Brighton Collaboration
Viral Vector Vaccines Safety Working Group

Global Collaborative Network for Vaccine Safety Studies
Veyrier-du-Lac, France
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Robert T. Chen MD. MA
HIV Vaccine & Special Studies Team
Centers for Disease Control & Prevention
Outline

Introduction

Maximizing value of pre-licensure vaccine safety data

Some suggestions for future
Are Vaccines Still SAFE?

As the list of recommended immunizations for children keeps growing, more and more parents are questioning whether every new shot is necessary.

By Maureen Connolly
“The windshield is larger than the rearview mirror”

Tom Daschle

via Barbara Law
## Life-saving vaccines on the horizon
*(source: www.path.org)*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number killed per year</th>
<th>Candidate vaccines</th>
<th>Research</th>
<th>Preclinical</th>
<th>Clinical/regulatory approval</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrheal</strong></td>
<td></td>
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<tr>
<td>Enterotoxigenic <em>Escherichia coli (ETEC)</em></td>
<td>380,000</td>
<td>6</td>
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<tr>
<td>Rotavirus*</td>
<td>527,000</td>
<td>7</td>
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<tr>
<td>Shigellosis</td>
<td>1 million</td>
<td>7</td>
<td></td>
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<tr>
<td><strong>Respiratory</strong></td>
<td></td>
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<tr>
<td>Influenza*</td>
<td>300,000–500,000</td>
<td>11</td>
<td></td>
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<tr>
<td>Pneumococcus*</td>
<td>2 million</td>
<td>5</td>
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<tr>
<td>Tuberculosis</td>
<td>1.6 million</td>
<td>11</td>
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<tr>
<td><strong>Vector-borne</strong></td>
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<tr>
<td>Japanese encephalitis (JE)**</td>
<td>10,000–15,000</td>
<td>4</td>
<td></td>
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<tr>
<td>Malaria</td>
<td>1.3 million</td>
<td>23</td>
<td></td>
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<tr>
<td><strong>Other</strong></td>
<td></td>
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<tr>
<td>HIV/AIDS</td>
<td>2.8 million</td>
<td>20</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Human papilloma virus (HPV)</td>
<td>250,000</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal A*</td>
<td>6,000–20,000***</td>
<td>4</td>
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</tr>
</tbody>
</table>
Opportunities to Improve Vaccine Safety Data

- Pre-Licensure
- Post-Licensure

Developed Settings
- a
- b

Less Developed Settings
- c
- d
FIGURE 11: **The R&D Process: Long, Complex, and Costly**

- **Drug Discovery**: 5,000–10,000 Compounds, 3–6 years.
- **Preclinical**: 250.
- **Clinical Trials**: PHASE 1 (20–100 volunteers), PHASE 2 (100–500 volunteers), PHASE 3 (1,000–5,000 volunteers), 6–7 years.
- **FDA Review**: 1/2–2 years.
- **Large-Scale Manufacturing**: ONE FDA-APPROVED DRUG.

“The most reliable way to assess causality is in a controlled study, but clinical trials of new vaccines are typically too small to detect rare but serious effects. If the size of these trials were increased, much more could be learned about the safety of a vaccine prior to its exposure to entire populations. “

Some Ideas to Improve Vaccine Safety during Pre-Licensure Clinical Trials

- Lessons from Rotashield and Intussusception:
  - Larger (vs. maximizing value of available) sample size

“Hindsight is always 20/20”  *Sarcastic Americanism*

vs.

“Those who cannot learn from history are doomed to repeat it. ...”  *Santayana*
Some Ideas to Improve Vaccine Safety during Pre-Licensure Clinical Trials

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“Those who cannot learn from history are doomed to repeat it. ...”  
Santayana
“Intussusception occurred during the first 12 months of life in 1 of 4633 placebo recipients (0.022%) vs. 5 of 10 054 (0.05%) of all rotavirus vaccinees, which included 2 of 8240 (0.024%) given the tetravalent rotavirus vaccine at the dosage proposed for licensure. These differences were not significant by Poisson regression analysis, $P = 0.45$ and 0.92, respectively.”

Lack of an apparent association between intussusceptions and wild or vaccine rotavirus infection. PIDJ 1998; 17:924-925.
“A Rotavirus Working Group of the ACIP was established.... composed of experts in pediatric ID, vaccinology, epidemiology, & public health. As part of the review process, a member reviewed all SAE reported in all of the industry-sponsored trials of all of the RRV candidates and noted 5 cases of intussusceptions among 10,054 vaccinees, 3 of which occurred during the week postvaccination, and 1 case among 4,633 placebo recipients. None of these cases had been judged by the clinical study investigators to be attributable to the vaccine.

