Tidsskriftet Tidsskrift for Den norske legeforening

Nursing home deaths after COVID-19 vaccination

ORIGINAL ARTICLE

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BACKGROUND

In the period 27 December 2020 to 15 February 2021, about 29 400 of Norway's roughly 35 000 nursing home patients were vaccinated with the mRNA vaccine BNT162b2. During the same period, the Norwegian Medicines Agency received 100 reports of suspected fatal adverse reactions to the vaccine. An expert group has examined the reports and assessed the extent of a causal link between vaccination and death.

MATERIAL AND METHOD

The expert group worked in two pairs, each of which examined 50 anonymised reports. Each member first examined the reports alone and classified the causality as unlikely, possible, probable, certain or unclassifiable. Each pair then discussed their results until they reached a consensus. All four experts assessed a random sample of 20 reports. The degree of agreement was assessed using weighted kappa and McNemar's test of symmetry.

RESULTS

The mean age of the patients was 87.7 years (range 61–103 years). Among 100 reported deaths, a causal link to the vaccine was considered probable in 10 cases, possible in 26 and unlikely in 59. Five were unclassifiable. Weighted kappa was 0.40 and 0.38 in the two expert pairs, respectively.

INTERPRETATION

Most nursing home patients have a short remaining life expectancy, but vaccination may, in a few cases, have accelerated a process of dying that had already begun. Nursing home patients should still be given priority for vaccination, but the benefits versus risk must be carefully weighed up for the frailest patients.

Main findings

For the majority of nursing home patients, there was no obvious link between vaccination and death.

A few very frail patients experienced adverse effects from the vaccine that are likely to have accelerated a process of dying that had already begun.

The first COVID-19 vaccination was given in Norway on 27 December 2020. Priority was given to nursing home patients because they have the highest risk of a fatal outcome from COVID-19 (1, 2). However, frail elderly people and those with multiple chronic diseases were underrepresented in the vaccine trials, so little is known about safety and efficacy in these groups (3, 4). In the clinical trial that formed the basis for approval of the Pfizer/BioNTech vaccine BNT162b2 (Comirnaty), the participants' median age was 52 years, ranging from 16 to 91 years (5). A total of 4.4 % were 75 years of age or older, and only 10 of the total 36 621 participants were over 85 years of age. At least one comorbid condition that worsens the prognosis of COVID-19 (heart disease, pulmonary disease, obesity, diabetes, liver disease or HIV) was reported in 46.2 % of the participants, but only 0.1 % had dementia, 0.5 % heart failure and 1.0 % cerebrovascular disease (6). No information was given regarding degree of frailty of the patients.

There are around 35 000 nursing home patients in Norway and about 45 deaths among these patients per day (7). In the period 27 December 2020 to 15 February 2021, approximately 29 400 nursing home patients received the first vaccine dose against COVID-19; all were given the mRNA vaccine BNT162b2 from Pfizer and BioNTech (Norwegian Institute of Public Health, personal communication). The first report of a possible vaccine-related death was sent to the Norwegian Medicines Agency on 4 January 2021, and by 15 February, 100 such reports had been submitted through the spontaneous reporting system for adverse drug reactions. As of 12 May 2021, the number of such reports had risen to 142.

The relatively high number of reported deaths has attracted attention both in Norway and internationally (8). From a clinical perspective, it seems plausible that otherwise mild adverse effects from vaccination could potentially hasten death in particularly vulnerable patients and patients who were already in the final stages of life before vaccination. However, since the mortality rate in this group is very high anyway, a fatal outcome soon after vaccination may also be coincidental. It is important to assess whether there is a causal link between vaccination and death as this can help to guide the ongoing vaccination strategy.

The Norwegian Medicines Agency and the Norwegian Institute of Public Health asked an expert group (TBW, BRK, AHR and MM) to assess the first 100 reports of potentially fatal adverse reactions to Comirnaty and to take a position on whether there was a probable causal link between vaccination and death in each case.

Material and method

The work was organised according to a pre-defined plan published online (9). The expert group consisted of four senior consultants who are specialists in internal medicine. Three of them are also specialists in geriatric medicine and one is a specialist in infectious diseases. In addition to clinical experience from the assessment and treatment of frail elderly patients, all four are also experienced researchers. The group received anonymised adverse reaction reports and worked in two pairs. Each pair assessed 50 of the 100 deaths. The group was blinded to the Norwegian Institute of Public Health's initial causality assessments, but was subsequently sent them after it had completed its own classification.

