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SAFETY PROFILE OF COVID-19 VACCINES AMONG HEALTHCARE WORKERS: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Healthcare workers were among the first groups offered COVID-19 vaccines in late 2020 and 2021, so they supplied much of the early real-world safety information. This narrative review summarises published trial reports, surveillance analyses and surveys on the safety of mRNA, adenoviral-vector and inactivated vaccines in this population. Local pain, fatigue, headache, myalgia and fever are common and usually short-lived, more frequent after the second mRNA dose and in younger people and women. Anaphylaxis, vaccine-induced thrombosis with thrombocytopenia and myocarditis are rare but important. Evidence rests largely on self-reported symptoms and passive reporting systems, with limited long-term follow-up. This review reports no new observational data.

1. INTRODUCTION

When the first COVID-19 vaccines were authorised for emergency use at the end of 2020, health systems had to decide quickly who would be offered them. Healthcare workers were placed near the front of the queue in nearly every national plan. Their risk of infection at work was higher than that of the general community, and an infected worker could pass the virus to patients who were already vulnerable [1, 2, 3]. Protecting the workforce also protected the capacity of hospitals to keep running. In many hospitals the first doses were given within days of the first delivery of vaccine.

That decision made healthcare workers a very large, closely watched population. Within weeks, millions had received a dose, many of them with occupational health departments, hospital pharmacies and employee surveys recording what happened next. The result was a stream of early safety information that complemented the pivotal trials, which had been designed principally to show efficacy and which, for practical reasons, included few people over 65 or with significant comorbidity [4, 5, 6].

Safety questions arrived in layers. First came the everyday effects: a sore arm, a day of tiredness, a fever that sent a nurse home before a night shift. Then came the questions about uncommon but serious events, including allergic reactions in the first minutes after injection and, later, unusual clotting disorders and inflammation of the heart muscle [7, 8, 9]. Each layer needed a different kind of evidence, from symptom diaries to national spontaneous-reporting systems [10, 11, 12].

Why were healthcare workers such a rich source of information? One reason is that they are employed, identifiable and contactable, so follow-up is easier than in the general public. Another is that they understand symptom reporting and are, on the whole, willing to complete questionnaires. A third is that vaccination of a whole hospital workforce within a few weeks creates a natural experiment in which hundreds or thousands of people receive the same product at around the same time [10, 13, 14]. The same features also bias the data: workers are not typical of the population, and they are likely to over-report minor symptoms when asked to look for them.

This review draws together published trial reports, surveillance analyses and cross-sectional surveys to describe what was known about vaccine safety in healthcare workers up to mid-2021. It does not report original data from any cohort. The sections below cover the vaccine platforms and why they differ in reactogenicity, the experience of healthcare workers, rare serious events, the methods used to monitor safety, and the main limitations of the evidence.

2. VACCINE PLATFORMS AND REACTOGENICITY

Three main platform types were in use among healthcare workers by mid-2021. Messenger RNA vaccines (BNT162b2 and mRNA-1273) deliver nucleoside-modified RNA in lipid nanoparticles that is translated into the spike protein in host cells [15, 16, 17]. Adenoviral-vector vaccines (ChAdOx1 nCoV-19, Ad26.COV2.S and the Russian Sputnik V) carry spike-protein DNA in a replication-incompetent virus [6, 18, 19, 20]. Inactivated whole-virion vaccines (CoronaVac and BBV152) use chemically killed virus with an aluminium adjuvant [21, 22].

The mechanisms behind reactogenicity differ somewhat between platforms but share a core. Innate immune sensors recognise components of the vaccine, including the lipid nanoparticle and RNA, the viral vector, or the adjuvant, and release cytokines such as interleukin-6, tumour necrosis factor and type I interferons [15, 23]. Those cytokines act on the hypothalamus and on pain receptors, producing fever, malaise and local tenderness. The more vigorous the early innate response, the more noticeable the symptoms, although the link between symptoms and later antibody titres is weak at best [23, 24].

