Medicines & Healthcare products Regulatory Agency

Research and analysis

ARCHIVED - Coronavirus vaccine - summary of Yellow Card reporting

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days after vaccination. Adverse reactions were generally milder and reported less frequently in older adults (65 years and older) than in younger people.

The monovalent COVID-19 Vaccine Moderna was evaluated in clinical trials involving more than 30,000 participants. The most frequent adverse reactions (https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna/information-for-healthcare-professionals-on-covid-19-vaccine-moderna) in these trials were pain at the injection site, fatigue, headache, myalgia (muscle pains), arthralgia (joint pains), chills, nausea/vomiting, axillary swelling/tenderness (swelling/tenderness of glands in the armpit), fever, injection site swelling and redness; these were each reported in more than 1 in 10 people. These reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. Adverse reactions were reported less frequently in older adults (over 65 years) than in younger people.

The COVID-19 Vaccine Novavax was evaluated in clinical trials involving more than 30,000 participants. The most frequently reported adverse reactions (https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-nuvaxovid) in these trials were headache, feeling sick (nausea) or getting sick (vomiting), muscle ache, joint pain, tenderness or pain where the injection is given, feeling very tired (fatigue) and generally feeling unwell; these were each reported in more than 1 in 10 people. These reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. Adverse reactions were reported less frequently in older adults (over 65 years) than in younger people.

The MHRA continually monitors safety during widespread use of a vaccine. We have in place a proactive strategy to do this (https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance). We also work closely with our public health partners in reviewing the effectiveness and impact of the vaccines to ensure the benefits continue to outweigh any possible side effects.

Part of our monitoring role includes reviewing reports of suspected side effects. Any member of the public or health professional can submit suspected side effects through the Yellow Card scheme (https://yellowcard.mhra.gov.uk/). The nature of Yellow Card reporting means that reported events are not always proven side effects. Some events may have happened anyway, regardless of vaccination. This is particularly the case when millions of people are vaccinated, and especially when vaccines are being given to the most elderly people and people who have underlying illness.

As of 23 November 2022, for the UK, 177,925 Yellow Cards have been reported for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, 246,866 have been reported for the COVID-19 Vaccine AstraZeneca, 47,045 for the monovalent and bivalent COVID-19 Vaccine Moderna, 52 for the COVID-19 Vaccine Novavax and 2,130 have been reported where the brand of the vaccine was not specified.

For the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca and monovalent and bivalent COVID-19 Vaccine Moderna the overall reporting rate is around 2 to 5 Yellow Cards per 1,000 doses administered.

In the 28 days since the previous summary for 26 October 2022 we have received a further 2,499 Yellow Cards for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, 228 for the COVID-19 Vaccine AstraZeneca, 1,099 for the monovalent and bivalent COVID-19 Vaccine Moderna, 15 for the COVID-19 Vaccine Novavax and 154 where the brand was not specified. The increase in reports for Pfizer and Moderna COVID-19 vaccines is due to the bivalent vaccine use in the national autumn booster campaign. Our review to date of suspected adverse events since the launch of the campaign has not revealed any new safety concerns.

It is important to note that Yellow Card data cannot be used to derive side-effect rates or compare the safety profile of COVID-19 vaccines as many factors can influence ADR reporting. Additionally, it is important to consider that a Yellow Card report can include reference to more than one vaccine associated with a suspected reaction where different vaccines have been used as third or booster doses.

For all COVID-19 vaccines, the overwhelming majority of reports relate to injection-site reactions (sore arm for example) and generalised symptoms such as ‘flu-like’ illness, headache, chills, fatigue (tiredness), nausea (feeling sick), fever, dizziness, weakness, aching muscles, and rapid heartbeat. Generally, these happen shortly after the vaccination and are not associated with more serious or lasting illness.

These types of reactions reflect the normal immune response triggered by the body to the vaccines. They are typically seen with most types of vaccine and tend to resolve within a day or two. The nature of reported suspected side effects is broadly similar across age groups, although, as was seen in clinical trials and as is usually seen with other vaccines, they may be reported more frequently in younger adults.

