Expert Report for the UK Covid-19 Inquiry

Module 4 – Vaccines and Therapeutics

Hurdles and Nets: Authorising and Monitoring Vaccines

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Author statement

"I confirm that this is my own work and that the facts stated in the report are within my own knowledge. I understand my duty to provide independent evidence and have complied with that duty. I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer."

Stephen JW Evans

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Appendix 1 is a note on statistical terminology and reference will be made to it at various points Appendix 2 provides an international comparison by way of an overview of the USA's FDA Regulatory process for the Pfizer vaccine.

1. Preamble

1.1 My first degree (BSc 1966) was from Keele University in physics and chemistry; I also had a year (1964-5) on a scholarship in the US doing physics and philosophy. Having worked in the computer industry and at CERN, Geneva, I worked in computing at The (Royal from 1990) London Hospital and Medical College (LHMC) from 1970 and did the MSc in Medical Statistics (1978) at The London School of Hygiene and Tropical Medicine (LSHTM). I taught on that MSc course from 1978 onwards. I was Senior Lecturer (1979), Reader (1986) then made Professor of Medical Statistics at LHMC in 1990. My role was in teaching medical students and postgraduates, together with participating in research across most academic departments of the Medical College. In 1991, I was a member of the Working Party of the Royal Statistical Society on statistics in drug regulation[1]. At that time, although there were statisticians on advisory committees, there were no statisticians on the staff of the Medicines Control Agency.

1.2 When I left LHMC in 1995 to go to be Head of the Epidemiology Unit at the UK Medicines Control Agency (MCA, now MHRA), I was made Honorary Professor of Medical Statistics at LSHTM as well as at LHMC. While at the MCA I was a lead assessor for major safety issues such as Hormone (Replacement) Therapy and breast cancer; vitamin K and childhood cancer; MMR and autism. I worked briefly (1999/2000) at Quintiles (now IQVIA) mainly providing statistical input to the Bristol Royal Infirmary Inquiry, before returning to the MCA in 2000 as a Specialist in Epidemiology. I became Professor of Pharmacoepidemiology at LSHTM (half-time) on retirement from the MCA in 2002.

1.3 From 2006 to 2018, I was on the EU committees on medicines safety becoming a European Commission appointed independent Expert member of the Pharmacovigilance (Drug Safety) and Risk Assessment Committee at the European Medicines Agency from 2012. My role was as a statistical epidemiologist assessing those aspects of issues around the safety of medicines.

1.4 I was a member of the WHO Global Advisory Committee on Vaccine Safety (2006-12), where I provided a statistical view of proposed and completed studies. I was also on various WHO groups before and during the Covid-19 pandemic, where again I provided statistical advice. In particular, I was on the Scientific Advisory Committee on

[1]Working Party of the Royal Statistical Society. Statistics and Statisticians in Drug Regulation in the United Kingdom. J. R. Statist. Soc. A 1991; 154: 413-419.

no-fault compensation for the WHO COVID-19 Vaccines Global Access (COVAX) initiative from March 2021 to October 2022.

1.5 I was Chair of the Royal Statistical Society Medical Section (1994-96). I was elected President of the International Society of Pharmacoepidemiology for 2010/2011.

1.6 I have been on many committees monitoring the conduct of randomised trials of medicines, both drugs and vaccines, all publicly funded. The role of these "Data Monitoring Committees" or "Data and Safety Monitoring Boards" is to ensure the safety of participants as an independent group having access to the accumulating data from the trial. During the Covid-19 pandemic, I was an independent statistician on the Data Monitoring Committee for the Com-Cov Trials, which compared different combinations of vaccines for first and second doses.

1.7 I am the statistician to the "Safety Platform for Emergency vACcines" (SPEAC) project for the "Coalition for Epidemic Preparedness Innovations" (CEPI) meta-Data and Safety Monitoring Board. This oversees all trials of vaccines funded by CEPI for diseases mainly affecting low and middle-income countries. Its role is to ensure that an overview of the trials is taken so that any new adverse reactions are assessed as rapidly as possible, utilising information from all trials.

1.8 I was involved with the OpenSAFELY collaboration from 2020 and continue with minor involvement, including being on its Oversight Board. This was a collaboration between Oxford University and LSHTM to utilise electronic health record data collected by GPs on a large proportion of the population of England. The research was done under the Covid-19 emergency legislation and enabled an important series of studies to be carried out while preserving the confidentiality of all the patient records. The first paper described the risk factors for death from Covid-19 and was helpful in setting global priorities for vaccination. Further research was done on issues around ethnic factors, vaccines and possible treatments for Covid-19. I presented some of the results, with colleagues, to JCVI (UK Joint Committee on Vaccination and Immunisation), but was not a member of JCVI or involved in its decision-making.

1.9 I had no involvement with MHRA during the Covid-19 pandemic, except for attending a Scientific Workshop on Head-to-Head Randomised Clinical Effectiveness Trials of Licensed Covid-19 Vaccines.

1.10 I sat on two ad hoc independent expert panels providing advice to UK Government bodies during the pandemic: the Vaccine Effectiveness Expert Panel from June 2021 to October 2022, organised by the Cabinet Office, and the Vaccine Effectiveness

expert working group from December 2020 to September 2022, organised by PHE/UKHSA. Neither of these groups were involved in Policy advice. I had no involvement with the Scientific Advisory Group for Emergencies (SAGE).

1.11 I was a participant (as a volunteer aged over 70, not as a scientist), in the Oxford/AstraZeneca trial of the ChAdOx vaccine in 2020/21.

1.12 I was convenor of the Statistics Expert Group at the Infected Blood Inquiry (Chair: Sir Brian Langstaff) which published its final report in May 2024. Our task was to estimate numbers of people who had been infected by diseases transmitted through blood products during the period when these products were infected.

1.13 I retired from LSHTM in October 2022, becoming Emeritus Professor, and continue to do some teaching and research.

1.14 My name is on about 100 publications since 2020, with over 300 since 1968. Most of my publications have resulted from collaboration with medical research colleagues. I have contributed statistical advice and analysis for many of these across a great variety of medical specialties. Some of my work has involved methods of checking on safety, particularly on the analysis of spontaneous reports ("Yellow Cards"). I have also done innovative work on checking for misconduct in research, especially in randomised trials.

1.15 I have been on various editorial boards, including the *British Journal of Clinical Pharmacology* and was an Associate Editor of *Pharmaco-epidemiology and Drug Safety.* I was a statistical advisor to the *British Medical Journal* and a member of its editorial review committee for over 15 years.

1.16 I am a substantive Fellow of The Royal College of Physicians of Edinburgh (relatively unusual for someone not medically qualified) and an Honorary Fellow of The Royal College of Physicians of London.

1.17 I was appointed a Member of the Order of the British Empire (MBE) for Services to the Safety of Medicines in January 2024.

Introduction: the regulatory process for medicines

1.18 The systems and processes which apply to the marketing authorisation for any medicine, including a vaccine, consist of a number of regulatory 'hurdles'. These hurdles aim to ensure three things: 1) that a new medicine has the beneficial effect claimed for it; 2) that, in the context of its intended use, any harms are minor compared with the benefits; and 3) that when delivered to a patient it meets standards of quality and does not contain impurities. These three aims can be summarised as: efficacy, safety and quality.

1.19 Once a medicine is authorised, regulators set up a series of 'nets' with which to capture unintended adverse effects of the medicine. Such nets represent post-marketing surveillance, or pharmacovigilance, systems and processes. This report will analyse the 'hurdles' and 'nets' put in place in respect of the Covid-19 vaccines in the UK.

2. The usual systems and processes which apply to the marketing authorisation of medicines

Scientific aspects of the process

2.1 The process begins with laboratory studies testing the biochemical effects related to efficacy and safety. These start as "in vitro" (Latin for "In glass") studies, conducted in test tubes or similar apparatus. They then move on to "In vivo" (Latin for "in the living") studies, which may involve whole cell organisms, plants or animals. For safety, animal studies are conducted, especially to check for cancers and other conditions that can take many years to develop in humans; the timescale for detection of such conditions in whole cell or animal studies is much shorter. These are called "pre-clinical studies". Many products fail at this stage, but the fact that they pass does not automatically mean they will have the desired benefits and lack of harms in humans.

2.2 When the pre-clinical studies have been completed satisfactorily, including deciding what approximate dose is appropriate, clinical studies start in human beings in successive phases. In phase 1, the basic clinical and physiological response is studied in a few (perhaps in groups of 5 to 10) healthy volunteers. Different doses will usually be given to find an optimal dose in humans.

2.3 Major lessons were learnt from a disastrous phase 1 study of a new drug carried out in 2006 at Northwick Park Hospital.[2] Six volunteers were simultaneously given the new drug and all six became very ill within 90 minutes (two volunteers were given a placebo). This was totally unexpected since the preclinical testing would usually prevent this type of thing happening. The MHRA commissioned a report[3] and the Royal Statistical Society set up its own Working Party on "First-in-man" studies.[4] A key problem was that this drug of a new type was given to all six volunteers at the same time; this was not sensible.

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[2] NIBSC (no date) TGN1412 10 years on - learning from a clinical trials disaster. Available at: https://nibsc.org/about_us/latest_news/nibsc_and_tgn1412.aspx (Accessed: 10 December 2024).
[3] MHRA (2006) Clinical trial final report - Press release, The National Archives. Available at: https://webarchive.nationalarchives.gov.uk/ukgwa/20141206051830/http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON2023822 (Accessed: 10 December 2024).
[4] The Royal Statistical Society (2012) Statistical Issues in First-in-Man Studies. Available at: https://web.archive.org/web/20120105003015/http://www.rss.org.uk/site/cms/contentviewarticle.asp?article=523 (Accessed: 10 December 2024). {the FOI annex is also of interest}

2.4 Phase 2 studies include quite small numbers, perhaps in the range 20 to 50. The clinical response is studied in patients who have the disease which the drug is aimed at treating. For vaccines in phase 2 the participants may be exposed, just through normal activity, to the virus that is the target of the vaccine. In some instances, volunteers may be exposed to the virus under controlled conditions: these are called "challenge trials". Phase 2 trials for vaccines will measure the immune response to the vaccine to ensure that it is likely to have a beneficial effect. In all phases patients are carefully monitored for adverse events (AEs), and if even a single serious AE occurs the entire development programme may be stopped.

2.5 For most trials in Phase 2, and for all trials in Phase 3, the allocation of a treatment to a patient is done on a random basis. This means that the treating doctor does not decide whether a particular patient will get the real drug or vaccine being studied or a placebo (or other "control" treatment). The consequence is that the group receiving the real vaccine and the control group will, on average, have similar people included. They will be the same age, gender, height, weight etc. on average. Any difference between them will be due to chance, and statistical methods can calculate probabilities of differences that would occur by chance. The groups will not just be similar for the characteristics listed above which are measurable, but they will be balanced for unmeasured and unknown characteristics. These trials are called "randomised Controlled Trials" or "RCTs". The strength of evidence for deciding whether a vaccine has caused an effect is much higher when the evidence is based on an RCT than when based on other study designs. This is why regulators require evidence from RCTs in almost all instances before authorising (licensing) a new medicine.

2.6 In Phase 3, larger numbers are studied. For drugs, this usually involves hundreds of participants, but for vaccines it involves thousands or tens of thousands of participants because the clinical outcomes being assessed are rarer (see sections on Statistical Power and Statistical Significance, Appendix 1). If 10% of participants have the clinical outcome in the control group, to show that halving the rate - a reduction to 5% - is "statistically significant" would require about 435 participants per group. If it is only 1% in the control group and 0.5% in the treated (e.g. vaccinated) group, then over 4,600 per group is required. So, for very rare outcomes the trial size has to be of the order of 30,000 participants or more. These trials are conducted under scrutiny by regulators and used to provide the primary evidence on clinical safety and efficacy for authorisation of the product. For drugs they almost always compare the active product with a placebo and both groups get the best available standard of care. For vaccines, the clinical outcomes are dependent on the target virus circulating at a high enough

level to cause infection in sufficient numbers among the population from which participants are recruited.

2.7 In respect of vaccines, some studies will allow use of a placebo as the comparison (control) group, while in others (sometimes because of ethical objections to injecting a placebo, especially in children) an alternative, previously authorised, vaccine is given as the control. An example would be the meningococcal vaccine used as a control in the Oxford/AstraZeneca trials of a Covid-19 vaccine. This control vaccine will have some benefit to the individual receiving it, since it is effective in preventing another disease, but it will have no effect on the infection the vaccine is intended to prevent. The individual obtains a benefit from the control injection, but it will not interfere with the assessment of the new vaccine. This prospect of benefit may help with recruitment and encourage participation.

2.8 Using an alternative vaccine rather than a placebo as the control will also result in reactogenicity (the general effects like fever, sore arm, redness and headache which tend to follow vaccine injections). This allows for a comparison of whether the new vaccine is better, similar or worse than an existing vaccine in terms of reactogenicity. It also helps with "blinding" vaccinees (the study participants receiving the vaccine) and the investigators as to whether the new vaccine or a control was administered. Not knowing which treatment is given and not knowing which treatment has been received is an important aspect of reducing bias in randomised trials. Concealment of which treatment will be given to the next patient is vital even if it is impossible to "blind" the investigator or patient once the treatment has been given.

Measuring efficacy

2.9 The RCTs should be designed with enough participants (see Appendix 1 on "Sample Size") to give evidence of benefit (efficacy) in terms of the outcome to be studied (the outcome is also usually pre-agreed with regulators). The outcome may be clinical such as prevention of a heart attack or death, or it may be a surrogate, that is, something that is easier to measure but is a good predictor of the effect on a clinical outcome. For example, reducing cholesterol is a surrogate for prevention of a heart attack, because we have very good evidence that high cholesterol can lead to heart attacks, and that in many trials reduction in cholesterol has led to reduction in heart attacks.

2.10 For vaccines the measured clinical response is preventing the actual disease or the infection, following exposure to the virus which is circulating in the population. The

vaccinees may or may not be exposed to the virus in varying doses and the trial has no control over this exposure (except in the case of "human challenge" studies where the volunteers are deliberately exposed to a controlled dose of the virus). The measurement of the clinical response may or may not include asymptomatic infection. An alternative, requiring smaller sample sizes, is measuring the "immune response" which is effectively a surrogate. At early stages of knowledge with a new virus, it will not be known whether the measurement of immune response does correlate with the clinical response, so for licensing of a vaccine with a new disease the relevant part of the immune response is not known, and regulators will require evidence of efficacy in terms of a clinical response. This will require larger trials than those using a surrogate.

2.11 There are various components of the body's response to a vaccine, notably B-cells which produce antibodies to fight the infection and T-cells which act directly against cells infected with the virus. It is possible to measure these in everyone whether they are exposed to the virus or not. At later stages, when a vaccine has demonstrated clinical efficacy, the relevant measures of the immune response that have been shown to relate to the clinical response ("correlates of protection") are characterised. Measuring these correlates of protection in smaller phase 2/3 trials will allow for authorisation of new vaccines as long as they have been sufficiently validated and provide sufficient evidence for efficacy. Thus, these smaller trials may be used to target a new variant of a virus with a modified version of the existing vaccine. These trials are also not dependent on the participants being exposed to the virus.