Phase 1 and 2 studies gave early signals. Dose-related fever, chills and fatigue were reported after the second dose of the mRNA candidates, and older participants usually described milder symptoms than younger ones [16, 17, 24]. For the ChAdOx1 vector vaccine, reactions were common after the first dose and could be reduced with paracetamol [20]. These patterns anticipated what healthcare workers later reported in much larger numbers.

Dose scheduling shaped what workers experienced. The mRNA vaccines were licensed on two-dose schedules three or four weeks apart, whereas the vector and inactivated vaccines were frequently given at longer intervals, and in the United Kingdom the interval for BNT162b2 was extended to as long as twelve weeks to reach more people with a first dose [14]. A longer interval changes the timing of the reactions but not their nature. Workers vaccinated early in the

campaign thus had two reaction episodes within a month, while those vaccinated later might have the second months after the first. Studies that pooled symptoms across doses obscured this pattern [10, 13, 25].

Phase 3 trials confirmed that the mRNA vaccines were efficacious and well tolerated in the sense of a regulatory benefit-risk assessment. Local pain at the injection site was the most frequent complaint, systemic reactions were more common after the second dose, and serious adverse events were balanced between vaccine and placebo groups [4, 5]. The adenoviral-vector trials reported a similar overall pattern with, in several analyses, more frequent early systemic symptoms after the first dose [6, 18, 19]. Inactivated vaccines generally produced lower rates of systemic reactions than the other platforms [21, 22]. Where available, pooled estimates from several surveys would give a firmer basis than any single report.

A comparison of platforms from trial data alone is not straightforward. Populations, solicited-symptom definitions, follow-up periods and severity grading differ among studies, and none of the pivotal trials compared vaccines head to head. Self-reported symptom surveys give a partial substitute, although they bring their own biases [10, 25, 26].

Some host factors have been identified consistently. Younger recipients, women and people who had previously been infected with SARS-CoV-2 reported more systemic effects, particularly after the first dose in the previously infected [10, 13, 27]. The finding for previously infected workers fits immunological data showing a rapid, strong antibody response to a single dose in seropositive people, which suggests a primed immune system responding more vigorously to the first exposure [27, 28]. For occupational health planning, this meant that staff with prior infection could expect symptoms after dose one that resembled those other staff would feel after dose two.

Immunogenicity and reactogenicity are not simple mirror images of each other. Early mRNA studies showed robust antibody and T-cell responses at doses that produced mild to moderate reactions, and older adults responded well even though they reported fewer symptoms [16, 17, 20, 24]. Antibody titres after one dose of an mRNA vaccine in previously infected workers were comparable with those after two doses in uninfected workers [27, 28]. Together these observations argue against the idea that a person who has no symptoms has not been protected, an idea that circulated widely among staff and was occasionally repeated by colleagues.

3. SAFETY IN HEALTHCARE WORKERS

Several large observational studies described the early experience of healthcare workers. A prospective study of users of a symptom-tracking smartphone application in the United Kingdom reported that systemic side effects were reported by a minority after the first dose of either BNT162b2 or ChAdOx1, that they were more frequent after the second dose of BNT162b2, and that local effects were common with all vaccines [10]. Most symptoms were mild and lasted around a day or two. Participants who reported symptoms were not exclusively health workers, but this occupational group was strongly represented.

Cross-sectional surveys of healthcare workers give a closer view of daily experience. Questionnaires from groups of workers given BNT162b2 recorded injection-site pain in most recipients, with fatigue, headache and muscle pain next, and fever reported by a smaller proportion, more often after the second dose [13, 25, 26]. A survey of workers in the Czech Republic, most of whom had received BNT162b2, found a similar gradient of symptoms and again reported that younger workers and women were affected more often [29]. By contrast, the phase 3 trial of the inactivated CoronaVac vaccine reported fewer systemic reactions than are described for mRNA vaccines, although the populations are not directly comparable [21].

