Complications of Vaccine-Preventable Diseases: View From A Children’s Hospital

Brian P. Lee, MD, FAAP
Division of Infectious Diseases
• I have no relevant financial relationships with a commercial interest to disclose

• I will not discuss any off-label use and/or investigational use in my presentation
Immunizations: A Public Health Miracle

- Immunizations are one of the most miraculous achievements in modern medicine and public health
  - If not for vaccines, 300 million people would have died of vaccine-preventable diseases in the 20th century
  - Compare that with the 160 million people estimated to have been killed in all wars combined during the same period

Kimberlin DW. AAP News April 1, 2012;33:1.
Immunizations: A Public Relations Challenge

• When a vaccine works, the benefits are not “seen” (and thus are often taken for granted)

• When a vaccine fails or purportedly causes harm (whether real or perceived), the risks appear immediate and tangible

Kimberlin DW. AAP News April 1, 2012;33:1.
Fear of Vaccines > Fear of Diseases

- Although parental concerns vary, the underlying premise is fairly constant: fear that vaccines are unsafe in some way

  Benjamin Franklin was a prominent early anti-vaccination campaigner…

  But he regretted his skepticism after his 4-year old son died from smallpox

Healy CM, Pickering LK. *Pediatrics* 2011;127:S127-S133.
Immunizations: View from a Children’s Hospital

• Review a series of cases from our hospital that highlight where appropriate immunization of the individual and the community around them may have prevented morbidity and mortality
  • For some, anecdotes can be powerful tools for education
  • Reminder that these diseases still exist and can rear their ugly head if we become complacent

• Discuss approaches to dealing with vaccine-hesitant parents
Case #1: A 15-year-old teenage girl

- Presented with 3-4 days of fevers, chills, malaise, generalized body aches, severe throat pain, cough, and difficulty breathing
- Previously healthy but completely unimmunized
- Seen at outside ED and prescribed Vicodin and ibuprofen
- Returned to ED with fever, tachycardia, severe respiratory distress, and O2 saturation of 80%
- Transferred to PICU and promptly intubated and mechanically ventilated
Case #1:  
A 15-year-old teenage girl

- Diagnosis: Influenza A (H1N1) with bacterial superinfection with methicillin-susceptible *Staphylococcus aureus*

- Treatment: oseltamivir (x 10 days) and antibiotics (x 1 month)

- Clinical course: intubated x 9 days; hospitalized x 27 days

- Outcome: recovered (one lucky teenager)
## Influenza: Putting Things in Perspective

<table>
<thead>
<tr>
<th>Infection</th>
<th>Annual Number of Cases in US</th>
<th>Annual Number of Deaths in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola (2014 only)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Influenza</td>
<td>&gt;200,000 (hospitalizations)</td>
<td>23,607</td>
</tr>
</tbody>
</table>

Complications Among Children Hospitalized with Influenza (US, 2003-2010)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>28%</td>
</tr>
<tr>
<td>Asthma exacerbation (age ≥2 years)</td>
<td>22%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>21%</td>
</tr>
<tr>
<td>Intensive care</td>
<td>14%</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>5%</td>
</tr>
<tr>
<td>Positive bacterial culture (most commonly <em>Streptococcus pneumoniae</em> and <em>Staphylococcus aureus</em>)</td>
<td>2%</td>
</tr>
<tr>
<td>Lung abscess/empyema, tracheitis, encephalopathy, bacteremia/sepsis, acute renal failure, myocarditis</td>
<td>≤2% each (but 48-70% in intensive care)</td>
</tr>
<tr>
<td>Death</td>
<td>1%</td>
</tr>
</tbody>
</table>

Case #2: 23-day-old female infant

- Presented with 4 days of congestion, fever, cough and difficulty breathing
- Intubated at outside hospital and promptly transferred to PICU
- WBC 36,600 (S10, B8, L67)
- CXR normal
- Nasopharyngeal sample positive for Influenza A
Case #2: 23-day-old female infant

