Name: Ulrike Baum

<she/her/hers>

Country: Finland

Affiliation: Finnish Institute for Health and Welfare

Function:

- **Statistical Researcher**
- **Coordination of vaccination register related tasks**

Main expertise:

- **Epidemiology**
- **Vaccine effectiveness studies based on cohort data**

Seasonal influenza vaccination

Conducting register-based research in real-time

Adult Immunization Board

Country meeting

Helsinki, Finland

4 December 2024

Finnish Institute for Health and Welfare

Ulrike Baum

Outline

- Recap: influenza vaccination program and vaccination register
- Vaccination coverage
- Effectiveness studies
  - Cohort study
  - Case-control study
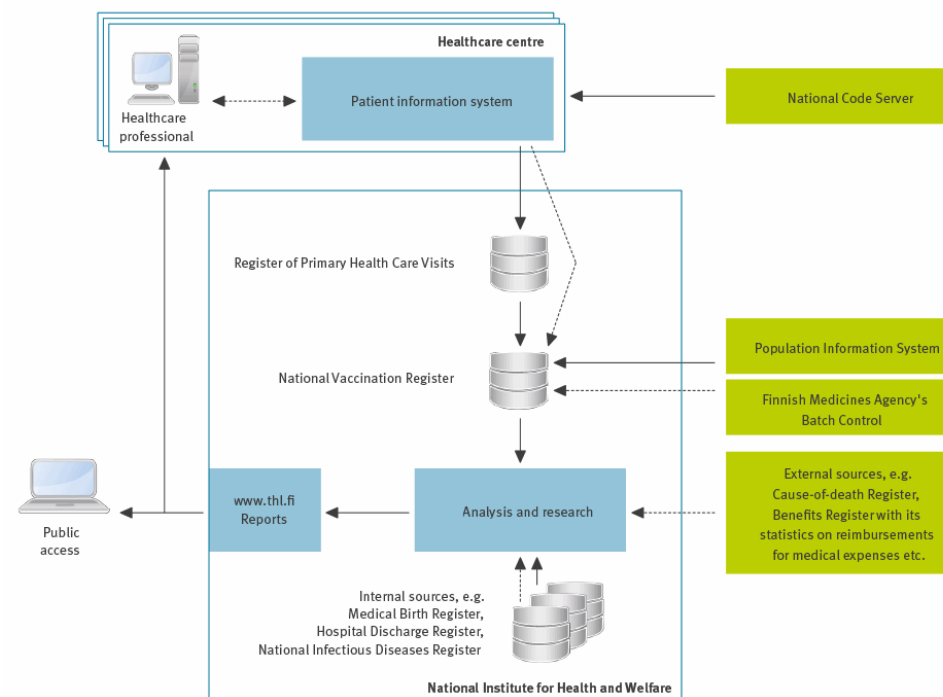 - Randomized trial
  - Target trial emulation
- Discussion

The hierarchy of evidence

https://www.mdpi.com/1660-4601/15/8/1726
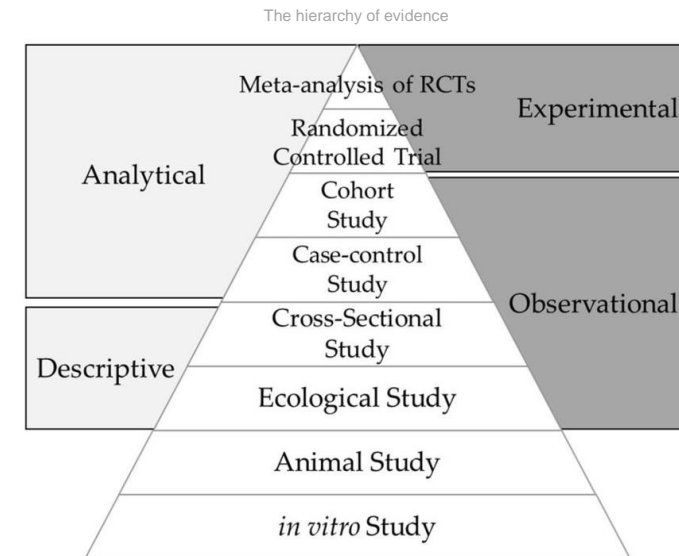
Recap: Influenza Vaccination Program and Vaccination Register

