Expert Report for the UK Covid-19 Public Inquiry

Module 4 - vaccines and therapeutics

Covid-19 vaccines: risks, benefits and how to prepare for the next pandemic

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Authors' statement

We confirm that this is our own work and that the facts stated in the report are within our knowledge. We understand our duty to provide independent evidence and have complied with that duty.

The opinions we have expressed represent our true professional opinions on the matters to which they refer. These opinions are based on relevant scientific evidence referenced in this report, but we have not pursued a full systematic review of the literature. The studies and reports quoted in this report are therefore a selection of the most important published literature, but not a full and complete search of the thousands of case reports and manuscripts available on this topic. It is therefore possible that other literature not mentioned in this report can provide different findings on some of the issues discussed. However, we are presenting here the most relevant literature that led to what we think is our best current knowledge at the time we wrote this report.

In addition to all the cited literature, I as Lead Author received and read with interest all the relevant material made available to the Covid-19 Inquiry, including MHRA and CHM statements and accompanying documents, and the experiences of those who suffered injuries and bereavement following vaccination. I was sorry to read about those who suffered serious disease or even death after receiving a vaccine, and was profoundly touched reading about these experiences. I am not an expert in law, litigation, or compensation rules related to vaccine/s injury, and these matters are therefore not discussed in my report.

Prof Daniel Prieto-Alhambra and co-authors

Oxford, September 2024

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1. Preamble

Qualifications and experience

Professor Daniel Prieto-Alhambra, MD MSc (Oxon) PhD

1.1. As lead author for this report (DPA), I have a long track record of experience in the discovery, curation, analysis and interpretation of routinely collected healthcare data (sometimes known as real world data) for pharmacoepidemiology. Pharmacoepidemiology is a discipline that mixes knowledge of clinical sciences, pharmacology and epidemiology to generate insights into the use, safety and benefits of medicines and vaccines in large populations and beyond well-controlled research settings. A subset of my research focuses specifically on vaccines and I have led or participated in national and multinational analyses of methods research (Catala et al., 2024a, Li et al., 2021a), on the use and distribution of Covid-19 vaccines (Roel et al., 2022), and on their benefits (Cabezas et al., 2021a, Catala et al., 2024b, Hermosilla et al., 2022, Trinh et al., 2024, Xie et al., 2022a) and risks in the UK and internationally (Burn et al., 2022a, Burn et al., 2022b, Li et al., 2022a, Li et al., 2021b, Li et al., 2022b, Xie et al., 2022c). I also have some experience with the mathematical modelling of vaccine distribution at the population level (Catala et al., 2021) and some knowledge and understanding of how national and international regulators evaluate and mitigate risks in the context of post-marketing surveillance.

1.2. I trained and have practised for many years as a medical doctor, trained in general practice and having completed a Masters (MSc Oxford) in Musculoskeletal Sciences and practised in Rheumatology in the NHS in England. Therefore, I have knowledge and experience of the clinical diagnosis and management of some conditions that are known to be associated with vaccination.

1.3. I have no knowledge or expertise on the mechanisms (desired or available) for the purchasing or manufacturing of vaccines, or on the logistics related to their distribution in the population, nationally or internationally. I also have no knowledge or experience with any legal aspects related to the compensation of potential harm caused by vaccines or medicines, including the *UK Vaccine Damage Payment Scheme*.

1.4. As an epidemiologist familiar with analysing large population-level datasets to assess causality rather than detailed laboratory or autopsy studies of pathology, I have limited specialist knowledge of the basic/immunological mechanisms underpinning vaccine safety events. However, I provide an overview of published literature describing pathological mechanisms where relevant. This is by no means a complete and exhaustive review of literature, but an attempt to summarise the existing knowledge on the biology and mechanisms underpinning some of the reported potential vaccine adverse events.

1.5. A number of potential conflicts of interest were raised with the Covid-19 Inquiry's legal team and I set these out for completeness:

- My current collaboration with the UK Health Security Agency (UKHSA) as a Honorary Consultant and supervisor for a PhD student in my group who also works

at UKHSA. This collaboration and studentship started more than a year after the relevant study period for this report and the Covid-19 Inquiry.

- Research funding from the European Medicines Agency in the form of competitive tenders for the investigation of Covid-19 vaccine safety and on other unrelated research questions.
- Consultancy work contracted through and paid to the University of Oxford (with no personal payments) to provide expert advice to AstraZeneca from March to September 2021. This work involved providing AstraZeneca with general advice on how to design observational studies for the monitoring of vaccine safety. I did not conduct any studies for, or funded by, AstraZeneca, nor was I given access to any data from AstraZeneca. Coagulation disorders were among the list of events monitored for all Covid-19 vaccines, as they usually are for any new vaccine; however, I was not aware of an association between coagulation disorders and adenovirus vectors before vaccine-induced thrombocytopenia and thrombosis (VITT) became apparent. I did not have any involvement in AstraZeneca's pharmacovigilance systems or reports, including its adverse event logging or analysis systems.
- On 1 March 2024 I was awarded a small grant (£50,000) to create a proposal for a national network to generate real world evidence to be used by the MHRA, under a competitive process funded by Innovate UK: UK Regulatory Science and Innovation Networks – Discovery phase (UKRI, 2023).

1.6. I do not consider that any of the above matters has affected my ability to prepare an objective and impartial report. The majority of my research to date has been funded by public or charitable sources, which include the NIHR, European Union and Arthritis Research UK (now known as Versus Arthritis).

Additional background information

Additional co-authors

1.7. The co-authors mentioned of this report set out above (Dr Annika Jödicke, Dr Edward Burn, Dr Junqing Xie and Dr Xintong Li) are experts in pharmacoepidemiology and drug and vaccine safety that work within my team at the Pharmacoepidemiology Research group at NDORMS, University of Oxford. They have all participated in or led analyses of Covid-19 vaccine safety or effectiveness and have contributed to the drafting of this report in line with my instructions and directions.

Consulted literature and materials

1.8. During the writing of this report, we consulted hundreds of manuscripts published and available in one of the most widely known repositories (PubMed) as well as documents, reports and any other useful documentation published by the key national stakeholders involved in the approval and post-marketing monitoring of vaccines in the UK: the Medicines and Healthcare products Regulatory Agency (MHRA), the Joint Committee on Vaccination and Immunisation (JCVI), and the UKHSA. We have considered published scientific papers from many countries around the world, including some data from the devolved nations of the UK. However, specific organisational responsibilities in Wales, Scotland and Northern Ireland were not within the scope of this report. We focussed most of our efforts on the review of literature published during the 'relevant period' as set in the

Letter of Instruction provided to us as expert witnesses: between 30 January 2020 and 28 June 2022. However, we did use later evidence or publications where necessary or relevant, particularly for the study of adverse events raised by the Inquiry's Material Providers.

1.9. I (Prof DPA) also received and read all the materials shared by the Covid-19 Inquiry staff, including witness statements and accompanying documents from the MHRA and CHM, and witness statements and accompanying documents provided by UK Covid Vaccine Adverse Reaction and Bereaved Groups (comprising the Scottish Vaccine Injury Group, the UK CV Family and the Vaccine Injured and Bereaved (VIBUK)). I have also read the evidence provided by Covid-19 Bereaved Families For Justice, Northern Ireland Covid-19 Bereaved Families For Justice, Scottish Covid Bereaved, Covid-19 Bereaved Families for Justice Cymru, Migrant Primary Care Access Group, Federation of Ethnic Minority Healthcare Organisations, Clinically Vulnerable Families, Traveller Movement and Disabled Peoples' Organisations.

1.10. This information was used to inform additional detail in some of the sections of this report.

1.11. We did not search government meeting minutes, or those of any other of their advisory committees, e.g. Scientific Advisory Group for Emergencies (SAGE) or the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG).

2. Background

Report structure

The report is structured as follows:

1. First, we provide a brief introduction to the types of Covid-19 vaccine available in the UK, with a particular focus on the initial stage of the vaccine rollout in 2021, when most of the population were vaccinated for the first time.
2. Second, we explain how vaccine safety was regulated and monitored during that same period.
3. Third, we summarise the intended effects of Covid-19 vaccines, including the prevention of infection and related complications in the short and long term. As part of this section, we address the potential and observable effects of Covid-19 vaccines to prevent community transmission of the (SARS-CoV-2) virus.
4. Fourth, we provide information on unwanted effects of the Covid-19 vaccines, including common and mild, and more rare and severe ones.
5. Fifth, we set out some concluding thoughts and make 10 recommendations to improve the UK's readiness for the safe deployment of vaccines in the scenario of a future pandemic

How we assessed the quality of evidence for this report

2.1. In some sections of this report, we were asked to assess the quality of evidence to the effect that the Covid-19 vaccines caused specific effects, including benefits as well as adverse drug reactions. As mentioned above, we did not conduct systematic reviews of the literature. Therefore, we cannot use standard definitions for the quality of evidence. Additionally, none of the most important and severe drug reactions would have been detectable with sufficient certainty in randomised controlled trials - these studies are the type of evidence on vaccines and therapeutics accepted as gold-standard in the scientific community. This is because the important and severe side effects turned out to be rare or very rare, and were hence unlikely to be picked up in a trial of a few thousands or tens of thousands of participants.

2.2. The following was therefore used to assess the quality of evidence available:

Quality of evidence	**Studies identified**	**Interpretation / intended meaning**
Very low	Case reports and anecdotal evidence	It is impossible to know if an association exists based on the available data
Low	Spontaneous report disproportionality analyses, cross-sectional studies, case-control or cohort studies without adequate confounding control	The true effect might be markedly different from the estimated effect

Moderate	At least one cohort or self-controlled study with adequate confounding control	We believe that the true effect is possibly close to the estimated effect
Moderate-high	Numerous cohort studies or self-controlled case series with adequate confounding control, or systematic reviews of observational data	We have some confidence that the true effect is likely close to the estimated effect
High	Randomised controlled trial evidence	We have a lot of confidence that the true effect is similar to the estimated effect

Introduction to Covid-19 vaccines

2.3. Numerous vaccines have been approved for the prevention of Covid-19 at the time of writing this report. The most important ones, covered in subsequent chapters, are classified in three main groups depending on their mechanism and structure:

- **Messenger RNA (mRNA) vaccines**: these instruct human cells to make units of the S protein typically found on the surface of the SARS-CoV-2 virus. Once vaccinated with an mRNA vaccine, human cells make copies of the S protein. This triggers your immune system to create antibodies and defensive white blood cells against this S protein, which will help you fight the virus once you are infected. Once the S protein copies have been made, your cells then destroy and eliminate the mRNA (European Medicines Agency: Amsterdam, 2021b, European Medicines Agency: Amsterdam, 2021a). The mRNA in the vaccine does not enter the nucleus of human cells, and it therefore does not mix with our DNA. The Pfizer-BioNTech ("BNT162b2", referred to hereafter as "the Pfizer vaccine") and the Moderna ("mRNA-1273", referred to hereafter as "the Moderna vaccine") vaccines are monovalent mRNA-based Covid-19 vaccines, "monovalent" being a vaccine designed to target a particular strain, generally the original "wildtype" variant. Bivalent mRNA vaccines, covering two strains - the "wildtype" variant and the Omicron variant - were introduced in summer 2022 after the end of this Inquiry's relevant period. They are therefore not a focus of this report.

- **Adenovirus vector vaccines**: these vaccines use a modified adenovirus to induce an immune response. Adenovirus are a family of viruses, some of them commonly infecting humans and causing cold or respiratory symptoms. This adenovirus, also known as a 'viral vector', is modified in two ways before inoculation: 1) it is made unable to reproduce/replicate; and 2) it is modified to include instructions on how to express one or more parts of the SARS-CoV-2 virus, specifically the spike protein (also known as the S protein). Once vaccinated with these viral vectors, human cells learn to make copies of the SARS-CoV-2 S protein, which triggers the creation of antibodies and defensive white blood cells. Similar to mRNA vaccines, these newly generated antibodies then protect against Covid-19 when the vaccinated person is exposed to SARS-CoV-2. Both ChAdOx1 (referred to hereafter as "the AstraZeneca vaccine") and Ad26.COV2.S ("the Janssen vaccine") are adenovirus vaccines.

- **Protein subunit / glycoprotein vaccines**: these vaccines contain S protein copies surrounded/wrapped by proteins to avoid their immediate destruction. As soon as the human immune system encounters these S proteins, it creates antibodies and defensive cells. These then protect the vaccinated person when they encounter an actual SARS-CoV-2 exposure. Nuvaxovid ("the Novavax vaccine") is a protein subunit vaccine.

2.4. There is a fourth type of commonly used vaccine: the inactivated viral vaccine. This uses inactivated (dead) viruses combined with an adjuvant and has a long history of being used for protection against many diseases, including polio and influenza. The only inactivated viral vaccine approved for use in respect of Covid-19 during the relevant period was the Valneva vaccine; however, this was never deployed in the UK. At least two inactivated vaccines were used in other parts of the world to protect against Covid-19: the Sinovac-Coronavac vaccine and the Sputnik V vaccine. These are not covered in detail in this report as they were never approved for use in the UK, but they are mentioned where relevant.

3. Vaccine safety regulation and monitoring

The UK regulatory system and the international context

3.1. The UK's regulator of medicines, including vaccines, is the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA is an executive agency of the Department of Health and Social Care (DHSC) and is responsible for ensuring the safety, quality and effectiveness of medicines, medical devices and blood components for transfusion.

3.2. In making its decisions, the MHRA receives advice from a number of independent advisory bodies, including the Commission on Human Medicines (CHM). The CHM is an advisory non-departmental public body, sponsored by the DHSC, and is the Government's independent expert scientific advisory body on medicines. During the pandemic, the CHM formed a number of Expert Working Groups (EWGs), including the Covid-19 Vaccine Benefit-Risk EWG (VBREWG).

3.3. Many western nations have vaccine (and medicines) evaluation processes similar to those in the UK. EU member states each have regulatory agencies like the MHRA and with similar functions, e.g. the Spanish Agencia Española de Medicamentos y Productos Sanitarios, the Dutch Medicines Evaluation Board (CBG for its initialism in the Dutch language) or the Danish Medicines Agency (Laegemiddelstyrelsen).

3.4. A key difference between these and the MHRA is that, since 2021, the former remain members of the collaboration of EU national agencies through the European Medicines Agency (EMA). This collaboration allows for both central (through the EMA) and national (through national agencies) approval and monitoring of medicines. The MHRA was part of the EMA and the EU framework during the first year of the pandemic (2020), but left it, with effect from 1 January 2021.

3.5. Other relevant national regulatory agencies of international reputation are the US Food and Drug Administration (US FDA) and Health Canada, among others. All these national agencies (including the MHRA) share similar functions, responsibilities and remits, including the monitoring of vaccine safety after approval through spontaneous reports and post-authorisation safety studies (PASS).

3.6. One apparent difference between the EMA, US FDA, and Health Canada on the one hand, and the MHRA on the other, is the availability of mechanisms for the commissioning of PASS. The EMA regularly opens competitive tenders for specific studies of regulatory interest, and some of these covered issues related to Covid-19 vaccine safety (e.g. EUPAS 39361, EUPAS 44469). More recently, the EMA funded the Data Analysis and Real-World Interrogation Network (DARWIN EU) to generate faster and better evidence, including on vaccine and medicine safety. The US FDA and Health Canada have similar platforms for the request and rapid execution of regulatory studies, namely the Sentinel and C-NODES initiatives respectively.

3.7. To the best of my knowledge, the MHRA does not have an equivalent mechanism for the commissioning of rapid analyses for timely evidence for regulatory purposes. While PASS studies can be commissioned by the MHRA (see below), it does not have the same rapid and stable mechanisms to commission them when compared to other regulators. However, the MHRA does have access to data from primary care and linked hospital records in the form of the Clinical Practice Research Datalink (CPRD). These data are available to the MHRA for analysis, but have certain limitations including geographic coverage and lack of information on most hospital treatments.

3.8. Recently, Innovate UK opened a call for the setting up of UK Regulatory Science and Innovation Networks. This is a promising development which could be the seed or pilot for a national infrastructure for the generation of regulatory evidence similar to those available to the EU EMA's DARWIN EU, Canada's C-NODES and the US FDA's Sentinel systems.

Authorisation of Covid-19 vaccines in the UK

3.9. In response to the pandemic, the MHRA modified its procedures to expedite the review and authorisation of the Covid-19 vaccines. This included a 'rolling review' procedure, whereby the MHRA received and assessed clinical trial data from pharmaceutical companies on a rolling basis rather than requiring that all data be presented at the same time. Once the MHRA had formed a positive opinion in relation to the safety and efficacy of a candidate vaccine, it sought advice from the CHM. The CHM then advised the UK government on each vaccine's quality, safety and potential risk-benefit balance, with a final decision on authorisation taken by a Minister acting as the 'Licensing Authority'.

3.10. The first Covid-19 vaccines, including the Pfizer, AstraZeneca and Moderna vaccines, were initially authorised for supply in the UK on a temporary basis under Regulation 174 of the Human Medicines Regulations 2012. Regulation 174 operates to disapply, on a temporary basis, the standard authorisation procedures and regulations where that is in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation, which may cause harm to human beings. The Covid-19 pandemic met this definition. Use of Regulation 174 also ensured that the vaccines could be supplied across the whole of the UK at the same time as, once the UK left the EU on 1 January 2021, Northern Ireland remained subject to the EU's medicines regulatory regime.

Post-marketing surveillance of Covid-19 vaccines in the UK

3.11. Once a Covid-19 vaccine had received approval for use, the MHRA was then responsible for the monitoring of post-marketing safety. Post-marketing safety data typically includes spontaneous reports made by affected people and healthcare professionals, and PASS. Spontaneous reports are often directly received and processed by the MHRA through the Yellow Card scheme. PASS are usually observational by nature. These studies use routinely collected health data from electronic medical records, registries or health claims, and utilise different study designs, including case-control, cohort and self-controlled methods (Lai et al., 2022). PASS are commonly conducted by various entities, including pharmaceutical companies (marketing authorisation holders), independent or academic

groups, national regulatory agencies (like the MHRA), or other national and international consortia, sometimes including contract research organisations (CROs).

3.12. Following advice from the CHM, the MHRA set up a four-strand approach to post-marketing surveillance of the Covid-19 vaccines:

1. Enhanced Yellow Card passive surveillance through an interface to the Yellow Card scheme specifically for the Covid-19 vaccines.

2. Rapid cycle analysis (proactive - as opposed to passive - analysis of pre-defined events) and ecological analysis (proactive analysis of trends within particular populations).

3. Targeted active monitoring through the Yellow Card Vaccine Monitor (invitations of a random selection of vaccinees to register on the Monitor, and then pro-active follow up to ascertain whether any suspected adverse reactions had occurred).

4. Formal epidemiological studies to confirm and quantify a suspected side effect.

3.13. In addition to the MHRA and CHM, other important stakeholders played a role so as to maximise the transparency and completeness of information on Covid-19 vaccines, both in terms of risks and benefits. Important relevant bodies included the Joint Committee on Vaccination and Immunisation (JCVI) and public health agencies like the UK Health Security Agency (UKHSA, formerly Public Health England) and equivalent bodies in Wales, Scotland and Northern Ireland. The JCVI focused on recommendations on the best strategies for prioritising vulnerable populations and for determining dosing regimens, while the UKHSA took responsibility for the monitoring of vaccine uptake and of vaccine effectiveness over time, particularly in the context of emerging SARS-CoV-2 variants. More detail on their respective roles and recommendations are covered in subsequent sections of this report.

The risk-benefit balance

3.14. Vaccines are not medicines used to treat existing conditions, but are used to prevent possible future outcomes. Safety is therefore particularly relevant in their evaluation and monitoring, and the risk-benefit balance is required to be very favourable to justify rollout to large numbers of people not currently suffering from the infection. To our knowledge, there are no pre-specified or universally accepted risk-benefit thresholds. Instead, vaccines are proposed for use when their potential risks are much rarer and/or less severe than the consequences of the infection they prevent or mitigate. In the case of Covid-19, and as detailed in subsequent sections, the vaccines prevented hundreds of thousands or millions of deaths worldwide, therefore proving to be extremely beneficial against a virus that was killing large numbers of people globally. As we will also describe in subsequent sections, the risks of serious adverse events associated with the UK-approved Covid-19 vaccines were very rare overall. However, some of them were more common in specific population subgroups, leading to changes in the use of the vaccines for the groups affected.

3.15. That said, the risk-benefit balance was also affected by the high incidence of Covid-19 during the pandemic and the high likelihood of almost everyone eventually becoming infected based on models that were later proved to be correct (Office for National Statistics, 2023). To keep the risk-benefit balance updated and accurate, all available and upcoming

data on overall effectiveness over time, impact on specific subpopulations and emerging risks of side effects had to be considered together.

Overall assessment of the UK's regulatory system

3.16. Based on the author's research and experience, it is my view that the modifications made to the UK's safety regulatory system in response to the pandemic and detailed in the following paragraphs of this section did not negatively affect the system's ability to effectively identify and respond to safety issues associated with the Covid-19 vaccines. The rolling review of clinical trial findings accelerated the process of systematic evaluation of vaccines' risk-benefit profiles at the time of approval. However, none of the potential serious adverse effects identified post-approval were known at that time, as they were too rare to be detected even in a very large clinical trial. Other regulators, like the EMA, followed similar processes with a similar result, as detailed in later sections of this report.

3.17. In terms of post-marketing surveillance, the continuous and enhanced review and analysis of spontaneous reports submitted using the bespoke Covid-19 vaccine Yellow Card scheme enabled very rapid identification of potential adverse effects. This was equivalent to the work done by other countries in Europe, such as Spain and its system for the notification of suspected adverse reactions. The Covid-19 vaccine Yellow Card scheme allowed the MHRA to identify safety issues in a timely manner, and to produce swift guidance and/or documentation to alert patients and clinicians and healthcare professionals. More details on the timings for each of these are provided in subsequent sections of this report.

3.18. The formation of VBREWG (the CHM Covid-19 Vaccines Benefit Risk Expert Working Group), and other advisory groups relating to emerging signals, was also fundamental to positively inform decision-making based on the potential impact of any changes in the vaccination campaign.