2.12 In respect of the Covid-19 vaccines, at the stage when there was no idea of how effective they were likely to be, there was a consensus among regulators that clinical outcomes must be used for the first authorisations. It would be insufficient to show only immune response, since it was not known which measures of immune response would reflect genuine clinical protection. The guidance from the FDA was that the observed vaccine efficacy (VE, see Appendix 1) should be at least 50%. Any estimate of VE like 50% will have some uncertainty around that value. It is possible to calculate the amount of uncertainty due to the numbers who have been studied using statistical methods. There is more detail about confidence intervals and limits in Appendix 1, but a confidence limit is a statistical measure of the uncertainty with which the VE is measured. The uncertainty becomes less the more data are available; that is mainly determined by the number of participants. The FDA guidance required a lower 95% confidence limit for VE of at least 30%. Other regulators and WHO set out similar

guidance for what might be acceptable were a new vaccine to show a VE that would lead to an authorisation. The EMA (and hence the UK prior to January 2021) had the same point estimate of 50% but allowed for a lower confidence limit of 20%, but preferably 30%.[5] This wider confidence interval would allow for a slightly smaller number of participants (see Appendix 1 on confidence intervals). The clinical outcome would generally be expected to be symptomatic infection. This is based on balancing several considerations: which outcomes are important; which are common enough to be detected statistically; and which are easy to identify - for example, an asymptomatic positive test may be common but would require testing all participants regularly, a significant logistical exercise. Asymptomatic infection would also be an acceptable outcome. The expected efficacy for a brand-new vaccine was expected to be similar to that of a flu vaccine which often has a VE of about 50%, though this varies considerably from year to year. Using the assumptions around infection rates then in order to meet the requirement on uncertainty, trial sizes of about 30,000 would be required.

Measuring Safety

2.13 Safety itself cannot be measured; it is the relative absence of harm that demonstrates safety. Harms are called adverse effects or adverse reactions. These are regarded as attributable to the vaccine. "Adverse events" (AEs) are bad outcomes which occur during a trial or in general clinical use of a vaccine, but which are not necessarily caused by that vaccine. They may be coincidental or may be caused by the disease the vaccine is targeted at, or another disease. When they occur after a vaccine is given, they are called "Adverse Events Following Immunisation" (AEFI).

2.14 The WHO has issued guidance on assessing individual AEFIs for causality,[6] but such judgements are subject to error. Ideally, to provide the strongest evidence that an AEFI is causally linked to a vaccine, randomisation in a clinical trial is required. As noted above, the strongest evidence for causal effects arises when an RCT is conducted, and a statistically significant difference in the rate of occurrence of the AE is shown between the vaccine and control groups. In all trials, AEs are counted. These may be

[5] European Medicines Agency (2020) EMA considerations on COVID-19 vaccine approval. Available at: https://www.ema.europa.eu/en/documents/other/ema-considerations-covid-19-vaccine-approval_en.pdf (Accessed: 10 December 2024).
[6] World Health Organisation (2002) Adverse Events Following Immunization (AEFI): Causality Assessment. Available at: https://iris.who.int/bitstream/handle/10665/191391/a87773_eng.pdf (Accessed: 10 December 2024).

actively sought by interviewing the participant or a health professional caring for them. A series of questions is asked, relating to expected AEs: have they occurred; if so, for how long; and how severe were they? Usually there will be an additional open-ended question asking whether any other AEs have been experienced. This may lead to the reporting of events that are totally unrelated to the medicine.

2.15 As noted above, all injected vaccines will have some reactogenicity,[7] i.e. the body's response when the immune system is activated. It does not necessarily show that the vaccine will produce longer lasting adverse effects or that the vaccine will work to prevent disease in that individual. On the other hand, the total absence of any reactogenicity would suggest the vaccine has no effect.

2.16 These effects are very frequent, with at least one generally occurring in most recipients. They do not usually last longer than a few days. In early trials, if these are very severe it may lead to a dose reduction or to cessation of development of the vaccine. The trials will easily be able to show if these occur at a higher rate or with greater severity than is usual in vaccines in general. Reactions such as anaphylaxis (allergic reactions that are particularly severe, leading to tissue swelling in the throat and/or tongue that can affect breathing) that occur soon after administration will be detected if they occur fairly frequently in trials.

2.17 Most adverse reactions to vaccines occur soon after vaccination, usually within 2-3 weeks. There are some reactions that can take longer to appear or may occur earlier but only get diagnosed at a later stage.

2.18 For example, Immune thrombocytopenia (previously called idiopathic thrombocytopenic purpura- ITP, "idiopathic" means "of unknown cause") is an autoimmune disorder with a reduction in platelets in the blood (thrombocytopenia) and appearing as bruising (purpura) or small red spots under the skin, usually on the chest and neck. It can be caused by vaccines, notably the mumps, measles, rubella vaccine. It is rare somewhere around 1 to 10 in 100,000 cases and can appear up to six weeks after vaccination. It in most cases is transient, and current advice from the ITP Association says:[8]

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[7] Hervé, C. et al. (2019) 'The how's and what's of vaccine reactogenicity', npj Vaccines, 4(1), p. 39. Available at: https://doi.org/10.1038/s41541-019-0132-6.

[8] ITP Support Association (2022) 'MMR and ITP', 3 August. Available at: https://itpsupport.org.uk/mmr-and-itp/, https://itpsupport.org.uk/mmr-and-itp/ (Accessed: 10 December 2024).

"Advice from the Association's medical advisors is that the fear of ITP is no reason to avoid vaccination, either for children who have had ITP before or for those who have never had it. Children are much more likely to come to harm from the diseases the vaccine prevents than from the few and rare side effects (such as ITP) associated with the injection.

MMR booster vaccinations

Parents of children who develop ITP as a result of the MMR jab can request a serum test before the booster is due to see if full immunity has been achieved, and if so, the booster jab will not be necessary. If the serology testing suggests that a child is not fully immune against measles, mumps and rubella then a second dose of MMR is recommended by the Dept of Public Health."

2.19 Current estimates suggest an incidence of about 1 in 20,000 but this is much lower than occurs following measles or rubella where the risk can easily be 1 in 3,000.

2.20 Another reaction that was delayed was that of narcolepsy (excessive daytime sleepiness) following one of the 2009 pandemic flu vaccines. This could appear up to twelve months after vaccination,[9] and may have occurred in about 1 in 34,500 doses. It took a study conducted seven or eight years after the vaccinations were given to realise that there was an increase in risk up to 12 months after vaccination. Earlier studies suggested the increase was only seen up to six months after vaccination.

2.21 These delayed onset reactions seem to be very rare, and their rarity will mean they are unlikely to be detected in RCTs because the numbers of participants is too low. In addition, intensive follow-up is usually limited to about 3 months in most vaccine trials. For example, at the time of authorisation of the Pfizer Covid-19 vaccine, the median time of follow-up was about two months. This means that the trials cannot be expected to detect effects with very long delays, and experience suggests these are rare. In my view, not universally acknowledged, most if not all very rare adverse reactions arise

[9] Stowe J et al. Reassessment of the risk of narcolepsy in children in England 8 years after receipt of the AS03-adjuvanted H1N1 pandemic vaccine: A case-coverage study. PLoS Med. 2020; 17:e1003225.

from what is called a "multi-hit or multi-step process" and evidence for this has arisen in other fields of medicine.[10] [11] This concept was first noted in relation to cancer. It was clear that there was no single factor or genetic mutation that caused a particular cancer, but it was realised that a combination of factors was necessary to cause a cancer to manifest itself. Some of these factors were genetic and some were from exposure to things like tobacco smoke in the environment. This seems to apply to other diseases in addition to cancer. For an individual to get a particular disease, they might need to have a specific genetic mutation and then be exposed to one or more factors in the environment. Sometimes there is a single mutation or exposure that is necessary for the disease but sometimes there are several genes or factors any of which provide the necessary "step" or "hit" in the process of developing the disease. For example, most people with narcolepsy have the HLA-DQB1*06:02 variation, and some have other, closely related genes, but the vast majority with those genes do not have narcolepsy. The genetic mutation is not a sufficient cause on its own to get the disease. Similarly, exposure to the pandemic flu vaccine was by no means sufficient to get narcolepsy, it was probably one of many different factors in the history of an individual that led to the very unfortunate outcome of getting narcolepsy. The consequence is that with multiple factors needing to be present, it may take some time before they have all occurred and an adverse effect is seen. For drugs as opposed to vaccines, this is more of a problem, since exposure to a drug takes place in almost all instances over a long period, often months or years, so the opportunity for such delayed effects is greater.

2.22 Inevitably, the total numbers of patients in an RCT - the sample size (see Appendix 1) - whether measuring immune or clinical responses, will be insufficient to detect very rare adverse effects (reactions, not events) and so further monitoring is required. Even if 30,000 people are vaccinated in a trial, an adverse effect that only occurs in say one person in 200,000 will probably not be observed. Even if it is observed, it is impossible to demonstrate that the vaccine is the cause of that rare event, given its rarity. These are considerations relating to what is called the "statistical power" of a study to detect an effect (see Appendix 1).

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[10] Pfeffer T et al (2020). Common genetic predisposition for heart failure and cancer. Gemeinsame genetische Prädisposition für Herzinsuffizienz und Krebs. Herz. 45. 632-636 doi.org/10.1007/s00059-020-04953-9 They say the multi-hit hypothesis "… supports the observation that cancer patients often do not show any acute cardiovascular effects, but years later cardiovascular pathologies emerge that are likely to be late effects of antitumor therapies.

[11] Al-Chalabi A et al. Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. Lancet Neurol. 2014;13:1108-1113.

2.23 If it were to be argued that a trial should be large enough to rule out very rare events, this raises ethical issues. Continuing a trial when we know the vaccine is effective, just to gain enough data to rule out very rare adverse effects, would mean delay in the provision of an effective vaccine to both the control group (i.e. those given a placebo) and the wider population. Such trials cannot be done because of the ethical issues, unless there is an effective treatment available to the control group. In the situation of a pandemic especially, but generally where a vaccine is preventing a disease with serious consequences, it would not be ethical to say to participants, 'there is an effective vaccine for this disease, but we want you to be prepared to take a placebo in order for us to have longer follow-up to detect some rare adverse effect that may not exist.' Recruitment would be difficult if not impossible even if the trial were to be regarded as ethical. During the pandemic, once the trial results were known, the investigators accepted that, although they would like to have continued follow-up without participants knowing whether they had received the vaccine or the control, they had to offer to "unblind" participants so that they could choose whether to have the vaccine if they had received the placebo.[12]

2.24 It could be said that safety is always provisional, in the sense that, with rare events, it may take some time for them to be detected. As part of that process for both drugs and vaccines there may be adverse events that are fairly rare, but which may be predicted or deemed possible, either from previous experience with similar products or by theoretical considerations. Companies are required to pay special attention to them, and there will usually be special surveillance in trials to actively look for these "Adverse Events of Special Interest" (AESI).

2.25 There has been international collaboration in defining AESI for different vaccines and the Brighton Collaboration[13] has had a major role in the process which utilises international collaboration. In 2019, prior to the Covid-19 pandemic, the "Coalition for Epidemic Preparedness Innovations" (CEPI) and the Brighton Collaboration came together to launch the Safety Platform for Emergency Vaccines (SPEAC) project.[14]

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[12] Cohen, J. (2020) *Makers of successful COVID-19 vaccines wrestle with options for placebo recipients*, *ScienceInsider*. Available at: https://www.science.org/content/article/makers-successful-covid-19-vaccine-wrestle-options-many-thousands-who-received-placebos (Accessed: 11 December 2024).

[13] This started in 1999 to be analogous to the Cochrane Collaboration but focussed on vaccines. They have made major contributions to setting out case definitions for adverse effects that might be caused by vaccines. Brighton Collaboration (2021) 'History'. Available at: https://brightoncollaboration.org/history/ (Accessed: 11 December 2024).

[14] SPEAC (2023) 'AESI Lists', 15 February. Available at: https://speacsafety.net/tools/aesi-lists/ (Accessed: 11 December 2024).

Their definitions of AESI for the Covid-19 vaccines were widely utilised during the pandemic, as the project worked on issues around Covid-19 vaccines, some of which had been partly funded in their development by CEPI.

2.26 As noted above in paragraph 2.14, the WHO[15] has issued guidelines on causality assessment and has various tools available for evaluating individual case reports.

2.27 In summary, it is relatively easy to detect frequent and rapid-onset adverse effects, but rare and delayed effects are much more difficult. They will generally require post-marketing surveillance rather than relying on pre-marketing trials.

Trial monitoring

2.28 For almost all major trials there will be a "Data Monitoring Committee" (DMC) or "Data and Safety Monitoring Board" (DSMB). These terms are synonymous. While individual DMCs will have slightly different roles according to their (usually published) charter, the basic functions are the same. They will generally have access to "unblinded" data both for efficacy outcomes and harms. They will know whether individual patients have received a vaccine or a control. They will meet regularly and the basic advice they give to the investigators' "Trial Steering Committee" (TSC) is whether to continue the trial as it is, to amend it in some way, or to pause or stop the trial. The independence of DMCs is a vital component of their organisation to ensure confidence in their working. They must not have vested interests in the success or otherwise of the product under trial but must have a range of clinical and statistical expertise to judge whether a trial should continue. They should also be independent of the investigators.

2.29 The TSC will include investigators and independent scientists who are responsible for the conduct of the trial. It will often have representatives of the sponsoring (funding) organisation (industry, academic or health service) as non-voting members. They will be there to give technical advice, but the main membership is intended to be independent of the sponsor. In "blinded" trials they will only see overall results, not those split by treatment group. It is their decision, based on advice from the DMC,

[15] World Health Organisation (2021) *Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, 2nd ed., 2019 update*. Available at: https://www.who.int/publications/i/item/9789241516990 (Accessed: 11 December 2024).

whether to continue, amend or stop the trial. If the DMC has advised stopping, I know of no instance where they have carried on recruiting, but there have been occasions where they have stopped a trial where the independent advice was to carry on.[16]

2.30 It is a general principle that DMCs do not have the sponsor or investigator(s) present when discussing "unblinded" data in the "closed" part of DMC meetings. There may be an "open" session where the TSC representatives or investigators may explain what is going on in the trial, in particular any recruitment or logistical issues.

Assuring Quality

2.31 As a separate area, a great deal of attention is paid to quality, and this will include what are called "excipients". For example, with any drug such as aspirin, the tablet that is taken is not simply aspirin but has other constituents to enable the aspirin (the "active ingredient") to remain in tablet form, to dissolve and release the aspirin during the digestive process. For aspirin these components of the tablet are typically starch, saccharin, lactose, citric acid, calcium carbonate and other things to ensure the taste is acceptable. For vaccines the excipients may be much more complex, even though the total volume of the vaccine that is injected may be quite small. In relation to vaccines, as biological products (rather than chemical products), there are complex requirements in the full checks that are done before a vaccine is authorised. In addition, each batch of vaccine is tested to ensure it meets the quality standards. In the UK, the MHRA's laboratories (formerly the National Institute for Biological Standards and Control (NIBSC)), are responsible for testing of vaccines and are recognised as the world leader in this field.[17]

2.32 Very occasionally there is a problem with a particular batch of a vaccine, for example, when impurities cause increased risks of fever or the vaccine dose is too low and there is a lack of efficacy. Most of these issues are detected by the manufacturer or regulatory authority so the batch is not released. Historically (from the 1950s and 1960s) there were definite batch problems, but lessons learnt have resulted in more careful checks. Batch problems can also occur after manufacturing during transport, storage and final delivery, especially with vaccines that need to be kept cold.

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[16] Evans S, Pocock S. Societal responsibilities of clinical trial sponsors. Lack of commercial pay off is not a legitimate reason for stopping a trial. BMJ. 2001;322:569-70. doi.org/10.1136/bmj.322.7286.569

[17] NIBSC (no date) *International standards*. Available at: https://nibsc.org/standardisation/international_standards.aspx (Accessed: 11 December 2024).

Regulatory aspects of the process

2.33 All countries have laws in place for regulating the marketing of medicines (both drugs and vaccines). In most countries including the UK, these laws apply to the marketing and supply of medicines and have a direct impact on the pharmaceutical industry. These laws do not, in the UK, directly regulate health professionals who have clinical freedom to prescribe medicines according to their view of what is in their particular patient's interests. The Bolam test is used to determine if a doctor's action would be classed as negligent: *"If a doctor reaches the standard of a responsible body of medical opinion, he is not negligent"*. It is the case that if a doctor follows the instructions for a medicine that is laid down by the regulatory authority, then this would be regarded as a *prima facie* defence against any claim for negligence, as it would meet the Bolam test. Not following those instructions is not necessarily negligent, but a doctor would have to show there was a responsible body or weight of medical opinion that agreed with the action of the doctor.

