Primary Vaccine Container Selection in Developing Countries

Safety

Neal Halsey

Johns Hopkins Bloomberg School of Public Health
Issues Requested to Cover

1. Rates of contamination, needlesticks, etc. due to vial size
2. Adherence to multi-dose vial policies
3. Presence or absence of preservatives
4. Practices in handling vaccines, reuse of needles, etc.
Preventable Medical Errors Occur in all Countries

U.S. ~1.5 million preventable adverse drug events/ year

No comparable estimates for immunization related errors in any country
Comparative Effectiveness

Comparing treatment options for different health conditions. For more information, select:
Effective Health Care Program.

TV & Radio Ads

Questions are the Answer

Questions Are The Answer
The top 10 questions to ask your doctor.

Explore Your Treatment Options
Explore the right treatment for you.
Minimal capacity includes:

- National Pharmacovigilance capacity
- Clear strategy for risk communication
- National pharmacovigilance resources
- National reporting form for AEFI
- National database or system for collating, managing & retrieving AEFI reports
- Harmonized set of standards implemented
- National AEFI expert review committee
- Health-care workers & others encouraged to report vaccine safety issues

Health-care workers & others are encouraged to report vaccine safety issues.

Courtesy P Zuber WHO
GVS Blueprint overview – CDC 15 December 11
### Indicator PM06: Capacity to detect and investigate significant vaccine safety issues according to WB income status (end 2009)

<table>
<thead>
<tr>
<th>Group of countries</th>
<th>Number of Countries</th>
<th>Number of Countries with data available</th>
<th>Number of Countries with Indicator Implemented</th>
<th>% Implemented (of those with data available)</th>
<th>% Implemented out of the total countries in the region</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Industrialized</td>
<td>48</td>
<td>48</td>
<td>45</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>B. Upper middle income</td>
<td>39</td>
<td>13</td>
<td>5</td>
<td>38</td>
<td>13</td>
</tr>
<tr>
<td>C1. Lower middle income</td>
<td>57</td>
<td>17</td>
<td>5</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>C2. Low income</td>
<td>49</td>
<td>17</td>
<td>2</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

Courtesy P Zuber WHO
GVS Blueprint overview – CDC 15 December 11
Problems in Answering Questions

- No true rate data
- Inadequate surveillance systems for detecting, reporting, and investigating adverse events.
- Inadequate training and supervision in many settings
- Underreporting, suppression/hiding of mistakes
Needlestick Injuries

- Safety devices: lower rates
- Automatic (passive) lower than manual
- France: overall rate: 2.05 injuries per 100,000 safety devices purchased.
- Developing countries: ?

Autodestruct vs. Safety Devices

Syringex Safety Syringe

- To destroy: Snap off plunger
- Needle locked to tip of plunger
- Needle retracted into barrel
- Needle hub remaining attached to Luer Lok
Around 30 WHO approved AD syringes (Belgium, China, Denmark, India, Indonesia, Korea, Malaysia, Singapore, Spain, UAE, USA, Vietnam) and 50 WHO prequalified RUP for therapeutic use.

Disposable syringes: ± 3 cts
AD & RUP syringes: 4.5 to 6 cts per unit
Retractable syringes: 6 to 9 cts per unit

Courtesy P. Duclos, WHO
Vaccines Available in a Variety of Presentations
Mixing and Reconstituting is More Complicated

1. Removing the cap from the vial
2. Inserting the needle into the vial
3. Placing the vial upright
4. Depressing the plunger to remove air

Important:
- Adjuvant
- Antigen

10 doses
Preventing Errors in Vaccine Administration

Simpler = Better

The more steps involved, the greater the chance for errors
Single Dose Vials or Prefilled Syringes
Prefilled Single Use Syringes

- Easiest
- Safest
- Most expensive per dose
- Least wastage
- Bulkiest: added shipping costs
- Most cold chain space requirements
- Practical developing country settings?
Note: a single country may procure more than one vaccine presentation in a given year; thus, one country may be counted in more than one vial size category.
DTP-HepB

2004-2005 Increase in global supply

Number of countries


Weighted avg price / dose (USD)

2 dose 10 dose 2 dose price 10 dose price

Jodi Liu Sage 2012
Bacterial Contamination of Multidose Vials
### Three Outbreaks of Group A Streptococcal Abscesses Following DTP Immunization 1985

