Pertussis Vaccine-Derived Protection: Immunological Perspective

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Immunological Correlates of Vaccine-Derived Protection
Annecy, France
Outline

- Correlates of protection
- *Bordetella pertussis* pathogenesis
- Immune response to infection
- Immune response to whole cell vaccines
  - Humoral
  - Cell mediated
- Immune response to acellular vaccines
  - Humoral
  - Cell mediated
- Effect of adjuvants on the immune response
- Duration of protection
Whole cell pertussis vaccine

- Medical Research Council trials in 1950’s
  - High levels of pertussis agglutinins correlated with protection
    - Medical Research Council, BMJ 1956
  - Predictive on population basis but were not predictive of protection on an individual level
- Agglutinins correlate best with antibody against fimbriae
  - Also with pertactin and lipooligosaccharide
WCV in animal model

- Protection against intracerebral challenge with virulent B. pertussis correlated with vaccine efficacy from the MRC vaccine efficacy studies
  - Kendrick test used to evaluate potency of whole cell vaccines
ACV in animal models

- Acellular pertussis vaccines do not pass the original Kendrick test (unless contaminated with PT with residual toxin activity)
  
  - The respiratory model by aerosol or intranasal has been used to study pertussis pathogenesis and immunity
    
    - Can correlate with vaccine efficacy of ACVs as determined in efficacy studies
    - Not accepted as a regulatory tool
Immune correlates of protection with acellular pertussis vaccines

- Household contact study nested within the Swedish and German efficacy studies of DTaP vaccines
  - Antibody correlate of protection
    - PRN, FIM, PT
    - No correlate with FHA
    - No protective level discernible
      - Swedish study used antibody break point of 5 EU/mL
      - German study found PRN levels ≥7 and PT values ≥66 EU/mL correlated with protection
        - Storsaeter et al. Vaccine 1998
        - Cherry et al. Vaccine 1998
Serological correlate of protection

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Storsaeter et al. Vaccine 1998
PT as protective antibody

- Household study as part of the Gotteborg Swedish efficacy trial of monocomponent PT vaccine
- Mean post immunization anti-PT levels
  - 79 EU/mL severe pertussis
  - 156 EU/mL mild pertussis
  - 246 EU/mL no pertussis
- Taranger et al. J Infect Dis 2000
Serological Correlates in Pertussis

- No single antibody has been demonstrated to be a correlate (surrogate?) of protection.
- Likely relates to the complexity of the immune response to pertussis.
- Finding correlates of protection for pertussis and enshrining them in regulation is important for evaluating vaccines only if the mechanism of protection for the new vaccine is identical to the vaccine for which the correlate was established.
Pathogenesis

- Attachment
- Evasion of host defenses
- Local damage
- Systemic manifestations

Hewlett, PIDJ 1997
Pertussis pathogenesis

- Attachment
  - Filamentous hemagglutinin
  - Fimbriae
  - Pertactin
  - Pertussis toxin

- Evasion of host defense
  - Adenylate cyclase toxin
  - Pertussis toxin

- Local damage
  - Tracheal cytotoxin
  - Dermatonecrotic toxin

- Systemic manifestations
  - Pertussis toxin
Immune response to infection

- Immunity to *B. pertussis* is complex
  - Multiple toxins (including a lipopolysaccharide), many of which act as virulence factors and are immunogenic
  - Binds to respiratory ciliated cells and multiplies extracellularly
  - Although doesn’t systemically disseminate, is taken up by macrophages and other cells and survives intracellularly
  - Both humoral and cell-mediated immunity may be important in protection
Immune response to *B. pertussis*

- A broad variety of immune responses can be demonstrated after infection
  - Includes antibodies and cellular responses to most of the toxins, surface components, and other unidentified antigens
  - Whether these contribute to protection is unknown
  - Mucosal antibody may also be important in bacterial clearance

- Immune response to vaccines in animal models demonstrates that responses to a variety of antigens can be protective suggesting that a single protective mechanism is unlikely

Immune response to current whole-cell vaccines mimics the response to infection in animal models and differs from the response to acellular vaccines
Immune response to infection

A variety of human and animal studies suggest that natural infection induces a Th1 type of response

- IFN-gamma, IL-2
- Little IL-4 or IL-5
Humoral response to whole-cell vaccine

- Antibody responses to pertussis antigens is variable amongst whole cell vaccines, likely related to the variability of antigen content amongst whole cell vaccines
  - WCVs standardized by protection in the mouse cerebral test, not by specific antigen content
  - PT is particularly variable in WCVs
- Antibody primarily IgG2a (Th-1) bias
- Little IgA response to WCV
Cell-mediated response to whole-cell vaccine

