PRAGMATIC CLINICAL TRIALS IN VACCINE EVALUATION

Arto A. Palmu, Chief Research Officer, Finnish Vaccine Research Center Finvac, Finland

Future Clinical Trials – from tomorrow to 2030 – Why choose the Nordics?
Helsinki, June 8, 2022
FINNISH VACCINE RESEARCH CENTER FINVAC LTD

- Rokotetutkimuskeskus Finvac Oy - Vaccinforskningscentralen Finvac Ab
- VAT 3256659-4 / FI32566594
- Home municipality TAMPERE (Finvac oy, Technopolis Asemakeskus, Peltokatu 26, 33100 Tampere)
- Formed via a merger of
  - Tampere University Vaccine Research Center and
  - THL clinical vaccine research group
  - Transfer of businesses/operations expected after the summer (operational Q3/2022)
- Owned by:
  - 51% State of Finland
  - 49% Tampere University Foundation sr.
- Website opened at www.finvacresearch.com

Pragmatic clinical trials

June 8, 2022
DISCLOSURE

My previous employer, The Finnish Institute for Health and Welfare (THL) has endorsed public-private partnership and has received research funding

- From Sanofi Pasteur
- From GlaxoSmithKline Biologicals SA
- From Pfizer Inc.

AA Palmu

Investigator in the research projects above
No other personal conflict of interest

Finnish Vaccine Research Center Finvac will collaborate with all major vaccine manufacturers

Pragmatic clinical trials

June 8, 2022
NEED OF PHASE IV EVIDENCE FOR VACCINES

- Effectiveness in real life circumstances, not only licensure studies
- Earlier licensure of vaccines with post-licensure commitments
- Different target groups, dosing schedules, combinations
- Indirect impact of vaccination programmes
- Long-term effects
- Rare adverse reactions
- Data for cost-effectiveness evaluations
- Data for mathematical modeling
Vaccines are at their best when implemented as large-scale vaccination programmes. Therefore, vaccines should be considered primarily as important public health tools.

The most important public health outcome, and thus critical in decision-making, is the absolute net reduction in overall disease burden.

Therefore, all reduction in disease should be measured.

Thus, sensitivity is more important than specificity.
CHALLENGES IN PHASE IV VACCINE RESEARCH

Design selection
- High vaccination coverage: cohort and case-control studies problematic
- Ecological before-after comparison susceptible to secular trends and changes in time (access to care, diagnostics, treatment resources, health care organization, other interventions, risk factors, demographics, etc. ...)

Bias
- Selection bias
- Confounding (by indication)
- Healthy vaccinee bias
- Misclassification (sensitivity/specificity)
- Heterogeneity (lack of standardization)
- Publication bias
- Lack of precision for rare outcomes

Pragmatic clinical trials
REGISTERS PROVIDE OPPORTUNITIES FOR PHASE IV RESEARCH

Large populations (low selection bias, adequate power)
Long-term follow-up feasible (indirect effects, waning, adequate power)
Documentation of routine care (generalizability)

BUT

Data available based on the purpose of the (administrative) register

Misclassification (sensitivity/specificity)

Heterogeneity
  - lack of standardization
  - high number of service providers

Confounding (by indication)

Differences in access to care
REAL-WORLD EVIDENCE STUDIES ENABLED BY EXCEPTIONAL INFRASTRUCTURE IN FINLAND

Data are nationwide, complete, real-time, linkable, affordable = UNIQUE

- **Digital and Population Data Services Agency** Digi- ja väestötietovirasto, [www.dvv.fi](http://www.dvv.fi) Real-time population data
- **Finnish Institute for Health and Welfare** Terveyden ja hyvinvoinnin laitos (THL) [www.thl.fi](http://www.thl.fi)

  Finnish National Infectious Diseases Register; Care Register for Health Care (hospital discharge register, HILMO), Register of Primary Health Care visits (AvoHILMO); Medical Birth Register, Cancer register, etc.

- **The Social Insurance Institution of Finland** Kansaneläkelaitos (KELA) [www.kela.fi](http://www.kela.fi)

  Kanta archive (national patient data repository) and data on purchases of prescription medicines, reimbursement for medicine expenses, cost of examinations and treatments, rehabilitation, sickness allowance, pensions, etc.

