Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

The case may be made public.

Norwegian Institute of Public Health, Division for Metal and Physical Health 4

Institution: Norwegian Institute of Public Health
Administrative unit: Division for Metal and Physical Health
Title of case study: Real-time surveillance of covid-19 immunization program in Norway
Period when the underpinning research was undertaken: 2012-2024
Period when staff involved in the underpinning research were employed by the submitting institution: 2004 - 2024
Period when the impact occurred: 2020-2024

1. Summary of the impact (indicative maximum 100 words)

The **covid-19 immunization** program has been the largest ever vaccination program in Norway. We developed an innovative surveillance system for adverse event monitoring using real time data from the Emergency Preparedness Register. The ability to rapidly establish Nordic collaboration studies to verify findings and increase study population size was crucial. This system was used for systematic monitoring and was especially important in signal evaluation. Our analyses underpinned governmental decision to exclude virus vector vaccines (AstraZeneca Vaxzevria) from the immunization program after acute severe events post-vaccination (VITT - Vaccine-induced Immune Thrombotic Thrombocytopenia). Our data later indicated an excess risk of heart inflammation (myocarditis) in young males after receiving mRNA-vaccines, leading to recommendations to preferentially use Comirnaty over Spikevax for young persons.

2. Underpinning research (indicative maximum 500 words)

The Norwegian Institute of Public Health (NIPH) is a central part of the Norwegian health authorities, delivering recommendations, reviews and research summaries to the Norwegian government. The Department of Chronic Diseases in Division for Mental and Physical Health engages in high-quality research on epidemiology and risk factors of somatic chronic diseases, and has had as a main responsibility surveillance of these. Earlier research has been on environmental factors (such as e.g infections and vaccines during the 2009 swine flu pandemic) and later development of immune-mediated diseases. The department has had a long-standing research focus on use, safety and effect of pharmaceuticals in the general population and among specific groups, such as those with chronic diseases or pregnant women. The department has expertise in epidemiology, statistics, data management and harmonization, and usage of health and administrative register data for research is a core part of the research activity. The department has longstanding collaboration with researchers in all Nordic countries and have extensive experience in combining Nordic register data in research studies. This prior expertise and experience in the department was perfectly suited to take responsibility of surveillance and research on vaccine safety when the SARS-CoV-2 pandemic hit, and to rapidly establish collaborative studies with other Nordic countries. This highlights the importance of establishing and investing in strong research groups to ensure high quality of evidence used in government decision-making processes during “normal” times to have organizational preparedness and expertise to handle health crises like a pandemic. The research underpinning the impact described in section 3 can be broadly grouped into three categories: **1. Supporting the government's efforts in handling the pandemic** through reports and commissioned tasks to the Ministry of Health and Care Services. For instance, our research contributed to estimating prevalence and geographic distribution of individuals at risk for severe COVID-19 outcomes. These figures were utilized in planning vaccination strategies and allocation of vaccines among municipalities. **2. Continuous surveillance of potential vaccine**

adverse events during the pandemic in close collaboration with the Norwegian Medicines Agency (NOMA), by performing repeated analyses in real-time register data as well as in-depth analyses of signals detected in adverse event reporting systems in Norway and the EU. **3. Performing scientific studies** on specific signals of serious vaccine adverse events including EMA- commissioned study on vaccine safety in children and adolescents and disseminating findings to relevant authorities in the Nordic countries and EMA, ECDC, FDA, WHO, and other authorities.

It is worth noting that most of the research results were used and shared during the pandemic prior to publication, which usually takes a long time, and that many results have yet to be published.

