Effectiveness isn’t enough: Why we need to evaluate the impact of vaccines, and how we should do it

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Conflicts of Interest

• I have received ad hoc consulting fees from Pfizer, Merck, GSK, and Affinivax
• I am PI on a research grant from Pfizer to Yale
**Topics to discuss today**

- Vaccine effectiveness and its limitations
- Using effectiveness vs transmission to understand impact
- Estimating vaccine impact from messy real-world data

### Diagram

- **Ear/eye infections**
  - All-cause pneumonia
    - Lab-confirmed Pneumococcal Pneumonia
    - Outpatient
    - Death
  - IPD

- **Children's ages**
  - Age of Children, months

- **Deaths per 100,000 population**
  - 1-11 months

- **Timeline**
  - Jan-00, Jan-01, Jan-02, Jan-03, Jan-04, Jan-05, Jan-06, Jan-07, Jan-08, Jan-09, Jan-10, Jan-11, Jan-12, Jan-13
Direct effects, indirect effects, and vaccine impact

- **Direct effect**: benefit an individual receives from getting a shot (or their baby??)

- **Indirect effect**: benefit of vaccine that results from disrupting transmission
  - Adds to the benefit for *vaccinated* individuals
  - Provides a benefit to *unvaccinated* individuals and age groups

- Direct + indirect effect = total effect = **vaccine impact**
Effectiveness or impact: who is asking?

Licensure organizations

Public Health advisory panels

Mom and Dad

Does the vaccine have a biological effect in preventing disease caused by the targeted pathogen?

What is the reduction in disease rates and costs savings that we can expect from this vaccine?

How will this vaccine reduce my risk of developing disease?

**Effectiveness against a specific outcome**  
**Impact, effectiveness**  
**Effectiveness—against a non-specific outcome**
Effectiveness, against what?

Pneumococcus

- Ear/eye infections
- All-cause pneumonia
  - Lab-confirmed Pneumococcal Pneumonia
  - Hospitalized
  - Outpatient
- IPD
- Death
- Colonization/transmission
The importance of defining your outcome

Effectiveness: 49%
Incidence: 39.9 cases/100,000
Preventable Incidence: 19.7 cases/100,000
Cost effectiveness: $$

8%
891 cases/100,000
72.2 cases/100,000
$$$$

Feikin, Scott, and Gessner, *Lancet* 2014
Madhi and Klugman, *Vaccine*, 2007
Gessner et al, *Vaccine*, 2019
Limitations of effectiveness
The public health impact of PCVs depends on both the direct effect and indirect/herd effect that results from blocking transmission.

90% of the reduction in disease burden is in unvaccinated adults.
- Vaccine is effective against vaccine serotypes and disrupts transmission
- This leads to impact in unvaccinated age groups
- Impact in adults depends on effectiveness against colonization AND replacement
Policy question: Should adults in the US be vaccinated with PCV13 given the high rates of vaccination in children?
Trends in PCV13 serotypes in adults ≥65 years

Use of PCV13 in children reduced PCV13 serotypes by ~60%

Mostly serotype 3 remaining

Additional impact of introduction in adults not obvious, but estimate that still prevented >8400 cases of CAP/year in US based on VE

Pilishvili, Lessa
ACIP presentations
Oct 2018
Dan, should we get our “pneumonia shot”? 
What do Mom and Dad really want to know?

Is this vaccine going to protect me from *pneumonia*?

NOT

Is this vaccine going to protect me against pneumococcal pneumonia caused by a serotype that is included in PCV13, if I happen to be exposed to that serotype?
How much does PCV13 protect an adult who is immunized compared to someone who is unimmunized?

40% reduction in pneumococcal pneumonia caused by vaccine serotypes comparing vaccinated with placebo

Bonten et al NEJM
How much does PCV13 protect an adult who is immunized compared to someone who is unimmunized?

<table>
<thead>
<tr>
<th>Infection with any pneumococcal strain</th>
<th>Confirmed pneumococcal community-acquired pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-protocol analysis</td>
<td>244 100 144 30.6 (9.8 to 46.7) 0.008</td>
</tr>
<tr>
<td>Modified intention-to-treat analysis</td>
<td>309 135 174 22.4 (2.3 to 38.5) 0.05</td>
</tr>
</tbody>
</table>

20-30% reduction in pneumococcal pneumonia cause by any serotype comparing vaccinated with placebo

Bonten et al NEJM
How much does PCV13 protect an adult who is immunized compared to someone who is unimmunized?

