The influence of maternal antibodies on active pertussis infant vaccination-human challenge studies (project)

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Human Challenges for *Bordetella pertussis*: A way forward?

Definition

- Human Challenge Experiment
  - The deliberate infection of human volunteers with a pathogenic strain of a virus, parasite, bacteria or fungus.
  - Used to study the pathogenesis, transmission and disease course of a particular infectious agent and to test the efficacy of candidate prophylactic or therapeutic agents.

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Kalil et. al. Future Microbiol 2012
Miller and Grady, Clin Infect Dis 2001
Rosenbaum and Sepkowitz Clin Infect Dis 2002
Acad Med Science 2005

Human Challenge Studies Background

- Useful for non-fatal infections where there is proven therapy that can minimize morbidity, complications and other serious outcomes
  - Not ethical where there is fatal outcome or where treatment may not be effective
    - Eg HIV infection, pandemic influenza, meningococcal infections
- Well-established for both transmission studies to understand pathogenesis (eg rhinovirus) or for treatment or prevention (eg influenza)

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The value of challenge research

1. Protection against a defined drug-sensitive strain of microbe can be evaluated in a controlled setting.
2. Potential efficacy of a vaccine or drug can be assessed in a smaller number of volunteers and more rapidly than through natural exposure.
3. The contribution of many biomarkers to resistance and protection against infection, such as various vaccine-induced immune responses, can be assessed relatively efficiently.

(Academy of Medical Sciences 2005)

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Vaccine Challenge – Benefits

- Capability of doing quick and cost effective efficacy studies at early stages of vaccine development
- Provides the opportunity to make formulation adjustments prior to full scale phase 3 efficacy studies
- Can more efficiently evaluate the effect of immunization on carriage, transmission, and severity of disease
- Can assess the safety, immunogenicity, and environmental shedding of attenuated or genetically modified live vaccines under controlled conditions
- Provides the opportunity to study vaccine route of administration, adjuvants etc with respect to protective efficacy

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Principles of pathogen selection

- The pathogen is well-characterized
- The disease is self-limiting in healthy individuals, and/or
- A rescue therapy is available to bring the participant back to good health
- The pathogen is approved by FDA CBER/Health Canada BGTD for use in humans

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Infection prevention and control

Appropriate infection prevention and control procedures are essential, requiring adequate trial facilities and well-trained staff with competency in Routine Practices and Additional Precautions.

Considerations:

- ✓ Are appropriate biological containment techniques in place to handle the challenge organism?
- ✓ Are there risks to contacts, within or outside the institution, as well as to the challenged individual?
- ✓ Is treatment available should the participant develop symptoms?
- ✓ Are there adequate safety follow-up procedures?

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(Academy of Medical Sciences 2005)

Bordetella pertussis: Uses of a human challenge model

- Incubation period
- Early clinical manifestations
- Pathogenesis
- Nature of the immune response (innate and adaptive)
- Transmission
- Protective antigens
- Strain contribution to pathogenesis
- Diagnostic tests
- Chemoprophylaxis and therapy
- Regulatory pathway for novel vaccines

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History of Pertussis Human Challenge

- NIH Protocol (DMID, NIAID)
  - 4 May 2004
    - Sylvia Yeh/Joel Ward
    - Harbor-UCLA
- Pre-IND meeting with FDA
  - July 26, 2004
    - responses and correspondence through June 2005
    - September 2005: DMID, NIAID decided not to pursue protocol

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History of Pertussis Human Challenge

- FDA feedback to investigators
  - Need for longer hospitalization and more extensive household and contact follow up
  - Inability to genetically mark challenge strain
- DMID NIAID
  - Decision that due to
    - increased cost of complying with FDA requirements
    - Tdap for adults was now available and the landscape of pertussis would dramatically change

  the challenge study was no longer as important or feasible

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Has the landscape changed again for human pertussis challenges?

