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Deaths in nursing homes after covid-19 vaccine

COVID-19 ENGLISH

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Torgeir Bruun Wyller, Bård Reiakvam Kittang, Anette Hylen Ranhoff, Pernille Harg, Marius Myrstad *About the authors*

SAMMENDRAG

BACKGROUND

In the period 27.12.2020–15.2.2021, about 29,400 of Norway's approx. 35,000 nursing home patients vaccinated with the mRNA vaccine BNT162b2. In the same period, the Norwegian Medicines Agency received 100 reports of suspected fatal side effects of the vaccine. An expert group has examined the reports and assessed the degree of causality between vaccination and the deaths.

MATERIAL AND METHOD

The expert group worked in two pairs who examined 50 anonymised messages each. Each member first examined the messages alone and classified the relationship as unlikely, possible, probable, certain or unclassifiable. Each pair of experts then deliberated to reach a consensus. All four experts assessed a random sample of 20 messages. The degree of agreement was assessed with weighted kappa and McNemar's symmetry test.

RESULTS

The patients' average age was 87.7 years (range 61–103 years). Among 100 reported deaths, a connection with the vaccine was assessed as probable in 10 cases, as possible in 26 and as unlikely in 59 cases. Five were unclassifiable. The weighted kappa was 0.40 and 0.38 in the two expert pairs, respectively.

INTERPRETATION

Most nursing home patients have a short expected remaining life, but in a few cases the vaccination may have contributed to accelerating an ongoing death process. Nursing home patients should still be given priority for vaccination, but in the most frail patients benefit versus risk should be thoroughly weighed.

MAIN FINDINGS

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

A few patients with a high degree of frailty suffered vaccine side effects that probably accelerated an already ongoing death process.

INNLEDNING

Vaccination against covid-19 started in Norway on 27 December 2020. It was decided to start with nursing home patients, as they have the highest risk of fatal outcomes from covid-19 (1, 2) . However, the frail elderly and people with many chronic diseases were poorly represented in the vaccine trials, so there is little knowledge about safety and efficacy in this group (3, 4) . In the study that formed the basis for the approval of the Pfizer/BioNTech vaccine BNT162b2 (Comirnaty), the median age of the participants was 52 years, with a spread of 16–91 years (5). 4.4% were aged 75 or over, and only 10 out of a total of 36,621 participants were aged over 85. 46.2% were

reported to have at least one comorbid condition that worsens the prognosis of covid-19 (heart disease, lung disease, obesity, diabetes, liver disease or HIV), but only 0.1% had dementia, 0.5% heart failure and 1, 0% cerebrovascular disease (6) . Information on frailty was not provided.

There are around 35,000 nursing home patients in Norway, and around 45 of them die every day (7) . In the period 27.12.2020–15.2.2021, approx. 29,400 nursing home patients the first vaccine dose against covid-19, all with the mRNA vaccine BNT162b2 from Pfizer and BioNTech (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 up to 15 February 100 such reports had been submitted through the spontaneous reporting system for drug side effects. As of 12 May 2021, the number of such messages had reached 142.

The relatively high number of reported deaths attracted attention both in Norway and internationally (8) . From a clinical perspective, it seems plausible that otherwise mild vaccine side effects can potentially hasten the time of death in particularly vulnerable patients and patients who were already in the end of life before vaccination. But since the mortality rate in this group is very high in any case, a fatal course in the days after vaccination could also be accidental. It is important to assess whether there is a causal link between vaccination and death, as this can help guide the further vaccination strategy.

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

MATERIALE OG METODE

The work was laid out according to a pre-defined, online published plan (9) . The expert group consisted of four senior doctors who are specialists in internal medicine. Three of them are also specialists in geriatrics and one is a specialist in infectious diseases. In addition to clinical experience from the examination and treatment of frail elderly patients, all four also have a background as researchers. The group received anonymised side effect reports and worked in pairs. Each pair considered 50 of the 100 deaths. The group was blinded to the Institute of Public Health's initial assessment of any causal relationships, but was sent these 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 the notifiers. For each of the deceased patients, we asked whether the patient was in a short-term or long-term care facility, a complete list of diagnoses, regular medications, height and weight, whether the patient was permanently bedridden at the time of vaccination, bedridden for more than half the day or up most of the day, whether the patient on at the time of vaccination mostly ate by themselves or had to be fed and whether the patient was mostly in nutritional balance or lost weight, whether the reporter at the time of vaccination expected the patient to die within a month, and whether the reporter believed that there was probably a causal relationship between the vaccination and the death.

Based on the text of the submitted adverse event 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 central objective was to assess whether each individual patient at the time of vaccination was in a downward course that continued at roughly the same rate until the patient died, or whether there was a clearly accelerated course in connection with the vaccination. We placed particular emphasis on the expected remaining lifespan at the time of vaccination, new symptoms that occurred after vaccination and the duration from vaccination to new symptoms and to death. In addition, we classified the patients using the Clinical Frailty Scale (CFS), an internationally widely used scale for frailty, which has also been translated into Norwegian(10) . The scale runs 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 adverse drug reactions (11) . Each pair then met for a review of their classifications. In those cases where the individual classification was different, the pairs discussed each other to reach a consensus assessment.