A number of detailed assessments of safety topics have been undertaken and we have updated our advice on these topics accordingly. Overall, our advice remains that the benefits of the vaccines outweigh the risks in the majority of people. Further comments on use in specific populations and details on the specific safety topics can be found within Section titled Analysis of data.

Conclusion

Vaccines are the best way to protect people from COVID-19 and have already saved tens of thousands of lives. Everyone should continue to get their

Up to and including 23 November 2022, the MHRA received and analysed 177,925 UK Yellow Cards from people who have received the monovalent or bivalent COVID-19 Vaccine Pfizer/BioNTech. These reports include a total of 511,776 suspected reactions (i.e., a single report may contain more than one symptom). The first report was received on 9 December 2020.

Up to and including 23 November 2022, the MHRA received and analysed a total of 246,866 UK reports of suspected ADRs to the COVID-19 Vaccine AstraZeneca. These reports include a total of 874,912 suspected reactions (a single report may contain more than one symptom). The first report was received on 4 January 2021.

Up to and including 23 November 2022, the MHRA received and analysed a total of 47,045 UK reports of suspected ADRs to the monovalent and bivalent COVID-19 Vaccine Moderna. These include a total 151,628 suspected reactions (a single report may contain more than one symptom). The first report was received on 7 April 2021.

Up to and including 23 November 2022, the MHRA received and analysed a total of 52 UK reports of suspected ADRs to the COVID-19 Vaccine Novavax. These include a total of 106 suspected reactions (a single report may contain more than one symptom). The first report was received on 21 November 2021.

Additionally, up to and including 23 November 2022, the MHRA received 2,130 Yellow Card reports where the brand of vaccine was not specified by the reporter.

In the 28 days since the previous summary for 26 October 2022 we have received a further 2,499 Yellow Cards for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, 228 for the COVID-19 Vaccine AstraZeneca, 1,099 for the monovalent and bivalent COVID-19 Vaccine Moderna, 15 for the COVID-19 Vaccine Novavax and 154 where the brand was not specified. Please note that a Yellow Card report can include more than one vaccine suspected to have caused a reaction where different vaccines have been used as third or booster doses.

It is important to note that Yellow Card data cannot be used to derive side effect rates or compare the safety profile of COVID-19 vaccines as many factors can influence ADR reporting.

Table 4: Number of suspected ADR reports received in the UK up to and including 23 November 2022.

Number of reports

Country	COVID-19 Pfizer/ BioNTech Vaccine (monovalent and bivalent)	COVID-19 Vaccine AstraZeneca	COVID-19 Vaccine Moderna (monovalent and bivalent)	Brand unspecified
England	138,610	203,063	37,408	1,214
Wales	8,628	10,922	2,841	114
Northern Ireland	3,087	3,020	202	27
Scotland	13,254	17,608	3,891	239

The majority of COVID-19 Vaccine Novavax reports are from England.

The figures in Table 4 are based upon the postcode provided by the reporter. The sums of the reports in the table will not equal the total reports received for the vaccines as a postcode may not have always been provided or may have been entered incorrectly. It is important to note that the number of reports received for each country does not directly equate to the number of people who may have experienced adverse reactions and therefore cannot be used to determine the incidence of reactions. ADR reporting rates are influenced by many aspects, including the extent of use.

We are working with public health bodies and encouraging all healthcare professionals and patients alike to report any suspected ADRs to the Yellow Card scheme. As expected, reports gradually increase in line with an increase in doses administered.

The overall reporting rate for first, second and third or booster doses is in the order of 2 to 5 Yellow Cards per 1,000 doses administered for the monovalent and bivalent COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca and monovalent and bivalent COVID-19 Vaccine Moderna. There is insufficient experience with COVID-19 Vaccine Novavax to be able to make similar estimates of reporting rates. It is known from the clinical trials that the more common side effects for all vaccines can occur at a rate of more than one in 10 doses (for example, local reactions or symptoms resembling transient flu-like symptoms).

3. Analysis of Data

AstraZeneca. It has also considered other blood clotting reports (thromboembolic events) alongside low platelet levels.