With the aim of giving the expert group a better basis for its assessments, the Norwegian Medicines Agency sent a request for additional information to all parties that had submitted reports. For each of the deceased patients, we requested a complete list of diagnoses and medications, height and weight of the patient, and asked whether the patient had a short-term or long-term nursing home stay, whether the patient at the time of vaccination was permanently bedridden, bedridden for more than half the day or mobile most of the day, whether the patient at the time of vaccination mostly fed themselves or had to be fed, and whether the patient was generally well nourished or had

lost weight, whether the reporting party at the time of vaccination expected the patient to die within one month, and whether the reporting party believed there was probably a causal link between vaccination and the patient's death.

Based on the text of the submitted adverse reaction reports and the additional information, we structured the available information to form a picture of the patient's clinical course before and after vaccination. A key objective was to assess whether each patient at the time of vaccination had already entered the final stage of life and then progressed at approximately the same rate until they died, or whether there was a clear acceleration in the clinical course in connection with vaccination. We placed particular emphasis on the patient's expected remaining life expectancy at the time of vaccination, new symptoms following vaccination and the period of time from vaccination until the onset of new symptoms and until death. In addition, we classified patients using the Clinical Frailty Scale (CFS), a widely used and internationally recognised scale for frailty, which has also been translated into Norwegian (10). The scale goes from 1 (very fit) to 9 (terminally ill).

Each of the experts independently classified the relationship between vaccination and death into one of five mutually exclusive categories: unlikely, possible, probable, certain and unclassifiable, according to the World Health Organization's classification system for monitoring adverse drug reactions (11). Each pair then met to review their classifications. In cases where the individual classification was different, the pairs discussed them until reaching a consensus.

The initial assessments were compared within each pair based on weighted kappa. This is a statistical measure of agreement between two assessments, and varies between 0.0 (no greater agreement than what can be expected from chance alone) and 1.0 (complete agreement). A kappa value of 0–0.20 is conventionally considered poor, 0.21–0.40 is fair, 0.41–0.60 is moderate, 0.61–0.80 is good and 0.81–1.0 is very good (12). Linearly increasing weights for degree of disagreement were used to place greater emphasis on the cases where the two experts had given a completely different classification. McNemar's test of symmetry was used to assess whether one expert in a pair systematically tended to consider the causal links to be more certain than the other expert (12). The agreement in CFS scores within each pair was assessed in the same way.

To uncover any systematic differences in the assessments between the two pairs, a random sample of 20 reports (ten from each of the pairs' original portfolio) was assessed by both pairs, and the degree of agreement was assessed using the same methods as described for the assessments within each pair.

Results

All the adverse reaction reports were from healthcare personnel. The reports were submitted in free text and varied considerably in the level of detail. Many contained sparse information. Fifty-seven of the reporting parties responded to

the request for additional information.

Background data for the 100 reported cases are shown in Table 1. Of the 79 patients for whom it was possible to estimate a CFS score, three were considered to have a score of 6, 28 a score of 7, 41 a score of 8, and 7 a score of 9. In cases where CFS scores differed, the lowest value was chosen.

Table 1

Descriptive data for the material as a whole (N = 100) and according to the probability of a causal link between vaccination and death, assessed by the expert group (excluding unclassifiable, n = 95). CFS = Clinical Frailty Scale. Mean (range) unless otherwise specified.

Variable	Material as awhole (n = 100)	Probable (n = 10)	Possible (n = 26)	Unlikely (n = 59)
Age (years)	87.7 (61–103)	83.9 (61–96)	89.5 (75–103)	87.5 (73–97)
Sex, men, number (%)	38 (38)	5 (50)	11 (42)	21 (36)
2nd vaccine dose, number (%)	14 (14)	1 (10)	5 (19)	6 (10)
Time from vaccine to symptoms (days)[1]	3.7 (0–19)	1.4 (0–4)	2.5 (0–7)	4.7 (0–19)
Time from vaccine to death (days)[2]	7.7 (0–21)	3.1 (1–6)	8.3 (1–21)	8.2 (0–21)
CFS score[3]	7.8 (6–9)	7.7 (7–8.5)	7.6 (7–8.5)	7.9 (6–9)

[1]Data missing for n = 2, n = 3 and n = 16 respectively, in the groups with a probable, possible and unlikely causal link.