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 would be expected based on chance alone) and 1.0 (complete agreement). A kappa value of 0–0.20 is conventionally considered poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good and 0.81–1.0 as very good (12) . Linearly increasing weights for degree of discrepancy were used to give greater weight to those cases where the two experts had assessed completely differently. McNemar's symmetry test was used to assess whether one expert in a pair systematically tended to assess the causal relationships as more certain than the other (12). The agreement in CFS scores within each pair was assessed in a similar way.

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

RESULTATER

All side effect reports came from healthcare professionals. The reports were submitted in free text and varied considerably in their level of detail. Many contained sparse information. 57 of the notifiers responded to the request for additional information.

Background data for the 100 reported cases appears in table 1. Of the 79 patients where it was possible to estimate a CFS score, three were assessed to have a score of 6, 28 a score of 7, 41 a score of 8 and seven a score of 9. In cases where there were different assessments of the CFS score, the lowest value was chosen.

TABLE 1

Descriptive data for the material collected (N = 100) and by degree of probability of causality between vaccine and death, assessed by the expert group (non-classifiable omitted, n = 95). CFS = Clinical Frailty Scale. Average (spread) if not stated otherwise.

In ten of the cases, a causal link between vaccine and death was assessed as probable, in 26 cases as possible and in 59 cases as unlikely. None were considered safe. 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 causality within the two expert pairs. The weighted kappa for the assessments of causality between vaccine and death was 0.40 for one pair and 0.38 for the other. For one pair of experts, there was a statistically borderline significant bias in the assessments ($p = 0.05$, McNemar's test), i.e. one expert tended to assess the causal relationships as more probable than the other. For the second pair, there was no significant bias ($p = 0.28$).

TABLE 2

The two expert pairs' assessments before consensus discussion

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

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

TABLE 3

Messages assessed by both pairs of experts, n = 20

The Institute of Public Health had initially categorized the connection between vaccine and death as possible in 83 of the cases, as improbable in 14 and as non-classifiable in three cases. Of the 14 cases that the Norwegian Institute of Public Health classified as unlikely, the expert group came to the same conclusion in 12, while two were classified as possible.

DISKUSJON

Of the 100 reported deaths, the expert group classified 10 (10%) as most likely related to the vaccine, and considered 26 (26%) to be a possible connection. It must be emphasized that these estimates are highly uncertain, which is illustrated by moderate kappa values for agreement between the initial assessments. The spontaneous reporting system for drug side effects is primarily hypothesis-generating and difficult to use as a basis for assessing causality. In many cases, the messages contained too little clinical information for it to be possible to form an impression of the patient's clinical course and thus a possible causal link between vaccination and death. Almost half of the notifiers did not submit additional information. In particular, there was a lack of information about the phase of life the patients were in, and whether they already had rapidly or slowly declining health and general condition before vaccination. All patients were in a complex clinical situation characterized by old age, frailty and many chronic diseases, so that many factors may have contributed to the deaths. It is therefore in practice impossible to determine with certainty how big a role the vaccination played in the death process.

Since the mortality rate in nursing homes is very high, it is expected that some patients will die by pure chance shortly after being vaccinated. It cannot be ruled out that some of the deaths that were classified as probable are in reality due to such random coincidences. We still find it reasonable to assume that vaccine side effects in very frail patients can start a cascade of new complications which, in the worst case, end up speeding up the time of death.

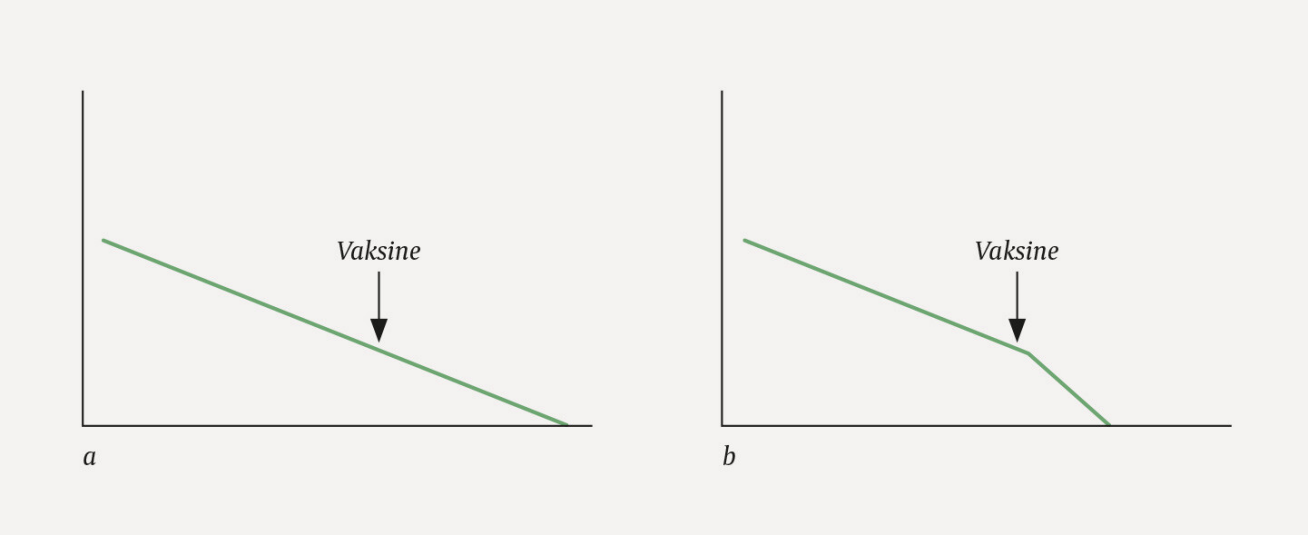
The categories probable and unlikely were used in those cases where the expert group believed that there was a clear preponderance of probability one way or the other, and the category possible where it was just as likely that there was a causal connection between vaccination and death as that there was no connection. The cases classified as possible are therefore in many cases very uncertain, and