Magnitude confirmed by CDC study (6-11% effectiveness) and re-analysis of CAPITA data (8.1% effectiveness)

5% reduction in pneumonia cause by any pathogen comparing vaccinated with placebo.

Bonten et al NEJM
Use of PCV13 in adults

- Has moderate effectiveness against *vaccine-targeted* serotypes
  - But vaccine-targeted serotypes are a small fraction of all CAP, so effectiveness against pneumonia is low
- But pneumonia is very common, so even low effectiveness might lead to a large savings in hospitalizations and cost
- But vaccine is very costly...
Effectiveness vs Impact?: It depends who you ask

CDC estimates PCV13 prevented >8400 cases of CAP/year in US based on VE*

PCV13 is effective and prevents lots of disease, even if impact is not obvious

So this vaccine will reduce my risk of pneumonia by 5-10%?

And it costs how much?!?

* Lessa, 2009 ACIP
Why is effectiveness not enough?

- For some stakeholders it is...
- Direct effect tells you the biological effect against a specified endpoint
- Can be misleading if not taken in the context of disease burden
- Serotype replacement can counteract some of the vaccine benefit
Part 2: Using data on direct effects on colonization to understand impact
Decline in IPD in unvaccinated age groups is *later* and *slower* than in children.
What could explain these patterns of indirect protection in adults?

- Need to reach some ‘critical threshold’ of coverage?
  - Critical thresholds needed for elimination, not for start of decline
- Need to wait until kids vaccinated as infants age into an older age stratum?
Intense transmission among toddlers, preschoolers

Navajo

Nurhonen PLOS one 2013

Finland
-44% of transmission events came from a child <7 years of age

Althouse et al, Epidemiol Infect 2017
Direct effect of PCVs is high against disease, lower against colonization

- Invasive pneumococcal disease
- Colonization

Vaccine effectiveness

- 1 primary dose
- 2 primary doses
- Booster dose

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Population direct effect on carriage

- Population direct effect: expected effect of vaccine on carriage of vaccine serotypes *if there was no effect on transmission*
- Calculate for different age groups based on age-specific uptake

Uptake of dose $i$ * Efficacy of dose $i$ * Rate of waning

**Provides a measure of vaccine uptake, adjusting for dose-specific effectiveness**
Population direct effect on carriage, by age

Weinberger et al., AJE 2019
Direct effect of vaccine against carriage in 36-60 month olds is best correlated with pneumococcal disease in adults

Weinberger et al., AJE 2019
Bonus observation:
Serotypes colonizing older kids (3-5 years) vs younger kids (<2 years) best correlates with IPD patterns in adults

- ST3 is 1.5 times as prevalent in older kids vs younger kids
- ST8 is a major emerging serotype in adults

Wyllie et al., in preparation
Individual-level vaccine status (infants) → Carriage of pneumococcus in the nasopharynx (infants) → Exposure of adults to pneumococcus → Pneumococcal disease in adults

Individual-level vaccine status (Toddlers) → Carriage of pneumococcus in the nasopharynx (toddlers) → Exposure of adults to pneumococcus → Pneumococcal disease in adults

Caption: "Exposure of adults to pneumococcus"
What do these analyses tell us?

- Effectiveness against colonization is useful to understand impact
  - Need to combine with information about dose-specific vaccine uptake, waning of immunity, correct age group of children

- Future trials evaluating VE against carriage could incorporate later timepoints to evaluate protection in kids who transmit
  - Could help to understand persistence of ST3 and replacement patterns
Part 3: Estimating vaccine impact from messy real world data
Challenges in estimating Impact

• ‘Pre-post’ comparisons can be biased by:
  – Short term epidemics due to RSV, influenza, others can obscure vaccine effects
  – Long term trends in underlying health, access to healthcare, etc can bias trends

• We are often evaluating non-specific endpoints (‘pneumonia’)
X-Ray confirmed pneumonia