3.19. In relation to complementary and proactive monitoring using PASS studies: UK-based data sources including pseudonymised NHS records and linked data, for example from the National Immunisation Management System (NIMS) registry, allowed quality and timely research on the safety and effectiveness of vaccines nationally.

3.20. The establishment of NIMS and similar registries in the devolved nations (e.g. the Vaccination Management Tool (VMT) in Scotland) was a key development in the monitoring of vaccine safety. It allowed national stakeholders to monitor the rollout, coverage, effectiveness and safety of Covid-19 vaccines in England (Tessier et al., 2023). NIMS provided a unique data asset that, linked to other national data sources, allowed for the continuous study of vaccine safety and effectiveness. This enabled the UK to be at the forefront in tracking vaccine effectiveness over time and to evaluate the impact of emerging SARS-CoV-2 variants.

3.21. The access to a complete view on the exposure to Covid-19 vaccines in the UK thanks to NIMS made it possible for many groups across the country, including government actors but also independent and academic groups, to conduct PASS studies to monitor safety and effectiveness across multiple populations and over time. This is demonstrated by the large number of high impact manuscripts cited in this report, including in top international scientific journals like the New England Journal of Medicine, the Lancet and the BMJ.

3.22. This complex system allowed the generation of timely evidence that resulted not only in multiple public and scientific communications on the risks and benefits of the Covid-19 vaccines, but also in swift action by the MHRA when potentially serious adverse effects were identified. The time lag between the identification of new adverse effects and the corresponding actions (e.g. notifications, change in indication, etc.) was similar to some countries but longer than others. This led to relatively minor differences in the timing of actions based on safety signals across the western world, detailed in subsequent sections of this report.

3.23. In this context it is important to note that decisions about when to act upon a safety issue in the middle of a pandemic involve a difficult trade-off between restricting access to a beneficial vaccine and minimising any related risks. Importantly, the context of community transmission and alternative vaccine availability had to be considered when making these decisions. In the UK, as in many other countries, such decisions were made not only by the regulator (the MHRA) but also by committees like the JCVI.

3.24. Other relevant initiatives that contributed positively to the monitoring and evaluation of vaccine safety nationally included Public Health Scotland's EAVE II (Early Pandemic Evaluation and Enhanced Surveillance of Covid-19), the SARS-CoV-2 immunity and reinfection evaluation (SIREN) study and other National Core Studies funded by the National Institute for Health and Care Research (NIHR). These programmes played significant roles in improving the understanding and evaluation of vaccine effectiveness.

3.25. In our opinion, despite the potential challenges and changes arising from the departure from the EU/EMA framework during the pandemic, the UK's investment in new or updated monitoring systems and research studies allowed the UK to monitor the risk-benefit of Covid-19 vaccines as quickly and effectively as many other similar countries. As I detail in subsequent sections, most relevant serious adverse events were noticed and acted upon by the MHRA within days or weeks before or after other international regulators from Europe or North America.

4. Intended effects of vaccines

4.1. In this section we briefly summarise most of the knowledge about the beneficial effects of Covid-19 vaccines available in the UK based on studies published in peer-reviewed journals before 28 June 2022. More recent studies are included for the section on beneficial effects of vaccines against Long Covid.

Initial estimates of the effectiveness of Covid-19 vaccines

Summary:

- We had high quality evidence from phase 3 trials suggesting that the Covid-19 vaccines prevented symptomatic Covid-19 at the time when they were approved.
- Some of these trials demonstrated an effect against asymptomatic infection, and some against severe Covid-19 (e.g. hospitalisation).

4.2. Initial estimates on how well vaccines protect against severe Covid-19 came from large, randomised clinical trials (also known as Phase III trials) including tens of thousands of people without previous SARS-CoV-2 infection, conducted mostly in 2020. The numbers of participants in these Phase III trials were comparable with those used for other recent vaccines, like those conducted for the study of vaccines against respiratory syncytial virus (Walsh et al., 2023, Wilson et al., 2023).

4.3. These first studies reported on the AstraZeneca (Voysey et al., 2021), Pfizer (Polack et al., 2020) and Moderna (Baden et al., 2021) vaccines in December 2020 and the Janssen vaccine (Sadoff et al., 2021) in April 2021. Despite differences in study populations, the geographical location from which participants were recruited and choice of comparator (placebo in most trials, non-Covid active vaccines in others), they all showed high protection against symptomatic Covid-19.

4.4. All four vaccines were subsequently approved and recommended for use in the UK and in the European Union based on these data. In February 2022, the Novavax vaccine became the fifth Covid-19 vaccine authorised for use in the UK (MHRA, 2022).

4.5. The efficacy of 2 doses of the AstraZeneca vaccine against symptomatic Covid-19 (positive test and at least one symptom) was reported to be 70.4% [95% Confidence intervals 54.8 to 80.6] at >14 days after the second dose in an interim analysis (Voysey et al., 2021). Interestingly, efficacy was higher (around 90%) in a subgroup of people who received a lower vaccine dose as their first dose, followed by a normal dose for the second.

4.6. It is worth mentioning that the timing between people receiving their first and second vaccine dose in this trial varied. While most UK participants received their booster dose ≥12 weeks after the first dose, those recruited in Brazil received their second dose within 6 weeks of the first. Exploratory analyses of these data suggested that efficacy for this vaccine was similar, if not better, with a longer time lapse between doses (<6 weeks vs ≥6 weeks), which is important when considering the subsequent UK-wide decision to prolong dosing intervals (see paragraphs 4.40 to 4.46).

4.7. Notably, this trial used regular PCR testing in a subset of participants, therefore providing evidence for a protective effect against asymptomatic as well as symptomatic Covid-19. Vaccine efficacy against asymptomatic infection in this study was estimated based on small numbers of participants and found to be around 50% in those receiving low dose/standard dose vaccination.

4.8. The first interim results from a large clinical trial on the efficacy of the Pfizer vaccine showed an efficacy of 95.0% [90.3 to 97.6] to prevent laboratory-confirmed Covid-19 ≥7 days after the second dose when administered 21 days after the first (Polack et al., 2020).

4.9. Similarly, high vaccine efficacy was shown for the Moderna vaccine, with 94.1% [89.3 to 96.8%] protection against symptomatic Covid-19 at least 14 days after the second dose when given 28 days after the first (Baden et al., 2021).

4.10. The Janssen vaccine was the only one-dose vaccine approved by the MHRA. At ≥14 days after a first dose, efficacy was 66.9% [59.0 to 73.4] against moderate-severe Covid-19, and 76.7% [54.6 to 89.1] against severe–critical Covid-19 (Sadoff et al., 2021).

4.11. Finally, 2 large clinical trials in the US/Mexico and the UK showed effectiveness of 90.4% [82.9% to 94.6] and 89.7% [80.2 to 94.6] at ≥7 days after 2 doses of the Novavax vaccine against Covid-19 (Dunkle et al., 2022, Heath et al., 2021).

Analyses of vaccine effectiveness in specific population subgroups of interest

Summary:

- We have moderate to moderate-high quality evidence suggesting that the initially approved Covid-19 vaccines prevented infection (at the time of analysis) and Covid-19 hospitalisations for specific subgroups of interest, including immune-suppressed patients, nursing home residents, and pregnant women.
- Additionally, we have high quality evidence that the approved mRNA vaccines were highly effective to prevent Covid-19 in children aged 5 to 15 at the time of approval for paediatric use.

4.12. With the roll-out of the vaccination campaign and increasing numbers of people vaccinated, the effectiveness of the vaccines "under real-world conditions" was monitored by multiple academic groups and by national agencies like the UKHSA (then known as Public Health England), Public Health Scotland, Public Health Wales and the Public Health Agency in Belfast, Northern Ireland. This included studies to establish the effectiveness of the approved Covid-19 vaccines in the general population and in subgroups of people not included or under-represented in the initial phase III trials.

4.13. Due to the observational nature of these data, it is difficult to establish comparisons between vaccinated and unvaccinated subjects. This is because vaccination was not randomly allocated (like in phase III trials) but instead offered based on important risk factors for infection (e.g. healthcare workers) or for severe disease (e.g. old age or clinical vulnerability). Multiple different methods were used to minimise the impact of this, and

some of these methods and analytical strategies have been further validated and shown to provide valid estimates of effectiveness, similar to those seen in phase III trials (Catala et al., 2024).

4.14. Among 383,812 people tested for SARS-CoV-2 as part of the Office for National Statistics' Covid-19 Infection Survey between 1 December 2020 and 8 May 2021, 12,826 people tested positive. This was one of the largest of such infection surveys conducted internationally at the time. Vaccine effectiveness in this population for the AstraZeneca and Pfizer vaccines at ≥21 days after the first dose was measured as 61% [54 to 68] and 66% [60 to 71] respectively. Higher effectiveness was reported after a second dose: 79% ([65 to 88] and 80% [73 to 85] respectively. While estimates for vaccine effectiveness varied between studies, they consistently showed that both vaccines were effective to substantially reduce the risk of symptomatic and severe Covid-19 when used under "real-world" conditions (Pritchard et al., 2021). All ethnic groups benefited from vaccination according to similar analyses (Glampson et al., 2021, Whitaker et al., 2022).

4.15. In addition, several studies were conducted among populations previously under-represented in trials, including individuals with clinical conditions that place them at high risk for severe Covid-19 (so called "clinical risk groups"). Whitaker et al. reported no overall reduction in vaccine effectiveness for at-risk clinical risk groups compared to the general population. However, substantially reduced vaccine effectiveness against infection was seen in the immunosuppressed group, with only 22-24% effectiveness of a first dose of the AstraZeneca or Pfizer vaccines, and 60% effectiveness for a second dose (Whitaker et al., 2022). Vaccine effectiveness against Covid-19 related hospitalisation after 2 doses was somewhat reduced in these people; fortunately, however, it remained substantial: 77% [74 to 80] (Embi et al., 2021).

4.16. Studies among residents of long-term care facilities in England showed vaccine effectiveness (against SARS-CoV-2 infection) of around 50% 4 weeks after a first vaccine dose and 60% in the month after a second dose (Paranthaman et al., 2022, Shrotri et al., 2021). A complementary study from Catalonia (Spain) focussing on severe outcomes reported effectiveness of 2 Pfizer vaccine doses against Covid-19 related hospitalisation or death in nursing home residents to be very high, with 95% [93 to 96] and 97% [96 to 98] protection respectively (Cabezas et al., 2021b).

4.17. Vaccination in pregnancy was a specific concern in the early days of the vaccination campaign, probably due to the exclusion of pregnant women from Covid-19 vaccine trials internationally. This exclusion led to uncertainty around the safety and efficacy of the approved vaccines in pregnant women, resulting in uncertainty for healthcare professionals giving individual advice about risks and benefits, and probably contributing to a low uptake during the beginning of the vaccine rollout. mRNA-based vaccines were later shown to be similarly safe and beneficial in pregnant women as in the general population, with 97% and 89% effectiveness against symptomatic Covid-19 and Covid-related hospitalisation after 2 doses of the Pfizer vaccine (Dagan et al., 2021). Later studies have provided additional reassurance on the effectiveness of these vaccines against Covid-19 complications and severe disease in pregnant women (Mercade-Besora et al., 2024). This information on risks and benefits was particularly relevant given the high rates of severe Covid-19 outcomes observed among pregnant women.

4.18. Following the vaccination of adults, the MHRA extended the approval of the Pfizer vaccine to allow its use in 12- to 15-year-old children (MHRA, 2021b), with vaccination of younger age groups advised later by the JCVI (JCVI, 2022). A phase III randomised clinical trial reported the vaccine to be highly effective against Covid-19 in children aged 12 to 15, and to produce an even greater immune response than in young adults (Frenck et al., 2021). Similarly, high vaccine effectiveness in younger children aged 5 to 11 was reported (90.7% [67.7 to 98.3]) with only 1/3 of the dose for adults being used in that age group (Walter et al., 2022).

Diversity in clinical trials

Summary:

- The initial AstraZeneca trials included a lower than desirable number of elderly people, particularly given the emphasis on protection of severe Covid-19, more common in older people. This led to some criticism about the potential efficacy of this vaccine in older populations, and likely encouraged some decision-makers in Europe to prioritise its use for middle-aged people.
- Sex representation was approximately balanced, but the exclusion per protocol of pregnant women from all phase III vaccine trials likely contributed to a slow uptake of the Covid-19 vaccines in pregnant women. This was unfortunate given pregnant women had poor outcomes when they had Covid-19.
- Most ethnic groups were included in the Phase III trials for all three vaccines, albeit in lower proportions than their representation in the overall population. Given the rarity of the later identified serious adverse events, it is unlikely that including a higher proportion of people from specific ethnicities would have affected our ability to identify specific safety issues.
- It remains important that efforts are made in the future to improve the diversity of phase III trials before products and vaccines are approved during a future pandemic. This would probably improve our understanding of the risk-benefit for specific subgroups and reduce vaccine hesitancy among the under-represented groups.

4.19. Regulators including the MHRA typically request that clinical trials include participant populations including those who are likely to receive the vaccine/medicine under study. This is based on European guidelines ICH E8 (r1) (EMA, 2022), which state: "*The population to be studied should be chosen to support the study objectives and is defined through the inclusion and exclusion criteria for the study. The degree to which a study succeeds in enrolling the desired population will impact the ability of the study to meet its objectives.*"

4.20. However, safety considerations for trial participants are also important when clinical trials are designed, and the same ICH E8 (r1) guidelines state: "*The study population may be narrowly defined to reduce the risk to study participants or to maximise the sensitivity of the study for detecting a certain effect. Conversely, it may be broadly defined to more closely represent the diverse populations for which the drug is intended. In general, studies conducted early in a development programme, when little is known about the safety of the drug, are more homogeneous in study population definitions. Studies conducted in the later phases of drug development or post-approval are often more heterogeneous in study*

population definitions. Such studies should involve participants who are representative of the diverse populations which will receive the intervention in clinical practice. Available knowledge about participant characteristics that may predict disease outcomes or effects of the intervention can be used to further define the study population."

4.21. Therefore, decisions on eligibility criteria for participants when designing a trial are typically based on a trade-off between including populations representative of those to be treated/vaccinated and excluding those at high risk of serious adverse effects. As far as I know, it is the responsibility of the trial sponsor to decide on these criteria.

4.22. Finally, an important factor contributing to the composition of a trial population is the willingness and/or ability of potential participants to enrol, and the ability of the investigators to attract diverse population groups to participate in the trials. Even if eligibility criteria are broad and inclusive, it is often the case that not all population subgroups are able or interested to participate in trials in sufficient numbers.

4.23. Regarding age, the AstraZeneca vaccine trials included low numbers of elderly people, with between 84% and 100% of participants aged 55 years or younger and only 0% to 10% aged 70 or older in the 4 pooled phase III trials (Voysey et al., 2021). Median (range) age in the Pfizer vaccine trial was 52 (16-91), and in the Moderna trial 51 (18-95) years old.

4.24. Sex representation was not remarkable in any of the phase III trials, with female participants 41% to 61% in the AstraZeneca trials, 49% in the Pfizer trial, and 47.3% in the Moderna trial.

4.25. Regarding ethnicity, over 90% of the participants in the UK-based AstraZeneca vaccine trials were white, but the smaller trial for this same vaccine conducted in South Africa included about 65% black participants, and the one conducted in Brazil included 10% black and over 20% mixed ethnicity participants. As for the Pfizer vaccine phase III trial (Polack et al., 2020), almost 83% of participants were white, about 9% black, 4% Asian and 2% multiracial. In the Moderna phase III trial (Baden et al., 2021), almost 80% were white, 10% black or African American, almost 5% Asian and about 2% multiracial.

4.26. All four AstraZeneca vaccine trials excluded pregnant and breastfeeding women (Voysey et al., 2021), and both the Pfizer and Moderna phase III vaccine trials excluded pregnant people (Polack et al., 2020, Baden et al., 2021).

Changes in vaccine effectiveness with the appearance of new variants, and waning immunity over time

Summary:

- Waning immunity is a known issue for many other vaccines, particularly for respiratory virus vaccines.
- Waning immunity for Covid-19 vaccines was monitored, and increased with the appearance of new variants, especially Omicron in late 2021. Waning immunity affected the vaccines effect against infection, but the vaccines remained (and remain) protective against hospitalisation and severe health outcomes despite waning

immunity.

- The UKHSA was world-leading in the monitoring of vaccine effectiveness over time, and action was taken to organise booster vaccination to confer additional protection to the population when Omicron appeared.

4.27. Multiple studies have assessed the effectiveness of vaccines against new variants and the waning of vaccines over time. For this summary, I predominantly refer to estimates provided by the UKHSA and Public Health Scotland based on data from the UK, sometimes working alongside public health colleagues from Wales and Northern Ireland. They continuously monitored the effectiveness of the Pfizer, AstraZeneca and Moderna vaccines. This monitoring covered periods when different variants were predominant, and later booster doses as well as the original two-dose schedules. In summary, their analyses showed that the protection vaccines offered against (symptomatic) SARS-CoV-2 infection was higher for the alpha variant compared to delta, and much higher for delta compared to omicron. This reduction in vaccine effectiveness could be the result of vaccine-induced immunity waning, adaptation of the virus, or a combination of both.

4.28. The effectiveness of Pfizer or AstraZeneca vaccines was lower against the delta variant compared to the alpha variant, with 30.7% [25.2 to 35.7] vs. 48.7% [45.5 to 51.7] effectiveness for both vaccines after one dose, with less noticeable differences after 2 doses: 88.0% vs. 93.7% for the Pfizer vaccine, and 67.0% vs. 74.5% for AstraZeneca respectively (Lopez Bernal et al., 2021). Fortunately, both the Pfizer and AstraZeneca vaccines preserved high levels of effectiveness in protecting against Covid-19 hospitalisation and death in relation to the delta variant, with limited waning over the follow-up available at the time (Andrews et al., 2022b, Sheikh et al., 2021).

4.29. Similar findings were reported from the US for 2 doses of the Moderna vaccine, with vaccine effectiveness against SARS-CoV-2 infection of 86.7% [84.3 to 88.7] against delta compared to 98.4% [96.9 to 99.1] against alpha (Bruxvoort et al., 2021).

4.30. After two doses of the AstraZeneca vaccine, effectiveness against Delta started at 82.8% [74.5 to 88.4] after 2 to 4 weeks but waned to 43.5% [42.4 to 44.5] after 25 or more weeks. Effectiveness of 2 doses of mRNA vaccines remained high in all periods, but there was also evidence of waning (Andrews et al., 2022a). This is in line with a meta-analysis estimating that during delta-dominant times, the protection against symptomatic Covid-19 decreased from 1 month to 6 months after full vaccination by 24.9% [13.4 to 41.6] in people of all ages. Fortunately, protection against severe Covid-19 decreased in a lesser fashion, only by 10% (Feikin et al., 2022).

4.31. Finally, substantial waning of AstraZeneca effectiveness was described by UKHSA after Omicron became the dominant variant nationally in late 2021, from around 50% at 2-4 weeks after the second dose to almost no protective effect from 20 weeks. Similarly, vaccine effectiveness for the Pfizer vaccine dropped from 65.5% [63.9 to 67.0] at 2 to 4 weeks after the second dose to 15.4% [14.2 to 16.6] after 15 to 19 weeks and 8.8% [7.0 to 10.5] after 25 weeks or more. The effectiveness of the 2-dose Moderna vaccine declined similarly over time, from 75.1% [70.8 to 78.7] to 14.9% [3.9 to 24.7] (Andrews et al., 2022a). No reductions in vaccine effectiveness against symptomatic disease were reported with Omicron sub-lineages BA.2 compared to BA.1. Booster doses with either mRNA vaccine

after a 2-dose primary course vaccination with the AstraZeneca or Pfizer vaccines substantially increased protection (Andrews et al., 2022a).

4.32. Importantly, while effectiveness of the booster dose also showed waning over time, mRNA booster vaccination was shown to remain highly protective against severe outcomes including hospitalisation and death due to Omicron (Nyberg et al., 2022, Stowe et al., 2022).

Estimates of vaccine effectiveness against Long Covid

Summary:

- Although Long Covid was not studied as a health outcome during the initial trials, we have moderate-high quality evidence to suggest that the existing Covid-19 vaccines are protective against the development of Long Covid.
- Overall, most good quality studies available to date continue to suggest that Covid-19 vaccines are either neutral or protective against the development of Long Covid.
- The effect of Covid-19 vaccines in people with pre-existing Long Covid remains unclear.

4.33. In February 2022, the UKHSA published a rapid review summarising the available evidence on the effectiveness of vaccines to prevent Long Covid (UKHSA, 2022c). All studies were observational, and hence provide weaker evidence than a properly conducted randomised controlled trial because the studies could not completely rule out factors other than vaccination. Most studies that assessed the association of pre-infection vaccination and long-term complications at that time showed a reduction in risk for Long Covid associated with vaccination. Eight of the studies reviewed assessed the effectiveness of vaccination before SARS-CoV-2 infection. Six of these studies showed that vaccinated people were less likely to develop symptoms of Long Covid after infection. However, all these studies were restricted to participants who suffered Covid-19, therefore neglecting the well-known effectiveness of the Covid-19 vaccines to reduce infection in the first place. Overall, this review and our knowledge suggests no association between vaccination itself and persistent symptoms of Long Covid. Although phase 3 trials showed that all approved Covid vaccines increased a risk of fatigue, this was self-limited and brief in duration. Two relevant studies were conducted using data from the US based on the Veteran Affairs national healthcare database and from a newly developed multicentre cohort called N3C, respectively. Both showed a reduced risk for post-acute Covid-19 complications in people with Covid-19 who had been previously vaccinated, compared to unvaccinated subjects (Al-Aly et al., 2022). Similarly, a UK-based study using digital self-reported data collected using the ZOE app reported lower odds (OR 0.51 [0.32 to 0.82]) of persistent symptoms (≥28 days) following full two-dose vaccination (Antonelli et al., 2022).

