Clinical trials: an overview of issues to be considered

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**THE VACCINE DEVELOPMENT PARADIGM**

**Public perception**

**Disease Burden**

**Scientific feasibility**

**Basic vaccine research**

**Vaccine candidates**

**Pre-clinical**

**Phase I**

**Phase II**

**Phase III**

**NRA**

**LICENCED PRODUCT**

**Phase IV**

**Time & costs:**
8-15 years
$60-900 million

**Pilot lots**

**Large-scale manufacture**

**Refinement of process & scale-up**

**Process development**

**Phase II**
The vaccine trials paradigm

• **Phase I** - Preliminary safety & immune response in small numbers of subjects

• **Phase II** - Safety & immunogenicity in larger groups; target populations; determine immunization schedule; choose the formulation; show compatibility with concomitant vaccines

• **Phase III** - Efficacy in large-scale trials (randomized, controlled, double-blind design, when possible)

**LICENSURE**

• **Phase IV** - Impact & safety post-licensure under real-life conditions; modifications in formulation and immunization schedule
<table>
<thead>
<tr>
<th>Category</th>
<th>Example Diseases</th>
<th>Burden and Market Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global market vaccines</strong></td>
<td>e.g., Hepatitis B, Hib, rotavirus, pneumo</td>
<td>Burden in both industrialized and developing countries; Markets in industrialized countries drive development</td>
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<tr>
<td><strong>Industrialized market vaccines</strong></td>
<td>e.g., Lyme disease; nicotine</td>
<td>Burden &amp; markets in industrialized countries drive development</td>
</tr>
<tr>
<td><strong>Impeded vaccines</strong></td>
<td>e.g., RSV, group A Streptococcus pyogenes</td>
<td>Markets exist but safety questions raise the risk and create barriers</td>
</tr>
<tr>
<td><strong>Developing market vaccines</strong></td>
<td>e.g., malaria, Shigella, Leishmania</td>
<td>Burden in developing countries; few “reliable” or “mature” markets</td>
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<tr>
<td><strong>Biodefense vaccines</strong></td>
<td>e.g., anthrax, tularemia, Ebola, smallpox</td>
<td>Burden is theoretical; governments create the market</td>
</tr>
<tr>
<td><strong>Pandemic vaccines</strong></td>
<td>e.g., Swine flu 1976 &amp; 2009, Avian flu 2006</td>
<td>Burden sometimes unclear; gov’ts must guarantee a market</td>
</tr>
<tr>
<td><strong>Emerging pathogen vaccines</strong></td>
<td>e.g., Ebola 2014-2015, Zika 2016</td>
<td>GAVI &amp; gov’ts must guarantee a market; industry sees some market</td>
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</tbody>
</table>
“Special” Phase I vaccine trials

• What is the ultimate target population?
  – Infant vaccines often require small step-wise Phase I studies in older children before descending to infancy

• Live viral and bacterial vaccines
  – Often special precautions (e.g., physical containment)
  – Preliminary assessment of excretion and transmission to contacts

• Impeded vaccines
  – (e.g., RSV, group A Streptococcus pyogenes)
  – Trials involve particularly intensive clinical surveillance and regulatory oversight

• Unusual vaccines
  – (e.g., “edible vaccines” derived from transgenic plants)

• Public health emergency - Ebola 2014, Zika 2016
Lesson learned from Ebola –
The time lines for initiating and completing Phase 1 of vaccine candidates can be accomplished at “warp speed” in the face of a public health emergency

- August 10, 2014 – WHO solicited emergency Ebola vaccine testing consortium for NIH/GSK and Merck/Newlink vaccines
- WHO Ethics Consultation, August 11, 2014
- Oxford, CVD, CVD-Mali submit a Strategic Award grant to Wellcome Trust, Aug 13. Grant awarded Aug 18.
- Clinical protocols written & submitted for ethical review in late August/early September.
- CVD-Mali protocol reviewed by 5 IRBs (3 in Mali, UMB, WHO) and Approval obtained from Malian Minister of Health, PM & President
- DSMB for the Mali trial approved launch of the study
- 1st Malian HCW vaccinated Oct 8; 40th Nov 14; 91st Nov 26.
- Serologic results by mid-January, 2015; 1x10^{11} pu chosen
Use of ChAd3-EBO-Z Ebola virus vaccine in Malian and US adults, and boosting of Malian adults with MVA-BN-Filo: a phase 1, single-blind, randomised trial, a phase 1b, open-label and double-blind, dose-escalation trial, and a nested, randomised, double-blind, placebo-controlled trial


