Vaccine Efficacy, Effectiveness and Impact

G. HANQUET, KCE, 9 September 2017
Outline

- The confusion
- Vaccine effects
- Methodologies
- Challenges
- Implications for decision making
"Prior to licensure, a vaccine must demonstrate its safety and **efficacy** in phased clinical trials.

Postlicensure, continued close monitoring of the vaccine safety and **effectiveness** is needed"

Chen (WHO), 1996

"WHO recommends an assessment of the **impact** of programme-based introduction (of PCV or HibCV)"

WHO, 2012
Efficacy, effectiveness or impact?

Efficacy of 7-valent pneumococcal conjugate vaccination in Germany: An analysis using the indirect cohort method
Simon Rückinger*, Mark van der Linden*, Ralf René Reinert, Rüdiger von Kries

Impact of the 10-valent pneumococcal non-typeable Haemophilus influenzae Protein D conjugate vaccine (PHID-CV) on bacterial nasopharyngeal carriage
Roman Pyruma*, Irena Havocová*, Miroslav Siplí*, Pavla Kríž, Jitka Motlova*, Vera Lebedova*, Patricia Lommel², Eva Kalisková², Thierry Pascal², Dorota Borys², Lode Schuereman³

Efficacy of RIX4414 Live Attenuated Human Rotavirus Vaccine in Finnish Infants
Timo Vestikari, MD.*, Aino Karvonen, MD.*, Leena Puustinen, MS.*, Shang-Qin Zeng, MD.*, Evelyn Dora Szakal, MS.*, André Delem, MS,† and Beatrice De Vos, MD†

Impact of rotavirus vaccination on laboratory confirmed cases in Belgium
Germaine Hanquet*, Geneviève Ducoffre*, Anne Vergison⁵, Pieter Neels d,e, Martine Sabbe⁵, Pierre Van Damme⁵, Koen Van Herck⁵,g

Impact and effectiveness of meningococcal C conjugate vaccine following its introduction in Spain
Amparo Larrauri *, Rosa Cano, Martina García, Salvador de Mateo

Herd Protection by a Bivalent Killed Whole-Cell Oral Cholera Vaccine in the Slums of Kolkata, India
Mohammed Ali², Dijiba Sul¹, Rojay De You¹, Sumon Karanza¹, Biswas Sab¹, Gaurav Behari Murali², Mahesh Pandi², Thomas F. Werts¹, Alika Bonner², G. R. Babuwar², Shigir K. Bhattacharya², Manish C. Singh Wujara², Jyoti Bhattacharya², Anina Lena Leger³,° and John Cleare³,°

Effectiveness of Intranasal Live Attenuated Influenza Vaccine Against All-cause Acute Otitis Media in Children
Terho Heikkinen, MD, PhD,链, Suvi L. Block, MD,链, Seth L. Toback, MD,链, Xiaoyu Hu, PhD,链, and Christopher S. Ambrose, MD

Effectiveness of Serogroup C Meningococcal Polysaccharide Vaccine: Results from a Case-Control Study in Quebec
Philippe De Wolfs,链, Geneviève Becqueminck,链, Gaston De Serres,链, Jean-François Boivin,链, Bernard Duval,链, Robert Ronis,链, and Richard Mescon,链

Effects of Pneumococcal Conjugate Vaccine 2 Years after its Introduction, the Netherlands
Gerwin D. Rodenburg¹, Sabine C. de Greeff², Angelique G.C.S. Jansen¹, Hester E. de Melker³, Leo M. Scholtes¹, Eeiko Hak, Lodewijk Spanjaard, Elisabeth A.M. Sanders¹, and Arije van der Ende³

Early effectiveness of heptavalent conjugate pneumococcal vaccination on invasive pneumococcal disease after the introduction in the Danish Childhood Immunization Programme

Effectiveness of a 2+1 dose schedule pneumococcal conjugate vaccination programme on invasive pneumococcal disease among children in Norway
Didrik F. Vestreheim*, Øistein Løvoll, Ingeborg S. Aaberge, Dominique A. Cauquant, E. Arne Heiby, Hilde Bakke, Marianne R. Bergsaker

Division of Infectious Disease Control, Norwegian Institute of Public Health, Norway
# Existing definitions

