Name:Petteri Hovi

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Country: Finland

Affiliation: Finnish Institute for Health and Welfare (THL)

Function: Medical expert in vaccine safety group during 2021 and 2022

Main expertise (1-2 lines): MD, PhD, Paeditrician, Title of Docent, Register epidemiology, Nationwide analysis

Adult immunization in Finland: successes, lessons learned and the way forward

Finnish Institute for
Health and Welfare

4 – 5 December 2024

Objective and Potential conflicts

"Discuss the effectiveness of current **surveillance systems** in detecting and responding to vaccine-preventable diseases in adults."

Current presentation focuses on safety.

* * *

Author works for the Finnish Institute for Health and Welfare, which receives funding from pharmacological institutes. The funders have not influenced the analysis plans, analysis, interpretations nor decisions to publish

Petteri Hovi et al. declares the have no potential conflicts of interest

Related presentations

Register-based surveillance
Tuija Leino

Real time –data on influenza
Ulrike Baum

National information resource plan
Jukka Jokinen

Vaccine effectiveness in risk groups
Eero Poukka

Registers in clinical trials
Tuomo Nieminen

Vaccine safety monitoring
Petteri Hovi

Real time epidemiological analyses based on national health registers in Finland

Vaccine safety monitoring

Vaccine safety during the SARS-Cov2 pandemic

Petteri Hovi, MD PhD, specialist in paediatrics

4 – 5 December 2024

Some published results from COVID-19 vaccine safety analyses in Finland

Analysis started	Adverse event	Methods	Result	Conclusions
1 / 2021	**Anaphylaxis**	Comparison of different exposures. COVID-19 vaccination vs influenza vaccination. Logistic regression.	COVID-19 vaccination is associated with greater probability of Anaphylaxis than influenza vaccination.	**Those administering vaccines must be prepared to handle anaphylaxis.**
2 / 2021	**Death due to any cause**	Parallel cohort comparison. Covid-19 vaccination vs unvaccinated time, by product and dose. Survival analysis via Poisson regression.	The hazard of death during 9 weeks from any COVID-19 vaccination was on average approximately 50% of those unvaccinated.	**The vaccination program is not causing excess deaths.**
3 / 2021	**Cerebral Venous Sinus Thrombosis & Thrombocytopenia (CVST)**	Parallel cohort comparison. AstraZeneca (AZ) vaccination vs unvaccinated time. Survival analysis via Poisson regression.	After 200 000 AZ doses there were 2 CVST within 28 days from vaccination, corresponding to 40 times (IRR, 95% CrI: 6–160) the expected incidence.	**AZ is associated with an increased risk of CVST.**
3 /2021	**Thromboembolic and Thrombocytopenic Events; multiple outcomes**	Meta analysis of country-specific self-controlled case series (SCCS) comparing 28 days after vaccination to time before vaccination. Conditional Poisson regression.	The rate of coagulation disorders was doubled (IRR 95% CI: 1.8-2.3) during 28 days following AZ vaccination and the rate of cerebrovascular disease was also higher (IRR 1.3, 95% CI: 1.2-1.5). Results for other outcomes and the mRNA vaccines were more unclear.	**AZ is associated with coagulation disorders and cerebrovascular diseases, especially cerebral venous thrombosis and thrombocytopenia.**
3 / 2021	**Myocarditis and Pericarditis (MP)**	Meta-analysis of country-specific parallel cohort comparisons (28 days following vaccination vs unvaccinated time). Gender- and age stratified survival analyses via Poisson regression.	Among males aged 16–24, those exposed to Spikevax experience 9–28 MP, and those exposed to Comirnaty 4–7 MP, per 100,000 vaccinated, during 28 days from vaccination.	**The mRNA vaccines are associated with increased risk of MP, especially among young males.**
1 / 2022	**Sudden Sensoneural Hearing Loss (SSNL)**	Historical cohort comparison. Time during 55 days from COVID-19 vaccination vs pre-pandemic time, by dose and product. Survival analysis via Poisson regression.	The incidence of SSNL within 55 days from any COVID-19 vaccination was not greater than before the pandemic.	**No evidence of a causal relationship between COVID-19 vaccination and SSNL.**

Case Anaphylaxis

- Threatens life
- Is not unexpected
- Question 1: What proportion of vaccinated?
- Question 2 (beyond us): Risk benefit for individuals & groups
- Problems due to setting
  - Comparison to everyday life? To the infection? To other vaccines?
  - Health care workers in the first wave of vaccinated
  - Awareness

Portion facing anaphylaxia (per 10^5 doses)

Exposure	Odds ratio*	Doses	Cases	Portion
Influenssa, 2019-2020	…	1201381	8	0,67
Influenssa, 2020-2021	…	1588905	13	0,82
Influenssa, 2021-2022	…	1872278	11	0,59
Influenssa, 2022-2023	…	128850	1	0,78
Comirnaty-1	3,1 (2,1 4,7)	3621255	82	2,26
Comirnaty-2	1,4 (0,9 2,3)	3629369	40	1,1
Comirnaty-3		2236195	11	0,49
Comirnaty-4		821740	2	0,24
Spikevax-1	1,7 (0,7 3,7)	558169	7	1,25
Spikevax-2	1,3 (0,5 3,0)	535970	6	1,12
Spikevax-3		821801	6	0,73
Spikevax-4		151275	0	0
Vaxzevria-1	3,4 (1,5 6,7)	361727	9	2,49
Vaxzevria-2	6,3 (1,8 17,5)	191818	4	2,09

