lockjaw)
Signs and symptoms include painful tightening of the muscles, usually all over the body.
Tetanus can lead to stiffness of the jaw so the victim can't open her mouth or swallow.
- Tetanus kills 1 person out of every 5 who get it.

3. Pertussis (Whooping Cough)
Signs and symptoms include violent coughing spells that can make it hard for an infant to eat, drink, or breathe. These spells can last for weeks.
Pertussis can lead to pneumonia, seizures, and brain damage.

4. Hib (*Haemophilus influenzae* type b)
Signs and symptoms. There may not be any signs or symptoms in mild cases.
Hib can lead to meningitis (infection of the brain and spinal cord coverings); pneumonia; infections of the blood, joints, bones, and covering of the heart; brain damage; and deafness.
- Before there was a vaccine, Hib disease was the leading cause of bacterial meningitis in children under 5 years of age in the U.S.

5. Hepatitis B
Signs and symptoms include tiredness, diarrhea and vomiting, jaundice (yellow skin or eyes), and pain in muscles, joints and stomach. But usually there are no signs or symptoms at all.
Hepatitis B can lead to liver damage, and liver cancer. Some people develop chronic (long term) hepatitis B infection. These people may not look or feel sick, but can infect others.
- Hepatitis B can cause liver damage and cancer in 1 child out of 4 who are infected.

6. Polio
Signs and symptoms can include flu-like illness, or there may be no signs or symptoms at all.
Polio can lead to paralysis (can't move an arm or leg, or sometimes can't breathe).
- In the 1950s, polio paralyzed about 37,000 people and killed about 1,700 every year in the U.S.

7. Pneumococcal Disease
Signs and symptoms include fever, chills, cough, and chest pain.
Pneumococcal disease can lead to meningitis (infection of the brain and spinal cord coverings), blood infections, ear infections, pneumonia, deafness, and brain damage.

8. Rotavirus
Signs and symptoms include diarrhea (sometimes severe), vomiting and fever.
Rotavirus can lead to dehydration and hospitalization.
- Up to 70,000 children were hospitalized each year in the U.S. because of rotavirus disease, and 20 to 60 died, before there was a vaccine.

Babies usually catch these diseases from other children or adults, who might not even know they are infected. A mother with **Hepatitis B** can infect her baby at birth. **Tetanus** enters the body through a cut or wound; it is not spread from person to person.

These diseases are much less common than they used to be, thanks to generations of parents who made sure their children were vaccinated. But even a disease that has almost disappeared will come back if we stop vaccinating. This has already happened in some parts of the world. When fewer babies get vaccinated, more babies get sick.

Six Childhood Vaccines can protect your baby from these eight diseases:

Vaccine	Number of Doses	Recommended Ages	Other Information
DTaP (Diphtheria, Tetanus, Pertussis)	5	2 months, 4 months, 6 months, 15-18 months, 4-6 years	Some children should not get pertussis vaccine. These children can get a vaccine called DT.
Hepatitis B	3	Birth, 1-2 months, 6-18 months	
Polio	4	2 months, 4 months, 6-18 months, 4-6 years	
Hib (*Haemophilus influenzae* type b)	3 or 4	2 months, 4 months, (6 months), 12-15 months	There are 2 types of Hib vaccine. With one type the 6-month dose is not needed.
PCV13 (pneumococcal)	4	2 months, 4 months, 6 months, 12-15 months	Older children with certain chronic diseases may also need this vaccine.
Rotavirus	2 or 3	2 months, 4 months, (6 months)	Not a shot, but liquid that is swallowed. There are 2 types of rotavirus vaccine. With one type the 6-month dose is not needed.

Your healthcare provider might offer certain **combination vaccines**. These are several vaccines given in the same shot. Combination vaccines are as safe and effective as the individual vaccines, and can mean fewer shots for your baby.

Some children should not get certain vaccines

Most children can safely get all of these vaccines. But be aware of these exceptions:

- A child who is sick on the day vaccinations are scheduled might be asked to come back for them at a later date.

- Any child who had a life-threatening allergic reaction after getting a vaccine should not get another dose of that vaccine.

- A child should not get a vaccine that contains a substance to which he or she has a severe allergy.
  Tell your doctor if your child has any severe allergies, or has ever had a severe reaction after any vaccination. Some of these vaccines contain neomycin, streptomycin, yeast, lactose, sucrose, or latex.

Talk to your doctor before your child gets . . .

. . . **DTaP vaccine**, if your child ever had any of these reactions after a dose of DTaP:
- A brain or nervous system disease within 7 days,
- Non-stop crying for 3 hours or more,
- A seizure or collapse,
- A fever of over 105°F.

. . . **Polio vaccine**, if your child has a severe allergy to the antibiotics neomycin, streptomycin or polymyxin B.

. . . **Hepatitis B vaccine**, if your child has a severe allergy to yeast.

. . . **Rotavirus Vaccine**, if your child has:
- SCID (Severe Combined Immunodeficiency),
- A weakened immune system for any other reason,
- Recently gotten a blood product, such as immune globulin,
- Ever had intussusception (a type of bowel obstruction that is treated in a hospital).

. . . **PCV13** vaccine, if your child has a severe allergy to yeast, or ever had a severe reaction after a dose of DTaP (or other vaccine containing diphtheria toxoid).

Risks of a Vaccine Reaction

Vaccines can cause side effects, like any other medicine.

Most vaccine reactions are **not serious**: tenderness, redness, or swelling where the shot was given; or a mild fever. These appear soon after the shot is given and go away within a day or two. They happen with about one-fourth to one-half of children, depending on the vaccine.

Polio, Hepatitis B and **Hib Vaccines** have been associated only with these kinds of mild reactions.

Other childhood vaccines have been associated with the following additional problems:

DTaP Vaccine
Mild Problems: Fussiness (up to 1 child in 3); tiredness or poor appetite (up to 1 child in 10); vomiting (up to 1 child in 50); swelling of the entire arm or leg for 1-7 days (up to 1 child in 30) – usually after the 4th or 5th dose.
Moderate Problems: Seizure (1 child in 14,000); non-stop crying for 3 hours or longer (up to 1 child in 1,000); fever over 105°F (1 child in 16,000).
Serious problems: Long term seizures, coma, lowered consciousness, and permanent brain damage have been reported following DTaP vaccination. These reports are so rare that it is hard to tell if the problems were really caused by the vaccine.

Pneumococcal Vaccine
Mild Problems: Drowsiness or temporary loss of appetite (about 1 child in 2); fussiness (about 8 children in 10).
Moderate Problems: Fever over 102.2°F (about 1 child in 20).

Rotavirus Vaccine
Mild Problems: Fussiness, mild temporary diarrhea or vomiting.
Serious Problems: *Intussusception* is a type of bowel blockage that is treated in a hospital, and could require surgery. There is a small risk of intussusception from rotavirus vaccination (between 1 in 100,000 and 1 in 20,000 children), usually within a week after the 1st or 2nd vaccine dose.

Problems that could happen after any vaccine:

- Brief fainting spells can happen after any medical procedure, including a vaccination. Sitting or lying down for about 15 minutes can help prevent fainting, and injuries caused by a fall.
- Severe shoulder pain and reduced range of motion in the arm where a shot was given can happen, very rarely, after a vaccination.
- Severe allergic reactions from a vaccine are very rare, estimated at less than 1 in a million doses. If one were to occur, it would usually be within a few minutes to a few hours after the vaccination.

As with any medicine, there is a very remote chance of a vaccine causing a serious injury or death.

The safety of vaccines is always being monitored. For more information, visit:
www.cdc.gov/vaccinesafety/

What if there is a serious reaction?

What should I look for?

- Look for anything that concerns you, such as signs of a severe allergic reaction, very high fever, or behavior changes.

  Signs of a severe allergic reaction can include hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, and weakness. These would usually start a few minutes to a few hours after the vaccination.

  Following rotavirus vaccine, also look for signs of stomach or bowel problems.

What should I do?

- If you think it is a severe allergic reaction or other emergency that can't wait, call 9-1-1 or get the person to the nearest hospital. Otherwise, call your doctor.
- Afterward, the reaction should be reported to the Vaccine Adverse Event Reporting System (VAERS). Your doctor should file this report, or you can do it yourself through the VAERS web site at www.vaers.hhs.gov, or by calling **1-800-822-7967**.

VAERS does not give medical advice.

The National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP) is a federal program that was created to compensate people who may have been injured by certain vaccines.

Persons who believe they may have been injured by a vaccine can learn about the program and about filing a claim by calling **1-800-338-2382** or visiting the VICP website at www.hrsa.gov/vaccinecompensation.

How can I learn more?

- Ask your doctor.
- Call your local or state health department.
- Contact the Centers for Disease Control and Prevention (CDC):
  - Call **1-800-232-4636 (1-800-CDC-INFO)**
  - Visit CDC's website at www.cdc.gov/vaccines or www.cdc.gov/hepatitis

Vaccine Information Statement (Interim)
42 U.S.C. § 300aa-26
[DATE]

6

Dated: November 4, 2013.

Bahar Niakan,

Director, Division of Policy and Information Coordination.

[FR Doc. 2013–27006 Filed 11–8–13; 8:45 am]

BILLING CODE 4165–15–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

National Vaccine Injury Compensation Program: Addition to the Vaccine Injury Table to Include All Vaccines Against Seasonal Influenza

AGENCY: Health Resources and Services Administration, HHS.

ACTION: Notice.

SUMMARY: Through this notice, the Secretary of the U.S. Department of Health and Human Services (the Secretary) announces that all FDA-approved vaccines against seasonal influenza are covered under the National Vaccine Injury Compensation Program (VICP), which provides a system of no-fault compensation for certain individuals who have been injured by covered childhood vaccines. Prior to this publication, trivalent influenza vaccines were included under Category XIV on the Vaccine Injury Table (Table) and will continue to be listed in that category. This notice serves to include all vaccines against seasonal influenza (not already covered under Category XIV) as covered vaccines under Category XVII of the Table (new vaccines covered under the VICP). This notice ensures that petitioners may file petitions relating to all vaccines against seasonal influenza (not already covered under the VICP) with the VICP even before such vaccines are added as a separate and distinct category to the Table through rulemaking.

DATES: This notice is effective on November 12, 2013. As described below, all vaccines against seasonal influenza (except trivalent influenza vaccines, which are already covered under the VICP) will be covered under the VICP on November 12, 2013.

FOR FURTHER INFORMATION CONTACT: Vito Caserta, M.D., M.P.H., Acting Director, Division of Vaccine Injury Compensation, Healthcare Systems Bureau, Health Resources and Services Administration, Parklawn Building, Room 11C–26, 5600 Fishers Lane, Rockville, Maryland 20857; telephone number (301) 443–5287.

SUPPLEMENTARY INFORMATION: The statute authorizing the VICP provides for the inclusion of additional vaccines in the VICP when they are recommended by the Centers for Disease Control and Prevention (CDC) to the Secretary for routine administration to children. See section 2114(e)(2) of the Public Health Service (PHS) Act, 42 U.S.C. 300aa–14(e)(2). Consistent with section 13632(a)(3) of Public Law 103–66, the regulations governing the VICP provide that such vaccines will be included as covered vaccines in the Table as of the effective date of an excise tax to provide funds for the payment of compensation with respect to such vaccines (42 CFR 100.3(c)(5)).

By way of background, trivalent influenza vaccines (meaning they each contain three vaccine virus strains which are thought most likely to cause disease outbreaks during the influenza season) are routinely given to millions of individuals in the United States each year. Trivalent influenza vaccines include an inactivated (killed) virus vaccine administered using a syringe as well as a live, attenuated product administered in a nasal spray. All trivalent vaccines have been covered under the VICP since July 1, 2005. On April 12, 2005, the Health Resources and Services Administration (HRSA) published a notice in the **Federal Register** announcing that such vaccines were covered under the category for new vaccines on the Table. See 70 FR 19092. Subsequently, the Secretary engaged in rulemaking to add trivalent influenza vaccines as a separate category on the Table (category XIV on the Table). See 76 FR 36367.

Since that time, quadrivalent influenza vaccines (meaning that they contain four vaccine virus strains which are thought most likely to cause disease outbreaks during the influenza season) have been approved by the Food and Drug Administration (FDA), and such vaccines are expected to be administered as an alternative to trivalent influenza vaccines during the upcoming and future flu seasons. On June 25, 2013, Public Law 113–15 was enacted, extending the applicable excise tax on trivalent influenza vaccines to also include any other vaccines against seasonal influenza. See Public Law 113–15 (amending 26 U.S.C. § 4132(a)(1)(N)).

The amendment included in Public Law 113–15 ensures that all FDA-approved seasonal influenza vaccines, including quadrivalent influenza vaccines, and other new seasonal influenza vaccines are covered under the VICP. Under the regulations governing the VICP, Category XVII of the Table specifies that "[a]ny new vaccine recommended by CDC for routine administration to children, after publication by the Secretary of a notice of coverage" is a covered vaccine under the Table (42 CFR 100.3(a), Item XVII). As explained in HRSA's notice of coverage with respect to the coverage of trivalent influenza vaccines, the CDC recommended in its May 28, 2004, issue of the Morbidity and Mortality Weekly Report (MMWR) that influenza vaccines be routinely administered to children between 6 and 23 months of age because children in this age group are at an increased risk for complications from influenza. That recommendation extends to seasonal influenza vaccines beyond trivalent vaccines. The latest CDC update of its annual influenza vaccination recommendation was published in the MMWR on September 20, 2013. MMWR 2013;62, No. 7. This report updated the 2012 recommendations by the CDC and its Advisory Committee on Immunization Practices regarding the use of influenza vaccines for the prevention and control of seasonal influenza. Routine annual influenza vaccination is recommended for all persons aged 6 months and older. For the 2013–14 influenza season, it is expected that trivalent live attenuated influenza vaccine (LAIV3) will be replaced by a quadrivalent LAIV formulation (LAIV4). Inactivated influenza vaccines (IIVs) will be available in both trivalent (IIV3) and quadrivalent (IIV4) formulations. No preferential recommendation was made for one influenza vaccine product over another for persons for whom more than one product is otherwise appropriate.

This notice serves to satisfy the regulation's publication requirement. Through this notice, all vaccines against seasonal influenza (beyond trivalent influenza vaccines, which are already covered under Category XIV on the Table) are included as covered vaccines under Category XVII of the Table (new vaccines).

Under section 2114(e) of the PHS Act, as amended by section 13632(a) of the Omnibus Budget Reconciliation Act of 1993, coverage for a vaccine recommended by the CDC for routine administration to children shall take effect upon the effective date of the tax enacted to provide funds for compensation with respect to the vaccine included as a covered vaccine in the Table. Under Public Law 113–15, the excise tax for vaccines against seasonal influenza (beyond trivalent influenza vaccines) "shall apply to sales and uses on or after the later of: (A) The first day of the first month which begins more than 4 weeks after the date of the enactment of this Act [i.e., Pub. L. 113–

15]; or (B) the date on which the Secretary of Health and Human Services lists any vaccines against seasonal influenza (other than any vaccine against seasonal influenza listed by the Secretary prior to the date of the enactment of this Act) for purposes of compensation for any vaccine-related injury or death through the Vaccine Injury Compensation Trust Fund." Public Law 113–15, § 1. The law further provides that if the vaccines were sold before or on the effective date of the excise tax, but delivered after this date, the delivery date of such vaccines shall be considered the sale date. *Id.*

Under this statutory language, the effective date of the excise tax for seasonal influenza vaccines other than trivalent influenza vaccines is the later of August 1, 2013 (which is the first day of the first month beginning more than 4 weeks after the effective date of Public Law 113–15, which was June 25, 2013), or the date on which the Secretary publishes a notice of coverage under the VICP for seasonal influenza vaccines not previously covered under the VICP. This publication is the notice referred to in the latter requirement. Because this publication is made after August 1, 2013, the effective date of coverage for all vaccines against seasonal influenza (beyond trivalent influenza vaccines, which are already covered by the VICP) is the effective date of this publication, November 12, 2013.

Petitions filed concerning vaccine-related injuries or deaths associated with all vaccines against seasonal influenza vaccines must be filed within the applicable statute of limitations. The filing limitations applicable to petitions filed with the VICP are set out in section 2116(a) of the PHS Act (42 U.S.C. 300aa–16(a)). In addition, section 2116(b) of the PHS Act lays out specific exceptions to these statutes of limitations that apply when the effect of a revision to the Table makes a previously ineligible person eligible to receive compensation or when an eligible person's likelihood of obtaining compensation significantly increases. Under this provision, persons who may be eligible to file petitions based on the addition of a new category of vaccines under Category XVII of the Table may file a petition for compensation not later than 2 years after the effective date of the revision if the injury or death occurred not more than 8 years before the effective date of the revision of the Table (42 U.S.C. 300aa–16(b)). Thus, persons whose petitions may not be timely under the limitations periods described in section 2116(a) of the PHS Act, may still file petitions concerning vaccine-related injuries or deaths associated with seasonal influenza vaccines (with the exception of trivalent influenza vaccines that are already covered under the VICP) until November 12, 2015, as long as the vaccine-related injury or death occurred on or before November 12, 2021 (8 years prior to the effective date of the addition of non-trivalent seasonal influenza vaccines as covered vaccines).

The Table will be amended through subsequent rulemaking to include all vaccines against seasonal influenza in place of only trivalent influenza vaccines under Category XIV of the Table. Once that is done, the Table's coverage provisions (codified at 42 CFR 100.3(c)) will explain that trivalent influenza vaccines are included on the Table as of July 1, 2005, and that other seasonal influenza vaccines are included on the Table as of November 12, 2013.

Dated: November 5, 2013.

Mary K. Wakefield,

Administrator.

[FR Doc. 2013–26992 Filed 11–8–13; 8:45 am]

BILLING CODE 4165–15–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review; Amended Notice of Meeting

Notice is hereby given of a change in the meeting of the Virology—A Study Section, October 03, 2013, 08:30 a.m. to October 04, 2013, 05:30 p.m., Embassy Suites Baltimore—Downtown, 222 St. Paul Place, Baltimore, MD which was published in the **Federal Register** on September 17, 2013, 78 FR 180 Pgs. 57169–57170.

The meeting will start on December 16, 2013 at 9:00 a.m. and end December 17, 2013 at 5:00 p.m. The meeting location remains the same. The meeting is closed to the public.

Dated: *November 5, 2013.*

Michelle Trout,

Program Analyst, Office of Federal Advisory Committee Policy.

[FR Doc. 2013–26894 Filed 11–8–13; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases; Amended Notice of Meeting

Notice is hereby given of a change in the meeting of the National Institute of Allergy and Infectious Diseases Special Emphasis Panel, October 10, 2013, 09:00 a.m. to October 10, 2013, 03:00 p.m., National Institutes of Health, 6700 B Rockledge Drive, 3137, Bethesda, MD, 20892 which was published in the **Federal Register** on September 16, 2013, 78 FR 56904.

The meeting notice is amended to change the date of the meeting from October 10, 2013 to December 5, 2013. The meeting is closed to the public.

Dated: November 5, 2013.

David Clary,

Program Analyst, Office of Federal Advisory Committee Policy.

[FR Doc. 2013–26906 Filed 11–8–13; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Heart, Lung, and Blood Institute; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: Heart, Lung, and Blood Initial Review Group; Heart, Lung, and Blood Program Project Review Committee.

Date: December 6, 2013.

Time: 8:00 a.m. to 4:00 p.m.

Agenda: To review and evaluate grant applications.

Place: Hyatt Regency Bethesda, One Bethesda Metro Center, 7400 Wisconsin Avenue, Bethesda, MD 20814.

Contact Person: Jeffrey H Hurst, Ph.D., Scientific Review Officer, Office of Scientific Review/DERA National Heart, Lung, and Blood Institute, National Institutes of Health, 6701 Rockledge Drive, Room 7208, Bethesda,

7

7.1

Herzog, Andrea (HRSA)

From: Andrea Herzog
Sent: Thursday, April 10, 2014 10:00 AM
To: Herzog, Andrea (HRSA)
Subject: Fwd: FW: National Vaccine Injury Compensation Program Question
Attachments: mmr_ii_pi.pdf

---------- Forwarded message ----------
From: **David King** <dking@salesmotion.com>
Date: Wednesday, April 9, 2014
Subject: FW: National Vaccine Injury Compensation Program Question
To: Andrea Herzog "Houston, Avril (HRSA)" <AHouston@hrsa.gov>

Annie & Avril,

Just making sure you have a copy of this – I know (believe) Vito has retired.

Thanks - Dave

From: Michael Vetter [mailto:michael.vetter@gmail.com]
Sent: Wednesday, April 09, 2014 4:48 PM
To: vcaserta@hrsa.gov
Cc: dking@salesmotion.com
Subject: National Vaccine Injury Compensation Program Question

Dear Dr. Caserta,

A quick question about the National Vaccine Injury Compensation Program's Vaccine Injury Table.

I believe my 17-month old son was injured by the MMR vaccine which caused or significantly aggravated his onset of diabetes mellitus to occur within 30 days of vaccination - with no prior signs, symptoms, or immediate family history. Merck lists diabetes mellitus as a possible adverse reaction to their M-M-R II vaccine in the product insert (see attached).

Why doesn't "the table" include diabetes mellitus for MMR when it is clearly identified by the manufacturer as a possible adverse result of the MMR vaccine?

I know the National Childhood Vaccine Injury Act of 1986 authorizes the ACCV to amend the Vaccine Injury Table used by the VICP. Would you consider adding diabetes mellitus as an adverse reaction to MMR?

Thanks in advance,

Michael Vetter

(585) 662-9401

7.2

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

M-M-R® II
(MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

DESCRIPTION

M-M-R* II (Measles, Mumps, and Rubella Virus Vaccine Live) is a live virus vaccine for vaccination against measles (rubeola), mumps, and rubella (German measles).

M-M-R II is a sterile lyophilized preparation of (1) ATTENUVAX* (Measles Virus Vaccine Live), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) MUMPSVAX* (Mumps Virus Vaccine Live), the Jeryl Lynn** (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) MERUVAX* II (Rubella Virus Vaccine Live), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts.[1,2]

The growth medium for measles and mumps is Medium 199 (a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum) containing SPGA (sucrose, phosphate, glutamate, and recombinant human albumin) as stabilizer and neomycin.

The growth medium for rubella is Minimum Essential Medium (MEM) [a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum] containing recombinant human albumin and neomycin. Sorbitol and hydrolyzed gelatin stabilizer are added to the individual virus harvests.

The cells, virus pools, and fetal bovine serum are all screened for the absence of adventitious agents.

The reconstituted vaccine is for subcutaneous administration. Each 0.5 mL dose contains not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus; 12,500 $TCID_{50}$ of mumps virus; and 1,000 $TCID_{50}$ of rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin. The product contains no preservative.

Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-M-R II, when reconstituted as directed, is clear yellow.

CLINICAL PHARMACOLOGY

Measles, mumps, and rubella are three common childhood diseases, caused by measles virus, mumps virus (paramyxoviruses), and rubella virus (togavirus), respectively, that may be associated with serious complications and/or death. For example, pneumonia and encephalitis are caused by measles. Mumps is associated with aseptic meningitis, deafness and orchitis; and rubella during pregnancy may cause congenital rubella syndrome in the infants of infected mothers.

The impact of measles, mumps, and rubella vaccination on the natural history of each disease in the United States can be quantified by comparing the maximum number of measles, mumps, and rubella cases reported in a given year prior to vaccine use to the number of cases of each disease reported in 1995. For measles, 894,134 cases reported in 1941 compared to 288 cases reported in 1995 resulted in a 99.97% decrease in reported cases; for mumps, 152,209 cases reported in 1968 compared to 840 cases reported in 1995 resulted in a 99.45% decrease in reported cases; and for rubella, 57,686 cases reported in 1969 compared to 200 cases reported in 1995 resulted in a 99.65% decrease.[3]

Clinical studies of 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II is highly immunogenic and generally well tolerated. In these studies, a single injection of the

vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible persons. However, a small percentage (1-5%) of vaccinees may fail to seroconvert after the primary dose (see also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*).

A study[4] of 6-month-old and 15-month-old infants born to vaccine-immunized mothers demonstrated that, following vaccination with ATTENUVAX, 74% of the 6-month-old infants developed detectable neutralizing antibody (NT) titers while 100% of the 15-month-old infants developed NT. This rate of seroconversion is higher than that previously reported for 6-month-old infants born to naturally immune mothers tested by HI assay. When the 6-month-old infants of immunized mothers were revaccinated at 15 months, they developed antibody titers equivalent to the 15-month-old vaccinees. The lower seroconversion rate in 6-month-olds has two possible explanations: 1) Due to the limit of the detection level of the assays (NT and enzyme immunoassay [EIA]), the presence of trace amounts of undetectable maternal antibody might interfere with the seroconversion of infants; or 2) The immune system of 6-month-olds is not always capable of mounting a response to measles vaccine as measured by the two antibody assays.

There is some evidence to suggest that infants who are born to mothers who had wild-type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.[5,6]

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components.[7-12] These studies also established that seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases.[13-15]

Following vaccination, antibodies associated with protection can be measured by neutralization assays, HI, or ELISA (enzyme linked immunosorbent assay) tests. Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination.[16-18] See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing.

The RA 27/3 rubella strain in M-M-R II elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine[19-25] and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies.[26,27] The RA 27/3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses.[27-29] The increased levels and broader profile of antibodies produced by RA 27/3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus,[27,29-31] and provide greater confidence for lasting immunity.

INDICATIONS AND USAGE

Recommended Vaccination Schedule

M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

Individuals first vaccinated at 12 months of age or older should be revaccinated prior to elementary school entry. Revaccination is intended to seroconvert those who do not respond to the first dose. The Advisory Committee on Immunization Practices (ACIP) recommends administration of the first dose of M-M-R II at 12 to 15 months of age and administration of the second dose of M-M-R II at 4 to 6 years of age.[59] In addition, some public health jurisdictions mandate the age for revaccination. Consult the complete text of applicable guidelines regarding routine revaccination including that of high-risk adult populations.

Measles Outbreak Schedule

Infants Between 6 to 12 Months of Age

Local health authorities may recommend measles vaccination of infants between 6 to 12 months of age in outbreak situations. This population may fail to respond to the components of the vaccine. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established. The younger the infant, the lower the likelihood of seroconversion (see CLINICAL

PHARMACOLOGY). Such infants should receive a second dose of M-M-R II between 12 to 15 months of age followed by revaccination at elementary school entry.[59]

Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

Other Vaccination Considerations

Non-Pregnant Adolescent and Adult Females

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see below and PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.[33]

Women of childbearing age should be advised not to become pregnant for 3 months after vaccination and should be informed of the reasons for this precaution.

The ACIP has stated "If it is practical and if reliable laboratory services are available, women of childbearing age who are potential candidates for vaccination can have serologic tests to determine susceptibility to rubella. However, with the exception of premarital and prenatal screening, routinely performing serologic tests for all women of childbearing age to determine susceptibility (so that vaccine is given only to proven susceptible women) can be effective but is expensive. Also, 2 visits to the health-care provider would be necessary — one for screening and one for vaccination. Accordingly, rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing — and may be preferable, particularly when costs of serology are high and follow-up of identified susceptible women for vaccination is not assured."[33]

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS).

Postpartum Women

It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period (see PRECAUTIONS, *Nursing Mothers*).

Other Populations

Previously unvaccinated children older than 12 months who are in contact with susceptible pregnant women should receive live attenuated rubella vaccine (such as that contained in monovalent rubella vaccine or in M-M-R II) to reduce the risk of exposure of the pregnant woman.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps, or rubella and import these diseases into the United States. Therefore, prior to international travel, individuals known to be susceptible to one or more of these diseases can either receive the indicated monovalent vaccine (measles, mumps, or rubella), or a combination vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella; and if monovalent measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.[34-36]

Vaccination is recommended for susceptible individuals in high-risk groups such as college students, health-care workers, and military personnel.[33,34,37]

According to ACIP recommendations, most persons born in 1956 or earlier are likely to have been infected with measles naturally and generally need not be considered susceptible. All children, adolescents, and adults born after 1956 are considered susceptible and should be vaccinated, if there are no contraindications. This includes persons who may be immune to measles but who lack adequate documentation of immunity such as: (1) physician-diagnosed measles, (2) laboratory evidence of measles immunity, or (3) adequate immunization with live measles vaccine on or after the first birthday.[34]

The ACIP recommends that "Persons vaccinated with inactivated vaccine followed within 3 months by live vaccine should be revaccinated with two doses of live vaccine. Revaccination is particularly important when the risk of exposure to wild-type measles virus is increased, as may occur during international travel."[34]

Post-Exposure Vaccination

Vaccination of individuals exposed to wild-type measles may provide some protection if the vaccine can be administered within 72 hours of exposure. If, however, vaccine is given a few days before

exposure, substantial protection may be afforded.[34,38,39] There is no conclusive evidence that vaccination of individuals recently exposed to wild-type mumps or wild-type rubella will provide protection.[33,37]

Use With Other Vaccines

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines.*

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including gelatin.[40]

Do not give M-M-R II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and PRECAUTIONS, *Pregnancy*).

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

Febrile respiratory illness or other active febrile infection. However, the ACIP has recommended that all vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper respiratory infection with or without low-grade fever, or other low-grade febrile illness.[41]

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;[41-43] cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis[60] (MIBE), pneumonitis[61] and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

WARNINGS

Due caution should be employed in administration of M-M-R II to persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur following vaccination (see ADVERSE REACTIONS).

Hypersensitivity to Eggs

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur (see PRECAUTIONS).[45]

However, the AAP has stated, "Most children with a history of anaphylactic reactions to eggs have no untoward reactions to measles or MMR vaccine. Persons are not at increased risk if they have egg allergies that are not anaphylactic, and they should be vaccinated in the usual manner. In addition, skin testing of egg-allergic children with vaccine has not been predictive of which children will have an immediate hypersensitivity reaction...Persons with allergies to chickens or chicken feathers are not at increased risk of reaction to the vaccine."[44]

Hypersensitivity to Neomycin

The AAP states, "Persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should not receive measles vaccine. Most often, however, neomycin allergy manifests as a contact dermatitis, which is a delayed-type (cell-mediated) immune response rather than anaphylaxis. In such persons, an adverse reaction to neomycin in the vaccine would be an erythematous,

pruritic nodule or papule, 48 to 96 hours after vaccination. A history of contact dermatitis to neomycin is not a contraindication to receiving measles vaccine."[44]

Thrombocytopenia

Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of M-M-R II (or its component vaccines) may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases (see ADVERSE REACTIONS).

PRECAUTIONS

General

Adequate treatment provisions including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

Special care should be taken to ensure that the injection does not enter a blood vessel.

Children and young adults who are known to be infected with human immunodeficiency viruses and are not immunosuppressed may be vaccinated. However, vaccinees who are infected with HIV should be monitored closely for vaccine-preventable diseases because immunization may be less effective than for uninfected persons (see CONTRAINDICATIONS).[42,43]

Vaccination should be deferred for 3 months or longer following blood or plasma transfusions, or administration of immune globulin (human).[44]

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.[33] However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see *Nursing Mothers*).

There are no reports of transmission of live attenuated measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R II.

Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine;[46] no studies have been reported to date of the effect of measles virus vaccines on untreated tuberculous children. However, individuals with active untreated tuberculosis should not be vaccinated.

As for any vaccine, vaccination with M-M-R II may not result in protection in 100% of vaccinees.

The health-care provider should determine the current health status and previous vaccination history of the vaccinee.

The health-care provider should question the patient, parent, or guardian about reactions to a previous dose of M-M-R II or other measles-, mumps-, or rubella-containing vaccines.

