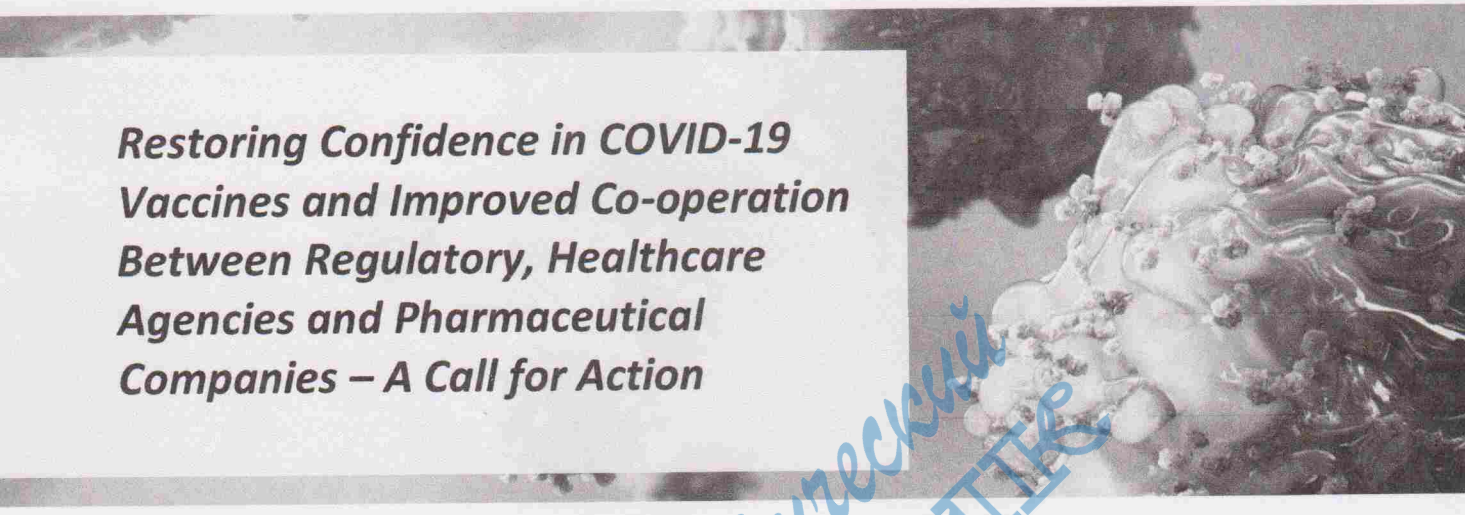
AstraZeneca



Restoring Confidence in COVID-19 Vaccines and Improved Co-operation Between Regulatory, Healthcare Agencies and Pharmaceutical Companies – A Call for Action

