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Pragmatic RCTs and the power of vaccine probe analysis:

The experience from Finland

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December 11, 2025

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Disclosures

AAP is currently employed by FVR – Finnish Vaccine Research, which conducts vaccine research funded by a number of vaccine manufacturers, including Pfizer, Inc., Moderna, Sanofi, GlaxoSmithKline SA, MSD, Seqirus, Osivax, and Abbott.
AAP has participated in advisory boards and speaker for MSD, Pfizer Inc., Janssen, Bionet, GlaxoSmithKline SA, and Vactech.

AA Palmu has received no personal remuneration from vaccine manufacturers.

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FVR in brief

Special-assignment company of the Finnish state: commercial vaccine research and related expertise for the needs of vaccine manufacturers public authorities, and society.

Ownership
Finnish government 51%; Tampere University Foundation 49%

Established in 2022 after merger of
- Tampere University Vaccine Research Center and
- clinical vaccine research group of the Finnish Institute for Health and Welfare (THL)

Customers
International vaccine manufacturers aiming for commercial licensure of their products and organizations looking for real-world evidence.

Phases 1 to 4, longterm experience and established performance
>170 trials conducted since 1990ies and numerous RWE studies at THL and FVR.

Network of clinics (Figure)
Extensive national network of clinical vaccine trial outpatient clinics.

Ongoing research (in 2025)
15 trials in various stages, against 10 different pathogens, 10 RWE studies

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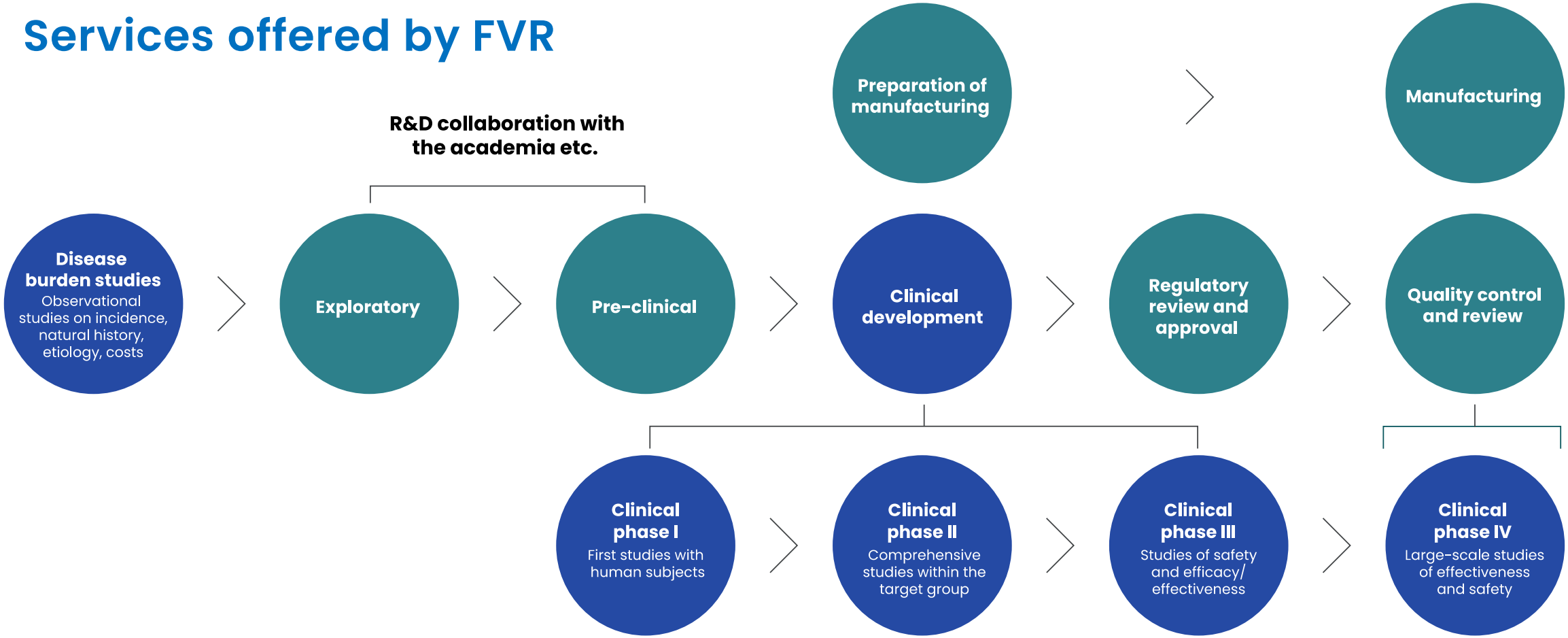
Services offered by FVR