4.34. Systematic reviews conducted later in 2022 and 2023 showed effect estimates to greatly vary between studies, largely depending on the Long Covid definition used, study population included and healthcare setting (Byambasuren et al., 2023, Notarte et al., 2022, Watanabe et al., 2023a). However, most of these studies published by Summer 2022 only included people with Covid-19, and the impact of vaccines to prevent Covid-19 in the first place was therefore not accounted for in any of these studies. More recently, analyses of

UK primary care data replicated in Estonia and Spain were published in 2023 and showed an overall effectiveness of a first vaccine dose to protect against development of Long Covid symptoms following SARS-CoV-2 infection to be around 50% in all adults (Catala et al., 2024b). These analyses were further replicated using nationwide Norwegian data with similar findings (Trinh et al., 2024).

4.35. The UKHSA Review mentioned above also looked at whether vaccination in people who were already suffering from Long Covid before being vaccinated had any effect on the symptoms of Long Covid. Four studies included in the review compared the reporting of Long Covid symptoms in the same person before and after vaccination, and three of these studies found that the majority of (but not all) participants had an improvement after vaccination. The review included three studies of people with Long Covid who were unvaccinated at the time of infection, to then compare those who subsequently were vaccinated to a separate group of Long Covid patients who were never vaccinated. All three studies reported a lower risk of Long Covid symptoms in the former vs the latter. In 3 of 5 studies reviewed looking at symptom changes following vaccination in people with Long Covid, there was a majority of people (close to 70%) who had no change in symptoms after vaccination (UKHSA, 2022c). A more recent systematic review (2023) highlights this inconsistency between studies, with some reporting improvement of Long Covid symptoms in 20.3% of people who had Covid-19 before vaccination, but 20.5 % showing symptomatic worsening, and 54.4% with no change/s in symptoms (Watanabe et al., 2023a).

Estimates of the overall population-level impact of vaccines on Covid-19 deaths

Summary:

- The best quality evidence available to date suggests that the Covid-19 vaccines saved millions of lives globally.

4.36. As detailed below, numerous studies have been conducted to understand the impact of Covid-19 vaccination on Covid-related and all-cause mortality. Overall, these suggest that Covid-19 vaccination had a substantial impact on the course of the pandemic, saving millions of lives globally. Directly measuring the impact of Covid-19 vaccination on Covid-19 related and excess mortality is difficult, as the counterfactual scenario without vaccination was not observed in most countries, and strong non-pharmacological (public health) restrictions would have likely been maintained to suppress transmission in the absence of vaccines. However, mathematical models have been published that estimate the number of deaths avoided by the vaccination program shortly after its roll-out.

4.37. Estimates published by Public Health England and Cambridge University's MRC Biostatistics Unit suggest that 127,500 deaths had been prevented in England as a result of the Covid-19 vaccination programme up to 24 September 2021 (UKHSA, 2021a). Meslé and colleagues estimated that between December 2020 and November 2021 the number of Covid-19 deaths directly averted in people 60 years and older as a result of Covid-19 vaccination in the WHO European region was 469,186 (sensitivity range 129,851–733,744). For England and Scotland, the estimates were 157,604 and 27,656 deaths averted by

vaccination respectively (Mesle et al., 2021). This study also suggests that the largest number of deaths across all countries were averted after vaccination of older people. The authors concluded that the largest reduction in expected deaths was seen in countries with "high early vaccine uptake" including England and Scotland. Overall, England and Scotland ranked among the top 10 countries (8th and 2nd respectively) in terms of deaths averted thanks to Covid-19 vaccination.

4.38. A more recent analysis (Mesle et al., 2024) estimated a total of 449,241 and 25,386 lives saved in England and Scotland respectively until March 2023. In this study, the UK was therefore estimated to be the country with the highest number of deaths averted due to Covid-19 vaccines in the WHO-Europe region, followed by Italy (203,026) and Germany (182,988). These estimates are based on mathematical models, and therefore limited by the underlying assumptions of the models used. For example, based on varying assumptions ("sensitivity analyses") about prior infection, vaccine efficacy, lag time until vaccines take effect, and waning immunity, the estimate provided for lives saved in England varied from 301,497 to 502,487 lives saved (reported in the paper's supplementary appendix pp.74-75). Unfortunately, the studies cited at paragraphs 4.37 and 4.38 did not include data from Wales and Northern Ireland.

4.39. Globally, the impact of the first year of Covid-19 vaccination programmes was estimated to have avoided 14.4 million [13.7 to 15.9] deaths from Covid-19 in 185 countries and territories, with an estimated 19.8 million [19.1 to 20.4) deaths from Covid-19 averted when excess deaths were included (Watson et al., 2022). However, the study also suggests that even more lives could have been saved globally if a more fair and equitable distribution of vaccines had been achieved.

Vaccine dosage intervals and their potential impact on vaccine effectiveness

Summary:

- Informed mostly by JCVI modelling, the UK extended the administration of second-dose vaccines to 12 weeks, instead of 3, as done in most of the randomised controlled trials.
- Data available later in the pandemic suggests that this strategy was highly beneficial, as it allowed the administration of at least one dose to more people, faster.
- Additionally, an analysis of phase 3 trials for the AstraZeneca vaccine suggest that a longer separation between doses provided higher protection against symptomatic infection.

4.40. At the start of the vaccination roll-out, both supply and deployment capacity were limited compared to the global demand for Covid-19 vaccines. In order to optimise the Covid-19 vaccination programme for maximum short-term impact, the JCVI issued a short statement on 31 December 2020 advising that the maximum intervals between a first and second vaccine dose should be extended from 3 to 12 weeks (JCVI, 2021b).

4.41. At that time, information on vaccine efficacy from the first dose of the Pfizer-BioNTech was available, suggesting a short-term vaccine effectiveness of around 90%. For the first dose

of the AstraZeneca vaccine, short-term efficacy was estimated to be around 70%. In its statement, the JVCI stated that *"given the high level of protection afforded by the first dose, models suggest that initially vaccinating a greater number of people with a single dose will prevent more deaths and hospitalisations than vaccinating a smaller number of people with two doses*".

4.42. Upon request, and in the preparation of this report, the JCVI confirmed that the output of those models is publicly available in document DHSC_00048398 (JCVI, 2021b), and was published in a research article in September 2021. Briefly, the JCVI models were based on data from the second wave in the UK (from 1 September 2020 until 21 December 2020) and focussed on the vaccination of the oldest age groups. While over 80-year olds only comprised 5% of the population, 60% of deaths due to Covid-19 occurred in this age group. The theoretical models first examined whether, given a limited supply of vaccine, it would be better to give as many people as possible one dose and provide them with partial protection, or to give two doses (and thus a higher level of protection) to a smaller number of people, focussing on those at highest risk for Covid-19 related mortality. The models showed that when supplies are limited, a greater number of deaths could be averted by covering more people with a single dose. However, models also showed that there is a point at which it is better to switch to giving two doses to people at highest risk. That point depended on both the vaccine uptake and the relative efficacy from one dose compared to two doses. Additional models were then developed to predict the optimal allocation of vaccine doses between first and second doses, by maximising the relative number of deaths averted when both first and second doses are used to vaccinate the oldest age-groups first. Recommendations for the application in the UK based on these models were therefore "*that for relatively high protection from the first dose (compared to the efficacy derived from two doses) a substantial number of first doses should be administered before attention switches to giving second doses*", and that the time of switching to prioritising second doses would depend on the relative vaccine efficacy and the speed with which the vaccination campaign could be rolled out.

4.43. Published efficacy of the first dose of the Pfizer vaccine against symptomatic Covid-19 14 days after vaccination was 89% [52 to 97]. In the Phase III randomised controlled trial, the 2nd dose was administered 21 days after the first dose. No intervals longer than 21-28 days were tested, and therefore no efficacy estimates were directly available. For the AstraZeneca vaccine, efficacy from 22 days after a first dose was 73% [48.79 to 85.76]. Subgroup analyses among people who received their vaccines <6 weeks or ≥6 weeks' apart from each other showed comparable vaccine efficacy if the interval was extended (53.4% [−2.5 to 78.8] vs. 65.4% [41.1 to 79.6]) (Voysey et al., 2021). The JCVI statement reported an exploratory analysis of vaccine efficacy of 73% [48.8 to 85.8] among people with a first AstraZeneca dose between 22 days after first dose until either second dose or 12 weeks. Despite this uncertainty, independent mathematical models led by international researchers backed up this decision, suggesting that if efficacy persisted for up to 12 weeks, the decision to separate vaccine doses would result in better effects on health and fewer public health (non-pharmacological) restrictions (Catala et al., 2021).

4.44. The decision to extend the interval between vaccine doses was met with controversy. Concerns were raised over the lack of evidence for the interval (predominantly for the Pfizer vaccine) and the potential for vaccine resistant variants to develop (Berkane et al., 2021, Mahase, 2021). On 8 January 2021, the WHO published interim guidance for the use of the

Pfizer vaccine, recommending that the interval between doses may be extended up to 42 days (6 weeks) based on available clinical trial data (WHO, 2021a).

4.45. The roll-out of the first vaccine doses was accompanied by UK-based studies to monitor the clinical effectiveness of first-dose vaccination against Covid-19 and severe Covid-19 early on, with data from Scotland indicating a substantial reduction in risk of hospital admission due to Covid-19 (Vasileiou et al., 2021). This study also did not report on data from Wales or Northern Ireland.

4.46. In retrospect, increasing the interval between first and second doses from 3 to 12 weeks (and later 8 weeks) was found "highly beneficial" to prevent Covid-19 related hospitalisation and deaths. Based on mathematical models published in 2023, an estimated 32,000 to 72,000 hospital admissions and 4,000 to 10,100 deaths had been averted by the policy during the first 10 months following the start of the vaccination campaign in England (Imai et al., 2023, Keeling et al., 2023).

The effect of Covid-19 vaccines in limiting transmission of the virus in the UK

Summary:

- The effect of the approved Covid-19 vaccines to reduce transmission could not be studied in the vaccine trials. Therefore, the data available are at best of moderate-high quality.
- Most or all of the studies available on this topic demonstrated that the Covid-19 vaccines would reduce transmission.
- However, the observed decline in vaccine effectiveness against infection with the emergence of new variants likely resulted in a reduced effect against transmission.

4.47. The concept of vaccine effectiveness to minimise transmission (VET) is distinct from the general term of vaccine effectiveness, which typically refers to preventing, at the person level, infection, symptomatic illness and severe disease, including hospitalisation and death. Instead, VET focuses on the role of vaccines in reducing the contagion from person to person (here related to the SARS-CoV-2 virus), a crucial aspect in controlling community transmission and spread across the population.

4.48. Measuring transmission is challenging, particularly in the context of randomised controlled trials, as it requires tracking both symptomatic and asymptomatic infections among participants and their close contacts. To overcome these challenges, a combination of study designs has been used to date, each with inherent limitations and strengths. Observational studies provide evidence that may be most directly applicable to real-world settings but could contain biases. Viral load studies offer insights into infectiousness but require careful interpretation of their implications in wider populations and more realistic scenarios. Modelling studies provide a broader view, but often rely on assumptions that are not verifiable.

4.49. The process by which vaccination can prevent SARS-CoV-2 virus transmission can be broadly divided into two independent steps: first, by reducing the likelihood of infection among the vaccinated; and second, by reducing the likelihood of transmitting the virus to others for individuals who experience a breakthrough infection after vaccination

(infectiousness given infection). This dual mechanism highlights the complexity of evaluating VET.

4.50. Despite these difficulties, a number of studies have been conducted on this topic. Most available evidence consistently shows that the Covid-19 vaccines used in the UK are and remain highly effective in reducing severe disease and mortality (see paragraphs 4.16 to 4.17). Early results also showed effectiveness in reducing infection and symptomatic disease, which indirectly contributes to VET, as uninfected individuals cannot transmit the virus. This argument, advocated by reports from the UKHSA [A rapid review (UKHSA, 2022b); A rapid evidence briefing update 1 (UKHSA, 2022a)], supports the indirect beneficial effect of vaccines on transmission dynamics. It is, however, unclear whether these vaccines are similarly effective in reducing asymptomatic infection, particularly after the emergence of Omicron.

4.51. Understanding the infectiousness or ability to pass on the infection in breakthrough Covid-19, among the vaccinated, is much more complex. Early UK-based studies consistently showed that Covid-19 vaccines reduced the risk of transmission by nearly 50% among household members from index cases when the Alpha variant was dominant (Harris et al., 2021, Shah et al., 2021). These findings were later corroborated by other studies with different designs, and in diverse settings and populations (de Gier et al., 2021, Prunas et al., 2022, Salo et al., 2022).

4.52. However, clear variability in VET was later observed when different SARS-CoV-2 variants became dominant. In the context of the Delta variant, vaccines remained effective against transmission, but showed a lower effectiveness compared to earlier strains. A contact tracing study gathering data from September 2020 to September 2021 and published in October 2021 of 602 community contacts of 471 UK Covid-19 index cases found that the secondary attack rate (SAR) in household contacts exposed to the delta variant was 25% for fully vaccinated individuals versus 38% for unvaccinated individuals (Singanayagam et al., 2022). In another study of 146,243 tested contacts of 108,498 index patients, vaccination with the Pfizer vaccine significantly reduced PCR positivity in contacts, particularly for the Alpha variant (SAR ratio 0.32) and less for the Delta variant (SAR ratio 0.50). This pattern was also observed for the patients receiving AstraZeneca vaccinations (Eyre et al., 2022). Of importance, a rapid decline was observed in VET over time after vaccination, particularly for the new variants researched in these studies.

4.53. Data from viral load studies present a mixed picture regarding the infectiousness of vaccinated individuals with Delta SARS-CoV-2 viral infection. Although many suggested no significant differences in viral clearance time between vaccinated and unvaccinated cases (Hagan et al., 2021, Pouwels et al., 2021, Salvatore et al., 2023), some studies found that full vaccination can reduce infectious viral load for Delta breakthrough cases compared to unvaccinated infected individuals (Bak et al., 2021). It is crucial to note that measuring viral RNA in swabs is only a proxy for transmission potential, and these results should therefore be interpreted with caution.

4.54. The emergence of the Omicron variant introduced further complexity. While vaccines are less effective in preventing Omicron infections, their impact on transmission is not straightforward and remains less well understood. A large study showed only marginal increases in transmission among unvaccinated individuals infected with Omicron compared

to Delta, but a more significant increase for vaccinated and booster-vaccinated contacts, suggesting a reduction in VET for Omicron-infected subjects (Lyngse et al., 2022).

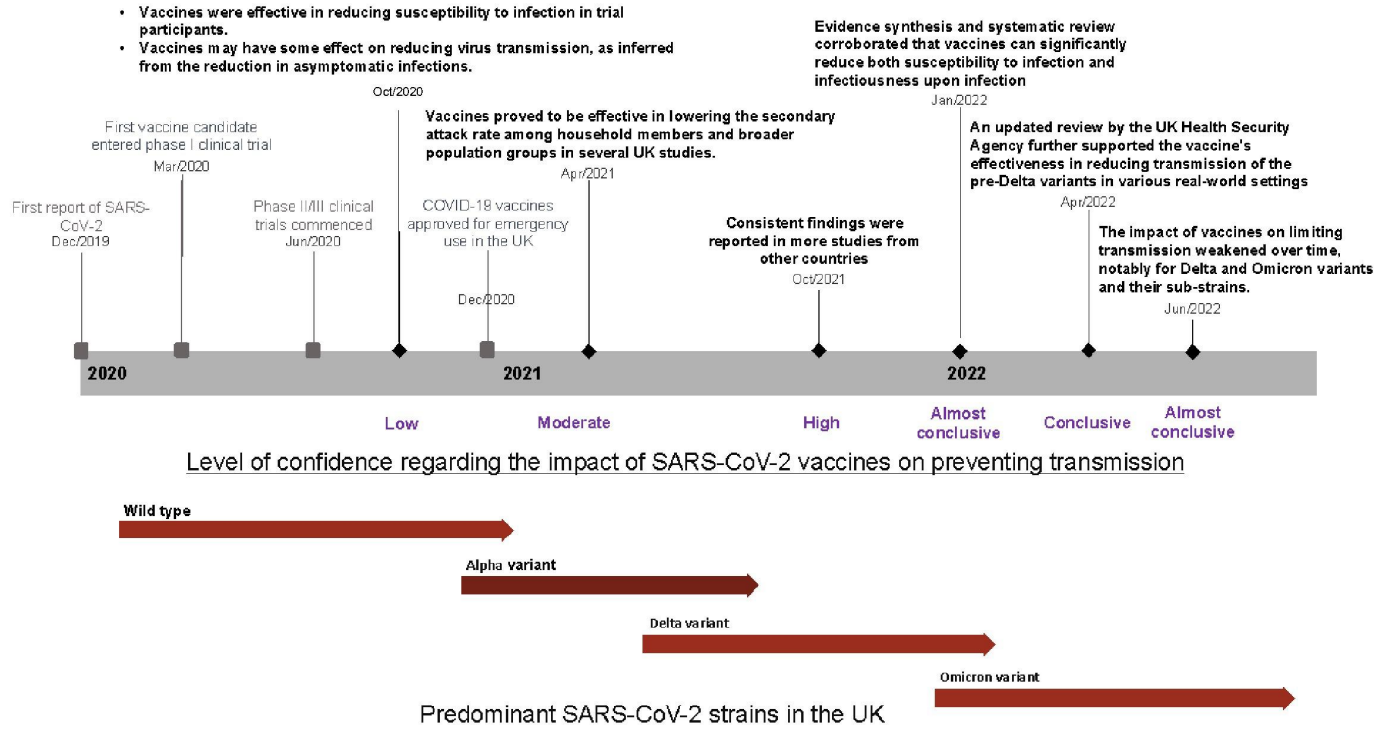
4.55. During the circulation of Omicron variants, the role of booster doses and hybrid immunity became a focal point. Data was available to support the contention that booster-vaccinated individuals are less infectious than those fully/primarily vaccinated, but it remains unclear if this enhanced protection (infectiousness given infection) offsets the reduced effectiveness of vaccines against Omicron (infection probability). A study in prisons in California supports the idea that a combination of previous infection and vaccination provides the most robust defence against transmission, compared to either previous infection or vaccination alone (Tan et al., 2023). How generalisable these findings are to the broader population remains an open question, as most post-marketing evidence on VET has been derived in somewhat closed research settings. The least indirect evidence from many modelling studies supports the effectiveness of vaccines in limiting transmission, yet these are based on assumptions that may not always reflect practical conditions.

4.56. In conclusion, while vaccines continue to play a crucial role in preventing serious illness, their effectiveness in preventing transmission appears to be more subtle, dynamic and intricate. Most evidence suggests that the effect of vaccines to reduce overall transmission (likelihood of infection + infectiousness given infection) increased with booster doses but declined over time since the last dose had been given and with the emergence of the Omicron variants. However, these studies are unlikely to reflect the complex dynamics of transmission in the community, and many other non-pharmaceutical factors and interventions play a role in community transmission, making it difficult to research VET in realistic settings.

4.57. Preliminary data indicated that Covid-19 vaccines reduced transmission by lowering the likelihood of infection among trial participants. While the evidence suggested a possible reduction in virus spread due to the vaccines' impact on asymptomatic infections, this inference was made with lower confidence (August 2020).

4.58. At the time of vaccine approval, there was no consensus in the scientific community about the vaccines' effectiveness in reducing transmission in real-world settings, as this was not directly assessed in the clinical trials (December 2020). Data was subsequently collected and analysed in subsequent months, and is summarised in the following sections.

Figure 1: Chronology - when the effect of the UK Covid-19 vaccines on transmission became known



4.59. As detailed above, all best evidence consistently showed the vaccines' effectiveness in preventing transmission, based on data emerging within a year of their approval and distribution across the UK (January 2022). There was a decline in vaccine effectiveness for preventing infection after the emergence of the Delta variant and other novel variants, suggesting VET may be less efficient in limiting these new variants compared to the wild type or pre-Delta variants (June 2022).

Summary of known estimates of vaccine effectiveness for vaccines not approved in the UK during 2020/2021

4.60. At the start of the roll-out of the vaccination campaign in the UK in December 2020, evidence about the effectiveness of other vaccines was still scarce.

4.61. The Sputnik V vaccine received emergency authorisation on 11 August 2020 in Russia, where it was developed.(SputnikV, 2022). However, results from phase 1-2 clinical trials were only published a month after vaccine approval, and concerns were raised by scientists about potential inconsistencies in the published data, as a result they requested that the raw data be shared with researchers (Bucci, 2020). Results from a large phase III trial, which was still ongoing at the time Sputnik was rolled-out in Russia, were published in early February 2021 (Logunov et al., 2021). The study reports 91.6% efficacy against Covid-19 and that the vaccine was well tolerated in the study population. However, concerns were again raised about the study, with scientists pointing out “numerical inconsistencies in the

statistics and results", as well as insufficient access to the original study data and full study protocol (Bucci et al., 2021). While the EMA started a rolling review of the Sputnik V in March 2021 (EMA, 2021e), the vaccine had not yet been authorised in the European Union as of November 2024 (EMA, 2024a).

4.62. Separately, in May 2021, the WHO recommended the inactivated Covid-19 vaccines BIBP (developed by China National Biotec Group (CNBG), Sinopharm) and CoronaVac (developed by Sinovac) for use as part of their "emergency use listing" (WHO, 2021b). However, at that time the vaccination campaign in the UK had already progressed efficiently using other previously approved vaccines. Results from Phase 1-2 trials for BIBP were published in August 2020 (Xia et al., 2020) and January 2021 (Xia et al., 2021). In May 2021, a large multinational phase III trial with 2 doses given 21 days apart from each other showed 79% efficacy [66 to 87] against symptomatic SARS-CoV-2 infection (Al Kaabi et al., 2021). The phase III trial was conducted in Brazil, with 2 doses of Sinovac-CoronaVac given 14 days after each other. This showed an efficacy of 51% [36 to 62] against symptomatic SARS-CoV-2 infection and 100% [17 to 100] against severe Covid-19. Results from Indonesia (65.3% [20.0 to 85.1]) and Turkey (83.5% [65.4 to 92.1]) against symptomatic SARS-CoV-2 infection showed comparable findings (WHO, 2021c). Again, these results were only available when the UK vaccination campaign had already progressed using previously approved vaccines, rendering these additional vaccines unnecessary at the time.

