Vaccine Hesitancy and the Safety of the Recommended Childhood Immunization Schedule

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Disclosures

- Jason M. Glanz, PhD, has documented no financial relationships to disclose or conflicts of interest to resolve.

- Jason M. Glanz, PhD, has documented that his presentation will not involve discussion of unapproved, off-label, experimental, or investigational use of any medical product.
Outline

- Vaccine hesitancy
- Vaccine safety monitoring in the US
  - Vaccine Safety Datalink (VSD), Vaccine Adverse Event Reporting System (VAERS)
  - Rotavirus vaccine (Rotashield) and intussusception
  - The safety of the recommended childhood immunization schedule
National Immunization Rates

Vaccine-specific coverage* among children 19-35 months, National Immunization Survey, 1994-2014

* The Healthy People 2020 target for coverage is 90% for all these vaccines with the exception of rotavirus (80%) and HepA (85%)

Source: Centers for Disease Control and Prevention
Exemption Rates

- All Schools
- Public Schools
- Private Schools
Ease of Obtaining Nonmedical Exemption


Figure created by Mother Jones
Nonmedical Exemption Rates by States, 2013-2014

Source: Centers for Disease Control and Prevention
Figure created by Mother Jones
Rates of Nonmedical Exemptions by Ease of Exemption, 2006–2011

Vaccine Hesitancy

- Expression of concern about the decision to vaccinate
- Often based on perceived risks and benefits of vaccination

Vaccine Hesitancy

- Contributors
  - Compulsory nature of vaccines
  - Coincidental temporal associations with adverse health outcomes
  - Lack of familiarity with VPDs
  - Distrust of government, pharma, medical establishment

Vaccine Hesitancy – Attitudes and Beliefs

Vaccine Hesitancy – A Continuum

Accept all vaccines, no concerns
Accept all vaccines, have concerns
Delay some vaccines
Delay all vaccines
Refuse some vaccines
Refuse all vaccines

Vaccine Hesitancy – A Nuanced View

Gust D, Brown C, Sheedy K et al. *Am J Health Behav*. 2005
Vaccine Hesitancy – 2010 HealthStyles Survey

Specific Vaccine Concerns

- Yes: 77%
- No: 23%

Kennedy A, Lavail K, Nowak G. Health Aff. 2011
Vaccine Hesitancy

- Concerns about the schedule
  - “Too many too soon”
  - “Ingredients” – aluminum, formaldehyde
- 10 – 15% parents requesting “alternative immunization schedules”

Vaccine Hesitancy – A Delicate Balance

Personal Liberty

Public Health
Vaccine Hesitancy

- Delaying and refusing vaccines puts children and communities at greatly increased risk for:
  - Measles
  - Pertussis
  - Pneumococcal
  - Varicella

- Maintaining public trust in our national immunization program is a high priority!

Vaccine Hesitancy

- Call to action:
  - Individual and health system interventions
    - Pregnant women
    - Web-based resources and engagement
    - Tailored messaging
  - Provider risk communication techniques

Glanz JM, Kraus CR, Daley MF. *Plos Biology* 2015
Vaccine Hesitancy

- Call to action:
  - Robust, national systems to monitor
    - Trends in vaccine hesitancy
    - Vaccine safety

Glanz JM, Kraus CR, Daley MF. *Plos Biology* 2015
Vaccine Safety Monitoring in the United States
The Vaccine Safety “Life Cycle” (I)

**Study characteristics**
- Randomized
- Select population
- Relatively small numbers
- Solicited adverse events

**Phase I**

**Phase II**

**Phase III**

**LICENSURE**

**VAERS**
**VSD**
**PRISM**
**CISA**

**Study characteristics**
- Not randomized
- General population
- Large numbers
- Unsolicited adverse events
Post-Licensure studies of vaccine safety

VAERS
VSD
PRISM
CISA

POTENTIAL OUTCOMES

Reassurance to public
Update to VIS forms
Change package insert
Change in ACIP recs
Clinical practice change
Removal from market

Kaiser Permanente
Vaccine Adverse Event Reporting System (VAERS)

- US postlicensure vaccine safety surveillance (1990)
  - Collects voluntary reports of adverse events following vaccination
  - Co-managed by Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA)
Vaccine Adverse Event Reporting System (VAERS)

- Healthcare providers encouraged to report clinically significant adverse events following vaccination
  - Anyone can submit a report to VAERS
- Receives approx 30,000 reports per year
- Data publicly available
VAERS Reports Can Be Filed Online

Report Adverse Event Online

Knowingly filing a false VAERS report with the intent to mislead the Department of Health and Human Services is a violation of Federal law (18 U.S. Code § 1001) punishable by fine and imprisonment.

