PRAGMATIC CLINICAL TRIALS IN VACCINE EVALUATION

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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

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

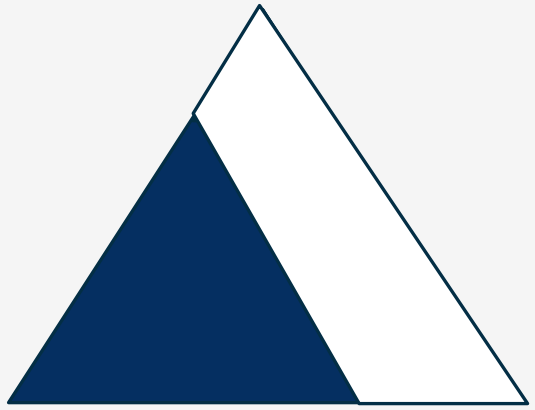
- Finnish Vaccine Research Center Finvac will collaborate with all major vaccine manufacturers

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

THE PUBLIC HEALTH PERSPECTIVE

- 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

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 Real-time population data
  - **Finnish Institute for Health and Welfare** Terveyden ja hyvinvoinnin laitos (THL) 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
    - 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 Cause of deaths, Background information

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

SOLUTION: PRAGMATIC RANDOMIZED CLINICAL TRIALS

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

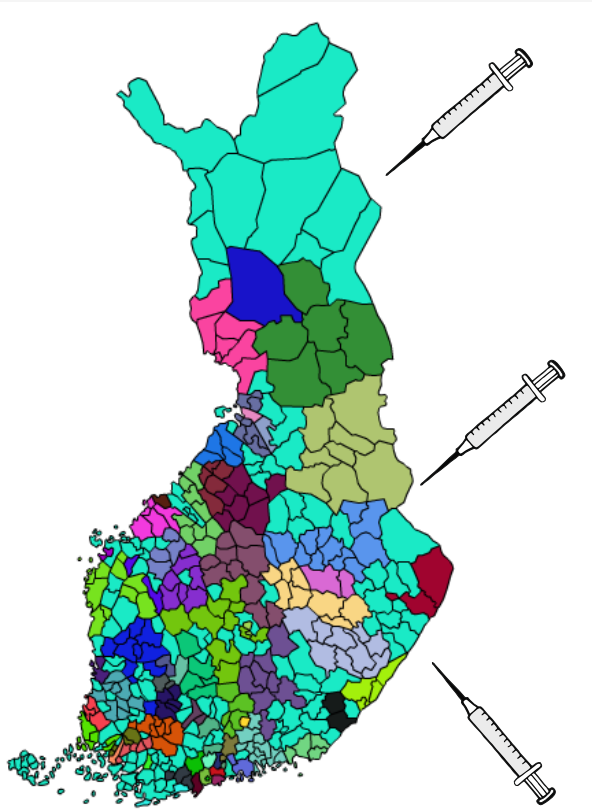
2) 1) RCT, the gold standard for proving causality
    1) Randomization will
        1) Control all confounding, known and unknown
        2) Facilitate blinding to assure balanced misclassification - Symmetric if present
3) 2) Registers allow the long-term follow-up in a feasible manner
4) 3) Collaboration with healthcare organizations allows large sample size
5)

EXAMPLES OF **PRAGMATIC VACCINE TRIALS** USING NATIONAL REGISTER DATA

- FinIP vaccine trial 2008-2018 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 **I**NVASIVE **P**NEUMOCOCCAL 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**