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Definitions as stated by the following agencies</th>
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<tbody>
<tr>
<td><strong>Vaccine efficacy</strong></td>
<td>EMA(^{11})</td>
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<td></td>
<td>Reduction in the chance of developing the disease after vaccination <strong>relative to the chance in unvaccinated</strong> as determined in a prospective <strong>randomised controlled study</strong>.</td>
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<td><strong>Vaccine effectiveness</strong></td>
<td>WHO(^{12})</td>
</tr>
<tr>
<td></td>
<td>Reduction in the chance or odds of developing clinical disease after vaccination relative to the chance or odds when unvaccinated. Vaccine efficacy measures <strong>direct protection</strong> (i.e. protection induced by vaccination in the vaccinated population sample).</td>
</tr>
<tr>
<td><strong>Vaccination impact</strong></td>
<td>CDC(^{21})</td>
</tr>
<tr>
<td></td>
<td>The ability of a vaccine to provide protection against disease under ideal circumstances (e.g. <strong>during a clinical trial</strong>).</td>
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<tr>
<td><strong>None found</strong></td>
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</table>

**Vaccination impact** None found

**Comparing the burden of disease** caused by the pathogen included in the vaccine, in a population that has received the vaccine, to the burden of disease in a population that has not received the vaccine. \(^{15}\)
Vaccine effects

- **Direct effect:**
  - Protection in vaccinated persons only
  - Induced by individual vaccination

- **Indirect effect:**
  - Effect of a vaccination programme
  - At population level, including non-vaccinated
Direct effect

- Depends on vaccine and host characteristics
- Compares disease in vaccinated to disease in and unvaccinated in one population
- Measured in clinical trials or in real life
  - **Efficacy**: protection measured in clinical trials
    - Ideal conditions of administration
    - Selected subjects (e.g. underlying diseases often excluded)
  - **Effectiveness**: protection if measured in real life situation
    - Routine vaccination, including incomplete schedule, delayed administration
    - Any person of the target group
Herd effects or indirect

Effect of widespread vaccination: protection by reduced transmission in the population, when large proportions are vaccinated

Figure 1. Diagram illustrating transmission of an infection with a basic reproduction number $R_0 = 4$ (see Table 1). A, Transmission over 3 generations after introduction into a totally susceptible population (1 case would lead to 4 cases and then to 16 cases). B, Expected transmissions if
Two vaccine exposures

- **Individual vaccination**
  Direct effect only

- **Vaccination programme**
  Direct + indirect effect

Effect of programme > sum of effects of vaccination on vaccinated

- If there is an indirect effect
How to measure vaccine effects?

Adapted from Halloran et al.

$R_{1V}$: rate in vaccinated group from population 1  
$R_{1u}$: rate in unvaccinated group from population 1  
$R_{2u}$: rate in (unvaccinated) from population 2  
$R_{1ave}$: average rate in population 1 (vaccinated and unvaccinated combined)  

$VE_{direct} = 1 - \frac{R_{1V}}{R_{1u}}$  
$VE_{indirect} = 1 - \frac{R_{1u}}{R_{2u}}$  
$VE_{total} = 1 - \frac{R_{1ave}}{R_{2u}}$
Direct effect

Direct effect of vaccination on those vaccinated
- Exposure = individual vaccination
- Vaccinated vs. non vaccinated, same population

Methods: study design must cancel the indirect effect of programme:
- cohort studies (from same population)
- case control studies
- screening methods
- Broome method

\[ VE_{direct} = 1 - \frac{AR_{1v}}{AR_{1u}} \]

Same population

Controls have same exposure/coverage than population giving rise to cases
An example of direct effect

- Case control for influenza vaccines

Samples positive (cases; n = 1,155) and negative (controls; n = 2,686) for influenza A and B according to vaccination status and vaccine effectiveness estimates, United Kingdom, October 2015–May 2016