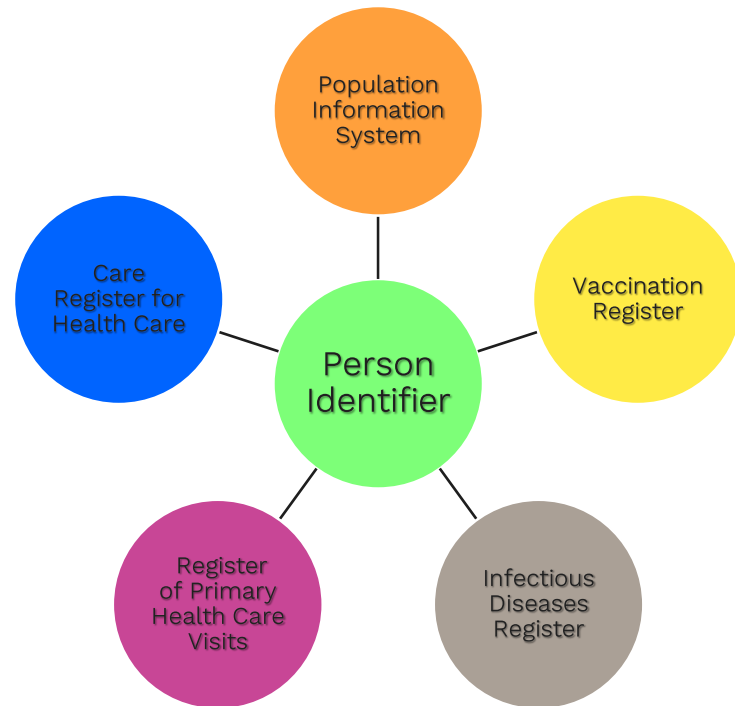## To whom is the influenza vaccine administered?

A free influenza vaccine is available as part of the national vaccination programme to those for whom influenza is an essential health risk, or who gain significant health benefits from the vaccination. Groups entitled to a free influenza vaccination are

- pregnant women
- everyone aged 65 and over
- children aged under 7
- those belonging to at-risk groups because of an illness or treatment
- those close to a person susceptible to serious influenza
- part of social welfare, healthcare and medical care personnel
- men starting their military service and women starting their voluntary military service

Persons who live or stay for long periods in institutional conditions, including prisons and reception centres, are also entitled to a free vaccination.

https://thl.fi/en/topics/infectious-diseases-and-vaccinations/vaccines-a-to-z/influenza-vaccine

Baum Ulrike, Sundman Jonas, Jääskeläinen Susanna, Nohynek Hanna, Puumalainen Taneli, Jokinen Jukka. Establishing and maintaining the National Vaccination Register in Finland. Euro Surveill. 2017;22(17):pii=30520.

Effectiveness Studies


- Vaccine effectiveness
  - Protective direct effect of vaccination
  - Vaccine-attributable relative reduction in disease incidence