4.63. Finally, some reassuring data is available on the efficacy of some of these vaccines mixed with those available in the UK. This could be important for people who migrated or travelled to or from the UK and therefore received different vaccines over time. Data from Brazil published in early 2022 demonstrated good clinical effectiveness against infection and severe Covid-19 when one dose of CoronaVac was followed by one of the Pfizer vaccine (Cerqueira-Silva et al., 2022).

5. Vaccine side effects

Introduction

5.1. Side effects are also known as Adverse Drug Reactions (ADRs). The EMA defines an ADR as "A noxious and unintended response to a medicine." A serious ADR is defined by the EMA as “An adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect.” (EMA, 2024b)

5.2. The large randomised trials conducted to test the vaccines before authorisation would have identified all common side effects (defined by the MHRA (MHRA, 2023c) as those affecting 1 in 10 to 1 in 100 of those who take the medicine or vaccine) and uncommon side effects (1 in 100 to 1 in 1,000), but not necessarily those that are rare (1 in 1,000 to 1 in 10,000). They were unlikely to detect very rare side effects (fewer than 1 in 10,000). Further detail on this issue can be found in Prof. Stephen Evans’ expert report **INQ000474707** paragraph 6.1.2

5.3. This report addresses the following categories of ADR:

- Those serious ADRs which were observed and recognised during the initial stage of the vaccine rollout in 2021, and which therefore had, or could have had, a significant effect on the UK’s vaccination campaign. This focus reflects the report’s key objective of making recommendations which will enable the UK to safely and effectively deliver a major vaccination campaign in the event of a future pandemic.
- ADRs of the Covid-19 vaccines raised by the Inquiry’s Material Providers who have particular concerns about vaccine safety, including vaccine injured and bereaved groups.
- Menstrual disorders.
- Mild adverse reactions to the Covid-19 vaccines. For the purposes of this report, a mild reaction is defined as one which typically disappears within hours or a few days, leaves no sequelae, does not require hospitalisation, and does not result in death.
- What we consider are the most prominent publicly reported ADRs which, upon investigation, were not confirmed, namely adverse pregnancy outcomes and fertility problems.

5.4. In addressing ADRs, we have had reference to the ‘known risks’ of the Covid-19 vaccines identified by the MHRA in its ADR chronologies. ‘Known risks’ are defined by the MHRA as adverse reactions where the evidence has shown a plausible causal association with a vaccine and as a result the MHRA has updated the product information for healthcare professionals, the Summary of Product characteristics (or SmPC) and the Patient Information Leaflet (or PIL). The scope of the report has not been limited to an examination of these ‘known risks’.

5.5. Finally, it is worth noting that in some parts of this section, and particularly in the ‘serious adverse events’ section, we refer to data on the existing association/s between Covid-19 itself and the ADR. This is to refer to scenarios where the ADR under discussion could be caused by Covid-19 itself as well as by the vaccine that could prevent or mitigate it. Such

situations are challenging for regulators when making risk/benefit assessments. Abnormal blood clotting is an important example: a specific type of clot was a side effect of the AstraZeneca vaccine, but was also a consequence of the infection itself (see paragraph 5.47).

5.6. Fortunately, multiple studies have examined not only the association between Covid-19 vaccines and ADRs but also between Covid-19 and the ADR of interest. See for example Li et al, Patone et al, Hippisley-Cox et al and Burn et al for relevant studies including UK data (Hippisley-Cox et al., 2021, Patone et al., 2021, Patone et al., 2022, Li et al., 2022b, Burn et al., 2022)).

Serious adverse events

Myocarditis/pericarditis

Summary:

- Myocarditis and pericarditis are inflammatory disorders affecting the heart.
- They have been reported as rare adverse events after the Pfizer and Moderna vaccines. Estimates of frequency vary across studies, typically between 1 in 100,000 and 1.5 in 10,000, and seem higher in younger men after the second dose.
- The quality of the evidence known to us now which suggests an association between the use of Pfizer or Moderna vaccines and the risk of myocarditis is moderate-high.
- Although some cases of post-vaccine myocarditis needed hospital admission, large studies have found very low or no associated fatalities.
- Myocarditis also occurs due to Covid-19 itself. Some epidemiological studies suggest a stronger association between Covid-19 and myocarditis than between Covid-19 mRNA vaccines and myocarditis.
- In my opinion, and based on the evidence summarised below, the UK regulatory response was appropriate in relation to safety signals concerning myocarditis/pericarditis. A key reason for this is that most studies suggested that Covid-19 itself could cause as much if not more myocarditis/pericarditis than the vaccines. Therefore, a risk/benefit assessment had to be made, taking into account that vaccination had other benefits, like the reduction in Covid-19 infections and severity.

5.7. Myocarditis is an inflammation of the heart muscle, while pericarditis is the inflammation of the outer heart lining. Most cases of myocarditis and pericarditis are caused by viral infections. Myo- and pericarditis had also been described in association with previous (non-Covid) vaccines, and therefore they were considered adverse events of special interest, and monitored from the beginning of the vaccination rollout. Both myocarditis and pericarditis are often mild, and symptoms usually resolve after a short time with standard treatment and rest. Some cases require intensive care support and fatal cases have been reported.

5.8. On 4 February 2021, the MHRA discussed with VBREWG for the first time a potential association between the Pfizer vaccine and the risk of myo/pericarditis in people aged <50

years old, based on Yellow Card reports and observed-vs-expected analyses. The number of cases at that time was small, and the evidence considered inconclusive. Further monitoring was advised.

5.9. In early June 2021, MHRA consulted VBREWG again on the risk of myo/pericarditis associated with the Pfizer and Moderna Covid-19 vaccines. Data for discussion included suspected cases reported through the Yellow Card system, an analysis by UKHSA of 'Secondary User Service' (SUS) data, international data (from US and Israel), and data provided by the manufacturers. At that time, the Yellow Card scheme had received 34 reports of suspected myocarditis and 26 of suspected pericarditis following almost 15 million first doses and almost 11 million second doses of the Pfizer vaccine; 31 reports of suspected myocarditis and 55 of suspected pericarditis after almost 25 million first doses and almost 16 million second doses of the AstraZeneca vaccine; and two reports of suspected myocarditis (0 pericarditis) following approximately 0.5 million first doses of the Moderna vaccine.

5.10. In late June 2021, and after a review of all data available, the VBREWG suggested that the product information for the Pfizer and Moderna vaccines should include a warning of potential risks of myocarditis and pericarditis, particularly for young males and following the second dose of the vaccine.

5.11. Myocarditis and pericarditis have been listed since then in the product information leaflets for both mRNA vaccines as "very rare" side effects, indicating that they may affect up to 1 in 10,000 people (MHRA, 2023e). Cases of myocarditis and pericarditis have been reported following mRNA SARS-CoV-2 vaccination in published post-authorisation safety surveillance since mid-2021, with reports predominantly within 14 days after the second dose of mRNA SARS-CoV-2 vaccines (Abu Mouch et al., 2021, Diaz et al., 2021a, Kim et al., 2021, Rosner et al., 2021).

5.12. Many research studies have been conducted to estimate the incidence of myocarditis, as well as their association with Covid-19 vaccines. A study using US safety surveillance data reported 10.1 extra cases per million doses in the 1- to 21-day period following the second dose of mRNA vaccines in those aged 12-39 (Klein et al., 2021). A large study in Israel found an incidence of 2.13 cases per 100,000 persons with at least one dose of the Pfizer vaccine, with the highest risk seen among males aged 16-29 (Witberg et al., 2021). Another study reported that among over 5 million Israeli residents who received two doses of the Pfizer vaccine, the highest risk was observed among 16-19 year old males, with 15.07 cases per 100,000 persons within 21 days after the second dose (Mevorach et al., 2021).

5.13. Many studies reported a higher risk of myocarditis among recipients of the Moderna vaccine compared with the Pfizer vaccine, and among young men. Husby and colleagues reviewed data from four million residents of Denmark age 12 and older who received one of the mRNA vaccines from October 2020 to October 2021, and reported an incidence of 1.4 per 100,000 Pfizer vaccinated individuals within 28 days, and incidence of 4.2 per 100,000 Moderna vaccinated individuals. In their post hoc analysis of male participants aged 12-39 years vaccinated after a second dose of the Pfizer vaccine, there was no significant increase in rates of myocarditis, and the absolute rate was 1.8 per 100,000 vaccinated individuals within 28 days of vaccination (Husby et al., 2021).

5.14. A meta-analysis of four cohort studies including a total of 23 million people showed excess events of 5.55 events per 100,000 vaccinees after the second dose of the Pfizer vaccine

and 18.39 events per 100,000 vaccinees after the second dose of the Moderna vaccine in 16-24 year old males during the 28 days after vaccination compared to the unexposed (Karlstad et al., 2022). A study from Canada found higher rates of myocarditis or pericarditis associated with receipt of the Moderna vaccine compared with the Pfizer vaccine as a second dose, particularly among younger males (Buchan et al., 2022).

5.15. The rates and excess risk reported in those studies varied depending on the data source (passive versus active surveillance), geographical region, time windows of risk assessed, outcome definition and ascertainment, and vaccination schedule between first and second doses (Gellad, 2021). In a systematic review of 46 studies, the authors concluded that the incidence of myocarditis is probably highest in males aged 12-29 years and more likely with Moderna than with the Pfizer vaccine. Yet the certainty about evidence using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) ranged from "very low" to "moderate" (Pillay et al., 2022).

5.16. It is important to understand that myocarditis can also occur after SARS-CoV-2 infection. A large UK-based study among over 42 million vaccinated individuals, led by Patone et al, found that the risk of myocarditis was overall higher after SARS-CoV-2 infection than after Covid-19 vaccination. This study also found that while a risk of myocarditis after vaccination exists, this risk was much lower compared to that seen following Covid-19 infection in the unvaccinated. The authors stated that this suggests vaccination provides some protection from the cardiovascular consequences of SARS-CoV-2. However, in the specific subgroup of males younger than 40 years old, this study found that the risk of myocarditis was higher after a second dose of the Moderna vaccine than after a positive SARS-CoV-2 test (Patone et al., 2022a). In another study by the same research team, increased risks of myocarditis after vaccination, and after a SARS-CoV-2 positive test, were reported. Among people aged under 40 years, the excess cases of myocarditis were 15 per 1 million people receiving a second dose of Pfizer or Moderna vaccines, compared to 10 following a SARS-CoV-2 positive test (Patone et al., 2022b).

5.17. The severity of myocarditis after vaccination has been reported in multiple international studies. A large study from Israel including over 2 million people vaccinated with the Pfizer vaccine observed 54 cases of myocarditis within 42 days of vaccination, among which 76% of cases were mild, 22% intermediate severity, and only 2% severe (Witberg et al., 2021). Using data from 26 paediatric medical centres across the United States and Canada, researchers reported that among 139 adolescents and young adults seen in these specialised centres with suspected myocarditis after mRNA vaccines, most were admitted for two or three days, about one in five (18.7%) in intensive care, and none died (Truong et al., 2022). Data from the US Vaccine Safety Datalink showed that 55%, 86% and 77% of reported myocarditis cases after mRNA vaccines were hospitalised among those aged 12-17 years, 18-29 years, and 30-39 years old respectively (Klein, 2021).

5.18. Based on UK data, Patone et al reported that among 140 patients who were admitted to hospital for myocarditis in the 1 to 28 days after a first dose of the AstraZeneca vaccine, 28.6% died within 28 days of hospital admission with myocarditis with a mean age of 62 years old, with an equivalent figure after a first dose of the Pfizer vaccine of 17.7% (Patone et al., 2022a).

5.19. Obviously, because myocarditis can be caused by some vaccines, but also by the infection that such vaccines prevent or mitigate, there needs to be a risk/benefit analysis. In this

analysis, the risk of myocarditis must be weighed against the overall benefits of vaccination. Bozkurt et al. summarised the benefit-risk assessment conducted by the US CDC (figure 2) and showed a positive risk-benefit balance for all age and sex groups (Bozkurt et al., 2021).

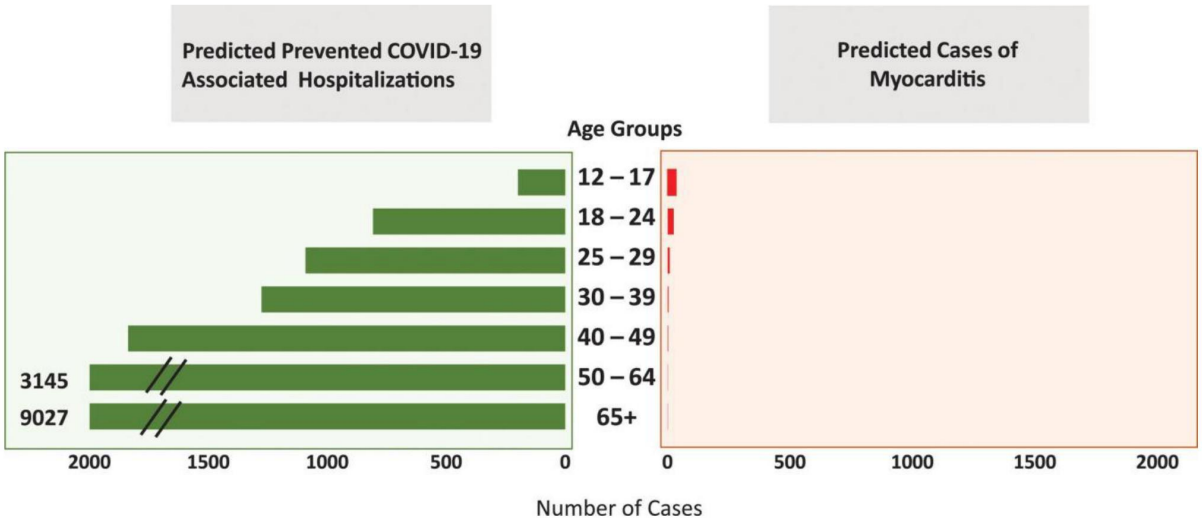


Figure 2 Predicted benefits of reduction in Covid-19–related hospitalizations and death and risks of myocarditis after second dose of mRNA Covid-19 vaccination by age group (Bozkurt et al 2021).

5.20. In the UK, an additional study quantified the risk-benefit of two doses of SARS-CoV-2 vaccination among adolescents in England (Gurdasani et al., 2021). Assuming an infection rate of 1,000 per 100,000 per week among 12–17 year olds as in late July 2021, vaccination could avert 287 Covid-19 hospitalisations, 19 Intensive Care Unit admissions, and 2 deaths per week, with an estimated disbenefit of 10 cases of vaccine-associated myocarditis/pericarditis.

5.21. Current evidence also suggests that vaccination may provide longer-term benefits by preventing infection-associated myocarditis in addition to the prevention of other post-acute Covid-19 complications, including respiratory disease and thromboembolic events (Al-Aly et al., 2022, Trinh et al., 2024, Xie et al., 2022b). However, many studies have limited follow-up, and the long-term consequences of vaccine- or Covid-19 associated myocarditis remain unclear (Pillay et al., 2022).

5.22. A systematic review and meta-analysis has synthesised both randomised clinical trials and observational studies, and myocarditis risk was estimated to be 1.8 per million (95% CI, 0.000%-0.001%) following the second injection of mRNA vaccines (Watanabe et al., 2023b). However, most of the included studies were of relatively small sample size. Another review study concluded that for girls and boys aged 5-11 years, incidence of myocarditis after vaccination with the Pfizer vaccine could be fewer than 20 cases per million, with low certainty (Pillay et al., 2022).

5.23. Following further studies of safety and efficacy in children, on 4 June 2021, the UK approval of the Pfizer vaccine was extended to 12- to 15-year-olds (MHRA, 2021b). On 25 June

2021, the MHRA added a warning to the product information for both monovalent mRNA Covid-19 vaccines (Pfizer and Moderna) to inform healthcare professionals and patients of these reports and provide advice and awareness of symptoms for myocarditis and pericarditis. In July 2021, the JCVI advised that vulnerable children aged 12 and over should be offered the Pfizer vaccine (JCVI, 2021d).

5.24. In November 2021, the UKHSA published guidance on myocarditis and pericarditis post-Covid-19 vaccination, as well as a clinical management guidance for healthcare professionals, updated in January 2023 (UKHSA, 2023). This guidance summarised the updated information on myocarditis and pericarditis following vaccination, and suggested that individuals who develop myocarditis or pericarditis following Covid-19 vaccination should be assessed by an appropriate clinician to determine whether it is likely to be vaccine related. If further doses were due, the Pfizer vaccine could be offered from 12 weeks after recovery from myocarditis or pericarditis following a Covid-19 vaccination. Updated guidance makes further recommendations to consider the context at the time of vaccination.

5.25. In terms of later national regulatory action, the MHRA updated information on Myo/pericarditis in March 2022, changing from a potential side effect of unknown frequency to "very rare" (MHRA, 2022b). The approval for use of the Pfizer vaccine was extended to 5 to 11 year olds in December 2021, and a half dose (50 micrograms) of the Moderna Covid-19 vaccine was approved for use in 6 to 11-year old children in April 2022.

Conclusion

5.26. We have moderate-high quality evidence to suggest an association between vaccination with Pfizer or Moderna Covid-19 vaccines and an increased risk of myocarditis. Similar quality of evidence exists to suggest an association between Covid-19 and an increased risk of myocarditis.

5.27. Overall, and based on the available evidence, the UK regulatory action taken in relation to myocarditis/pericarditis was in my opinion appropriate. As detailed, myocarditis occurred also after Covid-19 in the unvaccinated population and a risk/benefit balance had to be considered when taking action in the context of the pandemic. Given the additional benefits of vaccination, including the prevention of (SARS-CoV-2) infection and the mitigation of Covid-19 severity, the benefits of vaccination with mRNA vaccines during the period of interest outweighed the risks related to a potential excess risk of myocarditis after vaccination.

Blood clots with or without low platelet levels

Summary:

- Unusual combinations of blood clots and low platelet levels (thrombosis with thrombocytopaenia syndrome, or TTS) were reported as rare side effects from the AstraZeneca vaccine.
- Additionally, unusual blood clots in the brain called cerebral venous sinus thrombosis (CVST) were also reported after the AstraZeneca vaccine, sometimes associated with low platelet levels.
- The evidence for an association between the AstraZeneca vaccine on rare blood clots

(CVST) and blood clots with low platelets (TTS) is of moderate-high quality. Estimates of frequency vary widely, but seem higher in women aged 40 years or younger.

- According to the last published 'Summary of Yellow Card reports' the estimated rate of TTS is 21.8 per million doses in people under 50 and 11.3 per million in those aged 50 or older after the AstraZeneca vaccine.
- TTS is a serious, rapidly developing, and sometimes fatal condition. The case fatality rate was overall, according to MHRA estimates, about 1 in 4 cases. This proportion was even higher early on in the rollout when the condition was first recognised.
- Blood clots, including those with low platelets and CVST, are even more commonly associated with Covid-19 itself in the unvaccinated population, calling for continued risk-benefit analyses.
- Due to this side effect, the JCVI advised on 7 April 2021 that young people under 30 years old should be offered an alternative to the AstraZeneca vaccine, as based on the available evidence, the risks were deemed to outweigh the benefits for that age group. This recommendation was extended to those aged 30 to 39 years old on 7 May 2021.
- In my opinion, and based on the evidence available to date, the UK regulatory response was appropriate. A potential reason for some differences in recommendations internationally was the recommended use of the AstraZeneca vaccine in Europe, where it was prioritised for younger populations, likely at higher risk of CVST and TTS. This contributed to an earlier detection of this ADR in countries like Denmark or Germany.
- As recommended later in this report, a better and/or more formal collaboration with international regulators and the existence of faster mechanisms for the commissioning of epidemiological studies would have allowed the MHRA and JCVI to have more and better information to act upon earlier.

5.28. It was known from early on in the pandemic that Covid-19 tended to cause blood clots in infected people (Thomas et al., 2020). However, although blood clots were monitored as potential adverse events of interest, it was not expected that there might be a risk of vaccines causing rare brain blood clots (CVST) or TTS. Additionally, no evidence of a risk of blood clots was found in the large randomised trials before authorisation.

5.29. In early 2021, following the introduction and rollout of millions of doses of the AstraZeneca vaccine, cases of cerebral venous sinus thrombosis (CVST), which are rare blood clots in the brain, were reported in Norway, Germany, and Austria, often accompanied by thrombocytopenia (low platelet levels) (Greinacher et al., 2021, Schultz et al., 2021). The term Thrombosis with Thrombocytopenia Syndrome (TTS) was coined to describe a new and very rare event potentially linked to adenovirus vector-based vaccines including AstraZeneca and Janssen (WHO, 2021d) . The most common initial symptom reported among TTS cases was headache.

5.30. Post-vaccination thrombosis and/or TTS led to hospital admission in most cases, with some reports of cases leading to sequelae or life-threatening complications, and some resulting in death. According to the summary of Yellow Card reporting, up to 23 November 2022 there

were 445 cases of TTS reported following the AstraZeneca vaccine, with an overall case fatality rate of 18% (MHRA, 2023a).

5.31. A previous UK-based multicentre cohort study included 70 people with cerebral venous thrombosis with thrombocytopenia after vaccination, 47% of whom died or were dependent on others for personal care at the end of hospital admission (Perry et al., 2021). A study pooling results from various case series and case reports of 64 TTS cases after the AstraZeneca vaccine concluded that the overall mortality of the condition was 35.9% (Hwang et al., 2021).

5.32. During February 2021, a total of 3 cases of TTS were reported to the MHRA among over 8 million people vaccinated with the AstraZeneca vaccine. These were discussed at a VBREWG meeting on 25 February 2021 and close monitoring of this issue was agreed, without further regulatory action. In March 2021, a number of European countries reported similar events, and some of them (e.g. Denmark) stopped using the AstraZeneca vaccine altogether. To our knowledge, this decision was taken by their health authorities (e.g. the Danish Health Authority), and not by national regulators or the EMA.