Step 1 of 5: Person Reporting Event

Form Completed By: [Help]

[Relation to Patient: Choose a Relation ▼] [Help]

First Name: ___________________________ MI: ___________________________ Last Name: ___________________________

Address: __________________________________________ __________________________________________ __________________________________________

City: ___________________________ State: ___________________________ Postal Code: ___________________________

Phone Number: ___________________________ Email Address: ___________________________

Information Kept Confidential [Help]
VAERS Strengths

- Can detect rare adverse events
- Generates hypotheses
  - Helps identify new or rare adverse events
  - Helps determine if further studies are needed
- Monitors trends of already known adverse events
- Monitors vaccine lot safety
VAERS Limitations

- Possible risk of underreporting
- Stimulated reporting during media attention
- Possible incomplete data on report form
VAERS Limitations

- No denominator
  - No information on number of persons vaccinated
  - No information on background rates of adverse events in the population

- Cannot establish causation (hypothesis generating)
VAERS Reports

- 92% of VAERS reports are “non-serious”
- Most frequent reports:
  - Local reactions
  - Fever
  - Rashes and itching
  - Headache
  - Dizziness
VAERS Data Can Be Readily Misrepresented

Deaths in the U.S. during the past 10 years:
2004 to 2015

Due to Measles
ZERO
Source: CDC

Due to Measles Vaccines
108
Source: VAERS database

Zero U.S. measles deaths in 10 years, but over 100 measles vaccine deaths reported

Tuesday, February 10, 2015 by: Natural News Editors
Tags: measles deaths, MMR vaccine, immunization dangers

(NaturalNews) With the measles and measles vaccine debate reaching a near

Click here!

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FREE REPORT: Reveals The 1 Simple Ingredient That DESTROYS Cancer, Diabetes, And Other Debilitating Diseases....
Learn all about the incredible cure that Big Pharma doesn't want you to know about.
Vaccine Safety Datalink (VSD)

- Created in 1995
- Collaboration between 8 managed care organizations and the Centers for Disease Control and Prevention (CDC)
- >9,000,000 children and adults
- Integrated delivery systems, enrolled populations, electronic health records

Baggs et al. *Pediatrics* 2011
Vaccine Safety Datalink (VSD)

- Highly accurate vaccine data
- Case ascertainment
  - ICD-9 codes
  - Medical record review
- Study Designs – Denominator
  - Cohort, case-control, self-controlled cases series
  - Can establish causality (hypothesis testing)

Baggs et al. *Pediatrics* 2011
Broad Spectrum of VSD Work

- Autism
- Rapid cycle surveillance
- Hypothesis testing
  - Febrile seizures (+)
  - Immune thrombocytopenia (+)
  - Diabetes (-)
  - Multiple sclerosis (-)
- Methods development
- Under-vaccination / Alternative schedules
Rapid Cycle Surveillance

Historical Background Rate

Calendar Year

2001 2005 2006 2013
Broad Spectrum of VSD Work

- Autism
- Rapid cycle surveillance
- Hypothesis testing
  - Febrile seizures (+)
  - Immune thrombocytopenia (+)
  - Diabetes (-)
  - Multiple sclerosis (-)
- Methods development
- Under-vaccination / Alternative schedules
Rhesus Rotavirus Vaccine and Intussusception: A Safety Monitoring Example
Rhesus Rotavirus Vaccine and Intussusception

- Pre-licensure trials (thousands of children)
  - 5 cases of intussusception in vaccinees, 1 case in controls (not statistically significant)
- Vaccine (Rotashield) licensed in 1998
- May 1999: “signal” noted in VAERS
  - 9 cases in 6 months
  - Cluster of 4 cases in April – May 1999