Cohort Study

- Population: all people aged 65–100 years living in Finland
  - Cohort of ~ 1 million individuals
  - Individual follow-up from start till end of season
- Exposure: seasonal influenza vaccination
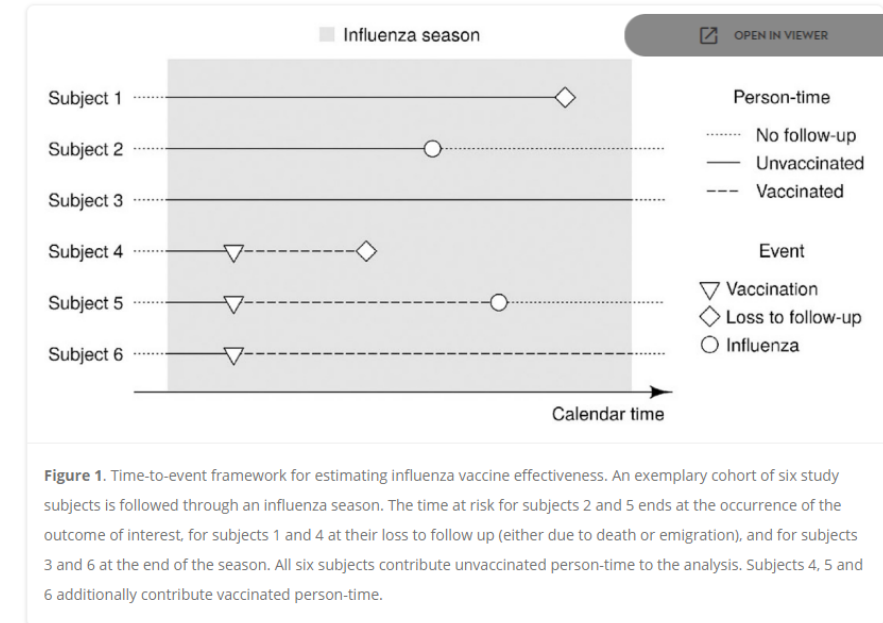- Outcome: laboratory-confirmed influenza

thl
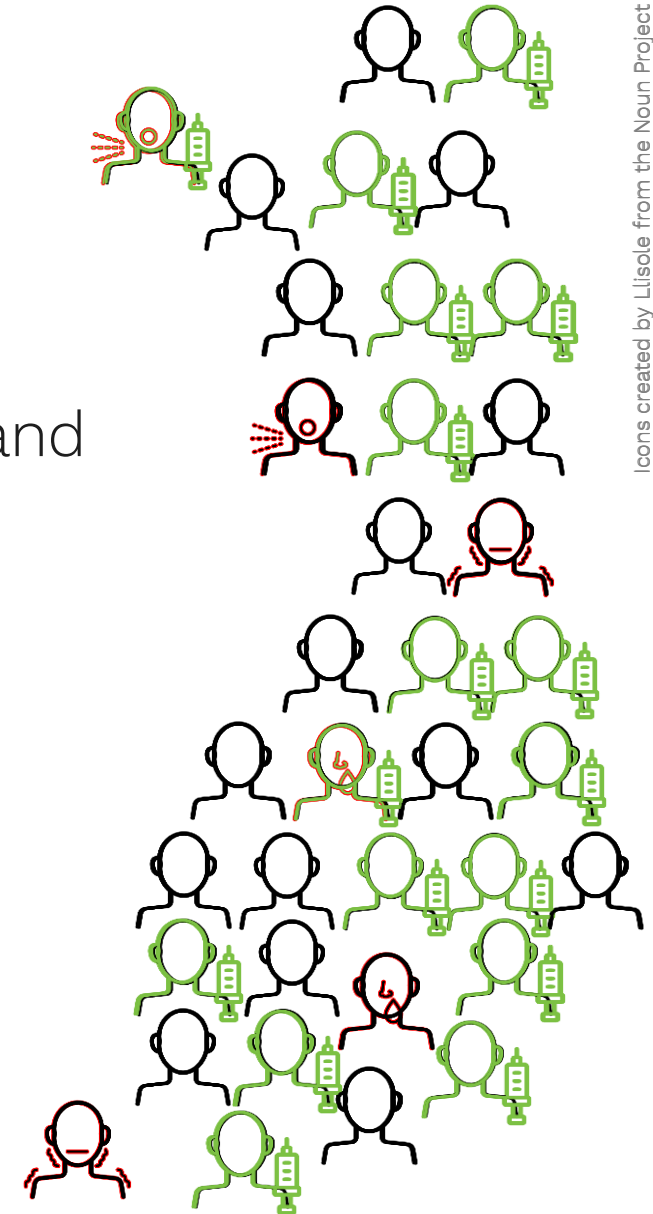
Cohort Study

- Population: all people aged 65–100 years living in Finland

  - Cohort of ~ 1 million individuals

  - Individual follow-up from start till end of season

- Exposure: seasonal influenza vaccination

- Outcome: laboratory-confirmed influenza

- Time-to-event analysis: VE = 1 - HR

Figure 1. Time-to-event framework for estimating influenza vaccine effectiveness. An exemplary cohort of six study subjects is followed through an influenza season. The time at risk for subjects 2 and 5 ends at the occurrence of the outcome of interest, for subjects 1 and 4 at their loss to follow up (either due to death or emigration), and for subjects 3 and 6 at the end of the season. All six subjects contribute unvaccinated person-time to the analysis. Subjects 4, 5 and 6 additionally contribute vaccinated person-time.