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Finland has a 70-year history of large pragmatic field vaccine trials

- Finland participated in the Salk polio vaccine trial in the 1950ies along with US and Canada
- First national large field trials started in 1970ies when meningococcus A epidemic hit Finland
  - Randomized field trials in the army and in children (Peltola 1977, Makela 1977)
- Followed by many others
  - Haemophilus influenzae type B polysaccharide and conjugate vaccine trials (Eskola 1990)
  - Pneumococcal polysaccharide and conjugate vaccine trials (e.g. Eskola 2001, Kilpi 2003, Palmu 2013)
  - HPV cluster-randomized trial (Lehtinen 2015)
  - High-dose influenza vaccine trial (Palmu 2024)
  - More to come….

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Need of phase IV evidence for vaccines

- Effectiveness of licensed vaccines in real life circumstances
- **Earlier licensure of vaccines with post-licensure commitments**
- Indirect impact of vaccination programmes
- Long-term effects
- Rare adverse reactions
- Expanded target groups with comorbidities, different dosing schedules, concomitant vaccines
- Data for cost-effectiveness evaluations
- Data for mathematical modeling

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The public health perspective

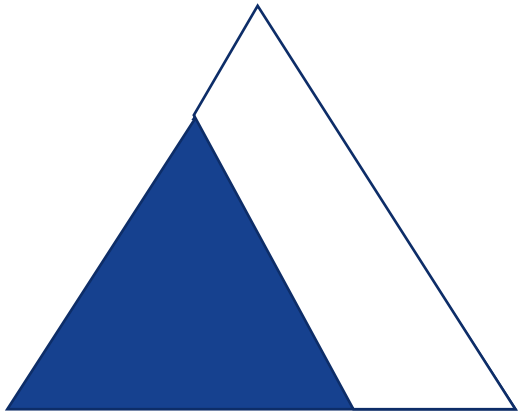
Vaccines are at their best when implemented as large-scale vaccination programmes

- Therefore, vaccines should be considered primarily as important **public health tools**

The most important public health outcome is the net reduction in overall disease burden

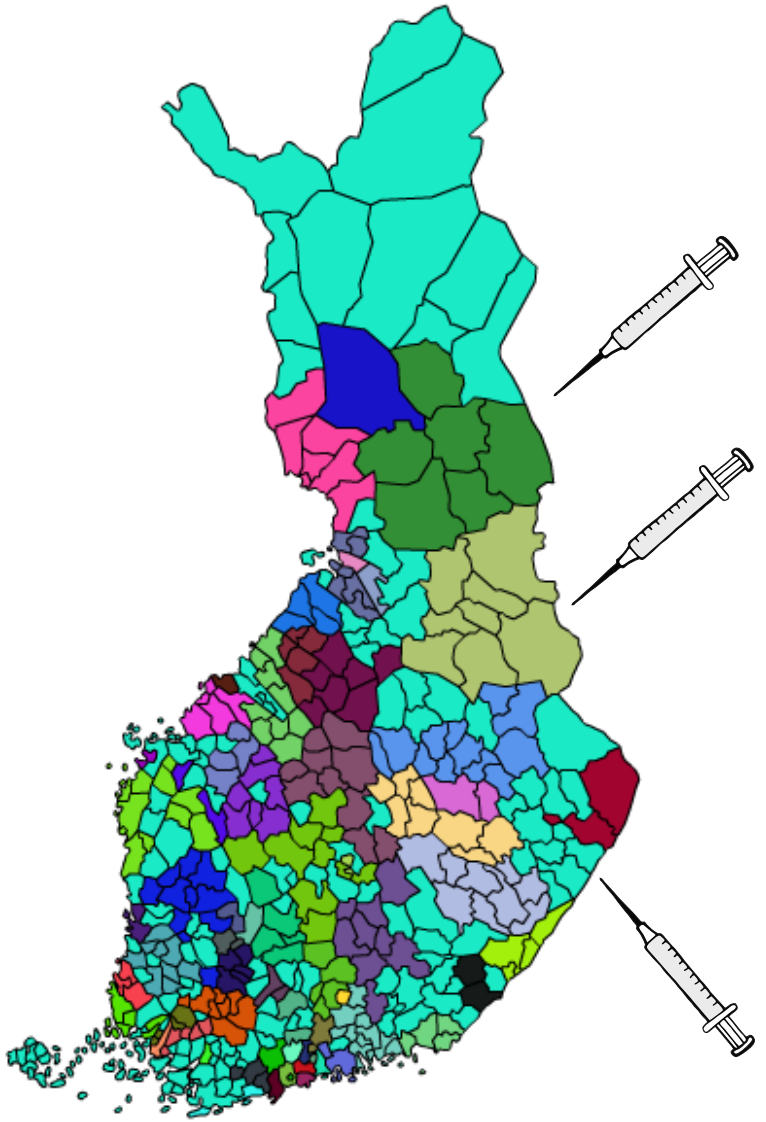
- Therefore, all reduction in disease should be measured
- Thus, sensitivity is more important than specificity