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Crude VE (95% CI)</th>
<th>Adjusted VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influenza A or B</strong></td>
<td>165</td>
<td>990</td>
<td>55.1 (45.0–62.7)</td>
<td>52.4 (41.0–61.6)</td>
</tr>
<tr>
<td><strong>Influenza A(H3N2)</strong></td>
<td>112</td>
<td>658</td>
<td>54.1 (43.7–63.7)</td>
<td>54.5 (41.6–64.5)</td>
</tr>
<tr>
<td><strong>Influenza A/68</strong></td>
<td>45</td>
<td>232</td>
<td>68.2 (28.8–62.8)</td>
<td>48.0 (26.4–64.5)</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>308</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Influenza B</strong></td>
<td>43</td>
<td>308</td>
<td>62.4 (47.7–73.0)</td>
<td>54.2 (33.1–68.6)</td>
</tr>
<tr>
<td><strong>Influenza B/ Victoria</strong></td>
<td>21</td>
<td>161</td>
<td>65.2 (44.6–78.0)</td>
<td>57.3 (28.4–74.6)</td>
</tr>
</tbody>
</table>

CI: confidence interval; RCGP: Royal College of General Practitioners Research and Surveillance Centre; VE: vaccine effectiveness.

* Adjusted for age group, sex, month, pilot area and surveillance scheme.

* Based only on data from RCGP and Scotland only.

Valenciano Vaccine 2010 and Pebody Eurosurv 2016
Indirect, total and overall effect

Comparing two separate but similar populations, one with vaccination, the other without:

- **Vaccinated persons:** total effect
- **Non-vaccinated:** indirect effect
- **All persons:** overall effect

**Design:**

- Population separated by time or place
  - Pre and post-vaccine comparison (time)
- Cluster randomized trials
- Statistical or mathematical modelling
Impact of vaccination programme

WHO: correspond to overall effect

Vaccination programme

Total population being compared

Hanquet, Vaccine 2011
## Major confusion: direct and overall

<table>
<thead>
<tr>
<th>Direct effect</th>
<th>Overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>of <strong>individual vaccination</strong></td>
<td>of a <strong>vaccination programme</strong></td>
</tr>
<tr>
<td>on <strong>vaccinated persons</strong></td>
<td>in a <strong>population</strong>, in which a fraction only is vaccinated</td>
</tr>
<tr>
<td>Pre or post-licensure</td>
<td>Post-licensure only</td>
</tr>
<tr>
<td>Does not include indirect effect</td>
<td>Direct + indirect effects</td>
</tr>
<tr>
<td></td>
<td>Potentially replacement disease</td>
</tr>
<tr>
<td>Compares groups from same population</td>
<td>Compares 2 populations</td>
</tr>
<tr>
<td>Need to know vaccine status</td>
<td>No need to know vaccine status</td>
</tr>
</tbody>
</table>

For PCV7, in clinical trials:
- 94-97% on vaccine types
- 89% on all IPD cases

Whitney NEJM 2003

For PCV7, in US in <2 years:
- 78% on vaccine types
- 69% on all IPD

Black PIDJ 2000
Efficacy, effectiveness or impact?

Vaccinated vs unvaccinated, same population

- **In clinical trials**
  - Efficacy of RIX4414 Live Attenuated Human Rotavirus Vaccine in Finnish Infants
    - Timo Vestikari, MD,* Aino Karvonen, MD,* Leena Puustinen, MS,* Shang-Qin Zeng, MD,* Evelyn Dona Szakal, MS,* Andrée Delem, MS,* and Beatrice De Vos, MD†
  - Effectiveness of Intrasanal Live Attenuated Influenza Vaccine Against All-cause Acute Otitis Media in Children
    - Terho Heikkonen, MD, PhD* Sue L. Block, MD† Seib L. Toback, MD,‡ Xiaohua Wu, PhD,‡ and Christopher S. Ambrose, MD‡

- **In real life setting**
  - Impact of the 10-valent pneumococcal non-typeable Haemophilus influenzae Protein D conjugate vaccine (PHID-CV) on bacterial nasopharyngeal carriage

Two populations: one vaccinated vs other unvaccinated

  - Elizabeth Koshy, Joanna Murray, Alex Bottle, et al.
  - Thorax 2010 65: 770-774
  - doi: 10.1136/thx.2010.137802

- Impact of rotavirus vaccination on laboratory confirmed cases in Belgium
  - Germaine Hanquet,‡, Geneviève Ducroître,‡, Anne Vergison,‡, Pieter Neels,‡, Martine Sabbe,‡, Pierre Van Damme,‡, Koen Van Herck,‡