Information for Patients

The health-care provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The health-care provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.[47]

Pregnancy should be avoided for 3 months following vaccination, and patients should be informed of the reasons for this precaution (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, CONTRAINDICATIONS, and PRECAUTIONS, *Pregnancy*).

Laboratory Tests

See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing, and CLINICAL PHARMACOLOGY.

Drug Interactions

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines.*

Immunosuppressive Therapy

The immune status of patients about to undergo immunosuppressive therapy should be evaluated so that the physician can consider whether vaccination prior to the initiation of treatment is indicated (see CONTRAINDICATIONS and PRECAUTIONS).

The ACIP has stated that "patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive live virus vaccines. Short-term (<2 weeks), low- to moderate-dose systemic corticosteroid therapy, topical steroid therapy (e.g. nasal, skin), long-term alternate-day treatment with low to moderate doses of short-acting systemic steroid, and intra-articular, bursal, or tendon injection of corticosteroids are not immunosuppressive in their usual doses and do not contraindicate the administration of [measles, mumps, or rubella vaccine]."[33,34,37]

Immune Globulin

Administration of immune globulins concurrently with M-M-R II may interfere with the expected immune response.[33,34,44]

See also PRECAUTIONS, *General.*

Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with M-M-R II. It is also not known whether M-M-R II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) In a 10-year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome;[48] (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans;[37] and (3) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to infection with wild-type measles during pregnancy.[57,58] There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects.

Nursing Mothers

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants.[49] In the infants with serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella.[50,51] Caution should be exercised when M-M-R II is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established (see also CLINICAL PHARMACOLOGY). Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

Geriatric Use

Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

ADVERSE REACTIONS

The following adverse reactions are listed in decreasing order of severity, without regard to causality, within each body system category and have been reported during clinical trials, with use of the marketed vaccine, or with use of monovalent or bivalent vaccine containing measles, mumps, or rubella:

Body as a Whole

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Pancreatitis; diarrhea; vomiting; parotitis; nausea.

Endocrine System

Diabetes mellitus.

Hemic and Lymphatic System

Thrombocytopenia (see WARNINGS, *Thrombocytopenia*); purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis and anaphylactoid reactions have been reported as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm in individuals with or without an allergic history.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. This type of involvement as well as myalgia and paresthesia, have also been reported following administration of MERUVAX II.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0-3%; women: 12-26%),[17,52,53] and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in women older than 35 years, these reactions are generally well tolerated and rarely interfere with normal activities.

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS); subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia.

Experience from more than 80 million doses of all live measles vaccines given in the U.S. through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine very rarely.[54] In no case has it been shown that reactions were actually caused by vaccine. The Centers for Disease Control and Prevention has pointed out that "a certain number of cases of encephalitis may be expected to occur in a large childhood population in a defined period of time even when no vaccines are administered". However, the data suggest the possibility that some of these cases may have been caused by measles vaccines. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with wild-type measles (one per two thousand reported cases).

Post-marketing surveillance of the more than 200 million doses of M-M-R and M-M-R II that have been distributed worldwide over 25 years (1971 to 1996) indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported.[17]

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with infection with wild-type measles, 6-22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Centers for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.[55]

Cases of aseptic meningitis have been reported to VAERS following measles, mumps, and rubella vaccination. Although a causal relationship between the Urabe strain of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Respiratory System

Pneumonia; pneumonitis (see CONTRAINDICATIONS); sore throat; cough; rhinitis.

Skin

Stevens-Johnson syndrome; erythema multiforme; urticaria; rash; measles-like rash; pruritis.

Local reactions including burning/stinging at injection site; wheal and flare; redness (erythema); swelling; induration; tenderness; vesiculation at injection site.

Special Senses — Ear

Nerve deafness; otitis media.

Special Senses — Eye

Retinitis; optic neuritis; papillitis; retrobulbar neuritis; conjunctivitis.

Urogenital System

Epididymitis; orchitis.

Other

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals (see CONTRAINDICATIONS). No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993.[56]

Under the National Childhood Vaccine Injury Act of 1986, health-care providers and manufacturers are required to record and report certain suspected adverse events occurring within specific time periods after vaccination. However, the U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) which will accept all reports of suspected events.[47] A VAERS report form as well as information regarding reporting requirements can be obtained by calling VAERS 1-800-822-7967.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravascularly.

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.

The recommended age for primary vaccination is 12 to 15 months.

Revaccination with M-M-R II is recommended prior to elementary school entry. See also INDICATIONS AND USAGE, *Recommended Vaccination Schedule.*

Children first vaccinated when younger than 12 months of age should receive another dose between 12 to 15 months of age followed by revaccination prior to elementary school entry.[59] See also INDICATIONS AND USAGE, *Measles Outbreak Schedule.*

Immune Globulin (IG) is not to be given concurrently with M-M-R II (see PRECAUTIONS, *General* and PRECAUTIONS, *Drug Interactions*).

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial — First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. If the lyophilized vaccine cannot be dissolved, discard. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. M-M-R II, when reconstituted, is clear yellow.

Use With Other Vaccines

M-M-R II should be given one month before or after administration of other live viral vaccines.

M-M-R II has been administered concurrently with VARIVAX* [Varicella Virus Vaccine Live (Oka/Merck)], and PedvaxHIB* [*Haemophilus b* Conjugate Vaccine (Meningococcal Protein Conjugate)] using separate injection sites and syringes. No impairment of immune response to individually tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed with M-M-R II were similar to those seen when each vaccine was given alone.

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concurrently with measles, mumps and rubella vaccines is not recommended because there are limited data relating to the simultaneous administration of these antigens.

However, other schedules have been used. The ACIP has stated "Although data are limited concerning the simultaneous administration of the entire recommended vaccine series (i.e., DTaP [or DTwP], IPV [or OPV], Hib with or without Hepatitis B vaccine, and varicella vaccine), data from numerous studies have indicated no interference between routinely recommended childhood vaccines (either live, attenuated, or killed). These findings support the simultaneous use of all vaccines as recommended."[32]

HOW SUPPLIED

No. 4681 — M-M-R II is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), **NDC** 0006-4681-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature.

Storage

To maintain potency, M-M-R II must be stored between -58°F and +46°F (-50°C to +8°C). Use of dry ice may subject M-M-R II to temperatures colder than -58°F (-50°C).

Protect the vaccine from light at all times, since such exposure may inactivate the viruses.

Before reconstitution, store the lyophilized vaccine at 36°F to 46°F (2°C to 8°C). The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. **Do not freeze the diluent.**

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 36°F to 46°F (2°C to 8°C) and discard if not used within 8 hours.

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

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7.3

03-09-06

GUIDING PRINCIPLES FOR RECOMMENDING CHANGES TO THE VACCINE INJURY TABLE

When recommending changes to the Vaccine Injury Table ("the Table"), members of the Advisory Commission on Childhood Vaccines (ACCV) shall utilize the following overarching guiding principles:

- The Table should be scientifically and medically credible; and
- Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

Recognizing that it would be virtually impossible to agree upon a precise definition of scientific and medical credibility, the ACCV adopts the following additional guiding principles in furtherance of the above overarching principles:

- To the extent that the Institute of Medicine ("IOM") has studied the possible association between a vaccine and an adverse effect, the conclusions of the IOM should be considered by the ACCV and deemed credible but those conclusions should not limit the deliberations of the ACCV.
- To the extent there are data sources other than an IOM report, ACCV members should make an effort to assess the relative strength of those data sources. When making such assessments, ACCV members should acknowledge that differing sources of data should be afforded different weight and should do so by adopting the following hierarchy (listed from strongest to weakest sources of data):

    - Clinical laboratory data (such as PCR confirmation of vaccine strain virus following immunization against varicella)
    - Challenge/re-challenge/de-challenge data involving non-relapsing symptoms or diseases (particularly when documented in multiple individuals)
    - Controlled clinical trials (including, but not limited to, double-blind, placebo controlled clinical trials)
    - Controlled observational studies such as cohort and case control studies, including but not limited to studies based upon data from the Vaccine Safety Datalink (VSD) database
    - Uncontrolled observational studies such as ecological studies
    - Case series
    - Data from passive surveillance systems, including but not limited to the Vaccine Adverse Event Reporting System
    - Case reports

- Editorial articles on scientific presentations
- Non-peer reviewed publications

However, ACCV members should also consider additional factors that may affect the relative weight of a particular source of evidence, including, but not limited to:

- Particular methodological limitations associated with a study or source of evidence
- Potential bias associated with the conduct of a particular study or source of evidence, including analytic bias or bias resulting from potential conflicts of interest among the investigators
- Potential confounding factors that may have impacted the results of a particular study
- Biologic coherence, including whether there is a scientifically viable mechanism by which the vaccine could be associated with the particular adverse event under consideration (*e.g.*, does it make sense to extrapolate the results of studies examining the health effects of wild type virus to a vaccine that is not a live attenuated viral vaccine?)

- Where appropriate, ACCV members should request assistance from members of the Health Resources and Services Administration, Division of Vaccine Injury Compensation or others associated with the Program in assessing the relative strength of the sources of evidence.

- In the absence of an IOM report or study considered to be definitive, ACCV members should assess not only the relative strength of the evidence but also the consistency of the evidence supporting the proposed change to the Table. Consistency across multiple sources of evidence generally should be considered an indication of credibility.

- When considering proposed changes to the Table, ACCV members should also remain cognizant of the important policy considerations underlying the Table. In an effort to give maximum effect to those policy considerations, where there is a split in credible scientific evidence supporting a proposed change to the Table:

  - In those instances where an Omnibus Proceeding under the VICP has addressed the particular injury under consideration, members of the ACCV should consider the causation finding(s) of the Special Master who presided over the Omnibus Proceeding but the finding(s) of the Special Master should not limit the deliberations of the ACCV; and
  - ACCV members should tend toward adding or retaining the proposed injury(ies).

Approved by ACCV: March 9, 2006

7.4

Adverse Effects of Vaccines: Evidence and Causality

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HARDBACK (2012)

Kathleen Stratton, Andrew Ford, Erin Rusch, and Ellen Wright Clayton, Editors; Committee to Review Adverse Effects of Vaccines; Institute of Medicine

Causality Conclusion

Conclusion 4.25: The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and arthropathy in men.

TYPE 1 DIABETES

Epidemiologic Evidence

The committee reviewed eight studies to evaluate the risk of type 1 diabetes after the administration of MMR vaccine. One study (Fescharek et al., 1990) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population. Two controlled studies (Karavanaki et al., 2008; Telahun et al., 1994) had very serious methodological limitations that precluded their inclusion in this assessment. Karavanaki et al. (2008) and Telahun et al. (1994) conducted case-control studies in diabetic children and hospital controls using a self-report questionnaire, but did not validate vaccination histories with medical records or adequately adjust for age or date of diagnosis.

The five remaining controlled studies (Altobelli et al., 2003; Blom et al., 1991; DeStefano et al., 2001; Hviid et al., 2004; Patterson, 2000) contributed to the weight of epidemiologic evidence and are described below.

Blom et al. (1991) conducted a case-control study in diabetic children (0 to 14 years of age) enrolled in the Swedish Childhood Diabetes Register from September 1985 through August 1986. A total of 393 children with type 1 diabetes were matched to 786 controls (two controls for each case matched on age, sex, and county) from the official Swedish population register. The dates of vaccination were ascertained from questionnaires that were sent to the parents of cases and their matched controls within 4 weeks of disease diagnosis. Questionnaires were returned for 86 percent of the cases and 67 percent of the controls. There were no systematic differences in the age, sex, and county categories of those that returned the questionnaire compared to those that did not, but other factors that were not reported in the study could suggest selection bias. Self-report vaccination data were compared to vaccination records from the local child health care centers and school health units. The authors were able to validate the vaccination status of 88.5 percent and 82.1 percent of the cases and controls, respectively. Since the relative risk ratio of matched and unmatched data remained close to 1, the case and control matching was removed to avoid losing information during the analysis. The odds ratio for diabetes diagnosis any time after vaccination was assessed for MMR vaccine, 0.95 (95% CI, 0.71–1.28); measles vaccine, 0.74 (95% CI, 0.55–1.00); mumps

vaccine, 1.75 (95% CI, 0.54–5.70); and rubella vaccine, 1.24 (95% CI, 0.41–3.73). The authors concluded that MMR vaccine does not increase the risk of type 1 diabetes in children, and measles vaccine may have a protective effect that should be investigated.

Patterson (2000) conducted a case-control study in children (under 15 years of age) with type 1 diabetes enrolled at seven centers participating in the EURODIAB ACE Group from 1989 to 1995. Controls were selected at each center from population registers, general practitioners' lists, or school rolls, and matched to cases by age. Of the 1,028 cases and 3,044 controls invited to participate in the study, 900 (87.5 percent) and 2,302 (75.6) responded, respectively. The authors did not provide any information on the nonresponders. Vaccination data were obtained from parent interviews or questionnaires depending on the center, and were validated with official records or child health care booklets in 74 percent of the cases and 78 percent of the controls. A diagnosis date was assigned to each control based on the midpoint of the recruitment period for the corresponding diabetic child. The Mantel Haenszel approach was used to stratify the analysis by center, and the odds ratio for diabetes diagnosis any time after rubella vaccination was 1.18 (95% CI, 0.91–1.53). A logistic regression analysis was used to adjust for confounding variables, and the odds ratio for diabetes diagnosis any time after rubella vaccination was 1.27 (95% CI, 0.93–1.72). The authors concluded that administration of rubella vaccine does not increase the risk of type 1 diabetes in children.

DeStefano et al. (2001) conducted a case-control study in children (10 months to 10 years of age) enrolled in four HMOs participating in the VSD. A total of 252 type 1 diabetes cases and 768 matched controls were included in the analysis. The study required participants to be born from 1988 through 1997, enrolled in the HMO since birth, and continuously enrolled for the first 6 months of life. Additionally, cases had to be enrolled at least 12 months before the diabetes diagnosis except when diagnosis occurred before 12 months of age. The case index date was defined as the first date of type 1 diabetes diagnosis in the medical record; controls were assigned the same index date as their matched case. At least three controls were matched to each case on sex, date of birth (within 7 days), HMO, and length of enrollment in the HMO (up to the index date). Trained chart abstractors obtained complete vaccination histories from the medical records of the cases and controls. Vaccination histories were similar for the cases and controls with 92.1 percent and 90.6 percent exposed to MMR vaccine, respectively. The results of two conditional logistic regression models were provided: Model 1 stratified by the matching variables; Model 2 stratified by the matching variables and race, ethnicity, and family history of type 1 diabetes (additional variables also obtained from medical records). The odds ratio for diabetes diagnosis any time after MMR vaccination using

Model 1 was 1.36 (95% CI, 0.70–2.63) and using Model 2 was 1.43 (95% CI, 0.71–2.86). The authors concluded that vaccination with MMR does not increase the risk of type 1 diabetes in children.

Altobelli et al. (2003) conducted a case-control study in children (under 15 years of age) with type 1 diabetes enrolled in the diabetes register of the Abruzzo region of Italy from 1990 through 1996. A total of 136 cases (52.9 percent men and 47.1 percent women) and 272 controls (50.7 percent men and 49.3 percent women) participated in the study. The controls were identified in the National Health System records and were matched to cases on age (within 1 year) and registration with the same family pediatrician. The pediatricians certified that all controls were free of diabetes and none were diagnosed with diabetes during the study period. Trained physicians collected immunization information from the parents of diabetic cases and controls using a questionnaire at the first diabetologic examination or pediatric examination, respectively. The vaccination data were verified with records from the National Health System. A larger proportion of the controls were exposed to MMR vaccine and measles vaccine when compared to the cases: MMR vaccination in 8.1 percent of cases and 18.7 percent of controls; measles vaccination in 10.3 percent of cases and 12.9 percent of controls. The odds ratio for diabetes diagnosis any time after MMR vaccination was 0.382 (95% CI, 0.201–0.798) and measles vaccination was 0.777 (95% CI 0.403–1.498). The authors concluded that administration of MMR vaccine or measles vaccine does not increase the risk of type 1 diabetes in children.

Hviid et al. (2004) conducted a retrospective cohort study in children born from January 1990 through December 2000 and who resided in Denmark through December 2001 (end of study period). The participants were identified in the Danish Civil Registration System, and linked to information on type 1 diabetes diagnosis in the Danish National Hospital Register and vaccination data from the National Board of Health. The children were followed from birth and removed from the study at the first occurrence of an outcome of interest. The study outcomes included diagnosis of type 1 diabetes, loss to follow-up or emigration, reaching 12 years of age, and death. Vaccination status was considered a time-varying variable and was classified according to the number of doses administered (zero, one, two, or three doses of each vaccine). A total of 739,694 children were included in the study, of whom 16,421 were prematurely removed from the analysis because of loss to follow-up, emigration, or death. The rate ratio for diabetes diagnosis any time after one dose of MMR vaccine (compared to the unvaccinated) was 1.14 (95% CI, 0.90–1.45). The study also evaluated the rate ratios of diabetes diagnosis 1, 2, 3, 4, and > 4 years after MMR vaccination and found no significant differences. The authors

concluded that MMR vaccination does not increase the risk of type 1 diabetes in children.

Weight of Epidemiologic Evidence

The five observational studies consistently reported no increased risks of type 1 diabetes following MMR vaccination, and two had negligible methodological limitations (Hviid et al., 2004; Patterson, 2000). The five studies had relatively large sample sizes and were representative of European and U.S. populations of children across a broad range of ages and varying time periods at risk of type 1 diabetes following vaccination. See Table 4-12 for a summary of the studies that contributed to the weight of epidemiologic evidence.

The committee has a high degree of confidence in the epidemiologic evidence based on five studies with validity and precision to assess an association between MMR vaccine and type 1 diabetes; these studies consistently report a null association.

Mechanistic Evidence

The committee identified five publications reporting type 1 diabetes developing after the administration of vaccines containing measles and mumps alone or in combination. The publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Ehrengut and Zastrow, 1989; Fescharek et al., 1990; Helmke et al., 1986; Otten et al., 1984; Sinaniotis et al., 1975). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. In addition, Otten et al. (1984) reported that one patient contracted mumps 2 years after vaccination and 4 years before development of type 1 diabetes making it impossible to attribute the development of type 1 diabetes to vaccination. Two publications studied antibodies to mumps in patients developing type 1 diabetes or autoantibodies associated with the development of type 1 diabetes in patients after mumps infection or vaccination. Vaandrager et al. (1986) tested sera from patients after mumps infection or vaccination for the presence of autoantibodies associated with type 1 diabetes. The authors isolated autoantibodies from patients after mumps infection or vaccination but reported that the patients did not develop type 1 diabetes. Hyoty et al. (1993) tested sera collected from patients before and after receiving an MMR vaccination. The authors reported a decline of mumps antibodies in type 1 diabetes patients. The publications did not contribute to the weight of mechanistic evidence.

TABLE 4-12 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Type 1 Diabetes

Citation	Operationally Defined Outcome	Study Setting	Defined Study Population	Study Design	Sample Size	Primary Effect Size Estimate[a] (95% CI or p value)	Heterogeneous Subgroups at Higher Risk[b]	Limitations (Negligible or Serious)[c]
Blom et al. (1991)	Type 1 diabetes reported to the Swedish Childhood Diabetes Register	Sweden	Children aged 0–14 years Cases were enrolled in the Swedish Childhood Diabetes Register from 9/1/1985 through 8/31/1986 Controls were identified in the official Swedish population register	Case-control	393 children with type 1 diabetes 786 controls matched on age, sex, and county	OR for type 1 diabetes diagnosis any time after MMR vaccination: 0.95 (95% CI, 0.71–1.28) OR for type 1 diabetes diagnosis any time after measles vaccination: 0.74 (95% CI, 0.55–1.00) OR for type 1 diabetes diagnosis any time after mumps vaccination: 1.75 (95% CI, 0.54–5.70) OR for type 1 diabetes diagnosis any time after rubella vaccination: 1.24 (95% CI, 0.41–3.73)	None described	Serious

Patterson (2000)	Type 1 diabetes diagnosed by the EURODIAB ACE Group	Europe (Austria, Latvia, Lithuania, Luxemburg, Romania, United Kingdom)	Children under 15 years of age enrolled at seven centers participating in the EURODIAB ACE Group from 1989 through 1995 Controls were selected at each center from population registers, general practitioners' lists, or school rolls	Case-control	900 children with type 1 diabetes 2,302 controls matched on age	OR for type 1 diabetes diagnosis any time after rubella vaccination using the Mantel Haenszel approach: 1.18 (95% CI, 0.91–1.53; $p = .21$) OR for type 1 diabetes diagnosis any time after rubella vaccination using a logistic regression analysis: 1.27 (95% CI, 0.93–1.72; $p = .13$)	None described	Negligible
DeStefano et al. (2001)	First date of type 1 diabetes diagnosis in the medical record	Four HMOs participating in the VSD	Children born from 1988 through 1997, ages 10 months to 10 years	Case-control	252 children with type 1 diabetes 768 controls matched on sex, date of birth, HMO, and length of enrollment in the HMO	OR for type 1 diabetes diagnosis any time after MMR vaccination using Model 1: 1.36 (95% CI, 0.70–2.63) OR for type 1 diabetes diagnosis any time after MMR vaccination using Model 2: 1.43 (95% CI, 0.71–2.86)	None described	Serious

continued

TABLE 4-12 Continued

Citation	Operationally Defined Outcome	Study Setting	Defined Study Population	Study Design	Sample Size	Primary Effect Size Estimate[a] (95% CI or p value)	Heterogeneous Subgroups at Higher Risk[b]	Limitations (Negligible or Serious)[c]
Altobelli et al. (2003)	Type 1 diabetes diagnosis in the diabetes register	Abruzzo region of Italy	Children under 15 years of age with type 1 diabetes in the diabetes register of the Abruzzo region from 1990 to 1996 Controls identified in the National Health System records of Italy	Case-control	136 children with type 1 diabetes 272 controls matched on age and registration with the same family pediatrician	OR for type 1 diabetes diagnosis any time after MMR vaccination: 0.382 (95% CI, 0.201–0.798) OR for type 1 diabetes diagnosis any time after measles vaccination: 0.777 (95% CI, 0.403–1.498)	None described	Serious
Hviid et al. (2004)	Type 1 diabetes diagnosis in the Danish National Hospital Register	Denmark	Children born from 1/1/1990 through 12/31/2000, residing in Denmark through 12/2001	Retrospective cohort	739,694 children	Rate ratio for type 1 diabetes diagnosis any time after one dose of MMR vaccine compared to the unexposed: 1.14 (95% CI, 0.90–1.45)	None described	Negligible

[a] The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

[b] The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

[c] Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

Weight of Mechanistic Evidence

The association of type 1 diabetes with wild-type mumps infection is controversial. Several publications have reported cases of type 1 diabetes developing after mumps infection (Litman and Baum, 2010). Epidemiologic studies report a 3- to 4-year lag time between mumps infection and type 1 diabetes (Litman and Baum, 2010), which would be consistent with a slow loss of islet cells not clinically apparent for several years; however, it would also be consistent with numerous other triggers. In addition, a decrease in the frequency of type 1 diabetes has not been associated with a decrease in the frequency of mumps infection after implementation of mumps vaccines (Litman and Baum, 2010). Owing to the uncertainty the committee did not consider mumps infection when determining the weight of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of type 1 diabetes. Autoantibodies, T cells, molecular mimicry, and complement activation may contribute to type 1 diabetes; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

The committee assesses the mechanistic evidence regarding an association between MMR vaccine and type 1 diabetes as lacking.

Causality Conclusion

Conclusion 4.26: The evidence favors rejection of a causal relationship between MMR vaccine and type 1 diabetes.

HEPATITIS

Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of hepatitis after the administration of MMR vaccine.

Weight of Epidemiologic Evidence

The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and hepatitis.

7.5

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Age at First Measles-Mumps-Rubella Vaccination in Children With Autism and School-Matched Control Subjects: A Population-Based Study in Metropolitan Atlanta

Frank DeStefano, Tanya Karapurkar Bhasin, William W. Thompson, Marshalyn Yeargin-Allsopp and Coleen Boyle

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Age at First Measles-Mumps-Rubella Vaccination in Children With Autism and School-Matched Control Subjects: A Population-Based Study in Metropolitan Atlanta

Frank DeStefano, MD, MPH*; Tanya Karapurkar Bhasin, MPH‡; William W. Thompson, PhD*; Marshalyn Yeargin-Allsopp, MD§; and Coleen Boyle, PhD§

ABSTRACT. *Objective.* To compare ages at first measles-mumps-rubella (MMR) vaccination between children with autism and children who did not have autism in the total population and in selected subgroups, including children with regression in development.

Methods. A case-control study was conducted in metropolitan Atlanta. Case children ($N = 624$) were identified from multiple sources and matched to control children ($N = 1824$) on age, gender, and school. Vaccination data were abstracted from immunization forms required for school entry. Records of children who were born in Georgia were linked to Georgia birth certificates for information on maternal and birth factors. Conditional logistic regression was used to estimate odds ratios (ORs).

Results. The overall distribution of ages at MMR vaccination among children with autism was similar to that of matched control children; most case (70.5%) and control children (67.5%) were vaccinated between 12 and 17 months of age. Similar proportions of case and control children had been vaccinated before 18 or before 24 months. No significant associations for either of these age cutoffs were found for specific case subgroups, including those with evidence of developmental regression. More case (93.4%) than control children (90.6%) were vaccinated before 36 months (OR: 1.49; 95% confidence interval: 1.04–2.14 in the total sample; OR: 1.23; 95% confidence interval: 0.64–2.36 in the birth certificate sample). This association was strongest in the 3- to 5-year age group.

Conclusions. Similar proportions of case and control children were vaccinated by the recommended age or shortly after (ie, before 18 months) and before the age by which atypical development is usually recognized in children with autism (ie, 24 months). Vaccination before 36 months was more common among case children than control children, especially among children 3 to 5 years of age, likely reflecting immunization requirements for enrollment in early intervention programs. *Pediatrics* 2004; 113:259–266; *autism, autism spectrum disorders, MMR vaccine, immunizations, epidemiology.*

ABBREVIATIONS. MMR, measles-mumps-rubella; IOM, Institute of Medicine; MADDSP, Metropolitan Atlanta Developmental Disabilities Program; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*; ASD, autism spectrum disorder; MR, mental retardation; OR, odds ratio; CI, confidence interval.

From the *National Immunization Program, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; ‡Battelle Memorial Institute, Centers for Public Health Research and Evaluation, Atlanta, Georgia; and §National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia.

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Reprint requests to (F.D.) Centers for Disease Control and Prevention (E-61), 1600 Clifton Rd, NE, Atlanta, GA 30333. E-mail: fxd1@cdc.gov

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Autism is a serious, life-long developmental disorder characterized by marked impairments in social interactions; communication skills; and repetitive, restrictive, or stereotyped behaviors, interests, and activities.[1] Recent studies have suggested that the prevalence of autism is higher (30–60 per 10 000 children)[2–5] than in studies conducted 15 to 20 years ago (4–5 per 10 000).[6–10] The apparent increase in prevalence, coupled with reports of increasing numbers of children with autism being served by schools and service agencies,[11–14] has prompted concerns that environmental exposures might be causing autism. Vaccines, particularly the measles-mumps-rubella (MMR) vaccine, are among the exposures for which there has been a great deal of speculation of a possible association with autism.

Wakefield et al[15] were the first to propose that MMR vaccine might be causally linked to autism. They published a report describing 12 pediatric patients with inflammatory bowel conditions and regressive developmental disorders, mostly autism. In 8 of the 12 cases, the children's parents or pediatricians suggested that MMR vaccine might have contributed to the onset of behavioral problems. The same investigators subsequently proposed a new syndrome consisting of certain gastrointestinal conditions associated with behavioral regression[16] and reported identifying laboratory evidence of measles virus genome in the peripheral white blood cells and bowel biopsy specimens of a few such patients. The investigators, however, did not distinguish whether the virus was wild measles virus or vaccine strain virus.[17,18] Several epidemiologic studies have not found an association between MMR vaccination and autism.[19–24] The Institute of Medicine (IOM)[25] reviewed the MMR-autism hypothesis and rejected a causal association at the population level but encouraged additional studies to evaluate more fully the possibility that there are subgroups of children who might be at increased risk of autism from MMR vaccination.

To examine further a possible relationship between MMR vaccine and autism, including in different subgroups of children, we conducted a large

case-control study in metropolitan Atlanta in which we compared the MMR vaccination histories of a population-based sample of children with autism and school-matched control children who did not have autism.

METHODS

Study Population

Children with autism were identified from the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP), a multiple-source, population-based surveillance program that monitors the occurrence of selected developmental disabilities among children in the 5-county metropolitan Atlanta area.[5,26] In 1996, the first year in which autism was included, MADDSP identified 987 children 3 to 10 years of age with autism, for a prevalence of 3.4 per 1000 children.[5] The autism cases were identified through screening and abstraction of source files at schools, hospitals, clinics, and specialty providers. Clinical psychologists with expertise in the diagnosis of autism reviewed the abstracted records according to a standardized coding scheme to determine the presence of behavioral characteristics consistent with the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV)[1] criteria for autism spectrum disorders (ASDs). The study was approved by the Centers for Disease Control and Prevention's institutional review board. Because the activity was considered public health surveillance, parental consent was not required. Instead, permission to access records was obtained from each data source.

For the current study, case children were derived from the 987 children who were originally identified in the 1996 MADDSP prevalence year. During the period from 1999 through 2001, we were able to locate school records with the required immunization documents for 660 case children. We were not able to find school immunization records for the remaining children because the children had moved out of state, transferred to a school in a county that was not under MADDSP's jurisdiction, transferred to a private school that was not accessible by MADDSP, or were being home schooled. When a child moved or transferred, the child's permanent school record, including immunization form, was transferred to the child's new school. We were not able to quantify how many children were lost for each of these reasons because of incomplete record keeping at the schools. An additional 17 case children were excluded from the study because we could not identify matched control children for them.

We attempted to match 3 control children to each case child and were successful for 97% of the case children; the remaining case children had fewer matched control children. Control children were selected from regular education programs and were matched to case children based on age in 1996 (within 1 year), gender, and school of attendance at the time of abstraction. However, when a case child was attending a psychoeducational school, a special school for children with behavioral and developmental difficulties, control children were selected from the school in the child's residential area that the child would have attended had the child not had a disability. In addition, when a case child was in the last elementary grade level before middle school and was older than other children in his or her grade level, control children were selected from the middle school that the case child normally would have attended.

We excluded case and control children from the study when they were missing a vaccination form (15 case children and 14 control children). We also excluded children with incomplete vaccination forms when the form did not list at least 1 diphtheria-tetanus-pertussis vaccine by 2 years of age or at least 1 MMR vaccination at any age (4 case children and 1 control child). Children with a religious or medical exemption (1 case and 1 control) were not excluded from the study. After all exclusions, 624 case and 1824 control children remained in the study.

Classification of Autism Subgroups

The MADDSP data files were reviewed by a developmental pediatrician (M.Y.A.) to identify subgroups of children with potentially different susceptibilities to development of autism from an environmental exposure, such as MMR vaccine. These groups, which were not mutually exclusive, included 1) children without any indication of developmental delay before 12 months of age (ie, before the recommended age of the first MMR vaccination) or a preexisting condition, 2) children with any indication of loss of age-appropriate developmental skills (regression) or appropriate skills that failed to progress (plateau), and 3) children with and children without coexisting mental retardation (MR). Children without any indication of developmental delay at <1 year of age were children who did not lack any speech at appropriate ages, including cooing and babbling, and were socially responsive in the first year of life (eg, cuddling, appropriate eye contact, responding to parents voices). Children without a preexisting condition included children who did not have a major birth defect, a co-occurring developmental disability, or a major perinatal or postnatal insult (eg, infection, injury) that could have contributed to developmental delays. Children without a preexisting condition and without evidence of delay before 1 year of age were grouped into a single category. MR was defined as an IQ of 70 or less on the most recent psychometric test. We also attempted to examine information on family history of autism spectrum conditions or other developmental disabilities, but this information was incomplete in the records and not useful for analysis.