MMWR 1999;48:577-581
FIGURE 2. Number of intussusception reports after the rhesus rotavirus vaccine-tetravalent (RRV-TV) — United States, September 1998–December 1999

## Rhesus Rotavirus Vaccine and Intussusception Validation Studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Setting</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>19 states</td>
<td>35.8</td>
</tr>
<tr>
<td>Cohort</td>
<td>10 MCOs</td>
<td>31.0</td>
</tr>
</tbody>
</table>

RRV & Intussusception: Summary

- Basis for studies = VAERS signal
- Case-Control and retrospective cohort studies were a collaboration between CDC, NIH, 19 states, MCOs, FDA, and industry
- Attributable Risk = approx. 1/10,000 doses
- Policy Implications:
  - Withdrawal of ACIP recommendation for RRV
  - Significant impact on developing countries
  - Stimuli for safer rotavirus vaccines (RV1, RV5)
What was learned from the Rotavirus Vaccine Story?

- Safety monitoring in the US was “sensitive” enough to detect unanticipated, rare adverse event
- Hypothesis testing vaccine safety studies are resource intensive
- Timeliness of risk assessment is important
- Independent systems running in parallel are needed for detecting signals and establishing causation.
The Safety of the Recommended Childhood Immunization Schedule: An Agenda Setting Example
Schedule timeline figure

Birth-2 years Vaccine Schedule 1983-2015

KEY
* = Recommended for special populations
** = Combo Vaccine Pediarix

CDC. Past Immunization Schedules. 2015
Retrieved http://www.cdc.gov/vaccines/schedules/past.html
Epidemiology of Under-vaccination and Alternative Immunization Schedules

- Alternative immunization schedules appear to be more common
- Safety of alternative schedules is unknown
- Vaccine Safety Datalink (VSD) – 8 MCOs
  - “Natural experiment” to study safety
  - Numerous challenges to studying safety
Epidemiology of Under-vaccination and Alternative Immunization Schedules

Objectives

- To examine patterns and trends of under-vaccination in a large cohort of children born 2004 – 2008
- Compare health care utilization rates between under-vaccinated children and children on the ACIP recommended schedule
- Assess risk of pertussis infection
Calculating Days Under-vaccinated

Total days under-vaccinated for DTaP = 291 days
Average Days Under-vaccinated

- HepB Delay: 0 Days
- DTaP Delay: 62 Days
- Hib Delay: 62 Days
- IPV Delay: 62 Days
- Pneumo Delay: 62 Days
- Varicella Delay: 242 Days
- Rotavirus Delay: 160 Days
- MMR Delay: 242 Days

Cumulative days undervaccinated:

\[ 0 + 62 + 160 + 62 + 62 + 62 + 242 + 242 = 892 \text{ days} \]

Average days undervaccinated:

\[ \frac{892}{8 \text{ vaccines}} = 112 \text{ days} \]
Epidemiology of Under-vaccination and Alternative Immunization Schedules

- 48.7% under-vaccinated
- 1/8 (13%) children under-vaccinated due to parental choice
- 1399 patterns of under-vaccination
- Significant differences in healthcare utilization

Glanz et al. *JAMA Pediatrics* 2013
Nested case-control to assess risk of pertussis

Vaccination History

- 3 vaccinations = Vaccinated
- 1-2 vaccinations = Under-vaccinated
- 0 vaccinations = Unvaccinated

Age at Calendar Time

2 months 6 months 20 months

Event
## Case-control results

<table>
<thead>
<tr>
<th>Vaccination status (doses refused/delayed)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vs. 0</td>
<td>2.3 (0.97 – 5.2)</td>
</tr>
<tr>
<td>2 vs. 0</td>
<td>3.4 (0.89 – 13.1)</td>
</tr>
<tr>
<td>3 vs. 0</td>
<td>18.6 (4.9 – 70.0)</td>
</tr>
<tr>
<td>4 vs. 0</td>
<td>28.4 (3.2 – 252.6)</td>
</tr>
</tbody>
</table>