Cohort Study

FIGURE 2

Influenza vaccine effectiveness against laboratory-confirmed influenza in people aged 65–100 years, stratified by vaccination status at the end of the previous season, Finland, August 2012–May 2020

Vaccine effectiveness, %

● Not vaccinated   ◆ Vaccinated
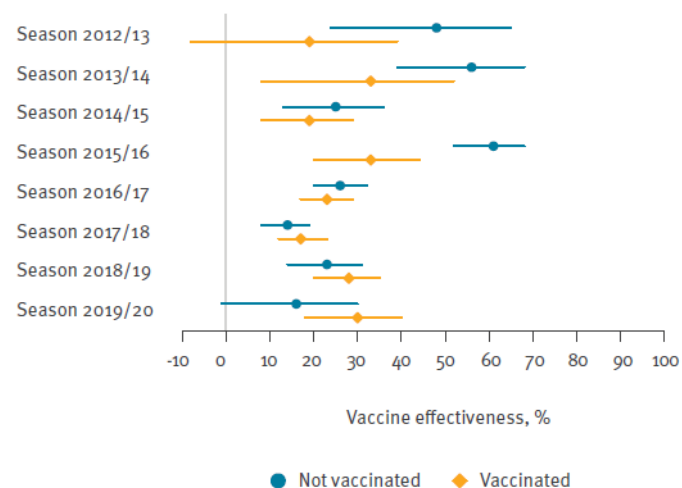
- Negative control outcome analysis
  - Off-season hospitalization for ARI
  - Assessment of residual confounding

TABLE 3

Hazard ratios comparing the hazards of off-season hospitalisation for acute respiratory infection in vaccinated and unvaccinated people aged 65–100 years, Finland, August 2012–May 2020

Off-season	Cohort size	Unvaccinated		Vaccinated		Crude HR		Adjusted HR[b]	
		Cases	Attack rate[a]	Cases	Attack rate[a]	Estimate	95% CI	Estimate	95% CI
2013	770,550	3,278	680	2,695	947	1.40	1.33–1.47	1.08	1.01–1.15
2014	799,926	3,405	736	3,112	932	1.27	1.21–1.33	1.00	0.94–1.07
2015	917,978	3,995	737	3,409	917	1.25	1.19–1.30	1.01	0.96–1.07
2016	957,252	4,347	811	,3634	872	1.08	1.03–1.12	1.00	0.94–1.05
2017	989,040	4,063	793	4,050	857	1.08	1.03–1.13	1.00	0.94–1.05
2018	1,033,957	4,164	779	4,266	862	1.11	1.06–1.16	1.01	0.95–1.06
2019	1,089,843	2,971	547	3,408	628	1.15	1.09–1.21	1.07	1.01–1.14

CI: confidence interval; HR: hazard ratio.
[a] The attack rate is presented as the cumulative risk at the end of the off-season multiplied by 105.
[b] The hazard ratio was adjusted for age, sex, 1-year vaccination history, nights hospitalised in the past 5 years and presence of underlying chronic conditions.