5.33. On 18 March 2021, after a review of further cases of TTS and CVST from national and international patients with VBREWG, the MHRA provided an update to the Licensing Minister and to JCVI. The latter decided that vaccination with the AstraZeneca vaccine should continue based on benefit-risk analyses. By this point, the MHRA had received 5 reports of TTS, 2 of them with a fatal outcome. Although causality could not be proven, the MHRA suggested it could also not be ruled out, and needed rapid investigation.

5.34. At a meeting on 27 March 2021, the CHM discussed potential mechanisms underlying the occurrence of TTS. Although they concluded that causality cannot be established, they advised that further research was needed, including on the background rates of TTS. At this time, the EMA had recently commissioned and funded an international study on this topic with the objective of estimating background (historical), post-Covid and post-vaccine rates of TTS (EMA, 2021a). This study reported an excess risk of CVST and thrombocytopenia following administration of the AstraZeneca vaccine, but also a much higher excess risk of blood clots and CVST following Covid-19 infection in the unvaccinated (Burn et al., 2022). This had been previously shown in other UK-based studies, including a large self-controlled analysis by Hippisley-Cox et al (Hippisley-Cox et al., 2021), which found a 5-fold increased risk of thrombocytopaenia and a 13-fold increased risk of venous thrombosis, and also increased risks of CVST and ischaemic stroke after Covid-19.

5.35. On 1 April 2021, the MHRA informed the CHM of an increasing number of (retrospectively reported) cases of CVST with thrombocytopenia, totalling 62 confirmed, probable, or possible cases, 19 of them with a fatal outcome. Three days later, the MHRA updated CHM with an overall and age-stratified analysis of risk-benefit for the AstraZeneca vaccine. At this time, the CHM considered that the risk-benefit of this vaccine was less favourable in people younger than 40 years old (with exceptions), and recommended that this should be reflected in this vaccine's authorisation documentation.

5.36. On 6 April 2021, AstraZeneca provided VBREWG with an analysis of global cases. AstraZeneca concluded that there was no clear age cut-off for TTS but CVST-TTS was seen more frequently in younger people.

5.37. On the same day, in light of the analysis provided by AstraZeneca, the CHM reconsidered its conclusion that the regulation 174 authorisation should be amended, advising instead that the product and patient information should be updated in relation to TTS but without giving a specific age cut off.

5.38. After a review of cases from spontaneous reporting systems of Europe and the UK on 7 April 2021, the EMA's Pharmacovigilance Risk eAssessment Committee (PRAC) reported a possible link between the AstraZeneca vaccine and the occurrence of unusual blood clots with low blood platelets, also known as TTS (EMA, 2021g).

5.39. On the same day, the MHRA reported this same potential link, with an estimated overall risk of about 4 cases per million doses of the AstraZeneca vaccine (MHRA, 2021a). This was based on an analysis with an expert panel including haematologists and the adjudication of 79 case reports, classified as 9 confirmed, 14 probable and 56 possible cases. Nineteen of these had a fatal outcome. The MHRA then updated the information for healthcare professionals and the UK recipients about extremely rare blood clots. MHRA suggested that anyone who experienced cerebral or other major blood clots occurring with low levels of platelets after their first dose of the AstraZeneca vaccine should not have their second dose. At that same time, the JCVI advised that alternative vaccines should be offered to individuals aged <30 years old without underlying health conditions (JCVI, 2021e). Later (on 7 May 2021 - see below), this advice was extended to those aged 30–39 years without clinical vulnerability at higher risk of severe Covid-19 disease, in line with recommendations issued by many other European countries (JCVI, 2021c).

5.40. On 15 April 2021, the MHRA took further regulatory action and added TTS to the AstraZeneca vaccine list of special warnings and precautions for use through regulation 174 and relevant information on related symptoms was added to the product information for vaccine recipients. The EMA took similar action at the EU level on that same date.

5.41. On 7 May 2021, the MHRA published an updated statement reporting on a total of 262 cases of suspected TTS following the AstraZeneca vaccine. The MHRA continued to monitor cases from then and into 2022, and convened an expert group to coordinate further research. Also on this date, the JCVI updated their guidance and recommended that an alternative vaccine be offered to those aged 30 to 39 years old.

5.42. In early May 2021, the EMA commissioned and funded international studies specifically to investigate the association between Covid-19 vaccines and the risk of TTS (EMA, 2021a).

5.43. In January 2022, the MHRA updated the information for healthcare professionals and vaccine recipients to include a warning about CVST without thrombocytopenia. The last published 'Summary of Yellow Card reports' from November 2022 provides an estimate of incidence rate of 21.8 per million doses in people under 50 and 11.3 per million in those aged 50 or older.

5.44. Since Autumn 2021, the JCVI has not recommended the use of the AstraZeneca vaccine for booster vaccination. In May 2024 AstraZeneca withdrew the product from the UK and EU markets.

5.45. While some risk-benefit analyses were conducted, risk-benefit analysis of vaccination has been very challenging due to the rapidly evolving data, changing levels of SARS-CoV-2 transmission and severity, and variations in rates and complications of TTS and Covid-19

among different groups (Lau et al., 2021). For example, a risk–benefit analysis among people aged 18-59 years in Australia showed that the potential risks of TTS after the AstraZeneca vaccine may outweigh the benefits in younger adults, as they were at low risk of dying from Covid-19 (MacIntyre et al., 2021). Another study targeting people under 60 in Italy concluded that among subjects aged 20–29 years the benefit–risk ratio was not clearly favourable, while the benefits of vaccination (with AstraZeneca) largely exceeded the risks in older age groups (Palladino et al., 2021).

5.46. While the reported incidence rates vary greatly by vaccine type, age, sex, geographical distribution, and case definition, it has been shown that the incidence of TTS is higher after the first dose of certain Covid-19 vaccines than following subsequent doses, and the younger age groups are more often affected (Kerr et al., 2022).

5.47. However, the extent to which that risk increased for the AstraZeneca vaccine varies across different studies:

- In one of the first large published studies, Pottegård et al (Pottegård et al., 2021) found increased rates of venous thromboembolic events (1.1 excess events per million vaccinations) among recipients of the AstraZeneca vaccine in Denmark and Norway, including cerebral venous thrombosis (0.25 excess events per million vaccinations).

- Soon after, an analysis of health records including over 29 million people in England by Hippisley-Cox et al reported an increased risk of thrombosis and thrombocytopenia after AstraZeneca vaccination as well as after SARS-CoV-2 infection (Hippisley-Cox et al., 2021). They reported elevated risks of thrombocytopenia both after the AstraZeneca vaccine and more after SARS-CoV-2 infection. Additionally, they found 7 and 20 CVST cases per 10 million individuals after the AstraZeneca vaccine and SARS-CoV-2 infection, respectively. The study highlighted that the risks of these events were notably higher and more prolonged after SARS-CoV-2 infection compared to vaccination in the same population.

- Similarly, Burn et al. conducted an analysis of UK primary care records, and found an excess risk of CVST equivalent to 3 cases per million people receiving the AstraZeneca vaccine (Burn et al., 2022a). However, this study also found a clear and stronger association with SARS-CoV-2 infection, with 9 excess cases of CVST expected per million Covid-19 cases.

- More recently, Kerr et al. found an additional 0.25 CVST events per million people given the AstraZeneca vaccine (Kerr et al., 2022).

- In a population-based cohort study of 46 million adults in England by Whiteley et al., compared with unvaccinated people, the excess risk of intracranial venous thrombosis (ICVT) was 0.9 to 3 per million AstraZeneca recipients, varying by age and sex (Whiteley et al., 2022).

- Finally, a matched cohort study using databases from multiple European countries showed a 30% increased risk of thrombocytopenia after a first dose of the AstraZeneca vaccine compared to a first dose of the Pfizer vaccine during the first 28 days after vaccination (Li et al., 2022b). In addition, when comparing the Janssen vaccine to the Pfizer vaccine, this study reported wide confidence intervals and a borderline (not

significant) increased risk of venous thromboembolism with thrombocytopenia, with an incidence rate ratio of 2.26 (95% confidence interval 0.93 to 5.52).

- To date and to my knowledge, we do not have clear evidence of differential TTS risk after adenovirus vector vaccines among pregnant women (Pischel et al., 2022).

Conclusion

5.48. Based on the evidence listed above, we have moderate-high quality evidence to suggest an association between vaccination with the AstraZeneca Covid-19 vaccine and an increased risk of CVST and TTS. Similar quality of evidence suggests an association between Covid-19 and an increased risk of CVST.

5.49. In summary, my opinion is that MHRA and other national bodies like JCVI took appropriate action related to the finding of an increased risk of thrombosis, CVST, and TTS after the AstraZeneca vaccine. Although this action was taken later than in other European countries, this could be due to differences in the use of the AstraZeneca vaccine in continental Europe, where it was initially recommended for younger people (age <40), who later were found to be at higher risk of these ADRs. More formal collaborations with European authorities could have enabled a closer interaction, leading to an earlier detection of these very rare ADRs. It is however also important to notice that very large UK-based studies reported during the period of interest found that Covid-19 itself could cause thrombosis, thrombocytopaenia and CVST, probably more than the AstraZeneca vaccine did. Therefore, there was a clear need for a fine benefit-risk balance in the decision making at a time when SARS-CoV-2 was circulating very rapidly in the UK.

Guillain-Barré Syndrome

Summary:

- Guillain-Barré Syndrome (GBS) is a rare neurological condition leading to sensory loss or abnormality and muscle weakness, sometimes leading to life-threatening disease.
- GBS had been previously associated with (non-Covid) vaccines, and was identified as a potential adverse event of special interest to be monitored during the vaccination campaign.
- Multiple analyses and epidemiological studies have suggested an association between AstraZeneca and Janssen vaccines and the risk of GBS.
- The quality of the evidence known to us suggesting an association between the AstraZeneca vaccine and the risk of GBS is moderate-high.
- GBS can also be caused by Covid-19, presenting a challenge for benefit-risk assessments.
- In summary, it is my opinion that the UK regulatory action taken in relation to post-vaccination GBS was appropriate, taking into account the risk-benefit balance of the available vaccines at the time.

5.50. Guillain-Barré Syndrome (GBS) is a rare condition where the immune system damages nerve cells, and typically presents with sensory abnormalities, muscle weakness and autonomic dysfunction (UKHSA, 2021b). The severity of GBS can range from mild transient weakness to complete and life-threatening paralysis that needs intensive care treatment and respiratory support.

5.51. Associations with other (non-Covid) vaccines and GBS have been inconsistently noted, including the shingles and seasonal influenza vaccinations. Additionally, one case of GBS was seen in the intervention arm of one of the AstraZeneca trials. All this led to the active monitoring of GBS as a potential side effect of Covid-19 vaccines as an 'adverse event of special interest'.

5.52. In early March 2021, MHRA consulted the VBREWG to discuss the data available from Yellow Card reports, where 24 cases of suspected GBS (1 fatal) had been observed following administration of the AstraZeneca vaccine, and 8 (2 fatal) after administration of the Pfizer vaccine. This was in the context of almost 12 and 11 million doses of each vaccine respectively having been administered in the UK by that date. The VBREWG advised there was a potential safety signal for GBS particularly after AstraZeneca vaccine administration, and advised close monitoring of case reports.

5.53. As reported cases continued to increase, the MHRA sought advice from the VBREWG again in April and May 2021. According to the MHRA, up until 29 April 2021, there had been 194 reports of suspected GBS (6 fatal) observed in almost 24 million people vaccinated with AstraZeneca, although 5 of these cases did not meet the diagnostic criteria for GBS. A further 29 reports (3 fatal) had been reported following the administration of almost 12 million first doses of the Pfizer vaccine. According to the MHRA, 85% of the reviewed suspected cases did not meet the diagnostic criteria for GBS. Based on this, the VBREWG advised that a formal epidemiology study should be conducted to characterise a potential association between the AstraZeneca vaccine and the risk of GBS.

5.54. In late July 2021, the MHRA consulted the VBREWG again, as the number of spontaneous reports of GBS after Covid-19 vaccines had continued to increase. Until then, 391 reports (5 fatal) of suspected GBS had been recorded after administration of the AstraZeneca vaccine, 40 (2 fatal) after the Pfizer vaccine, and 2 (none fatal) after the Moderna vaccine. At that time, almost 25 million, 20 million and 1.5 million first doses of each vaccine had been administered in the UK respectively. The VBREWG recommended updating the AstraZeneca vaccine product information to include GBS as an adverse reaction. The EMA's safety committee, PRAC, had taken similar action earlier that same month.

5.55. Further analyses and epidemiological studies performed by the MHRA, by AstraZeneca and by national and international researchers in the following weeks and months led to similar conclusions regarding an association between the AstraZeneca vaccine and the risk of GBS.

5.56. On 26 July 2021, the WHO Global Advisory Committee on Vaccine Safety (GACVS) subcommittee recommended that the potential benefits of both the Janssen and AstraZeneca Covid-19 vaccines continued to outweigh any potential risk of GBS, particularly given the increase in the more transmissible Delta (B.1.617.2) variant (WHO, 2021d). On 20 August 2021, the MHRA updated the Product Information Leaflets and

Summary of Product Characteristics to include new warnings on Guillain-Barre Syndrome, which was later characterised as a "very rare" side effect (MHRA, 2023f).

5.57. Epidemiological studies have shown small absolute excess risks of GBS after the AstraZeneca and Janssen vaccines:

- In an England-based study using data from over 32 million patients, an estimated 3.8 excess cases of Guillain–Barré syndrome per million people receiving the AstraZeneca vaccine were seen, compared to 14.5 excess cases per million people after a positive SARS-CoV-2 test (Patone et al., 2021).
- In a UK-wide study with similar study design, researchers found a small increased risk of GBS after a first dose of the AstraZeneca vaccine but not after the second dose, or after mRNA vaccines. This equated to 11 additional cases of GBS per million vaccinees (Walker et al., 2022).
- In a third smaller study using data from the UK and Catalonia (Li et al., 2022a), no consistent association with vaccination was found, but a very clear increase in risk of GBS was seen after Covid-19 infection.

5.58. Post-vaccination GBS led to hospital admission in over 90% of the reported cases (Abara et al., 2023, Tamborska et al., 2022), intensive care was needed among about 10% of cases with some reports of cases leading to sequelae or life-threatening complications (Hanson et al., 2022).

5.59. Since GBS was very rare after vaccination, studies among specific demographic groups, including pregnant women and children, and on risk factors of developing GBS after vaccines, remain limited.

5.60. Risk-benefit analyses of developing GBS after vaccination in terms of averted hospitalisation and death are limited. However, multiple studies showed that rates of GBS were much higher after Covid-19 infection compared with the risk following vaccination (Li et al., 2022a, Patone et al., 2021):

- In a binational study using data from the UK and Spain conducted by Li et al, the risk of GBS was more than three times higher than expected after Covid-19.
- In a larger study using UK data, Patone et al found a much higher risk of GBS after Covid-19 than after vaccination with the AstraZeneca vaccine: they estimated almost 15 excess cases of GBS per million people with Covid-19, compared to just below 4 per million people receiving the AstraZeneca vaccine.

Conclusion

5.61. We have moderate-high quality evidence suggesting an association between vaccination with AstraZeneca vaccine and an increased risk of GBS. Similar quality evidence suggests an even stronger association between Covid-19 and an increased risk of GBS.

5.62. In summary, and based on the available evidence, it is my opinion that the UK regulatory action related to post-vaccination GBS was appropriate. This is due to the repeated observation in independent studies of post-Covid GBS, meaning that slowing or stopping vaccination could have led to a higher number of people with Covid-19 and hence a likely increased risk of those people developing post-Covid GBS.

Bell's palsy

Summary:

- Bell's palsy is a rare weakness or lack of movement of one side of the face caused by a paralysis of the facial nerve.
- Although rarely serious or fatal, Bell's palsy may not always resolve completely.
- Bell's palsy was identified as a potential adverse drug reaction during clinical trials for the Covid-19 vaccines, and is a recognised rare side effect of the AstraZeneca, Janssen, Moderna and Pfizer vaccines.
- The quality of the evidence known to us suggesting an association between the use of AstraZeneca vaccine and the risk of Bell's palsy is moderate-high. To our knowledge, the evidence of an association with the other Covid-19 vaccines is of lower quality.
- Epidemiological studies are not conclusive on a causal association or on potential higher risk groups, but have shown an increased risk of Bell's palsy after Covid-19 infection.
- In summary, in my opinion the UK regulatory action was appropriate, given the rarity and relatively low-moderate severity of Bell's palsy, and the observation that it could also be caused by Covid-19 itself.

5.63. Bell's palsy is characterised by a weakness or lack of movement that usually affects one side of the face, related to a facial nerve paralysis.

5.64. A small imbalance in the number of cases of Bell's palsy was observed between vaccinated and control groups in trials for the Pfizer and Moderna vaccines (Polack et al. 2020; Baden et al. 2021). Similarly, clinical trials of the AstraZeneca vaccine conducted in the United States, Peru and Chile reported facial paralysis (or palsy) in five participants in the vaccine group, all events reported as non-serious. No cases of facial paralysis were reported in the placebo group.

5.65. Currently, "temporary one sided facial drooping" is listed as a rare side effect (may affect up to 1 in 1,000 people) for the Pfizer (MHRA, 2024) and Moderna vaccines (MHRA, 2023, b). Similarly, 'facial paralysis' is listed as a rare adverse drug reaction in the Summary of Product Characteristics (MHRA, 2023g) for the AstraZeneca and Janssen vaccines (MHRA, 2023f).

5.66. Evidence on the association between Covid-19 vaccines and Bell's palsy in real-world data and epidemiological analyses remains inconsistent. For example:

- Patone et al found an increased risk of hospital admissions with Bell's palsy during the 15–21 days following a first dose of the AstraZeneca vaccine (Patone et al. 2021).
- Walkers et al. found 17.9 cases of Bell's palsy per million vaccinees after the first dose of the AstraZeneca vaccine using data from England, and no association with the Pfizer vaccine (Walker et al. 2022).

- In a smaller study using UK primary care records and Spanish linked data, Li et al found no association between mRNA or adenovirus-based Covid-19 vaccines and Bell's palsy (Li, Raventós, et al. 2022).

- An observed-to-expected analysis of data from Israel reported that compared to historical unvaccinated populations, a higher standardised incidence ratio was reported after the first dose of the Pfizer vaccine, with a 30-day risk of 6.24 cases per 100,000 people given a first dose (Shibli et al., 2021).

- A comprehensive systematic review synthesised the data from multiple observational studies, and found that incidence of Bell's palsy after one of the mRNA vaccines did not significantly differ from those who did not receive any vaccine (odds ratio of 0.70; 95% CI, 0.42-1.16), and no significant difference among first-dose recipients of the Pfizer vaccine compared with the AstraZeneca vaccine. However, the between-study heterogeneity was high in the first analysis and the results need to be interpreted with caution (Rafati et al., 2023) - in other words, the studies were conflicting and further research could change the overall conclusion.

5.67. Similar to other serious adverse effects, various studies have shown that the risk of Bell's palsy is notably higher after having a SARS-CoV-2 infection, providing useful context on the risk-benefit of vaccination (Li et al., 2022a, Patone et al., 2021, Rafati et al., 2023).

5.68. Post-vaccination Bell's palsy rarely led to hospital admission, with very rare reports of cases leading to sequelae or life-threatening complications. According to an NHS publication of advice to patients with the condition (NHS, 2023), most people with Bell's palsy get better within 6 months. A review showed 69.2% of Bell's palsy cases after vaccination recovered by the end of follow-up, yet the follow-up time varies greatly across studies (Albakri et al., 2023).

5.69. The prognosis of Covid-19 vaccine related Bell's palsy remains unclear. The authors are unaware of any good quality longitudinal studies measuring how long it lasts, so this needs continued monitoring. Bell's palsy is very unlikely to be a fatal event.

5.70. Currently, there is insufficient information on whether Bell's palsy post vaccination is more common among particular demographic groups such as pregnant women. No published study focusing on risk-benefit analysis of Bell's palsy was found by the time of writing this report.

Conclusion

5.71. We have moderate-high quality evidence suggesting an association between vaccination with AstraZeneca vaccine and an increased risk of Bell's palsy. Similar quality of evidence suggests an association between Covid-19 and an increased risk of Bell's palsy.

5.72. In my opinion, the UK regulatory action related to Bell's palsy was appropriate, given the low frequency and low-moderate severity of this ADR compared to the benefits of the vaccine, including the reduction of severe Covid-19 outcomes.

Transverse myelitis

Summary:

- Transverse myelitis (TM) is a serious, very rare disease caused by inflammation of specific parts of the spinal cord.
- TM had been associated with previous viral infections and vaccines, and was monitored as an adverse event of special interest during the roll out of the Covid-19 vaccines.
- TM has been recognised as an extremely rare event following the AstraZeneca and Janssen vaccines, with less than 1 event reported per each 100,000 doses administered. The quality of the evidence suggesting this association is low.
- Good quality epidemiological studies are scarce and causality difficult to interpret due to the rarity of this event.
- In summary, in my opinion the UK regulatory action was appropriate given the extreme rarity of this event, and the potential that Covid-19 itself might cause this condition.

5.73. Transverse myelitis (TM) is a rare acute neurological disorder where parts of the spinal cord are dysfunctional due to inflammation. The long-term effects of TM vary among people: about one third of people with TM have a full or near-full recovery; one-third have fair recovery with some retaining their symptoms; and the last third recover poorly and have significant physical disabilities (Johns Hopkins Medicine, n.d.). TM is known to be associated with several viruses, such as the herpes and influenza virus (MHRA, 2023a)

5.74. In the UK-based phase I trial of the AstraZeneca vaccine, 1 case of TM was reported, which led to a temporary halt in the study recruitment until further analyses were completed and the trial continued in September 2020 (Voysey et al. 2021). Given previous knowledge and these trial findings, TM was identified as an adverse event of special interest and monitored since the start of the vaccination programme.