Pneumococcal pneumonia

Clinical pneumonia

Hypoxic pneumonia

Mackenzie, Lancet ID 2018
Example 1: RSV epidemic masks the impact of PCV7/13 on radiologically-confirmed pneumonia

Ignore effect of RSV: vaccine impact through 2010/11 = -5%
Adjust for RSV: vaccine impact through 2010/11 = 28%

Weinberger et al., EID, 2013
Adjusting for broader trends

Step 1: Fit a regression model using data from the pre-vaccine data to establish a relationship between pneumonia and a control disease. 
E.g., \( \log(\text{pneumonia}) = b_0 + b_1 \log(\text{control disease}) \)

Step 2: Plug in observed value from control disease in post-vaccine period into the model and compare projected values with observed values to estimate impact.
Adjusting for broader trends: PCV impact in S. Africa

- PCV introduced against a background of increasing HAART use
- How do we tease out vaccine effect?
- Adjust for other causes of death in a regression model
- Data-driven ‘synthetic controls’ method to identify adjustment variables

Jackie Kleynhans, Cheryl Cohen, NICD
Data-driven selection of controls:
Infants: B50-B89: Protozoal diseases, Helminthiases, Pediculosis, acarasis, and other infestations

Older children and adults: A16-A19: Tuberculosis

Results robust to which specific controls were used to adjust trends

Jackie Kleynhans, Cheryl Cohen, NICD
Measuring impact

• Use of appropriate control conditions is critical to adjust for short and long term trends
• Data-driven methods can help identify the best control for each age group/population
Conclusions

- Impact vs effectiveness: depends who is asking
- Indirect protection is critical for evaluating vaccine programs
- Data on VE on colonization can help understand which risk groups drive vaccine impact
- Estimating Impact from real-world data is challenging but possible with appropriate statistical tools
Brief tangent for discussion: did the Novavax vaccine ‘fail’?

- 39% (97.5%CI, -1% to 64%) against medically significant RSV LRTI
- 44% (95%CI, 20% to 62%) against RSV LRTI hospitalizations
- 48% (95%CI, -8% to 75%) against RSV LRTI with severe hypoxemia

- Assignment as primary or secondary endpoints is arbitrary

In service of an arbitrary threshold, p-values often lead researchers to make poorly supported claims and ignore interesting but insignificant results, scientists argue.

- should be mechanism to synthesize these outcomes or evaluate them in totality
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Points for discussion
General points for discussion

• How do we evaluate multiple products or consider effects of previous vaccination status?
  – PPV23 history for pneumococcus, PCV13 history for PCV15/20
  – Brand-specific effectiveness for flu vaccines
  – Imprinting based on previous flu vaccines?
• In which risk groups do we evaluate effectiveness?
• Which public health agencies care about impact? Effectiveness?
Implications for influenza

• What endpoint do we care about?
  – Effectiveness against a specific subtype?
  – Effectiveness against any strain of influenza?
  – Effectiveness against Influenza-like illness or pneumonia?

• How do we measure effectiveness?
  – Test-negative design?
  – Randomization?

• How do we measure impact for influenza?
  – Epidemic disease, variable intensity by year and location
Effectiveness, against what?

Influenza

- All-cause pneumonia
- Flu pneumonia
- Death
- Lab-confirmed
- Outpatient
- Hospitalized
- ILI
Implications for RSV

• What endpoint do we care about?
  – Effectiveness against lab-confirmed RSV
  – Effectiveness against bronchiolitis
  – Outpatient vs inpatient?
  – Other secondary endpoints like asthma?

• Novavax: Medically-significant RSV vs RSV hospitalization
Effectiveness, against what?

RSV

- All-cause pneumonia
- Hospitalized
- Lab-confirmed
- Death
- Bronchiolitis
- Asthma?
Some reading


• Bruhn et al. Estimating the population-level impact of vaccines using synthetic controls. PNAS 2017 Feb 14;114(7):1524-1529
Extra slides
Correlation of *carriage prevalence* in different groups of kids and IPD in adults
How do we measure direct effects?

- Individually-randomized RCTs
- Post-licensure/Phase 4 studies with ‘real-world’ data
  - Case control studies
  - Test negative design
  - Broome method
  - Correlates of protection vs pathogen endpoints

[Diagram: Database linkage in Finland]

Baam, Euro Surveill 2017