* Odds ratio calculation

- referent; influenza vaccination
- time window: day 0
- Model: age group, sex, health care worker status, former allergy, former anaphylaxis

Case TTS

Flow chart

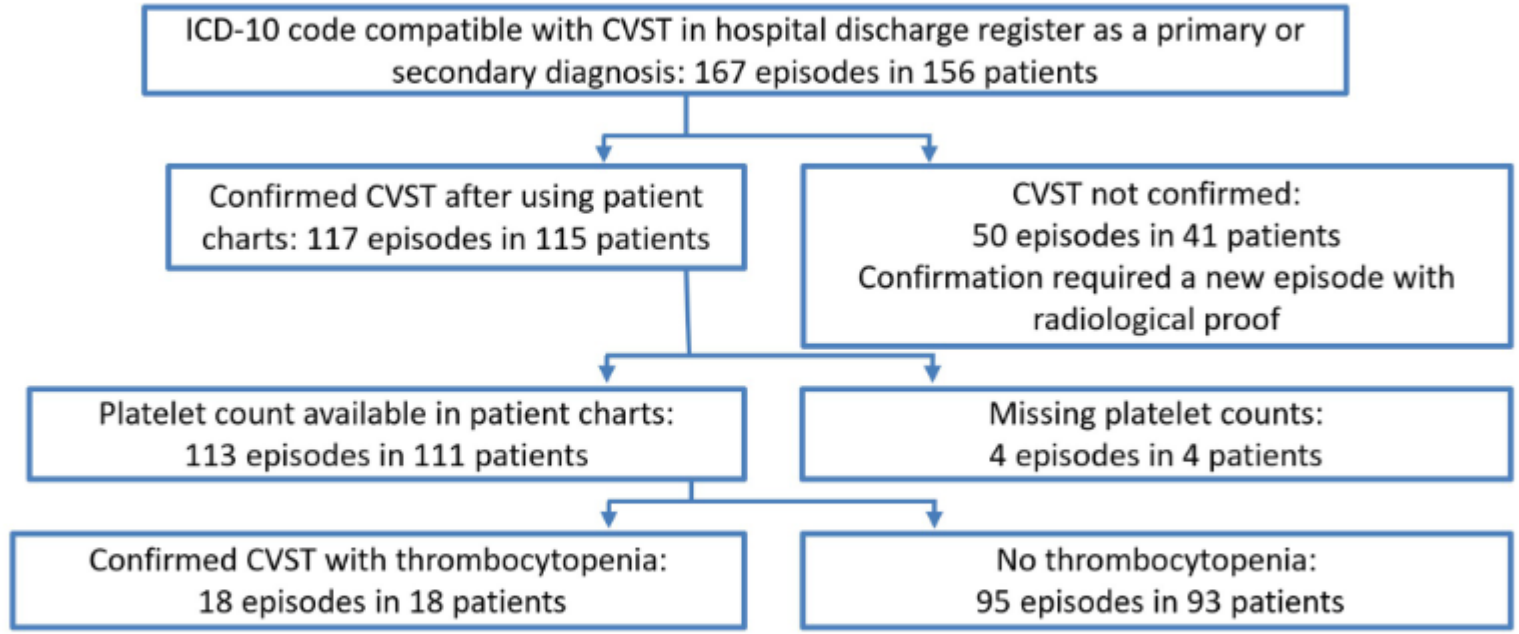
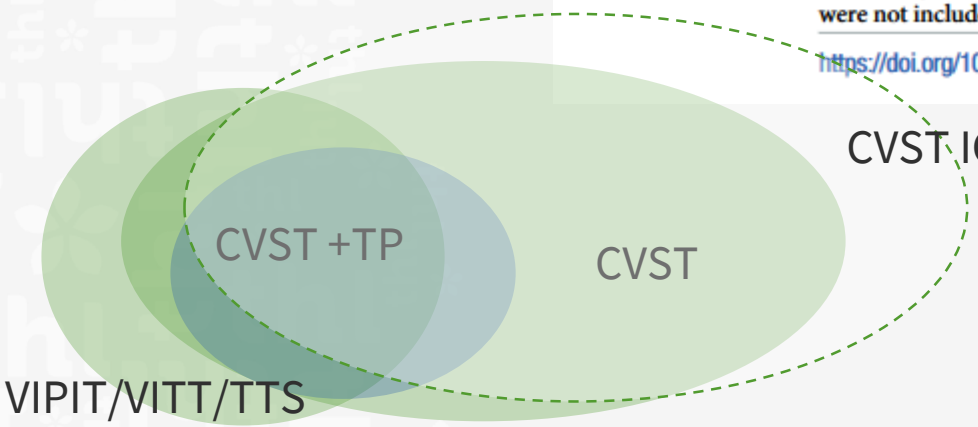


Fig 1. Flow chart. From top to bottom shows the extraction of confirmed cerebral venous sinus thrombosis (CVST) in combination with thrombocytopenia. Note that three register-based CVST episodes, one of which confirmed, are included here but occurred after the risk periods and were not included in the pre-vaccinated time.

https://doi.org/10.1371/journal.pone.0282226.g001



CVST ICD-10 codes found

Incidences

Incidences per 28 days per million persons of cerebral venous sinus thrombosis and thrombocytopenia during the 28-day risk periods after COVID-19 vaccinations and during the unexposed time preceding the vaccinations. Numbers of episodes provided in parentheses.

Conclusions.