5.75. In late February 2021, the MHRA consulted the VBREWG based on a total of 6 Yellow Card reports of suspected TM in association with the AstraZeneca vaccine. At that time, observed vs expected and rapid cycle analyses did not suggest a safety signal, and the VBREWG advised a review of reports but no further regulatory action. In mid May 2021, the VBREWG was consulted again, as 57 Yellow Card reports of suspected TM had been received following over 30 million doses of the AstraZeneca vaccine; and 18 reports following 20 million doses of the Pfizer vaccine (none with a fatal outcome). Observed vs expected analyses conducted by the MHRA showed a potential increased risk following the AstraZeneca vaccine, and for some age groups following the Pfizer vaccine, but rapid cycle analyses did not confirm this signal. The VBREWG concluded that monitoring was needed, but did not recommend regulatory action at the time.

5.76. On 29 October 2021, MHRA presented the latest data available to the VBREWG, including reports from clinical trials, published studies and Yellow Card report analyses. As of 12 October 2021, the MHRA had received 111 Yellow card reports of suspected TM following the administration of the AstraZeneca vaccine, 27 after administration of the Pfizer vaccine, and one after administration of the Moderna vaccine, none with fatal outcome. A signal was noted also from observed-vs-expected analyses. The VBREWG advised the addition of TM

to the AstraZeneca vaccine product information, and that a second dose of this vaccine should not be offered to people who had TM after the first dose.

5.77. On 14 January 2022, EMA's safety committee PRAC concluded that a causal relationship between the AstraZeneca and Janssen vaccines and TM is at least a reasonable possibility, and recommended a change to the product information for these two vaccines to include a warning to raise awareness among healthcare professionals and people receiving the vaccines of very rare cases of TM following vaccination (EMA 2022).

5.78. In the 8 March 2023 release of the "Coronavirus vaccine - summary of Yellow Card reporting", the MHRA suggested that an association between TM and the AstraZeneca vaccine is possible, whilst the risk of this adverse event with any of the Covid-19 vaccines used in the UK remained extremely rare (less than 1 report per 100,000 doses of each vaccine). It also reiterated that a further dose of the AstraZeneca vaccine should not be given to those who experienced symptoms of TM after a previous dose of this vaccine (MHRA. 2023i.

5.79. Evidence from epidemiological studies suggested that the incidence of TM after any Covid-19 vaccine is rare and an association remains unclear:

- Using data from >17 million patients in England, Walkers et al stated that there was no clear evidence of an increased incidence of transverse myelitis following the first dose of the AstraZeneca vaccine in the primary analysis. However, some sensitivity analyses suggested borderline significant evidence of increased risk within 28 days after vaccination (Walker et al. 2022).

- In another study with data from the UK and Spain, Li et al. identified <5 events of TM in all vaccinated cohorts, and risk analyses could not be completed due to the small number of cases.

5.80. In a summary of case reports from the literature, 42% of 24 included TM cases achieved complete recovery, and one died of poor general condition at the age of 85 (Rinaldi et al., 2022). According to the UK Yellow Card report, as of 26 October 2022, there were no reports with fatal outcome following suspected transverse myelitis (MHRA, 2023a).

Conclusion

5.81. We have low quality evidence suggesting an association between vaccination with the AstraZeneca vaccine and an increased risk of TM.

5.82. Due to the rarity of transverse myelitis following vaccination, observational data on the incidence, association, risk factors and specific demographic groups remain very limited.

5.83. In summary, in my opinion the UK regulatory action was appropriate given the extreme rarity of this event, which prevented the generation of good quality evidence on causality. Additionally, it is likely that Covid-19 itself might also cause TM, making decision-making even more challenging.

Immune thrombocytopaenia

Summary:

- Immune thrombocytopaenia (ITP) is a condition known to be associated with previous vaccines, including MMR, hepatitis and many others.
- The MHRA considered ITP an Adverse Event of Special Interest, and monitored its occurrence from very early on during the Covid-19 vaccination campaign.
- Although signals suggesting a risk of ITP emerged in April 2021, the difficulty of diagnosing ITP led to challenges in the classification of Yellow Card reports.
- In October 2021, the MHRA took regulatory action and added ITP to the product information of the AstraZeneca vaccine.
- Studies funded by international regulators (the EMA) have suggested a standardised incidence rate of about 14 events of ITP per 100,000 people per year following the first dose of the AstraZeneca vaccine, and a similar rate after Covid-19. This compared to a rate of 8/100,000 in the general population in 2019.
- There is low-moderate quality evidence suggesting an association between the AstraZeneca vaccine and the risk of ITP.
- In summary, the UK regulatory action was appropriate and in line with that of other international regulators. However, decisions were made approximately one month later than, for example, the EMA.

5.84. Immune thrombocytopenia (ITP) is an autoimmune disease characterised by isolated thrombocytopenia. It is diagnosed in patients with a platelet count below 100,000 per cubic millimetre in whom other causes of thrombocytopenia have been ruled out. Cases of ITP have been reported following several other vaccines, including MMR, Haemophilus influenza, hepatitis B virus, human papillomavirus, diphtheria-tetanus-acellular pertussis, varicella-zoster, pneumococcus and polio (David and Shoenfeld, 2020). Therefore, ITP was identified as an Adverse Event of Special Interest, and the MHRA monitored it from the beginning of the vaccination campaign. Based on international large data, the annual incidence of ITP in the general population ranges from 2 to 56 cases per 100,000 people per year (Cooper and Ghanima, 2019, Lambert and Gernsheimer, 2017, Li et al., 2021c).

5.85. The MHRA discussed Yellow Card cases of suspected ITP with the VBREWG on 25 February 2021. At that time, the MHRA had received 5 reports of suspected ITP following administration of the Pfizer vaccine, none fatal; and 17 following administration of the AstraZeneca vaccine, including one fatality among an estimated 8.4 million people vaccinated with this vaccine as of 21 February 2021. The VBREWG advised that judgments on causality could not be made and more data was deemed necessary.

5.86. Later, on 23 April 2021, further advice was provided by the VBREWG on ITP. Data up to 20 April 2021 contained 36 Yellow Card reports of suspected ITP (none fatal, 13 hospitalised) following administration of the Pfizer vaccine, and 121 of suspected ITP following administration of the AstraZeneca vaccine, 8 with fatal outcomes. Epidemiological analyses of observed vs expected rates performed by MHRA at the time showed no signal for the Pfizer vaccine, but a signal for potential excess risk of ITP after the AstraZeneca vaccine

was noted. On 6 and 7 May 2021, the MHRA consulted the CHM on the risk of ITP associated with the administration of Covid-19 vaccines. The VBREWG and CHM recommended consultation with consultant haematologists to develop case definition criteria for ITP reports and for case adjudication.

5.87. On 29 October 2021, the MHRA sought advice from the VBREWG on an analysis of confirmed ITP reports. At the time, there were 76 confirmed Yellow Card reports of ITP following administration of the AstraZeneca vaccine, including 2 fatalities; 40 following administration of the Pfizer vaccine; 2 following administration of the Moderna vaccine; and 12 following administration of the Janssen vaccine. Additional epidemiological analyses including survey data and published literature led to the conclusion that the available evidence warranted the addition of ITP to the product information of the AstraZeneca vaccine on 29 October 2021. The EMA PRAC Committee had reached a similar conclusion and imposed similar actions almost a month earlier, on 30 September 2021.

5.88. There is some published literature on the association between Covid-19 vaccines and ITP. Due to the rarity of ITP and the complexity of its diagnosis, there is a scarcity of epidemiological studies estimating the risk or relative risk of ITP. A Scottish case-control study of 2.53 million people receiving a first dose Covid-19 vaccination found a small increased risk of ITP with an estimated excess risk of 1.13 additional cases per 100,000 first doses of the AstraZeneca vaccine. The authors did not observe an increase in risk of ITP after the Pfizer vaccine (Simpson et al., 2021). A case-series study using the US Vaccine Adverse Event Reporting System (VAERS) reported the rate of thrombocytopenia was 0.80 per million doses for both mRNA vaccines. Although not able to separate ITP from all thrombocytopenia cases, the authors concluded that the number of post-vaccination ITP cases did not suggest a safety concern attributable to the mRNA vaccines at the time of analysis (4 February 2021) (Welsh et al., 2021).

5.89. A study funded by the EMA analysed UK primary care data and reported a standardised incidence rate of ITP of 7.9/100,000 person-years in historical general population data, compared to 14.1/100,000 person-years following vaccination with a first dose of the AstraZeneca vaccine, and 13.4/100,000 person-years following Covid-19. This study performed an analysis of observed vs expected rates, and found a potential excess risk of ITP following the AstraZeneca vaccine (Burn et al., 2022).

Conclusion

5.90. We have low to moderate quality evidence suggesting an association between vaccination with the AstraZeneca vaccine and an increased risk of ITP.

5.91. In my opinion, based on the best evidence available, the UK regulatory action related to ITP was appropriate and similar to other countries, albeit somewhat slower than that taken by the EMA. This is an example where a formal collaboration with EMA and/or the ability to commission rapid epidemiological studies could have led to earlier and better data and action.

Capillary leak syndrome

Summary:

- Capillary leak syndrome (CLS) is a very rare and potentially fatal condition where fluid leaks from small blood vessels, likely due to inflammatory reactions.
- Very low numbers of CLS cases have been reported following vaccination with the AstraZeneca vaccine: 5 suspected cases after over 40 million doses administered in the UK.
- A possible association with CLS flares has also been recognised following administration of the Moderna vaccine.
- To our knowledge, the quality of the evidence suggesting an association between the Covid-19 vaccines and the risk of CLS is low.
- It is likely that the association between Covid-19 vaccines AstraZeneca and Moderna and the risk of CLS is higher in people with previous CLS.
- Good quality studies are needed to further our understanding of the potential causality and mechanisms involved in this potential association.
- In summary, the UK regulatory action related to CLS was appropriate and similar to that proposed by other countries and regulators including the EMA.

5.92. Capillary leak syndrome (CLS) is a very rare and serious condition that causes fluid leakage from small blood vessels (capillaries), resulting in swelling mainly in the arms and legs, low blood pressure, thickening of the blood and low blood levels of albumin (an important blood protein). Very rare cases of CLS have been reported in the first few days after administration of the AstraZeneca vaccine. Some of the cases had a history of CLS, and fatal outcomes have been reported.

5.93. In April 2021, the MHRA discussed with the VBREWG that the EMA's PRAC committee was reviewing a possible association between the AstraZeneca vaccine and a potential risk of CLS. At that time, the MHRA had received 3 reports of possible CLS among more than 20 million people vaccinated with the AstraZeneca vaccine. As of 7 May 2021, the MHRA had received seven reports of suspected CLS (no fatality), all following administration of the AstraZeneca vaccine, and none following administration of the Pfizer or Moderna vaccines. Two of the seven cases had a history of CLS prior to vaccination, making causality assessments difficult. A week later, the MHRA consulted the VBREWG with information from Yellow Card reports and from international studies. No causality could be established, and no action was taken at that time.

5.94. Less than a month later (in early June 2021), the issue was discussed again with the VBREWG, as the EMA's PRAC had made a recommendation to include warnings in the product information for AstraZeneca regarding recurrent CLS as a risk associated with the vaccine in people with a previous history of the condition. At this time, the MHRA had received 3 further reports of suspected CLS after administration of the AstraZeneca vaccine. An adjudication of cases concluded that 5 (out of 10) of the cases could be classified as suspected CLS, of which 2 had a prior history of CLS. None of these had a fatal outcome. This was in a context where more than 40 million doses of the AstraZeneca

vaccine had been administered. However, the VBREWG advised the addition of a precautionary statement in the product information for this vaccine.

5.95. On 11 June 2021, the EMA's safety committee recommended that the product information for the AstraZeneca vaccine should be updated in respect of CLS (EMA, 2021h). Three days later (on 14 June 2021), the MHRA discussed this recommendation with the VBREWG, who advised that similar updates should be made to the UK AstraZeneca product information, including a contraindication in people with a history of CLS. On 16 June 2021, the MHRA submitted this advice to the Licensing Minister, who accepted the addition of this contraindication. Subsequently, the EMA also advised that people with a history of CLS should not receive the other adenovirus-based Covid-19 vaccine produced by Janssen (EMA, 2021d). Similarly, a contraindication for people with previous CLS was included in the UK equivalent (SmPC) for the Janssen vaccine (MHRA, 2023f).

5.96. Case reports of CLS after mRNA vaccines have also been reported (Inoue et al., 2022). According to the MHRA, 3 reports of 'probable' CLS had been recorded in the UK following vaccination with the Moderna vaccine by March 2022, and none after the Pfizer vaccine. The EMA's PRAC had recently concluded that a warning regarding recurrence of CLS should be added to the Moderna vaccine product information. The VBREWG advised similarly for the UK vaccine product information, which was updated on 15 June 2022.

5.97. To our knowledge, epidemiological studies on the incidence and/or risk of CLS after Covid-19 vaccination are very scarce and of limited quality. We identified one cross-sectional study that examined the individual case safety reports in the pharmacovigilance database EudraVigilance. The authors found a lower CLS reporting probability after vaccination with mRNA vaccines compared to viral vector-based ones (Ruggiero et al., 2022).

Conclusion

5.98. We have low quality evidence suggesting an association between vaccination with the AstraZeneca vaccine and an increased risk of CLS.

5.99. In summary, in my opinion the UK regulatory action related to CLS was appropriate and similar to that proposed by other countries and regulators including the EMA. In this case, action was taken within days of a similar decision made by the EMA to impose a contraindication of the AstraZeneca vaccine for people with a previous history of CLS.

Acute Disseminated Encephalomyelitis (ADEM)

Summary:

- Acute Disseminated Encephalomyelitis (ADEM) is an extremely rare but serious inflammation of specific parts of the central nervous system.
- ADEM has been previously associated with viral infections including Covid-19, and was monitored closely as an adverse event of special interest for the Covid-19 vaccines.
- Most international regulators did not take action regarding ADEM during the roll out of the Covid-19 vaccines. The MHRA added ADEM as an extremely rare event associated with the AstraZeneca vaccine in 2023.

- Epidemiological studies remain inconclusive in terms of causation. The quality of the evidence suggesting an association between the AstraZeneca vaccine and ADEM is low-moderate.
- In summary, the UK regulatory action related to the potential risk of ADEM was appropriate and more proactive than that taken by other international regulators.

5.100. Acute Disseminated Encephalomyelitis (ADEM) is a very rare but serious inflammatory demyelinating disorder of the central nervous system (Pohl et al., 2016). It predominantly affects children and young adults, and typically presents with an acute onset after a bacterial or viral infection, including SARS-CoV-2. Several studies, systematically compiled by Yumin Wang et al, have previously reported an increased incidence of ADEM after SARS-CoV-2 infection (Wang et al., 2021).

5.101. ADEM was identified as an adverse event of special interest and was monitored closely from the beginning of the Covid-19 vaccination campaign. AstraZeneca submitted monthly reports to the MHRA and other regulators for review. By the end of June 2021, the company had received 26 reports of ADEM following administration of the AstraZeneca vaccine, 9 of them from the UK. Observed-vs-expected analyses did not confirm a signal by that time and no regulatory action was taken.

5.102. In February 2022, the MHRA reviewed a new safety report submitted by the company, which contained updated analysis on reports of suspected ADEM which had been requested by the EMA. No regulatory action was taken (by the MHRA or the EMA) at the time, but close monitoring continued. The MHRA collaborated with UKHSA to conduct a self-controlled case series to investigate this further (see below).

5.103. In June 2022, the MHRA was informed that the Australian regulator was considering the addition of ADEM as an adverse drug reaction in relation with the AstraZeneca vaccine. In December 2022, the MHRA consulted international regulators in writing. According to the MHRA, six agencies responded (Australia, Canada, New Zealand, Singapore, Switzerland and the USA), and only Australia had taken action to list ADEM in the product information for the AstraZeneca vaccine.

5.104. Although epidemiological analyses continued to be inconclusive, MHRA and VBREWG took a precautionary approach and added ADEM as an extremely rare event in the 'Special warnings and precautions for use' of the AstraZeneca product information in November 2023.

5.105. Extremely rare cases of ADEM have been reported following both the AstraZeneca and Pfizer vaccines. However, a causal relationship has not been established in systematic reviews of the literature (Nabizadeh et al., 2023). For example, Li et.al compared the observed and expected incidence rates of immune mediated neurological events including encephalomyelitis using electronic health records data from the UK and Spain, and observed no safety signal between Covid-19 vaccines encephalomyelitis after first dose of the AstraZeneca or Pfizer vaccines (Li et al., 2022a). However, this study did not separate ADEM from overall encephalomyelitis. Conversely, a more recent large self-controlled analysis of data from the National Immunisation Management System (NIMS) and hospital discharge data from England did find an association when estimating the risk of ADEM 0 to

42 days after Covid-19 vaccination (Stowe et al., 2024). Stowe et al observed an increased risk of ADEM following the first dose of the AstraZeneca vaccine was observed (relative incidence (RI) = 3.13, 95% Confidence Interval (CI) [1.56–6.25]) with a vaccine attributable risk of 0.39 per million doses. No association was found with any of the other vaccines used in the UK.

Conclusion

5.106. We have low-moderate quality evidence suggesting an association between vaccination with the AstraZeneca vaccine and an increased risk of ADEM.

5.107. In summary, it is my opinion that the UK regulatory action relating to ADEM risk was appropriate. In this particular case, the MHRA took more precautionary action than other (international) regulators.

Anaphylaxis

Summary:

- Anaphylaxis is a rare and potentially fatal severe allergic reaction, typically observed within minutes of exposure to a specific food or medicine.
- Anaphylaxis cases were observed on the first day of Covid-19 vaccination following administration of the Pfizer vaccine.
- The evidence of an association between mRNA Covid-19 vaccines and a risk of anaphylaxis is, to our knowledge, of low quality.
- A number of changes were made to the vaccine information and vaccination campaign, including initial contraindications for those with previous allergies and the need to wait 15 minutes after the administration of the first dose for everyone receiving the Pfizer or Moderna vaccines.
- Most of these contraindications and warnings were removed in late 2021 during the Covid-19 vaccine booster campaign.
- In summary, the UK regulatory action related to post-vaccine anaphylaxis was appropriate, and changed over time as evidence emerged.

5.108. Anaphylaxis is a rare, severe, life-threatening allergic reaction with a rapid onset that involves multiple organ systems and can progress rapidly. Anaphylaxis can occur after vaccination, with onset typically within minutes to hours (McNeil and DeStefano, 2018). Therefore, it was pre-specified as an adverse event of special interest by many regulators and monitored from the beginning of the vaccination campaign.

5.109. Reports of anaphylaxis after the first dose of the Pfizer vaccine emerged on the first day of the vaccination campaign in the UK (8 December 2020). The next day (9th December 2020), a meeting of the VBREWG was held which was attended by experts in allergy and immunology. The VBREWG concluded that a causal association was likely. As a result, a warning was sent to the NHS and a press release issued by the MHRA to advise that vaccine recipients should be monitored for 15 minutes after vaccination. Additionally, VBREWG suggested that the Pfizer vaccine should be contraindicated for people with a

known allergy to polyethylene glycol (PEG), and that PEG content was made clearer in the Pfizer vaccine product information. Further, a contraindication should be considered for those with a previous food or vaccine allergy. These changes were implemented in the Pfizer vaccine product information promptly on 10 December 2020.

5.110. On 22 December 2020, the MHRA consulted the VBREWG and concluded that the contraindication for those with food allergies should be reconsidered so as to avoid their exclusion from vaccination. On 31 December 2020, the MHRA updated the information for the Pfizer vaccine, with the reference to previous allergies moving to the 'Warnings and precautions' section and being reworded as follows: 'Talk to your doctor, pharmacist or nurse before you are given the vaccine if you have: ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given Covid-19 mRNA Vaccine BNT162b2 in the past". This was further reworded in January 2021 as follows:

- *"Do not have the vaccine: If you have ever had a severe allergic reaction to any of the active substances or any of the other ingredients listed in section 6."*
- *"Tell your doctor, pharmacist or nurse before vaccination: if you have ever had a severe allergic reaction (anaphylaxis) after any other vaccine injection".*

5.111. Despite a lack of a similar experience with the Moderna vaccine in the UK, in January 2021, the MHRA took the precaution of adding a similar warning to the product information for this vaccine as well. Later that month, on 29 January 2021, the MHRA sought the VBREWG's advice concerning a total of 14 reports of suspected anaphylaxis following the AstraZeneca vaccine (after 3 million doses had been administered). These were less severe than those seen with the Pfizer vaccine. On 23 February 2021, the information for the AstraZeneca vaccine was updated to add anaphylaxis as an ADR with frequency as yet unknown.

5.112. In late September 2021, and following the collection of data and discussions with NHS England on the impact on vaccination speed and consultation with the VBREWG, it was decided that the requirement for a 15-minute observation period could be removed for those receiving a second (or further) dose of an mRNA vaccine they had previously received. On 14 December 2021, motivated by the need to roll out booster vaccinations as the Omicron variant spread rapidly, the MHRA removed the 15-minute observation period for the Pfizer and Moderna vaccines for most people (except for those with a history of allergies to these vaccines) (see MHRA statement INQ000474337).

5.113. Analysis using spontaneous report system EudraVigilance for the European Economic Area (EEA) and from the VAERS for the US reported incidence of anaphylactic reaction was 8.96 (95% CI 8.80–9.11) per million doses, and 1.46 (95% CI 1.39–1.52) per million doses for anaphylactic shock (Boufidou et al., 2023). A prospective cohort study from the US showed that during the 3 days following the administration of an mRNA vaccine, 0.025% [95% CI, 0.014%-0.040%] out of over 50,000 adult participants developed anaphylaxis (Blumenthal et al., 2021).

5.114. Later analysis, focused on children and adolescents, reported that the overall mean anaphylaxis rate was 12.81 [95% confidence interval (CI): 11.49–14.12] per million mRNA vaccine doses among children below 18 years old using EudraVigilance data (Maltezou et al., 2023). Covid-19 vaccines are within the range of anaphylaxis rates reported across several common vaccines in these two passive reporting systems (Maltezou et al., 2022).

Conclusion

5.115. We have low-moderate quality evidence suggesting an association between vaccination with mRNA vaccines and an increased risk of anaphylaxis.