The Rotavirus Vaccine Story: A Clinical Investigator’s View
Retrospective use of the newly developed person-time analysis of events indicates 3 prelicensure cases of intussusception occurring the week after vaccination was more cases than would have been anticipated. However, only 1 of these prelicensure cases fit the profile of vaccine-associated cases, and that child had not received Rotashield.
Some Ideas to Improve Vaccine Safety during Pre-Licensure Clinical Trials

Lessons from Rotashield and Intussusception:
- Larger (vs. maximizing value of available) sample size
- Single DSMB/integrated safety oversight of candidate vaccine
- Ensure DSMB includes safety/rare disease epi expertise

Use data linkage and pattern recognition to complement traditional clinician attribution of causality in clinical trials

Specimen collection for pharmacogenomic studies

Use/develop standardized Brighton Collaboration case definitions + other processes?

Chen RT, Vaccine 2008, Boston, MA => IABS 2011
New Brighton Collaboration (BC) Pre-Licensure Working Groups

• Viral Vector Vaccines Safety Working Group (V3SWG)
  – Cross-cutting issues currently
  – Launched Sept 2008: ~100 => 30 volunteers
  – Lead: Bob Chen
  – Future: vector-specific (e.g., adeno-, pox-, DNA)

• INYVAX: Safety Elements of a Protocol for Clinical Trial of Vaccines in Resource Limited Countries
  – EC funded, Launched March 2009
  – Lead: Jan Bonhoeffer + Uli Heininger
  – Future:
    • target disease-specific (HIV, Malaria, TB) vaccines
    • Vector-specific (e.g., adeno-, pox-, DNA)
V3SWG: The Need

- Live viral vectors provide effective means for heterologous antigen expression in vivo = promising platforms for novel vaccines.

- While preclinical evaluation of recombinant live viral vectors look promising, there is as yet limited clinical experience (efficacy, safety).

- Increasing number viral vectors entering clinical trials => need to establish appropriate regulatory requirements.

- The halt of the Merck STEP/Phambili trials in 2007 and the unexpected success of ALVAC canarypox HIV vaccine in RV144 trial have increased attention on safety of viral vector vaccines.

- Improving ability to anticipate safety issues, their assessment, and meaningfully interpret safety data from trials of such new vaccines will help their clinical development and aid in the likelihood of overall public acceptance should they be safe and efficacious.
HIV vaccine trials stopped

Cumulative Number of HIV Infections: MITT population (males)

Overall

- 49 Vaccine
- 33 Placebo

Ad5 > 200

- 21 Vaccine
- 9 Placebo

1-tailed p-value = 0.044 (for $VE_{\text{INF}} < 0$
2-tailed p-value = 0.077 (for $VE_{\text{INF}} \neq 0$

1-tailed p-value = 0.020 (for $VE_{\text{INF}} < 0$
2-tailed p-value = 0.029 (for $VE_{\text{INF}} \neq 0$

Cases accrued as of Oct 17, 2007
RV-144 efficacy varied by time

Year 1: 60%
Year 2: 36%
Year 3: 30%

Source: Donald Stablein, PhD, EMMES
## Viral Vaccine Vectors by Stage of Development

<table>
<thead>
<tr>
<th>Novel Viral Vectors already in Clinic</th>
<th>Viral Vectors in Advanced Pre-Clinical Stage, soon in Clinic</th>
<th>Vectors in Upstream Pre-Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad35</td>
<td>Sendai **#</td>
<td>NDV *</td>
</tr>
<tr>
<td>Ad26</td>
<td>Measles * #</td>
<td>CDV *</td>
</tr>
<tr>
<td>Ad5</td>
<td>Ad4 *</td>
<td>HSV-1 *</td>
</tr>
<tr>
<td>Tiantan Vaccinia *</td>
<td>Ad7 *</td>
<td></td>
</tr>
<tr>
<td>AAV2</td>
<td>PIV-1 *</td>
<td></td>
</tr>
<tr>
<td>VEE</td>
<td>CMV *</td>
<td></td>
</tr>
<tr>
<td>BCG*</td>
<td>Yellow Fever * #</td>
<td></td>
</tr>
<tr>
<td><em>Canarypox</em></td>
<td>VSV</td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td>AAV1</td>
<td></td>
</tr>
</tbody>
</table>