Baum Ulrike, Kulathinal Sangita, Auranen Kari. Spotlight influenza: Estimation of influenza vaccine effectiveness in elderly people with assessment of residual confounding by negative control outcomes, Finland, 2012/13 to 2019/20. Euro Surveill. 2021;26(36):pii=2100054. https://doi.org/10.2807/1560-7917.ES.2021.26.36.2100054

Case-Control Study

- To estimate vaccine effectiveness by mimicking a test-negative design study
- Population: all people aged ≥65 years living in the city of Tampere
  - Study population of ~ 40,000 individuals
- Cases: any hospitalization with lab-confirmed influenza A
- Controls: any hospitalization without lab-confirmed influenza
- Exposure: seasonal influenza vaccination
- VE = 1 - OR

Comparison of Study Designs

Seasonal influenza vaccine effectiveness (%)

Legend:
- Active TND study (green)
- Reg.-based case-control study (yellow)
- Reg.-based cohort study (magenta)

X-axis: 2015/16, 2016/17, 2017/18
Y-axis: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100
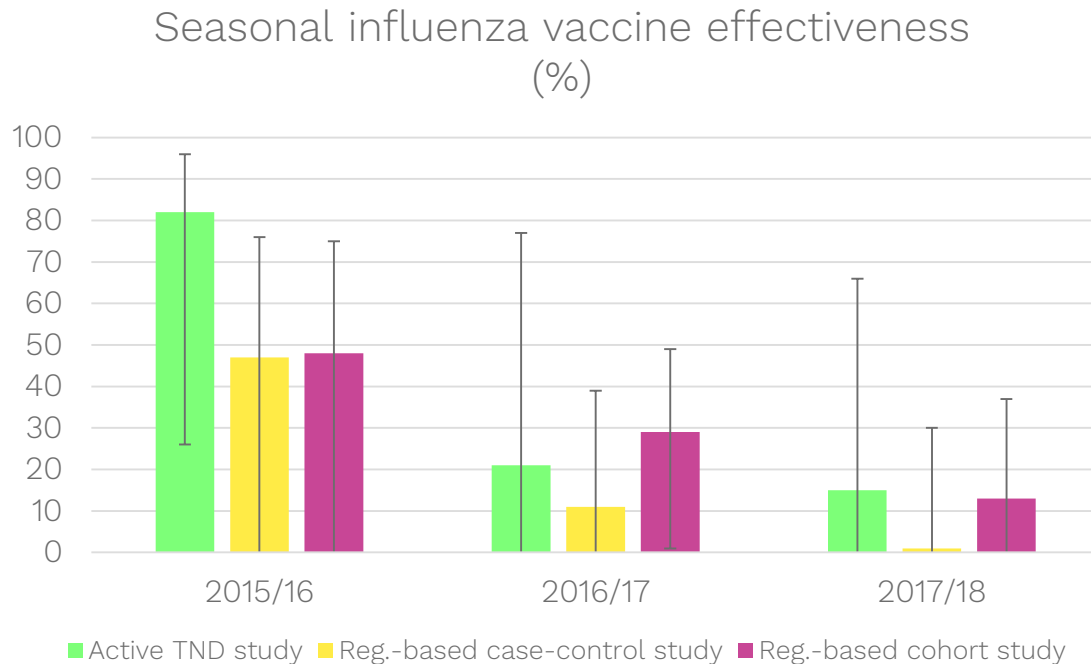
The register-based case-control design produced results that were less consistent with the active test-negative design than the register-based cohort design.

The register-based cohort design is the method of choice to continue the annual surveillance of seasonal influenza vaccine effectiveness.

Halme J, Syrjänen RK, Baum U, Palmu AA. Effectiveness of trivalent influenza vaccines against hospitalizations due to laboratory-confirmed influenza A in the elderly: comparison of test-negative design with register-based designs. *Vaccine* 2022; 40:4242–52.

FinFluHD Vaccine Trial

- To demonstrate superior relative VE of QIV-HD versus QIV-SD in a double-blind, randomized trial with register-based follow-up

- Population: people aged ≥65 years living in Finland

  - Study population of ~ 33,093 participants enrolled between Oct and Dec 2019

- Exposure:

  - Investigational vaccine, QIV-HD (Efluelda®, Sanofi)

  - Control vaccine, QIV-SD (Vaxigrip Tetra®, Sanofi)

- Outcome: cardiovascular or respiratory inpatient hospitalization

thl

Palmu AA, Pepin S, Syrjänen RK, Mari K, Mallett Moore T, Jokinen J, Nieminen H, Kilpi T, Samson SI and De Bruijn I. (2024), High-Dose Quadrivalent Influenza Vaccine for Prevention of Cardiovascular and Respiratory Hospitalizations in Older Adults. Influenza Other Respi Viruses, 18: e13270. https://doi.org/10.1111/irv.13270