- WCV induces interferon gamma production and can protect in animal models in the absence of substantial antibody
  - Also protects in the mouse IC test
- Cellular immunity may be required to clear intracellular bacteria
- WCV elicits a Th1 response, similar to infection
  - IFN-gamma and IL-2
  - No IL-4 or IL-5
  - Likely due to residual amounts of active PT and LPS in WCVs
Humoral response to acellular vaccine

- Antibodies are induced against each of the antigens in the acellular pertussis vaccines
  - These antibodies are protective when administered passively in the mouse respiratory infection model
  - Higher levels of antibody (e.g., PT) correlate with greater protection
    - However, protection can still be demonstrated after antibody levels have dropped, suggesting a role for cell mediated memory
- Antibodies primarily IgG1 (Th-2 bias)
Cell-mediated response to acellular vaccine

- Acellular vaccines induce a Th-2 type of response
  - Mixed Th-1/Th-2 after primary dose
  - More polarized Th-2 after booster
- Different cellular response to subsequent infectious challenge (in animal models)
  - Slower and less influx of neutrophils and lymphocytes to respiratory site of infection
- Adding IL-12 to acellular vaccine formulation can shift the response toward a Th-1 profile
Immune response to infection

Mills K, Microbes and Infection 2001
Immune response to immunization

Mills K, Microbes and Infection 2001
Duration of protection

- Antibody levels in humans (and in the mouse model) peak 1-2 months after a primary series and then decline quickly
  - Duration of protection can be years, beyond when antibody can be detected
  - In animal model, duration of protection is longer after WCV compared to ACV, suggesting a role for cell-mediated immunity for long term protection
- Depletion of T-cells leads to prolonged infection, regardless of antibody level
Effects of adjuvants on the immune response to pertussis vaccines

- Adjuvants non-specifically activate cells of the innate immune response
  - Stimulate immune response to co-administered antigen
- Until recently, alum was the adjuvant used in most human vaccines
  - Only adjuvant in licensed pertussis vaccines
  - Induces Th-2 biased response
Pertussis vaccines and adjuvants

- WCVs all adjuvanted with alum
  - Th-2 bias mitigated by residual LPS and PT
    - Potent toll like receptor (TLR) agonists
    - Results in a Th1 biased response
- ACV also adjuvanted with alum
  - Without the residual active toxin, Th-2 response induced
- Novel adjuvants can change this bias
  - TLR ligands such as CPG (bacterial DNA)
  - Cytokines such as IL-12
Novel adjuvants and pertussis vaccine

- Challenges with existing acellular vaccines
  - Th-2 bias
  - Require multiple doses
  - Poorly protective in newborns
- Gates Foundation Grand Challenge
  - Single dose pertussis vaccine effective in newborns
Novel adjuvant platform

- Cytosine phosphate guanosine oligodeoxynucleotides (CpG ODN)
  - TLR 9 ligand
- Polyphosphazene synthetic polymers (PPs)
  - depot effect with microspheres
- Innate defense regulator peptides (IDR)
  - recruitment of immune cells
IgG1 (Th-2) response in adult mice

Gracia, Polewicz, Halperin, Hancock, Potter, Babiuk, Gerdts, 2010 submitted
IgG2a (Th-1) response in adult mice

Weeks
IgG2a Antibody Titre

PBSA
PTd (0.1 µg)
PTd + CpG C (10 µg) + IDR-HH18 (10 µg) + VIDO-EP#3 (50 µg)
-IDR & CpG complexed
PTd + CpG C (10 µg) + IDR-HH18 (75 µg) + VIDO-EP#3 (50 µg)
-IDR & CpG complexed
PTd + CpG C (10 µg) + IDR-HH18 (75 µg) + VIDO-EP#3 (50 µg)
-not complexed

CpG, IDR, PP

Gracia, Polewicz, Halperin, Hancock, Potter, Babiuk, Gerdts, 2010 submitted
IgG2a response in neonatal mice

Gracia, Polewicz, Halperin, Hancock, Potter, Babiuk, Gerdts, 2010 submitted
Conclusions

- Immunity to pertussis is complex
  - Both humoral and cell-mediated immunity important
  - Immune response post pertussis vaccine depends on the vaccine
    - Whole cell vaccines Th-1 bias
    - Acellular vaccines Th-2 bias
    - Novel adjuvants may alter this in the future
  - Antibody levels against PT, PRN and FIM can be used as markers of protection
    - No established single correlate of protection
    - No established protective antibody levels
    - May not be relevant at all with novel vaccines