The published evidence is brought together in table 1, which sets out representative findings by vaccine platform and monitoring approach, and the number of entries per group is displayed in fig. 1. The rows are a synthesis of what was reported by each source in qualitative terms; where the original papers

gave counts, these are not reproduced because the denominators and symptom definitions differ too much to allow a simple comparison. The most robust message across sources is that common reactions are frequent but transient, and that serious events are uncommon [4, 5, 10, 11].

Table 1: Published safety findings for COVID-19 vaccines relevant to healthcare workers

Vaccine or topic	Reported finding	Ref.
BNT162b2 mRNA platform	Pain at the injection site most common; systemic effects more frequent after dose two and in younger recipients.	[4, 13, 25]
mRNA-1273 mRNA platform	Similar reactogenicity profile; delayed large local reactions reported about a week after dosing.	[5, 30]
Anaphylaxis after mRNA vaccines	Rare, mostly within 30 minutes; prompted observation periods and adrenaline availability.	[7, 31, 32]
Myocarditis after mRNA vaccines	Rare; mainly young males after dose two; usually mild and short-lived.	[9, 33]
ChAdOx1 nCoV-19 Vector platform	Frequent early systemic effects after dose one; reduced with paracetamol in early trials.	[6, 10, 20]
Thrombosis with thrombocytopenia	Rare, one to three weeks after ChAdOx1 or Ad26.COV2.S; antibodies to platelet factor 4.	[8, 34, 35]
Ad26.COV2.S Single dose	Early United States surveillance showed a generally mild event profile and a rare thrombosis signal.	[18, 36]
CoronaVac Inactivated	Lower rates of systemic reactions than are described for mRNA vaccines in the phase 3 trial; populations not directly comparable.	[21]
BBV152 Inactivated	Phase 1 trial reported mostly mild adverse events.	[22]
Passive reporting systems	Fast and sensitive to unexpected events but cannot estimate incidence.	[11, 12]
Symptom-tracking applications	Allow large prospective comparisons but depend on self-reporting.	[10]

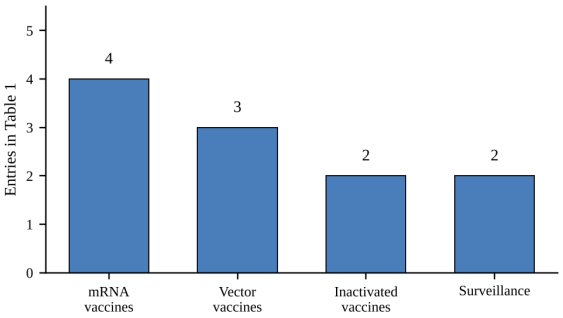


Fig. 1: Number of entries in table 1 by vaccine platform or monitoring approach

Surveillance data from the first weeks of the United States programme, which began with healthcare personnel, showed that most reports to the Vaccine Adverse Event Reporting System were of non-serious events such as headache, fatigue, dizziness and pain at the injection site, and that reports of serious events were rare relative to the number of doses given [11]. Reporting rates are, of course, affected by who reports and how easy reporting is, but the overall picture was consistent with trial findings. A later analysis of the single-dose Janssen vaccine followed the same pattern, with an additional signal that is discussed below [36].

Pharmacists and nurses delivering vaccines also saw the practical side of reactogenicity. Syncope and anxiety were noticeable at busy sites, injection technique and the choice of a deltoid site affected the pain reported, and the shoulder-injury problems recorded later in some surveillance reports were attributed to needle placement and not to the vaccine antigen [12, 32, 37]. Training vaccinators properly, which is cheap, therefore contributes to the safety profile as experienced by staff, even if it does not appear in trial tables.

Delayed local reactions attracted attention. Some people who received mRNA-1273 developed a red, itchy, sometimes warm and swollen area around the injection site, appearing about a week after the dose, and in a small series the reaction was described as a delayed large local reaction, resolving within days without treatment [30]. It was not a contraindication to a second dose, and most affected people were able to continue [30, 31]. Workers who developed it were sometimes alarmed, since it resembled cellulitis.