2.34 Sometimes, especially in paediatrics, there are no instructions regarding the use of a medicine. This is usually because the randomised trials (see paragraph 2.5) have not been carried out in children. However, the clinical need of a child will often mean that a medicine is prescribed outside the terms of its licence. Guidance on this is sometimes provided by doctors' professional bodies and bodies such as NICE.[18]

2.35 The regulatory authority in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA)[19] (until 2003 the Medicines Control Agency, MCA). The MHRA is responsible for regulating the marketing of medicines (drugs and vaccines) and, from 2003, medical devices. They are effectively part of the Department of Health and part of the Civil Service. They act as the Executive Arm of the Licensing Authority. It is seen as important that the legal decision-making responsibility is with Ministers of the Crown who form the Licensing Authority in law, but in almost all instances, Ministers will follow the advice from the MHRA, and in many instances before the pandemic, the decisions were delegated to the MHRA entirely.

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[18] NICE (2024) *British National Formulary for Children (BNFC)*. Available at: https://www.nice.org.uk/bnfc-uk-only (Accessed: 11 December 2024).
[19] MHRA (2023) *More information about the MHRA, GOV.UK*. Available at: https://www.gov.uk/government/publications/more-information-about-the-mhra/more-information-about-the-mhra--2 (Accessed: 11 December 2024).

2.36 Usually, the data on all studies from laboratory to phase 3 clinical trials are submitted to the MHRA (with a large fee from the pharmaceutical company developing the medicine to cover the cost of assessment). This happens when all studies have been completed and there is good evidence for efficacy, generally based on two major phase 3 trials, and no major safety issues.

2.37 The MHRA has many good scientists, pharmacists, medical doctors and statisticians within its staff of over 1,200 full-time equivalent employees,[20] but inevitably they will not have the leading experts in every area. The MHRA utilises standing advisory committees and will call on experts in very specialised areas when required. The MHRA staff write assessment reports on applications made by companies or on safety issues that may affect multiple companies, which are then considered carefully by the relevant advisory committees. The MHRA will also raise questions with relevant scientists etc. within companies, while conducting assessments.

2.38 The different parts of a particular submission will be assessed by MHRA scientists with good knowledge of a field such as lab studies or clinical trials. They also tend to have specialised knowledge within clinical fields such as cancer or infectious disease. The MHRA relies heavily on advice from committees of experts, almost always from academia. The most important is the Commission on Human Medicines (CHM), which, prior to 2005, was the Committee on Safety of Medicines (CSM).[21] Technically the CHM is there to advise the licensing authority, but it is the MHRA that conveys that advice to Ministers. The CHM generally operates by discussing the reports written by MHRA staff, which usually end with a series of questions to be answered by the Advisory Committee members, most often by consensus but sometimes with a vote.

2.39 Companies who have applications for an authorisation turned down have rights of appeal to have their application re-examined.

2.40 In addition to the CHM, there are about ten standing sub-committees called Expert Working Groups (EWGs)[22] which give advice to the CHM. Notable among these are the Clinical Trials, Biologicals and Vaccines EWG and Pharmacovigilance EWG

[20] MHRA statement INQ000474337_0009
[21] Prior to 2005 there was another body, the Medicines Commission which met less frequently and dealt with, among other things, appeals by companies against decisions taken based on CSM advice. This was merged with CSM to form CHM.
[22] Commission on Human Medicines (no date) *Membership*, *GOV.UK*. Available at: https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership (Accessed: 11 December 2024).

(post-marketing surveillance). In April 2020 a specific EWG for Covid-19 vaccines was set up, and there have been additional Working Groups on Covid-19 issues. Each of the sub-committees and Working Groups operate in the same way as the CHM, with a smaller membership than the CHM itself. The issue to be discussed will have an assessment report (AR) written by an MHRA staff member, sometimes in consultation with members of the CHM or its expert groups, but the CHM or sub-committee members will have read these before meetings and will discuss and may disagree with the AR. The MHRA employees as author(s) of the AR will be present at the relevant meetings, will present their report but do not have any voting rights and will usually not contribute to the discussion except for clarification or when the Chair asks them to contribute. For CHM meetings, which can take place on multiple days in a month, there may be many issues, each with an AR and questions to be decided. CHM has experts within specialties such as lab studies, cardiology, infectious disease and clinical trial methodology.

2.41 In most regulatory agencies, and for a long period at the MHRA, assessments were generally done by different people for pre-marketing and post-marketing aspects. In some senses this is a sensible split, since expertise in randomised trials and their analysis is different from epidemiological and pharmacovigilance expertise. The latter is usually the term used when considering spontaneous reports, but pharmacovigilance will require attention to randomised trials, epidemiology (non-randomised - NRSI - or observational studies: see below, paragraphs 4.15 to 4.16 for further explanation of NRSI) as well as to spontaneous reports. However there have been reorganisations (after 2002 when I left the MCA) that led to both pre- and post-marketing assessments being done within teams divided by clinical specialty. However, the current organisation has reverted to the more usual split between pre- and post-marketing issues.

2.42 Regulators and their advisory committees will appraise all types of new data that accrue. Companies are legally required to inform regulators of new data regarding their product. They may also be required by regulators to actively carry out studies to look for harms in general and to evaluate particular known or suspected harms. Regulators will occasionally carry out or commission research on particular safety issues.

2.43 A key aspect in terms of safety is the agreement with the company about the Summary of Product Characteristics (SPC or SmPC).

2.44 The SmPC is a legal document which is the responsibility of the pharmaceutical company. Its contents and wording are in a standard format and must be approved by a regulator as part of the authorisation process. The SmPC sets out what the product is used for, the conditions under which it should be used (including any groups who should not use it) and lists the "undesirable effects".

2.45 These undesirable effects, which could also be called adverse reactions, are those that are known at the time of authorisation but are regularly added to as experience accrues with the product. Much of the regulatory activity post-authorisation is directed at updating the SmPC and advisory committees may be asked for their opinion in some instances, but most activity is done in negotiation between the company and the regulator.

2.46 The EU guidance[23] states, in relation to "undesirable effects":

> "*This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC.*"

2.47 In my experience, terms for adverse reactions are added to the SmPC too readily. I have found the emphasis to be on how often the adverse events occur during treatment rather than emphasising differences from a control. I suspect that companies are often prepared to include things for which evidence is weak, but uncertain, so that if later studies strengthen the evidence, they will not be involved in litigation.

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[23] European Commission (2008) *A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC).* Available at: https://health.ec.europa.eu/document/download/6a043dea-7d0f-4252-947b-cef58f53d37e_en (Accessed: 11 December 2024).

2.48 The SmPC is targeted in its language at health professionals, and there is a "Patient Information Leaflet" (PIL) targeted at patients. Efforts are made to ensure that this is comprehensible to a lay person and the MHRA has commissioned research to improve the PIL, e.g. by Dolk S et al[24]. The UK published guidance to encourage companies to do this.[25] It is an absolute requirement that the PIL gives the same information as the SmPC. There is some evidence that many patients when first using a medicine do read the PIL[26] but there is considerable variation in the quality of PILs. The language used in PILs conforms to regulatory guidance, but words like "common" (1 to 10%) or "very common" (over 10%) have a very different understanding in the minds of patients[27]. The large number of side effects in these leaflets can lead to anxiety for patients. These long lists are necessary, despite the significant uncertainty, but they could likely be improved. Clarification of the meaning of words, and emphasis on excess risk when taking a medicine would help - many of the listed side effects would occur anyway at a background rate in the general population, i.e. those not taking the medicine. One study[28] found that nearly 20% never read the PIL and "Over half the respondents (56.0 %) never sought more information about possible side effects of medicines."

2.49 Different regulators have varying amounts of transparency around their decision-making on authorisation of medicines. The US FDA has the greatest transparency with assessment reports published on the web, and key meetings of advisory committees held in public and, recently, live-streamed. The European Medicines Agency (EMA) and the UK MHRA do not generally hold their advisory meetings in public, though they both involve the public on occasions on limited topics. They each produce a public version of their final assessment report, with, in my experience, most detail in the FDA and more in the EMA than the MHRA documents. There are arguments for not always having meetings in public so that experts can give their opinions without anxiety of press interference, but clearly there are also points in favour of greater transparency.

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[24] Dolk, S. *et al.* (2011) 'Headline section in patient information leaflets: Does it improve reading performance and perception?', *Information Design Journal*, 19(1), pp. 46–57. Available at: https://doi.org/10.1075/idj.19.1.05len.
[25] MHRA (2020) *Best practice guidance on patient information leaflets*, *GOV.UK*. Available at: https://www.gov.uk/government/publications/best-practice-guidance-on-patient-information-leaflets (Accessed: 11 December 2024).
[26] D K Raynor et al, How do patients use medicine information leaflets in the UK?, *International Journal of Pharmacy Practice*, 15:2007;209–218
[27] Webster RK et al. How does the side-effect information in patient information leaflets influence peoples' side-effect expectations? A cross-sectional national survey of 18- to 65-year-olds in England. *Health Expect*. 2017; 20: 1411–1420.
[28] Krska J & Morecroft CW. Patients' Use of Information about Medicine Side Effects in Relation to Experiences of Suspected Adverse Drug Reactions: A Cross-Sectional Survey in Medical In-Patients. *Drug Saf* **36**, 673–680 (2013)

2.50 It should be noted that the European system of regulation was in force in the UK until 1st January 2021. This is not a European version of the US system though they have many similarities, and the EMA is not a European version of the FDA. The FDA acts for the whole of the US and individual states have no role as states in the Federal decision making or assessment process. In the European Union (EU) the EMA acts as a co-ordinating centre, but it is the member states who do the assessment work (for which they receive fees) and the states are represented at the voting committees for pre- and post-marketing issues. The "centralised" system of regulation means that decisions are binding on all member states though the assessment process is done by two member states ("Rapporteur" and "Co-Rapporteur") using their own staff and scientific experts. There will be discussion with the EMA's own staff and sometimes review by one of the expert committees at the EMA such as the Vaccine Working Party. The other member states then vote on the issues raised and usually (but by no means always) these votes accord with the Rapporteur's advice, especially if the Co-Rapporteur is in agreement. Prior to the UK's vote to exit from the EU, the UK did a disproportionate amount of the assessment work (and hence received large amounts in fees). Following the UK's vote to leave the EU, the existing workload of the UK as Rapporteur or Co-Rapporteur was planned to be transferred to other EU member states before the UK left the EU. This transfer was noted to be largely complete by April 2018.[29] After 2018, the UK was no longer given new products to assess as Rapporteur or Co-Rapporteur.

2.51 As part of the EU system, there is provision in the EU legislation for decisions to allow supply of a product to be taken independently by a member state in a public health emergency. They also have accelerated or conditional approval mechanisms for innovative medicines.

Regulation of Clinical Trials

[29] European Medicines Agency (2024) *Annual reports and work programmes | 2018*. Available at: https://www.ema.europa.eu/en/about-us/annual-reports-work-programmes (Accessed: 11 December 2024).

2.52 For many years prior to 2003, the UK regulators have been responsible for approving the design of trials and monitoring the conduct of clinical trials when they were intended to support an application for a licence. In 2001 the EU set out a Clinical Trials Directive that gave guidelines for all clinical trials of medicines. This EU Directive was enacted in UK law by the "UK Medicines for Human Use (Clinical Trials) Regulations" which became effective in 2004. The newer UK laws applied to all interventional trials of medicines so applied to academic- as well as industry-sponsored trials. Prior to that time there were some laws that affected clinical trials under the Medicines Act of 1968.

2.53 The Directive of 2001 was implemented in rather different ways in the EU member states and in 2014 the EU Clinical Trial Regulation 536/2014 (EU-CTR) was agreed. An EU Regulation, in contrast to a Directive, is itself law and results in harmonised laws across the EU. This EU regulation only came into force in 2022, after the UK had left the EU, so that Regulation does not apply in the UK and the 2004 UK Regulations are in force, though they have had some amendments since 2004. In addition, the Human Medicines Regulations 2012 had incorporated EU regulations up to that point and was the law prior to exiting the EU. This was important in relation to the early Covid-19 vaccines.

2.54 A key principle set out in the 2012 Regulations, which reflects the remarks above about the function of the Regulations in general, is enshrined in Regulation 46, which states: "A person may not sell or supply, or offer to sell or supply, an unauthorised medicinal product." The 2012 Regulations were amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 and the Human Medicines (Amendment etc.) (EU Exit) Regulations 2020.

2.55 The major effect of all these laws was that interventional clinical trials, whether conducted by industry, the NHS or academia, became subject to more scrutiny by the UK regulatory authority, the MHRA. It also resulted in a unified requirement for ethics committee scrutiny prior to commencement of a trial. The 2001 EU Directive had not only resulted in a variety of implementations across different states but had increased the level of bureaucracy in starting trials. This was seen by many as disproportionate for some trials that were of very low risk to participants. This concern was addressed in the 2014 EU-CTR by allowing for different categories of risk, so trials being conducted with already licensed medicines had reduced requirements.

2.56 All these laws also had a clear system for the reporting of adverse events (not necessarily believed to be caused by the intervention) that occurred in trials. Prior to the trial starting there will be a set of adverse events that can be anticipated to occur, and which would not be unexpected. When the trial participants have a disease that is being treated, then there will be adverse events that are caused by that disease and so would be expected. If the product in the trial has a known adverse reaction profile, then again there will be some such reactions that will be expected, and these will be described in the trial protocol and listed in the patient consent form. Other adverse events would then be "unexpected", and any such that are serious will not only be considered carefully by the investigators and the trial sponsor, but they also must be reported to the relevant regulatory authority.

2.57 "Serious" Adverse Reactions (SARs) have a global regulatory definition: "An adverse reaction that is associated with death, inpatient hospitalization, prolongation of hospitalisation, or persistent significant disability or incapacity, or otherwise life-threatening".[30] Clinicians may regard "serious" as encompassing more than this definition. With a new vaccine for a healthy population there will be no expected serious adverse events so every such event will be unexpected.

2.58 During a trial, when a serious unexpected adverse event occurs, the investigators decide whether it is a suspected adverse reaction, i.e. it could be caused by the product. Such a suspected reaction is called a "SUSAR" ("Suspected Unexpected Serious Adverse Reaction"[31]). When a SUSAR occurs in a trial there is a requirement to report to regulators and the sponsor (usually the company making the relevant product). Depending on the nature of the SUSAR, trial recruitment may be paused while an investigation takes place. This investigation may be conducted by a Data and Safety Monitoring Board or a regulator like the MHRA but will involve close communication with the regulator and sponsor of the trial. It will usually also include specialists in the clinical area of the adverse event, and such an independent group of clinicians may carry out the entire investigation. Even if their judgement is that the event is a reaction, caused by the product under trial, they may recommend restarting trial recruitment with all trial sites being informed and asked to increase surveillance for that event. In some instances, if particular characteristics which are risk factors for the event are known and can be easily identified, then the trial design may be modified to

[30] https://cioms.ch/wp-content/uploads/2017/07/Int-Reporting-Adv-Drug-Reactions-1987.pdf
[31] SUSAR- the word ordering is now set in global regulation but is illogical and should have been "Serious Unexpected Suspected Adverse Reaction" in that it is the adverse reaction (not the unexpectedness) that is "suspected"- to be caused by the product.

exclude recruitment of participants with those risk factors. Usually these procedures are set out, at least in outline, in the study protocol.