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Executive Summary

- Vaccines and vaccination programmes are the cornerstone in tackling any pandemic.
- The available vaccines have already had a major, positive impact on COVID-19-related mortality, hospitalisation and socioeconomic disease burden.
- Over the past 4 months, Public Health England estimate 10,400 COVID-19-related deaths have been prevented by vaccination in adults aged over 60 years in England alone: 2,600 deaths prevented per month of vaccine roll out.
- While thrombosis events have been reported with all COVID-19 vaccines, very rare events of thrombocytopenia with cerebral venous sinus thrombosis have recently been identified following vaccination with adenoviral vectored vaccines including *COVID-19 Vaccine AstraZeneca*/AZD1222 (Vaxzevria) and *COVID-19 Vaccine Janssen* (JNJ-78436735).
- Some health agencies have responded to these very rare reports by restricting use of the vaccines, fuelling vaccine hesitancy and particularly in adenoviral vectored vaccines.
- In addition, there have been recommendations that people who received their first dose of *COVID-19 Vaccine AstraZeneca*/AZD1222 should receive an mRNA vaccine for their second dose. There are no clinical data to support such an approach and the World Health Organization (WHO), European Medicines Agency (EMA) and Joint Committee on Vaccination and Immunisation (JCVI) recommend against it.
- All available COVID-19 vaccines are associated with adverse safety events, however set against the death toll of COVID-19 the benefits of vaccination with any of the available vaccines far outweigh the risks at an individual and at a public health level as has been repeatedly stated by regulators around the world.
- Obtaining the data necessary for a full assessment of vaccine safety, such as listings of adverse events by age group and by comorbidities, is an ongoing process for all vaccine sponsors. A significant level of attention has focused on the rare events of thrombotic thrombocytopenia, but each vaccine will have different risks and it is important to consider the overall safety profile of each.
- Restoring confidence in vaccines requires a concerted effort involving regulatory and healthcare agencies and pharmaceutical companies, to ensure rapid access to the latest data and allow for transparent, consistent communications to the public.
- Precise data on all vaccines, adjusted by the demographics of each population, broken down by age, sex, vaccine status and vaccine type are needed to provide appropriate context to incidents of these rare events.
- Absolute numbers of COVID-19 cases, hospitalisations and deaths, ideally with real-time updates, could build on the existing post-vaccination surveillance strategies to allow for better evidence-based decision making and label adjustments to be based on a solid foundation of data.
- AstraZeneca remains committed to thorough ongoing data gathering on the safety and benefits of the vaccine and vaccination through collaboration with the National Immunization Technical Advisory Groups (NITAGs).

Introduction

Cases of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were first identified in Wuhan City, China in December 2019. Even before human-to-human transmission had been confirmed by Chinese authorities[1] and the WHO,[2] a scientific team based at the Jenner Institute in the University of Oxford in the UK had already begun designing a vaccine against SARS-CoV-2, based on an existing vaccine platform that was in clinical development for other infectious diseases.[3] Meanwhile, as COVID-19 rapidly spread worldwide, pharmaceutical companies were called into action in the race for solutions to rapidly combat the pandemic, as a worldwide humanitarian crisis unraveled in real time.

AstraZeneca supports a unified pharmaceutical research and development effort. Leveraging its heritage in research and development, AstraZeneca joined forces with the academic group from the University of Oxford, whose novel vaccine platform already had existing preclinical and clinical results. The academic team also shared AstraZeneca's vision of a not-for-profit vaccine programme, distributed in an equitable manner for all during the current COVID-19 crisis.

While much progress has been made and many deaths have been prevented, the pandemic is still ongoing and currently only around 7% of the world's population has received at least one dose of a COVID-19 vaccine.[4] The WHO and European Commission estimate effective COVID-19 vaccines must reach 70% of all humankind to effectively break the chain of SARS-CoV-2 transmission through 'herd immunity' - tenfold the current coverage achieved from vaccine rollouts.[5,6]

Benefits of Vaccination

Following a successful preclinical and clinical development programme, *COVID-19 Vaccine AstraZeneca*/AZD1222 currently has full licensure approval or emergency use authorisations in over 90 countries worldwide.[7] Robust effectiveness, against all severities of COVID-19, has now also been demonstrated in a wide range of real-world populations and environments.[8-12]

Countries enlisting effective immunisation strategies against COVID-19 that include multiple vaccine platforms are now experiencing striking reductions in COVID-19-related deaths, hospitalisations and overall burden of disease.[12] The Office of National Statistics and University of Oxford have released data from a UK study of >350,000 adults showing that one dose of either BNT162b2 (Pfizer) or *COVID-19 Vaccine AstraZeneca*/AZD1222 reduced the odds of contracting new SARS-CoV-2 infection by 65% ≥21 days.[13]

The European Centre for Disease Prevention and Control reports 662,622 COVID-19-associated deaths in the European union/European Economic Area (EU/EEA) to date.[14] At present, the average 14-day mortality risk rate in the EU/EEA is 77.6 (range: 0.0–353.4) deaths per million, with no change in the previous 7 weeks.[15] Clinical trial and real-world effectiveness data from *COVID-19 Vaccine AstraZeneca*/AZD1222 shows that hospitalisations, intensive care unit (ICU) admission and deaths from COVID-19 can be reduced by over 80% through vaccination.[11,16]