- Reemergence of pertussis
  - Outbreaks
- Duration of protection of acellular vaccines
  - After childhood and ? adolescent doses
- Vaccine coverage in adults
- New vaccines and need for a regulatory pathway
  - Live, attenuated vaccine
  - Novel adjuvants

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What is the way forward?

- Is there a renewed appetite for developing the pertussis human challenge model?
- Where could/should it be done?
- What would be the funding source?
  - For development of the strain?
  - For the funding the initial trials establishing the model?

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An open, phase 1 trial to determine the optimal dose and method of *B. pertussis* challenge administered to healthy adults 18–40 years of age to recover *B. pertussis* in nasopharyngeal cultures 3–7 days after challenge

Protocol

- Phase: 1
- Blinding: none
- Population: healthy adults 18-40 years of age
- Agent: live liquid culture of *Bordetella pertussis* BP D420
- Dose: dose ranging 100 CFU with 5 fold increases to maximum 1,000,000 CFU

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Objectives

- Primary
  - Safety and optimal dose and methods for *B. pertussis* challenge and evaluation
    - Route of delivery
    - Doses
    - Number of organisms
  - Achieve infection in 3 of 4 participants (as measured by positive nasopharyngeal culture or PCR) 3-7 days post challenge

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Objectives

- Secondary
  - Characterize incubation period and characterize early symptoms
  - Determine frequency of spontaneous clearance, or subclinical or symptomatic illness
  - Determine efficacy of azithromycin therapy in terminating infection/alleviating symptoms
  - Determine the optimal time frame to evaluate the innate immune response and humoral and cell-mediated immunity following challenge

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Clinical Evaluations

- Medical history
  - At screening
  - daily inpatient
  - outpatient visits and calls
- Symptom observation
  - 9-12 hours pre-challenge
  - Daily symptoms up to day 16 (inpatient)
- Symptom diary cards
  - Inpatient day 0-16
  - Outpatient day 17-42

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Data Monitoring and Safety Committee

- Review all serious adverse events
- Determine stopping rules related to safety

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Challenge Strain: Bordetella pertussis D420

- Provenance
  - Year and location of clinical isolate
  - Age and state of health of source patient
- Serotyping
  - Fimbriae 2
  - Fimbriae 3

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B. pertussis D420

- Genomic analysis
  - PCR
    - Promotor region of pertussis toxin gene (*ptx*P)
    - Subunit A of pertussis toxin gene (*ptx*A)
    - Pertactin (*prn*)
    - Type 2 (*fim*2) and type 3 (*fim*3) fimbriae
  - Pulsed field gel electrophoresis (PFGE)
  - Whole genome sequencing

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Preparation of *B. pertussis* inoculum

- General
  - Produced under GLP conditions
  - Produced in liquid, chemically defined medium (Stainer Scholte medium)
    - No animal products

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Single Harvest production

- Produced from seed lot aliquot
- Larger volumes in Stainer Scholte medium
- Grown to high titer
- Tested same as seed lot
- aliquoted

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Challenge dose

- Made from single harvest aliquot
- Resuspended to appropriate dose in PBS
- Tested for titer, identity, purity, and antimicrobial sensitivity

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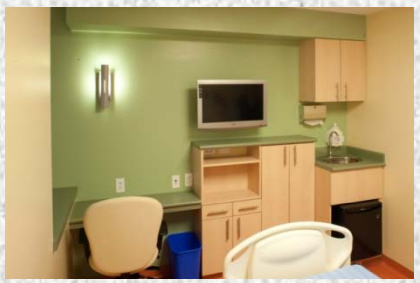
Facility:
CCfV Challenge Unit



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Progress Report

- Finally negotiation of the MTA to obtain *B. pertussis* D420 from the CDCa
- D420 being transferred to CCfV facility
  - Begin process of creating and characterizing the inocula
- Process of finding partners to fund the initial creation and characterization of the model

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Questions and Discussion

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