Palmu et. al. Lancet 2013;381:214–22

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

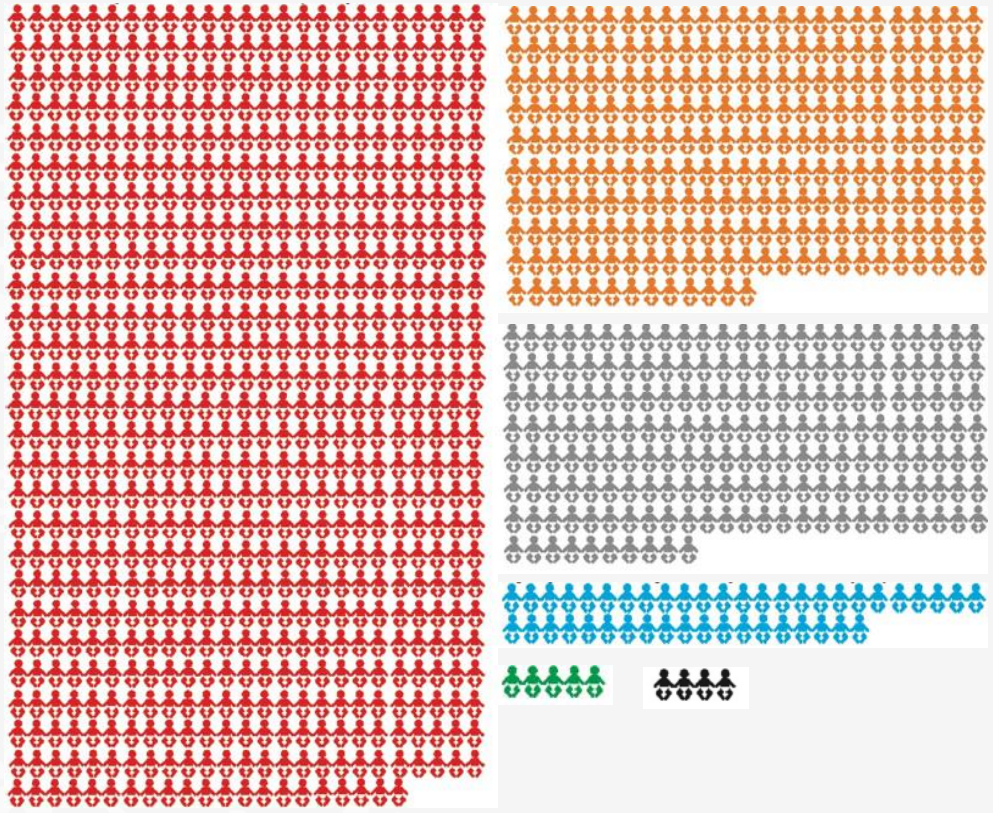
Outcomes	VE 3+1/2+1 95% CIs	Incidence per 100 000 Control 3+1/2+1	VPDI per 100 000
IPD (invasive pneumococcal disease) [1] Data: National Infectious diseases register	94% 77 to 99	80	75
Non-laboratory-confirmed IPD [2] Data: National hospital discharge register (HILMO)	50% 32 to 63	422	207
Pneumonia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

Palmu AA, et al. Vaccine 2018

VE, Vaccine Effectiveness; CI, Confidence Interval; VPDI, Vaccine-Preventable Disease Incidence; IPD, Invasive Pneumococcal Disease; AOM, Acute Otitis Media.

Original data published: [1]Palmu et al. Lancet 2013, [2]Palmu et al. Lancet Resp Med 2014, [3]Kilpi et al. Vaccine2018, [4]Palmu et al. Pediatr Inf Dis J 2015, [5]Palmu et al. Lancet Inf Dis 2014

Number needed to vaccinate to prevent one event during two-year follow-up: FinIP trial



Disease	NNV
Laboratory-confirmed IPD	671
Non-laboratory-confirmed IPD	238
Pneumonia	185
Tympanostomy tube placement	44
Antimicrobial purchase	5
Any of the outcomes above	4