[2]Data missing for n = 1 and n = 5 in the groups with a probable and unlikely causal link.

[3]In cases where two experts have given different CFS scores, the average score was used. In 21 of the 100 cases, the score could not be estimated due to a lack of information. This applied to n = 1, n = 8 and n = 7 in the groups with a probable, possible and unlikely causal link.

In ten of the cases, a causal link between vaccine and death was considered probable, in 26 cases as possible and in 59 cases as unlikely. None were considered to be certain. The expert group considered five of the cases to be unclassifiable. Table 1 shows descriptive data for the first three groups.

Table 2 compares the assessments of the degree of causal link within the two expert pairs. The weighted kappa for the assessments of causality was 0.40 for one pair and 0.38 for the other. For one pair of experts, there was a statistically

significant borderline bias in the assessments (p = 0.05, McNemar's test), which means that one expert tended to assess the causal links as more probable than the other. For the other pair, there was no significant bias (p = 0.28).

Table 2

The two expert pairs' assessments before discussion to reach a consensus

		Expert pair 1, n = 49 Expert B			Expert pair 2, n = 46 Expert B		
		Probable	Possible	Unlikely	Probable	Possible	Unlikely
Expert A	Probable	2	7	0	1	6	4
	Possible	2	8	5	0	3	2
	Unlikely	1	6	18	1	2	27

Unclassifiable cases are excluded.

For estimated CFS scores, the kappa values were 0.55 and 0.67 respectively, but there was nevertheless asymmetry within both pairs (p = 0.02 and p = 0.09, McNemar's test), i.e. one expert tended to assess the degree of frailty as more pronounced than the other.

Table 3 compares the conclusions of the two expert pairs for the 20 cases assessed by both pairs. The weighted kappa for this comparison was 0.70 and p = 0.85 (McNemar's test).

Table 3

Reports assessed by both expert pairs, n = 20

		Expert pair 1		
		Probable	Possible	Unlikely
Expert pair 2	Probable	3	1	0
	Possible	1	4	2
	Unlikely	0	1	8

The Norwegian Institute of Public Health had initially categorised the link between vaccine and death as possible in 83 of the cases, unlikely in 14 and unclassifiable in three. Of the 14 cases that the Norwegian Institute of Public Health classified as unlikely, the expert group came to the same conclusion in 12, but classified two as possible.

Discussion

Of the 100 reported deaths, the expert group classified 10 (10 %) as most likely related to the vaccine, and considered that there could be a possible link for 26 (26 %). It must be emphasised that these estimates are very uncertain, which is illustrated by the moderate kappa values for agreement between the initial assessments.

The spontaneous reporting system for adverse drug reactions is primarily useful for generating hypotheses and is not particularly suitable as a basis for assessing causality. Many of the reports did not contain sufficient clinical information to form an impression of the patient's clinical course and a possible causal link between vaccination and death. Almost half of the reporting parties did not submit additional information. In particular, there was a lack of information about which phase of life the patients were in, and whether their health and general condition were already rapidly or slowly deteriorating before vaccination. All patients were in a complex clinical situation characterised by old age, frailty and multiple chronic diseases, which means that a variety of factors could have contributed to the deaths. It is therefore practically impossible to determine with any certainty how much of a role the vaccine played in the deaths.

The extremely high mortality rate in nursing homes means that random factors will lead to a certain number of deaths shortly after vaccination anyway. It cannot be ruled out that some of the deaths that were classified as probable are in fact due to such random factors. Nevertheless, we find it reasonable to assume that adverse effects from the vaccine in very frail patients can trigger a cascade of new complications which, in the worst case, end up expediting death.

The categories 'probable' and 'unlikely' were used in cases where the expert group considered there to be a clear likelihood one way or the other, and the category 'possible' was used where a causal link between vaccination and death was just as likely as unlikely. Many of the cases classified as 'possible' are therefore very uncertain, and some of them could perhaps also have been categorised as unclassifiable. The group considered far more cases to be either probable or unlikely than the Norwegian Institute of Public Health in its initial assessment. This is probably due to access to more information as well as knowledge of typical clinical courses in frail elderly people.