- Diagnosis: pertussis
- Treatment: azithromycin
- Clinical course: developed worsening respiratory distress, with apnea and bradycardia, necessitating high frequency oscillatory ventilation & then extracorporeal membrane oxygenation (ECMO)
- Outcome: expired on hospital day #3 (nasopharyngeal culture from admission turned positive for *Bordetella pertussis* two days after death)
Pertussis Epidemics in California

- 2010: 9,146 cases reported (most in 63 years)
  - 10 deaths reported (90% Hispanic, 90% <2 months of age and had not received DTaP)
- 2014: 10,831 cases reported (most in 70 years)
  - Highest rate in Hispanic infants <1 year of age
  - 2 deaths reported (both ≤5 weeks of age)
Pertussis Mortality

- Death from pertussis occurs rarely but young infants <6 months of age are most at risk.
- Risk factors for mortality:
  - Female sex
  - BW <2500 grams
  - Apgar <8
  - Mother with <12 years of education
  - Hispanic infant <2 mos old (2.6x higher mortality)

Tdap: Immunize Pregnant Women to Convey Protection to Young Infants

- Advisory Committee on Immunization Practices (CDC) in 2012 recommended Tdap for pregnant women with every pregnancy irrespective of previous Tdap history

- Optimal timing for Tdap between 27 and 36 weeks GA to maximize maternal antibody response and passive antibody transfer to the infant

- Tdap coverage rate only 29.5% in 2012-13 and only 6.2% during most recent pregnancy

- Of pertussis cases <4 mos of age in 2014 in CA whose maternal vaccination history available, only 16% received Tdap between 27-36 weeks gestation

Maternal antepartum Tdap results in higher concentrations of pertussis antibodies in infants during the first 2 months of life

Antibody Levels to Pertussis Toxin

Tdap: Immunize the Reservoir to Protect Most Vulnerable (Coccooning)

Source of Pertussis in Infants

Tdap: Immunize the Reservoir to Protect Most Vulnerable (Cocooning)

- Adolescents and adults who have or anticipate having close contact with infant <12 months of age should receive single dose of Tdap (at least 2 weeks before contact)

- Despite recommendations for universal Tdap, coverage was 86% among adolescents in 2013 and only 14.2% among adults in 2012

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6305a4.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6329a4.htm

Case #3:
8-month-old male infant

- Presented with fevers to 102 F and refusal to roll and to move right leg (recovered from URI 3 days prior)
- Previously healthy, immunizations up to date
- T 39.6 C, WBC 26.9, ESR 55, CRP 8.7
- X-ray showed lucency at the right proximal femoral metaphysis, suspicious for osteomyelitis
- Ultrasound revealed moderate effusion at right hip joint
Case #3: 8-month-old male infant

- Diagnosis: *Streptococcus pneumoniae* osteomyelitis and septic arthritis (positive in blood and synovial fluid cultures)
  - Nonsusceptible to: amoxicillin, penicillin, cefotaxime, and meropenem
  - Susceptible to: vancomycin and linezolid
  - Isolate identified as serotype 19A (patient had only received PCV7 x3)

- Treatment: 6 weeks of antibiotics

- Clinical course: underwent surgical drainage of hip (twice), hospitalized x 17 days

- Outcome: recovered
Impact of 7-valent pneumococcal conjugate vaccine on invasive pneumococcal disease among children <5 years old, 1998-2009

Moore, IDSA, 2009 & CDC Unpublished
Increase in IPD Caused by Non-PCV7 Serotypes

- 29% increase in IPD by non-PCV7 serotypes
  - 255% increase in IPD caused by serotype 19A between 1998-9 and 2004-5
  - 19A was the most common serotype causing IPD as of 2005

- Incidence of penicillin-nonsusceptible IPD by non-PCV7 serotypes increased by 195%
  - PCN-NS 19A causing IPD increased by 238%

MMWR. February 15, 2008 / 57(06);144-148.
How will things change with PCV13?