Public Health England have estimated that 10,400 deaths have been prevented in adults aged over 60 years in England, in just 4 months of vaccine distribution (approximately 15 million doses) between December 2020 and March 2021. This equates to approximately 2600 deaths prevented per month due to a swift ongoing vaccine roll out.[17]

Associated Risks

Along with the substantial benefits of vaccination, vaccines are also associated with some risk. As the COVID-19 vaccination programmes roll out, pharmaceutical companies will continue their ongoing commitment alongside regulatory authorities to monitor safety.

All available COVID-19 vaccines have an adverse reaction profile, contraindications, warnings and precautions. The most common reactions seen with all vaccines are typically mild to moderate, self-limiting and include pain and/or tenderness at the site of injection, headache, fatigue, myalgia, arthralgia, nausea/vomiting, pyrexia and chills. [18–23] In addition, rare events have been reported and included in the product labels of all vaccines, including *COVID-19 Vaccine AstraZeneca*/AZD1222. [18–23]

Fatalities have been observed following COVID-19 vaccination. Unadjusted data relating to fatalities following vaccination per million doses of BNT162b2 (Pfizer), *COVID-19 Vaccine AstraZeneca*/AZD1222 and *COVID-19 Vaccine Janssen* (JNJ-78436735) are shown in **Table 1**. Further granularity of the data by age, sex, comorbidities and other demographic variables is urgently required to allow a more comprehensive evaluation of health outcomes and mortality following vaccination.

TABLE 1: Overview of vaccine fatalities as reported from government sources and related medical/pharmacovigilance agencies

	# Fatal cases			# Doses administered (millions)			# Fatal cases/million doses		
	Pfizer	AZ	J&J	Pfizer	AZ	J&J	Pfizer	AZ	J&J
USA[24]	999	-	54	99.5		7.2	10	-	7.5
France[25]	386	44	-	8.5	2.5	-	45.3	17.9	-
Germany[26]	321	19	-	10.7	2.9	-	29.9	6.5	-
UK[27]	302	472	-	14.6	19.5	-	20.7	24.2	-
Norway[28]	130	6	-	0.8	0.1	-	164.3	44.6	-
Austria[29]	57	3	-	1.2	0.4	-	47.5	7.5	-
Italy[30]	76	12	-	7.0	1.6	-	10.9	7.3	-
Argentina[31]	-	4	-	-	0.5	-	-	7.7	-
Brazil[32]	-	40	-	-	3.3	-	-	12.3	-
Chile[33]	1	-	-	0.3	-	-	3.4	-	-

NB. Cases are updated routinely and may be subject to change since latest report.
AZ, *COVID-19 Vaccine AstraZeneca*/AZD1222; J&J, *COVID-19 Vaccine Janssen* (JNJ-78436735); Pfizer (BNT162b2).

For all vaccines, the identification and characterisation of rare adverse events relies on full transparency and sharing of all available data. Due diligence commits regulatory bodies and pharmaceutical companies to ongoing safety monitoring and the transparent sharing of safety data, as this information arises post-authorisation. Through this ongoing collaborative monitoring of safety signals, AstraZeneca, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) and the EMA identified rare thrombotic thrombocytopenia events linked to COVID-19 illness and vaccination.[34] Cases were reported mainly from EU and UK spontaneous reporting systems, when around 25 million people had received the vaccine.[33]

As of 22 March 2021, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) reviewed 62 cases of cerebral venous sinus thrombosis (CVST) and 24 cases of splanchnic vein thrombosis together with low levels of blood platelets occurring after vaccination with *COVID-19 Vaccine AstraZeneca*/AZD1222. These events were reported in the EU drug safety database (EudraVigilance) and 18 cases sadly resulted in fatality. The PRAC concluded that although the unusual blood clots

with low blood platelets events should be listed as very rare side effects of *COVID-19 Vaccine AstraZeneca*/AZD1222, the overall benefits of the vaccine in preventing COVID-19 outweigh the risks.[35] Whilst there has been some speculation, currently there is no established mechanism that has been verified by which a vaccine could cause these rare events of thrombosis with thrombocytopenia, and it is too early to draw conclusions on causal links to the adenoviral vector platform.