Vaccination History

Trained abstractors collected vaccination histories for both case and control children from the standardized state immunization forms that are required for all children who attend school and early intervention programs in Georgia. The forms are placed in each student's permanent school file that is kept at the school where the child is enrolled. During the period in which children in our study would have enrolled in school, Georgia law required at least 1 dose of measles, mumps, and rubella vaccines, usually administered at 15 months of age as the combined MMR vaccine. Vaccination was also required for enrollment in preschool special education programs for 3- to 5-year-old children with disabilities.

Other Data Collection

For children with autism, additional developmental disability–related information was obtained from MADDSP data files. This included information on the presence of other developmental disabilities, epilepsy, and IQ level (for categorization of MR). In addition, we identified major birth defects among the case children by matching with Centers for Disease Control and Prevention's Metropolitan Atlanta Congenital Defects Program, a population-based surveillance program of major birth defects that covers the same geographic area.[27]

For all case and control children, we obtained demographic information, including date of birth, gender, race, and birth state, from the birth certificate or registration form that is kept in each child's permanent school record. We matched 355 (56%) case and 1020 (56%) control children to Georgia state birth certificate records, which allowed us to obtain additional information, such as each child's birth weight and gestational age and the mother's parity, age, race, and education.

Statistical Analyses

Determining exposure–disease associations requires knowledge of dates of exposure and onset of illness. Autism, however, usually does not have a well-demarcated date of onset. Other studies have tried to address the possible relationship to MMR vaccination by examining the temporal relationship between vaccination and onset of initial parental concern, date of first diagnosis of autism, or onset of regression (if present). We had incomplete information on these events, so we compared the distribution of ages at first MMR vaccination between case and control children. The assumption implicit in this exposure comparison is that if the MMR vaccine increases the risk of autism, which usually develops before 24 months of age, then children who are vaccinated at younger ages would have a higher risk of developing autism. The age at exposure was examined in a number of ways. First, we compared the overall distributions of age at vaccination. We then analyzed associations using 3 specific age cutoffs: 1) <18 months of age, as an indicator of "on-time" vaccination according to the recommended vaccination schedule for MMR vaccine[28]; 2) <24 months of age, the age by which atypical development has become apparent in most children with autism[23,29–32]; and 3) <36 months of age, the age by which autistic characteristics must have developed to meet DSM-IV criteria for autism.[1]

We used the χ^2 statistic for categorical comparisons of the

characteristics of case and control children. We compared the overall distributions of ages at first MMR vaccination using a likelihood ratio test in a conditional logistic regression model stratified by matched sets in which age at vaccination was included as a categorical variable with 5 age categories. We also used conditional logistic regression models to estimate the odds ratios (ORs) for the association between autism and age at MMR vaccination dichotomized according to the 3 prespecified age cutoffs (18 months, 24 months, and 36 months).

In the subgroup of children that we matched to birth certificate files, we were able to adjust for additional factors. Potential confounding variables were evaluated individually for their association with autism case status. Those with a $P < .20$ were included as covariables in conditional logistic regression models to estimate adjusted ORs.[33] In analyses stratified by birth or maternal characteristics, we were not able to maintain the matched sets in the analysis. However, we did include the matching factors (age, gender, and school) as covariables in the regression models.

RESULTS

Case Selection

The 624 case children included in the analysis and the 363 excluded case children were similar with respect to age and gender (Table 1). Although a somewhat larger proportion of included (60%) than excluded (56%) case children had evidence of MR, this difference was not statistically significant.

Clinical Features of Autism Cases

Among the 624 case children, 378 had MR, 31 had cerebral palsy, 8 had visual impairment, 7 had hearing loss, 49 had epilepsy, and 31 had congenital malformations. A total of 234 cases were identified with at least 1 preexisting condition (eg, congenital malformation, metabolic disorder, fetal alcohol syndrome, intraventricular hemorrhage) or indications of developmental delay before 1 year of age. On the basis of record review, we identified 80 case children with evidence of regression or plateau in developmental milestones after 12 months of age

Demographic Characteristics of Case Children and Matched Control Children

In the total sample, case and control children were matched appropriately on age and gender, with a preponderance of boys in both groups (Table 2). The racial distributions were also fairly similar, although a larger proportion of control (10%) than case (6%) children were classified as "other" race and both groups had an appreciable number for which race information was missing.

TABLE 1. Comparison of Demographic Characteristics and Cognitive Levels Between Included and Excluded Autism Case Children

Characteristic	Included Cases ($N = 624$)		Excluded Cases ($N = 363$)	
	n	%	*n*	%
Age group (y)				
3–5	214	34	131	36
6–10	410	66	232	64
Gender				
Male	500	80	292	80
Female	124	20	71	20
Mental retardation				
Yes	376	60	205	56
No	248	40	158	44

The similarities in age and gender were also observed in the 355 case and 1020 control children who were matched to the Georgia birth certificate files (Table 2). In this subsample, the racial distributions of case and control children were the same and no children had missing race data. Using data that were available only in the birth certificate files, we did find several differences between case and control children. Compared with control children, case children were significantly ($P < .05$) more likely to have had a low birth weight and to have been the product of a multiple-birth pregnancy. At the time of delivery, mothers of case children tended to be older and to have had higher levels of education.

Comparisons of Ages at MMR Vaccination

The overall distributions of ages at first MMR vaccination were similar ($P = .22$) for case and control children (Fig 1). Most case (70.5%) and control (67.5%) children were vaccinated between 12 and 17 months of age.

When we performed the analyses dichotomizing age at vaccination, we found that vaccination before 18 months or 24 months of age was not associated with case status, either overall or in the different gender or age subgroups (Table 3). Using a 36-month cutoff, more case children (93%) than control children (91%) were vaccinated before 36 months of age (OR: 1.49; 95% confidence interval [CI]: 1.04–2.14); the association was strongest in children 3-to-5 years of age (OR: 2.34; 95% CI: 0.99–5.54). Although the OR was higher among boys than among girls, the gender-specific ORs were not significantly different (likelihood ratio test P-value = 0.27 for the interaction of gender and age at vaccination <36 months).

In the analyses using the birth certificate subsample, we were able to adjust for potential confounding variables. All of the ORs were lower than those in the total sample, except those for the 3- to 5-year age group vaccinated before 24 months or before 36 months (Table 3). However, because of the smaller size of the birth certificate sample, the 95% CIs for all age categories were wider and included 1.0. Although the birth certificate sample results in Table 3 were adjusted for maternal and birth characteristics, the ORs were not different from unadjusted results for the birth certificate sample (data not shown), indicating that there was little to no confounding effect by these factors.

Results for Subgroups of Case Children

When we performed analyses within the nonmutually exclusive clinical subgroups of case children, we found no associations with vaccination before 18 months or 24 months of age among cases without preexisting conditions before 1 year of age, case children with regression or plateau, and case children with and without MR (Table 4). Using a 36-month age cutoff, the ORs in all subgroups of case children were above 1.0, but only the OR among case children without MR had a CI that excluded 1.0. None of the adjusted results using the birth certificate sample was statistically significant. In the birth certificate sample, however, only 3 case children without men-

TABLE 2. Characteristics of Cases and Control Subjects in the Total Sample and the Birth Certificate Sample

Variable Category	Total Sample				Birth Certificate Sample			
	Controls		Cases		Controls		Cases	
	n	%	*n*	%	*n*	%	*n*	%
Age (y) in 1996								
3–5	623	34	214	34	376	37	127	36
6–10	1201	66	410	66	644	63	228	64
Gender								
Male	1462	80	500	80	809	79	282	79
Female	362	20	124	20	211	21	73	21
Race								
White	918	50	333	53	571	56	199	56
Black	636	35	230	37	384	38	137	39
Other	174	10	40	6	65	6	19	5
Missing	96	5	21	3	0	0	0	0
Maternal age (y)								
<20					95	9	15	4
20–34					803	79	280	79
35+					122	12	60	17
Maternal education (y)								
≤12					466	46	135	38
13–15					253	25	100	28
16+					301	30	120	34
Birth weight (g)								
0–1499					11	1	12	3
1500–2499					52	5	37	10
2500+					957	94	306	86
Multiplicity								
Singleton					990	97	329	93
Twin+					30	3	26	7
Parity								
First born					452	44	149	42
Second or higher					560	55	204	57
Missing					8	1	2	1
Total	1824	100	624	100	1020	100	355	100

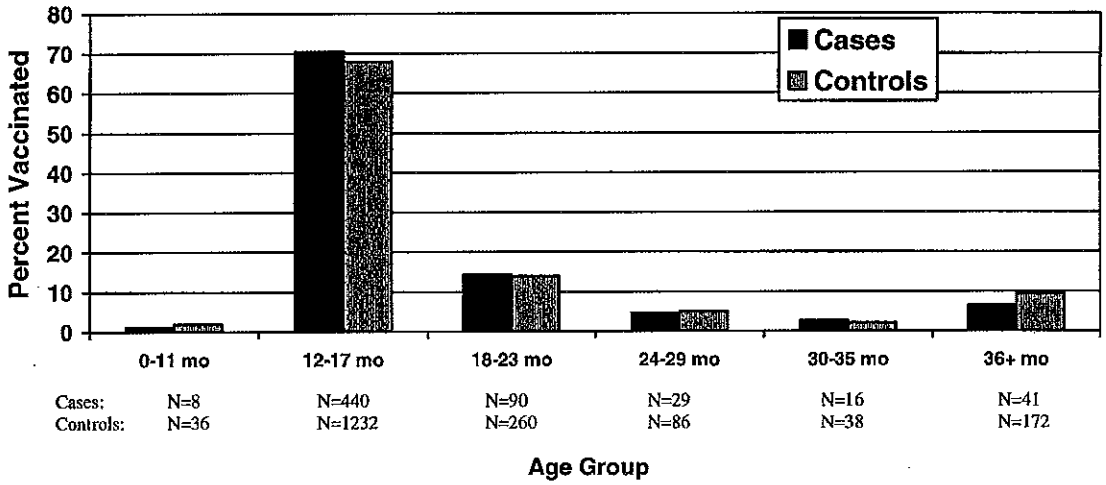

Fig 1. Age at first MMR vaccination by case status for total sample.

tal retardation were vaccinated after 36 months of age, resulting in a highly unstable OR estimate for this subgroup.

Results According to Race, Birth Weight, and Maternal Characteristics

We further examined associations according to selected maternal and birth characteristics that were available from the birth certificate files. For vaccination before 18 months or 24 months of age, all of the ORs according to different categories of race, birth weight, maternal age, and maternal education were <1.0 (Table 5). For the 36-month cutoff, there were suggestions of possible associations within the subgroups of children whose mothers were older or had more years of education, but the CIs were very wide and included 1.0.

DISCUSSION

In this population-based study in a large US metropolitan area, we found that the overall distribution of ages at first MMR vaccination among children

TABLE 3. Association Between Age at First MMR Vaccination and Autism Case Status for the Total Sample and the Birth Certificate Sample and According to Gender and Age

Sample	Case Subgroup	Cases	<18 Months, OR (95% CI)	<24 Months, OR (95% CI)	<36 Months, OR (95% CI)
Total sample	All cases	624	1.12 (0.91–1.38)	1.21 (0.93–1.57)	1.49 (1.04–2.14)
Unadjusted analyses*	Boys	500	1.22 (0.97–1.54)	1.29 (0.96–1.73)	1.67 (1.10–2.53)
	Girls	124	0.83 (0.52–1.30)	0.96 (0.55–1.68)	1.06 (0.51–2.20)
	Aged 3–5 y	214	1.08 (0.73–1.60)	1.66 (0.95–2.92)	2.34 (0.99–5.54)
	Aged 6–10 y	410	1.14 (0.90–1.46)	1.10 (0.82–1.49)	1.33 (0.89–1.98)
Birth certificate sample	All cases	311	0.93 (0.66–1.30)	0.99 (0.63–1.55)	1.23 (0.64–2.36)
Adjusted analyses†	Boys	243	0.94 (0.65–1.38)	1.01 (0.61–1.67)	1.64 (0.77–3.49)
	Girls	68	0.79 (0.33–1.86)	0.84 (0.26–2.77)	0.24 (0.04–1.47)
	Aged 3–5 y	112	0.77 (0.39–1.50)	1.67 (0.60–4.67)	2.63 (0.51–13.45)
	Aged 6–10 y	199	0.98 (0.65–1.47)	0.87 (0.51–1.46)	1.09 (0.52–2.30)

* Conditional logistic regression model stratified by the matching variables (age, gender, school).
† Conditional logistic regression model stratified by the matching variables (age, gender, school) and adjusted for birth weight, multiple gestation, maternal age, and maternal education. The number of cases ($N = 311$) is less than the number of cases with birth certificate data because some cases had no matched controls with birth certificate data.

TABLE 4. Associations Between Age at First MMR Vaccination and Autism Case Status Within Selected Clinical Subgroups of Cases for the Total Sample and the Birth Certificate Sample

Sample	Case Subgroup	Cases	<18 Months, OR (95% CI)	<24 Months, OR (95% CI)	<36 Months, OR (95% CI)
Total sample	No preexisting conditions <1 y‡	390	1.07 (0.83–1.39)	1.14 (0.82–1.59)	1.51 (0.96–2.37)
Unadjusted analyses*	Regression or plateau	80	1.37 (0.78–2.41)	1.30 (0.64–2.66)	1.45 (0.54–3.93)
	With MR§	376	1.06 (0.82–1.38)	1.09 (0.79–1.51)	1.21 (0.79–1.84)
	Without MR	248	1.23 (0.87–1.73)	1.46 (0.93–2.30)	2.45 (1.20–5.00)
Birth certificate sample	No Preexisting Conditions <1 y‡	187	1.05 (0.68–1.61)	1.02 (0.56–1.86)	1.82 (0.77–4.31)
Adjusted analyses†	Regression or Plateau	31	0.83 (0.23–3.09)	0.41 (0.07–2.29)	0.69 (0.14–3.30)
	With MR§	179	1.13 (0.72–1.79)	0.96 (0.54–1.71)	0.82 (0.38–1.79)
	Without MR	132	0.68 (0.40–1.16)	1.02 (0.47–2.22)	3.55 (0.74–17.07)

* Conditional logistic regression model stratified by the matching variables (age, gender, school).
† Conditional logistic regression model stratified by the matching variables (age, gender, school) and adjusted for birth weight, multiple gestation, maternal age, and maternal education.
‡ Includes children without any indication of developmental delay at <12 months, a major defect, co-occurring developmental disability, or a major perinatal or postnatal insult.
§ Defined as an IQ of ≤70 on the most recent psychometric test.

TABLE 5. Associations Between Age at First MMR Vaccination and Autism Case Status According to Race, Birth Weight, and Maternal Characteristics in the Birth Certificate Sample

Characteristic	Category	Cases	<18 Months, OR* (95% CI)	<24 Months, OR* (95% CI)	<36 Months, OR* (95% CI)
Race	White/other	218	0.87 (0.59–1.27)	0.77 (0.44–1.35)	0.89 (0.40–1.95)
	Black	137	0.83 (0.54–1.27)	0.98 (0.58–1.66)	1.68 (0.82–3.47)
Maternal age	<35 y	295	0.90 (0.67–1.22)	0.91 (0.61–1.35)	1.23 (0.71–2.11)
	35+ y	60	0.53 (0.24–1.17)	0.59 (0.16–2.23)	2.64 (0.22–31.72)
Maternal education	<16 y	235	0.94 (0.68–1.30)	0.94 (0.62–1.41)	1.18 (0.67–2.07)
	16+ y	120	0.60 (0.33–1.09)	0.61 (0.21–1.74)	2.76 (0.48–15.87)
Birth weight	<2500 g	49	0.50 (0.20–1.25)	0.48 (0.15–1.55)	1.41 (0.29–6.86)
	≥2500 g	306	0.91 (0.67–1.23)	0.93 (0.62–1.39)	1.26 (0.71–2.24)

* OR (95% CI) from unconditional logistic regression model adjusted for age, gender, school, and all factors listed in table.

with autism was similar to that of school-matched control children who did not have autism. Our hypothesis was that earlier age at vaccination, ie, before a possible critical time window for autism development, might be associated with an increased risk for autism. When we analyzed associations according to different age cutoffs, we found that similar proportions of case and control children had been vaccinated before 18 months or before 24 months of age. No significant associations for either of these age cutoffs were found for specific subgroups of case children, including children with some indication of regression or plateau in development, the group of most concern based on the clinical reports of Wakefield et al.[15] Vaccination before 36 months of age was more common among case children than control children, although only a small proportion of children in either group received their first MMR vaccination after 36 months of age.

We compared the distribution of ages at vaccination between case and control children because we lacked an unvaccinated comparison group and we had incomplete information for determining date of onset of autism. Determining onset of autism, however, is difficult even under the best of circumstances. In most instances, brain abnormalities associated with autism probably occur prenatally,[34–36] but parents might not become aware of their chil-

dren's problems until later in life, when communication delays and characteristic behaviors become apparent. Analyses of videotapes made of children before ASD diagnosis indicate that identifying onset of developmental problems is very difficult, especially retrospectively,[37,38] and that children who were reported as losing skills often had abnormal behaviors before the time when the loss was first noted.[32,39]

The US vaccination schedule recommends that the first dose of MMR vaccine be administered between 12 and 15 months of age.[28] Thus, our results for vaccination before 18 months of age evaluated possible increased risks of autism associated with vaccination by or shortly after the recommended age. Parental concerns about development or the first indications of atypical development usually occur before 24 months of age in children with autism,[23,30–32,40] and developmental regression, if it occurs, usually is noted between 12 and 24 months of age.[23,41–43] In Wakefield's case series, 10 of the 12 children had ASD and 9 (90%) of the ASD cases had atypical behaviors noted by 21 months of age.[15] Thus, we would expect that exposures that could be causally associated with autism would most likely occur before 24 months of age.

To meet DSM-IV criteria for autism, some manifestation of atypical development must be apparent before 36 months of age.[1] Of the 41 case children who were vaccinated after 36 months of age in our study, 32 (78%) had documented delays in development before 36 months of age. Rather than representing causal relationships, associations with the 36-month cutoff would be more likely than associations with earlier age cutoffs to have been influenced by factors related to the evaluation, management, and treatment of the child. For example, case children might have been more likely than control children to have been vaccinated as a requirement for enrollment in early intervention or preschool special education programs. This possibility is supported by the finding that the difference between case and control children in the proportion vaccinated before 36 months of age was strongest in the 3- to 5-year-old age group. In 1991, the Individuals with Disabilities Education Act[11] mandated the provision of special education programs for children with autism beginning at approximately 36 months of age. Thus, the case children who were 3 to 5 years of age in 1996 would have been most affected by the Individuals with Disabilities Education Act special education requirement and 98% of these children had been enrolled in preschool special education programs.

In addition to being a large, population-based study, our study had a number of other strengths. We included a detailed review of case records by a panel of autism experts to confirm the case definition for autism according to DSM IV criteria. We were able to obtain additional clinical information that allowed us to evaluate associations within subgroups of case children according to developmental course (eg, regression) or presence of other coexisting conditions (eg, MR). We ascertained vaccination histories from standard immunization forms, eliminating possible recall bias. Information bias was further reduced by the fact that the clinical and behavioral data and the vaccination data came from independent record sources and the information on both exposure and outcome was recorded before the publicity about a possible association between MMR and autism. Furthermore, by linking with birth records, we were able to evaluate and control for potential confounding by demographic and birth characteristics.

Although the original group of 987 autism case children identified by MADDSP in 1996 probably was a fairly complete enumeration of cases in metropolitan Atlanta, we were able to locate vaccination records for only approximately two thirds of these children during 1999 through 2001. This is primarily because when a child moved or changed schools, the permanent school record was transferred to the child's new school and we did not have access to records for children who were no longer attending a school in a metropolitan Atlanta public school district that participates in MADDSP. Thus, factors related to moving or changing schools might have influenced our results. However, we did not find any significant differences in demographic characteristics or cognitive level between case children who were included and those who were excluded from the study.

Among case and control children whose records we were able to match with Georgia birth certificate files, we performed a subanalysis to evaluate possible confounding by differences in birth and maternal characteristics. For the most part, the results were not greatly different from those in the total sample. The differences that were noted were predominantly of lower ORs in the birth certificate sample. These differences seemed to be primarily a result of restricting the analysis to children who were born in Georgia and could be matched to a state birth certificate and not to confounding by maternal or birth characteristics. Thus, the differences between the 2 samples could represent random fluctuation or a possible bias related to being born outside Georgia.

A number of other epidemiologic studies have failed to find an association between MMR vaccination and autism.[19–24] A recent retrospective cohort study from Denmark is particularly persuasive.[24] The study contained data on more than half a million Danish children, including nearly 100 000 who had not been vaccinated with MMR. Through linkages of various national registries and medical databases, the study found that the relative risk associated with MMR was 0.92 (0.68–1.24) for autistic disorder and 0.83 (0.65–1.07) for other ASDs. An Immunization Safety Review Committee of the IOM[25] reviewed the epidemiologic and other evidence on MMR vaccine and risk for ASDs and concluded that the evidence favors rejection of a causal relationship at the population level. Other review panels have reached similar conclusions.[44,45] The IOM committee, however, did recommend additional studies to evaluate potential high-risk subgroups of children.

The caveat by IOM relates primarily to "autistic enterocolitis," which has been proposed by Wakefield and colleagues[16,18] to be a new clinical syn-

drome that is associated with MMR vaccination as supported by laboratory evidence of persistent measles virus infection in the intestines of affected children. The syndrome is characterized by developmental regression along with gastrointestinal disturbances. We were not able to evaluate the syndrome because we lacked information on gastrointestinal symptoms, but we did not find an association between age at vaccination, most notably by 18 months or 24 months, and autistic regression. We found a lower proportion of cases with regression, however, than has been reported in other studies.[40,46] Our number of regression cases is likely to be an underestimation because we relied on abstracted information rather than interview with the parent and we may not have captured all of the behavioral information needed to determine whether the child had regression. Analyses by other investigators have found no support for a new variant of autism[40,46] or for the association of the MMR vaccination with regressive autism[23] or gastrointestinal disorders.[47]

In addition to regression, we evaluated other clinical subtypes of ASDs, including case children with and without MR, and case children who did not have congenital malformations or early evidence of developmental problems (and thus were at risk for onset of developmental disabilities at the recommended age for MMR vaccination). We generally did not find increased risks for any of these case subtypes associated with MMR vaccination at any age. The only exception was that case children without MR were more likely to have been vaccinated before 36 months of age than their matched control children.

Other concerns have been raised about vaccinations and autism, especially about thimerosal, the mercury-containing preservative that until recently had been included in multidose preparations of certain vaccines.[25] In the present study, we were not able to evaluate the potential association between thimerosal exposure and autism. The routinely recommended infant vaccines that used to contain thimerosal were diphtheria-tetanus-pertussis, hepatitis B, and *Haemophilus influenzae* type b. Hepatitis B and *Haemophilus influenzae* type b vaccines, however, were not required for school attendance during the period of our study, and they were incompletely recorded in the school records. MMR vaccine has never contained thimerosal. Single-antigen measles vaccine has been hypothesized to be safer than MMR,[48] but we had too few children who received measles vaccine alone to be able to evaluate this possibility. We performed an analysis in which we evaluated associations with any measles-containing vaccine; the results were similar to those for MMR vaccine (data not shown). We did not evaluate associations with the second dose of MMR vaccine because it is usually administered between 4 and 6 years of age, which is after the 36-month age limit for autism onset as defined by the DSM-IV.[1]

CONCLUSION

From a large population-based case-control study that included a well-defined case group and a comparison group of children selected from the same community, we found that, overall, the age at time of first MMR administration was similar among case and control children. Case children, especially those 3 to 5 years of age, were more likely than control children to have been vaccinated before 36 months of age. A majority of case children who were vaccinated after 36 months of age, however, had indications of developmental problems before 36 months of age. The difference in vaccination coverage by 36 months of age between case and control children is likely to be an artifact of immunization requirements for preschool special education attendance in case children.

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DISAPPOINTING RESULTS

"Lack of a measurable analgesic effect and absence of a beneficial effect on poor neonatal outcome do not support the routine use of morphine infusions as a standard of care in preterm infants who have received ventilatory support. Follow-up is needed to evaluate the long-term effects of morphine infusions on the neurobehavioral outcomes of prematurity."

Simons SHP et al. Routine morphine infusion in preterm newborns who received ventilatory support. *J Am Med Assoc.* November 12, 2003

Submitted by Student

Age at First Measles-Mumps-Rubella Vaccination in Children With Autism and School-Matched Control Subjects: A Population-Based Study in Metropolitan Atlanta

Frank DeStefano, Tanya Karapurkar Bhasin, William W. Thompson, Marshalyn Yeargin-Allsopp and Coleen Boyle

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7.6

ORIGINAL ARTICLE

Childhood Vaccination and Type 1 Diabetes

Anders Hviid, M.Sc., Michael Stellfeld, M.D., Jan Wohlfahrt, M.Sc., and Mads Melbye, M.D., Ph.D.

ABSTRACT

BACKGROUND

A link between childhood vaccinations and the development of type 1 diabetes has been proposed.

METHODS

We evaluated a cohort comprising all children born in Denmark from January 1, 1990, through December 31, 2000, for whom detailed information on vaccinations and type 1 diabetes was available. Using Poisson regression models, we estimated rate ratios according to vaccination status, including the trend associated with the number of doses, among all children and in a subgroup of children who had siblings with type 1 diabetes. Given recent claims of clustering of cases of diabetes two to four years after vaccination, we also estimated rate ratios during the period after vaccination.

RESULTS

Type 1 diabetes was diagnosed in 681 children during 4,720,517 person-years of follow-up. The rate ratio for type 1 diabetes among children who received at least one dose of vaccine, as compared with unvaccinated children, was 0.91 (95 percent confidence interval, 0.74 to 1.12) for *Haemophilus influenzae* type b vaccine; 1.02 (95 percent confidence interval, 0.75 to 1.37) for diphtheria, tetanus, and inactivated poliovirus vaccine; 0.96 (95 percent confidence interval, 0.71 to 1.30) for diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; 1.06 (95 percent confidence interval, 0.80 to 1.40) for whole-cell pertussis vaccine; 1.14 (95 percent confidence interval, 0.90 to 1.45) for measles, mumps, and rubella vaccine; and 1.08 (95 percent confidence interval, 0.74 to 1.57) for oral poliovirus vaccine. The development of type 1 diabetes in genetically predisposed children (defined as those who had siblings with type 1 diabetes) was not significantly associated with vaccination. Furthermore, there was no evidence of any clustering of cases two to four years after vaccination with any vaccine.

CONCLUSIONS

These results do not support a causal relation between childhood vaccination and type 1 diabetes.

From the Danish Epidemiology Science Centre, Department of Epidemiology Research (A.H., J.W., M.M.), and the Medical Department (M.S.), Statens Serum Institut, Copenhagen, Denmark. Address reprint requests to Mr. Hviid at the Danish Epidemiology Science Centre, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark, or at aii@ssi.dk.

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THE INCIDENCE OF TYPE 1 DIABETES mellitus is increasing in developed countries.[1] This fact — taken together with the seasonal variation in the incidence of the disease, differences in incidence between genetically similar populations including monozygotic twins, and epidemiologic studies showing that migration changes the risk of type 1 diabetes according to the country of residence — suggests that environmental factors have an important role in the development of type 1 diabetes.[2-4]

A link between childhood vaccinations and the development of type 1 diabetes has been proposed for several reasons. First, there is a temporal association between the widespread introduction of general childhood immunizations and the increase in the incidence of type 1 diabetes in developed countries. Second, it has been observed that specific vaccines prevent type 1 diabetes in murine models and others induce it. And third, some findings suggest an association between infections and type 1 diabetes.[2] In particular, it has been hypothesized that any vaccination after two months of age increases a person's risk of type 1 diabetes and that early vaccination (in the first month of life) protects against type 1 diabetes.[5-7] Vaccination against *Haemophilus influenzae* type b has been singled out, with claims of clustering of cases of type 1 diabetes three to four years after vaccination.[8] This hypothesis has recently been expanded to include bacille Calmette–Guérin vaccine; measles, mumps, and rubella (MMR) vaccine; and pertussis vaccine.[9] However, the majority of the evidence does not provide support for these specific hypotheses or for any other association between type 1 diabetes and childhood vaccination, yet there have been few analytic studies.[2,10,11]

We evaluated the relation between type 1 diabetes and routinely administered childhood vaccines in a cohort comprising all children born in Denmark from 1990 through 2000, with longitudinal information on the type and the number of doses of vaccine received and the possible diagnosis of type 1 diabetes. Vaccines against *H. influenzae* type b, diphtheria, tetanus, poliovirus, pertussis, measles, mumps, and rubella were evaluated with respect to the development of type 1 diabetes among all children and among a subgroup of children who had a sibling with type 1 diabetes. In a further analysis, we examined the cohort to see whether there was an excess of cases of type 1 diabetes during specific periods after vaccination.

METHODS

Since April 1968, people living in Denmark have been given a unique identification number in the Danish Civil Registration System.[12] Using this registry, we constructed a cohort of all children born in Denmark from January 1, 1990, through December 31, 2000. Using these unique personal identification numbers, we were able to link information on vaccinations, the diagnosis of type 1 diabetes, the presence or absence of siblings with type 1 diabetes, and potential confounders to the children in the cohort. The use of registries containing information on individual subjects was approved by the Danish Data Protection Agency.

VACCINATIONS

During the study period (1990 through 2001), Denmark had a nationwide policy of vaccinating children against pertussis, measles, mumps, rubella, diphtheria, tetanus, poliovirus, and *H. influenzae* type b. Table 1 provides an overview of the vaccines and schedules used in this period. The dates of vaccination with the first, second, or third dose of the vaccines were obtained from the National Board of Health. We did not obtain information on the second dose of the MMR vaccine, since administration of the second dose is recommended at 12 years of age, or on the diphtheria–tetanus booster, since the booster was introduced in January 1996 and administration is recommended at 5 years of age. In Denmark childhood vaccinations are administered solely by general practitioners, who are reimbursed when they report these data to the National Board of Health. The National Board of Health has kept a register of these reports since 1990. Data on the MMR vaccine have been available only since September 1991, and thus, children born in 1990 were classified as having unknown MMR vaccine status.

TYPE 1 DIABETES

Information on the diagnosis of type 1 diabetes from January 1, 1990, through December 31, 2001, was obtained from the Danish National Hospital Register.[13] From 1990 through 1993, Denmark used a modified version of the *International Classification of Diseases, 8th Revision* (ICD-8). From 1994 through 2001, the *International Classification of Diseases, 10th Revision*, was used. We used codes 249 and E10 (the code 249 does not exist in the standard World Health Organization version of the ICD-8) to iden-

Table 1. Overview of Childhood Vaccines Used in Denmark from 1990 through 2001.