Phase 3 question: Can the investigational vaccine prevent the target infection?
Phase 4 question: How much can the vaccine prevent the disease burden caused by the targeted microbe?



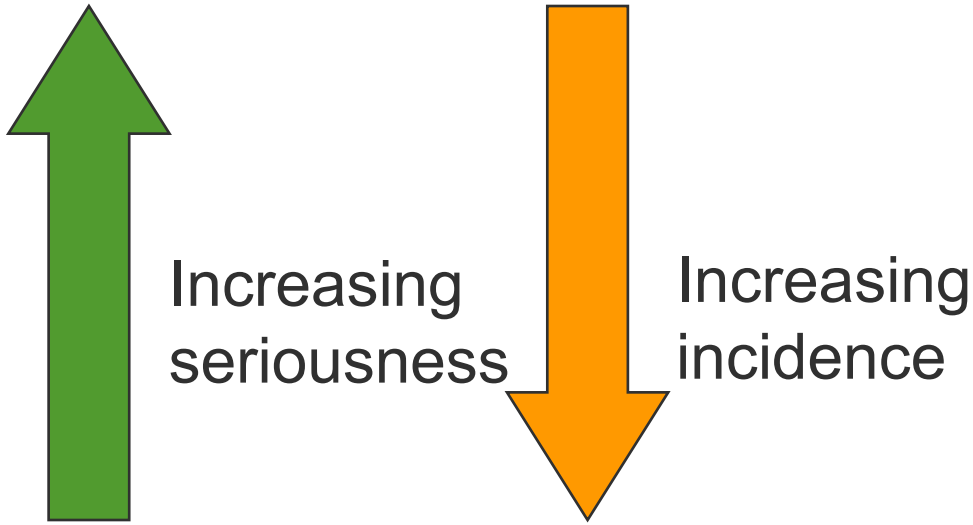
Combining register data with pragmatic RCT designs

- Finnish Invasive Pneumococcal disease vaccine effectiveness trial (FinIP)



Streptococcus pneumoniae (Pnc) causes a variety of clinical diseases

- Invasive Pneumococcal Disease (IPD)
  - Meningitis
  - Septicemia, bacteremia
  - Bacteremic pneumonia
- Non-bacteremic pneumonia
- Sinusitis
- Otitis media



- The public health perspective:
  - to prevent the full disease burden comprising of all the disease outcomes

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**
  - **No study visits, except for enrolment and vaccinations**

Palmu et. al. Lancet 2013;381:214–22

Register follow-up

- **THL Infectious disease register**
  - Laboratory-confirmed invasive pneumococcal disease (IPD), primary endpoint
- **THL Care register for Health care (hospital discharge register Hilmo)**
  - Clinically suspected IPD
  - Pneumonia
  - Tympanostomy tube procedures
- **National Insurance Institute of Finland (KELA)**
  - Antimicrobial purchases
  - Tympanostomy tube procedures (private)

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]	94% 77 to 99	80	75
Non-laboratory-confirmed IPD [2]	50% 32 to 63	422	207
Pneumonia[3]			
Tympanostomy tube			
Antimicrobial purc			