The role of the National Institute for Health and Care Excellence (NICE) and the Joint Committee on Vaccination and Immunisation (JCVI)

2.59 The MHRA and other regulators in most countries do not make decisions based on cost, and they do not advise on whether a product that can be licensed should actually be used in the NHS (or equivalent healthcare systems). For medicines in general the consideration of cost-effectiveness is the role of the National Institute for Health and Care Excellence (NICE) in England and Wales, though the devolved administration in Northern Ireland accepts NICE guidelines. Scotland has its own bodies (Scottish Intercollegiate Guidelines Network (SIGN) and the Scottish Medicines Consortium (SMC)) to provide similar advice and are generally aligned with NICE but neither these nor NICE are regulatory authorities, but are usually described as providing "Health Technology Assessment" (HTA). Organisations carrying out HTA take costs and usage into account when they provide national guidance and advice to improve health and social care, including several matters outside the use of medicines. As noted above they contribute to guidance for use of medicines in children where the evidence used by regulators is lacking. In England and Wales, NICE has not played a major role for individual vaccines, though they have examined vaccine uptake as a whole. They do not go into detailed recommendations as to which vaccines should be used and this is the role of the Joint Committee on Vaccination and Immunisation (JCVI) which provides advice to all UK Governments (while the JCVI has no statutory basis for providing advice to Ministers in Scotland or Northern Ireland, its terms of reference, "as defined in legislation", state "The Committee may also provide advice to Scottish and Northern Irish ministers" This is an expert scientific advisory committee like the CHM, but has a different role, not related to regulatory functions but focussed on what vaccines should be used in the UK and immunisation issues in general. The JCVI does take costs into account when giving its advice. Again, decisions are formally made by ministers responsible for health in the different countries in the UK, but they rarely ignore JCVI advice. They are an advisory body to the health departments and are not involved directly in routine surveillance of vaccines, though they do take any new knowledge on efficacy and safety into account and may change their advice on usage based on such information.

3. Was regulatory authorisation of Covid-19 vaccines different?

Legal processes

3.1 In respect of the first Covid-19 vaccines authorised for use in the UK, the MHRA did not take its usual role of delegated decision-making. Instead, the formal legal role of the Licensing Authority reverted to various ministers reporting to the Secretary of State for Health.[32]

3.2 The UK was not authorising any new products itself under the EU Brexit Withdrawal agreement, but under EU law as implemented in UK law a provision for temporary supply in a health emergency could be made.

3.3 It should be noted that the MHRA did not issue a Marketing Authorisation (MA) for the Covid vaccines initially. The first authorisation granted was for the Pfizer/BioNTech vaccine and this was for "Temporary Supply" under Regulation 174 of the Human Medicines Regulations 2012 (see below). The MHRA could not issue an MA under the EU law existing as at December 2020, but shortly afterwards the EMA did issue an MA for the Pfizer/BioNTech vaccine. Similarly, the Oxford/AstraZeneca and Moderna vaccines were granted "Temporary Supply" authorisation which were followed by EMA CMAs.

3.4 The basic principles of assuring efficacy, safety and quality as set out above were the same for authorisations of medicines (including vaccines) during the pandemic. A very clear illustration of the process, which is similar in all the major regulatory agencies, is provided in the US FDA documents and transcripts of their Advisory Committee. Appendix 2 illustrates this process. A simpler and very clear description of the process used at the EMA is also available.[33] As the UK was still operating under the EU system at the time of initiation of trials for Covid-19 vaccines (because of Brexit), they did not issue guidelines for vaccine efficacy etc. in the way that the FDA and EMA did, but accepted the EMA guidelines.[34] During the Covid-19 pandemic the UK continued to

[32] MHRA statement INQ000474337 paragraph 35

[33] https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/coronavirus-disease-covid-19/covid-19-public-health-emergency-international-concern-2020-23/covid-19-vaccines-development-evaluation-approval-and-monitoring

[34] MHRA statement INQ000474337 paragraph 129

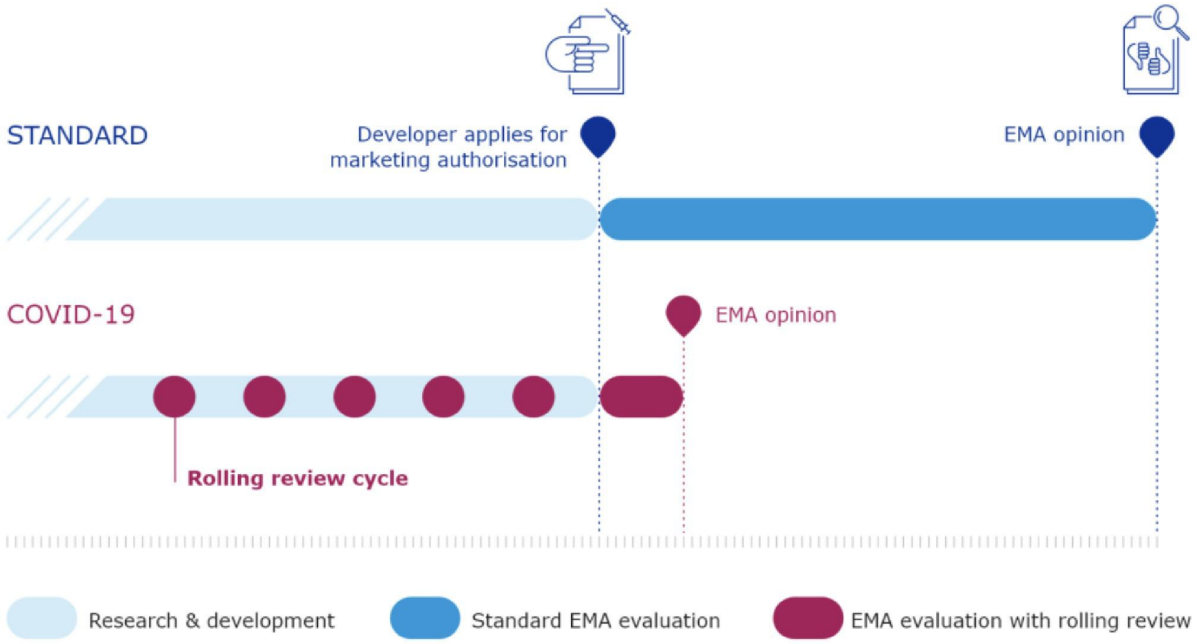
participate in the International Coalition of Medicines Regulatory Authorities (ICMRA) and other international activities as it had done since about 2012 when the ICMRA was established.

3.5 The key operational process used with assessment of the Covid-19 vaccines that led to a reduced time to obtain approval was a "Rolling Review", where data from the initial lab and clinical studies were submitted to regulators who assessed them as soon as they became available, rather than waiting for the full trial programme to be completed. This enabled the usual scrutiny of, say, the preclinical studies to be done well before the phase 3 trials were assessed. I emphasise that there was no reduction in the clinical studies, or in the scrutiny by the MHRA. It was simply that the "rolling" production of information and data to the MHRA meant that it could carry out its scrutiny in a more efficient manner, without having to wait until it had received the totality of all the data before commencing its review. Furthermore, this "Rolling Review" was used by the MHRA, the EMA and the US FDA. In addition, efforts were made to expedite the approval of trials and assist their execution. [35] The dramatically increased frequency of meetings of the advisory committees and working groups also made a notable contribution to a speeding up of the process. The scrutiny was intensive, with many academics giving of their time unstintingly, aware of the needs of the public.

3.6 The process, which was applied in the UK, is illustrated in an analogous diagram from the EMA website.[36]

[35] MHRA statement INQ000474337 paragraphs 139-141

[36] https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/coronavirus-disease-covid-19/covid-19-public-health-emergency-international-concern-2020-23/covid-19-vaccines-development-evaluation-approval-and-monitoring#related-documents-19306



3.7 The area in dark blue shows the usual process happening which does not start until the complete dossier on the product is submitted after all trials are complete. The total area in red indicates that all the assessments take place but start at an early stage, so that when the final trials are submitted, the earlier assessment is already complete and the time from final trial report to authorisation is reduced.

3.8 Even prior to the pandemic there were avenues to allow for more rapid authorisation when new innovative treatments became available, especially when no existing treatment existed. These would usually be given as "provisional authorisations" or "emergency use authorisations", where a single pivotal phase 3 trial, rather than two independent trials, would be accepted. In such cases, requirements for post-marketing surveillance were more stringent. In the US, the "Fast Track" process[37] was used before the pandemic and the possibility of rolling review was allowed as part of this process.

3.9 This pre-existing provision was in Regulation 174 of the 2012 UK Regulations which mirrored EU regulations and was used by the MHRA in authorising Covid-19 vaccines, as explained above.

[37] Office of the Commissioner (2023) *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, FDA*. Available at: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review (Accessed: 11 December 2024).

3.10 Regulation 174 states:

> *"The prohibitions in regulation 46 (requirement for authorisation) do not apply where the sale or supply of a medicinal product is authorised by the licensing authority on a temporary basis in response to the suspected or confirmed spread of—*
>
> *(a)pathogenic agents;*
>
> *(b)toxins;*
>
> *(c)chemical agents; or*
>
> *(d)nuclear radiation,*
>
> *which may cause harm to human beings."*

3.11 Hungary used the same procedure to authorise a Russian vaccine, which was again just for temporary use in Hungary and not for the EU more generally[38]. They may also have used the same procedure to authorise temporary supply of the AstraZeneca vaccine before the EMA approved it.[39]

3.12 The MHRA in its notice relating to the Temporary Supply of the Pfizer/BioNTech vaccine said:

> *Whilst an acceptable level of information has been received to provide assurance that appropriate standards of quality, safety and efficacy have been met for authorisation of specific batches for temporary supply under Regulation 174 of the Regulations, it should be noted that COVID-19 mRNA Vaccine BNT162b2 remains under review as MHRA continues to receive data from the company as it becomes available. This will include, for example, long-term follow-up efficacy and safety data. Further information that is received by the MHRA will be reviewed as part of the*

[38] Reuters (2021) 'Hungarian drug regulator approves Sputnik V vaccine', 20 January. Available at: https://www.reuters.com/business/healthcare-pharmaceuticals/hungarian-drug-regulator-approves-sputnik-v-vaccine-website-2021-01-20/ (Accessed: 11 December 2024).
[39] BBC News (2021) 'Coronavirus: Hungary first in EU to approve Russian vaccine', 21 January. Available at: https://www.bbc.com/news/world-europe-55747623 (Accessed: 11 December 2024).

ongoing assessment for this product and updates will be made to this PAR to reflect that in due course.

3.13 As noted above, the UK's exit from the EU meant that for over a year, by the end of 2020, the UK MHRA was not doing any assessment work for the EMA and was not yet doing assessments for new products that would usually be licensed centrally in the EU, for the UK itself. The EMA still had responsibility for assessing and authorising all "Centrally Authorised" products which includes all biological products and consequently all vaccines. The UK had to accept the EU decisions until the end of 2020 unless they were invoking an emergency procedure as outlined above. During the time when assessment of vaccines was happening in the UK it was clear that the MHRA staff, free from their usual EU workload, were working extraordinarily hard on the vaccines assessment. Their response times to interactions with companies was measured in minutes or hours rather than days.[40] The scrutiny was intense and although quicker than in normal times, was no less careful. The interaction with advisory committees was also very much more frequent as were the meetings of the advisory bodies.

Trials

3.14 The MHRA made major efforts to facilitate the approval and execution of clinical trials by devoting extra resources to the appraisal

3.15 The randomised trials for the Covid vaccines were conducted in many countries and many regulatory authorities were involved. For example, the Oxford/AstraZeneca vaccine had 20 trial sites in the UK,[41] as well as those in South Africa and Brazil.

3.16 In the report of these Oxford/AZ trials in the Lancet[42] the authors state: *"There were 175 [adverse] events (84 in the ChAdOx1 nCoV-19 group and 91 in the control group), three of which were considered possibly related to either the experimental or a control vaccine."* They go on to say *"Three cases of transverse myelitis were initially reported as suspected unexpected serious adverse reactions, with two in the ChAdOx1 nCoV-19 vaccine study arm, triggering a study pause for careful review in each case.*

[40] MHRA statement INQ000474337 paragraph 804
[41] The trial registration site, clinicaltrials.gov, for trial COV002 lists them at https://clinicaltrials.gov/study/NCT04400838#contacts-and-locations
[42] Voysey M, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111.

Independent clinical review of these cases has indicated that one in the experimental group and one in the control group are unlikely to be related to study interventions, but a relationship remained possible in the third case."

3.17 This was an example of pausing trial recruitment while review of SUSARs occurred. The participant had received a first dose and then some 10 weeks or so later, a booster dose. 14 days after receiving the booster they had symptoms described as transverse myelitis. The system of trial monitoring worked extremely well, with rapid reporting of the adverse event to the trial investigators and regulators. The pausing of recruitment showed a cautious approach, illustrating that the safety of trial participants is paramount. The fact that a similar event occurred in the control group shows that such events can occur without their being caused by the new vaccine under trial, but taking a cautious approach is sensible. The further monitoring did not show any increase in risk during the trial (see paragraphs 5.73 - 5.83 of Professor Prieto-Alhambra's report INQ000474703 for a full description of the pre- and post-authorisation evidence about transverse myelitis as a potential side effect).

Preparation for monitoring

3.18 In preparation for the anticipated authorisation of Covid-19 vaccines the MHRA and CHM set up an Expert Working Group to plan for surveillance of the vaccines. This met four times between May and October 2020, but it did not publish the report until after the first vaccines were being used in early February 2021 - Report of the Commission on Human Medicines Expert Working Group on COVID-19 vaccine safety surveillance (JR/51 INQ000274036). This will be discussed further below.

3.19 In summary, the authorisation process in the UK was appropriate to the circumstances and was based on a great deal of data. The fact that other countries also authorised the vaccine at about the same time suggests the assessment was up to standard. I know of nothing that the UK missed in comparison with other countries at that time.

4. The usual systems and processes for post-marketing surveillance of medicines

Spontaneous reports/Yellow Cards

4.1 For all medicines, spontaneous reporting of suspected adverse reactions to medicines has been encouraged since the 1960s, arising from the thalidomide tragedy. It will also include regular scrutiny of the spontaneous reports (called "yellow cards" in the UK).

4.2 Since the 2000s Spontaneous Reports (SRs) from patients have been accepted and encouraged, while prior to that time they were only accepted from health professionals and coroners. In the UK all reports originating in the UK from whatever source are included in the SR database. It is the responsibility of pharmaceutical companies to submit reports arising in other countries to the MHRA. They then form part of the same database, but their origin is noted. In 2019 the MHRA received 43,776 Yellow Card reports and in 2020 it received 40,764.[43]

4.3 The first source of information about possible new safety issues is usually the SRs, and since the mid 1990s, the scrutiny of them has included some statistical triage to focus on those reports which are observed more than might be expected, given the total number of reports for that product and that adverse event term. Since the 1980s, most regulators have had large databases of SRs which they were able to interrogate and use to produce reports for clinical assessors and advisory committees. The databases enabled scanning of every possible adverse event with every drug, producing an indication of how disproportionate the reporting was for each term. Those combinations of a drug with an adverse event with sufficiently high values of the observed count compared with what is expected are called "signals of disproportionality".[44] A possible new adverse reaction is called a "signal",[45] and it will not be accepted as being caused by the medicine without detailed scrutiny. A disproportionate count is not enough.

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[43] MHRA (2021) *Freedom of Information request on the number of cases reported to the Yellow Card Scheme in 2019 and 2020 (FOI 21-533)*, *GOV.UK*. Available at: https://www.gov.uk/government/publications/freedom-of-information-responses-from-the-mhra-week-commencing-14-june-2021/freedom-of-information-request-on-the-number-of-cases-reported-to-the-yellow-card-scheme-in-2019-and-2020-foi-21-533 (Accessed: 11 December 2024).