- CVST: Case definition based on ICD-10 code alone may work as a proxy for groups.
- Combination of two or more simultaneous side-effect by ICD-10 codes did not work

Haematologist Riitta Lassila, HUS was the clinical consultant

Case Definition and age group, years	Unexposed time	BNT162b2	ChAdOx1 nCov-19
CVST, register-based[a]			
0-15	0.49 (7)	NA	NA
16-29	1.22 (18)	0	153.63 (1)
30-54	1.73 (49)	14.59 (1)	24.99 (1)
55-64	2.72 (32)	0	0
65+	2.68 (54)	2.41 (1)	0
All ages	**1.79 (160)**	3.73 (2)	12.14 (2)
CVST, confirmed[b]			
0-15	0.28 (4)	NA	NA
16-29	1.02 (15)	0	153.63 (1)
30-54	1.23 (35)	0	24.99 (1)
55-64	1.87 (22)	0	0
65+	1.88 (38)	0	0
All ages	**1.28 (114)**	0	12.14 (2)
CVST, confirmed, with thrombocytopenia[c]			
0-15	0.21 (3)	NA	NA
16-29	0.07 (1)	0	153.63 (1)
30-54	0.04 (1)	0	24.99 (1)
55-64	0.51 (6)	0	0
65+	0.25 (5)	0	0
All ages	**0.18 (16)**	0	12.14 (2)

ChAdOx1 nCov-19 (Vaxzevria, AstraZeneca) BNT162b2 (Comirnaty, Pfizer–BioNTech). NA not applicable, for those under 16 years the COVID-19 vaccines were unavailable.
[a] CVST, cerebral venous sinus thrombosis: As a main diagnosis any of ICD-10 codes I636, I676, or G08 included. Only emergency-room visits and non-scheduled in-patient hospitalizations were included.
[b] CVST, confirmed: Episodes in registers that were confirmed by chart review (clinical radiological reports and clinical interpretations).
[c] CVST, confirmed, with thrombocytopenia: Platelet count < 150,000 per cubic millimetre within 14 days before and after episode start.
Note that the 28-day risk time after BNT162b2 was free from episodes with confirmed CVST. Note also, that risk time after mRNA-1273 (Moderna) was free from any CVST.

Administered doses by Apr 2, 2021 (end of follow-up time) of each vaccine and number of COVID-19 infections by age and risk group.

		Counts						Risk group proportions within vaccination*age group				
Age group	Risk group[a]	Total	BNT162b2	mRNA-1273	ChAdOx1 nCov-19	COVID-19 -infection		Total	BNT162b2	mRNA-1273	ChAdOx1 nCov-19	COVID-19 -infection
16-29	No risk	831712	16594	400	4914	18312		0.919	0.884	0.749	0.669	0.927
	Risk	73269	2167	134	2428	1445		0.081	0.116	0.251	**0.331**	0.073
	Total	904981	18761	534	7342	19757						
30-54	No risk	1504207	59165	1432	18580	25178		0.859	0.820	0.637	0.402	0.869
	Risk	246115	12986	816	**27641**	3812		0.141	0.180	0.363	**0.598**	0.131
	Total	1750322	72151	2248	46221	28990						
55-64	No risk	504340	25259	1000	13358	5072		0.689	0.666	0.444	0.193	0.696
	Risk	227584	12680	1250	**55917**	2218		0.311	0.334	0.556	**0.807**	0.304
	Total	731924	37939	2250	69275	7290						
65+	No risk	637774	265211	24820	20720	2660		0.488	0.453	0.395	0.267	0.442
	Risk	667912	**320665**	38025	56839	3363		0.512	0.547	0.605	**0.733**	0.558
	Total	1305686	585876	62845	77559	6023						
Ages 16 and above	No risk	3478033	366229	27652	57572	51222		0.741	0.512	0.407	0.287	0.825
	Risk	1214880	**348498**	40225	142825	10838		0.259	0.488	0.593	**0.713**	0.175
	Total	4692913	714727	67877	200397	62060						

ChAdOx1 nCov-19 (Vaxzevria, AstraZeneca) BNT162b2 (Comirnaty, Pfizer–BioNTech) mRNA-1273 (Spikevax, Moderna)

[a] A short version of a list of diseases yielding to vaccination priority. Codes were searched via registers from Jan 1, 2015 to Jan 1, 2021 and before the episode start: malignancy, type 2 Diabetes, severe lung disease, severe chronic kidney disease, History of transplantation, Down syndrome, congenital immunodeficiency, asthma, cardiovascular disease, immunosuppression, chronic severe liver disease, type 1 diabetes, adrenal disorder, sleep apnea, for details, see **S3 Table.**

International collaboration

When evidence of severe adverse events become available for the first time after licensure, the **events are almost always very rare**. The adverse events may also be associated with specific sub-populations, such as with myocarditis and COVID-19 mRNA vaccines in young males.

- It is then beneficial to collaborate internationally in order to estimate the associations more precisely.

During COVID-19 vaccine safety surveillance, THL collaborated with other Nordic countries in several studies, and provided statistical data to the Global Vaccine Data Network (GVDN).

- Due to data privacy regulations, it is a challenge to share individual-level data between countries. Therefore, the Nordic studies utilised aproaches where country-specific results were combined in meta-analyses.