2(3)+1 vaccine doses for infants

Palmu AA, et al. Vaccine. 2018

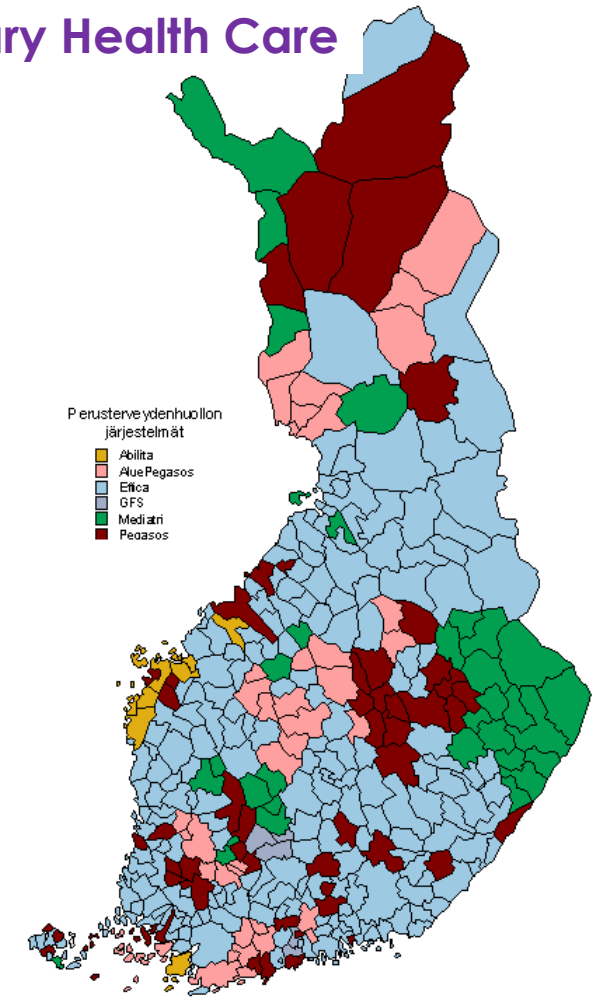
ADDITIONAL OPPORTUNITIES TO AUGMENT RESEARCH

Access to patient file data:
National Electronic Patient Data Repository (KANTA) and data lakes

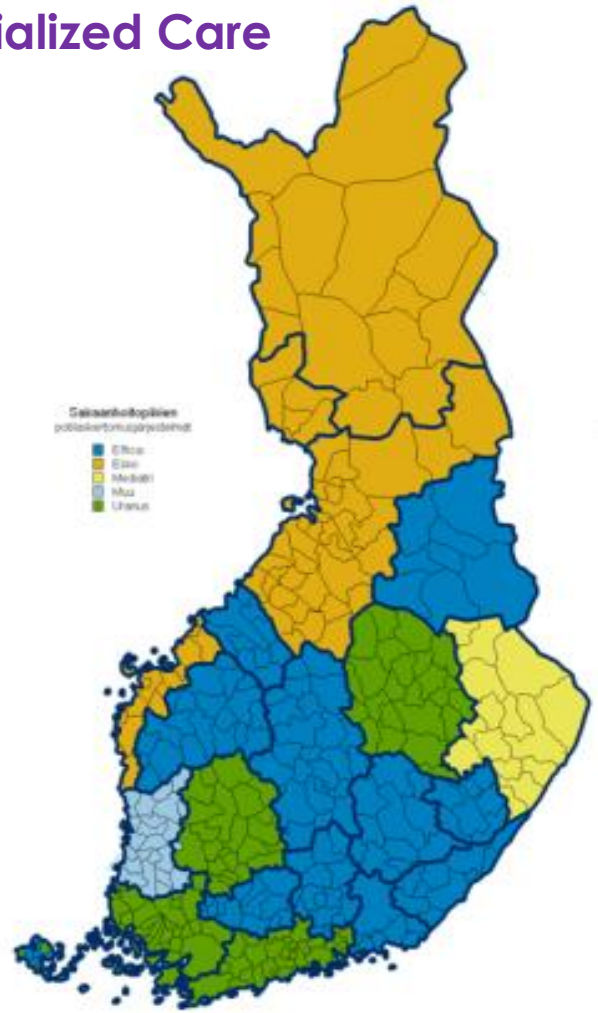
From Jan 1, 2023 in 21 wellbeing services counties

both primary and specialized care

Primary Health Care



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