This scientific review concluded that the evidence of a link with COVID-19 Vaccine AstraZeneca is likely and an announcement (https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots) was made on 7 April 2021 with a further statement on 7 May 2021. We have continued to publish the latest breakdown of all cases of these extremely rare side effects on a weekly and now monthly basis.

Anyone who experienced cerebral or other major blood clots occurring with low levels of platelets after their first vaccine dose of COVID-19 Vaccine AstraZeneca should not have further doses. Anyone who did not have these side effects should come forward for their second dose when invited.

Anyone who experiences any of the following from around 4 days after vaccination should seek medical advice urgently:

- a severe headache that is not relieved with simple painkillers or gets worse or feels worse when you lie down or bend over
- an unusual headache that may be accompanied by blurred vision, confusion, difficulty with speech, weakness, drowsiness or seizures (fits)
- rash that looks like small bruises or bleeding under the skin beyond the injection site
- shortness of breath, chest pain, leg swelling or persistent abdominal (tummy) pain.

Up to 23 November 2022, the MHRA had received Yellow Card reports of 445 cases of major thromboembolic events (blood clots) with concurrent thrombocytopenia (low platelet counts) in the UK following vaccination with COVID-19 Vaccine AstraZeneca. Fifty-one of the 445 reports have been reported after a second dose. Of the 445 reports, 221 occurred in females, and 219 occurred in males aged from 18 to 93 years. The overall case fatality rate was 18% with 81 deaths, six of which occurred after the second dose.

Cerebral venous sinus thrombosis was reported in 161 cases (average age 46 years) and 284 had other major thromboembolic events (average age 54 years) with concurrent thrombocytopenia. The estimated number of first doses of COVID-19 Vaccine AstraZeneca administered in the UK by 23 November 2022 was 24.9 million and the estimated number of second doses was 24.1 million.

The overall incidence after first or unknown doses was 15.9 per million doses. Considering the different numbers of patients vaccinated with COVID-19 Vaccine AstraZeneca in different age groups, the data indicates that there is a higher reported incidence rate in the younger adult age groups following the first dose compared to the older groups (21.8 per million doses in those aged 18-49 years compared to 11.3 per million doses in those aged 50 years and

over). The number of first doses given to those in the 18-49 years age group is estimated to be 8.5 million while an estimated 16.4 million first doses have been given to patients aged 50+ years. The MHRA advises that this evidence should be taken into account when considering the use of the vaccine. There is some evidence that the reported incidence rate is higher in females compared to men although this is not seen across all age groups and the difference remains small.

The overall incidence of thromboembolic events with concurrent low platelets after second doses was 2.1 cases per million doses. Taking into account the different numbers of patients vaccinated with COVID-19 Vaccine AstraZeneca in different age groups, the data indicates that there is a lower reported incidence rate in younger adult age groups following the second dose compared to the older groups (1.0 per million doses in those aged 18-49 years compared to 2.1 per million doses in those aged 50 years and over). The number of second doses given to those in the 18-49 years age group is estimated to be 8.0 million while an estimated 16.1 million second doses have been given to patients aged 50+ years. These rates after second doses should not be directly compared to the incidence rates reported after the first dose as the time for follow-up and identification of cases after second doses is more limited and differs across age groups. However, the data are reassuring, particularly regarding younger recipients where there is a significantly lower incidence after the second dose compared to the first, and there is overall no indication of an increased risk of these events after the second dose in any age group. Anyone who did not have these side effects should come forward for their second dose when invited.

These cases have also been analysed by the independent advisory body, the CHM's COVID-19 Vaccines Benefit Risk Expert Working Group, which includes lay representatives and advice from leading haematologists.

On the basis of this ongoing review, the advice remains that the benefits of the vaccine outweigh the risks in the majority of people.

Table 5: Number of suspected thrombo-embolic events with concurrent thrombocytopenia ADR cases received for the COVID-19 Vaccine AstraZeneca in the UK up to and including 23 November 2022.