[44] Evans, SJW. Pharmacovigilance: a science or fielding emergencies? Statist. Med. 2000; 19:3199-209.

[45] https://who-umc.org/signal-work/what-is-a-signal/

4.4 The major global databases of SRs are at the FDA, the EMA and at the Uppsala Monitoring Centre (UMC) which began as a part of the WHO in Geneva but is now independently funded and a WHO Collaborating Centre.[46] UMC collects SRs from national regulators, so there is inevitably a delay in their reports with some countries submitting within a month or so, but others several months or years behind. This delay is sometimes for technical reasons but is usually because it is not a priority for the country's own resources.

4.5 UMC is a particularly useful source for data from low and middle-income countries and they help such countries with resources for data collection, analysis and training. UMC does their own signal detection and produces reports both for industry and national regulators. They have made advances in signal detection and evaluation.

4.6 Databases of spontaneous reports are a biased set of observations about medicines and medical events. They are a very weak source of scientific evidence on causal effects of medicines. They can be like the warning light on a car dashboard, which might indicate a real problem with the vehicle, but may also be a fault in the warning system. The suspicion that a medicine caused an adverse event may be incorrect, and a majority of such reports are either about a well-known problem or are simply coincidental. The real value of SRs is in alerting regulators to a new problem which can then prompt further, targeted investigation.

4.7 More extensive data that are less biased have *all* observations on medicines and medical events. Analysing such data carefully is the field of pharmacoepidemiology. Formal studies using such data, often based on electronic records of data collected for the purposes of clinical care, are called "observational studies", in contrast to randomised trials where medicines are given in controlled conditions and treatments are allocated randomly so that valid comparisons can be made and the influence of other factors that might be systematically different between the groups (known as "confounding factors") can be eliminated. Further discussion of these appears at paragraph 4.15 below.

Signal detection

[46] Uppsala Monitoring Centre (no date) *About Uppsala Monitoring Centre*. Available at: https://who-umc.org/about-uppsala-monitoring-centre/ (Accessed: 11 December 2024).

4.8 The MHRA uses sophisticated software applied to their database of SRs to provide reports enabling signal detection and evaluation processes to be carried out, and it has developed from the first suggestions made in the mid-1990s.[47] The current software is based on Bayesian statistical methods to produce signals of disproportionality, that is to say, where there are more reports than might be expected given the total number of reports for that product and the total number of reports for a particular adverse event. In the US the databases for drugs (Adverse Event Reporting System - AERS) are separate from those for vaccines (Vaccine Adverse Event Reporting System - VAERS). It may be noted that the US system seems to collect "events", while most worldwide regulators collect "suspected adverse reactions". These latter systems use the reporter's suspicion rather than simply recording that an event has happened. In practice, looking at reporting rates worldwide, this distinction does not seem to make any major difference.

4.9 When a "signal" of a possible new adverse reaction is detected within the MHRA, an assessor responsible for that product, and similar ones, will review the cases and make a report at an internal meeting. In many instances the relevant pharmaceutical company will also have had similar data and they and the MHRA will also review international data. In most instances, if the signal is confirmed, then it will be added to the SmPC. Sometimes the signal is found first by the company (especially if the major use of the product is from outside the UK), then it will inform the MHRA and if they agree, the SmPC will be amended.

4.10 If the company does not agree to the SmPC being updated there will be discussion and possibly meetings, and in serious cases, advice from an advisory committee may be sought. The regulator will have the final say, but the company can appeal. Companies rarely go to court beyond the MHRA appeal process. Occasionally an epidemiological study will be conducted by the regulator or required by the regulator to be carried out by the company when there is doubt as to whether an effect is causal.

Signals from other sources

[47] Evans SJ et al. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10:483-6. For a review, see Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 2009; 18: 427-3

4.11 Some signals can arise from epidemiological studies, also called non-randomised studies of interventions (NRSI), perhaps most famously with the 3rd generation oral contraceptives causing a higher than usual rate of blood clots (venous thromboembolism). Three independent studies had been done, though none was yet published, but they were all submitted pre-publication to the MCA (now MHRA). Extremely careful review was done, and the advice of the Committee on Safety of Medicines (CSM) was sought.

4.12 Sometimes pharmaceutical companies are required to carry out NRSI as part of the agreement to authorise a medicine and the regulator will review these studies. Since electronic health record databases have been used for analysis, starting in the late 1980s, the use of such studies has increased enormously. The EMA, through a nominally independent group, the European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP),[48] has set standards for these studies. It has been largely controlled by the EMA and has commercial groups as well as academics involved. Many of the commercial groups are from "Contract Research Organisations" (CROs) which have been set up to carry out research for the pharmaceutical industry. These include randomised and non-randomised studies. Much of the epidemiological work on drugs, and some on vaccines, is carried out by these organisations, some of which are "not-for-profit" and value their independence.

4.13 A notable source of signals is also published literature reports, and while pharmaceutical companies are required to evaluate these and report to regulators on at least an annual basis, regulators will also scan publications of case reports for new signals when resources permit.

Evaluation of signals and observational studies

4.14 The MHRA have developed prioritisation for signals according to their impact on public health.[49] [50] [51] In most instances careful work around the totality of evidence available at the time results in a decision to include or not include changes to the product information. These changes may be warnings, restrictions on use or contraindications.

[48] European Union (2024) *ENCePP - European Network of Centres for Pharmacoepidemiology and Pharmacovigilance*. Available at: https://encepp.europa.eu/index_en (Accessed: 11 December 2024).
[49] Waller P et al. Impact Analysis of Signals Detected from Spontaneous Adverse Drug Reaction Reporting Data. Drug-Safety 28, 843–850 (2005)
[50] Heeley E et al. Testing and Implementing Signal Impact Analysis in a Regulatory Setting. Drug-Safety 28, 901–906 (2005)
[51] Seabroke S et al. Development of a novel regulatory pharmacovigilance prioritisation system: an evaluation of its performance at the UK Medicines and Healthcare products Regulatory Agency. Drug Saf. 2013;36:1025-32.

In the extreme they lead to suspension (temporary) or withdrawal (permanent) of a product. The latter will usually only occur when an alternative product for the same indication is available.

4.15 With Electronic Health Records (EHRs) becoming available for analysis since the 1980s, observational studies have been increasingly used for surveillance. These "observational" or "epidemiological[52]" studies rely on what has been recorded as occurring in clinical practice with no attempt to carry out a "trial" of any intervention. It is simply "observing" what has taken place. They are to be contrasted with randomised trials where treatments are decided by a random process that ensures comparability of the groups who receive, and those who do not receive, the treatment under trial. It is better to refer to them as "Non-randomised Studies of Interventions" (NRSI).[53] A buzz-word for them that has become commonly used is "Real World Studies" or "Real-World Evidence".[54] The implicit contrast with randomised trials suggests that RCTs are conducted in some unreal world, but the meaning is obvious. RCTs are carried out in clinical practice, but they exist on a spectrum from those that have highly selected participants included with extremely careful monitoring such as frequent blood tests (explanatory trials) to those that are much closer to ordinary clinical practice (pragmatic trials).[55]

4.16 With NRSI the lack of randomisation means that the treated and comparison (control) groups may differ in many ways, some unmeasured or unrecorded, which makes interpretation challenging at best and impossible at worst. It is the task of epidemiologists and statisticians who work in this field to try and design and conduct studies that minimise bias and attempt to suggest when effects are genuinely caused by the intervention of interest.

4.17 Regulators may require such studies to be planned at the time of authorisation or conducted in response to concerns raised by signals. They are likely to be funded by industry, though they are usually carried out by academics or contract research

[52] Some use "observational epidemiological studies", as opposed to "experimental epidemiology studies"
[53] Reeves, B.C., Deeks, J.J. and Cochrane Non-Randomized Studies of Interventions Methods Group (2024) 'Chapter 24: Including non-randomized studies on intervention effects', in *Cochrane Handbook for Systematic Reviews of Interventions*. 6.5. Available at: https://training.cochrane.org/handbook/current/chapter-24 (Accessed: 11 December 2024).
[54] European Medicines Agency (2023) *Use of real-world evidence in regulatory decision making – EMA publishes review of its studies*. Available at: https://www.ema.europa.eu/en/news/use-real-world-evidence-regulatory-decision-making-ema-publishes-review-its-studies (Accessed: 11 December 2024).
[55] Glasziou P et al. The differences and overlaps between 'explanatory' and 'pragmatic' controlled trials: a historical perspective. Journal of the Royal Society of Medicine. 2023;116:425-432.

companies. Regulators may also initiate and fund or carry out their own observational studies and the UK did this for a Parkinson's drug, selegiline,[56] and for MMR and autism.[57] Regular updates of analyses of all such studies, together with summaries of spontaneous reporting are submitted by industry to regulators. These emphasise safety but occasional studies of efficacy may be done. Much of the post-authorisation activity of regulators is devoted to assessing these reports and amending the product information (SmPC and PIL) where necessary.

4.18 One example where an observational study was carried out related to the mumps component of the MMR vaccine.[58] There was evidence from this study that the Urabe strain was associated with an increased risk of aseptic meningitis compared with the Jeryl Lynn strain. The vaccine with the Urabe strain was removed from use in the UK and most other countries, although the risk of meningitis from wild mumps is about 4 times higher than with the Urabe strain and a great deal higher than that with the Jeryl Lynn strain.

4.19 In 1995, CP Farrington developed a statistical and epidemiological method called the "Self-Controlled Case Series" method (SCCS).[59] This method has been possibly the most important methodological advance in studying vaccine safety in populations after vaccination. With SCCS a person acts as their own control, which has many advantages when studying vaccines. It is not based on a haphazard collection of cases but requires careful ascertainment of all those in a defined population who have been vaccinated and had the relevant outcome. Most epidemiological, non-randomised studies make comparisons between two groups. With a "cohort" design, the two groups are divided by whether they had a particular "exposure", for example a vaccine. The vaccinated group are those "exposed", and a comparison group - the people in the "control" group - are selected to be similar to the exposed group but are unexposed. The problem, especially with vaccine studies, is that those who are vaccinated can differ in many ways from those who are not vaccinated. The analysis of a cohort study can attempt to adjust for this using statistical methods. These require that all the factors by which the control groups differ are known and have been measured precisely. This is often not the case, and it cannot be known

[56] Thorogood M et al. Mortality in people taking selegiline: observational study. BMJ. 1998; 317(7153):252-4
[57] Taylor B et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet. 1999;353:2026-9
[58] Miller E et al. Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. Lancet. 1993;341:979-82.
[59] Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. Biometrics 1995; 51: 228–235.

whether all factors are taken into account. If the factors that differ are incorrectly or incompletely adjusted for, then the comparison may be invalid or biased.

4.20 By contrast, with a self-controlled design, comparisons are not made between groups of people but are made at different times within the same person. There will be time periods when they are exposed and time periods when they are not exposed. The result of this design is that factors which are fixed in time (like age, gender, medical history and others that may not be measured or even known) are the same for both the "exposed" and the "control" period and cannot then result in a biased comparison for that reason. There are assumptions for the SCCS method to be valid, but these tend to be easier to deal with than in a usual cohort study.

4.21 A 2011 paper[60] identified 40 studies where 11 different vaccines and at least 23 different outcomes had been studied. This paper also discussed the assumptions necessary for the SCCS method to be valid. The SCCS method was used to show a dramatic effect of the Urabe strain mumps vaccine, and several studies showed a lack of association between MMR vaccine and autism.[61] [62] [63] The first of these studies was done independently of, but funded by, the MCA (now MHRA), as noted above. This method is clearly capable of detecting and estimating the effect of very rare effects. It can also provide strong evidence against causal effects when there is no real effect. The method produces a measure of relative risk called the Incidence Rate Ratio (see Appendix 1) but requires extra data to obtain absolute risks.

4.22 Since 1990 a major contribution has come from the US where electronic healthcare records have been used to assess vaccine safety. The Vaccine Safety Datalink (VSD)[64] is a collaboration between the Centers for Disease Control and Prevention (CDC) and healthcare organisations that have electronic records. The inclusion of millions of individuals means that risks of the order of 5 per million can be detected, but the VSD can also provide quite tight confidence limits (see Appendix 1) where there is no genuine causal effect. The MHRA did conduct something similar using what

[60] Weldeselassie YG et al. Use of the self-controlled case-series method in vaccine safety studies: review and recommendations for best practice. Epidemiology and Infection. 2011;139:1805-1817.
[61] Taylor B, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet 1999; 353: 2026–2029.
[62] Farrington CP et al. MMR and autism: further evidence against a causal association. Vaccine 2001; 19: 3632–365.
[63] Andrews N et al. Recall bias, MMR, and autism. Arch Disease in Childhood 2002; 87: 493–494.
[64] McNeil MM et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine. 2014;32:5390-8.

it called "Rapid Cycle Analysis" (which was one of its four pillars of safety surveillance, as described in section 4 below). It also used electronic health records to which the MHRA had access. It scans for occurrence of pre-defined medical conditions associated with vaccine administration. The theoretical gains from using EHRs both to detect as well as evaluate signals are not always seen in practice. It requires very large numbers (tens of millions) of patients, together with very good recording of data and the ability to analyse the data very rapidly for signal detection to be effective. Most work with EHRs has concentrated on searching for a limited range of adverse events in a limited range of medicines rather than trying to be universal by looking at all medicines and all possible adverse events. This contrasts in the way that analyses of spontaneous reports can examine all reported medicines and all reported suspected adverse reactions.[65]

Phase 4 'trials'

4.23 These are conducted on authorised products, post-marketing, and can be used to assess safety. To a statistician or clinical trialist the word "trial" tends to be synonymous with "randomised controlled trials" but some do not use the word in that way. It is better to use "study" rather than trial for most studies conducted in Phase 4, since very few of them are randomised. Those that are randomised post-authorisation tend to be for new indications for authorised drugs. I know of no phase 4 RCTs for vaccines conducted to assess safety alone. There are new randomised trials of authorised vaccines but, rather than being done to assess safety, they are for extending the indication, for example to younger children or looking at the effects of having different vaccines for second or third doses. They will look for new harms and will report them, but their sample size is insufficient to detect rare harms.

4.24 In the late 1980s and early 1990s in the UK there was an era of phase 4 "trials" that were seen as marketing exercises by companies conducting them. It was concluded that most of these provided very limited information on the safety of medicines in general.[66] The advent of EHRs made many of these studies redundant. A more recent review, which used the US registry of trials, clinicaltrials.gov,[67] also highlighted the relatively small sample sizes for most of the studies even when focussed on safety.

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[65] Coloma PM et al. Postmarketing safety surveillance : where does signal detection using electronic healthcare records fit into the big picture? Drug Saf. 2013;36:183-97.
[66] Waller PC, Wood SM, Langman MJS, Breckenridge AM, Rawlins MD. Review of company postmarketing surveillance studies. Br med J 1992; 304: 1470-1472.
[67] Zhang X et al. Overview of phase IV clinical trials for postmarket drug safety surveillance: a status report from the ClinicalTrials.gov registry. BMJ Open 2016;6:e010643

4.25 In my view the ongoing VSD system is much more effective than most of the company-sponsored studies. Whether regulators apply sufficient scrutiny to company-sponsored studies or have enough powers to ensure compliance with high standards is difficult to say. Many fail to recruit enough participants and the general public's perception of companies using patient data tends to be adverse.

Requirements on companies for post-marketing surveillance

Risk management Plans

4.26 A key requirement in obtaining authorisation of any medicinal product, including vaccines, is having a "Risk Management Plan" (RMP). This is a document that sets out what is known and what is unknown at the time of authorisation, about the safety of a product. It has to be set out by a company at the time of an application for authorisation, with a plan to investigate any important unknown areas and known problems needing further characterisation. It was developed from suggestions made in a paper in 2003.[68] The EU introduced the requirement for an RMP in 2010.[69] There is a great deal of documentation and guidance for these RMPs which contain principles that have also been adopted outside the EU. The FDA has a "Risk Evaluation and Mitigation Strategy" (REMS) which has a similar purpose. The 2003 paper suggested that actively extending the knowledge on the safety of a product should be a requirement for all products. The regulatory implementation of the idea has tended to only require active (in the sense of conducting new studies) surveillance in respect of products deemed to be higher risk, while passive surveillance relying on spontaneous reporting is regarded as acceptable for low-risk products.