FinFluHD Vaccine Trial

Hospitalization indication (ICD-10 code)	QIV-HD (N=16,549)		QIV-SD (N=16,544)		rVE, % (95% CI)
	n	%	n	%	
65–74 years					
No. subjects with available data	11,410	–	11,415	–	
Any respiratory / circulatory (J/I)	120	1.05	151	1.32	**20.49 (−1.71 to 37.97)**
Respiratory (J)	42	0.37	48	0.42	12.46 (−35.28 to 43.55)
Circulatory (I)	78	0.68	105	0.92	25.68 (−0.57 to 45.28)
MACE (I20–I25 + I65)	37	0.32	55	0.48	**32.70 (−3.96 to 56.87)**
≥75 years					
No. subjects with available data	5138	–	5127	–	
Any respiratory / circulatory (J/I)	137	2.67	121	2.36	**−12.98 (−45.49 to 12.18)**
Respiratory (J)	46	0.90	45	0.88	−2.00 (−57.40 to 33.86)
Circulatory (I)	93	1.81	79	1.54	−17.47 (−60.61 to 13.91)
MACE (I20–I25 + I65)	36	0.70	41	0.80	12.38 (−40.54 to 45.59)
≥85 years					
No. subjects with available data	635	–	628	–	
Any respiratory / circulatory (J/I)	32	5.04	32	5.10	**1.10 (−66.73 to 41.34)**
Respiratory (J)	6	0.94	15	2.39	60.44 (−7.89 to 87.42)
Circulatory (I)	26	4.09	18	2.87	−42.85 (−176.60 to 24.63)
MACE (I20–I25 + I65)	6	0.94	7	1.11	15.23 (−194.58 to 76.46)

-100 -75 -50 -25 0 25 50 75 100
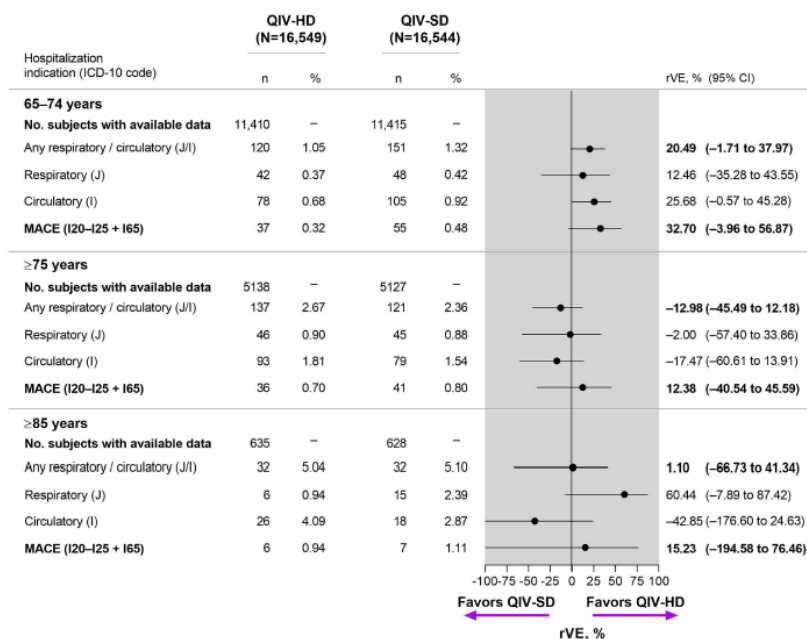Favors QIV-SD   Favors QIV-HD
rVE, %

FIGURE 3 | Relative Vaccine Effectiveness for Unscheduled Respiratory or Cardiovascular Hospitalizations, by Age Group. CI, confidence interval; ICD-10, International Classification of Diseases tenth revision; MACE, major acute cardiovascular events; QIV-HD, high-dose quadrivalent vaccine; QIV-SD, standard-dose quadrivalent vaccine; rVE, relative vaccine effectiveness.