- PCV7 was a huge success, but emergence of nonvaccine serotypes (especially 19A) and drug resistance had been a growing concern.
- PCV13 includes protection against serotype 19A.
- With PCV 13, the same questions that followed the introduction of PCV7 remain relevant:
  - Will there be serotype replacement in NP colonization and subsequent disease?
  - Will resistance increase among nonvaccine serotypes?
Case #4: 3-year-old girl

- Presented with fever and runny nose for 6 days and cough for 2 days
- In past day, she also developed
  - Red rash starting on face and spreading to torso, then arms/palms
  - Red, irritated eyes and dry, cracked lips
- Returned from 3-week trip to Philippines 4 days ago (2 days into illness)
- No ill contacts and no past medical history
- Unimmunized (5-year-old sibling also unimmunized but 4 other siblings immunized)
Case #4: 3-year-old girl

• Diagnosis: measles
• Treatment: vitamin A
• Clinical course: discharged from hospital within 1 day
• Outcome: recovered without complications (yet)
Case #5: 9-year-old boy

- Presented with 3-week history of “being kind of slow,” “staring nowhere,” and twitching of head and shoulders spreading to the legs over the last 3 days
- No fever, rash or other symptoms
- Born in Philippines, where he had history of measles at 8 months of age
- MRI of brain showed diffuse white matter edema
- EEG revealed high-amplitude bursts with background suppression
Case #5: 9-year-old boy

- **Diagnosis:** subacute sclerosing panencephalitis (SSPE)
  - CSF measles IgG 1:64 and serum measles antibody high

- **Treatment:** experimental only (nothing proven)
  - Trial of IV ribavirin and PO isoprinosine
  - Family declined intraventricular injections of alpha-interferon

- **Clinical course:** hospitalized 23 days; worsening myoclonic jerks, difficulty eating and drinking, inability to speak

- **Outcome:** progressive decline
Measles: Making a Comeback in US

2000
Measles elimination in US (no endemic spread)

2014
644 Cases
23 Outbreaks

*Provisional data reported to CDC’s National Center for Immunization and Respiratory Diseases

www.cdc.gov/measles/
Measles Outbreak 2014-15

- On Jan 5, 2015: CDPH received report of:
  - Unvaccinated 11 year old hospitalized with suspected measles with only travel to Disneyland
  - 4 additional suspect measles cases in California residents and 2 in Utah residents – all had visited Disneyland between Dec 17-20

- When outbreak declared over on Apr 17, 2015: 131 cases among California residents (+cases in 6 other states)

http://www.cdph.ca.gov/HealthInfo/discond/Pages/Measles.aspx
Vaccination Status of US Measles Cases in 2015

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6414a1.htm
# Measles: Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>8%</td>
</tr>
<tr>
<td>Otitis media</td>
<td>7%</td>
</tr>
<tr>
<td>Lower respiratory tract infection (with/without bacterial superinfection)</td>
<td>1 in 20 (but with mortality up to 60%)</td>
</tr>
<tr>
<td>Acute encephalitis</td>
<td>1 in 1000 (15% develop rapidly fatal form; 25% of survivors have neurologic sequelae)</td>
</tr>
<tr>
<td>Death (usually from pneumonia or encephalitis)</td>
<td>2 in 1000</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis (onset 4-8 years after infection)</td>
<td>1 in 100,000 (death within 6-9 months, only 5-10% with spontaneous resolution)</td>
</tr>
</tbody>
</table>

http://www.cdc.gov/vaccines/pubs/pinkbook/meas.html#complications
Case #6:
3-year-old boy

- 3-year old presented with 1 day of diarrhea and 12 hours of repeated emesis, then developed fever
- Seen at outside hospital where progressive purpuric rash and hypotension noted
- Patient required intubation and vasopressor support and was transported to PICU
- Previously healthy and immunizations up to date
Case #6:
3-year-old boy