Referent group: All vaccinations on time (1, 2, 3 and 4)
IOM Report

- In 2013, Institute of Medicine (IOM) issued a report on feasibility of studying the safety of recommended childhood immunization schedule
  - Reviewed scientific literature
  - Assessed stakeholder concerns
  - Identified and evaluated potential methodological approaches
IOM Report

- IOM concluded:
  - Few published studies have examined the entire current recommended schedule as a whole
  - Available evidence suggests current schedule is safe
  - Need more research (observational studies)
  - VSD represents an ideal research environment
IOM Report

- General recommendations
  - Focus on entire childhood schedule
  - Long term health outcomes
  - Susceptible subpopulations
IOM Report

- Specific recommendations
  - Compare health outcomes between:
    - fully immunized and completely unimmunized
    - fully immunized and partially immunized (those who omit certain vaccines/doses)
    - children who receive fewer doses per visit (spacing) and those who receive vaccines at later ages (but still within the recommended ages)
VSD White Paper

Objective:
To develop a comprehensive white paper that focuses on how the VSD can be used to assess the safety of the recommended childhood immunization schedule
Study Team

Kaiser Permanente Colorado
  Jason Glanz, PhD
  Matthew Daley, MD
  Sophia Raff Newcomer, MPH
  Jo Ann Shoup, MSPH

Group Health Cooperative, Seattle, WA
  Michael Jackson, PhD

Emory University, Atlanta Georgia
  Saad Omer, MBBS, PhD
  Robert Benarczyk, PhD

Centers for Disease Control and Prevention
  Frank DeStefano, MD, MPH
VSD White Paper

Specific Aims (3):

- Through stakeholder engagement
  1. Define a cohort based on IOM recommendations
  2. Identify plausible adverse event outcomes that could be related to recommended schedule
  3. Suggest methodological approaches that could be used to assess safety of recommended schedule
<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>8 mos</th>
<th>10 mos</th>
<th>12 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1</td>
<td>Hep B</td>
<td>DTaP- IPV - HepB, Hib, Pc, Rota</td>
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<td>DTaP- IPV - HepB, Hib, Pc, Rota</td>
</tr>
<tr>
<td>Child 2</td>
<td>Hep B</td>
<td>DTaP- IPV - HepB, Hib, Pc, Rota</td>
<td>DTaP- IPV - HepB, Hib, Pc, Rota</td>
<td>DTaP- IPV - HepB, Hib, Pc, Rota</td>
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<td>DTaP- IPV - HepB, Hib, Pc, Rota</td>
</tr>
<tr>
<td>Child 3</td>
<td>DTaP- IPV - HepB</td>
<td>DTaP- IPV - HepB, Hib</td>
<td>DTaP- IPV - HepB</td>
<td>DTaP- IPV - HepB</td>
<td>DTaP- IPV - HepB</td>
<td>DTaP- IPV - HepB</td>
<td>DTaP- IPV - HepB</td>
</tr>
<tr>
<td>Child 4</td>
<td>DTaP- IPV - HepB</td>
<td>DTaP- IPV - HepB</td>
<td>DTaP- IPV - HepB</td>
<td>DTaP- IPV - HepB</td>
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<td>DTaP- IPV - HepB</td>
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**X** = acute adverse outcome
**X** = long term adverse outcome

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</thead>
<tbody>
<tr>
<td>Child 1</td>
<td>Hep B</td>
<td>DTaP-IPV-HepB, Hib, Pc, Rota</td>
<td>DTaP-IPV-HepB, Hib, Pc, Rota</td>
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</table>
Methods – Stakeholder Engagement

- Identify 5 subject matter experts (SMEs)
- Two in-person meetings and 5 conference calls
Methods – Stakeholder Engagement

- Iterative process
  - Audio record discussions
  - Take detailed notes
  - Independently review notes to identify key themes
  - As a group, discuss and refine themes
Methods – Stakeholder Engagement

SMEs (n=5)

- General Vaccinologists
  - Walter Orenstein, MD, Emory University
  - Stanley Plotkin, MD, Univ. Pennsylvania
  - Edgar Marcuse, MD, MPH, Univ. Washington