Periodic safety update reports (PSURs)

4.27 As the EMA says, *"Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase."* These must be provided by a company at regular

[68] Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf. 2003;12:17-29.
[69] Butler D et al. Regulatory experience of handling Risk Management Plans (RMPs) for medicinal products in the EU. Expert Opin Drug Saf. 2021;20:815-826.

intervals after a product is authorised. They must include any new information a company becomes aware of that could affect the benefit-risk balance of the product. They are assessed by the regulator to whom the report is submitted.

5. Post-marketing surveillance of Covid-19 vaccines: similarities and differences

5.1 In the pre-authorisation Covid-19 vaccine trials many minor side effects were seen but none suggested the benefits would not greatly exceed the harms.

5.2 At the time of authorisation various adverse effects were known and listed in the SmPC. The MHRA Temporary Supply document also said, in respect of the Pfizer/BioNTech vaccine:

"… the following additional risks and safety measures have been proposed:

Important identified risks	*None*
Important potential risks	*Vaccine associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD)*
Missing information	*Use in pregnancy and lactation* *Vaccine effectiveness*

There are no important identified risks for BTN162b2 [the Pfizer vaccine]."

5.3 The potential risks were theoretical, since they had been seen in animal models for vaccines developed for SARS-CoV-1 and in some Respiratory Syncytial Virus vaccines. Pregnant and lactating women were excluded from the first trials.

5.4 Similarly, no SUSARs were recorded during the UK Moderna vaccine trials. In relation to the Oxford/AstraZeneca vaccine, in September 2020 the Phase I UK trial was suspended after a report of transverse myelitis in a trial participant. The trial was restarted later the same month following advice of the CHM and the DMSB. There were no reports of any signal for thromboembolic events in the Oxford/AstraZeneca vaccine trials.

5.5 The CHM established the Vaccine Safety and Surveillance Expert Working Group (VSSEWG) to advise on the safety monitoring strategy for the Covid-19 vaccines. The output of the meetings of the VSSEWG was the "Report of the CHM Expert Working

Group on COVID-19 vaccine safety surveillance". This defined four 'pillars' or 'strands' to the vigilance strategy. These were, in summary:

- Enhanced Yellow Card passive surveillance through a Covid-19 interface to the Yellow Card scheme.
- Rapid cycle analysis (proactive analysis of pre-defined events) and ecological analysis (proactive analysis of trends within particular populations).
- 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).
- Formal epidemiological studies to confirm and quantify a suspected side effect.

5.6 The four-pillar strategy, in essence, uses the same basic approach to monitoring and surveillance as for all new products before the pandemic. There was no reduction in the means used to monitor safety, rather there were extra things done in pillars 2 and 3 that had not been done before. The further follow-up of trial participants for two years was part of the trial protocols; the eight planned observational studies were greater in extent than would be usual. The usual follow-up of SRs was done. The rapid cycle analysis using electronic health records in the CPRD (Clinical Practice Datalink) was an innovation, though the MHRA had made use of CPRD for studying safety issues with drugs for many years.

5.7 Similarly, another innovation was targeted active monitoring through the "Yellow Card Vaccine Monitor" (YCVM). This was similar to a system suggested many years ago called "Prescription Event Monitoring". Instead of starting with a suspected adverse reaction for which the numbers "at risk" were unknown, it started with those prescribed a drug. The prescribing doctor was then asked to report any adverse events occurring after the prescription (on a green form). This enabled the rate at which adverse events occurred to be estimated because the "at risk" numbers were known. It did require the prescribers to respond by filling in the forms, and this adds to their workload. This process was carried out successfully by the Drug Safety Research Unit based in Hampshire, but its utility has been overtaken by the availability of EHRs, which do not add to the clinician's workload beyond clinical care.

5.8 For the YCVM a random selection of nearly 600,000 vaccinees were invited to register on the Monitor by the end of June 2021. Those who responded were contacted at

different times post-vaccination to ascertain whether any suspected adverse reactions had occurred. The report dated 26 August 2021 makes it clear that the response rate was very low. There were 29,832 who registered, said to be an uptake of 4.8% (this implies over 600,000 invited). Over 5,000 did not report actually receiving a vaccine so the volume of usable data, although large in absolute numbers, was a small proportion of those invited. It seems that the data were processed through the Yellow Card software system, and naming it a Yellow Card system might have been done to capitalise on the familiarity of the name. Its principles were quite different to Yellow Cards, and while it had some utility, the potential for notable bias with such a low response rate was very considerable.

5.9 The system was helpful in looking at menstrual disorders (no signal of a problem was found) and pregnant women were particularly encouraged to register with the system. A November 2021 report on a UKHSA Covid-19 pregnancy surveillance protocol[70] states:

> "In addition to random invitation, MHRA have collaborated with UKHSA to provide a leaflet to pregnant women who take the vaccine which encourages them to register with the Yellow Card Vaccine Monitor. This activity has contributed to over 2,200 pregnant women registering to 3 November 2021."

5.10 It is not clear whether the follow-up data have been published but there are a number of more useful studies that are less prone to bias which have been published and show the harms to pregnant women associated with catching Covid-19 disease and some benefits, but no harms, of being vaccinated.[71]

5.11 The rollout of Covid-19 vaccines was expected to involve vaccinating more people in a short time period than had ever occurred before. Large flu vaccination campaigns targeted very young and older people whereas the age range for Covid-19 vaccines was going to be a lot wider. Giving any vaccine to such a large number of people would result in very large numbers of reports of adverse events. In anticipation of large volumes of SRs, there were attempts to use artificial intelligence (AI) to analyse them

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[70] UK Health Security Agency (2021) *National surveillance and safety analysis of COVID-19 vaccination in pregnancy*. Available at: https://assets.publishing.service.gov.uk/media/619f89da8fa8f50382034dc9/UKHSA-Covid-19-pregnancy-surveillance-protocol.pdf (Accessed: 11 December 2024).

[71] E.g. Mensah, A et al. (2024), COVID-19 Vaccine Safety in Pregnancy, A Nested Case–Control Study in Births From April 2021 to March 2022, England. BJOG. https://doi.org/10.1111/1471-0528.17949

and also to use AI methods for scanning social media. Research on social media using AI carried out after the first year of Covid-19 vaccine use did not find any new "signals" that were not already under investigation.[72] The study only used English-language Facebook posts, so would not have been able to identify possible adverse events described in other languages. Obtaining international information on signals of possible adverse reactions is a vital component for the whole process of national surveillance.

5.12 The volume of reports received at the MHRA was extremely large with 2,000 reports a day,[73] approaching a 20-fold increase compared to the usual total volume of reports. There were specific studies set up independent of industry to look at areas of potential concern. The major difference from pre-pandemic surveillance was in the volume of SRs, and the large quantity of observational studies, often published on the internet without peer review, e.g. in the form of preprints. This was a global phenomenon, and the media were very sensitive to reports coming from any country. Large volumes of GP data became available in the UK, in many instances with new methods of linkage to other data, some with special attention to preserving privacy (see also the Goldacre review[74]). The overall MHRA strategy was reasonable, though I suspect was harmed by not being involved with the EMA as intimately as it was prior to the UK's exit from the EU. It is possible that the WHO/ICMRA collaboration was able to make up for this loss of access to data and discussion in the EU regulatory system. There may have been staff and resource limitations at the later stages of the pandemic, though the volume and quality of the work done was very high.

5.13 The "Four Pillar" strategy was definitely a strong attempt to monitor safety of vaccines and therapeutics in an active way and not simply to rely on passive surveillance. Whether the YCVM was worthwhile, I would question, but Rapid Cycle Analysis is useful.

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[72] Hussain Z et al. Artificial Intelligence-Enabled Social Media Analysis for Pharmacovigilance of COVID-19 Vaccinations in the United Kingdom: Observational Study. JMIR Public Health Surveill. 2022;8(5):e32543.
[73] MHRA (2022) *MHRA Annual Report and Accounts*. Available at: https://assets.publishing.service.gov.uk/media/62d98ce2d3bf7f28671e928d/MHRA_Annual_Report_and_Accounts_2021-22.pdf (Accessed: 11 December 2024).
[74] Goldacre, B & Morley, J. (2022). Better, Broader, Safer: Using health data for research and analysis. A review commissioned by the Secretary of State for Health and Social Care. Department of Health and Social Care. Available at: https://assets.publishing.service.gov.uk/media/624ea0ade90e072a014d508a/goldacre-review-using-health-data-for-research-and-analysis.pdf Accessed 11 December 2024

5.14 During the pandemic, there were some delays in getting permissions for data to be used, but the rate at which studies were conducted was very high, once data became available.

5.15 The speed with which studies were conducted often relied on other areas of work being suspended, with individuals working 60 to 80 hours a week, utilising on-line conferencing tools like Zoom for discussions. This meant that many potential safety issues were discussed rapidly among experts. While not part of the regulatory process, the use of non-peer reviewed internet archives like medRxiv[75] meant good (and bad) quality research became known very rapidly. This was not under the control of regulators or medical journals and was a notable change in the way that science was conducted. The peer review process took place after publication, so it often meant that investigators (and regulators) were aware of the findings earlier than usual, and these non-peer reviewed studies played a significant part in communicating about drugs and vaccines in relation to Covid-19.

5.16 There was a process in the UK to enable access to data that would not normally be available rapidly. Notices issued by the Secretary of State for Health under Regulation 3(4) of the Health Service (Control of Patient Information) Regulations 2002 (COPI Regulations), allowed for processing of confidential patient information for Covid-19 purposes under strict controls. These COPI regulations were only short-term permissions allowed because of the emergency of the pandemic, and it was delays in their renewal that caused problems for some research.

5.17 OpenSAFELY is a secure analytics platform for observational research using patient health records. The emphasis on privacy of the individual records was very high. Researchers did not have direct access to individuals' data but could execute computer programs within the secure servers of the data provider and then view the results. The data were up-to-date and linkage to other data such as vaccinations and hospital admissions was also done rapidly.

5.18 While not part of the regulatory process, the OpenSAFELY collaboration,[76] initially between Oxford University and The London School of Hygiene, had a very high output of publications on Covid-19 utilising the COPI regulations. Very large (17 to 25 million) numbers of patients' GP records, based initially on one GP service provider (TPP),

[75] https://www.medrxiv.org/
[76] https://www.opensafely.org/

became available for analysis. When a second provider of GP computer services (EMIS) was added more than 55 million patients' data could be used. Linkage to other data, including vaccinations, enabled research to be done within the GP service provider's secure environment, preserving confidentiality in a way that had not been done before. Having such large numbers of patients' health data available was totally new for the UK. At least 18 publications on vaccines have come from OpenSAFELY and (at end July 2024) more than 82 completed and published research papers on research related to Covid-19. From the first idea to use the TPP GP data it took only 42 days for the OpenSAFELY Collaborative to pre-print the world's largest Covid-19 study (on 7 May 2020) using 40% of the English population.[77] It examined factors associated with death from Covid-19. Decisions made by JCVI on priorities for vaccination also utilised those data.

5.19 There was a high level of communication between the MHRA and the public health agencies but as far as I am aware rather less between the MHRA and academic researchers. While a key paper from OpenSAFELY on neurological events and vaccines included MHRA authors,[78] this took a relatively long time to appear. The potential for rapid analyses requires resources of experts to carry out the studies in addition to the availability of data.

5.20 The workload on Covid-related issues was enormous. The processes for assessing safety of medicines were undoubtedly stretched globally. In the UK, Brexit had resulted in some key staff leaving the MHRA. As far as I can tell the processes followed the general principles pre-pandemic but had to operate more quickly with reduced and less-experienced staff than would be ideal. That the MHRA staff worked extraordinarily hard at peak periods is undoubtedly true. I do not know the details of how the MHRA interacted in the meetings of the ICMRA where in principle the FDA and the EMA were members as well as other countries like Canada and Australia. I do not think the FDA and EMA had all their discussions within the ICMRA meetings but rather fed their conclusions to those meetings. The Australian recognition of the UK contribution is noteworthy.[79] My view is that the MHRA had to rely on what was being done in the EU and the US as an outside agency and as the recipient of their information rather than a

[77] Collaborative, T.O. *et al.* (2020) 'OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients'. medRxiv. Available at: https://doi.org/10.1101/2020.05.06.20092999.
[78] Walker, J.L. *et al.* (2022) 'Safety of COVID-19 vaccination and acute neurological events: A self-controlled case series in England using the OpenSAFELY platform', *Vaccine*, 40(32), pp. 4479–4487. Available at: https://doi.org/10.1016/j.vaccine.2022.06.010.
[79] Para 360 of MHRA witness statement INQ000474337

full participant as it was when part of the EU system. However, vaccine safety is a global concern and the MHRA participated fully in the WHO and other international bodies like ICMRA. I do not think this led to errors or notable delays on major issues.

5.21 It is often difficult to disentangle a patient's or a group of patients' response to a medicine from their response to diseases they may also be experiencing. This is made worse in a pandemic, especially where the disease is new and has features that are not always easily distinguished from an effect of a medicine. There is a need for considerable expertise and experience in dealing with complex post-authorisation issues clarifying whether it is the vaccine causing the adverse event.

5.22 There is a great deal of informal exchange of information globally, and post-Brexit the MHRA has built some more formal links with regulators inside and outside the EU through the ICMRA. How much informal exchange there was with the EU I do not know, but losing a seat at the table within the EMA will have meant a major loss of information and the ability to discuss with other experts. Pre-2018 the location of the EMA in Canary Wharf had been extremely advantageous. With the safety of medicines there is a strong need to be able to access global data and to have the facility to discuss with the providers of data the interpretation of those data. Otherwise, an individual country with a relatively small population has to largely accept what is being done in the groups of countries with the largest amount of data.

6. How the above systems and processes reacted to apparent adverse reactions to Covid-19 vaccination

Analysis of the efficacy of the systems and processes concerning safety

Abbreviated time frames for the Covid-19 vaccine clinical trials and any effect on safety assessment

6.1 While resources and processes enabled a rapid development time and fast approval times, in my view the abbreviated time did not affect assessment of safety because:

6.1.1 The preclinical and early phase studies were done to the usual standard and were extensive.

6.1.2 The phase 2/3 clinical trials enrolled very large numbers of patients. It is not strictly the number of patients that needs to be large, it is the number of outcome "events" that needs to be large (see Appendix 1). An event in this context is for example a test-confirmed case of infection with SARS-CoV-2 having clinical symptoms. The trial is to demonstrate that the rate of occurrence of these events is reduced by the vaccine. The results were robust, both because the design of the trials ensured that efficacy, if it existed at a sufficiently high level, would be demonstrated clearly. They were able to estimate the unanticipated high efficacy with good precision because there were also sufficiently large numbers of cases of infection with the virus. It is the numbers vaccinated which affect assessment of safety. For the Pfizer/BioNTech vaccine there were 43,000 participants, so a total of over 20,000 vaccinated with the study vaccine, together with sufficient follow-up done carefully. By the time the final assessment was made, very large numbers (nearly 10,000 vaccinated with the study vaccine) had been followed up for at least two months, during which virtually all vaccine-related effects are likely to occur[80] (see also paragraph 2.21). The AstraZeneca vaccine trials had over 23,000 participants.[81] The Moderna vaccine trials had over 30,000 participants.[82] Even with these large numbers included in the trials, very rare events would not be found until millions had been vaccinated. The trials continued to be followed up after the submission for authorisation and results

[80] MHRA statement INQ000474337 paragraph 126
[81] MHRA statement INQ000474337 paragraph 222
[82] MHRA statement INQ000474337 paragraph 239.

communicated to regulators. The result of the large trials was that it could be shown clearly that adverse effects that occurred within the period most such effects occur (2 months) even if they were at a rate of 1 in 1,000, would have been detected and shown to be a causal effect. No such serious events occurred, and there is a "rule of 3"[83] that suggests the uncertainty in the true rate as a 95% upper bound of 3/N, where N is the number of participants studied, though it may well be better to use a "rule of 4" as a simple rule though more complex methods have been suggested.[84] With 20,000 studied, the upper limit might then be a rate of 1 in 5,000. So the trials were robust to rare events, but very rare events occurring at a notably lower rate such as 1 in 100,000 or 1 in 1 million would probably not be observed. From personal experience (as a participant in the ChAdOx vaccine trial), the questioning of participants was done very carefully to elicit expected and unexpected adverse events, and certainly any serious adverse events would be detected and reported.