some of them could perhaps also have been placed in the non-classifiable category. The group assessed far more cases as either probable or unlikely than what the Institute of Public Health had done in its initial assessment. This is probably due to both access to more information and knowledge of typical clinical courses in frail elderly people.

The side effect reports were submitted during approx. 50 days, a period of time in which it can be assumed that 2,000–2,500 nursing home patients died in Norway (7) . Whether one assumes that 10 or 36 of these deaths were hastened by the vaccine, the proportion is low anyway. In the same period, close to 30,000 nursing home patients were vaccinated, which means that there must very likely have been far more than 100 deaths in nursing homes in close temporal relation 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 emphasize that the vast majority of long-term patients in nursing homes have a short life expectancy. They are definitely in the last phase of life. This is emphasized by the fact that the expert group scored 48 out of 79 classifiable patients in CFS category 8 or 9, which indicates a life expectancy of less than six months. This has two important implications. The first is that the expert group's task in practice was to identify any acceleration of an already rapid downward 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 those cases where causation was classified as probable, death may have occurred only slightly earlier (days, weeks or a few months) than it otherwise would have done. This is an important point in the assessment. In these cases, too, the vaccination was most likely only a contributing cause of the death. The patient's frailty, comorbidity and age were also necessary links in the causal chain.

FIGURE 1



Theoretical connection between death process and vaccination, strongly schematized. The X-axis illustrates time and the Y-axis illustrates remaining life. a) The vaccination did not hasten death. b) The vaccination hastened death.

Our findings should not be interpreted as meaning that patients with a CFS score of 8 should generally not be vaccinated. On the contrary, frail patients can potentially benefit greatly from vaccination, both because they have a high mortality rate from covid-19 (13) , a high risk of long-term effects on function and quality of life (14) as well as great pleasure from less intrusive visiting restrictions in nursing homes.

Frailty assessments, on the other hand, can be used to identify patients who are particularly vulnerable to side effects of drugs and probably also vaccine side effects. It is reasonable to assume that the risk of fatal consequences of vaccine side effects can be reduced through preventive measures such as good hydration, drug review and optimized treatment of comorbid conditions. In addition, it is probably important to be clinically alert to acute functional impairment, for example due to intercurrent infection, around the planned vaccination time, so that the vaccination is possibly postponed. For those with the most reduced physiological reserves, the advantages and disadvantages of vaccination must be thoroughly assessed. In our opinion, this is adequately discussed in the current version of the Norwegian Institute of Public Health's guidance on the corona vaccine(15) .

The article is peer-reviewed.

LITERATURE

COMMENTS (3)

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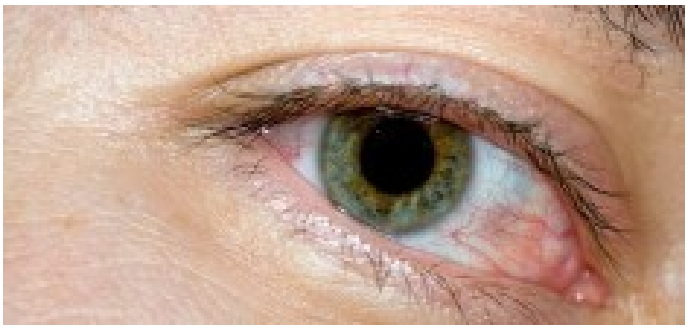

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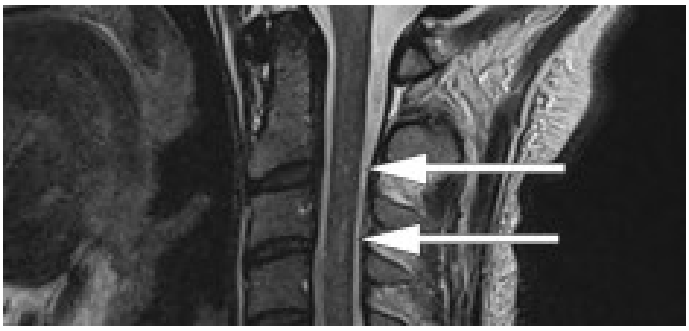

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