Vaccine	Period Used	Schedule	Composition
Haemophilus influenzae type b	June 1993–1995 1996 1997–2001	5, 6, and 16 mo of age* 5, 6, and 15 mo of age 3, 5, and 12 mo of age	Capsular *H. influenzae* type B polysaccharide conjugated to tetanus toxoid
Diphtheria, tetanus, and poliovirus†	1990–1996	5, 6, and 16 mo of age	Diphtheria and tetanus toxoids and inactivated poliovirus
Diphtheria, tetanus, acellular pertussis, and poliovirus†	1997–2001	3, 5, and 12 mo of age	Diphtheria, tetanus, and pertussis toxoids and inactivated poliovirus
Whole-cell pertussis	1990–1996	5 wk (½ dose), 9 wk, and 10 mo of age	Inactivated whole-cell pertussis
Measles, mumps, and rubella	1990–2001	15 mo of age and 12 yr of age	Live, attenuated measles (Moraten), mumps (Jeryl Lynn), and rubella (Wistar RA 27/3) virus
Oral poliovirus	1990–2001	2, 3, and 4 yr of age	Live, attenuated poliovirus (trivalent)

* Catch-up vaccination was initially offered to older children.
† The use of a diphtheria–tetanus booster at five years of age was introduced in January 1996.

tify all cases of type 1 diabetes. Beginning in 1995, visits to the emergency room and outpatient visits were included in the National Hospital Register.

HISTORY OF TYPE 1 DIABETES AMONG SIBLINGS

Information on a person's mother and father is potentially available for each person in the Danish Civil Registration System. We used this information to identify siblings. We defined siblings as children having the same mother. Information on the diagnosis of type 1 diabetes among siblings who were 0 to 14 years of age in the period from January 1, 1997, through December 31, 2001, was obtained from the Danish National Hospital Register, with the use of the above-mentioned diagnostic codes. Before January 1987, only one diabetes code (250) existed. Consequently, siblings who received a diagnosis of code 250 before January 1, 1987, and code 249 or E10 thereafter were considered to have type 1 diabetes.

POSSIBLE CONFOUNDING FACTORS

The following information on possible confounding factors was obtained from the Danish Civil Registration System, the Danish Medical Birth Registry,[14] and the National Hospital Register: the child's place of birth (Copenhagen; Copenhagen suburbs; an area with at least 100,000 population; an area with a population of 10,000 to 99,999; or an area with a population of less than 10,000), the child's birth weight (less than 2500 g, 2500 to 2999 g, 3000 to 3499 g, 3500 to 3999 g, or 4000 g or more), the mother's country of birth (Denmark or other), and the mother's age at the birth of the child (less than 20 years, 20 to 24 years, 25 to 29 years, 30 to 34 years, 35 to 39 years, or 40 years or greater). The percentage of missing values for the variables of child's birth weight, child's place of birth, and mother's country of birth were 5.2 percent, 0.03 percent, and 0.5 percent, respectively.

STATISTICAL ANALYSIS

Children in the cohort were followed from birth until December 31, 2001, or until they received a diagnosis of type 1 diabetes, died, were lost to follow-up or emigrated, or reached 12 years of age, whichever occurred first. The resulting incidence rates for type 1 diabetes were analyzed with the use of Poisson regression (log-linear regression on the incidence rates with the use of the logarithms of the follow-up times as offsets), which yielded estimates of rate ratios according to vaccination status.[15] Vaccination status (the receipt of zero, one, two, or three doses of any vaccine) was considered a time-varying variable — that is, the children could contribute person-years in the cohort as both unvaccinated and vaccinated subjects. The presence of siblings with type 1 diabetes was also considered a time-varying variable. Thus, children contributed person-years as children who had a sibling with type 1 diabetes only after a sibling received a diagnosis of type 1 diabetes, and not before.

We estimated the dose–response relation between vaccination and the development of type 1

diabetes as the increase in the rate ratio per dose (or per 0.5 ml in the case of the whole-cell pertussis vaccine). We determined whether there was clustering of cases of type 1 diabetes in the period after vaccination by subdividing this period (the first, second, third, or fourth years after vaccination and more than four years after vaccination).

We adjusted all rate ratios for the child's sex, the child's age (in six-month intervals), and the calendar period (in one-year intervals). In an additional analysis, we further adjusted rate ratios for the receipt of other vaccines (children were categorized as either unvaccinated or vaccinated with at least one dose), with the exception that the diphtheria, tetanus, and inactivated poliovirus vaccine; the diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; and whole-cell pertussis vaccine were not mutually adjusted for, owing to their strong intercorrelation. We also adjusted rate ratios for the potential confounding variables previously listed. In the analysis of the association between type 1 diabetes and vaccination among children who had siblings with type 1 diabetes, we also included the number of siblings as a time-varying variable.

Variables were identified as confounders in the analysis of the association between vaccination and type 1 diabetes if they changed the dose-specific rate ratios among all children by more than 10 percent. When adjusting for the potential confounding effect of variables with missing values, we used the method of single imputation, replacing a missing value with the most common value.

RESULTS

A total of 739,694 children were included in our cohort. During 4,720,517 person-years of follow-up, we identified 681 cases of type 1 diabetes. Of these, 26 cases during 4208 person-years were among children who had a sibling with type 1 diabetes.

The follow-up of 16,421 children was prematurely terminated because of death in 5131 children, emigration in 11,057, or loss to follow-up in 233. The mean (±SD) age at the diagnosis of type 1 diabetes was 5.2±2.8 years. The mean age at the end of follow-up was 6.4±3.2 years.

Table 2 presents rate ratios for type 1 diabetes according to vaccination status among all children and children who had at least one sibling with type 1 diabetes. No association was found between vaccination and type 1 diabetes. The rate ratio for type 1 diabetes was 40.05 (95 percent confidence interval, 26.90 to 59.63) among children who had at least one sibling with type 1 diabetes, as compared with children who had no siblings with type 1 diabetes.

To evaluate the possible independent effect of the components of the diphtheria, tetanus, and inactivated poliovirus vaccines, we combined receipt of diphtheria, tetanus, and inactivated poliovirus vaccine with receipt of diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and found rate ratios of 0.80 after one dose (95 percent confidence interval, 0.42 to 1.51), 0.90 after two doses (95 percent confidence interval, 0.51 to 1.58), and 0.79 after three doses (95 percent confidence interval, 0.45 to 1.38). We estimated rate ratios of type 1 diabetes in the period after the first, second, and third doses of vaccine.

We evaluated the clustering hypothesis by determining whether the models that included terms for the dose-specific time since vaccination were significantly different from the models that included only dose-specific vaccination terms. We found no significant differences: P=0.57 for diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine; P=0.67 for diphtheria, tetanus, and inactivated poliovirus vaccine; P=0.68 for *H. influenzae* type b vaccine; P=0.80 for whole-cell pertussis vaccine; P=0.34 for MMR vaccine; and P=0.11 for oral poliovirus vaccine. Likewise, we found no increase in rate ratios in the three or four years after vaccination.

For example, the rate ratios were as follows in the third year after vaccination with the last dose: 0.99 for diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine (95 percent confidence interval, 0.60 to 1.63); 0.86 for diphtheria, tetanus, and inactivated poliovirus vaccine (95 percent confidence interval, 0.55 to 1.35); 0.86 for *H. influenzae* type b vaccine (95 percent confidence interval, 0.59 to 1.26); 1.20 for whole-cell pertussis vaccine (95 percent confidence interval, 0.78 to 1.84); 1.50 for MMR vaccine (95 percent confidence interval, 0.98 to 2.28); and 0.83 for oral poliovirus vaccine (95 percent confidence interval, 0.49 to 1.42).

We further evaluated whether the total number of vaccinations was a risk factor for type 1 diabetes. Children who received at least one vaccination were compared with children who received no vaccinations whatsoever, resulting in a rate ratio of 1.24 (95 percent confidence interval, 0.48 to 3.18). We compared children who received the maximal number of vaccinations in this study (13) with children who received no vaccinations and found a rate ratio

Table 2. Rate Ratio for Type 1 Diabetes among Vaccinated Children as Compared with Unvaccinated Children.*

Vaccine	All Children			Children with at Least 1 Sibling with Type 1 Diabetes		
	Person-yr at Risk†	No. of Cases	Rate Ratio (95% CI)‡	Person-yr at Risk	No. of Cases	Rate Ratio (95% CI)§
Haemophilus influenza type b						
Unvaccinated	1,596,918	211	1.00¶	1419	7	1.00¶
1 Dose	835,833	123	0.87 (0.69–1.09)	799	7	1.62 (0.57–4.63)
2 Doses	850,946	114	0.97 (0.73–1.29)	709	2	0.66 (0.14–3.19)
3 Doses	1,436,820	233	0.99 (0.75–1.30)	1281	10	1.69 (0.63–4.54)
At least 1 dose			0.91 (0.74–1.12)			1.38 (0.58–3.31)
Increase in rate ratio per dose			1.00 (0.91–1.10)			1.13 (0.82–1.55)
Diphtheria, tetanus, and inactivated poliovirus						
Unvaccinated	1,110,803	110	1.00¶	258	1	1.00¶
1 Dose	276,557	33	1.02 (0.66–1.57)	1092	8	1.93 (0.12–31.17)
2 Doses	1,134,823	178	1.07 (0.79–1.46)	2136	16	3.22 (0.40–26.02)
3 Doses	2,198,334	360	0.95 (0.69–1.30)	723	1	2.92 (0.38–22.32)
At least 1 dose			1.02 (0.75–1.37)			3.03 (0.41–22.63)
Increase in rate ratio per dose			0.97 (0.88–1.06)			1.25 (0.78–1.99)
Diphtheria, tetanus, acellular pertussis, and inactivated poliovirus						
Unvaccinated	3,734,846	552	1.00¶	3437	21	1.00¶
1 Dose	296,026	39	0.96 (0.66–1.39)	258	4	3.02 (1.02–8.91)
2 Doses	242,792	24	0.93 (0.57–1.53)	167	0	
3 Doses	446,854	66	0.97 (0.67–1.41)	347	1	0.58 (0.08–4.38)
At least 1 dose			0.96 (0.71–1.30)			1.36 (0.50–3.70)
Increase in rate ratio per dose			0.99 (0.87–1.12)			0.93 (0.56–1.56)
Whole-cell pertussis						
Unvaccinated	995,949	109	1.00¶	721	2	1.00¶
1 Dose	382,317	54	1.24 (0.85–1.79)	349	8	1.59 (0.22–11.41)
2 Doses	1,383,584	194	1.02 (0.76–1.37)	1298	14	1.58 (0.33–7.53)
3 Doses	1,958,668	324	1.04 (0.77–1.41)	1841	2	1.74 (0.39–7.76)
At least 1 dose			1.06 (0.80–1.40)			1.68 (0.39–7.19)
Increase in rate ratio per 0.5 ml of vaccine			0.99 (0.94–1.04)			1.14 (0.76–1.73)
Measles, mumps, and rubella‖						
Unvaccinated	1,373,401	124	1.00¶	1053	6	1.00¶
1 Dose	2,934,287	499	1.14 (0.90–1.45)	2795	20	0.86 (0.34–2.14)
Unknown	412,830	58	1.04 (0.71–1.52)	361	0	
Oral poliovirus						
Unvaccinated	1,655,931	137	1.00¶	1030	2	1.00¶
1 Dose	742,807	95	1.06 (0.71–1.59)	591	3	1.87 (0.31–11.36)
2 Doses	825,780	137	1.07 (0.69–1.65)	837	5	1.68 (0.32–8.90)
3 Doses	1,496,000	312	1.12 (0.73–1.72)	1750	16	2.24 (0.50–10.06)
At least 1 dose			1.08 (0.74–1.57)			2.01 (0.46–8.71)
Increase in rate ratio per dose			1.04 (0.91–1.18)			1.24 (0.83–1.87)

* CI denotes confidence interval.
† Values for person-years at risk have been rounded.
‡ Rate ratios were adjusted for age, calendar period, and child's sex.
§ Rate ratios were adjusted for age, calendar period, child's sex, and the number of siblings.
¶ This group served as the reference group.
‖ Children received only one dose of measles, mumps, and rubella vaccine during the study period because administration of the second dose of vaccine is not recommended until 12 years of age.

of 1.32 (95 percent confidence interval, 0.42 to 4.10). We calculated the trend for the number of vaccinations received and found an increase in the rate ratio per vaccination of 1.00 (95 percent confidence interval, 0.96 to 1.05).

DISCUSSION

Diverse causal mechanisms have been proposed to explain a possible link between childhood vaccination and type 1 diabetes,[16] but the available evidence

is weak.[2,10,11] However, the process of detecting associations between vaccination and rare or long-term outcomes is complicated, and many negative studies have been statistically underpowered or have suffered from a lack of unvaccinated subjects. Issues that call into question vaccine safety have the potential to jeopardize vaccination programs; for these programs to retain the confidence of both the public and health professionals, continued safety evaluations are becoming an increasingly important part of public health procedures.

On the basis of ecologic evaluations, Classen and Classen have claimed that vaccination is associated with an increased risk of type 1 diabetes two to four years after vaccination.[8,9] We tested this hypothesis directly by examining data on individual subjects in a population-based cohort study. We found no support for the existence of a causal relation between type 1 diabetes and childhood vaccination overall or at any time after vaccination.

We speculated that any association between vaccination and type 1 diabetes would be more pronounced among children who were genetically predisposed to diabetes. Although we found that the risk of type 1 diabetes increased among children who had one or more siblings with diabetes, there was no apparent association between diabetes and vaccination among such children. However, the lack of statistical significance and inconsistency limit the conclusions that can be drawn from this analysis. If we consider the results for at least one dose of vaccine, the diphtheria, tetanus, and inactivated poliovirus vaccine and the oral poliovirus vaccine stand out, with rate ratios of 3.03 (95 percent confidence interval, 0.41 to 22.63) and 2.01 (95 percent confidence interval, 0.46 to 8.71), respectively. However, these increases are clearly based on reference groups that included only one and two unvaccinated children in the case of diphtheria, tetanus, and inactivated poliovirus vaccine and oral poliovirus vaccine, respectively. In a previous study, Hummel et al. evaluated the risk of developing islet autoantibodies during the first two years of life among children who had a parent with type 1 diabetes and found no association with vaccination.[17] A novel aspect of our study is the evaluation of the association between vaccination and type 1 diabetes among genetically predisposed children older than two years.

We identified cases of type 1 diabetes from discharge diagnoses in the National Hospital Register. Nielsen et al. evaluated the quality of data in this registry with respect to type 1 diabetes and found that in the period from 1987 to 1993, the specificity of the diagnosis was 96 percent and the completeness of the data was 91 percent.[18] Svensson et al. estimated the incidence of type 1 diabetes in Denmark from 1996 through 2000 on the basis of data in a national diabetes registry initiated in 1996.[19] Among children from birth to four years of age, the incidence was 12.73 per 100,000 person-years, and among children five to nine years of age, the incidence was 19.36 per 100,000 person-years. During the same period, we found similar rates of type 1 diabetes — 13.37 per 100,000 person-years among children from birth to four years of age and 18.12 per 100,000 person-years among children five to nine years of age. Consequently, the validity and completeness of the data on type 1 diabetes that we used are unlikely to be a cause for concern. Our main priority was obtaining a large cohort with a sufficient period of follow-up, and thus we chose the National Hospital Register, which allowed us to start our follow-up in 1990, rather than in 1996, as would have been the case had we used the national diabetes registry.

Analytic epidemiologic studies of a possible association between vaccination and type 1 diabetes are rare. Three case–control studies — one from Sweden,[20] a multicenter study by the Europe and Diabetes study group,[21] and one from the United States[22] — found no adverse effect of childhood vaccination on type 1 diabetes. In a recent review of the safety of immunization,[23] the Institute of Medicine recommended that existing vaccine surveillance systems be used in combination with disease registries to explore the association between immunization and type 1 diabetes. The advantage of our study is that we were able to evaluate the association between childhood vaccinations and type 1 diabetes in a nationwide cohort with longitudinal, individual-level information on vaccinations and type 1 diabetes. The use of a nationwide cohort and the independent and prospective ascertainment of vaccination history and the diagnosis of type 1 diabetes eliminate concern regarding selection bias and recall bias, commonly found in other types of post-licensure studies of vaccination safety. In conclusion, there appears to be no support for any causal relation between childhood vaccination and type 1 diabetes.

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DIABETES

Infections and risk of type I diabetes in childhood: A population-based case–control study

Emma Altobelli[1], Reimondo Petrocelli[2], Alberto Verrotti[3] & Marco Valenti[1]
[1]*Department of Internal Medicine and Public Health, University of L'Aquila;* [2]*Faculty of Medicine, Institute of Hygiene, University of Chieti;* [3]*Department of Pediatrics, Faculty of Medicine, University of Chieti, Italy*

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Abstract. *Objective*: This study focuses on the evaluation of some infectious diseases as risk determinants of type I diabetes mellitus (DM). *Methods*: A population-based case–control study was carried out by referring to the type I DM population-based register of the Abruzzo region of Italy as it includes all type I DM cases since January 1 1990, the point at which the register became operative. The pediatric population (age: 0–14), living in the same municipalities of the cases, was selected as the control population. Data were collected through questionnaires submitted by a physician to parents of cases and controls. Conditional logistic regression models were used to evaluate association between determinants and onset of type I DM. *Results*: The risk of diabetes for children exposed to only one infection (morbilli, parotitis, rubella, pertussis or varicella) is not statistically significant: OR: 0.778; CI: 0.427–1.370. On the contrary, when two infections are contracted statistically significant results occur: OR: 2.375; CI: 1.149–4.914; for more than two infections values are: OR: 6.786; CI: 2.881–17.877. No substantial difference in odds ratios (ORs) after adjustment for confounding variables was found. A significant decrease in OR was noted for pertussis and MMR vaccinations, respectively: OR: 0.015; CI: 0.001–0.251; OR: 0.400; CI: 0.201–0.799. *Conclusions*: Since the higher the number of contracted infections, the higher the risk of diabetes, contracted infections can be considered potential accelerating factors of clinical manifestation of type I DM. Therefore multiple exposures might speed up the onset of diabetes in children. This study suggests the utility of applying the risk model method to wider populations, especially if the geographical variability of standardised incidence rates of type I DM in pediatric age is taken into consideration.

Key words: Case–control study, Infections, Population register, Risk, Type I diabetes mellitus, Vaccinations

Abbreviations: CI = confidence interval; DM = diabetes mellitus; MMR = morbilli–parotitis–rubella; OR = odds ratio

Introduction

The natural history of type I diabetes mellitus (type I DM) still has many obscure aspects. The hypothesis of a potential role played by some environmental factors, such as viral agents, is well known, a fact which explains recourse to a pathogenic model based on an initial infection followed by a chronic development. Some studies on pancreas functionality in diabetic patients showed gland reduction followed by atrophy [1, 2]. Post-mortem analysis demonstrated that pancreas of type I DM patients is much lighter and smaller, and insulitis affects 23% of insulin-containing insulae [3, 4], while acute focal pancreatitis and widespread lymphocytic infiltrates were found in the exocrine pancreas [3]. The reason why the destruction of beta cells (which are just 2% of the gland) favours a remarkable reduction of the pancreatic exocrine tissue is still unknown. However, it has been demonstrated that diabetic patients have a reduced pancreas exocrine function and this reduction is closely related to the destruction of beta cells [5].

Some authors suggest that viruses are involved in the destruction of pancreatic beta cells and that this takes place before the clinical symptoms of diabetes appear [6, 7].

In 1969, Gable et al. [8] reported an association between the Coxsackie B4 virus and type I DM. The Coxsackie virus was then isolated in a child's pancreas with a death diagnosis of DM [9]. A study carried out by Menser et al. [10] showed that 20% of individuals with congenital rubella developed type I DM after a 10-year follow-up [10].

These discoveries have given new momentum to epidemiological research in the last 10 years and studies have tried to define a potential link between viral diseases and type I DM [11–18]. Considering

viruses as risk factors, it should be noted that the results of the most important studies are not consistent [19–22]. The possible association between infectious diseases and diabetes has also prompted an interest in vaccinations as possible risk factors for diabetes. Vaccines could either have a protective role or a triggering effect in the development of type I DM. In fact, results of related epidemiological studies are in disagreement [13, 19, 23–25].

This study focuses on the one hand on infectious diseases as factors involved in the development of the clinical phase of type I DM, and, on the other, on vaccines as a potential protective factor. This is achieved through a population-based case–control study, which was carried out by referring to the type I DM population-based register of the Abruzzo region (Central Italy) which includes all type I DM cases since January 1 1990 [26], the point at which the register became operative.

Methods

Patients

The register of type I DM pediatric patients was established in Abruzzo in 1990. It includes incident cases of diabetes with diagnosis before the age of 15, starting from January 1 1990. The case inclusion criteria were defined according to the DIAMOND Project research group [27]. The diagnostic criteria were defined according to the National Diabetes Data Group [28]. Two independent information sources were used to establish new cases of diabetes. One hundred and thirty-six new incident cases (males = 72, 52.9%; females = 64, 47.1%) were identified between 1990 and 1996, i.e. a 9.12 per 100,000 per year standardised rate (European standard population) with a 95% confidence interval (95% CI) of 7.56–10.68 [29]. By means of the capture–recapture method, we achieved a 98.1% register completeness, as well as a 95% CI of 134–141 established incident cases [30]. The mean age at onset was 9.4 (standard deviation = 4.0) in males and 7.5 (standard deviation = 3.8) in females. Children affected by diabetes contracted as a side effect of other diseases or pharmacological therapy were excluded.

As the control population, we used the pediatric population (0–14 years) of the Abruzzo Region listed in the records of the National Health System, which requires by law selection and registration of a family pediatrician. For the purposes of control random sampling, the list of children registered with the same family pediatrician of the matched case was used as the sampling frame. Thus, 272 age-matched (±1 year) controls (males = 138, 50.7%; females 134, 49.3%) were randomly selected. All controls were diabetes free, as certified by their pediatricians: moreover, no control subject developed diabetes during the period of recruitment of cases, nor during the conduct of the study.

Data were collected through questionnaires submitted by a physician trained on data collection, to parents of diabetic children during the first diabetologic examination. The same questionnaire was also submitted to parents of control children by the same physician, at the time of the firstly occurrent pediatric examination.

All parents of both cases and controls agreed to participate in the study and signed the informed consent form.

The questionnaire included the following key items: participants' personal data, breast feeding and time frame, dates of contracted infections taken into consideration, i.e. morbilli, rubella, varicella, parotitis epidemica (parotitis) and pertussis (criteria for infectious disease occurrence were referred to literature [31]), information about exposure to vaccinations (morbilli, rubella, parotitis, pertussis and combined vaccine morbilli–parotitis–rubella), information about other infectious diseases. For diabetic children, the date of first administration of insulin and exposure to the above-cited infections during the year before the onset of diabetes were also requested.

The validity of infection and vaccination data was verified by checking the records of the National Health System, for which registration of infections and vaccinations is compulsory. As data derive from an epidemiological register, which was built up to address public health strategies, further details on clinical conditions of cases and controls were not available.

Statistical analysis

Individual and multiple associations between onset of type I DM and contracted infections were evaluated. The association between onset of type I DM and breast-feeding was also analysed.

Conditional logistic regression models were used to evaluate the association between diabetes onset and the determinants taken into consideration. To adjust for potential confounders, logistic regression analysis was used with terms included in the model. The odds ratio (OR) values were calculated using the method of Mantel–Haenzel and each risk value is quoted with a 95% CI [32].

SAS software was used for the procedures of statistical analysis [33].

Results

Table 1 summarises all single and multiple infectious diseases contracted during the year before the diagnosis of diabetes. It clearly shows that total percentage of exposure to infections is higher in the cases

Table 1. Infections contracted during the last year before study enrollment: exposure in diabetic and control children

		Cases N = 136		Controls N = 272	
	Infection	Exposed	Percent	Exposed	Percent
1 infection	Morbilli	5	3.7	9	3.3
	Parotitis	4	3.0	9	3.3
	Rubella	0	0.0	1	0.4
	Pertussis	1	0.8	7	2.6
	Varicella	9	7.0	32	11.8
2 infections	Morbilli and Parotitis	3	2.2	2	0.8
	Morbilli and Varicella	2	1.5	4	1.5
	Morbilli and Rubella	1	0.8	0	0.0
	Morbilli and Pertussis	2	1.5	0	0.0
	Parotitis and Rubella	0	0.0	2	0.8
	Parotitis and Pertussis	1	0.8	2	0.8
	Rubella and Pertussis	2	1.5	0	0.0
	Parotitis and Varicella	5	4.0	5	2.0
	Rubella and Varicella	1	0.8	2	0.8
3 infections	Morbilli and Rubella and Varicella	4	3.0	1	0.4
	Morbilli and Parotitis and Rubella	1	0.8	1	0.4
	Morbilli and Parotitis and Varicella	4	3.0	2	0.8
	Parotitis and Rubella and Pertussis	2	1.5	2	0.8
	Parotitis and Pertussis and Varicella	3	2.2	0	0.0
	Parotitis and Rubella and Varicella	1	0.8	1	0.4
	Morbilli and Pertussis and Rubella	1	0.8	0	0.0
	Pertussis and Rubella and Varicella	1	0.8	0	0.0
>3 infections	Morbilli and Rubella and Parotitis and Pertussis	1	0.8	0	0.0
	Parotitis and Pertussis and Rubella and Varicella	1	0.8	0	0.0
	Morbilli and Parotitis and Pertussis and Rubella and Varicella	1	0.8	0	0.0
	Total	56	40.4	82	30.1

(n = 56, 40.4%) than in the controls (n = 82, 30.1%) (z test for comparison of proportions = 2.15, p = 0.015).

In analysing the disaggregated data regarding the types of contracted infections, it is important to emphasise that, with reference to individual viral exposures, the difference between cases and controls is not remarkable.

Information on other infections during childhood is the following: with regard to cases, one haemophilus influenzae, two exantema subitum; with regard to controls, two haemophilus influenzae, three exantema subitum. On account of such figures, these data were not considered in the analysis.

Table 2 shows the disease-specific risks, irrespective of the concurrent occurrence of more than one infection in the same subject.

Table 3 shows the OR estimates associated with various infection patterns. Our data demonstrate that the risk of diabetes for children exposed to one infection (measles or parotitis or rubella or varicella or pertussis) is not statistically significant, while, if more than one infection was contracted during the year before the onset of diabetes, the risk increases significantly. In particular, if two infections were contracted, values are: OR: 2.375; 95% CI: 1.149–4.914; for more than two infections, values are: OR: 6.786; 95% CI: 2.881–17.877. No differences in ORs after

Table 2. Disease-specific risks, irrespective of the concurrent occurrence of more than one infection in the same subject

Infection	Cases affected	Controls affected	OR	95% CI
Pertussis	16	11	3.16	1.33–7.76
Varicella	32	47	1.47	0.85–2.51
Rubella	17	10	3.74	1.56–9.41
Morbilli	23	19	2.71	1.35–5.48
Parotitis	27	24	2.58	1.36–4.90

Table 3. Risk of type I DM associated with the number of infections contracted during the last year before study enrollment

Infections	Cases N = 136		Controls N = 272		Logistic regression analysis		Logistic regression analysis adjusted for confounders[a]	
	N	Percent	N	Percent	OR	95% CI	OR	95% CI
No infection	80	58.9	190	69.9	1.0[b]	–	1.0[b]	–
1 infection	19	14.0	58	21.3	0.778	0.427–1.370	0.750	0.409–1.328
2 infections	17	12.5	17	6.3	2.375	1.149–4.914	2.274	1.091–4.744
>2 infections	20	14.7	7	2.6	6.786	2.881–17.877	5.798	2.427–15.430

[a] Confounding variables were: breast-feeding (<4 weeks, ⩾4 weeks), birth weight (<2500 g, ⩾2500 g), maternal age (<27 years, ⩾27years).
[b] Reference category.

adjustment for confounding variables were found (Table 3).

It is important to highlight that, contrary to three cases, no control was exposed to more than three of the infections considered in this study.

Table 4 summarises instances of single and multiple exposure to vaccinations. It clearly shows that total percentage of exposure to vaccinations is higher in the controls (n = 211, 72.6%) than in the cases (n = 44, 32.3%) (z test for comparison of proportions = 8.22, $p < 0.0001$).

When vaccinations were considered as risk factors for type I DM no significant increase in OR was noted, but a significant decrease in OR resulted for pertussis and MMR vaccinations, respectively: OR: 0.015; 95% CI: 0.001–0.251; OR: 0.400; 95% CI: 0.201–0.799.

Again, the combined MMR-pertussis vaccinated group of children showed a statistically significant decrease in risk of type 1 DM: OR: 0.260; 95% CI: 0.114–0.592.

No significant decrease in risk was found for morbilli vaccination: OR: 0.777; 95% CI: 0.403–1.498. With reference to the specific risk for parotitis and other associated vaccinations, due to the limited number of exposed controls and cases, the ORs were not estimated (Table 4).

Discussion

Following previous research on family diabetes as a risk factor [29], the population-based case–control study approach was chosen. It is commonly held in literature that this approach is very suitable for the study of possible risk factors in relation to relatively rare diseases, such as DM in pediatric age. None-

Table 4. Exposure to vaccinations in diabetic and control children

Vaccine	Cases N = 136		Controls N = 272			
	Vaccinated	Percent	Vaccinated	Percent	OR[a]	95% CI
Morbilli	14	10.3	35	12.9	0.777	0.403–1.498
Parotitis	0	0.0	1	0.4	–	–
Pertussis	0	0.0	52	19.9	0.015	0.001–0.251
MMR[b]	11	8.1	51	18.7	0.382	0.201–0.798
Morbilli and Pertussis	2	1.5	4	1.5	–	–
Parotitis and Rubella	0	0.0	4	1.5	–	–
Parotitis and Pertussis	2	0.8	0	0.0	–	–
Rubella and Pertussis	1	0.8	0	0.0	–	–
MMR[b] and Pertussis	7	5.2	47	17.3	0.260	0.114–0.592
Morbilli and Parotitis and Pertussis	2	1.5	1	0.4	–	–
Morbilli and Rubella and Pertussis	3	2.2	3	1.1	–	–
Parotitis and Rubella and Pertussis	2	1.5	0	0.0	–	–
Morbilli and Rubella and Parotitis and Pertussis	0	0.0	13	4.8	–	–
Total	44	32.3	211	77.6		

[a] Mantel–Haenszel OR: estimates were calculated only for contingency tables whose expected values were > 5 in each cell.
[b] Combined vaccine morbilli-parotitis-rubella.

theless, the case–control study has some limitations, such as the control population selection bias and the layer bias [34]. We tried to reduce the selection bias by randomly selecting the controls among children treated by the same pediatricians who also follow the cases. It is well known that environmental variations accross territory may play a key role in the actiology of diabetes. We have eliminated the layer bias by matching cases and controls by age. With reference to the type of interview, the personal interview was preferred over a telephone or mail interview. Although it is more expensive, the relation with the interviewee is closer and he/she is more willing to participate in the study, thus increasing the number of answers and total information. Nonetheless, it is not certain whether personal interviews increase accuracy [35]: hence we used an independent source of information to check the accuracy of information. In order to minimise costs only one trained interviewer was used to eliminate potential data-gathering. Moreover, our study analyses only certain infections, i.e. those infections with clear clinical signs for diagnosis and for which compulsory reporting is required.

In agreement with some authors [13–16, 21–22], our data show that single exposure to the infective agents taken into consideration does not increase the risk of type I DM: OR: 0.778; CI: 0.427–1.370.

We also evaluated the risk of diabetes associated with possible multiple patterns of exposure to infections throughout the year leading up to the clinical diagnosis of diabetes. In agreement with some other authors [13], our data confirm that the risk increases in cases of exposure to multiple infectious diseases. In fact, the risk is twice as high in cases of exposure to two infections and five times higher in cases of exposure to more than two infections. No substantial difference in ORs after adjustment for confounding variables was found.