Lancet Infectious Diseases, e-published Dec 2015
Phase II vaccine trials

- "Bread & butter" trials of vaccine development
- Pave the way for pivotal Phase III trials
- Often less "visible" than Phase I and III trials
- Sites and populations for Phase II trials
- Carefully select and validate the immune response(s) to be measured
- Finalize formulation as soon as possible
  - Communication with process developers
  - Communication with immune response measurers
- Harmony with existing immunization schedules
- Compatibility with concomitant vaccines
Phase II vaccine trials

Live vaccines

- Shedding pattern
- Transmissibility to contacts
- Environmental impact (GMOs)
- Genetic stability of isolates
Phase IIB volunteer challenge studies

- Characterize & compare the immune response to wild type pathogen and vaccines (link to re-challenge)
- Measure efficacy of candidate vaccines
- Identify vaccine-elicited correlates of protection
- Where challenge studies have been useful:
  - Pre-erythrocytic stage malaria vaccines
  - Cholera vaccines
  - *Shigella* vaccines
  - Enterotoxigenic *E. coli* vaccines
  - Influenza vaccines
  - Typhoid vaccines
THE TRUEST TEST

Studies that intentionally infect people with pathogens have a checkered past, but they are seeing a resurgence

By Jon Cohen

Science
20 May 2016
Efficacy of Vaxchora® (CVD 103-HgR) in preventing moderate and severe El Tor cholera when challenged 10 days after ingestion of a single oral dose of vaccine

<table>
<thead>
<tr>
<th>Cholera</th>
<th>Vacc*</th>
<th>Ctrls*</th>
<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>Attack Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>2/35</td>
<td>20/33</td>
<td>91%</td>
</tr>
<tr>
<td>(i.e., &gt; 3.0 liters)</td>
<td>5.7%</td>
<td>60.6%</td>
<td></td>
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</table>

Challenge with $10^5$ CFU of NIH El Tor Inaba N16961 frozen inoculum

*Includes increased proportion of blood group O subjects (high risk for cholera gravis)

This study design was finalized in consultation with the FDA

W Chen et al, Clin Infect Dis 2016
Assessing vaccine efficacy pre-licensure

- **“Gold Standard”** -- Large-scale, adequately-powered, randomized, controlled, double-blind trial with allocation at the level of the individual
- Trials with **cluster randomization** of larger units such as classes, schools, families, villages
- **Sero-protection** (immunologic correlate of protection known) or **serological non-inferiority**
- Mass interventions; “before and after” analysis
- Volunteer challenge studies
- FDA “**Animal model rule**” (e.g., biodefense vaccines, intermittent unpredictable burden, etc.)
- Accelerated approval
Large-scale Phase III vaccine field trials

- Selection and preparation of the study site
  - Impetus; incidence rate, seasonality, modes of transmission, adequacy of health care and microbiology infrastructure, census, migration data, etc.

- Protocol design ("pivotal study")

- Financing large-scale trials (industry; public; partners)

- Some ethical issues

- Nurturing political commitment and ownership

- Execution of the trial (logistics & management)

- Interaction with the DSMB

- Analysis of the data

- Post-trial commitments (to subjects & Ministry)
Phase III study protocol

Primary aim(s)

- Must be clear, precise, achievable
- Must provide the evidence base for:
  - Licensure
  - Public health use
- Sample size influenced by:
  - Number of study groups and comparisons
  - Out migration
  - Power to detect a true difference
  - Alpha value
  - Lower Limit of the 95% CI for vaccine efficacy
  - Herd immunity effect on incidence
Reasons to randomize by units other than individual subjects