Pregnancy and breastfeeding raised separate questions for the many women in the healthcare workforce. Pregnant women had been excluded from the pivotal trials, so the first guidance relied on biological plausibility and on the known risks of COVID-19 in late pregnancy, and early surveillance of pregnancy outcomes was reassuring but limited [11, 12, 37]. Professional bodies generally advised that pregnant staff could choose vaccination after discussion of risks and benefits. The reality for workers was a period of uncertainty during which individual counselling by occupational health clinicians mattered more than any published table, and the decision depended heavily on local exposure risk [4, 5, 12].

Work absence was a practical concern for employers. If a large share of a ward team received the vaccine on the same day, and a proportion developed a fever or flu-like illness the next day, staffing could be affected. Occupational health services responded by staggering appointments, advising workers about timing relative to shifts, and suggesting that paracetamol or other antipyretics be used for symptom relief after the dose, not before it, because of uncertainty about whether prophylactic use blunts the immune response [10, 12, 37].

Distinguishing vaccine symptoms from infection was another practical problem. Fever, headache and fatigue within two days of vaccination are expected, whereas symptoms starting later, or accompanied by cough or loss of smell, should prompt testing. Seroprevalence and cohort studies of healthcare workers showed that asymptomatic infection was not uncommon, so testing policies mattered for protecting patients as well as colleagues [1, 2, 38].

Evidence of effectiveness within the workforce provided the other half of the benefit-risk balance. The SIREN cohort in England found that previous infection was associated with substantial protection against reinfection, and later that BNT162b2 reduced infection risk in healthcare workers, with protection beginning after the first dose and increasing after the second [3, 14]. Interim analyses of American healthcare personnel and frontline workers reached similar conclusions for both mRNA vaccines [39].

Concern about vaccines among healthcare workers themselves was real, and it did not always follow scientific evidence. Surveys in several countries found that a sizeable minority of staff delayed or declined vaccination, citing worries about speed of development, effects on fertility or pregnancy and fear of side effects [25, 26, 29]. Studies that examined these decisions found that confidence rose when staff were given first-hand accounts from colleagues who had been vaccinated and when occupational health teams answered questions honestly, including questions about common symptoms [13, 25, 29]. Candid information about reactogenicity thus supports uptake instead of undermining it.

4. RARE AND SERIOUS EVENTS

Anaphylaxis was the first rare event to be characterised. In the United States, the first weeks of vaccination with BNT162b2 produced reports of severe allergic reactions at a rate of the order of ten per million doses, and a lower rate for mRNA-1273, nearly all within 30 minutes of vaccination, and most in people with a history of allergy [7, 31, 32]. All affected people recovered after treatment. These findings led to the 15-minute observation period for everyone vaccinated and the 30-minute period for those with a history of immediate allergic reactions, along with the requirement that adrenaline be at hand [7, 31, 32]. Prompt adrenaline is the key treatment, which is a good argument for keeping resuscitation equipment at every vaccination site.

Polyethylene glycol, present in the lipid nanoparticles of both mRNA vaccines, was suggested as a possible allergen, although the mechanism was not confirmed by 2021 and the role of other excipients, including polysorbate in the vector vaccines, was a matter of discussion [7, 31, 32]. Allergists generally concluded that people with a prior non-severe reaction could still be vaccinated under observation, while those who had a severe reaction to the first dose should be assessed individually before another [31, 32]. Healthcare workers, being close to emergency equipment, were well placed to be among the

first monitored under these procedures.

Vaccine-induced immune thrombotic thrombocytopenia was recognised in March and April 2021. Reports from Germany, Norway and elsewhere described cerebral venous sinus thrombosis and thrombosis in unusual sites, accompanied by low platelet counts and antibodies against platelet factor 4, one to three weeks after ChAdOx1 nCoV-19 vaccination, mainly in younger women [8, 34]. The syndrome resembles heparin-induced thrombocytopenia but occurs without heparin exposure. A similar pattern was later described after Ad26.COV2.S vaccination in the United States [35, 36].