- Dag Berild, J. et al. A. Analysis of Thromboembolic and Thrombocytopenic Events After the AZD1222, BNT162b2, and MRNA-1273 COVID-19 Vaccines in 3 Nordic Countries. https://doi.org/10.1001/jamanetworkopen.2022.17375.
- Karlstad, Ø. et al.. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. https://doi.org/10.1001/jamacardio.2022.0583.
- Husby, A, et al. Clinical Outcomes of Myocarditis after SARS-CoV-2 MRNA Vaccination in Four Nordic Countries: Population Based Cohort Study. https://doi.org/10.1136/bmjmed-2022-000373.
- Hviid, A, et al. Booster Vaccination with SARS-CoV-2 MRNA Vaccines and Myocarditis Risk in Adolescents and Young Adults: A Nordic Cohort Study of 8.9 Million Residents.. https://doi.org/10.1101/2022.12.16.22283603.

Background Rates Dashboards | Global Vaccine Data Network. https://www.globalvaccinedatanetwork.org/Data-Dashboards/Background-Rates-Dashboards (accessed 2023-06-01).

Summary and take home message

Published results summarized in Finnish:

Hovi, P.; Nieminen, T.; Artama, M. *Koronarokoteturvallisuus - Yhteenvetoraportti ajalta 1.1.2021-31.12.2022 : Kooste Terveyden ja hyvinvoinnin laitoksen lakisääteisen tehtävän toteuttamisesta*. http://urn.fi/URN:ISBN:978-952-408-125-2 (accessed 2023-08-07). Working paper that includes list of references

Multidiscipline

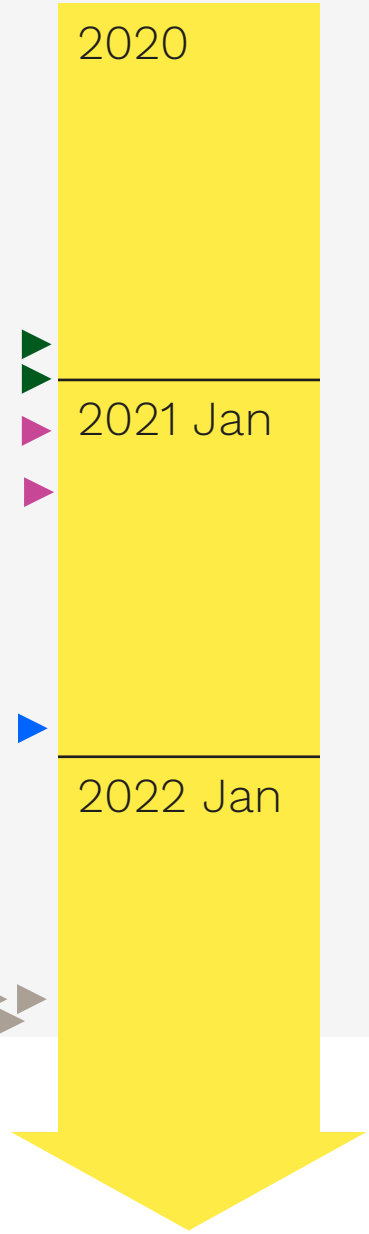
Whole country as a cohort, in real time

Focus

Disseminate

COVID-19 vaccinations in Finland

- mRNA vaccines
  - Comirnaty / Pfizer-BioNTech, Dec 21, 2020
  - Spikevax / Moderna, Jan 1, 2021
- Adenovirus vector vaccines
  - Vaxzevria / Oxford university and AstraZeneca, Jan 29, 2021
  - Johnson & Johnson vaccine, March 11, 2021
- Others:
  - Nuvaxovid by Novavax on Dec 20, 2021
- Variant vaccines:
  - Comirnaty BA.1, Sep 1, 2022
  - Comirnaty BA4-5, Sep 12, 2022
  - Spikevax BA.1 Sep 1, 2022.



- Priority groups
  - health care workers
  - elderly
  - those with pre-existing risk factors to severe COVID-19

- Register data was utilised to identify the risk factors of severe COVID-19*

Heini Salo, Toni Lehtonen, Kari Auranen, Ulrike Baum, Tuija Leino. **Predictors of hospitalisation and death** due to SARS-CoV-2 infection in Finland: A population-based register study with implications to vaccinations, https://doi.org/10.1016/j.vaccine.2022.04.055

- By 2022/09, 90% of the adult (18+) population had received at least one COVID-19 vaccine dose and coverage was 38% in those 0-17 years old.