Key researchers: Hanne Løvdal Gulseth, Research director/MD, 2020–2024; German Tapia, senior researcher, 2020–2024; Jesper Dahl, researcher/MD 2021–2024; Paz Lopez-Doriga Ruiz, researcher/MD 2020–2023; Øystein Karlstad, senior researcher, 2021–2024; Nina Gunnes, senior researcher/statistician, 2020–2023; Randi Selmer, senior researcher/statistician, 2021–2022; Inger Johanne Bakken, researcher/statistician 2023; Lars Jøran Kjerpeseth, researcher/MD 2023–2024

3. References to the research (indicative maximum of six references)

1. Lopez-Doriga Ruiz P, Gunnes N, Michael Gran J, Karlstad Ø, Selmer R, Dahl J, Bøås H, Aubrey White R, Christine Hofman A, Hessevik Paulsen T, Viksmoen Watle S, Hylen Ranhoff A, Bukholm G, Løvdal Gulseth H, Tapia G. Short-term safety of COVID-19 mRNA vaccines with respect to all-cause mortality in the older population in Norway. *Vaccine*. 2023;41(2):323-332. doi:10.1016/j.vaccine.2022.10.085
2. Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, Lidegaard Ø, Tapia G, Gulseth HL, Ruiz PLD, Watle SV, Mikkelsen AP, Pedersen L, Sørensen HT, Thomsen RW, Hviid A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. *BMJ*. 2021;373:n1114. doi:10.1136/bmj.n1114
3. Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, Hansen JV, Nohynek H, Gunnes N, Sundström A, Wohlfahrt J, Nieminen TA, Grünewald M, Gulseth HL, Hviid A, Ljung R. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. *JAMA Cardiology*. 2022;7(6):600-612. doi:10.1001/jamacardio.2022.0583
4. Husby A, Gulseth HL, Hovi P, Hansen JV, Pihlström N, Gunnes N, Härkänen T, Dahl J, Karlstad Ø, Heliö T, Køber L, Ljung R, Hviid A. Clinical outcomes of myocarditis after SARS-CoV-2 mRNA vaccination in four Nordic countries: population based cohort study. *BMJ Medicine*. 2023;2(1). doi:10.1136/bmjmed-2022-000373
5. *Report to EMA, Registration Number EUPAS48979: Association between COVID-19 Vaccines and Pediatric Safety Outcomes in Children and Adolescents Aged 5-19 in the Nordic Countries*.; 2023. Accessed April 27, 2023. https://www.encepp.eu/encepp/viewResource.htm?id=103722
6. Ihle-Hansen H, Bøås H, Tapia G, Hagberg G, Ihle-Hansen H, Berild JD, Selmer R, Karlstad Ø, Gulseth HL, Ariansen I. Stroke After SARS-CoV-2 mRNA Vaccine: A Nationwide Registry Study. *Stroke*. Published online 2023. doi:10.1161/STROKEAHA.122.040430

4. Details of the impact (indicative maximum 750 words)

During the pandemic, the NIPH gathered small teams of researchers to answer research questions deemed to be of urgent societal importance. By combining real-time data from several nationwide registries, developments during the pandemic could be followed and analysed. This was used to monitor infections, hospitalizations, deaths, and vaccination uptake in at-risk groups and the general population. A first milestone was defining which groups were at risk for severe SARS-CoV-2

disease, and these numbers were used to distribute the needed number of vaccine doses per health region/hospital/municipality, as at-risk groups were not uniformly distributed in Norway. This impacted the whole Norwegian society, by informing vaccination recommendations and guidelines, assess if any groups were lagging in their vaccination uptake, or needed higher prioritization due to high SARS-CoV-2 burden.

As vaccination unrolled, there were further impacts. During first-dose mRNA vaccine administration, there were concerns of vaccine-associated deaths in the elderly (January 2021), which gained media attention. Our analysis found no association between vaccination and mortality, which quelled fears and led to no vaccination pause or policy change. Later, ChadOx-1 vaccination was put on hold (March 2021) following reports of a novel adverse event with high mortality (VITT). Together with Danish researchers we reported an increased incidence of blood clots post-vaccination, as found in cases of VITT. Our results led to the NIPH recommending excluding vector vaccines from the vaccination program (April 2021), which directly informed policy as this became the official policy in Norway less than a month after the first results were presented (May 2021). Similarly, we reported increased incidence of myo- and pericarditis following mRNA vaccination, which was used by EMA for signal assessment and led to changes in recommendations in Nordic countries that younger individuals should choose Pfizer over Moderna mRNA vaccine in the Nordics (October 2021). The scientific article was published in Aprile 2022 and received the Paper of the Year award from the Norwegian Epidemiological Association for 2022. We have done commissioned studies by EMA (2022-2023), together with Scandinavian collaborators, on adverse events after vaccination in children and adolescents, which has informed policy for further vaccination of children and adolescents.