- **Statistics Finland Tilastokeskus** [www.stat.fi](http://www.stat.fi) Cause of deaths, Background information

+ national health insurance, public health care, universally accessible health services, skilled personnel and citizen’s trust

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Pragmatic clinical trials

June 8, 2022
SOLUTION: PRAGMATIC RANDOMIZED CLINICAL TRIALS

to evaluate the effectiveness of interventions in real-life routine practice conditions

1) RCT, the gold standard for proving causality
   Randomization will
   - Control all confounding, known and unknown
   - Facilitate blinding to assure balanced misclassification - Symmetric if present

2) Registers allow the long-term follow-up in a feasible manner

3) Collaboration with healthcare organizations allows large sample size
EXAMPLES OF **PRAGMATIC VACCINE TRIALS**
USING NATIONAL REGISTER DATA

**FinIP vaccine trial** 2008-2018 [www.finip.fi](http://www.finip.fi) in collaboration with GSK
- Pneumococcal conjugate vaccination in the infants
- Largest of its kind globally (N=47 000)
- Widely published 2013 to 2018 [Publications](#)

**FinFluHD vaccine trial** 2019- in collaboration with Sanofi Pasteur
- Influenza vaccine trial in the elderly
- Protocol: Am Heart J 2021 Jul;237:54-61
- The biggest vaccine trial of the modern era (N=121 000 planned), 33 000 enrolled in 2019-2020 influenza season
- Study discontinued in April 2022 due to the ongoing COVID-19 pandemic
**FINNISH INVASIVE PNEUMOCOCCAL DISEASE VACCINE EFFECTIVENESS TRIAL DESIGN**

- Phase III/IV cluster-randomized, double-blind trial in children <19 months of age at enrolment
- Vaccines
  - 10-valent PHiD-CV (GSK) in two thirds of clusters (N=52) OR hepatitis B or A vaccine as control in one third of clusters (N=26)
- GlaxoSmithKline as sponsor
- Conducted nationwide 2009 to 2011, follow-up until 2018
- Over 47,000 children enrolled in total
- Passive outcome follow-up from national health registers

### THE DISEASE BURDEN CAUSED BY *S. PNEUMONIAE* IN INFANTS AND THE VACCINE PREVENTABLE DISEASE INCIDENCES (VPDI)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>VE 3+1/2+1 95% Cis</th>
<th>Incidence per 100 000 Control 3+1/2+1</th>
<th>VPDI per 100 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPD (invasive pneumococcal disease) ¹</td>
<td>94% 77 to 99</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>Data: National Infectious diseases register</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-laboratory-confirmed IPD ²</td>
<td>50% 32 to 63</td>
<td>422</td>
<td>207</td>
</tr>
<tr>
<td>Data: National hospital discharge register (HILMO)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia ³</td>
<td>26% 8 to 41</td>
<td>1262</td>
<td>341</td>
</tr>
<tr>
<td>Data: National hospital discharge register (HILMO)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tympanostomy tube placement ⁴</td>
<td>13% -2 to 26</td>
<td>7887</td>
<td>1100</td>
</tr>
<tr>
<td>Data: KELA reimbursement register and HILMO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimicrobial purchases ⁵</td>
<td>8% 1 to 14</td>
<td>154900</td>
<td>11800</td>
</tr>
<tr>
<td>Data: KELA reimbursement register</td>
<td></td>
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</tr>
</tbody>
</table>

**Outcomes**

1. Palmu et al. Lancet 2013
3. Kilpi et al. Vaccine 2018
5. Palmu et al. Lancet Inf Dis 2014

VE, Vaccine Effectiveness; CI, Confidence Interval; VPDI, Vaccine-Preventable Disease Incidence; IPD, Invasive Pneumococcal Disease; AOM, Acute Otitis Media.
Number needed to vaccinate to prevent one event during two-year follow-up: FinIP trial

<table>
<thead>
<tr>
<th>Disease</th>
<th>NNV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory-confirmed IPD</td>
<td>671</td>
</tr>
<tr>
<td>Non-laboratory-confirmed IPD</td>
<td>238</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>185</td>
</tr>
<tr>
<td>Tympanostomy tube placement</td>
<td>44</td>
</tr>
<tr>
<td>Antimicrobial purchase</td>
<td>5</td>
</tr>
<tr>
<td>Any of the outcomes above</td>
<td>4</td>
</tr>
</tbody>
</table>

2(3)+1 vaccine doses for infants

Palmu AA, et al. Vaccine. 2018
ADDITIONAL OPPORTUNITIES TO AUGMENT RESEARCH
Access to patient file data: National Electronic Patient Data Repository (KANTA) and data lakes

From Jan 1, 2023 in 21 wellbeing services counties

both primary and specialized care
BIOBANKS: ADDITION OF LINKED GENOME DATA

**FinnGen** is a large public-private partnership aiming to collect and analyse genome and health data from 500,000 Finnish biobank participants. A gateway to personalized medicine projects.

**Fingenious®** is a digital portal that functions as the one-stop window to samples and biodata of Finnish public biobanks.
FINNISH VACCINE RESEARCH CENTER FINVAC WILL CONTINUE THE THL STRATEGY FOR PRAGMATIC CLINICAL TRIALS

Public health perspective
- Total effects, long-term effects, full population effects

The best possible design
- Large phase III and IV comparative randomized trials (RCT)

Use of national competition factors
- Collaboration with health care providers, register follow-up
FINVAC – PHASE I TO PHASE IV, WITH EXTENSIVE EXPERIENCE AND DOCUMENTED PERFORMANCE

WWW.FINVACRESEARCH.COM