Country	Number of cases
England	382
Wales	14
Northern Ireland	11
Scotland	36

Vaccination and surveillance of large populations means that, by chance, some people will experience and report a new illness or events in the days and weeks after vaccination. A high proportion of people vaccinated early in the vaccination campaign were very elderly, and/or had pre-existing medical conditions. Older age and chronic underlying illnesses make it more likely that coincidental adverse events including those with a fatal outcome will occur, especially given the millions of people vaccinated.

Part of our continuous analysis includes an evaluation of natural death rates over time, to determine if any specific trends or patterns are occurring that might indicate a vaccine safety concern. Based on age-stratified all-cause mortality in England and Wales taken from the Office for National Statistics (ONS) death registrations, several thousand deaths are expected to have occurred naturally, mostly in the elderly, within 7 days of the many millions of doses of vaccines administered so far.

For reference, weekly death registrations within England, Wales, Scotland and Northern Ireland are available from relevant statistical authorities. The most recent data during the preparation of the summary of Yellow Card reporting is summarised as follows:

- England and Wales (ONS (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/weeklyprovisionalfiguresondeathsregisteredinenglandandwales)): In the week ending 11 November 2022, 11,538 deaths were registered; of these deaths, 518 cited COVID-19, accounting for 4.5% of all deaths.
- Scotland (The National Records of Scotland (https://www.nrscotland.gov.uk/covid19stats)): In the week ending 20 November 2022, 1,271 deaths were registered; of these deaths, 40 cited COVID-19, accounting for 3.1% of all deaths.
- Northern Ireland (The Northern Ireland Statistics and Research Agency (https://www.nisra.gov.uk/statistics/death-statistics/weekly-death-registrations-northern-ireland)): In the week ending 18 November 2022, 386 deaths were registered; of these deaths, 8 cited COVID-19, accounting for 2.1% of all deaths.

The MHRA takes all reports with a fatal outcome in patients who have received a COVID-19 vaccine very seriously and every report with a fatal outcome is reviewed carefully. All reports with a fatal outcome regardless of the time period between receiving the suspect vaccine and the reported death are reviewed. All available information is assessed to consider whether the vaccine may have caused the reported death. Cumulatively, the Yellow Card data is thoroughly analysed for patterns or evidence which might suggest a causal link between the vaccination and the reported death alongside data available from international sources. This is further considered by the Commission on Human Medicines and its Expert Advisory Groups.

The MHRA has received 857 UK reports of suspected ADRs to both COVID-19 Pfizer/BioNTech Vaccines in which the patient died after vaccination, 1,334 reports for the COVID-19 Vaccine AstraZeneca, 111 reports for both COVID-19 Vaccines Moderna and 60 reports where the brand of vaccine was unspecified. The MHRA has received no fatal UK reports for COVID-19 Vaccine Novavax.

A report with a fatal outcome to the Yellow Card scheme does not necessarily mean that it was caused by the vaccine, only that the reporter has a suspicion it may have been. Underlying or previously undiagnosed illness unrelated to vaccination can also be factors in such reports. The relative number and nature of UK reports with a fatal outcome are subject to many factors that influence ADR reporting. They should therefore not be used to directly compare the safety of the different vaccines.

The number of UK reports with a fatal outcome following a specific COVID-19 vaccine should not be directly compared with each other. Table 11 and Table 12 provide a breakdown by age and sex for all UK reports with a fatal outcome following COVID-19 vaccination received by the MHRA. Where there are than 5 reports for a given category, report numbers have been replaced with a ^ in order to prevent patient/reporter identification in line with our duty of confidentiality to patients and reporters.

Table 11* / : Number of UK reports with a fatal outcome received for COVID-19 Vaccines by patient age up to and including 23 November 2022**

Age group (years)	COVID-19 Vaccine AstraZeneca	COVID-19 Vaccine Pfizer/BioNTech	COVID-19 Vaccine Moderna	Brand unspecified	All vacci
Under 18	^	6	-	^	9
18-29	29	19	^	-	49
30-39	49	34	6	^	90
40-49	97	32	6	^	138
50-59	158	45	^	10	218
60-69	205	78	13	9	305
70-79	267	179	19	6	471
80+	332	328	36	17	713
Unknown	195	136	25	13	369