The adverse reaction reports were submitted within a period of approximately 50 days, during which it can be assumed that 2000–2500 nursing home patients died in Norway (7). Whether 10 or 36 of these deaths were accelerated by the vaccine, the proportion is still low. In the same period, almost 30 000 nursing home patients were vaccinated, which means that there will most likely have been far more than 100 deaths in nursing homes in a close temporal relationship to vaccination in the relevant time period. Our findings cannot therefore be used to estimate the incidence of vaccine-related deaths.

It is important to emphasise that the vast majority of long-term patients in nursing homes have a short remaining life expectancy. They are definitely in the final stage of life. This is reflected in the expert group's scoring of 48 out of 79 classifiable patients in CFS category 8 or 9, which indicates an expected lifespan of less than six months. This has two important implications. The first is that the task of the expert group in practice was to identify a possible acceleration of an already rapidly deteriorating clinical course, which is schematically outlined in Figure 1. Such an assessment requires nuanced and detailed clinical information, which in many cases was not available. The estimates are therefore uncertain. The second implication is that even in cases where the causal link was classified as probable, death may have occurred only a little sooner (days, weeks or a few months) than would otherwise have been expected. This is an important aspect to consider. Also in these cases, vaccination was in all probability only a contributing factor to the cause of death. The patient's frailty, comorbidity and age were also necessary links in the causal chain.

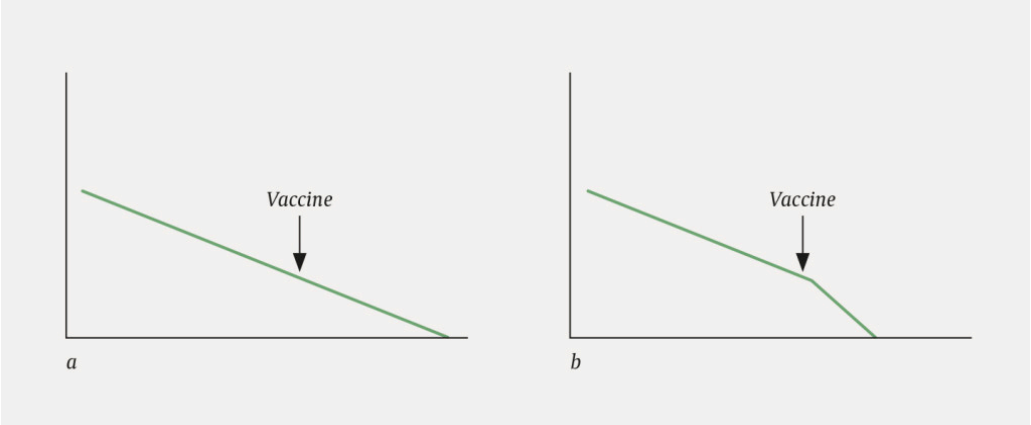

Figure 1 Theoretical link between the death process and vaccination, heavily schematised. The X-axis illustrates the time and the Y-axis illustrates the remaining life expectancy. a) Vaccination did not hasten death. b) Vaccination accelerated death.

Our findings should not be interpreted as implying that patients with a CFS score of 8 should not generally be vaccinated. Frail patients can potentially benefit considerably from vaccination because of the high mortality rate from COVID-19 (13) among this group, a high risk of long-term effects on function and quality of life (14) and the benefit from eased visiting restrictions.

Frailty assessments can, however, be used to identify patients who are particularly vulnerable to adverse drug reactions and probably also adverse reactions to the vaccine. It is reasonable to assume that the risk of fatal consequences from adverse effects of the vaccine can be reduced through preventive measures such as sufficient hydration, medication review and optimised treatment of comorbid conditions. Clinical vigilance for acute functional failure, for example due to an intercurrent infection around the scheduled time of vaccination, is also likely to be important, so that vaccination can be delayed if necessary. For those with the most impaired physiological reserves, the advantages and disadvantages of vaccination must be carefully considered. It is our view that this is adequately discussed in the current version of the Norwegian Institute of Public Health's COVID-19 vaccine guide (15).

The article has been peer reviewed.

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Publisert: 19 May 2021. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.21.0383
Received 6.5.2021, first revision submitted 13.5.2021, accepted 14.5.2021.