• Nature of the vaccine:
  – Live vaccine with potential for person-to-person transmission
  – Vaccine functions at the community level (e.g., transmission-blocking malaria vaccine)

• Logistics and practicality

• Attempt to measure herd immunity

• Mimic public health use (Ebola vaccine trial, Guinea)
Allocation to treatment groups in Santiago field trials of Ty21a

- Randomly allocated whole classes to receive Ty21a oral vaccine or oral placebo
- All children of consenting parents in a given class received the same product and regimen
- Vaccination during springtime (before school summer recess)
- Peak typhoid incidence during summer
### Efficacy of liquid formulation of Ty21a, Area SurOriente & Area Norte, Santiago

<table>
<thead>
<tr>
<th></th>
<th>Ty21a</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>No. classes</td>
<td>2,369</td>
<td>687</td>
</tr>
<tr>
<td>Classes with typhoid /10² classes</td>
<td>0.97</td>
<td>3.93</td>
</tr>
<tr>
<td>Efficacy</td>
<td>75%</td>
<td>-</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(56-85%)</td>
<td>-</td>
</tr>
<tr>
<td>No. children</td>
<td>36,623</td>
<td>10,302</td>
</tr>
<tr>
<td>Incidence/10⁵ children</td>
<td>63</td>
<td>272</td>
</tr>
<tr>
<td>Efficacy</td>
<td>77%</td>
<td>-</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(60-87%)</td>
<td>-</td>
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3 oral doses, every other day interval. 3 years of follow-up. Levine et al, Lancet 1990
Selecting the control preparation for vaccine efficacy trials

- **True placebo**
- A *licensed vaccine* against another infection that will have no effect on the study outcome events
  - provides a benefit for control subjects
  - sometimes difficult to find a suitable vaccine
  - may compromise double blindness
- An *experimental vaccine* against another infection that will have no effect on the study outcome events
  - good for efficacy but not for safety evaluation
Role of “luck” in large-scale vaccine field trials

- **Year to year variation** in disease incidence (e.g., cholera)
- **Antigenic change** in the circulating pathogen (e.g., influenza virus)
- **Geographic variability** within an endemic zone (e.g., meningococcus)
- Sometimes disease “hot spots” turn cold without precise explanations (e.g., malaria in some places in sub-Saharan Africa)
- Impact of other interventions (PREVAIL)
Strengthening infrastructure to support large-scale vaccine trials

- In large-scale trials in developing countries:
  - Microbiologic infrastructure often has to be strengthened
  - Health care infrastructure must often be reinforced
  - Intensive GCP training required

Automated blood culture machines introduced, Gabriel Touré Hospital bacteriology lab, Bamako, Mali, 2002
“Politics” and large-scale vaccine field trials

• Like it or not, in one way or another, politics always impinge on large-scale vaccine field trials
• The political aspects of vaccine trials must be recognized, considered and addressed

Ex-President of Mali, Amadou Toumani Toure
Organizing and executing large-scale vaccine field trials
It’s the LOGISTICS, darn it!!

Technical advances that have revolutionized large-scale field trials:
• Cell phones & satellite phones
• Notebook computers, tablet computers & PDAs
• Internet
• Skype & equivalent
• ICH (harmonization of Good Clinical Practices, etc.)
Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

Ana Maria Henao-Restrepo, Ira M Longini, Matthias Egger, Natalie E Dean, W John Edmunds, Anton Camacha, Miles W Carroll, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Stefanie Hossmann, Many Kader Kondé, Souleymane Kone, Eeva Kuisma, Myron M Levine, Selma Mandal, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, Conall H Watson, Sakoba Keita, Marie Paule Kieny, John Arne Rottingen

The Lancet
Published online July 31, 2015
http://dx.doi.org/10.1016/S0140-6736(15)6117-5
Primary analysis – all individuals assigned to immediate vaccination versus all individuals assigned to delayed vaccination

Vaccine efficacy = 100% (95% CI, 74.7-100), p=0.0036
Good Clinical Practice (GCP)

The comprehensive regulations and guidelines for conducting clinical trials that must be followed for results of those trials to be contained within an application requesting licensure of the vaccine.