thl

Multidiscipline

Thanks: Tuomo Nieminen

Multi-discipline team work

Vaccination campaign

Vaccine efficacy

Clinical care networks www

Data management

Statistics

Vaccinology

Register epidemiology

Vaccine epidemiology

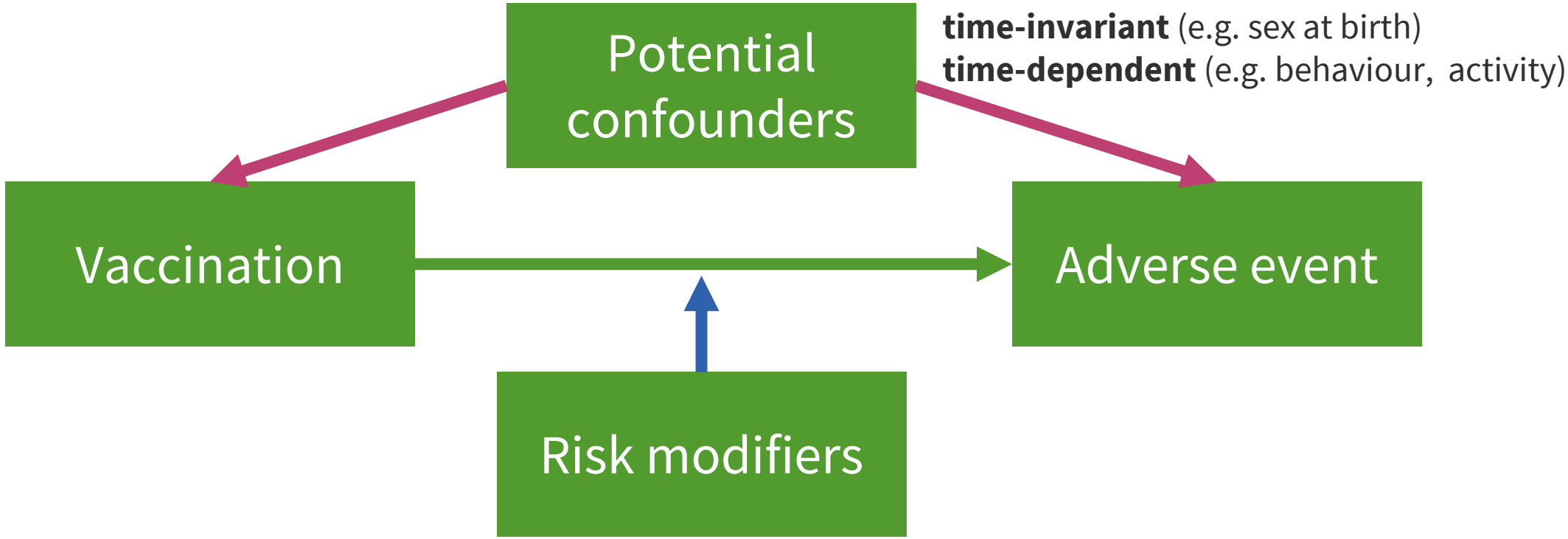
General management

Legislation

Communication

Research question

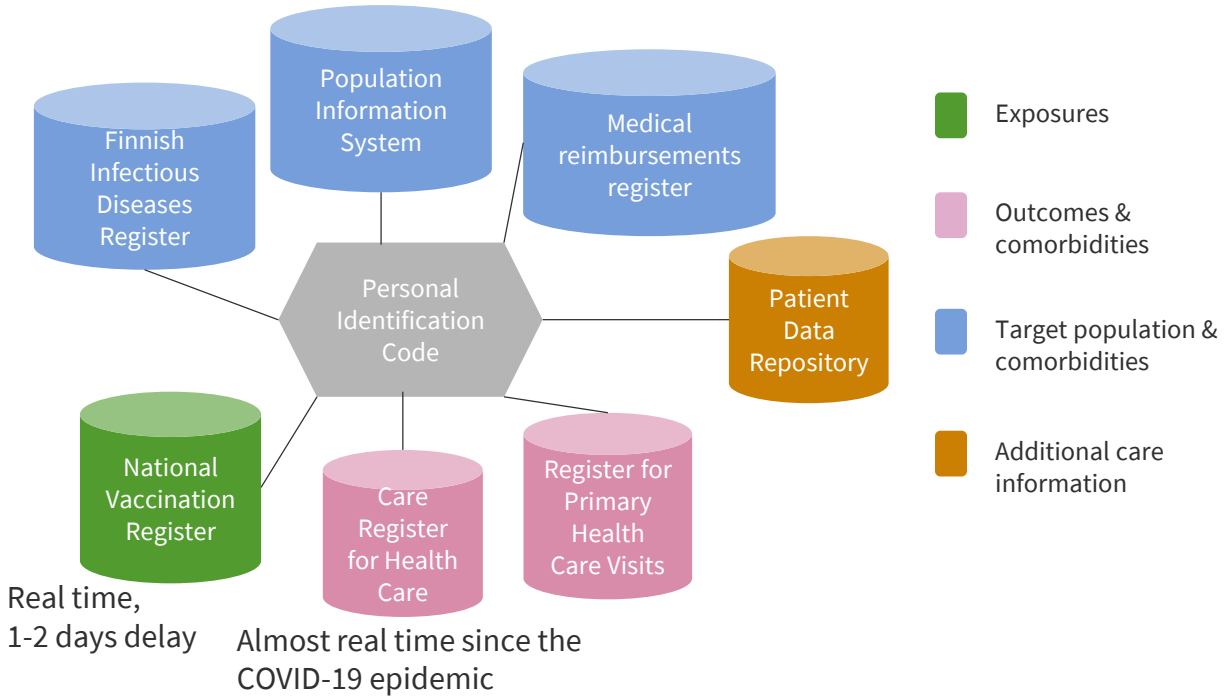
Is there an association between vaccination and an increased probability / HR / IRR of the adverse event occurring during a prespecified risk window?