QIV-HD was favored over QIV-SD for the prevention of respiratory and cardio-vascular hospitalizations in the population aged 65–74 years.

The FinFluHD vaccine trial demonstrated the feasibility of a pre-licensure pragmatic randomized trial with follow-up data from registries.

Target Trial Emulation

- To estimate vaccine effectiveness by mimicking a randomized trial

- Design: 1-to-1 matched cohort study
  - Matching of vaccinated individuals with individuals who have not yet received the vaccine
  - Matching on age, sex, etc.
  - Matched pair is followed since date of vaccination
  - Matched pair is right-censored when both are vaccinated
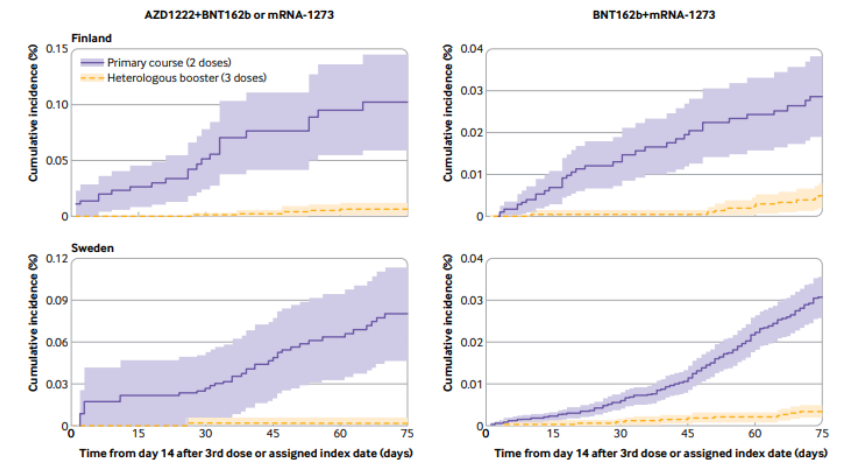
- Time-to-event analysis: VE = 1 - RR

Fig 2 | Cumulative incidence curves of death with covid-19 comparing heterologous AZD1222 (Oxford-AstraZeneca), BNT162b2 (Pfizer-BioNTech), and mRNA-1273 (Moderna) booster schedules with primary schedules in Finland and Sweden. Analysis was not possible in Denmark and Norway because of too few events