In addition to the examples listed above, we have also investigated several other suspected adverse events after vaccination (such as stroke, cardiac arrest, Guillain-barre syndrome, appendicitis, to name a few), with weekly monitoring of selected adverse events and at-need analysis of suspected adverse events. Most of these have been negative findings, and had less immediate impact, but these investigations have a crucial long-term impact in society at large as they develop trust and confidence in the vaccination programme by being open and responsive to the needs of the public. Also, each negative finding crucially adds to the knowledge of the safety of the covid/mRNA vaccines, which has a clear future impact. There have also been many requests where results have been sent directly to stakeholders, e.g requests from researchers, clinicians, interest groups, hospitals, journalists and the general population, with a high number of public information and transparency requests. Our results have been used extensively in the media and in debates, showing a clear impact in public discourse. Our published papers have generally attracted attention (e.g references 2, 3, 6 all have 99th percentile Altmetric attention scores compared to outputs of the same age). We have also advised and contributed to several governmental reports (such as reports on mortality, assessments on booster doses for at risk-groups, or assessments for vaccination of children), which have been used when planning future covid vaccinations and evaluate the handling of the pandemic. These have had a clear impact, such as vaccine recommendations in children and adolescents, although as part of a wider body of research.

Results were shared continuously with national and international authorities, such as ECDC, CDC, FDA, WHO and EMA, during the pandemic. This has clearly benefitted governing bodies and health authorities, the medical and academic community at large, and the general public in their charge. These impacts have all been quite substantial and immediate, with e.g the VITT study presenting combined results 14 days after the first reported death, and new recommendations <1 month after this, illustrating the impact on the Norwegian vaccination programme and policy.

5. Sources to corroborate the impact (indicative maximum of ten references)

- **NIPH changes in national vaccination recommendations**
  - Folkehelseinstituttet. Myokarditt hos gutter og unge menn kan forekomme oftere etter Spikevax-vaksinen fra Moderna. Published October 6, 2021. https://www.fhi.no/historisk-arkiv/covid-19/nyheter-2021/okt/myokarditt-spikevax/
  - Folkehelseinstituttet. Koronavaksinasjonsprogrammet: Anbefaling Om Videre Bruk Av AstraZeneca-Vaksinen. Folkehelseinstituttet; 2021. Published April 15, 2021. https://www.fhi.no/contentassets/3596efb4a1064c9f9c7c9e3f68ec481f/2021_04_14-anbefalingsnotat-oppdrag-21.pdf

- **EMA signal assessment report**
  - European Medicines Agency (EMA). Signal assessment report on myocarditis and pericarditis with Spikevax - COVID-19 mRNA vaccine (nucleosidemodified). Published December 2, 2021. https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-myocarditis-pericarditis-spikevax-previously-covid-19-vaccine-moderna-covid_en.pdf

- **EMA-commissioned study report on adverse events post-vaccination in children and adolescents**
  - Report to EMA, Registration Number EUPAS48979: Association between COVID-19 Vaccines and Pediatric Safety Outcomes in Children and Adolescents Aged 5-19 in the Nordic Countries.; 2023. https://www.encepp.eu/encepp/viewResource.htm?id=103722

- **National news prior to the stoppage of the AstraZeneca vaccine**
  - https://www.nrk.no/urix/na-begynner-selv-britene-a-tvile-pa-vaksinen-fra-astrazeneca-1.15487016

- **Presentation at award ceremony for Paper of the Year award from the Norwegian Epidemiological Association**
  - Award received for the paper *Karlstad Ø et al. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. JAMA Cardiology. 2022;7(6):600-612. doi:10.1001/jamacardio.2022.0583.* Presented at The 28th Norwegian Conference on Epidemiology, Tromsø 26 October 2022 https://nofe.no/arets-artikkel/.