<table>
<thead>
<tr>
<th>Cluster/Date</th>
<th>Number of Abscesses</th>
<th># Children w Positive Findings on Cultures</th>
<th>Streptococcus Type</th>
<th>Thimerosal Levels (wt/vol)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indiana</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Feb 1981</td>
<td>7</td>
<td>6</td>
<td>T-1, M-1</td>
<td>Not done</td>
</tr>
<tr>
<td><strong>Georgia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• July 1982</td>
<td>12</td>
<td>9</td>
<td>T-28, M nontypable</td>
<td>0.0092%</td>
</tr>
<tr>
<td><strong>Oklahoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oct 1982</td>
<td>5</td>
<td>4</td>
<td>T-3/13/B3264, M nontypable</td>
<td>0.0088%</td>
</tr>
</tbody>
</table>

* Normal Range = 0.0080-0.0120% (weight/volume)
Estimated Direct Medical Costs of 12 Cases of Group A Streptococcal Abscess in Georgia

<table>
<thead>
<tr>
<th>Service</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization (actual for 4 children)</td>
<td>$5,063</td>
</tr>
<tr>
<td>Surgical costs (actual for 12 children)</td>
<td>2,013</td>
</tr>
<tr>
<td>Pediatric re-visits (actual at $20/visit)</td>
<td>620</td>
</tr>
<tr>
<td>Outpatient antibiotics (estimated at $10/prescription)</td>
<td>120</td>
</tr>
<tr>
<td>Outpatient laboratory (estimated at $40/child)</td>
<td>320</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$8,136</strong></td>
</tr>
</tbody>
</table>
Multi-dose vials with a preservative can be stored for weeks or months

www2a.cdc.gov/.../pages/storage_practices.htm

1. Date opened
2. Care in alcohol prep for every entry
3. Keep in refrigerator- not at room temp
Multidose Vials Without Preservatives: 
Discard after 6 hours 

Following the open vial policy?

DANGER

BCG
Measles
freeze-dried
Hib Vaccine
Freeze-dried 
Vaccine
Yellow Fever

Must be discarded 6 hours 
after reconstitution

Adapted from poster CCPS/21, (4031) Freeze-dried Vaccine, World Health Organization (WHO)

Courtesy P. Duclos  WHO
BRIEF REPORTS

Toxic Shock Syndrome: An unforeseen Complication Following Measles Vaccination

to give a major setback to the programme. We herewith report the occurrence of a serious complication following measles vaccine administration, an aftermath possibly of contamination.

Material and Methods

In the month of July 1988, the authors visited Mandrup PHC and Bhandarkavathe subcentre in Solapur district to investigate a problem that occurred following measles vaccination.

On 16th July an ANM from Bhandarkavathe subcentre immunized 11 children with measles (and 10 with oral polio). Their ages ranged from 0 to 18 months. Within 3 hours of immunization, 4 children started getting diarrhea and vomiting. They were treated with ORT. Within 15 days...
Bacterial Contamination of Measles Vaccine Vials: India 1985-1994

- Multi-dose vials
- 39 clusters of fever, rash, shock: day of vaccination
- 81 deaths
- Bacterial contamination after reconstitution
  - Staph aureus and other

Prevention: discard vials after 2 (WHO 6) hours. Sterile syringe and needle for reconstituting. Smaller (5 dose) vials now used in most of India

### Bacterial Contamination of Measles Vaccine

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Time to Onset</th>
<th>Outcome</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire</td>
<td>1994</td>
<td>‘a few hours’</td>
<td>3 of 4 died</td>
<td>no information</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>1995</td>
<td>4-5 hours</td>
<td>4 of 5 died</td>
<td>S. aureus</td>
</tr>
<tr>
<td>India</td>
<td>1995</td>
<td>5 hours</td>
<td>All 3 died</td>
<td>‘contaminated’</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>1995</td>
<td>4-7 hours</td>
<td>3 of 7 died</td>
<td>S. aureus</td>
</tr>
</tbody>
</table>
10 Dose Measles Vaccine Vial plus Diluent
Toxic Shock after Measles Vaccine 2008

Death of Children after Measles Vaccination

According to reports in newspapers and television media, 4 infants died on 23 April 2008 within hours of taking measles vaccination in a village outreach clinic in Tiruvallur District in Tamil Nadu(1-4). No official or authenticated information on this issue is available on the websites of the Department of Family Welfare of the Government of India (GoI)(5). No official press release was referred to in any media report(1-4). An investigating committee was appointed by the GoI including the Director problems - systemic and specific. The lack of systematic monitoring of AEFI, of its professional management and of accountability to inform the public and health professionals of facts is obvious. The training of village health workers and the supervision of outreach vaccination clinics appear to be grossly inadequate. The incident-specific problem was responded to without collecting facts and details. The devil is indeed in the detail.