With regard to data showed in Table 2, the analysis of disease-specific risks could deserve attention for groups of patients in which only one infection had occurred, but this is not the case of our group of patients (except 19 of them, for five infections): given these conditions, the risk estimates for single diseases can be strongly biased.

Nevertheless, our results do not necessarily mean that multiple infections are initiating the beta-cell lesion, but rather, it is more likely that multiple infections are either accelerating or precipitating factors. In fact, the acute inflammation caused by infections could precipitate the on-going beta-cell destruction with consequent increase in the need for insulin, thereby masking the pre-existing insulin deficiency [36].

Vaccinations have been discussed as a potential risk factor for type I DM, since they can precipitate autoimmune response towards the beta cell. The results of a recent study show that no influence by vaccination on the development of islet autoimmunity was found in a cohort of first-degree relatives from the US [37].

In agreement with some authors, the present study shows a significant decrease in risk of type I DM in subjects receiving MMR vaccine [13].

Increased or decreased diabetes risk resulting from vaccines may only affect certain children at particularly high genetic risk for the disease. In fact, two reviews [38, 39] and a large population-based case–control study [40] have not found evidence of any effect of immunisation on the incidence of type 1 DM.

We have to underline that the Italian health law does not consider compulsory any of the vaccinations here analysed, so that they result a free choice of the families, suggested by the family pediatrician. As even the costs of non-compulsory vaccines are entirely covered by the National Health System, we have no reason to believe that attitudes to prescribe vaccination depend on socio-economic factors, but possibly on the personal experience of the pediatrician. Moreover, religious or cultural believes as potential determinants of variation of vaccination rates in populations do not apply to Italy and the Abruzzo Region in particular, where this kind of differences account for absolutely marginal figures.

As parents and the general public must be informed of possible vaccine risk, the results of this and other studies suggest that it is important to assure accurate and evidence-based information [41].

Due to lack of available studies, our results were not compared to those of other Italian regions. Therefore, this population-based case–control study indicate the need to apply the risk model methods to a wider population, including other Italian regions, especially if the geographic variability in Italy of standardised incidence rates of type I DM in pediatric age is taken into consideration.

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Address for correspondence: Dr Emma Altobelli, Dip. MISP c/o Facoltà Scienze Motorie, Università dell'Aquila, Via Cardinale Mazzarino, 67100 L'Aquila, Italy
Phone: +39-0862-432927; Fax: +39-0862-432929
E-mail: emmaalto@tin.it

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Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus

Frank DeStefano, John P. Mullooly, Catherine A. Okoro, Robert T. Chen, S. Michael Marcy, Joel I. Ward, Constance M. Vadheim, Steve B. Black, Henry R. Shinefield, Robert L. Davis and Kari Bohlke

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Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus

Frank DeStefano, MD*; John P. Mullooly, PhD‡; Catherine A. Okoro, MS*; Robert T. Chen, MD*; S. Michael Marcy, MD§; Joel I. Ward, MD‖; Constance M. Vadheim, PhD‖; Steve B. Black, MD¶; Henry R. Shinefield, MD¶; Robert L. Davis, MD#; Kari Bohlke, ScD#; and the Vaccine Safety Datalink Team

ABSTRACT. *Objectives.* To evaluate suggested associations between childhood vaccinations, particularly against hepatitis B and *Haemophilus influenzae* type b, and risk of developing type 1 diabetes; and to determine whether timing of vaccination influences risk.

Methods. We conducted a case-control study within 4 health maintenance organizations (HMOs) that participate in the Vaccine Safety Datalink project of the Centers for Disease Control and Prevention. Study eligibility was restricted to children who met the following criteria: 1) born during 1988 through 1997; 2) HMO member since birth; 3) continuously enrolled for first 6 months of life; and 4) at least 12 months of HMO membership before diabetes incidence date (or index date for controls) unless incidence date was before 12 months of age. All 4 HMOs maintain registries of their members who have diabetes, and we used the registries to identify potential cases of diabetes. We conducted chart reviews to verify that potential cases met the World Health Organization epidemiologic case definition for type 1 diabetes mellitus (ie, a physician's diagnosis of diabetes plus treatment with daily insulin injections). We defined the incidence date of diabetes as the first date that the child received a diagnosis of diabetes. We attempted to match 3 controls to each case. Controls had the same eligibility criteria as cases and were matched to individual cases on HMO, sex, date of birth (within 7 days), and length of health plan enrollment (up to the incidence or index date). The index date for controls was defined as the incidence date of the case to which the control was matched. Chart abstraction was performed by trained chart abstractors using standardized forms. In addition to complete vaccination histories, the chart abstraction forms for both cases and controls included information on sociodemographic characteristics, selected medical conditions, history of breastfeeding, and family medical history. We used conditional logistic regression to estimate the odds ratio (OR) of diabetes associated with vaccination, with vaccine exposure defined as before the diabetes incidence date (or index date for controls).

Results. Two hundred fifty-two confirmed cases of diabetes and 768 matched controls met the study eligibility criteria. The OR (95% confidence interval) for the association with type 1 diabetes was 0.28 (0.07–1.06) for whole cell pertussis vaccine (predominantly in combination as diphtheria, tetanus toxoids and pertussis vaccine), 1.36 (0.70–2.63) for measles-mumps-rubella, 1.14 (0.51–2.57) for *Haemophilus influenzae* type b, 0.81 (0.52–1.27) for hepatitis B vaccine, 1.16 (0.72–1.89) for varicella vaccine, and 0.92 (0.53–1.57) for acellular pertussis-containing vaccines. Compared with children who had not received hepatitis B vaccine, the OR of diabetes was 0.51 (0.23–1.15) for children vaccinated at birth and 0.86 (0.54–1.35) for those first vaccinated against hepatitis B at 2 months of age or later. Race and ethnicity and family history of diabetes were independently associated with risk of type 1 diabetes, but adjustment for these factors did not materially alter the ORs for any of the vaccines.

Conclusions. In this large, population-based, case-control study, we did not find an increased risk of type 1 diabetes associated with any of the routinely recommended childhood vaccines. Our study adds to previous research by providing data on newer vaccines, including hepatitis B, acellular pertussis, and varicella vaccines. For the older vaccines, our results are generally in agreement with previous studies in not finding any increased risks. Ours is the first epidemiologic study to evaluate the possibility that timing of vaccination is related to risk of clinical diabetes in children. Our results on hepatitis B vaccine do not support the hypothesis; risk of type 1 diabetes was not different between infants vaccinated at birth and those who received their first vaccination later in life. The results of our study and the preponderance of epidemiologic evidence do not support an association between any of the recommended childhood vaccines and an increased risk of type 1 diabetes. Suggestions that diabetes risk in humans may be altered by changes in the timing of vaccinations also are unfounded. *Pediatrics* 2001;108(6). URL: http://www.pediatrics.org/cgi/content/full/108/6/e112; *hepatitis B vaccine,* Haemophilus influenzae *type b vaccine, epidemiology.*

From the *National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia; ‡Center for Health Research, Northwest Kaiser Permanente, Portland, Oregon; §Kaiser Foundation Hospital, Panorama City, California; ‖Center for Vaccine Research, Harbor-University of California Los Angeles Medical Center, Torrance, California; ¶Pediatric Vaccine Study Center, Northern California Kaiser Permanente, Oakland, California; #Center for Health Studies, Group Health Cooperative, Seattle, Washington.

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Address correspondence to Frank DeStefano, MD, MPH, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, Mailstop F34, Atlanta, GA 30341-3724. E-mail: fdestefano@cdc.gov

ABBREVIATIONS. Hib, *Haemophilus influenzae* type b; HMO, health maintenance organization; OR, odds ratio; MMR, measles-mumps-rubella.

Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or juvenile diabetes) results from autoimmune destruction of pancreatic β-cells. Its cause is not known, although genetic and environmental factors are believed to be involved. Vaccinations are among the environmental

factors that have been studied, but most studies have not found an increased risk of type 1 diabetes associated with vaccination.[1–7] Most of the previous studies, however, were conducted before 1990 and do not provide information on many of the currently recommended childhood vaccines.

Classen and Classen[8,9] have hypothesized that certain vaccines (eg, hepatitis B, BCG), if given at birth, can decrease the risk of developing type 1 diabetes mellitus, whereas first vaccination at 2 months of life or later can increase the risk of type 1 diabetes. The few studies reported to date, however, have evaluated vaccine exposure without regard to timing. No controlled epidemiologic studies have been published concerning timing of vaccinations and diabetes risk.

Classen[8] has also hypothesized an association of *Haemophilus influenzae* type b (Hib) vaccination and diabetes. However, a 10-year follow-up study of over 100 000 Finnish children involved in a clinical trial of Hib vaccine did not find an increased risk of diabetes associated with vaccination or with number of vaccinations received.[10] The clinical trial compared children who had received 4 doses of vaccine at 3, 4, 6, and 14 to 18 months of age to children who received only 1 dose at 24 months of age. To provide a nonvaccinated comparison group, the follow-up study included data on a cohort of children born before the vaccination period. Thus, the nonvaccinated group was not concurrent with the 2 vaccinated groups.

We conducted a study in 4 large health maintenance organizations (HMOs). Our objectives were to evaluate the association between receipt of routine childhood vaccines and the risk of type 1 diabetes; to determine whether the timing of hepatitis B vaccine influences diabetes risk; and to assess associations between the schedule of Hib vaccinations and diabetes risk.

METHODS

We conducted a case-control study within 4 HMOs that participate in the Vaccine Safety Datalink project of the Centers for Disease Control and Prevention.[11] Study eligibility was restricted to children who met the following criteria: 1) born during 1988 through 1997; 2) HMO member since birth (ie, "born into the HMO"); 3) continuously enrolled for first 6 months of life; and 4) at least 12 months of HMO membership before diabetes incidence date (or index date for controls) unless incidence date was before 12 months of age.

Cases

All 4 HMOs maintain registries of their members who have diabetes, and we used the registries to identify potential cases of diabetes. In general, the registries include patients who have received a diagnosis of diabetes (*International Classification of Diseases, Ninth Revision* code 250) or filled a prescription for insulin or other glucose-lowering medication. We conducted chart reviews to verify that potential cases met the World Health Organization epidemiologic case definition for type 1 diabetes mellitus: a physician's diagnosis of diabetes plus treatment with daily insulin injections.[12] None of the cases had diabetes secondary to other conditions (eg, cystic fibrosis).

We defined the incidence date of diabetes as the first date that the child received a diagnosis of diabetes. Although the case definition required a physician's diagnosis at some time, the diagnosis for establishing the incidence date (ie, the first diabetes diagnosis) could have been made by a physician or other medical care provider (eg, physician's assistant or nurse practitioner). The diagnosis must have been a definite diagnosis of diabetes; "rule-out," "possible," or other indeterminate diagnoses were not accepted for the case definition or for establishing the incidence date.

Controls

We attempted to match 3 controls to each case. Controls had the same eligibility criteria as cases and were matched to individual cases on HMO, sex, date of birth (within 7 days), and length of health plan enrollment (up to the index date). The index date for controls was defined as the incidence date of the case to which the control was matched. Controls were selected from the HMOs' enrollment files.

Data Collection

Chart abstraction was performed by trained chart abstractors using standardized forms. In addition to complete vaccination histories, the chart abstraction forms for both cases and controls included information on sociodemographic characteristics, selected medical conditions, history of breastfeeding, and family medical history.

Analysis

We used conditional logistic regression to estimate the odds ratio (OR) of diabetes associated with vaccination. In the main analysis, relevant vaccine exposure was considered before the diabetes incidence date (or index date for controls). In the analyses of timing of hepatitis B vaccination, we categorized exposure according to age at first vaccination as follows:

- Never vaccinated (referent)
- Birth to 14 days of age
- Fifteen to 55 days of age
- ≥56 days of age

The vaccination timing hypothesis would predict that the OR should be <1.0 in the birth- to 14-day group and >1.0 in the ≥56-day group.

We also performed an analysis evaluating possible differences according to schedule of Hib vaccination, focusing on the schedules used in the Finnish Hib trial (ie, 3 doses in the first 8 months of life plus a fourth dose at 12–18 months vs only 1 dose at 21–27 months).

For each analysis, we present the results of 2 conditional logistic regression models. Model 1 is stratified by the matching variables: HMO, date of birth, sex, and length of health plan enrollment. Model 2 is also stratified by the matching variables and in addition includes covariables to adjust for race and ethnicity and family history of possible type 1 diabetes. We defined family history of possible type 1 diabetes as type 1 or unknown type of diabetes in a first-degree relative (ie, parent or sibling).

RESULTS

From the diabetes registries, we identified 318 potential cases, of which 255 met the study eligibility criteria and case definition after review of their medical records. An additional 3 cases were excluded because of missing vaccination records (2) or inconsistent data in the medical records (1). The remaining 252 cases were included in the analysis along with their 768 matched controls. The control-to-case ratio was slightly more than 3 to 1 because 1 HMO oversampled controls. A majority of cases were male, half were born during 1988 through 1990, and their ages at first diagnosis of diabetes ranged from 10 months to 10 years (Table 1). Because of matching, the controls had the same distributions as the cases for the preceding characteristics. The proportion of blacks and Hispanics were similar among cases and controls, whereas cases were less likely than controls to be Asians or Pacific Islanders and more likely to be white. Twenty-one percent of the cases had a family history of possible type 1 diabetes in a first-degree

TABLE 1. Characteristics of Cases and Controls

Characteristic	Cases (N = 252) N (%)	Controls (N = 768) N (%)
Gender		
Male	143 (56.8)	433 (56.4)
Female	109 (43.3)	335 (43.6)
Year of birth		
1988–1990	126 (50.0)	387 (50.4)
1991–1993	90 (35.7)	273 (35.6)
1994–1997	36 (14.3)	108 (14.1)
Age (incidence/index)		
10–28 mo	65 (25.8)	191 (24.9)
29–47 mo	64 (25.4)	200 (26.0)
48–72 mo	62 (24.6)	185 (24.1)
73–122 mo	61 (24.2)	192 (25.0)
Race/ethnicity		
Black	20 (7.9)	72 (9.4)
Asian/Pacific Islander	9 (3.6)	68 (8.9)
Hispanic	49 (19.4)	156 (20.3)
White	141 (56.0)	307 (40.0)
Other	7 (2.8)	35 (4.6)
Unknown	26 (10.3)	130 (16.9)
Family history of diabetes (possible type 1)	38 (21.1)	8 (4.0)
Breastfed (≥6 mo)	56 (22.2)	170 (22.1)

relative versus only 4% of controls. A similar proportion of cases and controls had been breastfed when they were 6 months or older.

The vaccination histories of cases and controls were similar (Table 2). Forty-four percent of cases versus 46% of controls had been vaccinated against hepatitis B before their incidence or index date, resulting in an OR of 0.81 with a 95% confidence interval of 0.52 to 1.27 (Model 1). Additional adjustment for race or ethnicity and family history of possible type 1 diabetes (Model 2) resulted in a small decrease in the OR to 0.73. Only 11 cases had not been vaccinated with Hib and 10 cases did not receive whole cell pertussis vaccine, resulting in less precise OR estimates for these 2 vaccines. Nonetheless, there was little evidence that either vaccine increased the risk of diabetes. In fact, the OR for whole cell pertussis vaccine suggested a decreased risk associated with this vaccine and the 95% confidence interval in the Model 2 results excluded 1.0. Vaccination with measles-mumps-rubella (MMR) vaccine was just over 90% in both cases and controls; the ORs in both models were around 1.4 with confidence intervals that overlapped 1.0. Acellular pertussis and varicella vaccines became part of the childhood immunization schedule during the later years of our study, and a minority of cases and controls had received these 2 vaccines. Neither vaccine showed an association with diabetes risk. Only 1 case and 3 controls had not received oral polio vaccine and thus we were not able to evaluate its association with diabetes.

The analysis of risk according to timing of hepatitis B vaccination indicated that the risk of diabetes was not related to timing of vaccination (Table 3). Children who were vaccinated within 14 days of birth had a risk about half of that of children who were not vaccinated (Model 1), but the confidence intervals around this estimate overlapped 1.0. The OR increased to 0.66 after adjustment for race or ethnicity and family history of type 1 diabetes (Model 2). Children who received their first hepatitis B vaccinations >14 days after birth also had lower risks than unvaccinated children, but again the 95% confidence intervals overlapped 1.0.

For hepatitis B vaccine, we also evaluated whether number of vaccine doses was related to risk of diabetes, but did not find any associations. Relative to unvaccinated children, the ORs (Model 1) were 0.63 (0.26–1.52) for children who had received 1 dose of vaccine and 0.85 (0.53–1.37) for children who had received 2 or more doses; the Model 2 results were not materially different.

For Hib vaccine, we evaluated relative risks according to different vaccination schedules. These analyses were restricted to children who were 27 months of age or older on their incidence or index date. We made this restriction because one of the schedules we compared involved receipt of a single dose of vaccine between 21 and 27 months. Using the currently recommended schedule (3 doses by 8 months of age with a fourth dose at 12–18 months of age) as the referent, the ORs were <1.0 for children who had received only 1 dose of vaccine at 21 to 27 months of age (Table 4). Only 8 cases, however, had been vaccinated according to the latter schedule and the confidence intervals were wide and overlapped 1.0. The ORs were also <1.0 for children vaccinated according to different schedules and those who were not vaccinated, but all the confidence intervals overlapped 1.0.

TABLE 2. Association Between Childhood Vaccines and Type 1 Diabetes

Vaccine	Vaccinated		OR (95% CI)	
	Cases N (%)	Controls N (%)	Model 1*	Model 2**
Hepatitis B	111 (44.0)	356 (46.4)	0.81 (0.52–1.27)	0.73 (0.45–1.19)
Hib	241 (95.6)	729 (94.9)	1.14 (0.51–2.57)	1.23 (0.53–2.89)
Pertussis (whole cell)	242 (96.0)	748 (97.4)	0.28 (0.07–1.06)	0.23 (0.06–0.93)
Pertussis (acellular)	58 (23.0)	177 (23.0)	0.92 (0.53–1.57)	1.12 (0.63–1.99)
MMR	232 (92.1)	696 (90.6)	1.36 (0.70–2.63)	1.43 (0.71–2.86)
Varicella	40 (15.9)	112 (14.6)	1.16 (0.72–1.89)	1.02 (0.61–1.72)

CI indicates confidence interval.
* Conditional logistic regression model stratified by matching variables (HMO, length of enrollment, gender, date of birth).
** As in Model 1, plus adjusted for race/ethnicity and family history of possible type 1 diabetes.

TABLE 3. Timing of Hepatitis B Vaccination and Risk of Type 1 Diabetes

Age at First Vaccination	Cases *N* (%)	Controls *N* (%)	OR (95% CI)	
			Model 1*	Model 2**
Not vaccinated	141 (56.0)	412 (53.7)	1.00 (referent)	1.00 (referent)
0–14 d	51 (20.2)	168 (21.9)	0.51 (0.23–1.15)	0.66 (0.27–1.59)
15–55 d	6 (2.4)	24 (3.1)	0.53 (0.18–1.52)	0.65 (0.21–2.0)
≥56 d	54 (21.4)	164 (21.4)	0.86 (0.54–1.35)	0.74 (0.45–1.21)

CI indicates confidence interval.
* Conditional logistic regression model stratified by matching variables (HMO, length of enrollment, gender, date of birth).
** As in Model 1, plus adjusted for race/ethnicity and family history of possible type 1 diabetes.

TABLE 4. Hib Vaccination Schedule and Risk of Type 1 Diabetes*

Schedule	Cases *N* (%)	Controls *N* (%)	OR (95% CI)	
			Model 1**	Model 2***
3 Doses by 8 mo plus 1 dose at 12–18 mo	52 (27.2)	135 (22.8)	1.00 (referent)	1.00 (referent)
1 Dose only at 21–27 mo	8 (4.2)	29 (4.9)	0.59 (0.22–1.57)	0.45 (0.15–1.30)
Other schedules	123 (64.4)	402 (67.8)	0.69 (0.41–1.16)	0.71 (0.41–1.24)
Not vaccinated	8 (4.2)	27 (4.6)	0.68 (0.26–1.81)	0.64 (0.22–1.81)

CI indicates confidence interval.
* Restricted to cases and controls ≥27 mo of age at incidence/index date.
** Conditional logistic regression model stratified by matching variables (HMO, length of enrollment, gender, date of birth).
*** As in Model 1, plus adjusted for race/ethnicity and family history of possible type 1 diabetes.

DISCUSSION

In this large, population-based, case-control study, we did not find an increased risk of type 1 diabetes associated with any of the routinely recommended childhood vaccines. Timing of hepatitis B vaccination also was not related to diabetes risk.

The possibility that vaccination may increase the risk of type 1 diabetes has been evaluated in a few epidemiologic studies. Classen[8] has provided the only evidence of a possible increased risk, but the nature of the evidence is strictly ecological, involving comparisons between countries or between different time periods in the same country. Such comparisons, however, may be influenced by many factors unrelated to vaccination, such as genetic predisposition and other environmental exposures. Moreover, similar ecological analyses conducted by other investigators have not found significant correlations between diabetes and several vaccines, including BCG, pertussis, and mumps.[2,3,5]

None of the epidemiologic studies that included control or comparison groups have found an increased risk of type 1 diabetes associated with vaccination. One of the largest and most comprehensive was a case-control study conducted in Sweden in the mid-1980s.[1] Overall, the 339 cases and 528 controls had similar vaccination histories for BCG, smallpox, pertussis, tetanus, rubella, and mumps vaccines. The only significant difference was a decreased risk of type 1 diabetes associated with measles vaccination. In a retrospective cohort study conducted in Canada, no association was found between BCG vaccine and risk of diabetes, although there was a suggestion that vaccination may have delayed the onset of diabetes.[4] A 10-year follow-up study of over 100 000 Finnish children who participated in a clinical trial of Hib vaccine also did not find an increased risk of diabetes associated with vaccination or with number of vaccinations received.[10]

Our study adds to previous research by providing data on newer vaccines, including hepatitis B, acellular pertussis, and varicella vaccines. For the older vaccines, our results are generally in agreement with previous studies in not finding any increased risks. We were not able to replicate Blom's finding that measles vaccine may decrease the risk of type 1 diabetes. All of the cases and controls in our study, however, had received MMR vaccine; thus, we could not evaluate the effect of single-antigen measles vaccine.

We also had limited ability to evaluate differences according to different Hib vaccination schedules. Only a few of the cases and controls in our study did not receive Hib vaccine or received only 1 dose at 21 to 27 months of age. Thus, our relative risk estimates for these groups were relatively unstable. The best data comparing different Hib schedules comes from the follow-up study of the Finnish clinical trial participants, and no significant differences were found in that study.[10] A remaining possible question is whether type of Hib conjugate influences risk,[13] but to address this question we would need additional data.

To our knowledge, ours is the first epidemiologic study to evaluate the possibility that timing of vaccination is related to risk of clinical diabetes in children. Classen[8,9] has suggested that certain vaccines, if given at birth, may decrease the occurrence of diabetes, whereas if initial vaccination is administered after 2 months of age, the occurrence of diabetes increases. The theory is based on results from experiments in laboratory animals, as well as comparisons of the rates of diabetes between countries with different immunization schedules. The possibil-

ity that vaccination shortly after birth may protect against the development of diabetes is supported by experiments in animal models conducted by other investigators.[7,14,15] Data in humans, however, have been lacking. Our results on hepatitis B vaccine do not support the hypothesis; risk of type 1 diabetes was not different between infants vaccinated at birth and those who received their first vaccination later in life.

Data from the Diabetes Autoimmunity Study also provides evidence against the notion that vaccination or timing of vaccination is associated with the development of type 1 diabetes.[16] This was a prospective study of 317 children who had a first-degree family member with type 1 diabetes. The children were monitored for the development of autoimmunity to pancreatic β-cells, an early precursor in the development of type 1 diabetes. No association was found between development of β-cell autoimmunity and receipt of any of a number of vaccines, including hepatitis B, Hib, polio, or diphtheria and tetanus toxoids and pertussis; nor was there an association with age at first vaccination with any of these vaccines.

Our main analyses evaluated the risk associated with ever being vaccinated. Several of our ORs were <1.0, so we further evaluated risk according to time since vaccination to investigate the possibility that vaccination of children with diabetes may have been deferred because they were in poor health before their diagnosis. If this were the case, we would have expected to see lower risks in time intervals closer to vaccination (ie, within 1 year) compared with more distant time periods (ie, >1 year). We did not see any decreased risks in the intervals closer to vaccination (data not shown); thus, it does not seem that deferral of vaccination because of poor health status influenced our results.

CONCLUSION

The results of our study and the preponderance of epidemiologic evidence do not support an association between any of the recommended childhood vaccines and an increased risk of type 1 diabetes. Suggestions that diabetes risk in humans may be altered by changes in the timing of vaccinations also are unfounded.

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Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus

Frank DeStefano, John P. Mullooly, Catherine A. Okoro, Robert T. Chen, S. Michael Marcy, Joel I. Ward, Constance M. Vadheim, Steve B. Black, Henry R. Shinefield, Robert L. Davis and Kari Bohlke

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Infections and vaccinations as risk factors for childhood Type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation

The EURODIAB Substudy 2 Study Group*

Abstract

Aims/hypothesis. To determine if vaccinations and infections are associated with the subsequent risk of Type I (insulin-dependent) diabetes mellitus in childhood.
Method. Seven centres in Europe with access to population-based registers of children with Type I diabetes diagnosed under 15 years of age participated in a case-control study of environmental risk factors. Control children were chosen at random in each centre either from population registers or from schools and policlinics. Data on maternal and neonatal infections, common childhood infections and vaccinations were obtained for 900 cases and 2302 control children from hospital and clinic records and from parental responses to a questionnaire or interview.
Results. Infections early in the child's life noted in the hospital record were found to be associated with an increased risk of diabetes, although the odds ratio of 1.61 (95 % confidence limits 1.11, 2.33) was significant only after adjustment for confounding variables. None of the common childhood infectious diseases was found to be associated with diabetes and neither was there evidence that any common childhood vaccination modified the risk of diabetes. Pre-school day-care attendance, a proxy measure for total infectious disease exposure in early childhood, was found, however, to be inversely associated with diabetes, with a pooled odds ratio of 0.59 (95 % confidence limits 0.46, 0.76) after adjustment for confounding variables.
Conclusion/interpretation. It seems likely that the explanation for these contrasting findings of an increased risk associated with perinatal infections coupled with a protective effect of pre-school day care lies in the age-dependent modifying influence of infections on the developing immune system. [Diabetologia (2000) 43: 47–53]

Keywords Type I (insulin-dependent) diabetes mellitus, epidemiology, risk factors, case-control study, perinatal, infection, vaccination, child care.

From as long ago as the introduction of insulin therapy a possible role of infections in the onset of childhood diabetes has been suspected [1]. Infections in the months [2, 3] or year [4, 5] preceding diagnosis are more common in children with Type I (insulin-dependent) diabetes mellitus than in control children and seasonal variation in onset with a peak in the winter months is evident throughout Europe [6]. This suggests that infections could play a part in precipitating Type I diabetes. The finding that a high proportion of children with fetal rubella embryopathy syndrome develop diabetes [7] suggests that infections early in life can also initiate autoimmunity. More recent observations indicate that coxsackie virus B infection during pregnancy is associated with an increase in diabetes risk [8–10].

Infectious diseases could be involved in the pathogenesis of autoimmune disease like diabetes in different ways. One is to directly attack the beta cell, an-

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Corresponding author: Dr. C.C. Patterson, Department of Epidemiology and Public Health, The Queen's University of Belfast, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BJ, UK

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other by affecting the developing immune system thus interfering with the future self/non-self discrimination capacity. This latter idea has been elaborated by immunologists based on experimental studies suggesting that infrequent infections and more widespread use of vaccinations lead to an increased risk of both atopic disease and childhood diabetes [11]. Other work from animal models has suggested that vaccinations can reduce the risk of diabetes [12]. Vaccinations have therefore been investigated as possible modulators of the risk of childhood diabetes. Several authors have looked for trends in childhood diabetes incidence rates after changes in countrywide vaccination policies. No detectable effect on incidence of Type I diabetes was reported after removal of either bacille Calmette-Guerin (BCG) [13] or pertussis [14] from the Swedish national immunisation programme. Although the elimination of mumps by a vaccination programme in Finland has been linked to the subsequent arrest of the incidence increase in diabetes among children aged 5–9 years, the incidence among children aged 0–4 years has continued to rise [15]. A recent analysis of diabetes incidence up to the age of 10 years in relation to differing *Haemophilus influenzae* type b vaccination regimes in Finland suggested that this vaccination and its timing were unlikely to be relevant [16]. The findings from various case control studies of vaccinations have been inconsistent. One study found mumps vaccination to be associated with a non-statistically significant reduction in diabetes risk [2], whereas another reported that measles vaccination, either alone or as a combined measles/mumps/rubella vaccination, was associated with a risk reduction [4]. Vaccination of BCG has been reported not to be associated with subsequent diabetes risk, although the data were suggestive of a possible protective effect under the age of 5 years [17]. Two other studies have reported that no vaccination was statistically significantly associated with risk [3, 18]. The findings of these case-control studies are difficult to interpret because vaccination uptake rates in some countries are so high that comparisons between cases and controls lack power. Also, isolated statistically significant findings are to be expected as a consequence of the multiple comparisons inherent in such studies, and should only be given credence if they can be replicated.

As part of a large, multicentre, population-based, case-control study to investigate early environmental exposures as possible risk factors for Type I diabetes, we have collected data on both vaccinations and infectious diseases in children who were diagnosed with diabetes before the age of 15 years and in an age-matched group of control children. We also report findings on perinatal infections, on some specific childhood infections and on a proxy measure of exposure to infections based on attendance at pre-school groups.

Methods and study design

Each of the eight participating centres had a population-based register of childhood onset diabetes operating in accordance with the standards of the EURODIAB ACE Group [19]. Cases were therefore obtained from a temporally and geographically well-defined study base in each centre. After consultation with the study coordinators, a population-based sample of control children, matched to the cases in age distribution, was obtained in each centre using sources which depended on local circumstances as previously described [20]. One centre (Bulgaria) had difficulty in complying with this element of the study and is excluded from this report. In the remaining seven centres 1028 children with diabetes onset before the age of 15 years and 3044 control children were invited to participate. Of these, 900 children with diabetes and 2302 control children participated giving response rates of 87.5% and 75.6%, respectively. A breakdown of numbers and response rates by centre is shown in Table 1.

An agreed set of core variables was then collected either by interview (Latvia, Luxemburg, Romania, UK-Leeds) or by questionnaire (Austria, Lithuania and UK-Northern Ireland). Information about maternal/perinatal infections and antibiotic treatment was obtained both from hospital records and from parental recall. Vaccination information was considered to be validated if obtained by the investigator from an official source or from a contemporary entry in a child health care booklet kept by the parent. If the parent was, however, able to provide exact dates of vaccination this was accepted as evidence of the existence of a contemporary record and the vaccination was considered to be validated even if the record was not actually seen by the investigator. Vaccination data obtained solely from parental recall was considered to be unvalidated. The child's history of five specific infectious diseases was obtained from parental recall. Pre-school group attendance was defined as regular attendance at a day-care centre, nursery or playgroup on three or more days a week for a minimum of 1 year. All information was transferred to a standardised coding sheet and anonymous records were dispatched to a single centre for data preparation and analysis.