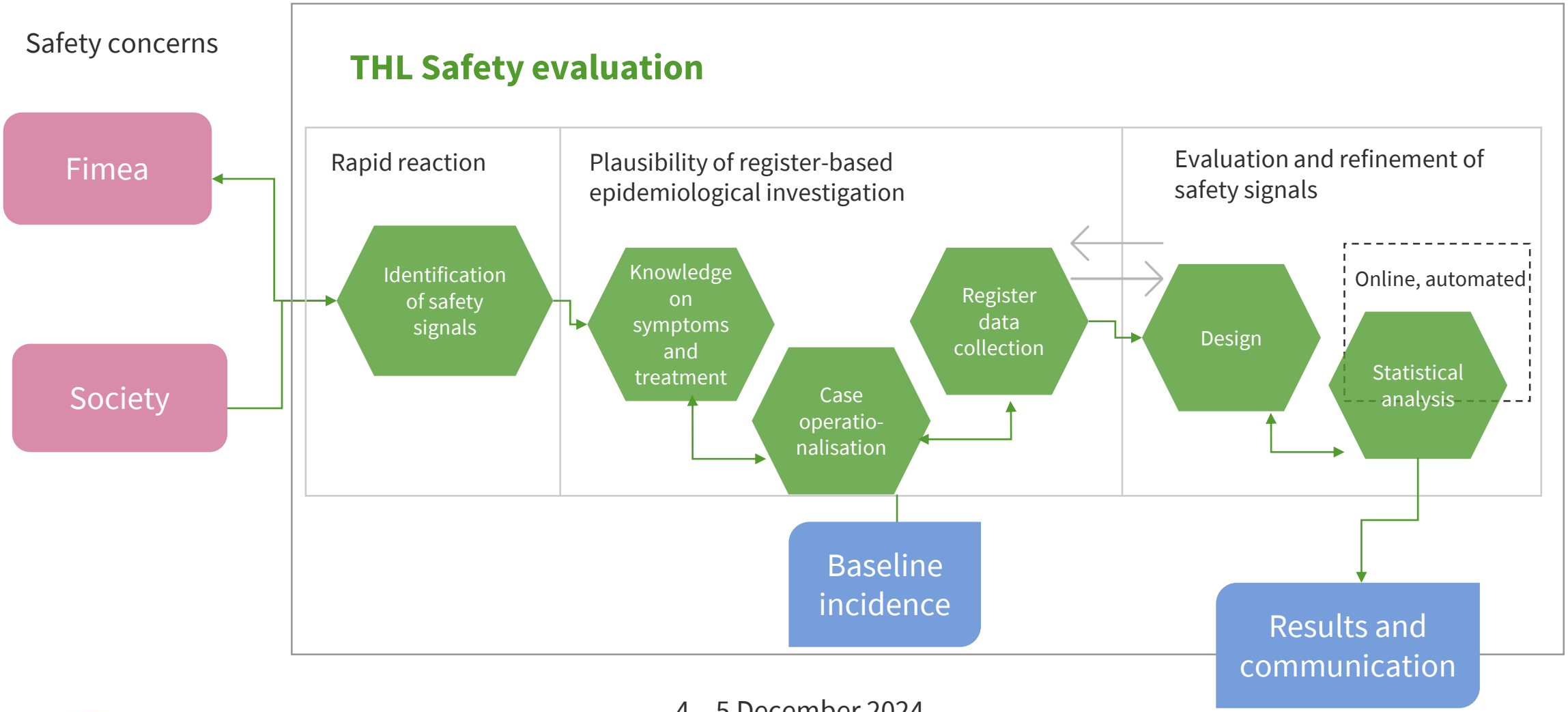
Country as a cohort: personal ID enables data linkage

In Finland, the **Population Information System** can be used to define the study population for vaccine safety analyses.

- Patient and date level data-linkage from population-wide registers
  - The **National Vaccination Register** includes all COVID-19 vaccinations administered in Finland.
  - The **Care Register for Health Care** includes data on discharge diagnoses from inpatient care.
- Possible comparator time can also be the unvaccinated population during any given time.
- The registers also include important information on demographics and comorbidities.



Reactive register-based safety surveillance



Which adverse events are important to study?

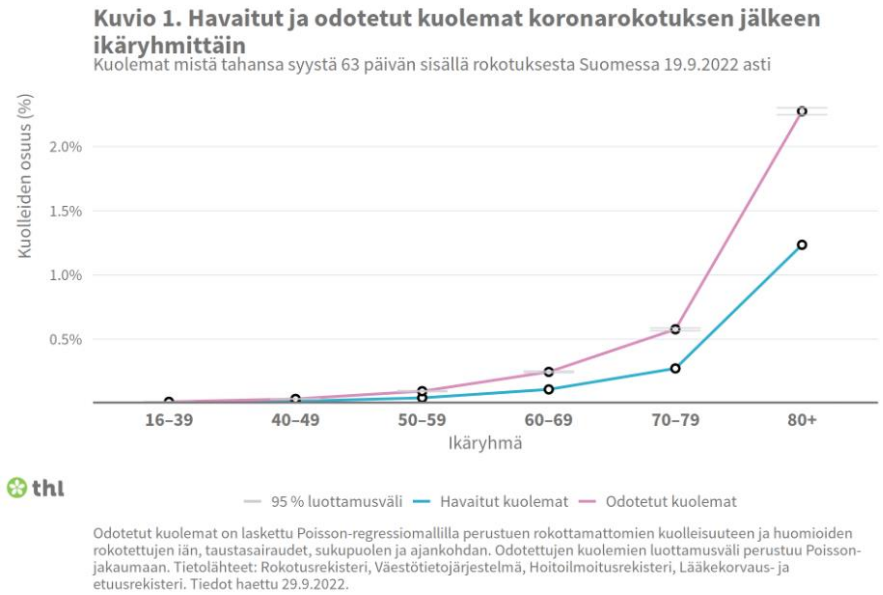
When a large group of individuals are vaccinated, many unwanted health conditions will occur in temporal relationship with vaccination.

➢ Most of these will have no causal relationship with vaccination.