- Diagnosis: meningococcemia (with purpura fulminans) and meningococcal meningitis
- Treatment: antibiotics (parents and twin brother given antibiotic prophylaxis)
- Clinical course: shock, DIC, multi-organ system failure including renal failure, cardiac arrest, ECMO
- Outcome: brain dead/expired on hospital day #4
As family began preparing for funeral…

- Twin brother developed cough, nasal congestion and fever to 104°F along with 2 episodes of emesis
- Admitted for antibiotics and observation
- Fortunately, blood cultures negative and probable diagnosis of viral syndrome plus otitis media
- Question: would you offer meningococcal vaccine to this child?
- Parents’ response: “If there was a vaccine that could have prevented my child’s death, why wasn’t it offered before?”
Rates of Meningococcal Disease by Age Group and Burden of Disease, United States, Active Bacterial Core Surveillance System, 2003-2012

For more information visit: http://www.cdc.gov/abcs/index.html
# Meningococcal Vaccines

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Serogroups</th>
<th>Age Group</th>
<th>Dose(s)</th>
<th>Who?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menactra</td>
<td>A, C, W-135, Y</td>
<td>9 mos – 55 yrs</td>
<td>1-2 (2-55 yrs) 2 (9-23 mos)</td>
<td>Adolescents, o/w high risk only</td>
</tr>
<tr>
<td>Menveo</td>
<td>A, C, W-135, Y</td>
<td>2 mos – 55 yrs</td>
<td>1-2 (2-55 yrs) 4 (2 mos-2 yrs)</td>
<td>Adolescents, o/w high risk only</td>
</tr>
<tr>
<td>MenHibrix</td>
<td>C, Y (+Hib)</td>
<td>6 wks – 18 mos</td>
<td>4</td>
<td>High risk only</td>
</tr>
<tr>
<td>Trumenba</td>
<td>B (4 strains)</td>
<td>10 – 25 yrs</td>
<td>3</td>
<td>≥10 yrs if high risk</td>
</tr>
<tr>
<td>Bexsero</td>
<td>B (3 strains)</td>
<td>10 – 25 yrs</td>
<td>2</td>
<td>≥10 yrs if high risk</td>
</tr>
</tbody>
</table>

AAP Committee on Infectious Diseases. *Pediatrics* 2014;134:400-3.

http://aapnews.aappublications.org/content/early/2015/03/02/aapnews.20150302-1
The Benefits of Immunization

• **Individual**
  - Prevents morbidity (prolonged debilitation and hospitalization) and mortality
  - Benefits more tangible with those diseases that remain common (e.g. pertussis, influenza, pneumococcus, meningococcus, hepatitis A and B, rotavirus)

• **Society**
  - Creates herd immunity that protects the broader population
  - Protects the most vulnerable groups who cannot be vaccinated, such as young infants or the immunocompromised (e.g. pertussis, measles)
  - When immunization rates dip, it puts the entire community at risk
## Parental Concerns

<table>
<thead>
<tr>
<th>Concern</th>
<th>Origin</th>
<th>Reality</th>
</tr>
</thead>
</table>
2010: *Lancet* issued formal retraction  
2010: Wakefield found guilty of “serious professional misconduct” by UK |
| Thimerosal        | 1997 US FDA Modernization Act required quantification of mercury in all foods and drugs | Ethylmercury in thimerosal is different than methlymercury (t½: 7 days vs. t½: 50 days in body) |
| Immune overload   | Popularized in 2008 because of the case of Hannah Poling who had neurodevelopmental decline after 5 vaccines (but was found to have mitochondrial enzyme defect) | Immunogens in vaccines given in first 2 years of life have decreased over the decades (>3000 in 1960s to <300 in 2015) |
## Parental Concerns