Local study leaders received detailed written instructions for the selection of control children, the conduct of interviews and the completion of the record sheet. Each centre was site-visited by a study coordinator and centre leaders participated in workshops to maintain uniformity in study standards. All centres adhered to the principle of obtaining informed consent, and the approval of local research ethics committees was obtained where they existed.

All data on exposure to vaccinations and infectious diseases were corrected back to date of diagnosis for the children with diabetes or a corresponding date for control children obtained as the midpoint of the centre's period of recruitment of children with diabetes. The analysis of pre-school care was restricted to children with disease diagnosed after their fifth birthday since the day care arrangements made for children diagnosed before that age might have been influenced by their disease. Data from only six centres contributed to the analysis of pre-school care because one of the centres had already reported a more detailed analysis of its data [21].

The Mantel Haenszel approach was used to pool the results across centres, separate odds ratios being obtained for each centre, and these being combined using a weighting based on the numbers of children with diabetes and control children in the centre and their rates of exposure [22]. In addition to a test of significance on the combined odds ratio, a test for heterogeneity was also obtained which provides a comparison of the separate odds ratio between the centres. To adjust for potential

Table 1. Summary of participants in the seven study centres

Centre	Status	Source	Number Eligible	Number Responding	Availability of vaccination information among responders[a]	Availability of validated vaccination information among responders[a]
Austria (Vienna)	Diabetic	1989–94 registrations	117	104 (88.9%)	88%	70%
	Control	Schools	477	380 (79.7%)	89%	74%
Latvia (one region excluded)	Diabetic	1989–94 registrations	143	141 (98.6%)	96%	87%
	Control	Population register	410	324 (79.0%)	95%	88%
Lithuania	Diabetic	1989–94 registrations	124	117 (94.4%)	100%	100%
	Control	Policlinics	369	269 (72.9%)	100%	100%
Luxemburg	Diabetic	1989–95 registrations	59	59 (100.0%)	90%	90%
	Control	Schools/pre-schools	188	178 (94.7%)	98%	98%
Romania (Bucharest)	Diabetic	1989–94 registrations	111	82 (73.9%)	100%	100%
	Control	Health service register	342	277 (81.0%)	100%	100%
United Kingdom (Leeds)	Diabetic	1993–94 registrations	234	208 (88.9%)	82%	40%
	Control	General practitioner registers	535	409 (76.4%)	83%	35%
United Kingdom (Northern Ireland)	Diabetic	1990–92 registrations	240	189 (78.8%)	99%	94%
	Control	General practitioner registers	723	465 (64.3%)	100%	94%
Total	Diabetic		1028	900 (87.5%)	93%	74%
	Control		3044	2302 (75.6%)	94%	78%

[a] Median of nine common vaccinations

confounders, logistic regression analysis was used with terms included in the model to represent centres. Statistical analyses were done using the SPSS and STATA (Stata Statistical Software, Release 6.0, Stata Corporation, College Station, Tex., USA) packages. A p value of less than 0.05 was considered significant in all tests.

Results

The Mantel Haenszel pooled odds ratios for nine vaccinations are presented in the first column of Table 2. None of the odds ratios was statistically significant and there was no evidence of heterogeneity between centres. The corresponding odds ratios obtained from logistic regression analysis adjusting for confounding variables are shown in the second column, and again none attained statistical significance.

The analyses of data on maternal and perinatal infections is summarised in Table 3. Maternal infections, whether recalled by the mother or recorded in the hospital notes, were not associated with any significant elevation in the child's risk of diabetes. In contrast, infections in the newborn child, particularly if recorded in the hospital notes, were associated with an increased risk although the finding only attained significance after adjustment for variables with the potential to confound the association [20, 23]. Birth weight was the most influential confounder, with low birthweight infants more frequently being recorded as having infections. The full extent of the excess risk of diabetes associated with infections in the newborn therefore only became apparent when the reduced risk of diabetes in low birth weight infants observed in our study was taken into account.

Table 2. Odds ratios for nine common vaccinations before and after adjustment for confounding variables

Vaccination	Mantel Haenszel analysis stratified by centre		Logistic regression analysis adjusted for confounders[a]	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Tuberculosis	0.91 (0.66, 1.25)	0.57	0.83 (0.57, 1.20)	0.32
Polio	1.03 (0.56, 1.90)	0.92	1.20 (0.57, 2.52)	0.64
Tetanus	1.20 (0.66, 2.19)	0.55	1.56 (0.73, 3.33)	0.26
Diphtheria	1.09 (0.62, 1.93)	0.76	1.27 (0.63, 2.56)	0.51
Pertussis/Whooping Cough	0.89 (0.71, 1.12)	0.32	0.83 (0.63, 1.09)	0.18
Rubella/German Measles	1.18 (0.91, 1.53)	0.21	1.27 (0.93, 1.72)	0.13
Morbilli/Measles	1.02 (0.82, 1.28)	0.86	1.10 (0.84, 1.42)	0.49
Parotitis/Mumps	1.00 (0.82, 1.22)	0.98	1.03 (0.82, 1.30)	0.80
Haemophilus influenza	1.16 (0.62, 2.18)	0.65	0.75 (0.30, 1.92)	0.55

[a] Confounding variables were: centre, age-group (< 5 years, 5–9 years, ≥ 10 years), breast feeding (< 2 months, ≥ 2 months), birth weight (< 2500 g, ≥ 2500 g), maternal age (≤ 25 years, > 25 years), jaundice at birth (yes, no), asthma before disease diagnosis (yes, no) and vitamin D supplementation (yes, no, unknown)

Table 3. Odds ratios for maternal and neonatal infections and antibiotic treatment, before and after adjustment for confounding variables

	Mantel Haenszel analysis stratified by centre		Logistic regression analysis adjusted for confounders[a]	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Maternal infection during pregnancy (maternal recall)	1.06 (0.86, 1.32)	0.58	1.17 (0.91, 1.50)	0.23
Maternal infection other than urinary tract infection during pregnancy (hospital notes)	1.07 (0.82, 1.40)	0.61	1.03 (0.78, 1.37)	0.82
Antibiotic treatment during pregnancy (maternal recall)	0.84 (0.62, 1.15)	0.28	0.86 (0.60, 1.23)	0.41
Antibiotic treatment during pregnancy (hospital notes)	1.22 (0.87, 1.73)	0.25	1.25 (0.87, 1.79)	0.24
Severe neonatal infection in child (maternal recall)	1.39 (0.91, 2.13)	0.13	1.58 (0.97, 2.57)	0.07
Neonatal infection in child (hospital record)	1.29 (0.92, 1.81)	0.14	1.61 (1.11, 2.33)	0.01
Antibiotic treatment for child (maternal recall)	1.40 (0.86, 2.28)	0.20	1.58 (0.86, 2.88)	0.14
Antibiotic treatment for child (hospital notes)	1.07 (0.77, 1.48)	0.68	1.33 (0.93, 1.91)	0.12

[a] Confounding variables were: centre, age-group (< 5 years, 5–9 years, ≥ 10 years), breast feeding (< 2 months, ≥ 2 months), birth weight (< 2500 g, ≥ 2500 g), maternal age (≤ 25 years, > 25 years), jaundice at birth (yes, no), asthma before disease diagnosis (yes, no) and vitamin D supplementation (yes, no, unknown)

The analysis of common childhood infections is summarised in Table 4. For none of the five specific infections considered was there evidence that the odds ratios was statistically significant. For morbilli this non-significant pooled odds ratio concealed, however, some heterogeneity between centres, significantly elevated odds ratios of 2.02 (95% CI 1.18, 3.47) for the Austrian centre and 3.50 (1.85, 6.03) for the Romanian centre being balanced by a non-significantly reduced odds ratio of 0.70 (0.47,1.02) in the UK (Northern Ireland) centre. No obvious explanation can be found to explain this result. The pooled odds ratios remained non-significant when the results were adjusted for confounding variables.

The analysis of pre-school care, which was restricted to those aged 5 or more at the time of diagnosis (children with diabetes) or qualifying (control children), is presented in Fig. 1. The frequency of pre-school care in the control groups varied widely between centres ranging from 17% in Luxemburg to 95% in Austria. The individual odds ratios associated with pre-school care were significantly less than one for three of the seven centres and the results approached significance for two of the remaining centres. The pooled odds ratio of 0.56 (0.45,0.70) was highly statistically significant ($p < 0.001$). There was some evidence of heterogeneity mainly attributable to the results from the Luxemburg centre although this centre contributed little weight to the pooled odds ratio estimate. As shown at the foot of Fig. 1, adjustment for potential confounding variables made little difference to the reduction in the risk of diabetes associated with pre-school care.

Table 4. Odds ratios for parental recall of five common childhood infections before and after adjustment for confounding variables

Infection	Mantel Haenszel analysis stratified by centre		Logistic regression analysis adjusted for confounders[a]	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Rubella/German Measles	0.87 (0.69, 1.08)	0.20	0.95 (0.72, 1.24)	0.68
Morbilli/Measles	1.16 (0.91, 1.47)	0.23	1.00 (0.73, 1.38)	0.98
Varicella/Chickenpox	1.03 (0.86, 1.23)	0.74	0.84 (0.68, 1.05)	0.12
Pertussis/Whooping Cough	1.01 (0.70, 1.45)	0.96	0.99 (0.63, 1.55)	0.96
Parotitis/Mumps	1.20 (0.93, 1.55)	0.16	1.14 (0.84, 1.54)	0.40
Any of these five infections	1.06 (0.88, 1.27)	0.53	1.07 (0.83, 1.37)	0.61

[a] Confounding variables were: centre, age-group (< 5 years, 5–9 years, ≥ 10 years), breast feeding (< 2 months, ≥ 2 months), birth weight (< 2500 g, ≥ 2500 g), maternal age (≤ 25 years, > 25 years), jaundice at birth (yes, no), asthma before disease diagnosis (yes, no) and vitamin D supplementation (yes, no, unknown)

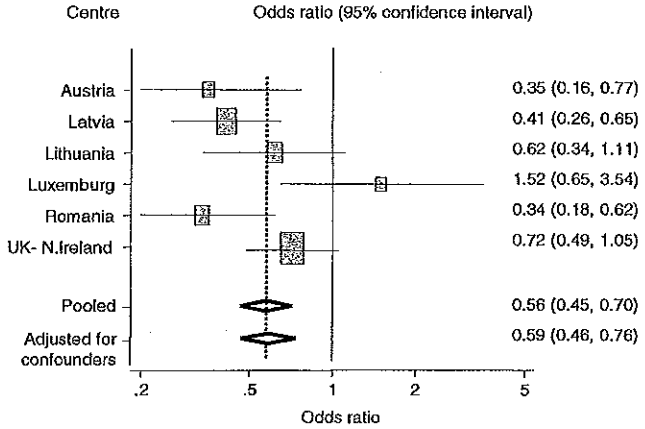

Fig. 1. Pooled odds ratio for pre-school day-care attendance with and without adjustment for confounding variables: the box size indicates the weight contributed by each centre to the Mantel-Haenszel pooled estimate

Discussion

This study shows that neonatal infectious diseases prospectively reported in hospital records are associated with a statistically significantly increased risk when adjusted for possible confounders. Because this significant finding was obtained in the context of multiple tests of hypothesis, some caution must, however, be exercised in its interpretation until corroborated by other studies. Nevertheless, the finding is consistent with previous studies showing a seasonality in the month of birth of children with diabetes [24] and simultaneous time and space clustering [25] suggesting that risk exposures operating around the time of birth and having an epidemic type of spread could be relevant. Furthermore, studies, from Sweden [8] and Finland [9] have shown an increase in comparison with control subjects' of coxsackie virus antibodies and antigens in maternal sera obtained during pregnancy from mothers of children who subsequently develop diabetes. The mechanism by which perinatal virus exposures could induce Type I diabetes has been debated since the observation that children with rubella embryopathy were at increased risk of diabetes. One possibility is that of a direct mimicry of autoantigens, this being supported by the observation that glutamic acid decarboxylase (GAD) carries sequence similarities not only with rubella virus capsid protein [26] but also to a sequence in the non-structural protein of coxsackie virus B [27]. Since the clinical onset of diabetes occurs several years after any early fetal or neonatal exposure, the early infection possibly only sensitises the organism through the GAD antigen and subsequent events could be necessary to activate the beta-cell destructive process. Such a mechanism could explain the widely reported occurrence of infectious disease just before the clinical onset of diabetes. On the other hand, fetal immunological events could have a specific effect on the developing immune system allowing other mechanisms to explain the association with early infections and autoimmunity. Due to lack of self/non-self discrimination of the fetal immune system, fetal viral infections could lead to persisting infection either in the beta cell or in the vicinity of the beta cell which might cause a slowly progressing inflammation or autoimmune development [28]. The dynamics of the developing immune system also introduces the potential for differential effects of infectious disease exposures in different time periods. The hygiene hypothesis claims that normal "education" of the immune system depends on a certain load of infections during the first years of life to avoid the occurrence of atopic and autoimmune diseases later in life. Some have warned of the potential for vaccinations to increase the risk of diabetes [29], whereas others have shown in animal models that non-specific stimulation of natural supressor activity associated with BCG vaccine or complete Freund's adjuvant could be protective [30–32]. The possible role of vaccinations in insulin-dependent diabetes continues to be debated [33] but there is a lack of reliable data. Our study, one of the largest case-control studies yet conducted to address this issue, found no evidence to support vaccination modulating the risk of childhood diabetes. We also looked specifically to see if the timing of BCG vaccination had any influence but we found no support for the hypothesis that early BCG vaccination was protective.

In most previous studies a history of specific childhood infections has been reported as frequently in diabetic as in control children [2, 4, 5] although one study did report that chickenpox was less common in diabetic children [3]. The limitations of parental recall of childhood infections are, however, well-documented [34], so it is notable that a study which used general practitioner records as an information source found that infections in the first year of life were associated with a reduction in the risk of diabetes in childhood [35]. Another study that used information recalled by parents showed the same pattern although the finding did not attain statistical significance [4]. Our own data, also based on parental recall, showed no link with any specific infectious diseases. In the light of the reported inadequacy of parental recall of the frequency and timing of non-specific infectious episodes [34] we did not, however, attempt to record the total infectious disease experience in the early years of life. Instead we used the proxy measure of pre-school day-care attendance which is known to be associated with an increased burden of infectious disease [36, 37]. We found that this measure had an inverse association with diabetes, a finding that is corroborated in a more detailed analysis of day-care arrangements in infancy in the study centre that we omitted from our analysis [21]. Contrary to our find-

ings, pre-school day-care attendance has previously been associated with an increased risk of diabetes [2, 38], although the findings in one study only just attained significance whereas in the other they were no longer significant after allowing for confounding variables. Since organised pre-school day-care has probably become more common in western European countries during the last few decades as mothers increasingly return to work after having their children, our finding of an inverse association with day-care attendance does not readily explain the recent widespread increase in the childhood diabetes incidence rate in European countries [39].

Other possible proxy measurements for infectious disease exposure in childhood have been studied. Three small-area analyses in the United Kingdom have reported lower rates of diabetes in children resident in areas of greatest material deprivation and of high population density [40–42], although an increased incidence in areas of material deprivation has also been reported [43]. Being the first child in the family could act as a marker for low exposure to infections, especially in the early years of life. Although generally birth order has not been found to be associated with diabetes [3, 44], there have been reports that diabetic children are more likely to be firstborn if attention is restricted to those with onset before the age of 5 years [18, 45]. Family size has also been investigated and although there has been a report that diabetic children are more often from smaller families than control children [2] others have found no such association [46]. The current study provided no evidence to support an association with either birth order or family size.

The hypothesis that early exposure to infections can reduce the risk of diabetes has advocates [11, 47]. The epidemiological evidence is, however, still weak and the hypothesis must remain speculative even though there is clear evidence to support it from animal models. Prospective monitoring of infectious disease exposures among large cohorts of children may be necessary to provide a reliable answer to this question.

In conclusion, our large multicentre case-control study covering a wide range of maternal and neonatal infections as well as validated vaccination data supports previous evidence of early perinatal infections as being risk factors for childhood onset of Type I diabetes. A proxy measure of the total load of infections during the pre-school years, on the other hand, gives support for a protective effect perhaps through a specific effect on the developing immune system. Our study indicates that vaccinations do not exert any major modifying effect on the risk of Type I diabetes.

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The EURODIAB Substudy 2 study group co-ordinators responsible for study design and preparation of the manuscript were: G. Dahlquist, Department of Clinical Science, Paediatrics, Umeå University, Umeå, Sweden; C. Patterson, Department of Epidemiology and Public Health, Queen's University Belfast, Northern Ireland, UK (also responsible for data processing and analysis); G. Soltész, Department of Paediatrics, University of Pecs, Hungary.

The study centre leaders were:
Austria: E. Schober and U. Schneider, Department of Paediatrics, University of Vienna, Vienna, Austria.
Bulgaria: S. Goranova, D. Stovanova and M. Ivanova, Children's Diabetic Centre, Sofia, Bulgaria
Lithuania: B. Urbonaite and A. Pundzuite, Department of Paediatrics, University of Kaunas, Kaunas, Lithuania.
Latvia: G. Brigis and I. Rubietza, Department of Public Health and Epidemiology, Medical Academy of Latvia, Riga, Latvia.
Luxemburg: C. de Beaufort, Paediatric Clinic, Luxemburg
Romania: A.-M. Konnerth and K. Ionescu-Tirgoviste, Department of Nutrition and Metabolic Disease, University of Bucharest, Romania.
United Kingdom (Leeds): P. McKinney, Institute of Epidemiology and Health Services Research, University of Leeds, Leeds, UK.
United Kingdom (Northern Ireland): C. Patterson, R. Greenlees and D. Hadden, Department of Epidemiology and Public Health, Queen's University Belfast, Northern Ireland, UK.

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Vaccination and risk of type 1 diabetes mellitus in active component U.S. Military, 2002–2008☆,☆☆

Susan K. Duderstadt[a,d], Charles E. Rose Jr[b], Theresa M. Real[a,d], Jennifer F. Sabatier[c], Brock Stewart[a,e], Guihua Ma[a,d], Uma D. Yerubandi[a,d], Angelia A. Eick[f], Jerome I. Tokars[a], Michael M. McNeil[a,*]

[a] Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, United States
[b] Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, United States
[c] Division of Global HIV/AIDS, Center for Global Health, Centers for Disease Control and Prevention, United States
[d] Logistics Health Incorporated, United States
[e] Science Applications International Corporation, United States
[f] Armed Forces Health Surveillance Center, U.S. Army Center for Health Promotion and Preventive Medicine, 11800 Tech Road, Silver Spring, MD 20904, United States

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ABSTRACT

Aims/hypothesis: To evaluate whether vaccination increases the risk of type 1 diabetes mellitus in active component U.S. military personnel.
Methods: We conducted a retrospective cohort study among active component U.S. military personnel age 17–35 years. Individuals with first time diagnoses of type 1 diabetes between January 1, 2002 and December 31, 2008 were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. We used Poisson regression to estimate risk ratios between individual vaccine exposures and type 1 diabetes. Secondary analyses were performed controlling for receipt of multiple vaccines and available demographic variables.
Results: Our study population consisted of 2,385,102 individuals followed for approximately 7,644,098 person-years of service. This included 1074 incident type 1 diabetes cases. We observed no significant increased risk of type 1 diabetes after vaccination with anthrax vaccine adsorbed (AVA) [RR = 1.00; 95% CI (0.85, 1.17)], smallpox vaccine [RR = 0.84; 95% (CI 0.70, 1.01)], typhoid vaccine [RR = 1.03; 95% CI (0.87, 1.22)], hepatitis B vaccine [RR = 0.83; 95% CI (0.72, 0.95)], measles mumps rubella vaccine (MMR) [RR = 0.71, 95% CI (0.61, 0.83)], or yellow fever vaccine [RR = 0.70; 95% CI (0.59, 0.82)].
Conclusions: We did not find an increased risk of diagnosed type 1 diabetes and any of the study vaccines. We recommend that follow-up studies using medical record review to confirm case status should be considered to corroborate these findings.

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1. Introduction

Type 1 diabetes is an autoimmune disorder characterized by the production of antibodies against pancreatic beta cells. The resulting destruction of these insulin-producing cells inevitably leads to impairment of insulin secretion, resulting in hyperglycemia and its associated complications. The etiology of type 1 diabetes is unknown, though both genetic and environmental risk factors are thought to play a role in its pathogenesis [1]. It has been hypothesized that vaccination could trigger type 1 diabetes in susceptible individuals [2]. Although post-vaccination type 1 diabetes may be biologically plausible [3], cumulative evidence has not supported an increased risk of type 1 diabetes following any vaccine [1].

The majority of studies to date assessing the risk of type 1 diabetes following vaccination has been limited to children or has been conducted in animal models. The few controlled epidemiological analyses that have examined diabetes following vaccination in adults have focused on anthrax vaccine adsorbed (AVA) and were conducted as part of more generalized anthrax vaccine adverse event surveillance efforts [4]. Two such analyses found no increased risk of ambulatory visits or hospitalizations for diabetes (type not specified), following administration of AVA to selected military groups [5,6]. As part of the Institute of Medicine's (IOM) review of the safety and efficacy of AVA, the Army Medical Surveillance Activity (AMSA) conducted additional analyses using the Defense Medical Surveillance System (DMSS) to address the

☆ *Disclaimer:* The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the Department of the Army, or the Department of Defense.
☆☆ The protocol for this study was determined to be non-research and therefore did not require review by the CDC Institutional Review Board (IRB), and was approved by the Armed Forces Health Surveillance Center (AFHSC).

* Corresponding author at: CDC, 1600 Clifton Road NE, MS D-26, Atlanta, GA 30333, United States. Tel.: +1 404 639 0542; fax: +1 404 639 8834.
E-mail address: mmm2@cdc.gov (M.M. McNeil).

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"healthy soldier" effect. A preliminary analysis by AMSA found post-vaccination hospitalization rates for diabetes (type not specified) to be significantly higher than pre-vaccination hospitalization rates. However, the follow-up analyses confirmed that pre-vaccination hospitalization rates were lower than rates in the group that was never vaccinated [7]. The IOM concluded that the perceived elevated risk was most likely the result of random chance or due to a "healthy soldier" or "healthy vaccinee" effect [4]. Nonetheless, the IOM recommended further investigation into the risk of diabetes following AVA.

None of the analyses examining diabetes following AVA distinguished between type 1 and type 2 diabetes, which have similar clinical manifestations but result from very different pathophysiological processes [8]. To date, there is no published evidence suggesting a link between vaccinations and type 2 diabetes, nor has a biologically plausible mechanism for post-vaccination type 2 diabetes been proposed. Type 2 diabetes accounts for 90–95% of all diabetes cases in adults [9], and despite strict physical standards for entry and retention [10], the incidence of type 2 diabetes has also been suggested to be several times that of type 1 diabetes in U.S. military personnel [11]. Given the likelihood that the large majority of diabetes cases in the analyses reviewed by the IOM had type 2 diabetes, these results provide little insight into the risk of type 1 diabetes, the form most plausibly related to vaccination, following AVA.

The objective of our study was to investigate a possible association between adult vaccination with selected vaccines and type 1 diabetes mellitus. To our knowledge, this is the first controlled epidemiologic study addressing this topic. Furthermore, this is the first study in any age group to investigate the risk of type 1 diabetes following several less common vaccines given to large proportions of military personnel, including AVA, smallpox vaccine, yellow fever vaccine, and typhoid vaccine.

2. Methods

2.1. Data source

The Defense Medical Surveillance System (DMSS) is an active surveillance system administered by the Department of Defense (DoD) to integrate data from medical treatment facilities, vaccination centers, and military personnel offices worldwide. Inpatient and outpatient diagnosis data are recorded using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes.

2.2. Study design

We conducted a retrospective population-based cohort study to investigate a possible association between receipt of selected vaccines and type 1 diabetes. The study population included U.S. military personnel in the Army, Air Force, Marines and Navy, age 17–35, who were in the active component at any time during the period January 1, 2002–December 31, 2008. In order to ensure that all subjects were disease-free at the start of the study period, individuals with evidence of diabetes or diabetes-related complications [polyneuropathy in diabetes (357.2), diabetic retinopathy (362.0), diabetic cataract (366.41), gestational diabetes (648.0) encounter for insulin pump training (V65.45), and transplantation of pancreas (Procedure code 52.8)] prior to January 1, 2002 were excluded from all analyses.

We used the 3-digit specification 250 (i.e., 250.XX) to identify individuals with "any" diabetes, and the 5th digit specifications 1 and 3 (i.e., 250.X1, 250.X3) to identify individuals with possible type 1 diabetes. In order to be considered a case, subjects were required to have at least two medical encounters with a type 1 diabetes mellitus code within one year after their first "any" diabetes diagnosis. We required that at least one of these encounters have a type 1 diabetes mellitus code as the primary diagnosis. Individuals who had ICD-9-CM codes for pregnancy-related diagnoses (630–679; V22, V23, V24, and V27) within 6 months prior to or following their first "any" diabetes diagnosis (250.XX) were excluded, given concerns that some women with gestational diabetes may be incorrectly assigned type 1 diabetes codes [11,12]. We also excluded subjects who had been assigned one or more ICD-9-CM codes suggestive of a possible non-autoimmune etiology, such as pancreatic cancer, a pancreatic injury, or a medical condition associated with pancreatic complications (Table 1). Individuals who had one or more "any" diabetes codes but did not meet the case classification criteria for type 1 diabetes were excluded from the study population.

We defined the *study start date* as January 1, 2002 or the date a person entered the active component, whichever was later. We defined the *study end date* as December 31, 2008, the date of the incident "any" diabetes diagnosis, the date a subject left the active component, or the subject's 36th birthday, whichever was earlier.

The date of exposure was defined as the day a subject received his or her first dose of the vaccine of interest. Vaccines were selected based on those evaluated in prior published studies of diabetes mellitus following childhood vaccination, and those vaccines most frequently reported to the Vaccine Adverse Event Reporting System (VAERS) in individuals with post-vaccination diabetes (CDC unpublished data). Selected vaccines included AVA, hepatitis B vaccine, smallpox vaccine, typhoid vaccine, and yellow fever vaccine. MMR was also included, given assertions by a few authors that measles-containing vaccines may be protective against childhood type 1 diabetes [13,14].

Subjects who had evidence of receipt of the vaccine of interest prior to their study start date were considered to be in the *exposed* group at study entry and contributed person-time to the exposed group until their study end date. Individuals with no evidence of prior exposure to the vaccine contributed person time to the *unexposed group* during the period from their study start date until the date they received the vaccine (i.e., date exposed) or until their end date, whichever was earlier. Individuals in this group who were subsequently vaccinated contributed person-time to the *exposed group* from the date of their first dose of the vaccine until their study end date.

We used Poisson regression to estimate risk ratios for this retrospective cohort study. *P*-values less than 0.05 were considered statistically significant. Multivariable modeling methods were used to examine the risk of diabetes following individual vaccines. There was one binary exposure variable for each of the six study vaccines, and we controlled for the following potential confounders: age, race, sex, service branch, military grade, occupation, deployment, and calendar year.

In order to address concerns regarding possible incorrect assignment of type 1 diabetes ICD-9 codes to individuals with type 2 diabetes, we performed a subanalysis restricted to non-Hispanic white males age 17–24. We suspect type 1 diabetes codes in this population may have higher positive predictive values (PPV) than those in other demographic groups. Non-Hispanic white adolescents (age 15–19) have been demonstrated to have a higher incidence of type 1 diabetes and lower incidence of type 2 diabetes than their African American or Hispanic counterparts [15], which should provide less opportunity for misclassification of type 2 diabetes. Rates of obesity, the primary factor associated with type 2 diabetes, have been found to be lower in young service members age 17–24 than in older military personnel [16], which supports the hypothesis that this younger age group may be less prone to type 2 diabetes than their older counterparts. Furthermore, the 17–24

Table 1
Medical exclusion criteria and the distribution for individuals with type 1 diabetes codes (not mutually exclusive).

Diagnosis	ICD-9-CM code	Number of people in the category excluded
Pregnancy code within 6 months of first diabetes diagnosis	630–679; V22, V23, V24, V27	29[a]
Disorders of pituitary gland and its hypothalamic control	253	11
Cushing syndrome	255.0	1
Polycystic ovaries	256.4	4
Disorders of iron metabolism	275.0	8
Dysmetabolic syndrome X	277.7	11
Neoplasm, pancreas, adrenal and other endocrine[b]	157, 194.0, 198.7, 211.6, 211.7, 227.0, 230.9, 234.8, 235.5, 237.28, 239.0, 239.7	2
Pancreatic trauma	863	0
Pancreatic surgery	251.3, Procedure code 52.8	0
Other	258.0, 271.4, 275.0, 277.0, 303.0, 577	0

[a] Mutually exclusive.
[b] Excluded if diabetes diagnosis occurs <1 year or any time after cancer diagnosis.

year old age group falls within the range examined in a study by Rhodes et al. who observed high accuracy for type 1 diabetes codes in individuals <26 years [17].

In order to account for possible changes in risk by time since vaccination, we performed additional analyses examining several time intervals (0 to <1 year, 1 to <2 years, 2 to <3 years, 3 to <4 years, 4 to <5 years, 5+ years after vaccination).

In addition to the Poisson regression models described above, we also considered negative binomial and generalized Poisson [18] models, as well as zero-inflated and hurdle models [19] based on the Poisson, negative binomial, and generalized Poisson probability distributions. Since the results obtained from these additional models were similar to those from Poisson models, we have presented results from only the Poisson models.

3. Results

We identified 2,402,976 individuals age 17–35 years who were in the active component (Army, Navy, Air Force, Marines) at any time during the period January 1, 2002 through December 31, 2008. A total of 17,874 were excluded from the study population because they had at least one code for diabetes or a diabetes-related complication assigned prior to January 1, 2002, or because they had a diabetes code after January 1, 2002 but did not meet the case definition (n = 8141). The final study population included 2,385,102 individuals.

We identified 1121 subjects who met our case definition. Of these, 29 were excluded because they had ICD-9-CM codes for pregnancy-related conditions within 6 months of their first diabetes diagnosis, and 18 were excluded for conditions known to predispose to diabetes (Table 1). The remaining 1074 type 1 diabetes cases were included in our analyses.

The observed overall incidence rate of type 1 diabetes was 14.1 per 1,00,000 persons per year. Among demographic characteristics examined, the incidence varied significantly according to service branch and grade category, being higher for enlisted service members than for officers (Table 2). Observed incidence was higher for blacks than whites, for men than women, and among older age groups. Factors not significantly associated with incidence included ethnicity, deployment, and occupational category.

Table 3 presents the results of the univariable (adjusted for each vaccine individually) and multivariable (adjusted for all vaccines simultaneously) analyses for each of the vaccines. In our multivariable analysis, we observed no significant increased risk of type 1 diabetes after vaccination with anthrax vaccine adsorbed (AVA) [RR = 1.00; 95% CI (0.85, 1.17)], smallpox vaccine [RR = 0.84; 95% (CI 0.70, 1.01)], typhoid vaccine [RR = 1.03; 95% CI (0.87, 1.22)], hepatitis B vaccine [RR = 0.83; 95% CI (0.72, 0.95)], measles mumps rubella vaccine (MMR) [RR = 0.71, 95% CI (0.61, 0.83)], or yellow fever vaccine [RR = 0.70; 95% CI (0.59, 0.82)].