- Methodologists
  - Martin Kulldorff, PhD, Harvard University
  - M. Alan Brookhart PhD, Univ. North Carolina
Defining Cohorts and Alternative Schedules (Specific Aim 1)

- Create distinct exposure groups
  - Average days under-vaccinated
  - Diagnostic codes for vx refusal (V64.05/06)
  - Specific schedules (Sears, Miller, Mumper, Cave)
  - Completely unvaccinated
Defining Cohorts and Alternative Schedules (Specific Aim 1)

- Create distinct exposure groups
  - “Shot limiting”
  - Delaying start to vaccination
  - Vaccine series not received
  - Doses not received
  - Spacing of vaccines
  - Exposure to non-antigen ingredients (e.g., aluminum, formaldehyde)
Defining Cohorts and Alternative Schedules (Specific Aim 1)

- Primary data collection
  - Medical record review
  - Survey/Interview parents
Identify Plausible Adverse Event Outcomes (Specific Aim 2)

- Identifying AE outcomes in typical VSD safety study
  - Step 1: ICD-9 CM diagnostic codes
  - Step 2: Abstractors conduct medical record review
  - Step 3: Clinician investigators adjudicate (validate) cases
  - Step 4: Validated cases linked immunization records and prepared for analysis
Identify Plausible Adverse Event Outcomes (Specific Aim 2)

- Which outcomes?
  - Related to schedule and not specific vaccine
  - Biologically plausible
  - Can be feasibly studied in VSD

- How to prioritize?
  - Public health significance
  - Public concern
Plausible Adverse Event Outcomes Identified in 4 Phases

- Phase 1 – Generate list of outcomes
  - Review of literature for AEs not captured in IOM reports
  - Organized outcomes by:
    - Organ system (respiratory, neurologic, autoimmune)
    - Reaction type (allergy, anaphylaxis)
Plausible Adverse Event Outcomes Identified in 4 Phases

- **Phase 1 (cont’d)**
  - Evaluate biologic/mechanistic plausibility
  - Assess appropriateness of evaluating outcome relative to entire schedule (acute/chronic, age a peak incidence)
  - Can outcome be clearly linked to a specific vaccine
    - Measles inclusion body encephalitis
    - Immune thrombocytopenia
Plausible Adverse Event Outcomes Identified in 4 Phases

- Phase 2 – SME engagement
  - Provide additional insight on:
    - Biologic plausibility
    - Relevance to entire schedule
    - Feasibility to study in VSD
  - Classify each outcome as “include” or “exclude”
Plausible Adverse Event Outcomes Identified in 4 Phases

- Phase 3 – Final prioritization
  - Examine incidence rate of each outcome in VSD
    - Classify outcomes as being feasible or not feasible to study in VSD
  - Each study team member rank each outcome on
    - Public health significance (1 to 5)
    - Public concern (1 to 5)
    - Sum together scores and average across study team (2 to 10)
  - Final Discussion to move outcomes up, down or off the priority list
Phase 1: Generate outcomes

Reviewed IOM reports & previous research
n= 75 outcomes

Identified plausible outcomes
n= 47

Phase 2: SME engagement

Subject matter expert review & prioritization
n= 47

Excluded and grouped outcomes
n= 31

Phase 3: Prioritization

Feasibility assessment based on incidence rates
n= 31

Ranked on public health significance & public concern
n= 20 outcomes
Ranking of outcomes

1. Asthma
2. Anaphylaxis
3. Encephalopathy
4. All-cause mortality
5. Meningitis
6. Learning & developmental disorders
7. Epilepsy
8. Type 1 diabetes
9. First demyelinating event
10. Allergy development
11. Attention deficit disorder
12. All-cause morbidity
13. Crohn’s disease & ulcerative colitis
14. Syncope & vasovagal reaction
15. Seizures
16. Kawasaki’s disease
17. Juvenile rheumatoid arthritis
18. Tics
19. Chronic urticaria
20. Bell’s palsy
Conclusions/Questions

- Vaccine hesitancy appears to be growing public health issue
- The US has a robust post licensure vaccine safety monitoring infrastructure
- Is studying the safety of the recommended schedule opening a can of worms?
- Should public concern be a criterion for studying safety?
Acknowledgements

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