As of 4 April 2021, 169 cases of this event were reported in the over 34 million people vaccinated with *COVID-19 Vaccine AstraZeneca*/AZD1222 in the UK.[35] The UK's JCVI issued the following new advice on the use of *COVID-19 Vaccine AstraZeneca*/AZD1222 based on the benefit-risk profile at a time when overall infection rate was low: adults aged under 30 with no underlying health conditions should be given the choice of an alternative vaccine where available.[36] Those that have received a first dose of *COVID-19 Vaccine AstraZeneca*/AZD1222 should continue to be offered a second dose of the same vaccine.[37] Health professionals have been alerted to this potential risk through labelling and healthcare provider letters, and as more is learned about thrombotic thrombocytopenia syndrome they can be prepared to diagnose earlier and manage such events promptly leading to better outcomes for patients.

Rare events of thrombosis with thrombocytopenia have also been reported for *COVID-19 Vaccine Janssen* (JNJ-78436735) and the mRNA vaccines from Pfizer (BNT162b2) and Moderna (mRNA-1273), including fatalities. **Table 2** summarises data shared by the EMA on thrombotic thrombocytopenia events by vaccine and the number of cases of thromboembolism from the Centers for Disease Control and Prevention's Vaccine Adverse Event Reporting System. Background incidence of thrombotic thrombocytopenia or thromboembolism pre- and post-pandemic are not provided. Precise data on all vaccines, adjusted by the demographics of each population, broken down by age, sex, vaccine status and vaccine type are needed to provide appropriate context to incidents of these rare events.

TABLE 2: Cases of thrombosis with thrombocytopenia and thromboembolism after selected COVID-19 vaccines

Vaccine	Developer	Thrombotic thrombocytopenia number of cases/implied Incidence[38,39]	Thromboembolism number of cases/implied incidence[40,41]
COVID-19 Vaccine AstraZeneca/AZD1222	AstraZeneca/University of Oxford/Vaccitech	169 in 35 million vaccinated 4.83 per million (both figures for EEA + UK)[38]	30 in 5,000,000 vaccinated 6 per million (both figures from EEA)[40]
COVID-19 Vaccine Janssen/JNJ-78436735	Johnson & Johnson	15 in 8 million vaccinated 1.90 per million (both figures US)[39]	55 in 4,917,225 vaccinated 11.2 per million (figures from US VAERS database)[41]
mRNA-1273	Moderna	5 cases WW; 4 million vaccinated --- (EEA + UK)[38]	550 in 51,079,761 vaccinated 10.8 per million (figures from US VAERS database)[41]
Comirnaty/BNT162b2	Pfizer/BioNtech	35 cases WW; 54 million vaccinated --- (EEA + UK)[38]	627 in 57,447,938 vaccinated 10.9 per million (figures from US VAERS database)[41]

NB. Background incidences pre- and post-pandemic are not provided. Characterisation of incidence broken down per population by age, sex, vaccine status and vaccine type are needed to provide appropriate context to incidents of these rare events.
VAERS, Vaccine Adverse Event Reporting System; WW, worldwide.

Providers of COVID-19 vaccines, including AstraZeneca, are committed to the reporting of all safety signals from vaccinated individuals post-authorisation, and over time these will become more fully characterised. Available evidence on an association between very rare thrombotic events with thrombocytopenia following vaccination is still unclear. There are limited age-adjusted data, and limited data on comorbidities or risk factors in individuals that experienced these events. Based on the currently available evidence, specific risk factors for all vaccines and different platforms have not yet been confirmed.