6.1.3 The size of the trials was very large because a clinical outcome was required rather than just looking for an immune response. For the 2009 flu pandemic, immune response was regarded as an adequate outcome because of the wide experience with flu vaccines and the trials tended to have hundreds of participants. For the HPV vaccines "experts agreed that ethical and time considerations make it necessary to use a surrogate endpoint, and not invasive cervical cancer, to define efficacy of HPV vaccines"[85] so the trials typically had 10,000 or fewer participants. For trials of the new respiratory syncytial virus (RSV) vaccines, trial sizes were intended to be about 10,000 or fewer maternal participants.[86] [87] The Covid-19 vaccine trials were larger than these and were clearly of adequate size to demonstrate the greater than expected efficacy.

6.1.4 As noted above, many non-randomised studies were done, and the regulators set out the plans for surveillance at the time of approval. In many instances these had even more participants than in the RCTs, so much rarer adverse events could be studied.

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[83] Eypasch E et al. Probability of adverse events that have not yet occurred: a statistical reminder BMJ 1995; 311 :619

[84] Turpin L et al. A modified rule of three for the one-sided binomial confidence interval. Int J Biostat. 2023 Sep 4. Epub ahead of print.

[85] Pagliusi SR & Aguado MT. (2004). Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine*, *23*(5), 569-578.

[86] Kampmann B et al. (2023). Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. *New England Journal of Medicine*, *388*(16), 1451-1464

[87] Dieussaert I et al. (2024). RSV prefusion f protein–based maternal vaccine—preterm birth and other outcomes. *New England Journal of Medicine*, *390*(11), 1009-1021.

6.1.5 As noted above, the rolling review was not a lesser review, but one that enabled the pre-clinical and early phase data to be fully assessed while the later phase trials were still ongoing. The usual system of starting the assessment process only when data from all phases of the trial were available leads to a much longer calendar period being required for assessment.

Oversight mechanisms in clinical trials

Reduction of bias in clinical trials

6.2 Trials conducted for regulatory purposes are very carefully designed. Concealment of allocation, with randomisation done centrally, is a vital aspect to avoid bias. While the placebo trials may have potential to "unblind" participants and investigators, there were large numbers of events reported in the placebo groups suggesting that the "blinding" process was done well. The trials were conducted to the usual standard of "Good Clinical Practice" (GCP, which is a standard for trial conduct and monitoring, as opposed to clinical practice). The Oxford based trials used an active vaccine as control and this can reduce bias for the reasons set out above at paragraphs 2.7 - 2.8. The major outcome events were assessed by multiple outcome evaluators who were "blind" to treatment allocation. The trials were subsequently published in high quality journals (New England Journal of Medicine and The Lancet) after rigorous peer review. The EMA Public Assessment Report (PAR)[88] stated, in relation to the Pfizer vaccine:

> "… *EMA gathered additional information as indicated below from EU and non-EU regulatory authorities …*
>
> - *a full inspection report from GCP inspection by Regierungspräsidium Karlsruhe and Paul-Ehrlich-Institut conducted at one of the investigator sites and at a CRO in Germany for the study BNT 162-01;*
> - *Establishment Inspection Reports from GCP inspection by Food and Drug Administrations (USA Regulatory Authority) of six investigator sites in USA for study C4591001 (BNT 162-02);*

[88] European Medicines Agency (2021) *Assessment report - Cominarty*. Available at: https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf (Accessed: 11 December 2024).

- *A full inspection Report and the summaries of the outcome from two GCP inspections by the National Administration of Drugs, Foods and Medical Devices (Argentinian Regulatory Authority) conducted at the single site located in Argentina for the study C4591001(BNT 16202)."*

6.3 The MHRA PAR said simply, *"All studies were conducted in line with current Good Clinical Practice (GCP)."*

6.4 My view is that the standards adopted were not different for Covid-19 vaccines; regulators were acutely aware that releasing an unsafe vaccine would have terrible consequences.

Ensuring accurate reporting of adverse events in trial data

6.5 Regulatory scrutiny was good in these trials. Processes for reporting are set out very clearly in the protocols, and although one can never guarantee that all investigators follow the protocol exactly, there was no reason to suspect any misconduct. We always have to rely on the integrity of investigators, but tests for misconduct are done routinely. If hints of a problem arise, more detailed investigation occurs. In the past it has been noted that published papers can be "spun" in some instances, though this is usually done to overstate the efficacy of medicines rather than their safety.[89] Regulatory scrutiny (in the US of the original raw data files, though only rarely done by other regulators) makes it very difficult to conceal AEs. The agreement among independent regulators and their advisory committees is another aspect that provides reassurance. In most trials the health professionals conducting them are not aware of which treatment an individual participant has received, and so adverse events are reported without knowledge of whether it is the study vaccine or not. This reduces bias in the trial results. For the Covid-19 vaccine trials, the overall publicity around the regulatory advisory committees meant that most of the scientific community was very well aware of the results and published data accorded with what was reported at the FDA (other regulators do not have open meetings in the same way). There was general surprise at the higher than expected efficacy of the vaccines, especially the mRNA vaccines. The design of the AstraZeneca trials was more complex, perhaps with the object of extracting as much scientific information as possible, rather than simply passing the regulatory hurdles.

[89] Chiu K et al. 'Spin' in published biomedical literature: A methodological systematic review. PLoS Biol. 2017;15:e2002173..

The diversity of clinical trials in terms of age (including children), ethnic background and sex, and the impact on assessing the safety implications for different groups.

6.6 It was clear that elderly people were at elevated risk from Covid-19, so considerable efforts were made to recruit a much higher proportion of elderly people than is usual in industry-sponsored trials. The Oxford trial particularly recruited over-70s but all the trials had some elderly people, and there was no evidence that the vaccine had markedly less efficacy among elderly people. There was discussion of this topic at the FDA VRBPAC public meeting and while elderly people in care homes (mainly for practical reasons) were not well-represented in the trials, extrapolation to older ages was not a major problem.

6.7 Children were not the main target of the vaccine since it was already clear that (in contrast to flu) they were not generally at high risk, in fact at surprisingly low risk. They were not well-represented in the trials, nor were they the group vaccinated initially, but then this is always an issue for all medicines independent of the pandemic. There are continual calls for children to be included in trials; however, recruiting them can be difficult. It is understandable, especially because of their low Covid-19 risk, that children were not included in trials until there was good general evidence in adults of the efficacy and lack of important harms. For those children who were clinically extremely vulnerable, they would not be included in trials of a very new vaccine given the uncertainty of benefit for them. In order to show evidence of efficacy in any sub-group that would require that the sub-group had tens of thousands of participants. This is impossible to achieve for sub-groups that are very small. We must use scientific medical knowledge on what might be expected in small sub-groups, when data on overall effects is obtained from large population-based trials, to decide when a new treatment is worthwhile in the sub-group.

6.8 Ethnic background is always an issue with trials, especially of new drugs or vaccines. Recruitment of minority groups is often a problem. Firstly, they form (by definition) a smaller proportion of the population and so will form a smaller proportion in trials reflecting the population, as found in a report from the National Institute for Health and Care Research.[90] Secondly, they may have poorer access to healthcare and

[90] National Institute for Health and Care Research (no date) *Randomised controlled trial participants: Diversity data report*. Available at: https://www.nihr.ac.uk/randomised-controlled-trial-participants-diversity-data-report (Accessed: 11 December 2024).

reluctance to participate in research. This is really only a scientific problem if there is a differential response in terms of efficacy or safety in different groups. It is a problem of equality and can contribute to vaccine hesitancy, but there does not seem to be any simple answer. Vaccine coverage in ethnic minority groups is consistently lower than in majority groups and this is a major topic in vaccine confidence generally. It is always better to describe this as "coverage" rather than "uptake", because the complex reasons affecting vaccine coverage is not simply whether people accept the vaccine (as implied by "uptake"), but whether they have had equitable access to the vaccines and information about them. Trials cannot be expected to overcome this problem until it is solved more generally in the population. The Covid-19 vaccine trials were at least as good as non-Covid-19 vaccine trials, and probably rather better, in trying to get important sub-groups included as participants (see for example, this small randomised trial[91] of a 2009 flu vaccine with or without adjuvant where 100% of the participants were reported as Caucasian).

6.9 It is also important to realise that even if a trial were to recruit participants from minority groups proportionately, the statistical power to show that the responses of such groups was different to the majority of responses is inevitably very low. In order to have good statistical power there would have to be highly disproportionate recruitment of all minority groups such that they had similar numbers of participants as the majority groups. We have to accept that we cannot answer all questions, even those of importance, in individually randomised trials. Ensuring diversity in clinical trial participants may be easier if trials are conducted in many different countries, rather than relying on smaller minorities in any one country.

6.10 There was no evidence of notable differential response in efficacy. The numbers having serious AEs in the trials were too small to show any heterogeneity in safety; it required later observational studies to confirm there was no excess risk in those groups.

The inclusion in clinical trials of the immunosuppressed, pregnant women and participants with co-morbidities, and the impact on assessing the safety implications for these groups

[91] Roman, François, et al. "Immunogenicity and Safety in Adults of One Dose of Influenza A H1N1v 2009 Vaccine Formulated with and without AS03A-Adjuvant: Preliminary Report of an Observer-Blind, Randomised Trial." Vaccine, vol. 28, no. 7, Feb. 2010, pp. 1740–45, https://doi.org/10.1016/j.vaccine.2009.12.014.

6.11 Investigators will be cautious in recruiting extremely vulnerable people until they are reassured about the general efficacy and safety of a new vaccine. It would then be unethical to include them in later placebo-controlled trials when a vaccine has already shown efficacy, so inevitably observational studies tend to be the only answer to increase knowledge. As with children and pregnant women, this is a general issue for all medicines and is not confined to vaccines or to the period of the pandemic. Once more than one vaccine has been approved for use, then trials comparing these vaccines in vulnerable (in a very general sense of being at higher risk of the effects of disease) populations are possible. It must also be realised, that had the trials in the wider population shown that a vaccine did not have overall benefits and did have harms, then there would have been major concern if vulnerable people had been included, then exposed to the vaccine and had thereby suffered without benefit. Making judgements over who should and should not be included when one knows a vaccine is generally beneficial, is not the same when very little is known.

6.12 Small numbers of those with co-morbidities were included in the trials, such as cancer, diabetes, and chronic lung disease, and particularly when the trials included older people, those with any co-morbidity not listed in the exclusion criteria could in principle be included. However, immune-compromised people were generally excluded.[92] The definition of immune-compromise used as an exclusion criterion in these trials was not exactly the same as the Clinically Extremely Vulnerable list maintained by the UK Government during the pandemic. That list changed considerably over time and was designed for different purposes. Rather, the exclusion criteria used in the drug trials was a general category of being on medication that suppresses the immune system, or having a medical condition where the immune system is compromised, as diagnosed by their doctor.

6.13 While this group might be at greatest risk from the virus (and also be at high risk of hospital admission and death from other causes), they could also be at risk of adverse effects of a new vaccine with unknown effects. Given the mechanism of vaccines (using an individual's own immune system to mount a response against the virus), the relative efficacy of a vaccine against infection is likely to be reduced in those with a compromised immune system. While the absolute effect may still be beneficial, it is a

[92] Polack, F.P. et al. (2020) 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine', New England Journal of Medicine, 383(27), pp. 2603–2615. Available at: https://doi.org/10.1056/NEJMoa2034577. Supplementary material lists comorbidities of participants.

difficult issue as to whether to include them in trials where any benefit or harm is uncertain. It must also be realised that simply including them in trials may not be sufficient to show that their response to a vaccine is the same or different to others. The sample size to show a differential response requires enormous numbers and this is unfeasible in early trials. The issue of generalisability of results is not simple[93]. This is a very important point and may not be generally understood. The issues around inclusion and exclusion of groups at potentially different risk of beneficial and harmful outcomes is a general problem and the article by Bukan et al[94] sets out some of the facts and the issues. They do not clearly distinguish between early trials of totally new vaccines from later ones, nor discuss the statistical issues of finding evidence for heterogeneous responses. Separate vaccine trials and observational studies were later organised to assess effectiveness in immunosuppressed populations (see Professor Prieto-Alhambra's report paragraph 4.15), as well as non-vaccine prophylactics that do not rely on the immune system (see Professor White's report, **INQ000474743).**

6.14 Pregnant women are rarely included in early trials as a precaution, though, like the elderly and immune-compromised, they were at risk of poor outcomes with Covid-19. Animal studies did not suggest problems, but again observational studies must be relied on for these groups. There were some trials done in small numbers of pregnant women, mainly I think for dosing purposes, but these were not done until after the early trials. As far as I know, no observational study has suggested any issue around congenital malformations for any Covid-19 vaccine and recent data[95] [96] [97] provide reassurance. Analyses of uncontrolled spontaneous reports are potentially at greater risk of bias and reliance on cohort studies is more reliable, though as noted above, non-randomised studies are generally much more subject to bias than randomised trials. Efforts were made in observational studies to check on outcomes in pregnancy, as noted above in paragraph 5.10.

Those with HIV were studied carefully and no notable issues either for efficacy or safety were found but the numbers generally were too small to draw firm conclusions.

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[93] Weiss NS et al. Generalizability of the Results of Randomized Trials. Arch Intern Med. 2008;168(2):133–135.
[94] Bukan K et al. Exclusion of older adults and immunocompromised individuals in influenza, pneumococcal and COVID-19 vaccine trials before and after the COVID-19 pandemic. Aging Clin Exp Res. 2023;35:917-923.
[95] Favre G et al. Risk of congenital malformation after first trimester mRNA COVID-19 vaccine exposure in pregnancy: the COVI-PREG prospective cohort. Clin Microbiol Infect. 2023;29:1306-12.
[96] Calvert C *et al.* A population-based matched cohort study of major congenital anomalies following COVID-19 vaccination and SARS-CoV-2 infection. *Nat Commun* **14**, 107 (2023)
[97] Rimmer MP et al, The risk of miscarriage following COVID-19 vaccination: a systematic review and meta-analysis, *Human Reproduction*, 2023;38: 840–852

For those with an impaired immune response, most of the concerns were around efficacy.

Changes to the regulatory process for marketing authorisation and the impact on safety

6.15 As noted above, the key aspect for safety is the numbers vaccinated. The trial size was enormous. Once efficacy had been shown, continuing to recruit sufficient numbers (millions, if extremely rare effects were to be detected and shown to be causal) would be unethical as it would prevent the vaccination of those allocated to the placebo group. Abbreviation of the process itself by using rolling review does not affect safety assessment, it is whether the numbers vaccinated and the follow-up time is adequate. Nearly all adverse effects of vaccines occur within 2 to 4 weeks. Occasionally something can occur which is not diagnosed until later (see paragraph 2.21) but continuing a placebo group follow-up for years and not allowing them to be vaccinated would be unethical, and once efficacy is shown convincingly, a vaccine must be made available. For participants in the trial, once efficacy was shown they could ask to know what treatment they had had and to have the vaccine if they were in the placebo group. Follow-up did continue for everyone to see if delayed adverse effects were seen and if the immune response was waning.