In COVID-19 vaccine safety surveillance, adverse events (AE) under investigation were chosen based on several factors such as:

- frequency of adverse reaction reports compared to known population incidence of the comparable disease
- the severity of the AE
- public interest
- other ongoing investigations
- available data
- available analytic skills and environment

Biological plausibility of a causal relationship did not affect the choice of which AE to study. For example, all-cause mortality immediately following COVID-19 vaccination was thoroughly studied during the vaccination campaign due to public interest in Finland.



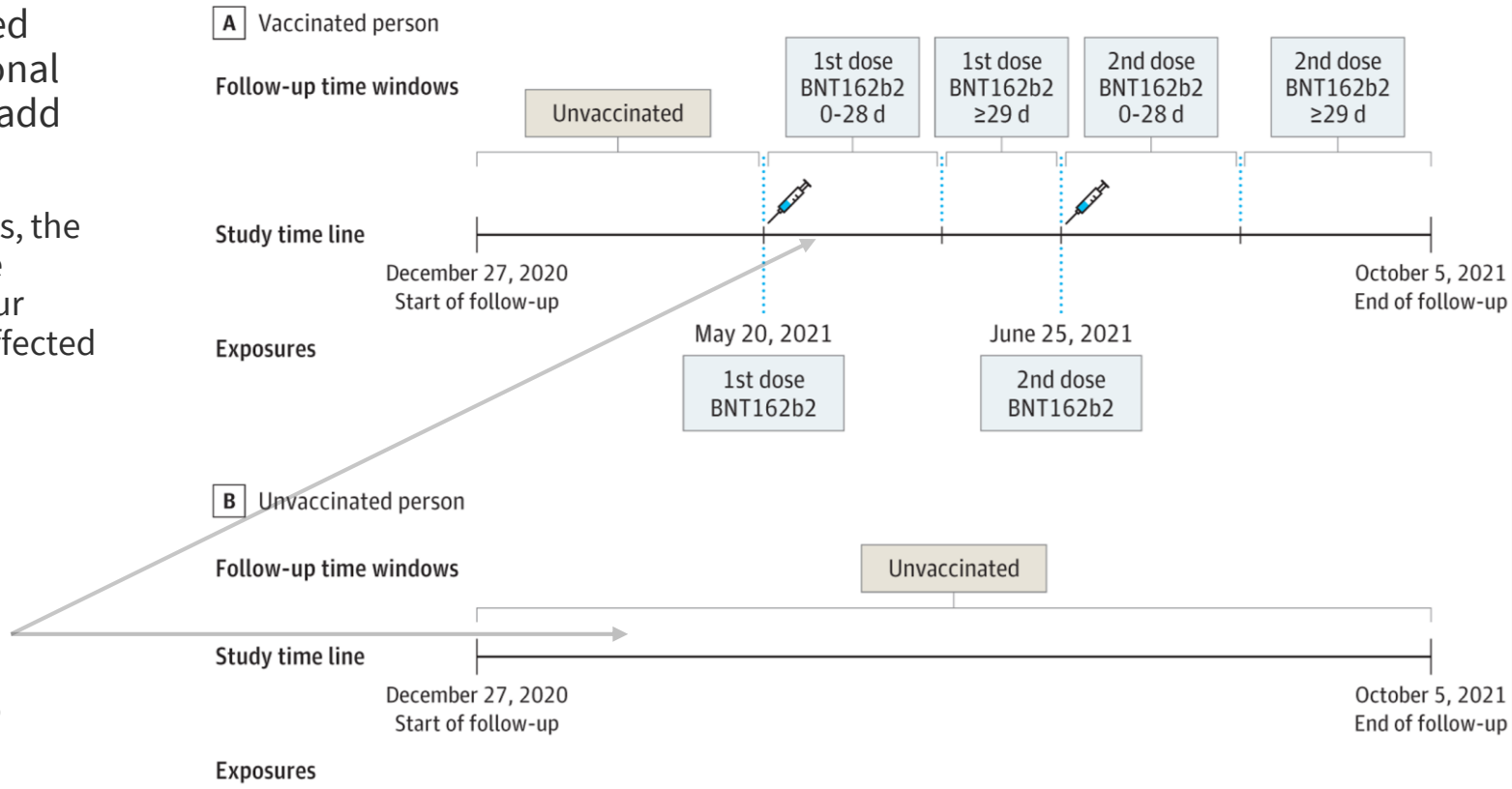
Tuomo Nieminen et al. Kuolleisuus välittömästi koronarokottamisen jälkeen [Hazard of death immediately following COVID-19 vaccination], THL Discussion Paper, https://urn.fi/URN:ISBN:978-952-343-981-8

Study designs: Parallel cohort comparison

Multiple study designs can and should be utilised when evaluating vaccine safety in an observational study, in order to assess possible biases and to add robustness.

- With COVID-19 vaccination adverse event analyses, the choice of main study design depended on e.g. the severity of the outcome, as care-seeking behaviour among vaccinated and unvaccinated was likely affected by the epidemic and lockdown measures.

When studying the association between **COVID-19 vaccination and Myocarditis**, a parallel cohort comparison design was utilised, and the incidence during 28 days following vaccination was compared to incidence during unvaccinated time in the population.