Current Status on Restrictions and Boosting (second dose) with *COVID-19 Vaccine AstraZeneca*/AZD1222 or mRNA Vaccines

Despite the substantial benefits associated with vaccination with *COVID-19 Vaccine AstraZeneca*/AZD1222, based on these findings, health agencies from some countries responded rapidly by restricting the use of *COVID-19 Vaccine AstraZeneca*/AZD1222 entirely or in certain age groups. [42,43] This is against the recommendation and a supporting analysis from the EMA, which reported the benefits of *COVID-19 Vaccine AstraZeneca*/AZD1222 outweigh the risks across all age groups.[35] The EMA's analysis looked at prevention of COVID-19-associated hospitalisations, ICU admissions and deaths, based on infection rates, to contextualise benefit-risk of vaccination post-first dose and the occurrence of blood clots with low platelets. Their results showed that the benefits of vaccination were higher with increasing age and infection rates, and that there were insufficient data available from the EU to provide further context on benefit-risk in terms of sex. The Committee recommended to continue giving a second dose of *COVID-19 Vaccine AstraZeneca*/AZD1222 between 4 and 12 weeks after giving the first one, in line with the product information.

Other health agencies have provided a recommendation that people who have received a first vaccination with *COVID-19 Vaccine AstraZeneca*/AZD1222 are offered an mRNA vaccine for their second dose, although there are currently no clinical data reporting the safety and efficacy/effectiveness of mixing vaccines on which to substantiate this off-label recommendation. Results from a single study in mice have rationalised further research into heterologous regimens,[44] and clinical research is ongoing in the COVID-19 Heterologous Prime Boost study (Com-CoV), although this clinical study of 720 participants is not large enough to detect rare safety events.[45] These advances are promising, yet they do not comprise suitable evidence to support a recommendation to mix vaccines, and the risks of such an approach without clear safety data must be highlighted. AstraZeneca do not recommend mixing vaccines at this time. In addition, this approach is not supported by the WHO, EMA or the JCVI.[41]

These rare events of thrombosis with thrombocytopenia are serious and the world has looked to health agencies for guidance. Decisions around COVID-19 vaccines have received significant media focus while the benefits of the current vaccine rollouts have received more limited coverage. The current reporting around vaccine safety may amplify the risks of vaccines in the minds of the public, while reducing confidence in effective vaccines with a positive benefit-risk profile, at a time when we remain in a pandemic situation that is far from under control in many countries.

With the limited data available, the current rate of thrombotic events in combination with thrombocytopenia following the second dose of *COVID-19 Vaccine AstraZeneca*/AZD1222 (3 per 2.54 million second doses administered) was observed. The benefit-risk profile of *COVID-19 Vaccine AstraZeneca*/AZD1222 in the context of other vaccines indicates that use of the two-dose regimen of *COVID-19 Vaccine AstraZeneca*/AZD1222 remains favourable and generally comparable to the benefit-risk profile of other COVID-19 vaccines.

Putting Data into Context

The way data is presented can be the most important tool available; data that is clear and easy to understand and is comparable across all COVID-19 vaccines. Data on incidence of rare adverse events, or deaths, in those who have been vaccinated need to be reported with the correct and appropriate context to avoid the very real possibility that people will make unsubstantiated and potentially incorrect conclusions that they must be related to treatment.

To put the data into context it is important to recognise that risks do exist with all medications. For example, and in no way trying to establish a comparison with vaccines, women using oral contraceptives compared with those who do not are at an elevated risk of venous thromboembolic events (300–900 per million),[46] thrombotic stroke (151–156 per million),[47] ischaemic stroke (99–162 per million),[48] myocardial infarction (37–58 per million)[47] and CVST (30 per million).[49]

It should also be taken into account that in unvaccinated individuals SARS-CoV-2 infection and COVID-19 can be associated with increased risk of thromboembolism events with an elevated risk of death.[50] Clear data on all vaccines, adjusted by the demographics of each population, broken down by age, sex, vaccine status (not vaccinated, partially vaccinated, fully vaccinated) and vaccine type is needed, to provide appropriate context to incidents of these rare events after vaccination.