As in the analysis investigating the full cohort (age 17–35), when fitting our models to the subset of non-Hispanic white males age 17–24, we observed no statistically significant increased risk ratios for MMR [RR = 0.73, 95% CI (0.55, 0.98)], yellow fever vaccine [RR = 0.69, 95% CI (0.50, 0.95)], hepatitis B vaccine [RR = 0.96, 95% CI (0.74, 1.26)], AVA [RR = 0.98, 95% CI (0.71, 1.36)], smallpox vaccine [RR = 0.90, 95% CI (0.62, 1.30)], or typhoid vaccine [RR = 0.91, 95% CI (0.67, 1.22)]. Results did not significantly vary by time since vaccination.

4. Discussion

This is the first epidemiologic study specifically investigating the risk of type 1 diabetes following vaccination in adults, as well as the first study evaluating the risk of type 1diabetes after AVA, smallpox, typhoid or yellow fever vaccines. In our investigation, we found no evidence of an increased risk of type 1 diabetes following receipt of any of the vaccines investigated in this military population. Although we noted statistically significant decreased risk ratios for hepatitis B, MMR, and yellow fever vaccines in our analyses, these should be interpreted with caution. The finding of significant risk ratios <1 cannot be viewed as evidence for a protective effect since even carefully conducted observational studies may have residual confounding. Controlling for multiple additional confounding variables may have been helpful, but additional relevant variables were not available in our dataset. Because it is often not possible to identify and control for all such confounding variables, the self-controlled case series method is often used in studies of vaccine adverse events [20]. This approach, however, requires identifying biologically plausible time windows when vaccine adverse events would be expected versus not expected, and precise information is not available for type 1 diabetes. Diabetes may have a long preclinical phase with development of autoantibodies possibly years before clinical onset. However, the possibility that vaccine exposure could "trigger" clinical diabetes in individuals with preclinical disease over a relatively short time period (weeks or months) should also be considered. Results of our evaluation did not vary when we examined several different times since vaccination.

Our results are consistent with investigations examining the risk of type 1 diabetes following childhood vaccines. The majority of epidemiologic studies that have included control or comparison groups have not found an increased risk of type 1 diabetes following childhood vaccination [1,13,21–24]. Findings of risk estimations (RR, odds ratio, etc.) less than one are not unique to our study but have also been reported in the literature for

Table 2
Demographics of cases and observed incidence[a] of type 1 diabetes in active component U.S. Armed Forces, 2002–2008.

Characteristic	Cases (n = 1074)		Person-years at risk	Rate per 100,000	Univariable analysis
	N	%			Risk ratio (95% CI)
Branch					
Army	366	34.1	2,767,033	13.23	1.0
Air Force	242	22.5	1,812,319	13.35	1.01 (0.86, 1.19)
Marine Corps	125	11.6	1,130,138	11.06	0.84 (0.68, 1.02)
Navy	341	31.8	1,934,608	17.63	1.33 (1.15, 1.54)
Grade category					
Officer	100	9.3	881,884	11.34	1.0
Enlisted	974	90.7	6,762,214	14.4	1.27 (1.03, 1.56)
Race					
White	712	66.3	5,287,360	13.47	1.0
Black	255	23.7	1,342,884	18.99	1.41 (1.22, 1.63)
Other	86	8.0	832,614	10.33	0.77 (0.61, 0.96)
Unknown	21	2.0	181,241	11.59	
Ethnic					
Non-hispanic	951	88.5	6,613,377	14.38	1.0
Hispanic	102	9.5	849,431	12.01	0.84 (0.68, 1.02)
Unknown	21	2.0	181,290	11.58	
Deployment					
No	638	59.4	4,510,144	14.15	1.0
Yes	436	40.6	3,133,954	13.91	0.98 (0.87, 1.11)
Sex					
Male	985	91.7	6,482,539	15.19	1.0
Female	89	8.3	1,161,516	7.66	0.50 (0.41, 0.63)
Occupation category					
Administrative/communication	529	49.3	3,581,944	14.77	1.0
Medical/scientific/research	74	6.9	583,904	12.67	0.86 (0.67, 1.09)
Hazardous	89	8.3	548,157	16.24	1.10 (0.88, 1.38)
Combat	382	35.6	2,928,884	13.04	0.88 (0.77, 1.01)
Unknown	0	0	1210	0	
Age category (years)					
17–24	495	46.1	4,002,108	12.37	1.0
25–29	320	29.8	2,035,304	15.72	1.27 (1.10, 1.46)
30–35	259	24.1	1,606,687	16.12	1.30 (1.12, 1.51)

[a] Based on automated data.

several childhood vaccines, including MMR [14,25], measles vaccine [13], and pertussis vaccine [25,26]. Several infectious agents, including enteroviruses, rotavirus, parvovirus, cytomegalovirus, mumps, and rubella have been suggested as possible modulators of type 1 diabetes [25,27] and a few authors have hypothesized that certain vaccines may have a protective effect by preventing natural infection [28]. However, studies by others have not been able to demonstrate similar protective effects [24,29,30].

Classen et al. have postulated associations between type 1 diabetes and a number of vaccines, including AVA, hepatitis B vaccine, MMR and others. However, much of the evidence cited to support this claim is either ecological and includes comparisons between countries or between different time periods in the same country [31], is based on the results of animal studies [32], or involves reanalysis of summary data published by other authors without adjusting for potential confounders [33]. Although ecological data may be useful in generating hypotheses regarding possible risk

Table 3
Results of Poisson regression analysis of type 1 diabetes mellitus in active component U.S. Armed Forces, 2002 through 2008.[a]

Vaccine Exposure	Cases	Person-years at risk	Rate per 100,000	Univariable analysis	Multivariable analysis
				Risk ratio (95% CI)	Risk ratio (95% CI)
Anthrax vaccine (AVA)					
Unvaccinated	598	4,181,732	14.30	1.0	1.0
At least 1 dose	476	3,462,367	13.75	0.96 (0.85, 1.08)	1.00 (0.85, 1.17)
Hepatitis B					
Unvaccinated	674	4,389,106	15.36	1.0	1.0
At least 1 dose	400	3,254,993	12.29	0.80 (0.71, 0.91)	0.83 (0.72, 0.95)
Measles, mumps, and rubella (MMR)					
Unvaccinated	369	2,215,350	16.66	1.0	1.0
At least 1 dose	705	5,428,749	12.99	0.78 (0.69, 0.88)	0.71 (0.61, 0.83)
Smallpox					
Unvaccinated	749	5,032,755	14.88	1.0	1.0
At least 1 dose	325	2,611,344	12.45	0.84 (0.73, 0.95)	0.84 (0.70, 1.01)
Typhoid					
Unvaccinated	323	2,098,989	15.39	1.0	1.0
At least 1 dose	751	5,545,110	13.54	0.88 (0.77, 1.00)	1.03 (0.87, 1.22)
Yellow fever					
Unvaccinated	424	2,704,252	15.68	1.0	1.0
At least 1 dose	650	4,939,846	13.16	0.84 (0.74, 0.95)	0.70 (0.59, 0.82)

[a] Adjusted for age, race, sex, service branch, military grade, calendar year, and receipt of one or more of the study vaccines.

factors for a disease, they cannot be used to determine causal relationships given the inability to account for other genetic or environmental risk factors that could vary by location or time. Similar ecological analyses conducted by other researchers have not supported a link between vaccination and type 1 diabetes in children [28,30]. Furthermore, it is difficult to extrapolate results of animal studies to humans, since development of diabetes in animal models may reflect different pathogenetic mechanisms than those operating in human subjects [34].

Strengths of our investigation include the availability of the DMSS, which contains more than 11 million person-years of data. Large linked databases, such as this one, are a valuable resource in the surveillance and timely assessment of rare vaccine adverse events, including chronic conditions with onset several years after vaccination [35]. Evaluation of such conditions is often not possible without access to very large numbers of individuals and high vaccination rates, such as those occurring in the military population. Furthermore, the quality of DMSS vaccine data from 1998 onward has been demonstrated to be suitable for post-marketing vaccine safety studies [36,37].

For this study we did not have access to medical records or pharmacy information, and were reliant on administrative data. As with any study relying solely on administrative data, an important limitation is the unknown quality of the diagnostic codes. The validity of diagnosis codes for diabetes mellitus has been shown to vary between databases and by medical center [38,39]. Although the nonspecific 3-digit ICD-9-CM code for diabetes mellitus (250) has been found to be adequately sensitive and specific for identifying diabetes mellitus cases (any type) in a number of databases [40], very little is known about the quality of 5-digit ICD-9-CM codes specific to type 1 diabetes. Rhodes et al., assessed the validity of diabetes ICD-9-CM codes in individuals <26 years of age (average 15.5 ± 4.8 yrs) in children visiting a pediatric endocrinology program and demonstrated codes for "type 1" diabetes (250.X1 and 250.X3) were highly accurate (PPV = 97.0%) [17]. However, it is unclear whether these findings can be extrapolated to other patient care settings or to older age groups, where the proportion of individuals with type 2 diabetes greatly outnumber that of type 1. The incorrect assignment of type 1 codes to individuals with type 2 diabetes especially those taking insulin, has been documented in the literature [8].

In order to address the issue of code quality, we applied algorithms designed to increase the PPV for case selection. The requirement for repeat codes on different days has been demonstrated to improve the PPV for both unspecified and insulin-requiring diabetes (e.g. people with type 1 diabetes or people with type 2 diabetes who are taking insulin) [41,42]. Codes in the primary position (principal diagnosis codes) have been demonstrated to be more accurate than those in other positions for several non-diabetes conditions [43], and a primary position requirement was also included in the case definition in a recent study by Greenburg et al., who estimated rates of diabetes mellitus in the U.S. military [11]. We also screened subjects for the presence of ICD-9-CM codes suggestive of non-vaccine diabetes etiologies (Table 1) and women who had codes for pregnancy within 6 months of their first diabetes diagnosis and may have had miscoded gestational diabetes.

Our observed incidence rate for all age groups was 14.1 per 100,000 persons per year, which falls within the range of published estimates for young adults in the United States (range 3.4 per 100,00 persons per year [11] (military personnel age 17–40), to 23.5 per 100,000 persons per year (civilian males, age 18–25) [44]. The relatively wide range of incidence estimates may be explained by a number of factors, including the study population, the chosen study period, and nature of information available to define cases (e.g. administrative data only, prescription information, chart review, serological studies for diabetes autoantibodies). Greenburg et al. used data from the DMSS to calculate the incidence of type 1 diabetes in military personnel age 17–40 years (1997–2007) and observed a rate of 3.4 per 1,00,000 persons per year, which was much lower than our calculated incidence using the same database. However, these authors excluded individuals who had type 2/unspecified codes (250.X0, 250.X2) during their case defining period, though these codes may be appropriately assigned to individuals under certain circumstances [45]. Indeed, 56% ($n = 602$) of the individuals in our case group were assigned 250.X0 or 250.X2 as their presenting code. Furthermore, of the 997 (93%) subjects in our case group who had at least one type 2/unspecified code, 309 (39%) also had at least one diagnosis of diabetic ketoacidosis, which occurs predominantly in individuals with type 1 diabetes [46].

We noted several demographic factors that influenced the risk of type 1 diabetes. From the multivariable model, risk was lower in women than in men [RR = 0.46; 95% CI (0.36, 0.57] which is consistent with previous reports [47,48]. Our calculated incidence of type 1 diabetes also increased with age. While similar trends have been noted in some studies [11,44,48] others have demonstrated declines in type 1 diabetes incidence from adolescence through the mid to late thirties [47], as well as variability in age trends among different ethnic groups [48]. We observed a higher calculated incidence of type 1 diabetes in blacks than in whites in the multivariable model [RR = 1.42; 95% CI (1.23, 1.65)]. This has also been observed in other studies using DMSS and other military administrative databases [11,42], however none of these studies formally validated their type 1 cases with medical record review. Although studies using rigorous case validation methods have confirmed that the incidence of type 1 diabetes in adolescents is higher for non-Hispanic whites than for other racial and ethnic groups [15], similar studies addressing type 1 diabetes incidence in U.S. adults are lacking.

Our study is subject to several limitations. The inclusion of individuals with type 2 diabetes as type 1 diabetes cases could have biased risk estimates towards the null [49]. We were unable to identify vaccines that were administered prior to entering the active component. Furthermore, the quality of vaccine data prior to 1998 is unknown, and we are unable to confirm the completeness of vaccine data in the pre-1998 period. Some individuals in our study population may have received MMR or hepatitis B vaccine as part of the routine childhood/adolescent immunization schedule and may have been incorrectly classified as "unexposed." Results for these two vaccines must be interpreted with this in mind, and are reflective only of vaccines received while in the military. By contrast, vaccines such as AVA and smallpox are unlikely to be received outside of the military setting. Although typhoid and yellow fever vaccines are occasionally administered to civilians traveling to endemic areas, their use is much more common in the U.S. military where service members are frequently deployed to high-risk areas. Hence, it is likely that most of our subjects who were vaccinated with AVA, smallpox vaccine, yellow fever vaccine and/or typhoid vaccine received them for the first time during military service.

We were unable to control for certain established or proposed non-vaccine risk factors in our analysis. Family history was not available. Although ICD-9-CM codes exist for several of the proposed infectious risk factors, we would not have been able to identify individuals who did not present for medical care, who were not tested for specific agents, or whose illness occurred prior to military entry. For example, Gorham et al. [42] hypothesized that their observed higher incidence of insulin-requiring diabetes in black military personnel could be due to a higher prevalence of vitamin D deficiency, a proposed risk factor for autoimmune diabetes [50]. We found only four individuals in our type 1 diabetes group who had codes for vitamin D deficiency, none of whom were black. Given the high prevalence of vitamin D deficiency in African American civilian men [51], we suspect this condition may be

undercoded and/or underdiagnosed and, hence, underrepresented in the DMSS.

The findings of this study are reassuring. However, follow-up investigation incorporating medical record review to formally validate case status should be considered. This may be especially important for the accurate evaluation of subpopulations with high rates of type 2 diabetes, where greater opportunity may exist for misclassification of diabetes type and/or incorrect assignment of diabetes codes. Evaluation for diabetes autoantibodies may also be important in the correct identification or classification of individuals with certain diabetes types. These include subjects with the latent form of autoimmune diabetes (Latent Autoimmune Diabetes in Adults, or LADA), frequently misdiagnosed as type 2 diabetes [52], as well as subjects with idiopathic or "type 1b" diabetes mellitus, which occurs more commonly in individuals with African or Asian ancestry [8]. Such patients are not identifiable using ICD-9-CM codes.

The results of our study do not support an association between vaccination during military service and type 1 diabetes in this population of young adults. These findings are consistent with those from previous epidemiological studies investigating childhood vaccines. The observed decreased risk of type 1 diabetes following MMR, yellow fever and hepatitis B vaccines may merit further investigation using medical record review and possibly serum assay to formally validate type 1 diabetes cases.

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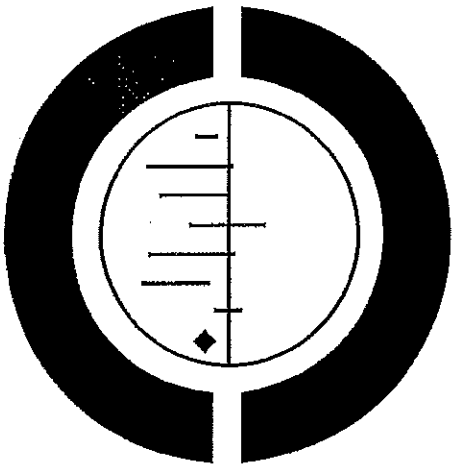
7.11

Vaccines for measles, mumps and rubella in children (Review)

Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C



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Leukaemia

The case-control study of Ma 2005 was realised within the Northern California Childhood Leukaemia Study (NCCLS) and assessed whether vaccination with MMR (and other vaccines) plays a role in the aetiology of leukaemia. In NCCLS (active since 1995) incident cases of newly diagnosed leukaemia in children aged between 0 and 14 years and ascertained from major paediatric clinical centres within 72 hours after diagnosis were collected (Table 12). Analyses had been carried out for both total leukaemia cases and control (323 and 409, respectively) and for acute lymphoblastic leukaemia (ALL) subset (282 cases and 360 controls). Considering leukaemia as case definition, OR estimates for any MMR dose before the reference date in all populations was 1.06 (95% CI 0.69 to 1.63). Considering ALL as case definition the OR estimate for any MMR dose before the reference date in all populations was 0.87 (95% CI 0.55 to 1.37).

Hay fever

Two case-control studies (Bremner 2005; Bremner 2007) investigated the risk of hay fever in MMR-vaccinated children in the UK (using the same data source).

Bremner 2005 focused particular attention on the timing of MMR vaccination to identify a critical period for MMR immunisation and hay fever risk (see Table 13 for definition). The nested case-control study was conducted within two large databases, the General Practice Database (GPRD) and Doctors' Independent Network (DIN) and involved 7098 hay fever cases and controls. After performing a conditional logistic regression the authors reported that infants who received MMR vaccination did not have a greater or lesser risk of developing hay fever than unvaccinated children. MMR unvaccinated children compared with vaccinated in month 14 (base group) had an OR of 0.79 (95% CI 0.78 to 1.08). A reduced risk of hay fever was noted after completing MMR after two years of age (OR 0.62; 95% CI 0.48 to 0.80).

Bremner 2007 specifically investigated if exposure to MMR vaccination during the first grass pollen season of life influences the risk of hay fever more than any other time of the year. The study was conducted within GPRD and DIN Databases and involved 7098 hay fever cases matched with controls. The risk of later hay fever following exposure to MMR vaccine within the first grass pollen season of life was not statistically different from that observed when MMR administration occurred outside of it (OR 1.05; 95% CI 0.94 to 1.18; P = 0.38).

Type 1 diabetes

Hviid 2004 was a retrospective cohort study carried out in Denmark aiming to evaluate if there was an association between childhood vaccinations and the onset of type 1 diabetes. A cohort of children born from 1 January 1990 to 31 December 2000 from the Danish Civil Registration System was individuated. The Danish Civil Registration System identified with a unique number all people living in Denmark. This number made it possible to obtain linked information on vaccination, diagnosis of type 1 diabetes (Table 14), the presence or absence of siblings with type 1 diabetes and potential confounding factors. The vaccination data were obtained from the National Board of Health, where the General Practitioners reported data. The results of this study do not sustain the hypothesis that there is a link between vaccinations and type 1 diabetes (measles, mumps and rubella (all children): rate ratio 1.14; 95% CI 0.90 to 1.45).

Gait disturbance

Association between MMR vaccination and gait disturbance was assessed by means of a self controlled case series study (Miller 2005) and considered as cases hospital admissions or general practice consultations in children within the Thames regions of England. Hospital admission cases were obtained from hospital computerised records for the period April 1995 to June 2001, considered those relative to children aged 12 to 24 months with ICD-10 diagnoses related to acute gait disorder (G111, G112, G25, R26, R27, R29, H55 and F984). Cases were validated by reviewing hospital case notes and grouped into five categories (Table 15). Vaccination history of cases was obtained from immunisation records. In all, 127 cases with available immunisation status were identified. Out of these, 65 belonged to category 4 (i.e. non-ataxic, non-viral origin) and were excluded from analysis. No cases corresponding to category 1 definition were found. Relative incidence (RI) within and outside post-vaccination time risk (0 to 30 and 31 to 60 days) was calculated after age stratification in one-month intervals. RI estimates for pooled two, three and five categories were not statistically relevant (RI 0.83; 95% CI 0.24 to 2.84 for 0 to 30 days risk time and RI 0.20; 95% CI 0.03 to 1.47 for 31 to 60 days risk time).

As gait disturbance does not require hospitalisation, authors carried out a further analysis based on cases observed in General Practices using the General Practice Research Database (GPRD) as the source, and considered children aged 12 to 24 months, born between 1988 and 1997. Read and OXMIS codes indicating a possible consult for gait disturbance were identified in GPRD by mapping ICD-9 codes and by searching keywords 'ataxia', 'gait', 'coordination', 'mobility' and 'movement'. Diagnoses were grouped into six categories (Table 15). Vaccination history was obtained from prescription records. In all, 1398 children with diagnoses A-F and known immunisation history were included. Since, in the authors' opinion, a vaccine-specific effect would appear one week after immunisation (an excess of B and C diagnoses was observed on vaccination day) the risk period zero to day five was separately considered. In any other considered risk periods (six to 30, 31 to 60 and six to 60 days after MMR immunisation) RI did not have a statistically relevant increased incidence. Early administration of thiomersal-containing DTP/DT vaccine did not influence this estimate.

8

8.1

As Michigan's vaccine exemption rate rises, doctors urge parents to immunize kids

Sue Thoms | sthoms1@mlive.com By **Sue Thoms | sthoms1@mlive.com**

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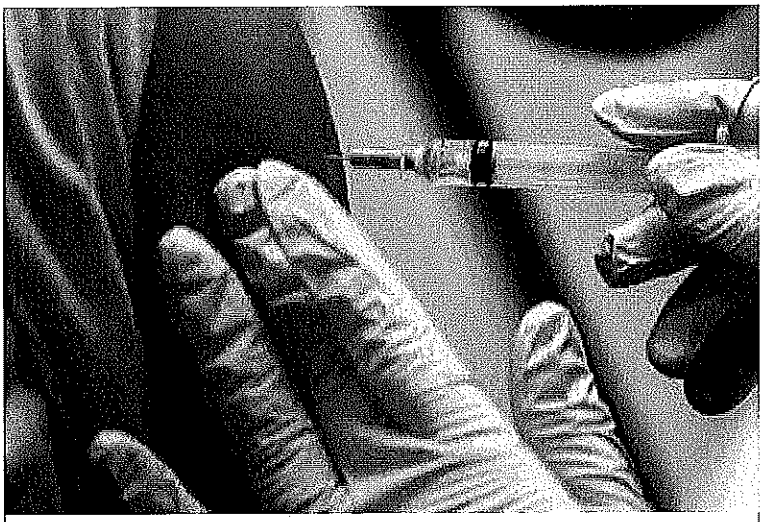
on April 29, 2014 at 6:00 PM, updated April 29, 2014 at 6:01 PM



File photo | MLive.com

GRAND RAPIDS, MI – Local doctors are urging parents to get their children vaccinated against childhood illnesses, as health statistics show Michigan has the fourth highest rate of non-medical exemptions for immunizations.

A group of physicians, nurses and educators on Tuesday, April 29, spoke at Cherry Street Health Services about immunizations for measles, mumps, polio, rubella and other diseases.

In Michigan, 5.3 percent of parents choose not to immunize their children for non-medical reasons, according to the Centers for Disease Control. It is one of four states with an exemption rate above 5 percent. The others are Oregon, Vermont and Idaho.

Dr. James Applegate, a Grand Rapids doctor and past president of the Michigan Academy of Family Physicians, said many parents don't realize how deadly the illnesses can be because the immunizations have been so effective in reducing numbers who become sick. But as vaccination rates have lagged, there have been outbreaks nationwide of measles and whooping cough, or pertussis.

Related: After losing baby to whooping cough, parents work to save lives

In Michigan, there were nearly 1,000 cases of whooping cough last year, an increase of almost 18 percent over 2012.

"One of the things we don't realize is because so many children are in day care and so many of us travel and are exposed to people who travel, the risks are a lot a higher than if we just lived in isolated little communities," Applegate said. "The world has changed a lot."

Getting older children immunized helps protect infants, said Dr. Rose Ramirez, a Spectrum Health doctor.

"Diseases like whooping cough can be severe in infants less than 6 months of age, who are at highest risk of severe illness, complications and even death," she said.

Applegate acknowledged that some parents are worried about potential side effects from vaccines, about the number of shots children receive and misinformation about potential dangers.

"I think if people are worried about shots and side effects and complications, that's when they should start a conversation with their doctor," he said.

In some cases, he said a physician can work out a way to change the number of shots a child receives at each visit and still make sure the child receives the correct vaccines in sequence.

"It is very stressful to see your child poked two or three times," he said. "But I can tell you the safest and best way to keep your child healthy is to immunize."

Sue Thoms covers health care for MLive/The Grand Rapids Press. Email her at ***sthoms1@mlive.com*** *or follow her on* ***Twitter, Facebook*** *or* ***Google+****.*

8.2

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People,™
Morbidity and Mortality Weekly Report (*MMWR*)

Benefits from Immunization During the Vaccines for Children Program Era — United States, 1994–2013

Weekly
April 25, 2014 / 63(16);352-355

Cynthia G. Whitney, MD1, Fangjun Zhou, PhD2, James Singleton, PhD2, Anne Schuchat, MD1
(Author affiliations at end of text)

The Vaccines for Children (VFC) program was created by the Omnibus Budget Reconciliation Act of 1993 (*1*) and first implemented in 1994. VFC was designed to ensure that eligible children do not contract vaccine-preventable diseases because of inability to pay for vaccine and was created in response to a measles resurgence in the United States that resulted in approximately 55,000 cases reported during 1989–1991 (*2*). The resurgence was caused largely by widespread failure to vaccinate uninsured children at the recommended age of 12–15 months. To summarize the impact of the U.S. immunization program on the health of all children (both VFC-eligible and not VFC-eligible) who were born during the 20 years since VFC began, CDC used information on immunization coverage from the National Immunization Survey (NIS) and a previously published cost-benefit model to estimate illnesses, hospitalizations, and premature deaths prevented and costs saved by routine childhood vaccination during 1994–2013. Coverage for many childhood vaccine series was near or above 90% for much of the period. Modeling estimated that, among children born during 1994–2013, vaccination will prevent an estimated 322 million illnesses, 21 million hospitalizations, and 732,000 deaths over the course of their lifetimes, at a net savings of $295 billion in direct costs and $1.38 trillion in total societal costs. With support from the VFC program, immunization has been a highly effective tool for improving the health of U.S. children.

Data from the 1980s suggested that measles outbreaks were linked to an ongoing reservoir of virus among high-density, low-income, inner-city populations (*2*). Although most children in these settings had a health-care provider, providers missed opportunities to give measles vaccine when children were in their offices, sometimes referring low-income children to another clinic where vaccines were available at no cost (*3*). Approximately 50% of children aged <19 years are eligible to receive vaccines through VFC (Immunization Services Division, National Center for Immunization and Respiratory Diseases, CDC, unpublished data, 2014).* Children can receive VFC-provided vaccine if they are Medicaid-eligible, uninsured, American Indian/Alaska Native, or, for underinsured children (i.e., whose health insurance does not fully cover immunizations), when they are receiving services at a federally qualified health center or rural health clinic (*1*). By providing vaccine for eligible children, at no charge, to public and private health-care providers who are enrolled in VFC, the program helped reinforce the "medical home." Inclusion of specific vaccines in VFC is determined by recommendations of the Advisory Committee on Immunization Practices (ACIP).

To assess improvements in coverage during the VFC era, data were obtained from the United States Immunization Survey (USIS) for the period 1967–1985, the National Health Interview

Survey (NHIS) for 1991–1993, and NIS for 1994–2012 (*3,4*). Children included in USIS and NHIS were aged 24–35 months and those in NIS were aged 19–35 months. USIS and NHIS data were from parental recollection of vaccines received, and NIS data were obtained through provider report.

The cost-benefit model for U.S. children born during 1994–2013 employed methods previously used for children born in 2009 (*5*). A decision analysis birth cohort model was constructed using data on immunization coverage; vaccine efficacies from published literature; historical data on incidence of illnesses, hospitalizations, and deaths from vaccine-preventable diseases before immunization was introduced; and recent vaccination period data (through 2013, if available; otherwise 2012 data were used for 2013) on these same disease outcomes. Vaccines included all those universally recommended for children aged ≤6 years except influenza vaccine, which has been modeled separately (*6*), and hepatitis A vaccine. Infants in hypothetical birth cohorts from the period 1994–2013 were followed from birth through death. Benefits of immunization included savings in direct and indirect costs that accrued from averting illnesses, hospitalizations, and deaths among the 20 birth cohorts. Program costs included vaccine, administration, vaccine adverse events, and parent travel and work time lost. Costs were adjusted to 2013 dollars, and future costs related to disease were discounted at 3% annually. The cost analysis was conducted from both health-care (direct) and societal (direct and indirect) perspectives, and net present value (net savings) was calculated.†

When the VFC program began in 1994, vaccines targeting nine diseases were provided: diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b disease, hepatitis B, measles, mumps, and rubella (Figure). During 1995–2013, five vaccines were added for children aged ≤6 years: varicella (1996), hepatitis A (1996–1999 for high-risk areas, 2006 for all states), pneumococcal disease (7-valent in 2000, 13-valent in 2010), influenza (ages 6–23 months in 2004 and ages 6–59 months in 2006), and rotavirus vaccine (2006). Since 1996, coverage with 1 dose of a measles-containing vaccine has exceeded Healthy People§ targets of 90%, up from <70% before the 1989–1991 outbreak (Figure). For other vaccines licensed before VFC, coverage also was higher in the VFC era, as measured by NIS, than in the pre-VFC era, as measured by USIS. In general, coverage for new vaccines introduced during the VFC era increased rapidly.

Among 78.6 million children born during 1994–2013, routine childhood immunization was estimated to prevent 322 million illnesses (averaging 4.1 illnesses per child) and 21 million hospitalizations (0.27 per child) over the course of their lifetimes and avert 732,000 premature deaths from vaccine-preventable illnesses (Table). Illnesses prevented ranged from 3,000 for tetanus to >70 million for measles. The highest estimated cumulative numbers of hospitalizations and deaths that will be prevented were 8.9 million hospitalizations for measles and 507,000 deaths for diphtheria. The routine childhood vaccines introduced during the VFC era (excluding influenza and hepatitis A) together will prevent about 1.4 million hospitalizations and 56,300 deaths.

Vaccination will potentially avert $402 billion in direct costs and $1.5 trillion in societal costs because of illnesses prevented in these birth cohorts. After accounting for $107 billion and $121 billion in direct and societal costs of routine childhood immunization, respectively, the net present values (net savings) of routine childhood immunization from the payers' and societal perspectives were $295 billion and $1.38 trillion, respectively.

Discussion

This report shows the strength of the U.S. immunization program since VFC began; coverage with new vaccines increased rapidly after introduction, and coverage for older childhood vaccines remains near or above 90%. The ability of VFC to remove financial and logistical barriers hindering vaccination for low-income children likely played a significant role in obtaining high coverage. Successful delivery of vaccines to children of all income levels relies on participation of public and private health-care providers, insurance companies, state and federal public health officials, vaccine manufacturers, and parents. For pediatric health-care providers, VFC supported the "medical home" and reduced barriers to integrated, quality pediatric care with immunizations as the backbone of well-child visits. VFC also supports state-based immunization programs, which have transitioned from service delivery in public health clinics to quality assurance of private sector immunization and oversight of approximately 90 million VFC and other public sector doses distributed annually (Immunization Services Division, National Center for Immunization and Respiratory Diseases, CDC, unpublished data, 2013).

This analysis demonstrates the large number of illnesses, hospitalizations, and deaths prevented by childhood immunization. Because of sustained high coverage, many vaccine-preventable diseases are now uncommon in the United States. Measles was declared no longer endemic in the United States in 2000 (*2*), in contrast to model estimates that 71 million cases would have occurred in children born in the VFC era without immunization. Economic analysis for 2009 alone found that each dollar invested in vaccines and administration, on average, resulted in $3 in direct benefits and $10 in benefits when societal costs are included (*5*). Although the data presented here were generated with U.S. disease estimates and costs, the benefits are relevant to other countries where policymakers are considering return on investment in their immunization programs.

The model estimated more illnesses prevented by vaccination during the lifetimes of 20 birth cohorts than a report published in 2013 that found 26 million illnesses prevented in the U.S. population over the last decade (*7*) and a report published in 2007 that found prevention of 1 million to 2 million illnesses per year (*8*). These earlier assessments used disease reported through passive public health systems for baseline burden estimates, did not adjust for the increase in U.S. population over time, and assessed fewer vaccines than the model presented here, all factors that could explain their lower estimates.