* Replication-competent  
# Non-recombinant virus also tested in humans as vaccine  
*Older vectors tested in humans for more than a decade*

Source: JL Excler, IAVI
V3SWG Membership/Secretariat

- ~30 volunteers from stakeholders representing academia, industry, and government
- balance between virology and safety expertise
- Global (current/past members from): Nigeria, Brazil, S Africa, Belgium, Netherlands, Germany, India, Jordan, Spain, Canada, U.K., and U.S.
- Meet during monthly one hour conference calls, supplemented by ad hoc off line discussions.
- Supported by secretariat (one MPH work-study student, toll free phone number).
- Akin to BC Local Rxn WG (multiple issues)
V3SWG Standard Template

- Collects standardized data re: each viral vector allowing greater ability to compare
- Identifies safety and regulatory issues needing consideration at the pre-clinical and clinical development stages
- Volunteer expert (or grad student) completes
- Second expert comments on the completed template and modify as necessary
- A neutral moderator resolves any disputes with the help of the workgroup => usual BC peer review
- Eventual web-posting and maintain “wiki-style”; more actively evolving science vs. case definitions
3. Characteristics of wild type agent

3.1. Please list any disease(s) caused by wild type, the strength of evidence, severity, and duration of disease fn
- healthy people
- Immunocompromised
- neonates, infants, children
- During pregnancy
- in the unborn
- any other susceptible populations
- In Animals

Characteristics of proposed vaccine vector

4.1. What is the basis of attenuation/inactivation?
4.2. What is the risk of reversion to virulence or recombination with wild type or other agents?
4.3. Is the vector genetically stable during multiple passages?
4.4. What is known about the genetic stability during in vivo replication?
4.5. Will a replication competent agent be formed?
4.6. What is the potential for shedding and transmission?
Recs on issues needing study: 2003 WHO informal consultation on characterization/quality aspect of vaccines based on live viral vectors

1. The potential for vector recombination with wild type pathogenic strains
2. Implications of prior infections on safety
3. Genetic stability of replicating vaccine viruses in vivo
4. Potential changes of vaccine viral tropism
5. Tests for absence of reversion to virulence
6. Absence of replication-competent virus when replication incompetent vectors are used

7. Vaccine effects on innate immunity and on the induction of an immuno-suppressive window or immune-activation

8. Length of time for monitoring Adverse Events

9. Possible secondary transmission of vaccine virus

10. Inclusion of adventitious agents in cell culture
Risk of Transmissibility

• Draft guidance outlines steps to be taken based on a high-medium-low risk assessment for different vectors
• How to define level of risk?
• Current solution: adapt from risk classification system for genetically modified organisms.
Latest “Black Swan” in Human Use of Technology

Disaster-hit Japan faces protracted nuclear crisis

719 people recommend this. Be the first of your friends.
Other “Black Swan” Events:

- **Non-vaccine:**
  - HIV contamination of blood products
  - BSE (Mad Cow Disease) and meat (bovine serum?)

- **Vaccine:**
  - SV40 and polio vaccine
  - Thimerosal preservative
  - Avian leukemia virus + endogenous avian virus in vaccines derived from chicken cells
  - Porcine Circovirus Type 1 (PCV1) in Vaccine-Related and Other Cell Lines
Issues raised by PCV contamination of rotavirus vaccine

• Vaccines are complex biological endproducts (e.g., virus, cultures, adjuvants, stabilizers)
• Potential for (relatively) universal inadvertent exposure of human populations
• May wish to archive vaccine specimens for future testing by new assays
• No standard guidance available on:
  - Which samples to archive?
Who is actively studying the complex immunization system to prevent future black swans?
Summary

• Good progress attained in post-licensure vaccine safety infrastructure, esp in some developed countries.
• Major challenges remain in extending to other realms.
• Opportunities exist to maximize value of pre-licensure safety data/processes.
• BC V3SWG represent first steps.
• Need to remain humble re: risk for “black swan” situations; lucky so far?
Acknowledgement

- Current and past members of V3SWG
  - Jean-Louis Excler
  - Bettina Klug
  - Jim Robertson
  - Rich Condit
  - Marian Laderoute
- Secretariat
  - Christina Via
  - Baevin Carbery

Disclaimer

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