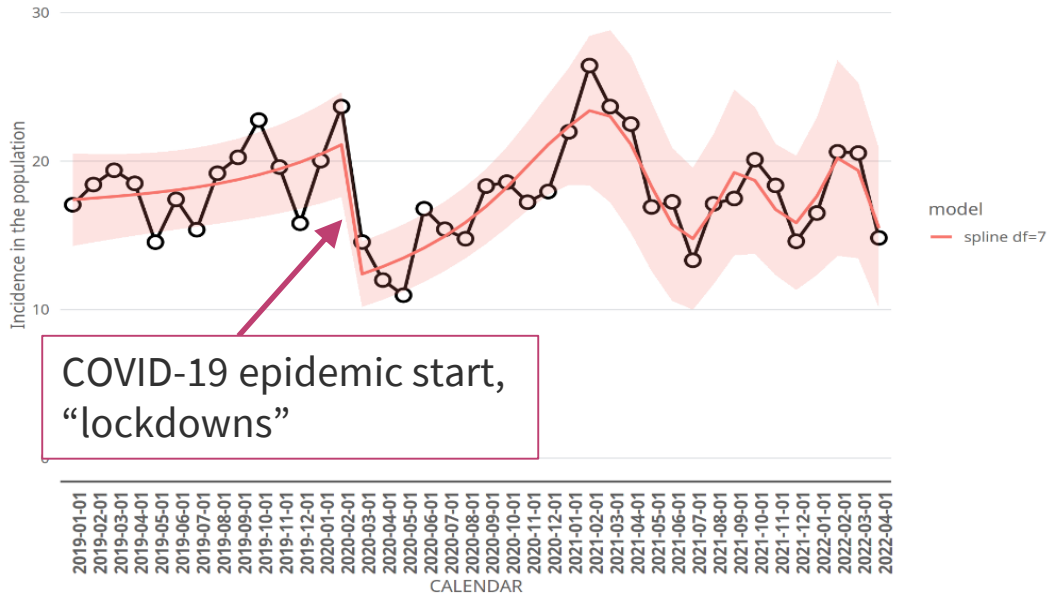


Karlstad Ø, Hovi P, Husby A, et al. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. *JAMA Cardiol.* 2022;7(6):600–612. doi:10.1001/jamacardio.2022.0583

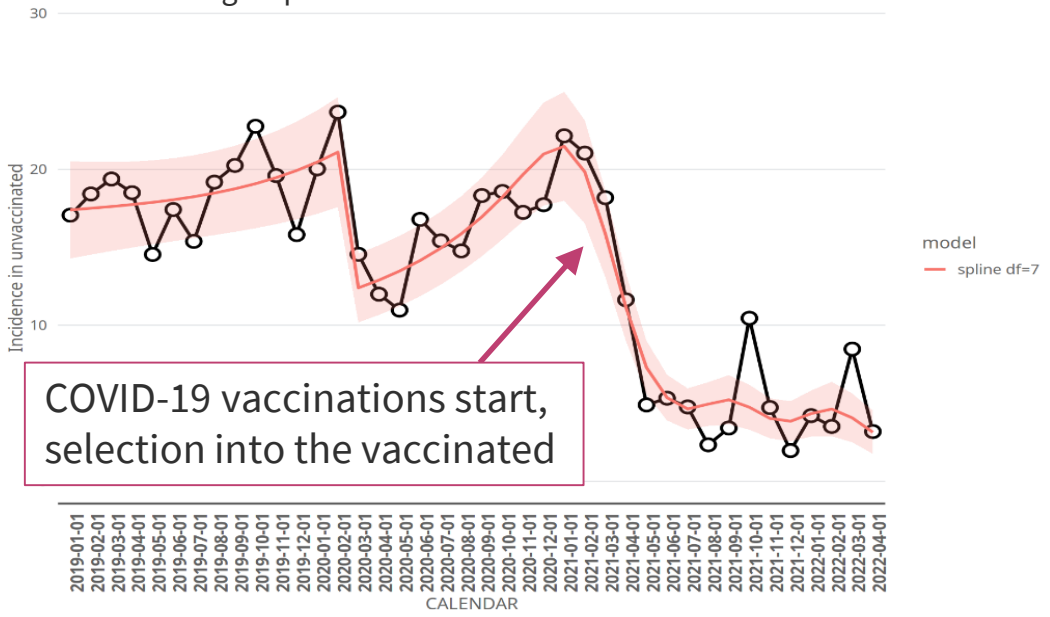
Study designs: Historical cohort comparison

When studying the association between **COVID-19 vaccination and sudden sensoneural hearing loss (SSNHL)**, a historical cohort comparison design was utilised, and the incidence of SSNHL during 55 days following vaccination was compared to incidence before the COVID-19 epidemic.

Incidence of SSNHL in the Finnish population. There was a decline in the utilisation of health services during the beginning of the COVID-19 epidemic



Incidence of SSNHL during unvaccinated time. The age-related selection to vaccinate affects the incidence in the unvaccinated group.



Nieminen TA, Kivekäs I, Artama M, Nohynek H, Kujansivu J, Hovi P. Sudden Hearing Loss Following Vaccination Against COVID-19. *JAMA Otolaryngol Head Neck Surg.* 2023;149(2):133–140. doi:10.1001/jamaoto.2022.4154

Dissemination of the work

- Internal research notes
- Open data
- Web site
- Social media
- Preprint
- Peer reviewed articles
- Review

Thank you to the COVID-19 vaccine safety group and others

- Tuomo Nieminen
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- Terhi Kilpi
- Ulpu Elonsalo
- Timo Koskenniemi
- Anniina Virkku
- Mika Muhonen

...

- Maija Kaukonen, Tiina Karonen et co (FIMEA)
- Anders Hviid (Statens Serum Institute, Copenhagen) + other Nordic collaborators
- GVDN network


Thank you