Protocol design  Informed consent
Record keeping  Data reporting
Laboratory SOPs  Adverse event reporting
Performing vaccine trials

- The TRIAL PROTOCOL, a key document, is a “bible” for those conducting the study.
- WRITE in the protocol exactly what you propose to do.
- DO what you wrote you would do.
- LEAVE a pristine document trail so that an independent interested party, monitor or auditor can verify that you DID WHAT YOU WROTE YOU WOULD DO.
Assessing vaccine safety during efficacy trials

Nested reactogenicity/immunogenicity trial

- Reactogenicity/immunogenicity of actual field trial lots
- Typically includes 1-5% of total trial participants
- Usually involves active surveillance

Surveillance for serious adverse events (SAEs)

- All hospitalizations and deaths monitored
- Adapt surveillance to fit local setting
- In developing country settings, repeated census and verbal autopsies may be required
Unexpected morbidity and mortality detected during pre-licensure efficacy trials

**Phase III trials of formalin-inactivated RSV vaccine, USA**

Increased incidence of severe RSV disease in vaccinees vs controls

Post-licensure impact and safety of vaccines

• *Disappointment* - Rotashield®
  (intussusception)
Post-licensure impact and safety of vaccines

- **Disappointment** - Rotashield®
  (intussusception)

- **Serendipity** - Hib & pneumo conjugates
  (indirect protection)
Phase IV surveillance to document product safety and impact

- Surveillance for rare adverse events
- Effectiveness/impact
  - Fall in incidence
  - Case/control studies
  - Large-scale post-licensure selective vaccination and intensive surveillance
  - Probe studies
Post-licensure impact of Prevnar® on invasive pneumococcal disease in USA

C Whitney et al, NEJM 2003
Impact of Hib vaccine introduction on invasive Hib disease in infants, Bamako, Mali

- **36-month Baseline Period**, 7-02 to 6-05
- **12-month Transition Period**, 7-05 to 6-06
- **23-month Intervention Period**, 7-06 to 5-08

Invasive Hib cases/10^5 infants per 6-month intervals

88% reduction

S Sow et al 2009
Prevalence of serum Hib PRP antibodies in Malian infants 6-7 months of age before and 18 & 30 months after the introduction of Hib conjugate into the EPI for Malian infants

Serum antibody levels:

- 0.15 mcg/ml
- 1.00 mcg/ml

N=200
N=201
N=200

S Sow et al, AJTMH 2009
Incidence of Invasive Streptococcus pneumoniae Infection in Bamako 0- to 23-month olds

Incidence per 100,000 population

- Baseline
- Intervention

S Sow et al, AJTMH 2009

Lack of impact of Hib vaccine introduction on invasive pneumococcal hospitalizations
**Vaccine effectiveness** -- Hib cases during 30 mos. of follow-up among children assigned to the two sets of health centers during the selective vaccination

<table>
<thead>
<tr>
<th>Santiago Health Centers:</th>
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<tbody>
<tr>
<td>DTP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assigned population:</td>
<td>46,948</td>
<td>48,080</td>
</tr>
<tr>
<td>No. Hib cases</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Effectiveness</td>
<td></td>
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</tr>
</tbody>
</table>

Effectiveness: 90% (CI=75-100%)*

* (95% Confidence Interval)
Lagos et al, Ped Infect Dis J 1996
Santiago, Chile
Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial


• 3rd trimester immunization of 4193 pregnant women
• **Primary aim** - determine if infants born to immunized mothers are protected against lab-confirmed influenza
• Randomized controlled trial:
  ▪ Flu vaccine (N=2108) vs quadrivalent meningococcal conjugate (Menactra™) (N=2085)
Enjoy ADVAC 2016
and Lake Annecy!!

Thanks
Merci
Gracias
Grazie
Danke
Obrigado