Discussion

- Heavy focus on elderly adults; neglection of other risk groups ?
- Strengths and limitations of register-based studies
    + Population-based estimates are more precise
    + Saving time and other resources
    – Bias e. g. due to unmeasured differences health-seeking behavior
    – History of infections
    – Negative test results
- Future focus on Nordic collaboration, risk group analyses and brand-specific VE
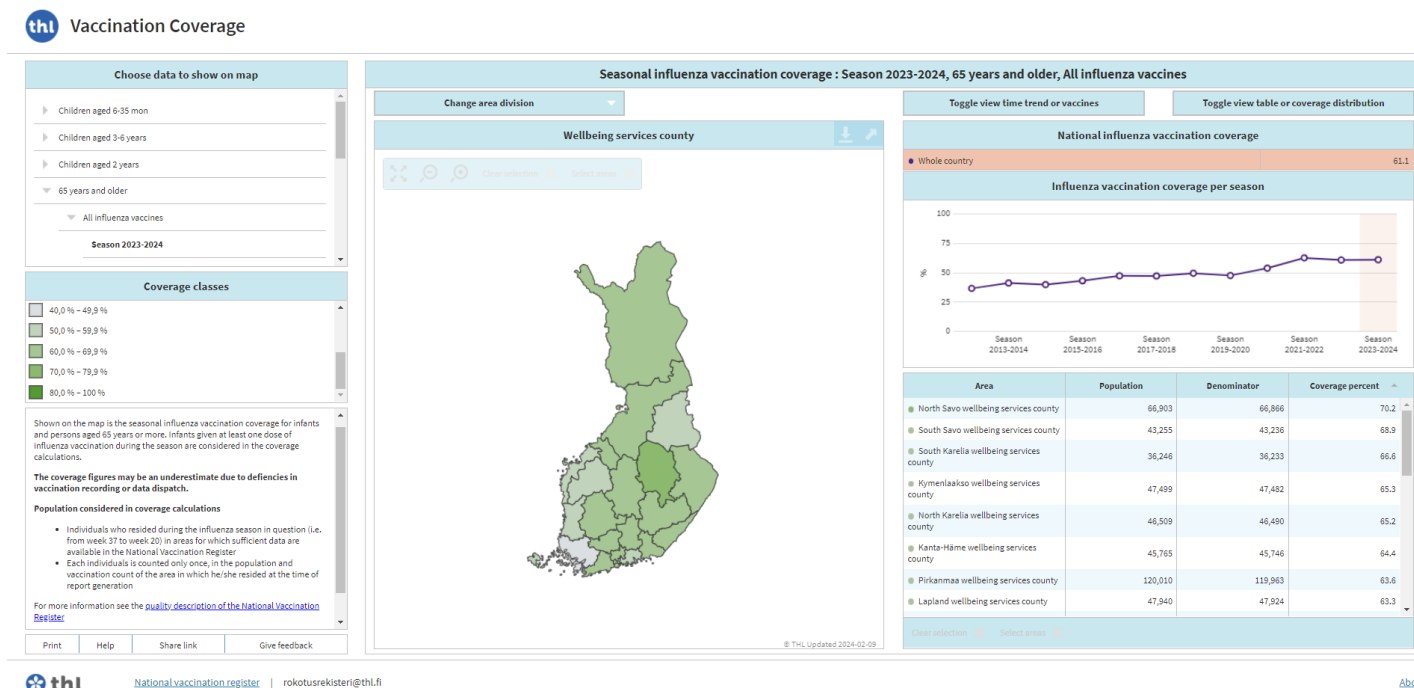
thl

Seasonal influenza vaccination

Conducting register-based research in real-time

Adult Immunization Board

Country meeting

Helsinki, Finland

4 December 2024

Finnish Institute for Health and Welfare

Ulrike Baum

Vaccination coverage atlas

https://www.thl.fi/roko/vaccreg/atlas/public/atlas-en.html?show=influenza

Vaccination coverage data cube

Left panel menu:

- **▼ Age**
  - ▼ All ages
    - ▼ 0-17
      - 0-6
      - 7-17
    - ▼ 18-64
      - 18-29
      - 30-49
      - 50-64
    - ▼ 65+
      - 65-79
      - 80+
- **▼ Area**
  - ▶ All areas
- **▶ Vaccination season**
- **▶ Reporting week**
- **▼ Measure**
  - ▼ Measure
    - Persons vaccinated in population
    - Persons in population
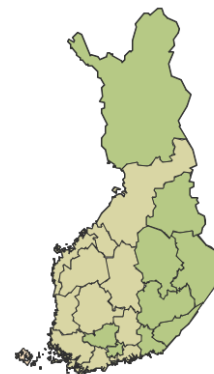   - Vaccination coverage
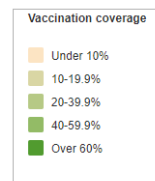
Influenza vaccination coverage by area

This page shows weekly updated seasonal influenza vaccination coverage by region. Data are available by week, vaccination season and age group. The data is presented as a map and as a downloadable table. You can make selections using the drop-down menus on the left-hand side of the page. You can select the week, vaccination season and age group to view. You can choose between welfare areas or municipalities for the regional breakdown of the map presentation. In the table view, you can compare the data of the regions with each other.

The contents source is the Vaccination registry at THL. The report contains vaccinations for persons that are found in the Finnish Population Information System. The age and home municipality of vaccinated persons are derived from the current situation and vaccination coverage is estimated based on the latest population information.

Vaccination coverage by area on a map (Season 2024-2025, Week 47, All ages)

Export table ▾

Vaccination coverage
- Under 10%
- 10-19.9%
- 20-39.9%
- 40-59.9%
- Over 60%

Leaflet

https://sampo.thl.fi/pivot/prod/en/vaccreg/influseason

thl

17