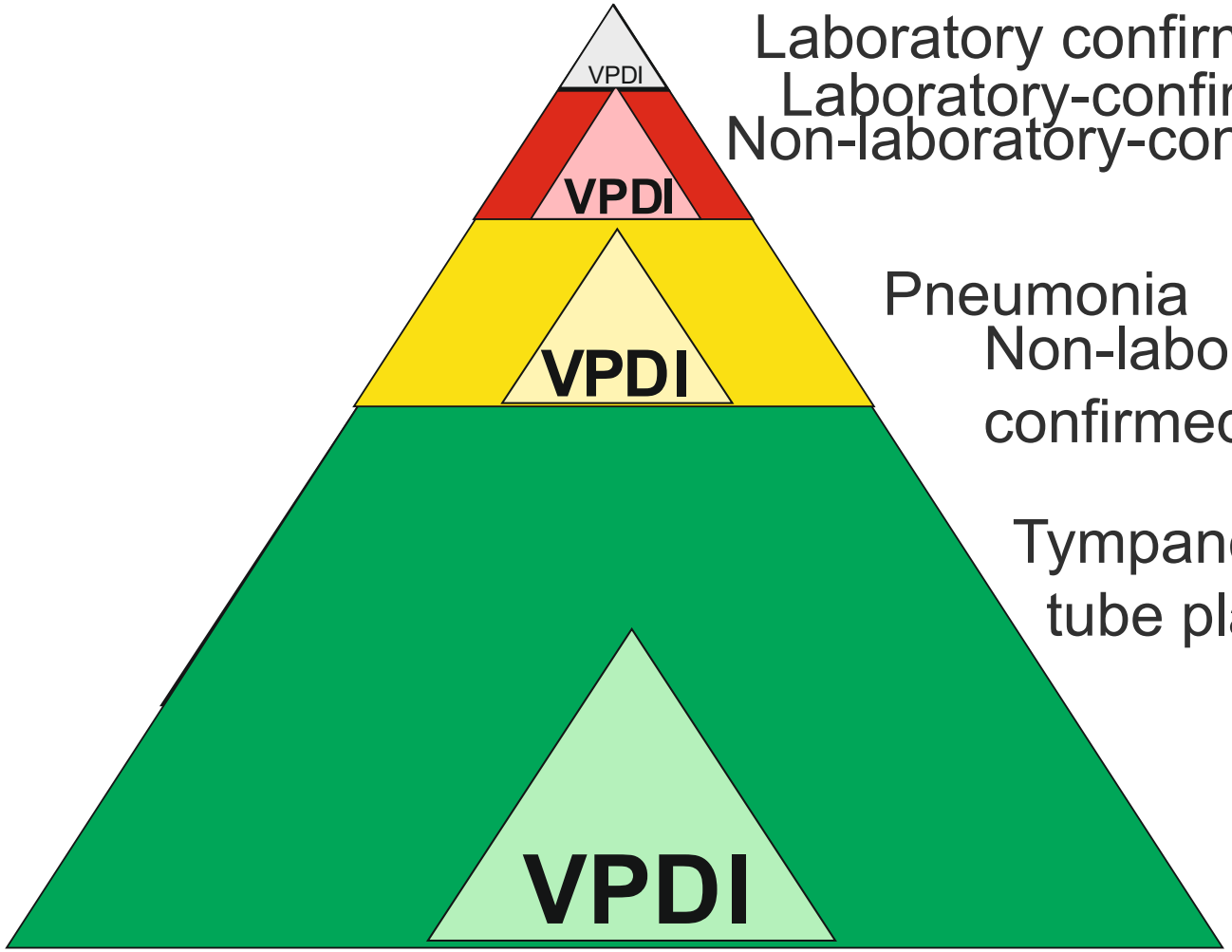
ICD-10 code	Diagnosis
A40.3 *	Sepsis due to Streptococcus pneumoniae
G00.1 *	Pneumococcal meningitis
M00.1 *	Pneumococcal arthritis and polyarthritis
B95.3 *	Streptococcus pneumoniae as the cause of diseases classified elsewhere
A40.9	Streptococcal sepsis, unspecified
A41.9	Sepsis, unspecified organism
A49.9	Bacterial infection, unspecified
G00	Bacterial meningitis, not elsewhere classified
G00.9	Bacterial meningitis, unspecified
I30.1	Infective pericarditis
M00	Pyogenic arthritis
B95.5	Unspecified streptococcus as the cause of diseases classified elsewhere

Palmu AA, et al.

VE, Vaccine Effectiveness; C
Pneumococcal Disease; AOM

Original data published: [1]Palmu et al 2015, [5]Palmu et al. Lancet Inf Dis 20

Disease burden and vaccine-preventable disease incidence (VPDI) in children vaccinated in infancy. Graphics based on true incidences.



