Potentially fatal side effects of COVID-19 vaccination in Norwegian nursing home residents. Protocol for a review of the first 100 cases

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Background

Vaccination against COVID-19 started in Norway 27th December 2020. It was politically decided to start vaccination of nursing home residents, known to have the highest risk for a fatal outcome of COVID-19 (1, 2). However, older people with co-morbidities and frailty have largely been excluded from the vaccine trials, and there are no published data on safety and efficacy in this group (3, 4).

About 35,000 persons are institutionalised in nursing homes in Norway, and about 45 deaths occur daily in this patient group (5). In the period from 27th December 2020 to 15th February 2021, approximately 29,400 nursing home residents got the first vaccine dose, all of them with the Pfizer vaccine (*Comirnaty*®). The first report of a death potentially linked to coronavirus-vaccination was sent to the Norwegian Medicines Agency on 4th January, and per mid-February 100 such reports had been sent through the Norwegian spontaneous reporting system. Healthcare professionals, as well as lay people, can submit reports on suspected adverse drug reactions through this system, and are encouraged to report potential fatal side effects, also if they find it unlikely to be a causal relationship between the drug use and the death. Healthcare professionals submitted all the reports about potential fatal side effects of *Comirnaty*.

This relatively high number of potential vaccine related deaths among nursing home residents attracted attention in Norway as well as internationally (6). Vaccination can potentially induce side effects causing a lethal course in seniors with very high degree of frailty, but since the mortality in this group nevertheless is high, a fatal course during the days after vaccination may also be coincidental. It is important to assess whether there is a causal relationship between vaccination and death, since this may help to guide the further vaccination strategy.

Thus, the Norwegian Medicines Agency and the National Institute of Public Health has asked four of us (TBW, BRK, AHR and MM) to scrutinize these first 100 reports and evaluate if it is likely to be a causal relationship between vaccination and death in each individual case. All four members of the expert group are physicians, PhD, specialists in general internal medicine, and working as clinicians. Three (TBW, AHR and MM) are also specialists in geriatric medicine,

whereof two (TBW and AHR) are professors in geriatric medicine. The fourth (BRK) is specialist and professor in infectious diseases and section head physician in nursing home medicine in the municipality of Bergen.

Study procedures

The reports are made completely anonymous before they are sent to the experts. The experts work in two pairs (TBW + MM and AHR + BRK), and each pair of experts assesses 50 of the reported deaths.

The work starts by scrutinizing the reports. They are presented in free text, with a considerable variable level of detail supplied. The National Institute of Public Health makes a preliminary assessment of the potential causal relationship between vaccination and death based on the reports received, but the experts are blinded regarding this assessment. In order to acquire a sufficient level of clinical details for each case, a structured request for further information is sent to the health personnel delivering the initial reports. We ask them to provide the following information for each deceased patient:

- Long-term or short-term nursing home stay
- Diagnoses / chronic disorders
- Regular medication
- Height and weight
- Whether, at the time of vaccination, the patient was permanently bedridden, bedridden more than half the day, or ambulatory most of the day
- Whether, at the time of vaccination, the patient mostly ate himself/herself, or had to be fed by others
- Whether, at the time of vaccination, the patient mostly was in nutritional balance or was in a phase of losing weight
- Whether or not the reporting personnel, at the time of vaccination, expected the patient to die within one month
- Whether or not, in the opinion of the reporting personnel, there is likely to be a causal relationship between the vaccination and the death of the patient.

Based on the text of the submitted reports and the additionally obtained details, we will, for each case, retrieve or derive information on the following features

- Age
- Gender
- Type of nursing home stay (long-term or short-term)
- Chronic diseases
- Medication
- Clinical Frailty Scale (CFS) score (7) as assessed by the experts based on all available information
- Expected remaining life time at time of vaccination (more or less than 1 month)
- New symptoms emerging after vaccination

- Number of days from vaccination to new symptoms
- Number of days from vaccination to death
- Most likely cause of death

Each expert will then, independently, classify the potential relationship between vaccination and death in one of five mutually excluding categories: Unlikely, Possible, Likely, Definite, and Not classifiable. When the two members of each pair of experts have classified each case differently, they will later make a common consensus classification.

Based on each expert's initial assessment (made unaware of the assessment made by the other expert in that pair), we will assess the degree of accordance within each pair of experts by using weighted kappa statistics and McNemar's test of asymmetry. We will also assess the accordance within each pair regarding the CFS classification and the assessment of expected remaining lifetime as more or less than one month on the time of vaccination. In order to disclose whether there exists systematic differences in the evaluations between the two pairs of experts, a random sample of 20 patient reports will be evaluated by both pairs, and the degree of agreement will be assessed by the same methods as described for the within-pairs assessments. Further, we will compare our assessments with the initial assessments made by the National Institute of Public Health upon receipt of the reports.

Publication

The result of the expert group's evaluation will be presented as a report to the Norwegian Medicines Agency and the National Institute of Public Health. We also intend to publish the results in a peer-reviewed international journal, as they are presumed to be of great interest for the international community.

Accountability statement

Before this study protocol was written, the experts made their first, preliminary assessments of the submitted side effect reports, in order to plan the further work, an decide upon supplementary information needed. The protocol was written and published on-line before any final assessment of the cases had been made.

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Oslo/Bergen, 6th April 2021

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