- Effectiveness of a 2+1 dose schedule pneumococcal conjugate vaccination programme on invasive pneumococcal disease among children in Norway
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  - Division of Infectious Disease Control, Norwegian Institute of Public Health, Norway

**Measured in:**
- vaccinated: total
- non-vaccinated: indirect
- all: overall
Methodological challenges

Assumption: "all other things being equal"

Same distribution among vaccinated and non-vaccinated
- Equal probability to be exposed to infection
- Equal susceptibility to the disease: probability of being vaccinated independent from the probability of developing the disease
- Equal probability to be detected and reported

When comparing two populations, they should have:
- Similar baseline transmission
- Similar characteristics of population and cases
- Similar medical practices / other interventions
- Similar case detection, reporting and data collection

Part of confounders can be addressed by adjustment in analysis
An example: rotavirus

**Table 3.** Rotavirus Vaccine Effectiveness Estimates Against Rotavirus Gastroenteritis Hospitalization\(^\circ\) in US Commercially Insured Infants and Children 8–20 Months of Age, 2007–2010

<table>
<thead>
<tr>
<th>Calendar Year by Effectiveness</th>
<th>Vaccinated With (\geq 1) Dose of RV5 or RV1, %</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
<th>Total (Vaccinated and Unvaccinated)</th>
<th>Vaccine Effectiveness(^b)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Direct effectiveness</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>2007</td>
<td>51.3</td>
<td>3</td>
<td>68,380</td>
<td>87</td>
<td>58,96</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>65.9</td>
<td>23</td>
<td>175,890</td>
<td>87</td>
<td>80,92</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>80.3</td>
<td>22</td>
<td>250,035</td>
<td>87</td>
<td>87,95</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>85.9</td>
<td>8</td>
<td>254,377</td>
<td>87</td>
<td>75,96</td>
<td></td>
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<tr>
<td>Indirect effectiveness</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>2007</td>
<td>51.3</td>
<td></td>
<td>60</td>
<td>14</td>
<td>–14,36</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>65.9</td>
<td></td>
<td>91</td>
<td>44</td>
<td>30,55</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>80.3</td>
<td></td>
<td>74</td>
<td>50</td>
<td>24,53</td>
<td></td>
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<tr>
<td>2010</td>
<td>85.9</td>
<td></td>
<td>13</td>
<td>82</td>
<td>70,90</td>
<td></td>
</tr>
<tr>
<td>Total effectiveness</td>
<td></td>
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<td>63</td>
<td>40</td>
<td>20,54</td>
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<tr>
<td>2008</td>
<td>65.9</td>
<td></td>
<td>114</td>
<td>75</td>
<td>69,79</td>
<td></td>
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<tr>
<td>2009</td>
<td>80.3</td>
<td></td>
<td>96</td>
<td>83</td>
<td>79,86</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>21</td>
<td>96</td>
<td>93,97</td>
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Implication for decision making

For vaccine authorisation (efficacy)

First information available when deciding to introduce a vaccine

Depends on:
1. The vaccine
   • Type of vaccine
   • Vaccine schedule and age
2. The host:
   • Immune response
   • Pre-existing immunity

Depend on:
1. The vaccination programme:
   • Type of vaccine (prevents transmission)
   • Proportion vaccinated (uptake)
   • Vaccine schedule (number doses) and age
2. The population:
   • Social contact patterns, high transmitters
3. The pathogen:
   • Modes and intensity of transmission

Represent the real public health benefit

To achieve wide reduction of disease

To protect population not responding well (elderly, neonates)
Conclusions

1. The type of effect to measure depends on the question
   - Regulatory (efficacy) vs. public health decision (impact)
2. Direct effect is the main information when deciding on a vaccine, but overall effect represents best the public health benefit of a vaccination programme
3. Effectiveness and impact measures are less robust than efficacy, but more representative of the real life
4. To know which effect has been measured in a study, need to assess which populations and groups are being compared
Thank you

If enough people are vaccinated against a disease (typically 83–85%), it has trouble spreading. This protects people who are not vaccinated, either because they are too young or have an allergy or other underlying medical condition.

In herd immunity, the vaccinated protect the unvaccinated.