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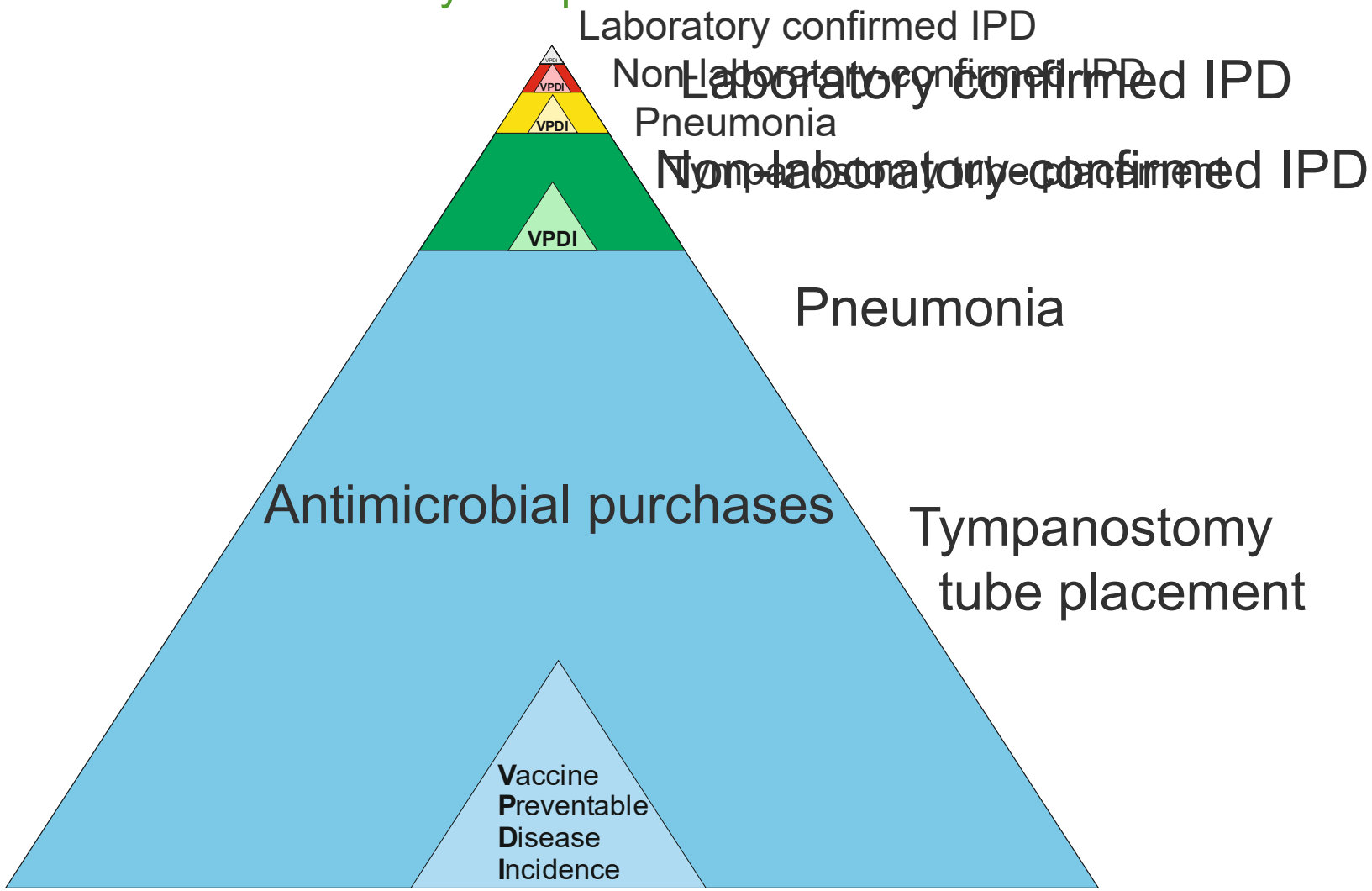
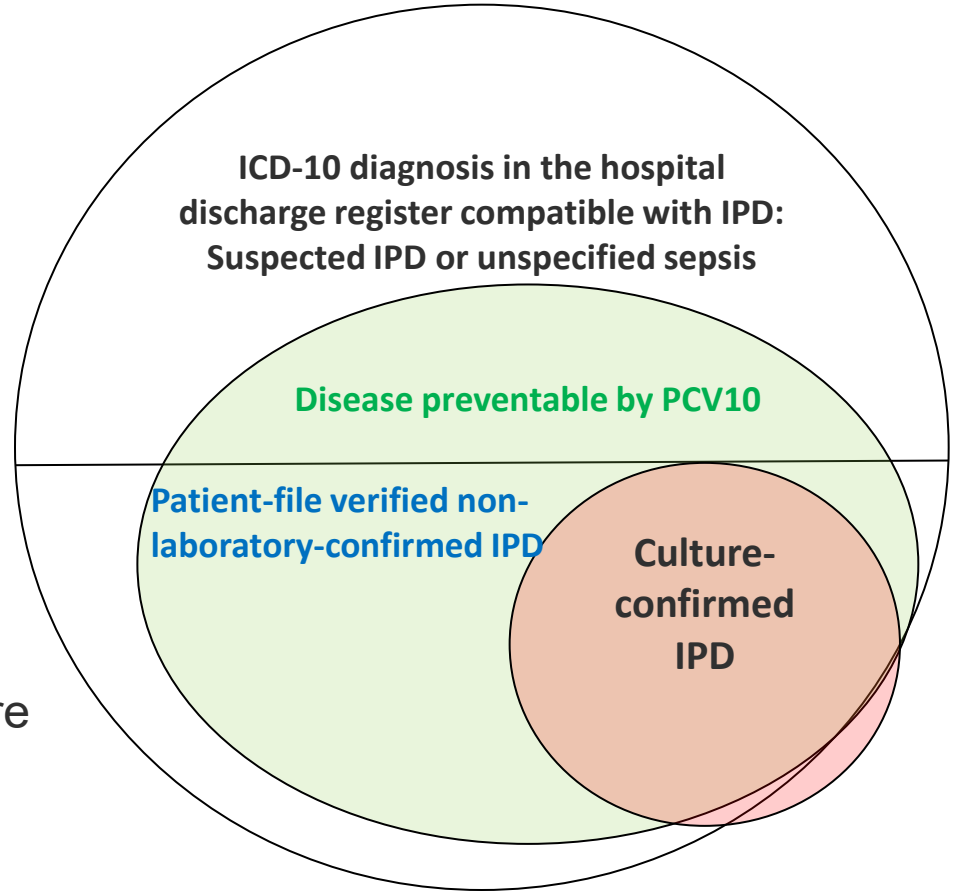