AstraZeneca has several ongoing studies investigating the efficacy, effectiveness, and safety of the AZD1222 vaccine in different contexts and population subgroups. Enhanced, active surveillance, combined with observational studies utilising existing secondary health data sources, ensure AstraZeneca continues its commitment to addressing knowledge gaps surrounding COVID-19 and building public trust.

Due to the approach of prioritising vaccinations based on age and other risk factors, the proportions vaccinated will vary by age groups, and currently younger people will most likely only have been vaccinated if they have pre-existing conditions that put them at high risk, confounding analysis of events that may occur more frequently in younger people. Absolute numbers for COVID-19 cases, hospitalisations and deaths, ideally with real-time updates, could build on the existing post-vaccination surveillance strategies, to allow better evidence-based decision making and label adjustments to be based on a solid foundation of data.

AstraZeneca's Commitment to Fighting COVID-19 and Restoring Vaccine Confidence

AstraZeneca is committed to partnering with NITAGs and regulatory bodies to restore confidence in COVID-19 vaccines and vaccination. The current available vaccines for COVID-19 are effective, well tolerated and all have an essential role in vaccinating the world's population now and in the future. As new variants continue to emerge, having vaccine platforms that can rapidly adjust is critical to win this war against SARS-CoV-2.

Even with effective vaccines, a certain proportion of the population will still get COVID-19, some may be hospitalised, and some may still be fatal. However, vaccines significantly reduce the prevalence in all three of these categories – cases, hospitalisations and deaths.

There is an urgent need to assess and evaluate COVID-19 safety in the same way and across all vaccines, so that clear and consistent guidelines on use can be provided by health agencies. This requires complete data that is clear and easy to understand, and for what we know to be true across all vaccines to be made clear. AstraZeneca supports this mission to restore confidence in approved and effective vaccines that will supply the global vaccination effort.

Summary

Vaccines and vaccination programmes are the cornerstone in tackling any pandemic. Every pharmacological intervention carries a certain inherent risk with use and vaccines are no different in that respect. However, it is important to place those risks into context with the benefits of vaccination, especially during a global health crisis and to ensure any decisions and recommendations are based on the most recently available robust scientific data.

Vaccination is essential for reducing the impact of the COVID-19 pandemic and has already demonstrated large significant reductions in ICU admission, hospitalisation and death in countries with widespread vaccination programmes as reported by the WHO, EMA and MHRA in April 2021. There is increasing hesitancy to use adenoviral-vectored vaccines with restrictions placed on their use, much of which can be attributed to the presentation of data looking at potential casual links between the vaccines and extremely rare thrombotic thrombocytopenia. A decision made against one vaccine can potentially further erode public confidence against all vaccines, from a global public health perspective. Lack of widespread vaccination will unnecessarily prolong the pandemic. More epidemiologic data, ideally real-world data, is needed to support recommendations on vaccine distribution.

Immune correlates of protection that adequately substitute vaccine efficacy against COVID-19 disease are not fully established. As such, a method to assess long-term protection of vaccines is not yet available.[51]

As this dynamic situation evolves, AstraZeneca remains committed to active collaboration in an effort to monitor and rapidly gather high quality data to further characterise benefits and safety through effective pharmacovigilance and safety programmes and understand the underlying epidemiology and mechanisms.

Key Resources

There is an urgent need to assess and evaluate COVID-19 safety in the same way and across all vaccines, so that clear and consistent guidelines on use can be provided by regulators. This is echoed in the report from the Tony Blair Institute of Global Change to truly understand the nature of these extremely rare events across all COVID-19 vaccines.

Wain R and Miller B. Restoring Confidence in the Workhorse Covid-19 Vaccines. Tony Blair Institute for Global Change. 2021. https://institute.global/policy/restoring-confidence-workhorse-covid-19-vaccines