According to media reports, 5 infants were ill within about half to one hour after getting measles vaccine in the morning session of an outreach clinic and 3 died(1-4). In the afternoon session two more

Reconstituting vials the day before campaigns

4 deaths: Media labeled “Killer Vaccine”

Bacterial Contamination of Multi-dose vials Associated with Severe Disease

- DTP
- Measles
- Yellow fever
- BCG

Contamination by health care worker after opening the vial
Still some poor practices

A typical case from a district hospital in a country with endorsed national plans, a national committee for infection control and using safety boxes and an operating treatment technology.

And poor management

Courtesy P. Duclos WHO
Respiratory Arrest and Deaths Following Measles and BCG Vaccines

- Mexico, Kenya, Lesotho, other
- Paralyzing agents: Succinyl choline, Pavalon, or pancuronium bromide mistaken as vaccine diluent
- Diluent and drug vials identical size, color, and print type.
  - Stored together

Weekly Epi Record 1996;71(32):239.
Injection safety

Newly published

WHO Guidelines on drawing blood: best practices in phlebotomy

Phlebotomy uses large, hollow needles to remove blood specimens for lab testing or blood donation. Each step in the process carries risks - both for patients and health workers. Patients may be bruised. Health workers may receive needlestick injuries. Both can become infected with bloodborne organisms such as hepatitis B, HIV, syphilis or malaria. Moreover, each step affects the quality of the specimen and the diagnosis. A contaminated specimen will produce a misdiagnosis. Clerical errors can prove fatal.

The new WHO guidelines provide recommended steps for safe phlebotomy and reiterate accepted principles for drawing, collecting blood and transporting blood to laboratories/blood banks.

Full document (Chinese, English, French and Portuguese)

Phlebotomy job aids

NEW DOCUMENTS

WHO Guidelines on drawing blood: best practices in phlebotomy
Preservatives in Multi-dose Vials
## Preservatives in Vaccines

<table>
<thead>
<tr>
<th>Preservative</th>
<th>Vaccine</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td>Typhim Vi</td>
<td>Typhoid</td>
</tr>
<tr>
<td></td>
<td>Pneumovax23</td>
<td>Pneumococcal Polysaccharide</td>
</tr>
<tr>
<td></td>
<td>ACAM2000</td>
<td>Smallpox</td>
</tr>
<tr>
<td>Benzethonium Chloride</td>
<td>Biothrax</td>
<td>Anthrax</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Biothrax</td>
<td>Anthrax</td>
</tr>
<tr>
<td></td>
<td>IPOL</td>
<td>Polio (IPV)</td>
</tr>
<tr>
<td>2-phenoxyethanol</td>
<td>IPOL</td>
<td>Polio (IPV)</td>
</tr>
<tr>
<td>non-US formulations</td>
<td>Hiberix</td>
<td>Hib</td>
</tr>
<tr>
<td></td>
<td>Pediarix</td>
<td>HepB</td>
</tr>
<tr>
<td></td>
<td>Kinrix</td>
<td>DTaP+IPV</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>Afluria (multi-dose)</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>DT</td>
<td>DT</td>
</tr>
<tr>
<td></td>
<td>Flulaval</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Fluvirin (multi-dose)</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Fluzone (multi-dose)</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>JE-Vax</td>
<td>Japanese Encephalitis</td>
</tr>
<tr>
<td></td>
<td>Menomune (multi-dose)*</td>
<td>Meningococcal</td>
</tr>
<tr>
<td>non-US formulations</td>
<td>Sii Q-Vac</td>
<td>DTP+HepB</td>
</tr>
<tr>
<td></td>
<td>Gene Vac-B</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td></td>
<td>MenAfriVac</td>
<td>Meningococcal A</td>
</tr>
<tr>
<td></td>
<td>Tetanus Toxoid</td>
<td>Rabies</td>
</tr>
<tr>
<td></td>
<td>Sii Rabivax</td>
<td></td>
</tr>
</tbody>
</table>

* in diluent  

Source: Package Inserts & RBall Presentation 4/4/12
Comparative Assessment of Prev(e)nar 13™ Multi-dose Formulations in Preservative Effectiveness by the Single-challenge Method

Comparative Assessment of Prev(e)nar 13™ Multi-dose Formulations in Preservative Effectiveness by the Multi-challenge Method 22-24°C vs 2-8°C

Vulnerabilities

- Single manufacturer of pharmaceutical grade Thiomersal.
- Declining market for Thiomersal
- One year’s assured stock of Thiomersal
- Basle Convention on movement of hazardous waste may prevent movement of raw material (mercuric chloride)
- In 2012 UNICEF has interruptions in supply for DPT, YF, PCV & RV.
Conclusions

- Errors in vaccine administration occur
- True rates unknown
- Improved surveillance and supervision to prevent errors should be priorities
- Unit dosing is simplest and safest
  - not practical at the present time in some settings
Maintaining public confidence should be our highest priority