The condition is rare, and the estimated risk varies with age and sex, which led to different national responses. Some countries restricted the use of the vector vaccines to older age groups, while others continued to offer them to all adults, weighing the risk against local infection rates [8, 35, 36]. Recognition of the syndrome changed clinical practice: patients with severe headache, abdominal pain, leg swelling or neurological symptoms in the weeks after vaccination needed urgent blood counts and imaging, and treatment with non-heparin anticoagulants and immunoglobulin was recommended [8, 34, 35].

Myocarditis and pericarditis after mRNA vaccination emerged as a signal in spring 2021, chiefly among adolescent boys and young men, usually within a few days of the second dose, and typically with mild illness and rapid recovery [9, 33]. Advisory committees concluded that the benefits of vaccination outweighed the risk for all age groups but acknowledged that the risk estimate was highest in young males [33]. For healthcare workers, most of whom are adults over 18, the risk was lower than for adolescents, but occupational health teams were asked to advise on the symptoms to watch for.

Other conditions were investigated and found no clear association. Bell palsy, miscarriage and stroke were all examined in early safety analyses, with no consistent causal association identified in the data available by mid-2021, though continued monitoring was recommended [11, 12, 37].

Counselling people about rare risks calls for careful wording. Telling a worker that anaphylaxis occurs at roughly one in a hundred thousand doses is accurate, yet comparisons with everyday risks and with the risk of severe COVID-19 help put the figure in context [7, 32, 33]. For vaccine-induced thrombosis, communication focused on recognising symptoms rather than on avoiding the vaccine, as early treatment was associated with better outcomes [8, 34]. Providing a leaflet listing warning symptoms and who to call became standard in several countries and was well received by staff.

Interpretation of rare-event data demands caution. Passive reports record temporal association and not causation, and the background incidence of many of these conditions in the general population is substantial. In a group of millions of newly vaccinated workers, some will have strokes or miscarriages purely by chance. Regulators therefore compare the number of reports with the number expected, using background rates by age and sex, before deciding that a signal is real [12, 37, 40].

5. SAFETY SURVEILLANCE AND STUDY DESIGN

Passive reporting systems such as VAERS in the United States, the Yellow Card scheme in the United Kingdom and EudraVigilance in Europe formed the backbone of post-authorisation safety monitoring. They are quick and sensitive to unexpected events, but they cannot give incidence, as the denominator is unknown and under-reporting is variable [11, 12]. The World Health Organization manual on vaccine safety surveillance set out the definitions and reporting responsibilities that most countries followed, using standard terms for adverse events following immunisation [12, 40].

Active systems complement passive reporting. The American v-safe smartphone programme invited vaccinated people to complete daily symptom checks in the first week and periodic checks later, and a similar approach was used in the United Kingdom symptom study [10, 11]. Cohorts of healthcare workers within hospital systems and national studies such as SIREN offered a

defined population with regular contact, making it possible to link vaccination with testing and clinical outcomes [3, 14]. Data from such cohorts fed into the safety evaluation more quickly than formal studies could have done.

Cross-sectional surveys, which supplied much of the published symptom data in 2021, have well-known weaknesses. Participants choose whether to respond, those with symptoms may be more motivated to do so, symptoms are recalled or recorded using non-standard checklists, and no control group of unvaccinated people is available to estimate the background rate of headache or fatigue [13, 25, 26, 29]. Nocebo effects are real: in the placebo arms of the large trials, a substantial minority of participants also reported systemic symptoms after an injection that contained no vaccine [4, 5, 6].

Data quality is a recurring issue. Records of brand, batch number and date of vaccination must be accurate for a report to be useful, and in busy vaccination centres these details were sometimes entered late or incompletely. Batch information matters because it allows regulators to look for clusters linked to a specific lot, which was used in early investigations of allergic reactions [11, 12, 32]. Electronic vaccine registries linked to health records reduced this problem in countries that had them, and the lesson has been to build such linkage into the programme before launch, not afterwards [37, 40].