5.116. In summary, it is my opinion that, based on the existing evidence, the UK regulatory action related to post-vaccine anaphylaxis was appropriate, fast and more aggressive than that taken by other countries. The initial precautionary advice was modified as reassuring evidence emerged which enabled a faster rollout of vaccines during the emergence of the Omicron variant.

Adverse events raised by the Inquiry's Material Providers who have particular concerns about vaccine safety, including vaccine injured and bereaved groups

Summary:

- Multiple case reports and patient/carer experiences describe possible adverse effects. Most of these are complex and rare, precluding or limiting our ability to establish any possible causal associations.
- We conducted a rapid review of the literature, and identified low-moderate quality studies on the following 14 conditions: Chronic Obstructive Pulmonary Disease (COPD), Varicella-zoster-virus (VZV) reactivation / Shingles, Seizures, Shoulder Injury Related to Vaccine Administration (SIRVA), Tinnitus, Autoimmune connective tissue disease and alopecia, Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus, Fibromyalgia, Graves' disease, Depression, Postural Orthostatic Tachycardia Syndrome (POTS), Optic Neuritis, and heart failure.
- The current evidence suggests that there is no association between Covid-19 vaccination and an increased risk of developing COPD.
- There is low-moderate quality and inconsistent data on an association between Covid-19 vaccines and VZV reactivation/shingles. Additionally, we found moderate-high quality and more consistent evidence of a small increase of herpes zoster infection after vaccination with the Pfizer or Moderna vaccines. Further research would be needed to elucidate this potential association.
- There is moderate-quality and inconsistent evidence studying the association between Covid-19 vaccines and seizures.
- No quality evidence exists on the potential association between Covid-19 vaccination and the risk of Shoulder Injury Related to Vaccine Administration (SIRVA).
- There is moderate-high quality but inconsistent evidence studying the association between Covid-19 vaccination and the risk of tinnitus.
- We found a single study of moderate quality studying the association between Covid-19 vaccines and autoimmune connective tissue disease and alopecia. The study findings were inconsistent and therefore inconclusive.
- The identified studies on the association between Covid-19 vaccines and the development of RA or RA flares is scarce, of moderate quality, and inconsistent.
- We found moderate quality but inconsistent evidence on the association between

Covid-19 vaccination and the risk of developing SLE. Additionally, we identified moderate quality and consistent evidence to suggest no association with SLE flares.

- We found only one study, of moderate quality, suggesting an association between vaccination with the Pfizer Covid-19 vaccine and the risk of fibromyalgia in elderly people. More research is needed to elucidate this potential association.
- We identified moderate-high quality evidence, suggesting that there is no association between Covid-19 vaccines and the risk of Graves' disease.
- We only found poor quality studies on the association between Covid-19 vaccines and the risk of depression. Good quality studies should be conducted to understand this.
- We found evidence of a possible association between Covid-19 vaccines and the risk of POTS. However, the overall risk is low, and much lower than that seen following Covid-19 infection in unvaccinated people.
- We identified moderate quality data and inconsistent studies on a potential association between Covid-19 vaccination and the risk of optic neuritis.
- The data identified on the association between Covid-19 vaccines and heart failure suggested a reduced risk among vaccinated compared to unvaccinated individuals.

Introduction

5.117. I, as lead author, have received and read the evidence submitted to the Inquiry by vaccine injured and bereaved groups. This includes multiple case reports and patient and carer experiences from people who suffered other suspected adverse effects of vaccination.

5.118. Many of these conditions are rare or have multiple contributing causes, which makes it challenging to investigate them and establish the requisite degree of causation so as to permit the conclusion they are directly related to the Covid-19 vaccines. A systematic literature review on their association with the Covid-19 vaccines or the conducting of epidemiological studies would be resource-intensive and is beyond the scope of this report. However, the co-authors and I have conducted a high-level literature review in order to identify those potential ADRs where there is some evidence to suggest the need for further research in the form of a formal systematic review of the literature and/or bespoke good quality epidemiological studies. In the following subsections, we summarise the methods used for our literature review, and then compile the knowledge we extracted from the published studies deemed of sufficient quality at the time of writing this report (November 2024). I make a recommendation at the end of this report to the effect that the MHRA should consider whether any of the ADRs raised by Material Providers warrant further examination by way of systematic reviews and/or epidemiological studies.

Methods for our rapid literature review

5.119. We started our literature review with a long list of conditions and health outcomes distilled from relevant witness statements. These were: Acquired Amegakaryocytic Thrombocytopenia, Acute kidney Injury, Acute onset Reactive Arthritis, Acute onset Autoimmune Hepatitis, Acute Necrotising Pancreatitis, Alopecia, Atrial fibrillation, Autonomic Nervous System Dysfunction, Brain haemorrhage, Bullous Pemphigoid, Cancer,

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), Chronic Mononeuritis Multiplex, Chronic Obstructive Pulmonary Disease, Chronic Pain Syndrome, Connective Tissue Disorders, Depression, Dorsal Root Ganglionopathy, Dysautonomia, Dystonia, Erythromelalgia, Exacerbation of Hemicrania Continua, Essential tremor, Fibromyalgia, Gastroparesis, Giant Cell Arteritis, Graves Disease, Heart Failure, Hemiplegic Migraine, Hyperacusis, Hypothyroidism Myxedema, Hyper immune response to Covid 19 vaccination, Hypoaldosteronism, Hyperprolactinaemia, Inappropriate Sinus Tachycardia, Intercranial Hypertension, Lupus, Mast Cell Activation Syndrome (MCAS), Medical Post Traumatic Stress Disorder, Mastocytosis, Motor Neurone Disease, Migraines with Aura, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Neurogenic Bladder, Nodular Paniculitis, Non-Hodgkin's Lymphoma, Nystagmus, Optic Neuritis, Pericardial Effusion, Peripheral Neuropathy, Pernicious Anaemia, Polymyositis, Postural Orthostatic Tachycardia Syndrome (POTS), Post Traumatic Stress, Post-Vaccination Syndrome, Pneumonitis, Progressive Bulbar Palsy, Psychosis, Pulmonary Sarcoidosis, Pudendal Neuralgia, Rapid Onset Glioblastoma, Reactivated Epstein Barr Virus, Reactivated Lyme Disease, Reactivated Shingles, Rheumatoid Arthritis, Secondary Hypogonadism, Scleroderma, Seizures, Sjogren's Syndrome, Shoulder Injury Related to Vaccine Administration (SIRVA), Small Fibre Neuropathy, Stevens-Johnson Syndrome, T-Cell Lymphoma, Thyrotoxicosis, Tinnitus, Trigeminal Neuralgia, Uveitis, Vaccine-induced Raynaud's Syndrome, Ventricular Tachycardia, Vasculitis, and Vestibulopathy.

5.120. For each of these, we conducted a query in the largest repository of medical research, the PubMed library. The literature search focussed on at least moderate quality studies on the association between Covid-19 vaccination and the risk of developing each of the events listed above. We restricted the search to large spontaneous report database analyses (e.g. US VAERS), case-control, self-controlled-case series and cohort studies, considered in this report as at least moderate quality evidence on vaccine safety. We also limited our search to studies mentioning each of the potential ADRs in the study title or abstract. We did not limit our search by language or date of publication. With all this in mind, the five co-authors of this report worked using a consistent and reproducible search query and a structured form for the extraction of findings. These, together with the list of identified manuscripts, are available as an Appendix (INQ000474569) alongside this report.

5.121. The following subsections summarise the findings obtained for the potential ADRs where we found at least moderate quality studies on the association with Covid-19 vaccines, regardless of their results. The potential ADRs to which this applied were the following 14: Chronic Obstructive Pulmonary Disease (COPD), Varicella-zoster-virus (VZV) reactivation / Shingles, Seizures, Shoulder Injury Related to Vaccine Administration (SIRVA), Tinnitus, Autoimmune connective tissue disease and alopecia, Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus, Fibromyalgia, Graves' disease, Depression, Postural Orthostatic Tachycardia Syndrome (POTS), Optic Neuritis, and heart failure. For all other events listed above, we did not find any moderate or high-quality evidence in the literature search we conducted. This does not mean that there is no association, it just means that we did not find published studies demonstrating such a link.

Chronic Obstructive Pulmonary Disease (COPD)

5.122. We only found one study that would pass our inclusion criteria on the association between Covid-19 vaccination and the risk of developing COPD (Huh et al., 2024). This retrospective cohort study utilised a combined database of nationwide healthcare claims data, Covid-19

patient registry and vaccination records from South Korea. Individuals diagnosed with Covid-19 in the Omicron variant-dominant period of January-March 2022 were tracked for 30-120 days post-infection. The exposure of interest was the receipt of primary and third doses of a SARS-CoV-2 vaccine. Compared with unvaccinated individuals, vaccination with at least two doses was associated with a 25% reduced risk of COPD.

5.123. Although the evidence is limited and only of moderate quality, the current evidence suggests that there is no association between Covid-19 vaccination and an increased risk of developing COPD.

Varicella-zoster-virus (VZV) reactivation / Shingles

5.124. Varicella-zoster virus is the virus that causes chickenpox. If it reactivates later on in life, it causes shingles, a painful blistering rash. Anecdotal cases of shingles after Covid-19 vaccination have been reported worldwide in case reports and case series analyses. Shafiee et al. conducted a systematic review and meta-analysis focusing on reactivation of human herpesviruses following administration of Covid-19 vaccines (Shafiee et al., 2023). Nine observational studies on shingles were compiled, showing that the rate of varicella-zoster virus (VZV) reactivation among those who received Covid-19 vaccine was 14 persons per 1,000 vaccinations (95% CI 2.97–32.80).

5.125. In terms of associations or causality, Birabaharan et al. analysed data from large health records databases and reported no difference in VZV reactivation during the 28 days after vaccination with mRNA vaccine compared to a propensity score matched contemporary control cohort (Birabaharan et al., 2021). Conversely, a similar study using similar data led by Hertel et al. analysed individuals given mRNA or adenovirus vector-based Covid-19 vaccines compared to unvaccinated people, and found an 80% excess risk of shingles/VZV reactivation during the 60-day period after vaccination (Hertel et al., 2022).

5.126. Increased risks of herpes zoster have also been reported in other observational studies. Barda et al. analysed observational data from Clalit Health Services from Israel with a target trial emulation design. The study found a 40% elevated risk of herpes zoster infection during the first 42 days after administration of the Pfizer vaccine compared with unvaccinated people, equivalent to an absolute increased risk of 16 events per 100,000 persons (Barda et al., 2021). A cohort study using electronic health records from the US including over 3 million people estimated the risk of herpes zoster within 90 days after receiving the second dose of mRNA vaccine/s. They found that compared to unvaccinated people, those vaccinated with the Moderna vaccine had a small (15%) excess risk of herpes zoster infection, and those vaccinated with the Pfizer vaccine had a 12% increased risk (Florea et al., 2023). Finally, Wan et al conducted a self-controlled case series analysis using data from Hong Kong, and identified an excess risk of approximately 7 cases of herpes zoster-related hospitalisations after every 1,000,000 doses of the Pfizer vaccine (Wan et al., 2022).

5.127. In summary, there is low-moderate quality and inconsistent data on an association between Covid-19 vaccines and VZV reactivation/shingles. We also found moderate-high quality and more consistent evidence of a small increase of herpes zoster infection after vaccination with the Pfizer or Moderna vaccines. Further research would be needed to elucidate this potential association.

Seizures

5.128. In a systematic review and meta-analysis of clinical trials reporting seizure incidence with Covid-19 vaccines, Rafati et al. pooled six RCTs and found no statistically significant difference in the incidence of new-onset seizure between Covid-19 recipients and placebo group (odds ratio 2.70; 95% CI, 0.76-9.57) (Rafati et al., 2024.

5.129. Evidence from observational studies has been inconsistent. Frontera et al. analysed data from the US Vaccine Adverse Events Reporting System (VAERS), and compared the rates of post-vaccination neurological events, including seizures, to age-matched baseline incidence rates in the US and rates of neurological events following Covid-19 infection. This study reported an increased observed-to-expected ratio of seizures following the Janssen vaccine but not other vaccines. However, the rate of seizure after acute Covid-19 infection was much higher than after Covid-19 vaccination (Frontera et al., 2022). Another study using the VAERS data showed that incidence rates of seizures were 35-fold higher after Covid-19 vaccine compared to influenza vaccines. However, these two studies were limited by the nature of spontaneous report data, and could be biased due to the differential nature of Covid-19 and influenza vaccines (Avasarala, 2022). A Malaysia-based self-controlled case-series study reported a small increased risk of seizure-related hospitalisation during the 21 days after either dose of the Pfizer vaccine, with an incidence rate ratio of 1.26 (95% CI 1.07-1.48) (Ab Rahman et al., 2022). Conversely, another self-controlled case-series analysis using electronic health records data from Hong Kong has reported no increased risk of seizures in the first 28 days after the Pfizer vaccine (Wan et al., 2022).

5.130. Seizures after Covid-19 vaccination have been studied in specific populations. Using healthcare data from 3 commercial claims databases in the US, sequential testing methods were applied to detect safety signals after Covid-19 vaccination among US children aged 6 months to 17 years. The study found that seizure met the statistical threshold for a signal in respect of Pfizer (for ages 2-4 years) and Moderna (for ages 2-5 years) vaccinations. However, these results should be interpreted cautiously because the methods only screened for potential statistical signals, requiring further investigation in a robust epidemiologic study with confounding adjustment (Hu et al., 2024).

5.131. In summary, there is moderate-quality and inconsistent evidence studying the association between Covid-19 vaccines and seizures. More and better-quality research is needed if this potential association is to be studied.

Shoulder Injury Related to Vaccine Administration (SIRVA)

5.132. Maliwankul et al. reported a series of seven SIRVA cases following a Covid-19 vaccination in Thailand, and suggested that all the SIRVAs were from an incorrect injection technique and not actually the vaccination (Maliwankul et al., 2022). A prospective study in Turkey included 65 patients who were diagnosed with unilateral shoulder impingement and/or bursitis, and concluded that exacerbation of symptoms may occur if symptomatic shoulders are vaccinated (İğrek et al., 2023).

5.133. No quality evidence exists on the potential association between Covid-19 vaccination and the risk of SIRVA.

Tinnitus

5.134. Observational studies on the association between tinnitus and Covid-19 vaccines have been inconsistent. Using electronic health records data on >2.5 million people who received mRNA Covid-19 vaccine in the US, Dorney et al reported a lower risk of tinnitus after mRNA Covid-19 vaccine dose 1 than after influenza, Tdap (tetanus, diphtheria and pertussis) or pneumococcal vaccination (Dorney et al., 2023).

5.135. With general practice data from Australia, Shetty et al. conducted a self-controlled case series analysis to assess the relative incidence of audio-vestibular conditions after Covid-19 vaccination. They found an increased risk of tinnitus in the 42 days following the AstraZeneca (relative incidence: 2.25, 95 %CI 1.45, 3.50) and mRNA vaccines (relative incidence: 1.53, 95 %CI 1.25, 1.87) compared to baseline periods (Shetty et al, 2024). However, this study was limited by not being able to capture Covid-19 infection in the database.

5.136. A US-based study analysed data from both the Vaccine Adverse Event Reporting System and Vaccine Safety Datalink, and concluded that there was no evidence to support an increased risk of tinnitus following Covid-19 vaccination but cannot definitively exclude the possibility (Yih et al., 2024).

5.137. Tinnitus has also been documented in patients infected with SARS-CoV-2. A retrospective study included 272 children aged 5–11 years from Italy, and found that compared to children who received two doses of the Pfizer vaccine, those infected with SARS-CoV-2 had a higher frequency of tinnitus (Aldè et al., 2022).

5.138. In summary, there is moderate-high quality but inconsistent evidence studying the association between Covid-19 vaccination and the risk of tinnitus. Therefore, further studies would be needed to assess the absolute and relative risk of tinnitus following Covid-19 vaccination and the association with Covid-19 infection are needed.

Autoimmune connective tissue disease and alopecia

5.139. Jung and colleagues (Jung et al. 2024) conducted a population-based cohort study involving 9 million individuals from Korea to evaluate the association between mRNA vaccination and the risk of autoimmune connective tissue diseases. They reported no increased risk of alopecia or most autoimmune connective tissue diseases following mRNA vaccination, except for systemic lupus erythematosus where they observed a 16% increased risk. However, a booster vaccination was associated with a 12% increased risk of alopecia areata, 16% increased risk of psoriasis and a 14% increased risk of rheumatoid arthritis.

5.140. Overall, we found only one single study of moderate quality on the association between Covid-19 vaccines and autoimmune connective tissue disease and alopecia. The study findings were inconsistent, and further research would be needed in order to assess the potential association with autoimmune connective tissue diseases and alopecia.

Rheumatoid arthritis (RA)

5.141. The largest cohort study on the association between Covid-19 vaccines and the risk of developing RA is the Korean analysis of 9 million participants mentioned above (Jung et al., 2024). This analysis found no association with primo-vaccination, but a small (14%)

increased risk of RA after booster vaccination. Conversely, a large good quality cohort study (Peng et al., 2023) showed inconsistent results, with a 30% increased risk of RA development after Covid-19 infection in unvaccinated people, but no increased risk of RA after vaccination.

5.142. Additionally, 4 different cohort studies have reported on the risk of flare/s after vaccination in people with pre-existing RA. Three of them found no association between Covid-19 vaccination and the risk of flares (Cruz et al., 2024; Jung et al, 2024; Li et al., 2022d)), whilst one reported a potential increased risk after the AstraZeneca vaccine compared to the Pfizer vaccine (Rider et al., 2022).

5.143. In summary, the data on the association between Covid-19 vaccines and the development or flares of RA is scarce, of moderate quality, and inconsistent. Further research would be needed to elucidate this potential association.

Systemic Lupus Erythematosus (SLE)

5.144. Two large population-based cohort studies examined the association between Covid-19 vaccination and the risk of developing SLE. Whilst one found a small increased risk after vaccination with mRNA vaccines (Jung et al., 2024), the other one found an association between Covid-19 infection and the risk of SLE and anti-phospholipid syndrome, but an attenuation in this association following vaccination (Peng et al., 2024).

5.145. An additional two studies were found on the potential association between Covid-19 vaccination and acute flares of SLE, both of them showing no association (Mok et al., 2022; Yoshida et al., 2022).

5.146. In summary, we found moderate quality but inconsistent evidence on the association between Covid-19 vaccination and the risk of developing SLE, and moderate but consistent evidence to suggest no association with SLE flares. More research would be needed to clarify the association between Covid-19 vaccines and the risk of SLE.

Fibromyalgia

5.147. We identified only one relevant study on the association between Covid-19 vaccines and the risk of Fibromyalgia (Shani et al., 2024). This observational retrospective cohort study was based on electronic medical records of Clalit Health Services (CHS) members, the largest healthcare organisation in Israel. Vaccinated (N = 2,455,207) and Unvaccinated (N = 594,879) subjects were compared, and multivariate models were used to account for differences between them in terms of age, sex, population sector, socioeconomic status, residency, obesity, smoking, history of immune-mediated disease, hypertension, hyperlipidaemia, cancer, depression and anxiety. The analysis suggested an almost 50% increased risk of fibromyalgia associated with vaccination with the Pfizer Covid-19 vaccine in people aged 65 years or older, and no association in younger people.

5.148. There is only one study, of moderate quality, suggesting an association between vaccination with the Pfizer Covid-19 vaccine and the risk of fibromyalgia in elderly people. More research would be needed to understand the potential causality of this association.

Graves' disease

5.149. We identified five studies on the association between Covid-19 vaccination and the risk of Graves' disease. In a small Israeli case-control study including just over 2,000 participants, no association was found (Gorshtein et al., 2024). Two self-controlled case series analyses were included, a small one from a single centre and a large one including over 2 million potential participants from Hong Kong. While the former found an association between Covid-19 vaccination and the risk of thyroid eye disease (not specifically Graves') (Muller et al., 2024), the latter did not find evidence of an association between the Pfizer vaccine and the risk of developing Graves' disease (Wong et al., 2022a). Finally, two cohort studies were analysed, none of them finding an association between Covid-19 vaccines and the risk of Graves' disease (Censi et al., 2023; Peng et al., 2023).

5.150. Overall, we found moderate-high quality evidence suggesting no association between Covid-19 vaccines and the risk of Graves' disease.

Depression

5.151. A population-based cohort study (Kim et al., 2024) using the Korean National Health Insurance Service (KNHIS) claims database assessed the potential association of psychiatric adverse events following Covid-19 vaccination. The study compared vaccinated and unvaccinated people, and reported a 70% higher risk of depression at three months after vaccination compared to the unvaccinated people. However, baseline characteristics showed substantial differences between groups, with vaccinated people being older and with more comorbidities. Imbalances between groups can lead to relevant bias and confounding, and it is unclear if the study adequately accounted for differences in baseline characteristics.

5.152. Given the study limitations and the scarcity of data on this topic, the quality of the evidence is of low quality. Future well-conducted studies using state-of-the-art methods to adequately account for confounding would be needed to adequately assess the association between Covid-19 vaccines and the risk of depression.

Postural Orthostatic Tachycardia Syndrome (POTS)

5.153. A large cohort study (284,592 individuals) found an increased risk of POTS within 90 days post-vaccination compared to pre-vaccination, but the risk was lower than that following SARS-CoV-2 infection (Kwan et al., 2022). Pooled incidence rates indicate 3.94 cases per 10,000 vaccinated individuals (95% CI: 0 to 16.39), compared to 107.75 cases per 10,000 post-infections (95% CI: 9.73 to 273.52) (Yong et al., 2023).

5.154. Despite the observed possible association, the overall risk is low, and much lower than that associated with Covid-19 infection, calling for a risk-benefit analysis. Further research would be needed (Rubin, 2023) to improve our understanding and to inform future vaccination campaigns.