<table>
<thead>
<tr>
<th>Concern</th>
<th>Origin</th>
<th>Reality</th>
</tr>
</thead>
</table>
| Aluminum (used as adjuvant for >70 years)                              | ?      | Aluminum exposure in first 6 months of life  
Breastfeeding: 7 mg  
Formula: 38 mg  
Soy formula: 117 mg  
Vaccines: 4.4 mg                                                                                                          |
| Formaldehyde (used to inactivate viruses and bacterial toxins)         | ?      | Normal by-product of protein/DNA synthesis  
Average 2 month old has 1.1 mg in their circulation vs. average exposure of ≤0.2 mg at one time from vaccines                                                                 |
Addressing Parental Concerns

- Establish a non-confrontational dialogue by acknowledging:
  - That the parent is trying to do their best for their child
  - The difficulties of the decision, especially given many conflicting sources of information

- Listen carefully to identify parental concerns around immunizations and target education appropriately

Healy CM, Pickering LK. *Pediatrics* 2011;127:S127-S133.
Vaccine Message Framing Studies: Does vaccine education help?

- Web-based nationally representative survey of 1759 parents
- Assessed vaccine attitudes and effect of 1 of 4 interventions:
  - Autism correction (correct misinformation)
  - Disease risks (present information on disease/vaccine risks)
  - Disease narrative (present dramatic narrative of child with measles)
  - Disease images (display visual images of children with each disease)

None of the interventions increased parental intent to vaccinate

- Providing information refuting MMR/autism link reduced the misperception but nonetheless decreased intent to vaccinate among parents who had the least favorable vaccine attitudes
- Dramatic narrative about an infant ill with measles actually increased concern about serious side effects from the vaccine

Conclusion: pro-vaccine education/messages may not be effective and, for some parents, may increase misperceptions or reduce vaccine intention

Vaccine Message Framing Studies: Does provider communication approach help?

- Cross-sectional observational study of parents with children aged 1-19 months old screened with Parent Attitudes about Childhood Vaccines survey
- Provider-parent vaccine discussions videotaped during health supervision visits
- Examined association between provider communication practices and parent resistance to vaccines

Vaccine Message Framing Studies: Communication approach used by provider

- Overall: 74% Presumptive, 26% Participatory
- Non-VHP: 89% Presumptive, 11% Participatory
- VHP: 59% Presumptive, 41% Participatory
Vaccine Message Framing Studies: Parental Resistance Rate by Provider Approach

<table>
<thead>
<tr>
<th>Resistance Rate</th>
<th>Overall</th>
<th>VHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumptive</td>
<td>26%</td>
<td>30%</td>
</tr>
<tr>
<td>Participatory</td>
<td>83%</td>
<td>89%</td>
</tr>
</tbody>
</table>
Vaccine Message Framing Studies: What if provider pursues initial recommendation in face of parental resistance?

Only 50% of providers pursued their initial plan.
Vaccine Message Framing Studies: Does emphasis on benefits help?

- National online survey of 802 parents of infants <12 months old
- Randomly assigned to receive 1 of 4 MMR vaccine messages
  - CDC’s Vaccine Information Statement (VIS) only
  - Vaccine’s direct benefit to child (+VIS)
  - Vaccine’s societal benefit (+VIS)
  - Vaccine’s benefit to both child and society (+VIS)

Vaccine Message Framing Studies: Does emphasis on benefits help?

Parents’ MMR Vaccine Intentions

- Benefits to Both + VIS: 90% (P = .03)
- Benefits to Child + VIS: 95% (P = .01)
- Benefits to Society + VIS: 85%
- VIS: 80%

Vaccine Message Framing Studies: Does emphasis on benefits help?

- Conclusions:
  - Providers should emphasize benefits directly to the child
  - Mentioning societal benefits seems to neither add value to nor interfere with information highlighting benefits directly to the child

What It Comes Down To: TRUST

- Health care providers are the most important influence in a parent’s final decision on immunizations
  - Use presumptive approach and be persistent
  - Emphasize direct benefits to the child
  - Scare tactics may backfire with some vaccine-hesitant parents

- Trusted resources for providers/parents:
  - Vaccine Education Center – Children’s Hospital Philadelphia
    - http://www.chop.edu/service/vaccine-education-center/home.html
  - Centers for Disease Control and Prevention