Statistical signal detection relies on comparing observed with expected events. Methods used by the regulators include proportional reporting ratios for passive data and sequential testing in linked electronic health records, in which events within a risk window after vaccination are compared with events in a control window [11, 12, 40]. These methods can be applied quickly, but they work best for outcomes that are well coded and have stable background rates. For syndromes that are new, such as vaccine-induced thrombosis with thrombocytopenia, case definitions needed to be written while the cases were arriving [8, 34, 40].

The Brighton Collaboration and CIOMS case definitions enabled consistent classification of events across countries and are the reason that data on anaphylaxis from different sources can be compared at all [32, 40]. Healthcare workers who reported events were often familiar with these definitions, which improved report quality relative to the general population.

6. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations apply to the evidence summarised here. Most healthcare worker data describe short-term effects within days to weeks of a dose. Medium- and long-term outcomes, such as menstrual changes, autoimmune disease and effects on pregnancy, were hardly addressed by mid-2021, and pregnancy was an exclusion criterion in the pivotal trials [4, 5, 6, 11]. Healthcare workers also tend to be younger and healthier than the population in the highest-risk groups, and so safety conclusions may not transfer directly to older adults [24].

A second limitation concerns comparisons between vaccines. Because most workers in a given country received whichever vaccine was supplied to them, the comparisons are confounded by age, sex, timing, prior infection and the type of reporting system. Naive comparison of reaction rates between vaccines is therefore unreliable, and the apparent differences between platforms should be treated as hypotheses [10, 25, 29]. Randomised head-to-head trials of platforms, where ethically and logistically possible, would resolve this far better than any amount of adjustment in observational data [6, 21].

Reporting bias deserves one more mention because it works in both directions. Media coverage of a safety signal tends to increase reports of the relevant condition, as seen after the announcements about thrombosis, while the sheer volume of vaccinations in spring 2021 produced an enormous number of reports that required triage [8, 11, 12]. Careful interpretation therefore needs the denominator of doses given, the age and sex of those vaccinated, and the background rate. Healthcare worker cohorts, in which these three are often known, are well suited to this

kind of analysis [14, 39].

Future work should include standardised symptom definitions, follow-up with validated instruments, linked electronic records and inclusion of control groups. Sharing of de-identified data across institutions would allow rarer events to be detected earlier, and studies of third doses and of heterologous schedules, which were being planned, would need the same rigour [10, 39, 40]. Clear communication with staff about the balance between common mild effects and rare serious ones remains central to maintaining confidence in vaccination programmes [4, 23, 37].

Finally, new variants and changing recommendations make the benefit-risk balance a moving target. As immunity builds in the community and as new platforms are introduced, safety findings from the first generation of vaccines will need to be revisited, and the experience of healthcare workers will remain a valuable source of information for that task [14, 39].

7. CONCLUSION

The published evidence up to mid-2021 shows that COVID-19 vaccines given to healthcare workers produced frequent but short-lived local and systemic reactions, with differences by platform, dose number, age, sex and previous infection [4, 5, 6, 10, 13]. Rare serious events, namely anaphylaxis, thrombosis with thrombocytopenia and myocarditis, were identified quickly through surveillance and resulted in practical changes in monitoring and age-based recommendations [7, 8, 9, 33].

Most of the data come from trials with limited representativeness, self-reported surveys and passive reporting, which have known weaknesses, and long-term outcomes remain unstudied. Better-designed active surveillance, standard definitions and transparent communication will be needed to sustain confidence among staff who must both receive vaccines and advise patients about them [11, 12, 39, 40].

8. ABBREVIATIONS

ADR-Adverse drug reaction, CIOMS-Council for International Organizations of Medical Sciences, COVID-19-Coronavirus disease 2019, mRNA-Messenger ribonucleic acid, SARS-CoV-2-Severe acute respiratory syndrome coronavirus 2, SIREN-SARS-CoV-2 Immunity and Reinfection Evaluation, VAERS-Vaccine Adverse Event Reporting System, WHO-World Health Organization

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Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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