Optic Neuritis

5.155. A total of 6 studies passed our inclusion criteria, including two self-controlled case series, an analysis of spontaneous reports and three cohort studies. The first self-controlled case series was a nation-wide analysis of Korean data which did not find an association between

mRNA vaccines and the risk of optic neuritis (Hwang et al., 2024). The second was an analysis of England-based paediatric data (Copland et al, 2024), which found a small increased risk of demyelinating disease including optic neuritis in females following a second dose of the Pfizer vaccine. The risk was small, estimated at 4 cases per million people. This same study showed SARS-CoV-2 infection was associated with increased risks of hospitalisation from seven outcomes including multisystem inflammatory syndrome, with these risks largely absent in those vaccinated prior to infection, therefore calling for a risk-benefit balance.

5.156. Additionally, an analysis of US VAERS spontaneous reports data (Jaffry et al., 2023) found reporting rates within the incidence range of optic neuritis in the general population. Using a self-controlled analysis, the same data suggested an increased risk of optic neuritis after Covid-19 vaccination compared to the control/unexposed time period.

5.157. The remaining were three cohort studies. First, an analysis of US data found the risk of optic neuritis after mRNA Covid-19 vaccination was rare, lower than that seen after influenza vaccination and decreased compared with Covid-19 infection in unvaccinated people (Shukla et al., 2024). Second, a large cohort study of almost 8.5m patients found no association between Covid-19 vaccination and optic neuritis risk (Han et al., 2023). Finally, a Japanese matched cohort study of composite ocular adverse events found an increased risk for the composite outcome after the second dose, not specific for optic neuritis; however, a self-controlled case series analysis using the same data showed no increased risk (Hashimoto et al., 2023).

5.158. Overall, there is moderate quality data but inconsistent findings on a potential association between Covid-19 vaccination and the risk of optic neuritis. More research would be needed to further our understanding of this potential association.

Heart Failure

5.159. A recent nation-wide study (Xu et al., 2024) based on Swedish health registry data assessed post-vaccination risk of cardiovascular events, including heart failure. The study showed a significantly reduced risk of heart failure in the first 6 weeks after vaccination in people aged 41 years and older.

Menstrual disorders

Summary:

- Temporary and minor changes to menstruation, in particular cycle length, were reported fairly commonly after Covid-19 vaccinations.
- Causality is not well established due to limitations in the available evidence, which we would classify as of moderate quality.
- Data on menstrual disorders is not typically well recorded in routine health records. To our knowledge, no good quality studies have found evidence of a long-term impact of Covid-19 vaccines on menstruation.
- International regulatory authorities including the MHRA did not restrict any vaccine due to this side effect, as based on the available evidence throughout the Inquiry's

relevant period, the risks were not deemed to outweigh the benefits.

- In summary, UK regulatory action was appropriate and similar to that taken by other international regulators.

5.160. Anecdotal reports of menstrual irregularities after receiving Covid-19 vaccines were received early on during the rollout of these vaccines. They took the form of spontaneous reports and were also often reported in social and traditional media following the launch of the Covid-19 vaccine programme (MHRA, 2023a).

5.161. Assessing the association between Covid-19 vaccines and menstrual disorders is particularly challenging because of difficulties in outcome ascertainment, with menstrual disorders not typically available or well recorded in routinely collected health data.

5.162. A number of observational studies have been conducted, and a systematic review of menstrual cycle changes after Covid-19 vaccinations included 14 studies with data from 78,138 vaccinated females. Of them, a striking 52% reported some form of a menstrual problem after vaccination (Nazir et al., 2022).

5.163. While most studies on Covid-19 vaccines and menstrual disorders were based on cross-sectional data, one cohort study used prospectively collected menstrual cycle data from a mobile phone application (Edelman et al., 2022). This study included 3,959 individuals from the United States and found vaccination to be associated with a small change in cycle length that was not considered to be clinically significant. In another prospective study, 79 individuals who had received a Covid-19 vaccine were seen to have a delay to the next period. However, this change was not sustained subsequently and causality was not well-established (Alvergne et al., 2022). At least one good quality study using population-based rich data from Norway supported the finding of an increased risk of menstrual disturbances after the first dose of the Pfizer vaccine (Caspersen et al., 2023). More recent studies have obtained contradictory conclusions (Blix et al., 2023).

Conclusion

5.164. The quality of the evidence suggesting an association between Covid-19 vaccines and (temporary) menstrual disorders is moderate.

5.165. During the Inquiry's relevant period, the MHRA kept the condition under review but took no regulatory action. This was a result of a lack of evidence of causality at this time; establishing causality was complicated by the fact that menstrual disorders can be caused by other factors such as stress and illness, and by the scarcity of relevant information for epidemiological research. In late 2022, the product information for the Pfizer and Moderna vaccines was updated to include heavy menstrual bleeding as an adverse effect.

5.166. In summary, and based on the available evidence, the UK regulatory action related to the association between Covid-19 vaccines and menstrual disorders was appropriate, and in line with that taken by international regulators. The temporary and self-limited nature of these ADRs meant they were unlikely to change the benefit/risk assessment of the vaccines during the deployment campaigns.

Mild adverse reactions

Summary:

- Mild and temporary side effects were identified early on, during phase III trials for all approved Covid-19 vaccines. Therefore, the quality of the evidence on these mild adverse reactions is high.
- Causality for these is very well established as it is based on randomised controlled trial data and was later confirmed in multiple larger observational studies.
- Mild ADRs were common and similar for all relevant vaccines covered in this report, and included temporary injection-site reactions, fever, fatigue, and headache.

5.167. Mild side effects were identified before marketing authorisation and were observed in phase III trials. These included injection-site reactions, fever, fatigue and headache. All of these were further confirmed in much larger post-marketing studies, as outlined in this section.

5.168. According to a study where self-reported side effects were prospectively collected and self-reported by vaccinated subjects using a UK-based Covid-19 symptom study app, the most commonly reported systemic side-effects were fatigue (8.4% after the first-dose of the Pfizer vaccine and 21.1% after the first dose of the AstraZeneca vaccine) and headache (7.8% and 22.8% respectively). In the same study, the most frequently reported local effects were tenderness (57.2% after Pfizer first-dose; 49.3% after AstraZeneca first dose) and local pain (29.2%; 19.1% respectively) around the injection site. Menni et al also found that both systemic and local effects were more frequent among individuals with previous SARS-CoV-2 infection (Menni et al., 2022).

5.169. In a large study using data from US-based active surveillance through the smartphone-based system V-SAFE, the most common local effect was injection-site pain (66.2% of participants after the first dose, and 68.6% after dose two of either the Pfizer or Moderna vaccines). Fatigue was reported among 33.9% participants after dose one and 55.7% after dose two. A total of 27% of participants after dose one and 46.2% of participants after dose two reported headache. Rosenblum et al found these reactions were more frequently reported following the Moderna vaccine than following the Pfizer vaccine, and more frequently following dose two of either vaccine compared with dose one. Female participants and individuals younger than 65 years reported adverse events and reactions more frequently than male participants and those aged 65 years and older (Rosenblum et al., 2022).

5.170. Both studies (and many others) concluded that most of these common side effects were mild, appearing within 1–2 days following vaccination and resolving without treatment (or with symptomatic treatment) within a week. These studies were limited to self-reported data and may have selection bias, under-representing older and socioeconomically disadvantaged populations who may have less or worse access to electronic devices (Krantz and Phillips, 2022).

5.171. National data on spontaneous reports in the form of Yellow Card reports were recorded by the MHRA and shared in the public domain in the form of weekly updates. For all the original Covid-19 vaccines most reported side effects were 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. These data suggest the most common adverse reactions for all the Covid-19 vaccines were mild and self-limiting 'reactogenicity'-type events which happen shortly after vaccination and are not associated with more serious or lasting illness (MHRA, 2023a).

5.172. Similar information is available for less commonly used Covid-19 vaccines nationally during the relevant period. Based on the Summary of Product Characteristics, pooled analysis from clinical trials of the Janssen vaccine showed that the most common local adverse reaction reported was injection site pain (54.3%), and the most common systemic adverse reactions were fatigue (44.0%), and headache (43.0%) (MHRA, 2023f). According to the Summary of Product Characteristics for the Novavax vaccine, the pooled data from two phase III studies showed that the most frequent adverse reactions were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%) and headache (50%) (MHRA, 2023d).

5.173. There was no clear evidence of differences in these side effects among pregnant women compared to non-pregnant women (Sadarangani et al., 2022, Shimabukuro et al., 2021).

Prominent publicly reported side effects which were not confirmed upon investigation

5.174. The sources of information on suggested but unconfirmed side effects are multiple, from anecdotal cases documented in the form of spontaneous reports (e.g. Yellow Card submissions) to more complex and poorly documented sources, like social media, self-reported alleged reactions, etc. It is therefore impossible to produce an exhaustive list of suggested but unconfirmed side effects for this report. We have focussed on what, in our opinion, are the most widely reported and investigated suggested but unconfirmed reactions: excess deaths, adverse pregnancy outcomes, and fertility problems.

Adverse pregnancy outcomes

Summary:

- Pregnant women were excluded from all the phase III Covid-19 vaccine trials. As a result, data on pregnancy outcomes was not available during the vaccine campaign.
- To our knowledge, more recent data has not shown an association between Covid-19 vaccines and adverse pregnancy outcomes.

5.175. Initial randomised controlled trials of Covid-19 vaccines excluded pregnant women and when the Covid-19 vaccine programme was launched in December 2020 pregnant women were advised by the JCVI not to have a vaccine until more information became available. Only in April 2021 did the JCVI announced that it would offer all pregnant women the Covid-19 vaccine in line with the vaccine rollout plan for the UK (Royal College of Obstetrics and Gynaecology, no date). However, Covid-19 vaccine acceptance was particularly low among pregnant women, with safety concerns a commonly given reason for vaccine hesitancy (Golder et al., 2023, Skjefte et al., 2021).

5.176. Several studies have assessed the risk of adverse outcomes amongst pregnant women. One systematic review of studies assessing the safety of Covid-19 vaccines during pregnancy included 71 studies involving over 17 million pregnant women (Ciapponi et al., 2023). Meanwhile, another systematic review included 14 studies with over 350,000 pregnant women (Tormen et al., 2023). The studies identified were generally observational, and most women identified who had been vaccinated had received an mRNA vaccine. The studies that informed these systematic reviews were generally found (by the authors of the reviews) to have moderate or high risks of bias, particularly relating to confounding and selection of participants.

5.177. Studies have not found evidence of an increased risk of maternal complications following receipt of a Covid-19 vaccine. In a meta-analysis of eight observational studies that compared maternal complications during pregnancy in vaccinated versus unvaccinated women, there was no significant differences for composite pregnancy complications (Odds Ratio [OR] 0.99, 95% Confidence Interval [CI] 0.81 to 1.21), hypertensive disorders and pre-eclampsia (OR 1.11, 95% CI 0.86 to 1.42), placental abruption (OR 0.60, 95% CI 0.29 to 1.21), thromboembolism (OR 2.44, 95% CI 0.12 to 51.05), postpartum haemorrhage (OR 0.89, 95% CI 0.62 to 1.29), puerperal fever (OR 0.91, 95% CI 0.55 to 1.50) or maternal death (OR 2.19, 95% CI 0.09 to 53.82) (Tormen et al., 2023).

5.178. Similarly, studies have also not found evidence of an increased risk of foetal or neonatal complications. In a meta-analysis of nine observational studies that compared maternal complications during pregnancy in vaccinated versus unvaccinated women, there was no significant differences for pregnancy loss (OR 1.04, 95% CI 0.96 to 1.13), foetal abnormalities (OR 0.91, 95% CI 0.40 to 2.07), small for gestational age (OR 1.01, 95% CI 0.87 to 1.17), intrauterine growth restriction (OR 0.97, 95% CI 0.62 to 1.52), preterm birth (OR 0.82, 95% CI 0.64 to 1.06), stillbirth (OR 0.73, 95% CI 0.28 to 1.87), meconium-stained amniotic fluid (OR 0.78, 95% CI 0.58 to 1.05), neonatal ICU admission (OR 0.91, 95% CI 0.58 to 1.44) or hypoxic ischaemic encephalopathy (OR 4.42, 95% CI 0.18–108.91).

Fertility problems

Summary:

- Concerns over the possible impact of the Covid-19 vaccines on fertility arose early during the vaccination campaign, based on anecdotal experience and opinions.
- To our knowledge, no study to date has demonstrated an association between the Covid-19 vaccines and a risk of developing female or male fertility problems.

5.179. Concerns about the possible impact of Covid-19 vaccines on fertility arose during the initial vaccine rollout. These concerns were not driven by spontaneous reports, but appear to have been driven largely by anecdotal experience and opinions (Diaz et al., 2021b).

5.180. A systematic review of the impact of Covid-19 vaccines on the fertility of men and women of reproductive age included 29 studies (Zace et al., 2022). These studies were limited in terms of how representative their study populations were: over half the studies were of patients undergoing In Vitro Fertilization (IVF), and follow-up time ranged from a minimum of 7 days to a maximum of 9 months after vaccination.

5.181. In terms of female fertility, studies found no evidence of Covid-19 vaccines having a detrimental impact on trigger day estradiol and progesterone concentrations, serum and follicular fluid estradiol and progesterone, number of oocyte implantation rate, or pregnancy rate. Meanwhile in terms of male fertility, no evidence was found of Covid-19 vaccines having an adverse effect on sperm volume and concentration, motility or morphology. Overall, pregnancy rates did not differ among vaccinated and non-vaccinated groups (Zace et al., 2022).

Excess deaths

Summary:

- Some reports have suggested that Covid-19 vaccines might have caused an excess in mortality after vaccine rollout started or after the pandemic.
- However, the best quality evidence available to us suggests that, in fact, the Covid-19 vaccines saved millions of lives that would have otherwise been lost due to Covid-19 and related complications.

5.182. Some reports have suggested that Covid-19 vaccines could have led to an excess in mortality after the rollout started or after the pandemic. One paper recently published in the BMJ Public Health (Mostert et al., 2024) was cited in some media outlets as suggesting that Covid-19 vaccines may have contributed to excess deaths, but it did not in fact analyse vaccination rates as a factor, and the BMJ Public Health issued an expression of concern about the article pending further investigation. The Expression of Concern (BMJ Public Health, 2024) stated:

5.183. "*The integrity team and editors are investigating issues raised regarding the quality and messaging of this work. The Princess Máxima Centre, which is listed as the affiliation of three of the four authors, is also investigating the scientific quality of this study. The integrity team has contacted the institution regarding their investigation.*

5.184. *Readers should also be alerted to misreporting and misunderstanding of the work. It has been claimed that the work implies a direct causal link between Covid-19 vaccination and mortality. This study does not establish any such link. The researchers looked only at trends in excess mortality over time, not its causes. The research does not support the claim that vaccines are a major contributory factor to excess deaths since the start of the pandemic…*"

5.185. While some of the serious ADRs reported above can lead to death, the Covid-19 vaccines also reduced Covid-19 and related severity and related health outcomes, as demonstrated by good quality data from clinical trials and large cohort studies outlined above. There is to our knowledge no good quality data suggesting that the Covid-19 vaccines have led to an increase in overall mortality at the population level. On the contrary, many good quality national and international studies have reported on a great number of lives saved by the Covid-vaccines: see estimates from academic research groups (Mesle et al., 2021; Watson et al., 2022). Updated estimates of the number of lives saved in the UK alone by the Covid-19 vaccines has been recently published, adding to hundreds of thousands of deaths

averted during the period up to March 2023 (Mesle et al., 2024) (see paragraphs 4.36 to 4.39).

5.186. In summary, the evidence supporting an association between the Covid-19 vaccines and an excess mortality at the population level is of low quality, and has been in many cases misinterpreted.

6. Conclusions and recommendations for a future pandemic

6.1. Due to the quality and quantity of data available, and to the longstanding experience of the MHRA and UKHSA, the UK had timely information on the risk-benefit balance of the Covid-19 vaccines. Compared to other countries, the ability of UK-based researchers and stakeholders to link vaccine records to patient records allowed for the study of changes in the use and effects of the approved vaccines over time and across population subgroups. Specifically, UK agencies reacted promptly to safety events, typically within days of other larger regulatory agencies such as the US FDA or the EU's EMA. This is detailed in previous sections of this report.

6.2. Regarding the monitoring of effectiveness, the MHRA and public health agencies like the UKHSA and Public Health Scotland generated very rapid data on the impact of Covid-19 variants on vaccine effectiveness, sometimes being the first in the world to generate such evidence. This was only possible due to the existence of world-leading virus genomic testing capacity linked to unique expertise and rich NHS data. These mechanisms should continue to exist, and national agencies should continue to be provided with the resources to obtain and deliver the necessary knowledge at speed and with enough quality.

6.3. Finally, the early vaccination rollout campaign resulted in hundreds of thousands of deaths being averted, making the UK the country with the highest number of lives saved during the pandemic due to Covid-19 vaccines in the whole WHO-Europe region. However, certain population groups had a lower uptake of vaccines, including groups at high risk of severe outcomes such as ethnic minority groups and pregnant women.

6.4. In summary, the UK national vaccine regulatory and public health systems reacted in a similar manner to those in other comparable nations when it came to the approval and post-marketing surveillance of vaccines. However, there are opportunities for improvement that should be established in preparation for the next pandemic.

6.5. Our key recommendations are:

A. **Ensure that regulatory rolling review is replicated in the face of a future pandemic.** The MHRA should be resourced to conduct these, including staff as well as funding for education, training and knowledge sharing and acquisition.

B. **Create a system whereby regulators can access joined up, detailed and anonymised health records to track vaccine risks and benefits in real time during a pandemic.** The resources required to achieve this include:

    i. Staff with expertise in pharmacovigilance and in the analysis of spontaneous reports. The system should be flexible to recruit or increase the number of staff involved in this process in situations like a national vaccination campaign, when the number of spontaneous safety reports is expected to exceed usual business.

    ii. Timely access to relevant data with information on complete vaccine exposure and linked patient records and outcomes. Multiple such data assets are available, but access to them is not homogeneous, with different data access or ethics committees involved, and different data formats. The MHRA should have access to a secure data

environment compliant with current regulations and recommendations holding as many relevant data assets as possible, harmonised to a common data standard and with linkage across databases where possible. This would be in line with recent recommendations in the Sudlow review 'Uniting the UK's Health Data: A Huge Opportunity for Society' (Sudlow, 2024). Given its regulatory role, the MHRA should have priority access to these data, and/or a rapid approval process.

iii. An established and adequately funded system for the generation of regulatory evidence, similar to the US Sentinel or the EU DARWIN EU systems. Currently, and to the best of my knowledge, the MHRA lacks a national infrastructure ready and available to generate regulatory evidence in a timely fashion. Investment in such a system is necessary to speed and scale up the generation of knowledge on the use, safety and effectiveness of vaccines as well as other key medicines and potentially medical devices. Based on existing models in Europe, Asia, and North America, these systems can be successfully set up in collaboration with academic experts, and funded based on competitive calls/tenders open to national applicants.

C. **The MHRA should invest in and prioritise relationships and information sharing with other global regulators.** Following the departure from the EU, furthering collaborations and partnerships with international regulators including the EMA, the US FDA and others would accelerate the MHRA's ability to identify very rare safety events that require very large numbers of data points.

D. **The MHRA should generate or have mechanisms to commission and fund specific studies needed to prepare the nation for the study of post-marketing vaccine safety.** The list of necessary studies should be completed by experts in regulatory science, but would likely include analyses of background incidence rates of all potential adverse events of special interest related to a new vaccine before it is launched. Ideally, these should be conducted using linked primary care and hospital data, and stratified by relevant socio-demographics, including age, sex, ethnicity, region and subgroups of particular interest, like pregnant women and people with disabilities.

E. **The MHRA to consider whether any of the ADRs raised by Material Providers warrant further examination by way of systematic reviews and epidemiological studies**. In particular, those potential ADRs in respect of which we identified that there was at least some evidence of a possible association, namely: VZV (infection and reactivation), seizures, tinnitus, autoimmune connective tissue disorders and alopecia, RA (development and flares), SLE, fibromyalgia, depression, POTS and optic neuritis.

F. **The MHRA should have timely access to all relevant data necessary to monitor vaccine effectiveness.** This should include variant surveillance data, similar to that available to the UK's public health agencies during the pandemic. Ideally, this data should be available to the MHRA as part of the set-up described in 2b above. This is necessary for the continuous analysis of benefit/risk, and would facilitate analyses of specific regulatory interest, e.g. on subgroups affected by specific safety concerns that could affect the benefit/risk balance.

G. **An expert group with knowledge of clinical trials, real world evidence, spontaneous reports analysis/pharmacovigilance, and pharmacoepidemiology should be formed and active in preparation for future national vaccination campaigns.** This group should interact with and coordinate all stakeholders involved in the monitoring of vaccine risk-benefits, including the MHRA, public health agencies across the four nations of the UK, the JCVI, NHS

and academic experts. While a number of such groups exist, and VBREWG took a similar role during the pandemic, a joint group including all these bodies and interests would catalyse the integration of timely evidence on vaccine risks and benefits at both the authorisation and post-authorisation stage.

H. **Greater requirement / drive to achieve diversity in vaccine clinical trials.** Depending on epidemiology and severity data, those at highest risk of severe disease should be prioritised for pre-authorisation trials. Specific subgroups considered at high risk of severe disease like pregnant women should not be systematically excluded from phase III trials.

I. **Greater obligations on pharmaceutical companies to conduct early post-authorisation safety studies, with a particular focus on the risk-benefit of vaccines among groups under-represented in or excluded from phase III trials.** This work should be done as early as possible after marketing approval. Ethnic minorities, elderly people with frailty or multiple comorbidities, pregnant women and people with disabilities should be among the groups prioritised in these studies.

J. **An expert communications team should be set up to inform the public on the existing mechanisms for the reporting of adverse reactions (i.e. Yellow Card) and to train and support healthcare professionals for the communication of vaccine risks in the context of vaccine benefits.** This team should work closely and have access to the expert group described in Recommendation G, and make the best efforts to tailor messaging to successfully reach minority groups across the country.

K. **Additional efforts should be made to vaccinate subgroups at highest risk of severe outcomes.** These efforts should be supported by bespoke evidence generation efforts (see recommendations H and I) and by dedicated communication campaigns, among other measures.

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