The findings in this report are subject to at least three limitations. First, the benefits of hepatitis A vaccine, annual childhood influenza vaccine, and adolescent vaccines were not included. Second, the model did not account for all indirect vaccine effects on disease burden; for some vaccines, reduced transmission to unvaccinated populations has been a powerful driver of cost-effectiveness (*9*). Finally, for some diseases such as diphtheria, factors other than immunization might have contributed to lower disease risks in recent decades, and reductions resulting from these contributions have not been incorporated into the model; if such reductions were substantial, the model would overestimate the vaccine-preventable burden. However, a sensitivity analysis of the 2009 birth cohort model using the same methods suggested that, even with "worst case scenario" assumptions, early childhood immunization was cost-saving (*5*).

Although VFC has strengthened the U.S. immunization program, ongoing attention is needed to ensure that the program addresses challenges and incorporates methods that could improve delivery. Approximately 4 million children are born in the United States each year, each of whom is vulnerable to vaccine-preventable pathogens that continue to circulate. Importations from areas where measles is endemic are an ongoing challenge for public health workers and

clinicians. Coverage with human papillomavirus vaccine for adolescent girls has not yet reached optimal levels. Essential program functions such as monitoring vaccine safety, coverage, and effectiveness and managing supply interruptions need ongoing attention, although the VFC stockpile has helped mitigate the impact of shortages (*10*). VFC, in conjunction with provisions of the Affordable Care Act that eliminate many co-payments for ACIP-recommended vaccines, minimizes financial barriers and thereby helps protect children from vaccine-preventable diseases.

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1National Center for Immunization and Respiratory Diseases, CDC; 2Immunization Services Division, National Center for Immunization and Respiratory Diseases, CDC (Corresponding author: Cynthia Whitney, cwhitney@cdc.gov, 404-639-4727)

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* Additional information available at http://www.cdc.gov/vaccines/programs/vfc/awardees/program-management/surveys/pes-estimates.html.

† Additional information available at http://www.cdc.gov/vaccines/programs/vfc/pubs/methods/.

§ Additional information available at http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=23 .

What is already known on this topic?

Vaccination is one of the most effective public health interventions. The Vaccines for Children (VFC) program was created by the Omnibus Budget Reconciliation Act of 1993 and implemented in 1994. VFC was created in response to low immunization coverage and the 1989–1991 measles outbreak in the United States.

What is added by this report?

In the 20 years since the VFC program was implemented, five new vaccines have been added to the routine infant immunization program, increasing the number of diseases prevented to 14. Vaccination coverage has remained near or above 90% for older vaccines. Because of vaccination, approximately 322 million illnesses, 21 million hospitalizations, and 732,000 premature deaths will be prevented among children born during this period, at a cost savings to society of $1.38 trillion.

What are the implications for public health practice?

The findings indicate the ongoing importance of maintaining and monitoring the U.S. immunization program.

FIGURE. Vaccine coverage rates among preschool-aged children* — United States, 1967–2012

8.3

The Journal Gazette

Published: May 1, 2014 3:00 a.m.

CDC, state seek to boost on-time infant vaccinations

SUMMER BALLENTINE | Associated Press

AVON – Indiana and national health officials launched a campaign Wednesday to ramp up infant vaccinations in the wake of recent whooping cough and other disease outbreaks.

State Health Commissioner William VanNess and an official from the U.S. Centers for Disease Control and Prevention announced the initiative at Indiana University Health West in Avon during National Infant Immunization Week.

While Indiana is third in the nation for adolescent tetanus, diphtheria and pertussis vaccines and meningococcal vaccines, the state falls in the bottom half for on-time infant immunizations at only 61 percent for children ages 19 to 35 months, health department spokeswoman Amy Reel said.

Arranging shots locally

- To make an appointment at the Allen County Immunization Clinic or for more information, call 449-7514 or go to www.allencountyhealth.com
- To make an appointment at Super Shot Inc., call 424-7468 or go to www.supershot.org for a schedule and more information
- To access the Indiana State Department of Health's Immunization Information System, known as CHIRP (Children and Hoosiers Immunization Registry Program), or to share data with schools or medical providers, go to myvaxindiana.in.gov

"Today we take for granted the low disease rates that we have," said Anne Schuchat, director of the CDC's National Center for Immunization and Respiratory Diseases and assistant surgeon general. "But diseases are still all around the world."

While the latest effort to raise awareness of the need for childhood immunizations is a state initiative, officials at the Fort Wayne-Allen County Department of Health said early and necessary vaccinations have always been promoted in county clinics.

"Obviously, health department staff will follow up with any new parents who receive the cards and come into our clinics," health department spokesman John Silcox said Wednesday. "We certainly support the state's initiative to educate parents about the importance of vaccinations and to have children vaccinated according to the recommended schedule."

VanNess will send a congratulatory card with a vaccine checklist to parents of every newborn in Indiana as part of a statewide push for higher rates of on-time infant vaccination. Hallmark pays for the greeting cards, which first were used in Missouri and Kansas almost two decades ago.

VanNess said parents sometimes wait until their children are about to enter school, where vaccinations are required for entry. But that could mean putting children at risk for the months or weeks before they get the shots, he said.

"We were going to do it regardless," said Craig Monnett of Brownsburg, who along with wife Amy received the first congratulatory card for 4-month-old son Liam during Wednesday's announcement. "It was never a question."

But some parents fear that vaccinations could lead to autism – which VanNess disputes – and never vaccinate their children.

Indiana excuses vaccine requirements if parents cite a religious or medical concern.

Only about 1 percent of children nationwide are not vaccinated, but Schuchat said communities with higher rates of unvaccinated children have a greater risk of outbreaks of diseases that have been virtually eliminated in the country. Indiana ranks comparably to national rates for nonmedical vaccine exemptions, but four states, including Michigan, have exemption rates higher than 5 percent.

Officials say that could mean a greater risk of catching diseases that could be prevented with vaccination.

For example, the CDC classified measles as virtually eradicated in 2000, but this year has brought the highest number of cases so far since 1996.

Diseases often are contracted outside of the United States and brought here, Schuchat said. One case of whooping cough was reported in a Carmel elementary school in March, and the Marion County Public Health Department announced this week that visitors to a tea shop in Indianapolis could have been exposed to hepatitis A.

Reel said outbreaks of whooping cough, measles, mumps and chickenpox have hit the state in recent years.

Schuchat said parents who never have seen measles or other now-preventable diseases might not realize their dangers, and diagnosing the diseases can be difficult because fewer doctors have seen cases of them.

VanNess said getting children vaccinated in time can save lives.

"These outbreaks really do not need to happen," VanNess said. "They are preventable."

8.4

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Perceptions of personal belief vaccine exemption policy: A survey of Arizona vaccine providers

Steven D. Haenchen[a,*], Elizabeth T. Jacobs[a,b], Kristin N. Bratton[a], Aubri S. Carman[a], Eyal Oren[a], Heidi L. Pottinger[a], Jessica A. Regan[a], Kacey C. Ernst[a]

[a] Mel and Enid Zuckerman College of Public Health, University of Arizona, 1295N. Martin Avenue, Tucson, AZ 85724, United States
[b] University of Arizona Cancer Center, University of Arizona, 1515N. Campbell Avenue, Tucson, AZ 85724, United States

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ABSTRACT

Background: As exemptions to school-entry requirements rise, vaccination rates in Arizona school children are approaching levels that may threaten public health. Understanding the interactions physicians have with vaccine-hesitant parents, as well as the opinions physicians hold regarding vaccination, exemption, and exemption policies, are critical to our understanding of, and ability to affect, vaccination exemption rates among children.

Methods: Survey responses were elicited from practitioners listed in The Arizona Partnership for Immunization and the Arizona Medical Association databases using a multi-pronged recruitment approach. Respondents provided data regarding their practice, comfort with parental refusal of individual vaccines, opinions about the beliefs held by parents that seek exemptions, parent education strategies, issues regarding providing care to unvaccinated children, and potential changes to Arizona policy.

Results: A total of 152 practitioners providing care to a wide geographic and economic population of Arizona responded to the survey. Respondents were generally strong advocates of all immunizations but were more accepting of parents' desires to refuse hepatitis B and rotavirus vaccines. Almost all providers indicated that they see patients whose parents request to refuse or delay from vaccinations at least occasionally (88% and 97%, respectively). Only 37% of respondents indicated that they would be supportive of a policy requiring them to sign off on a parent's decision to refuse vaccination.

Conclusions: Vaccination providers in Arizona are generally very supportive of childhood immunizations but have varying comfort with exemption from individual vaccines. Responding providers tended to not support a requirement for a physician's signature for vaccine exemptions due to varying concerns regarding the implementation of such a practice.

1. Introduction

Clinicians who routinely administer childhood immunizations are facing increasing vaccine hesitancy and refusal from parents [1–3]. A survey of the fellows of the American Academy of Pediatrics revealed that 70% of pediatricians had a parent refuse an immunization for their child in the previous 12 months [4]. A recent national survey found that, in a typical month, 8% of family practitioners and pediatricians reported that ≥10% of parents refused a vaccine and 20% reported that ≥10% of parents requested a delayed or alternative vaccination schedule [2]. It is important to also note that some vaccines are more likely to be refused than others. Various studies have shown measles-mumps-rubella (MMR) vaccine, varicella and hepatitis B to have higher refusal rates [4–8].

Clinician response to the increase in vaccine refusal has been variable. In a nationally representative survey, some pediatricians and family medicine practitioners (53% and 31%, respectively) reported their practice required parents to sign a form if they refused vaccination [2]. Some take more extreme action. For example, nationally, 15% of physicians responded that they dismiss patients from their practice for vaccine refusal [2] and in Connecticut, as many as 30% of pediatricians excluded vaccine-refusing patients [3]. In contrast, there are clinicians who accept

Abbreviations: MMR, measles mumps and rubella vaccine; CI, confidence interval.

* Corresponding author at: Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, 1295N. Martin Ave., Tucson, AZ, 85724, United States. Tel. +1 7857278584.
E-mail addresses: shaenchen@arizona.edu, haenchensd@gmail.com (S.D. Haenchen).

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or promote vaccine refusal. One study indicated that nationally 64% of all physicians would agree to delay administration of the primary series of vaccinations at least sometimes [2]. Evidence of promotion of vaccine refusal was noted in 14% of family practitioners stating they do not recommend parents receive all available vaccines [9]. This trend is exacerbated by high-profile clinicians who publicly promote alternative vaccination schedules [10].

All 50 states in the U.S. have requirements for childhood immunization prior to entry into school. However, all states allow exceptions when medically necessary and 48 allow for exemptions from these school-entry requirements due to religious or personal beliefs. As one of the most trusted sources for vaccine-related information, clinicians play an important role in parental decisions about school-entry immunization exemptions [11]. Furthermore, the ease of exemption protocols has been positively correlated with exemption rates [12–14]. To reduce the ease by which exemptions are obtained, physicians have been included in the exemption process. This approach has demonstrated modest success. In Washington state, for example, vaccination exemption rates fell from 6% for the school year beginning in 2010 to 4.5% in 2011 after the enactment of a policy requiring physician signature on all exemptions [15].

In Arizona, on the other hand, exemption from school-entry vaccine requirements has risen from 2.4% in 2008 [16] to 4.2% in 2012 [17]. In 2010, as many as 8% of schools reported vaccination exemption rates exceeding 10% for kindergarten-entry requirements [18]. We conducted a survey of clinicians who provide childhood immunizations in Arizona in an effort to determine: (1) their perceptions regarding vaccine refusal among patients, (2) their comfort levels with parental refusal of individual vaccine types, (3) how their interactions with families who have refused to vaccinate against one or more vaccine-preventable diseases may change, and (4) their support for a hypothetical change in current philosophical/personal belief vaccination exemption procedures.

2. Methods

2.1. Study design and data collection

A cross-sectional study design was used targeting clinicians in Arizona that administer childhood immunizations. An online survey was developed to determine providers' experience with, and perception of, parental refusal of childhood immunization. Questions about provider demographics (gender, time since attainment of degree, degree type), practice characteristics (practice size and type, patient demographics) and the providers' role in childhood immunizations (frequency of providing vaccinations for children) were included in the questionnaire. The questionnaire was adapted from previous vaccination-related physician surveys [2,9].

The survey was disseminated to the target population in two ways: (1) the survey link was distributed through The Arizona Partnership for Immunization listserv, which includes all providers listed in the Arizona State Immunization Information System database, and e-mail reminders were sent two and four weeks after the initial recruitment email; (2) participants were also recruited via a monthly newsletter distributed by the Arizona Medical Association where potential participants were either provided a link or could fax in a paper survey. Participants were directed not to respond to the survey more than once and no incentive was provided.

A series of screening questions were used to target only participants that treat or provide vaccinations to children. Questions pertaining to vaccinations included the frequency with which parents refuse or request a delay for immunizations and what changes in care, if any, follow such a request. For each vaccine, participants rated their comfort level with parental refusal of a particular vaccine using a five-point Likert scale, with responses ranging from "very uncomfortable" to "very comfortable".

Though the primary scope of our survey was to assess providers' opinions about vaccination, we also assessed opinions toward a hypothetical policy change requiring their signature prior to exemption from vaccination requirements for school-entry. Participants indicated their level of support with the proposed change, how they felt it would impact their practice, and if they thought it would impact the exemption rates. Finally, an open comment field was provided for respondents to express additional opinions about immunizations or exemptions.

The survey was anonymous and no identifiable information was collected. This study was reviewed and approved by the institutional review board of The University of Arizona.

2.2. Statistical analysis

Frequencies and percentages were calculated for all categorical responses. Respondents who did not choose that they would monitor health of patients differently or refuse to provide care were coded that they would not make any change in care. Likert scale questions regarding comfort levels were dichotomized to comfortable (responses of "somewhat comfortable" or "very comfortable") or uncomfortable (all other responses), as responses were heavily skewed toward discomfort. McNemar's test was used to compare comfort levels of different vaccine types using polio vaccine as the reference group with confidence intervals (CIs) [19]. Polio vaccine was chosen as the reference group based upon its high utilization and low refusal rate [3,20]. The presence of a trend between comfort by vaccine type and year of vaccine introduction was explored using the Mantel-Haenszel chi-square test. Supporters of the proposed change in the exemption protocol were compared to non-supporters using chi-square tests or Fisher's exact test, as appropriate. Open-ended responses regarding vaccine exemptions were categorized according to common themes (with similar exemption and vaccine refusal themes being combined), totaled, and a representative quote for each theme was selected.

3. Results

Of approximately 1200 participants invited to participate, 152 responses were collected (for a response rate of approximately 13%). Participants were directed to not complete the remaining questions about vaccination perceptions if they did not offer immunizations or only cared for adults; 36 individuals (24%) did not complete the entire survey. Only the remaining 116 individuals are included in the analyses presented here. Characteristics of these participants are presented (Table 1). Participants were largely female (73%) and almost all (98%) received their training in the United States. Physicians represented 63% of the participants but a diverse group of other vaccine providers responded, including nurses, nurse practitioners, physician assistants, and medical assistants. The majority (58%) of respondents indicated they had been practicing for at least 15 years and 12% had completed their degree within the previous five years. Most participants were from pediatric (60%) or family practices (29%), and 55% of practices represented were small (three or fewer physicians), though 28% of respondents were from large practices with eight or more physicians. Participants indicated that they provided care to a wide range of patient demographics of varying geographic locations, incomes, and ages. Nearly all (97%) of the participants indicated that they routinely provide immunizations; 2% responded that they never provide immunizations but continued to respond to the vaccine-opinion related portion of the survey.

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Table 1
Characteristics of survey respondents.

Characteristics	$n=116$ n (%)[a]
Female	85(73)
Trained in United States	114(98)
Type of degree received	
Doctor of Medicine	42(63)
Registered Nurse	8(12)
Other[b]	17(25)
Years since completion of degree	
<5 years	14(12)
≥5 and <10 years	13(11)
≥10 and <15 years	22(19)
≥15 years	67(58)
Practice type	
Pediatrician	69(60)
Family practitioner	33(29)
Public health clinic	6(5)
Other specialty	7(6)
Practice size	
3 or fewer physicians	64(55)
4 to 7 physicians	19(16)
8 or more physicians	33(28)
County of practice	
Maricopa	60(52)
Pima	32(28)
Other	24(21)
Proportion of patients receiving medical assistance	
<10%	21(18)
≥10% and <40%	31(27)
≥40% and <60%	31(27)
≥60% and <80%	18(16)
≥80%	13(11)
Proportion of patients under 5 years of age	
<10%	14(12)
≥10% and <40%	29(25)
≥40% and <60%	53(46)
≥60%	19(16)
Frequency of offered immunizations	
Routinely	112(97)
When requested	2(2)
Never	2(2)

[a] Totals for each category may not sum to total sample size due to non-response. Percentages represent percentages among those responding. Percentages may not sum to 100 due to rounding.
[b] This category includes licensed practical nurses, nurse practitioners, medical assistants, physician assistants, and registered pharmacists.

Clinician perceptions and experiences with exemptions and vaccination delay were variable (Table 2). Almost all participants indicated that they are at least occasionally asked by a parent to delay or refuse vaccination for their child (97% and 88%, respectively). A smaller fraction, 8% and 4%, reported that parents frequently or always request delayed or skipped vaccinations, respectively. Nearly half (67%) of the healthcare providers indicated that refusal to be vaccinated does not change the way they provide care to those patients; however, 10% indicated they would refuse to provide care following a vaccine refusal. When asked if they would support a change in vaccination exemption policies such that exemption requests would require physician signature, only 37% were supportive. Approximately half (51%) of all participants felt that such a procedure would fail to reduce the number of vaccine exemptions and just over half (55%) felt that it would constitute a burden on their practice to sign off on exemptions. However, respondents did not always hold these two opinions at the same time; only 33% of all respondents indicated that they felt this procedure would be both a burden and ineffectual.

Table 2
Characteristics of survey respondents' perceptions regarding vaccination refusal and exemptions.

Characteristics	$n=116$ n (%)[a]
Frequency of parents requesting a delayed immunization schedule	
Never	4(3)
Rarely	55(48)
Sometimes	47(41)
Frequently	9(8)
Frequency of parents refusing administration of a vaccine	
Never	14(12)
Rarely	72(62)
Sometimes	26(22)
Frequently	3(3)
Always	1(1)
How care changes for children following vaccine refusal	
Child's health is monitored differently	39(34)
Refuse to provide regular care	6(5)
Both monitor differently and refuse care	4(3)
No change in care noted	67(58)
Opinions regarding a protocol of physician signature for vaccination exemptions[b]	
Would support such a protocol	41(37)
Would educate parents before providing signature	110(96)
Believe this practice would fail to reduce exemptions	57(51)
Believe this practice would be a burden	63(55)
Believe this practice would not reduce exemptions and would be a burden	37(33)

[a] Totals for each category may not sum to total sample size due to non-response. Percentages represent percentages among those responding.
[b] Multiple responses were allowed for this prompt; percentages may exceed 100%.

Clinicians were more comfortable with parents refusing certain vaccines than others (Table 3). Vaccines are listed in order of their year of licensure in the United States [21–23] to examine the hypothesis that providers would be more comfortable with parents refusing recently introduced vaccines (this order was not observed in the design of the survey); however, no time trend for comfort with vaccine refusal was observed. Compared to polio vaccine, the only two vaccines for which providers were more comfortable with parents refusing were hepatitis B (16%; 95% CI = 6.1–18.0) and rotavirus (18%; 95% CI = 7.5–20.1).

There were differences between those who were supportive of the protocol change for exemptions and those who were not (Table 4). A larger proportion of those supportive of a change in exemption requirements (64%) indicated that they would not change patient care for those who refuse vaccination, as compared to those not supporting this directive (53%; $P=.03$). Supportive participants were also significantly more likely to believe that this change would reduce the number of exemptions (83% vs. 29% for non-supportive; $P<.001$). Finally, only 34% of respondents supportive of changes to exemption procedures felt that these would be a burden on their practice, in contrast to 68% of non-supporters

Table 3
Proportion of vaccine providers expressing at least some comfort with parents refusing specific required childhood immunizations.

Vaccine	Year licensed	$n=116$ n (%)	95% CI of difference relative to polio (%)
Inactivated polio vaccine	1955	5(4)	–
Measles, mumps, and rubella	1971	3(3)	−4.1 to 0.7
Hepatitis B	1981	19(16)	6.1–18.0[a]
Haemophilus influenzae type B	1985	4(3)	−3.8 to 2.1
Diphtheria, tetanus, and pertussis	1991	4(3)	−3.8 to 2.1
Varicella	1995	9(8)	−0.6 to 7.6
Pneumococcal conjugate vaccine	2000	4(3)	−3.8 to 2.1
rotavirus	2006	21(18)	7.5–20.1[a]

[a] $P<.05$ when compared to those comfortable with inactivated polio vaccine refusal, calculated by McNemar's test.

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Table 4
Differing opinions regarding vaccination for providers who are supportive of or against a protocol requiring physician signature for vaccination exemptions.

Characteristics	Supportive of protocol $n=41$ (37%) n (%)[a]	Not supportive of protocol $n=71$ (63%) n (%)[a]	P
Frequency of parents refusing administration of a vaccine			
Never	6(15)	8(11)	80[c]
Rarely	25(61)	45(63)	
Sometimes	8(20)	16(23)	
Frequently	1(2)	2(3)	
Always	1(2)	0(0)	
How care changes for children following vaccine refusal			
Child's health is monitored differently	15(37)	22(31)	0.67[c]
Refuse to provide regular care	1(2)	5(7)	
Both monitor differently and refuse care	2(5)	2(3)	
No change in care noted	23(56)	42(59)	
Opinions regarding a protocol of physician signature for vaccination exemptions[b]			
Would educate parents before providing signature	41(100)	66(93)	16[c]
Believes this practice would reduce exemptions	34(83)	20(29)	<.001[d]
Believes this practice would be a burden	14(34)	48(68)	<.001[d]

[a] Totals for each category may not sum to total sample size due to non-response. Percentages represent percentages among those responding.
[b] Multiple responses were allowed for this prompt; percentages may exceed 100%.
[c] P-value calculated using Fisher's exact test.
[d] P-value calculated using chi-square test.

Table 5
Categorization of open-field comments made by survey respondents pertaining to refusal or exemption from vaccines.

Category	$n=37$ n (%)[a]	Example quotation from this category
There is a need to provide better vaccine related education	10(26)	"We need legislators to understand vaccines and put those with incorrect info[rmation] on the spot. Schools should also require more parent education for exemptors."
Exemptions should not be allowed	7(18)	"We believe that every child should be vaccinated, period."
Dismay or futility to change parental opinions	6(16)	"Parents who are set against immunizations from the start are not going to be swayed by any evidence or explanation the physician can give."
Do not want to validate parental choices or fear of liability	6(16)	"Asking me to approve a parent's philosophical/personal belief would be asking me to violate my own philosophical/personal beliefs and makes it appear that medical providers approve of these decisions."
Treat exemptors differently	6(16)	"To have a parent understand that their child poses a health risk to others, I have different appointment times for them, 'ALERT' stickers on their chart and have them sign the . . . refusal form for their chart."
Physicians should not be responsible for signing exemptions	3(8)	"If the parent chooses not to immunize – for personal reasons of any kind – it is their signature the school should get not the medical providers."
Supportive of parent's right to exempt	3(8)	"I strongly believe in vaccinating my patients; however, ultimately the decision is up to the parents. I consider myself a resource for parents who are either unwilling or uncomfortable with vaccines. After discussion some change their minds, others do not. I am comfortable with that and do not want to feel like I am 'coercing' parents into doing something they are not comfortable doing."

[a] Responses do not sum to 100%, as some general comments did not discuss vaccine refusal or exemptions. Responses could fit into multiple categories.

($P<.001$). No difference was noted in the frequency with which providers experienced vaccine refusal by parents.

Open-ended comments demonstrated broad support of vaccination in participants, though some (8%) were more supportive of a parent's right to refuse vaccination or choose exemption (Table 5). The open-ended field elicited greater detail about the concerns participants had about requiring physician signature for exemptions. These included fear of liability issues and concern that it is not the responsibility of the physician to authorize a parent's decision not to vaccinate (16%) and that this might be interpreted as approval of the decision (8%).

4. Discussion

The results of this study indicate that Arizona immunization providers may not be supportive of a policy requiring their signature prior to exemption from school vaccination requirements. To our knowledge, this is the first study to examine physicians' opinions of a hypothetical vaccination exemption policy. It does not appear that these opinions were driven by a difference in overall opinions of vaccination, as both groups were very supportive of vaccines in general. Providers indicating a lack of support for a new policy were significantly less likely to believe that this policy shift would be effective in reducing exemptions and twice as likely to indicate this process would be a burden upon their practice. Proposals to change vaccination exemption policy should inform stakeholders of the potential effectiveness for increasing vaccination rates, as well as attempt to reduce the perceived burden of such a change.

Effectiveness in involving physicians in the exemption process can be addressed by providing current evidence revealing that increasing the difficulty of the exemption process leads to lower exemption rates at both state and national levels [12–14]. Lower exemption rates have been correlated with a lower disease burden, specifically pertussis rates, at both the state and census tract levels [12,24]. Trends based on aggregate data do not necessarily demonstrate an effect of policy on the health choices that individuals make. However, evidence from Washington state, where a recent policy requiring physician signatures on exemptions was enacted, demonstrated a 25% decrease in exemptions in the year following its implementation [15]. These data may sway those who are judging the effectiveness of a policy change based upon a belief of futility in changing parental opinions. Indeed, while there are individuals who may not alter their opinions about vaccination, it is likely that such a policy would decrease the proportion of parents obtaining exemptions for reasons of convenience, and may also provide some hesitant parents with the necessary information to make a decision to vaccinate.

Any potential policy change must also address concerns expressed by physicians regarding the burden that will be placed upon them. The language expressed in the legislation requiring physician signature in Washington state does not address liability of the approving provider [25]. We would recommend that any future attempts at changing exemption rates through a legislative process include statements that limit healthcare providers' liability, in addition to providing education to parents about vaccination. We also suggest that providers use a form such as that provided by the American Academy of Pediatrics to document that they have

informed parents of the risks associated with vaccine refusal and that parents assume these risks for their child [26].

The results of the present study demonstrate that perceptions regarding vaccination exemption are not consistent among all providers or for all vaccines. Most vaccines failed to elicit responses from providers that they were comfortable with patients refusing vaccination. However, providers were more likely to indicate they were comfortable with refusals to be vaccinated against hepatitis B or rotavirus. These opinions may be based upon recent discussions regarding the current and historical safety of these vaccines [27–30]. Additionally, a minority of pediatricians and family practitioners has indicated that they have little or no confidence in pre- and post-licensure studies of vaccines [31]. Still, other reasons may influence provider comfort with vaccine refusal, including relative transmissibility of different diseases and awareness of outbreaks. While most research examines clinician approval of the entire vaccine schedule, our results indicate that determining opinions by individual vaccines could be more revealing.

Previous research has attempted to characterize how frequently physicians exclude vaccine-refusing patients from their practice [3,4]. The exclusion rates reported by our respondents following vaccine refusal were similar to those noted in a national survey (5%) [4] but were considerably lower than the exclusion rate reported by Connecticut physicians (30%) [3]. However, it is unclear if these differences are true or due to varying definitions of the practice of excluding patients. While this process may be considered necessary by some practices, there are ethical and legal considerations that must be made [32–36]. Furthermore, the process should be implemented with care, as exclusion of patients may have an unintended consequence of creating clusters of practices with high exemption rates. Parents of excluded patients may seek care from those practices that are more tolerant of the exemption process or avoid utilization of the medical system [34,35]. These clusters of elevated exemption rates create an excessive burden on providers who do not exclude vaccine exemptors and place the patients served in these clusters at an elevated risk for vaccine-preventable diseases.

The current study has important strengths and limitations. This is the first study to examine vaccine provider opinions regarding a hypothetical policy requiring their signature for vaccine exemptions and potential changes to current policy, and one of very few that examines their opinions about individual vaccine types. This study extended beyond only physicians and invited all Arizona vaccine providers to participate, thus including the opinions of other vaccine providers such as nurses and public health clinics.

Bias may be present due to low sample size as a result of low response rate. Previous work has demonstrated low response rates are common in physician surveys, particularly in those administered online and similar response rates have been captured in other Arizona physician surveys [37,38]. Follow-up indicates that office policies may be partly responsible for low clinician response rates but research indicates that low response rates in physician surveys produces minimal bias [38,39]. We are unable to distinguish response rates by recruitment method, as with the exception of five faxed surveys all responses were collected through a single online survey. However, based upon date of submission and date of invitation at least 73% of all responses originated from the state immunization provider database. This result is expected as this invitation was delivered first and includes all immunization providers in the state.

Assessing generalizability of these data to all Arizona providers is difficult, as the invitation was made to all providers in the state immunization system database, which does not track the demographics of database members. Distribution lists were confidential and dissemination was made through the holding organization, which prevented tracking response rates in detail. In comparison to all practicing United States physicians, our respondent sample was comprised of a much greater proportion of females (73% vs. 28%) [40]. Further examination by practice type reveals that among physicians in our sample from pediatric practices 69% (22 of 32 physicians) were female while 58% of pediatricians are female nationally [41]. Similarly, 57% of physicians from family practices were female (4 of 7) compared to 34% nationally [41]. There may appear to be a slight overrepresentation of female physicians, but it is important to note that our survey was targeted at all vaccine providers and not just physicians. A previous vaccine-focused survey that examined healthcare providers (as opposed to physicians) obtained a gender distribution similar to that obtained in the current study with 72.9% of respondents being female [42].

Those responding to this survey may be more likely to feel strongly about vaccine provision in general and as such, may be more likely to support increasing restrictions on vaccine exemptions. Even so, the results of this study may not be generalizable to vaccination providers in other states or at the national level. The actual rate at which Arizona vaccine providers exclude patients from regular care due to vaccine refusal may be overestimated by this survey by either the aforementioned potential selection bias for those with very strong vaccine opinions or as a result of the data collection being based upon self-report and not observed practice. Though possibly due to differing definitions or levels of exclusion, previous research has indicated a discrepancy between reported exclusion in a hypothetical situation (39%) vs. actual observed practice (5%–30%) [3,4]. However, the reported exclusion rate is fairly low (9%) and is unlikely to be a significant overestimation.

Our research may fail to accurately estimate the proportion supportive of the hypothetical policy change. Previous research has demonstrated the existence of hypothetical bias [43]. This bias results from subjects typically overvaluing the costs associated with a hypothetical situation, such as anticipating a greater aminstrative burden on a medical practice than would actually occur. However, the same analysis revealed the magnitude of this bias was lessened when participants were given discrete choices as has been done in our survey. While we acknowledge the potential disparity between reported and actual support of this hypothetical policy, this does not detract from the importance of examining opinions held by physicians.

5. Conclusions

Arizona vaccine providers may not support a policy that would require physician signature prior to exemption from vaccine requirements for school-entry. The primary reasons for providers holding this opinion appears to be a lack of belief in the efficacy of this policy and a concern that it would overly burden their practices. Opinions of providers should be examined when implementing new vaccination-related policies to ensure the most effective delivery. Furthermore, research should be conducted in locales where policies have been implemented in order to learn how these opinions have changed after implementation.

Author contributions

All authors have contributed to the conception and design of the study or analysis and interpretation of data, and drafting the article or revising it critically for important intellectual content. All authors have provided approval of the final version as submitted.

Conflict of interest

The authors have no financial or personal interests that could inappropriately influence this research.

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