Invasive pneumococcal disease syndromes in children



FinIP trial design

- Phase III/IV randomized, double-blind trial
- children <19 months of age
- Vaccines
  - 10-valent PHiD-CV (GSK) OR
  - hepatitis B or A vaccine as control
- Over 47,000 children enrolled
- Passive outcome follow-up from national health registers

Sensitivity of blood culture in the detection of IPD estimated at 31%

Palmu AA, et al. The Lancet Respir. Med. 2014

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What was needed to demonstrate the hidden disease burden

1. Strong study design with clear interpretation: RCT
2. Large enough sample size
3. An effective vaccine
4. A specific enough disease syndrome
    1. Recognized by the physicians to the extent that relevant ICD-10 codes were used
    2. Competing diagnoses not very common

Is it also present in the older adults?

- Yes, but it is more difficult to demonstrate….

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What happened next?

- The finding in a pRCT was repeated in observational studies
  - In Finland
  - In Australia
  - In abstract in NZ
- Dozens of repeated international presentations on this exciting finding
- And then….

NOTHING!

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External stakeholders reactions

Regulatory: Nothing, but major development due to

- EU clinical trial regulation 2014/2022: low-intervention trial
- GCP R3: *risk-based approach, fit-for-purpose, avoiding unnecessary complexity*
    - Annex 2 provides additional GCP considerations, focusing on examples of trials that incorporate decentralised elements, pragmatic elements and/or real-world data (RWD).
        - Awaits adoption in 2025

Public health institutes: Nothing

NITAGs: Nothing

Scientists: the entity of clinically diagnosed case definition not included in any international collaboration

Pharma

- One report by GSK
    - A reflection on invasive pneumococcal disease and pneumococcal conjugate vaccination coverage in children in Southern Europe (2009–2016)
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC5489303/

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Benefits of a phase IV pragmatic trial

- Superior trial design for effectiveness evaluation after licensure
- High sample size to reach adequate power
  - Simplicity in practical conduct
  - RWD collection through registers with complete evaluation of disease burden
  - Long-term follow-up feasible
- Vaccine probe analyses
- Generalizability high with permissive inclusion criteria
- Low cost compared to traditional trials

- **Valid and important real-world evidence!**
- **Beneficial in providing scientific evidence, also in the presence of high-quality phase 3 trial data!**
- **Conservatism in science results in slow reactions to innovative ideas**
  - Presence of accepted yet deficient case definitions
  - Inability for worldwide methods to produce the results

www.fvr.fi

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Kiitos!

Phases 1 to 4,
longterm experience and established performance

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