6.16 All this is summarised by the MHRA statement (INQ000474337) para 154 which says-

"I am satisfied that the disapplication of the standard authorisation procedures via regulation 174 had no impact on the MHRA's rigorous assessment of the safety of the Covid19 vaccines. The MHRA's scientific standards remained unchanged and in line with international standards during the pandemic. The rigour of our scientific scrutiny of the vaccines for authorisation, and in post-marketing surveillance, was exactly the same as it would have been for a CMA or MA process. In addition, the amendment to the Human Medicines Regulations 2012 to insert a new regulation 174A on 17 October 2020, made it clear that the MHRA was able to define conditions and safeguards for the supply and use of products authorised for supply under regulation 174. This precisely mirrored the conditions of a licence (CMA or MA). In addition, the new regulation 174A set out the statutory framework for the action to be taken in the event of a breach of the conditions. It is relevant that the temporary authorisation of supply of Covid-19 vaccines under regulation 174 was accompanied by terms set out in Regulation 174 Information for UK Healthcare Professionals and

Patients [JR/46 INQ000507357– *], and that the subsequent approvals by other jurisdictions, in particular by the EMA and FDA, did not differ in any material respect."*

6.17 My view is that there was no slippage in standards in respect of efficacy or safety, especially in the context of a pandemic virus, which, in the UK alone, was causing tens of thousands of deaths and many more adverse outcomes.

Whether mRNA or viral vector vaccines should have been characterised as "gene therapies" or "pro-drugs" as distinct from traditional vaccines

6.18 I know of no reason why mRNA or viral vector Covid-19 vaccines could or should have been regarded as "gene therapies" - they are nothing like other gene therapies. The target was not to modify any genes, either of the virus or the recipient but to provoke a defensive response by the recipient's immune system. Similarly, the mRNA and viral vector Covid-19 vaccines are definitely not "pro-drugs", which are drugs that are inactive until they are metabolised in the body to an active metabolite. Tamoxifen (for breast cancer) is an example which is metabolised to endoxifen, which then acts against the cancer. Tamoxifen itself has little direct beneficial effect on cancer. Vaccines are not like drugs in their action; they are not metabolised to produce an effect. The regulatory processes for true gene therapies, where the target is altering individuals' genes, is very different but would have been totally inappropriate for the Covid-19 vaccines.

Efficacy of post-marketing surveillance systems and processes for Covid-19 vaccines

6.19 The UK may ultimately have had the most transparent (to the public, etc.) data on SRs, which was very up to date. I am unsure when this was first made available to the public, but it was quite soon after the vaccines were introduced. The data on Yellow Cards was available prior to the pandemic, but was made easier to view for vaccines soon after the vaccines were rolled out.

6.20 Many observational studies were set up, either with specific sources of data relevant to the pandemic or using existing electronic health records like CPRD. The fourth pillar of the MHRA strategy states this clearly, and PHE (later UKHSA) conducted many studies and published these. OpenSafely, as described above in paragraphs 5.17 to

5.19, was specifically mentioned in the strategy document setting out the four pillars for safety surveillance.

6.21 The use of OpenSafely to monitor vaccine safety was, from my view and experience, not done in the most effective or rapid way as was possible. This may have been the result of a lack of funding. They key aspects of the OpenSAFELY collaboration that helps with this are: 1) The very large numbers of patient records with up-to-date (daily update) full medical histories available; 2) the ability to obtain and link vaccination records very rapidly; 3) software expertise and developers who make access to data both highly privacy-preserving with efficient access; 4) the availability of skilled epidemiologists who can design, analyse and report studies to minimise bias in assessment of effects of vaccines. Phase 4 randomised trials were not relevant. Many observational studies were done, and the UK was at the forefront of these. For example, the UKHSA study that showed the Delta variant of the virus escaped the vaccines was published in the New England Journal of Medicine showing its global relevance.[98] Its data were up to the end of May 2021 and first published in July 2021 which is rapid for such a major study.

6.22 The UK reporting of myo/pericarditis was very rapid, with cases being reported before the end of January 2021 (MHRA statement INQ000474337 paragraph 645) and the MHRA consulted their advisory committee also in February 2021. They noted this was prominent among younger adults, but with very small numbers of reports. The MHRA also noted that myo/pericarditis was strongly increased following infection with SARS-CoV-2. The magnitude of this increase was dramatically more than any increase seen with any vaccines, which makes it more difficult to be sure of a causal effect (see paragraphs 5.7 - 5.27 of Prof Prieto-Alhambra's report INQ000474703).

6.23 Internationally this issue was mainly considered in later months, and it is possible that the increases following second doses seen in the US and Israel may have been associated with a shorter interval between doses than was adopted in the UK.[99]

6.24 The MHRA in making an announcement in June 2021 saw an immediate increase in reporting. This illustrates the problems associated with spontaneous reporting in that it is strongly affected by publicity. One thing they noted was their awareness of what

[98] Lopez Bernal J et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021;385:585-594.
[99] MHRA statement INQ000474337 paragraph 652

other countries were reporting and this illustrates the global nature of pharmacovigilance, especially in a pandemic.

6.25 A large UK study[100] showed the slight increase in risk, stronger following a second dose of the Moderna vaccine. It also showed a bigger increase following a SARS-CoV-2 positive test. The consequence of this is that with that virus still circulating, the benefit/harm balance was still in favour of giving the vaccine.

The ability to interrogate the Yellow Card database for batch-related issues and other temporal associations

6.26 It was possible for members of the public to access Yellow Card data and interrogate it at an early stage. There is no doubt the MHRA has sophisticated software to do this.

6.27 Batch number is sought for vaccine Yellow Card reports but is not always given, but dates and locations can be used to determine whether there are batch-related problems and these have been detected in the past. There is no reason why such problems, had they occurred, would not have been detected.

MHRA follow-up on Yellow Card reports in order to determine, for example, if symptoms have worsened over time

6.28 As a routine the MHRA will sometimes follow-up reports for extra information that would clarify medical history etc. in order to help the assessment of causality. This occurs particularly with fatal reports. In some instances where a suspected reaction is continuing at the time of the report, then knowing if it has resolved, continued or worsened may be important, but would not be routine. Those who send in Yellow Card reports can provide unsolicited follow-up and this is done regularly, but pressures on health professionals (GPs particularly, who are key reporters) may have reduced the likelihood of this during the pandemic, and the MHRA requesting follow-up does not mean it will be received. The use of electronic health records provides a much better, less biased and more detailed picture than spontaneous reports. The MHRA policy on privacy is set out clearly but in order to do things that could benefit public health, such

[100] Patone, M et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 28, 410–422 (2022)

as linking a Yellow Card with a patient's EHR GP record, requires the reporter to give the relevant NHS number. There can be reluctance to do this.

6.29 The MHRA witness statement makes it clear that they did continue to follow-up reports and that they also allowed for users including patients to initiate their own-follow-up via the website.[101]

Whether it should be made mandatory for healthcare professionals to report suspected adverse reactions via the Yellow Card system in the future

6.30 For a long time, some countries like France had "mandatory" reporting for health professionals but their reporting rates were lower than the UK. It is impossible to enforce; there is no way someone's thoughts ("suspicions") can be interrogated. Electronic health record systems make it easier in many cases to report. It is already mandatory for marketing authorisation holders to report.

6.31 The best review on what works to improve spontaneous reporting did not find any evaluations of mandatory reporting,[102] but included this section:

> ***Enforcement strategies***
>
> *No enforcement strategies (eg, mandatory reporting) featured in any of the 101 papers included in the six systematic reviews. However, in some countries governments have sought to use enforcement to encourage ADR reporting. On 25 May 1984, the French government decreed that all prescribing physicians, midwives or dentists should report all unexpected or toxic drug reactions to their regional monitoring centre. Reporting "serious" or "unlabelled" ADRs to the French Regional Centres subsequently became a mandatory legal requirement (underpinned by article R-5144-19) for any prescriber, physician, dentist or midwife in France in 1995. We are not aware of any data showing the impact of these requirements on reporting rates and are not aware of any countries which have followed France in making reporting of certain ADRs mandatory for individual prescribers. However, an international comparison of reporting by countries to Vigibase® indicated that France (with 174 reports/million inhabitants/year) had an average rate after the law had come into force (13th highest out of 36 high-income countries between 2000 and 2009).*
>
> *As a result of the 2014 Protecting Canadians from Unsafe Drugs Act (Vanessa's law), several amendments were made to Canada's Food and Drugs Act. As from 16 December 2019, serious ADRs and medical device incidents were required to be reported, in writing, to Health Canada within 30 calendar days from the date of their first documentation within a hospital. However, the mandatory*

[101] MHRA statement INQ000474337 paragraphs 372 & 374
[102] Routledge, P. A. and Bracchi, R. (2023). Improving the spontaneous reporting of suspected adverse drug reactions: an overview of systematic reviews. British Journal of Clinical Pharmacology, 89(8), 2377-2385.

reporting requirement applies to the hospital rather than to the individual HCPs working there. Concern has been expressed that because of their frequency and the subjectivity involved, Canadian hospitals will face difficulties reporting all serious ADRs. It will be important to evaluate the impact of this new requirement on the reporting of serious ADRs from the hospital sector in Canada.

6.32 It must also be realised that simply increasing the number of spontaneous reports does not necessarily provide a public health gain. Firstly, the number of reports does not measure the likelihood of a reported event being caused by the drug or vaccine, and secondly does not necessarily markedly improve the ability of a spontaneous reporting system to find "signals" of potential problems. The witness statement from Dame June Raine shows the MHRA take a similar view (INQ000474337, para 836 and JR/441). The EMA conducted a study following the introduction of mandatory reporting for industry[103] and found a very small impact following a large increase in the number of non-serious reports:

"Addition of non-serious reports to the signal detection process resulted in a small overall increase in signals of disproportionate reporting with some new signals of disproportionate reporting appearing and some existing signals of disproportionate reporting disappearing; the sensitivity of the signal detection system was slightly increased and the proportion of signals of disproportionate reporting that corresponded to known adverse drug reactions (a measure of efficiency) was unchanged."

6.33 For healthcare professionals including (but not limited to) general practitioners, it is a matter of their index of suspicion[104]. Education, including pharmacovigilance as part of regular training for healthcare professionals may help; making reporting logistically easier may help, but with an increasing workload, it can be difficult to get healthcare professionals to prioritise reporting when the demands placed on them for individual care are very high. They include the relevant data in the GP electronic health record (EHR) used for direct patient care and it is better to utilise these data. The MHRA have suggested linkage between Yellow Card reports and GP EHR data, but in my view such linkage would provide relatively little extra gain. It is better to utilise the EHR data

[103] Candore, G., Monzon, S., Slattery, J. et al. The Impact of Mandatory Reporting of Non-Serious Safety Reports to EudraVigilance on the Detection of Adverse Reactions. Drug Saf 45, 83–95 (2022)
[104] "Index of suspicion means the degree to which a healthcare provider suspects that a patient may be suffering from a particular illness or injury based on the provider's training and experience, the patient's clinical presentation of signs and symptoms, and the mechanism of injury if applicable." Available from: https://www.lawinsider.com/dictionary/index-of-suspicion (Accessed 11 December 2024)

directly using scanning methods and software applied to EHR databases[105] to look for signals.

6.34 Using the suspicion of healthcare professionals can be very important in noting a previously unknown adverse reaction. Following my suggestion to the MHRA that a prize be awarded to the first healthcare professional who noted an important ADR the then Chair of CHM and subsequently the MHRA noted my suggestion in a public lecture and the Dunlop prize was instituted, named after Sir Derrick Dunlop.[106] The first award for a new ADR was for noting and reporting thrombotic microangiopathy with recombinant Interferon beta. It was given to Doctor, now Professor, David Hunt,[107] in 2015. Professor Hunt became a member of the CHM in 2022. It can certainly be argued that, first, it is the early reports of a previously unknown reaction that are much more important than having many reports about known reactions, and second, that having an incentive to report these new reactions would make a better contribution to public health than compulsory reporting. As far as I know the prize has not been awarded for any vaccine adverse reaction, and indeed I do not believe that a second prize has ever been awarded. Assuming the MHRA is still prepared to make such an award, it would be good to publicise this, and it could be effective when new vaccines are introduced.

Pharmacovigilance systems and potential signals from the coronial process

6.35 Reports from coroners in England, Wales and Northern Ireland, and in Scotland the Crown Office and Procurator Fiscal Services, are submitted to the MHRA when it is suspected that an adverse reaction to a drug has caused a fatality. This is a requirement when it is believed that future deaths may be prevented[108]. Such reports have been included in UK Yellow Cards for many years. They are rarely looked at on their own but contribute to routine surveillance. I know of no adverse reaction to the Covid-19 vaccines detected by coroners that was not detected through other means – this is clear from the MHRA's statement which details the sources of the various safety

[105] Coste A et al. Methods for drug safety signal detection using routinely collected observational electronic health care data: A systematic review. Pharmacoepidemiol Drug Saf. 2023; 32: 28-43.
[106] Royal College of Physicians (1980) *Sir Derrick Melville Dunlop*. Available at: https://history.rcp.ac.uk/inspiring-physicians/sir-derrick-melville-dunlop (Accessed: 11 December 2024).
[107] University of Edinburgh (2016) *Dr David Hunt awarded drug safety prize by the MHRA*. Available at: https://institute-genetics-cancer.ed.ac.uk/news-and-events/news-2015/david-hunt-awarded-drug-safety-prize-by-the-mhra (Accessed: 11 December 2024).
[108] UK Government (2009) *Coroners and Justice Act 2009*. Available at: https://www.legislation.gov.uk/ukpga/2009/25/schedule/5/paragraph/7 (Accessed: 11 December 2024).

signals for the Covid-19 vaccines.[109] Coroners and Procurator Fiscals did pay attention to deaths where Covid vaccines might be thought to be responsible, and these supplemented knowledge obtained from other case reports. The MHRA publicly available database does not seem to have coroners' reports categorised separately for the interactive drug analysis profiles for vaccines. Spontaneous reports of deaths are taken very seriously by the MHRA and from my experience, most, but not all, cases reported by coroners had been previously reported by a health professional so their contribution to signal detection itself is not great, but they influence responses to signals as part of the appraisal process. In a 2018 review covering coroners' reports since 2009[110], the authors noted four instances of the MHRA issuing safety warnings for medicines following such reports. A more recent review[111] covering reports on preventable deaths from July 2013 to February 2022 does not mention vaccines, with most reports related to opioids. We know that death certificates completed by coroners for children with cerebral palsy, for example, are not necessarily more accurate than other sources for cause of death[112]. A recent review[113] from the USA in relation to myocarditis has suggested that coroners' reports add something to assessment of Covid-19 vaccines for a specific issue that was known previously, but these reports are most useful in understanding mechanisms of action and confirming known reactions rather than in detecting new effects.

Was the relevant data on safety signals obtained as quickly as possible?

6.36 Speed of ascertainment is largely dependent on usage. If a medicine is very heavily used, then the opportunity for observation of rare adverse effects is increased. The UK was rapid in its reporting on adverse effects. However, having immediate access to many countries' data on reporting from a much larger population allows for a better response. It also helps to spread the load of evaluation when a very large number of signals must be processed. As far as I know, following the UK's exit from the EU, the UK no longer had immediate access to the complete EU database on reported suspected adverse reactions (Eudravigilance) and so had to rely on the, possibly

[109] INQ000474337 paras 361-363, 687 and 691 for mention of coroners, 431-789 for specific risks
[110] Ferner RE et al. Deaths from Medicines: A Systematic Analysis of Coroners' Reports to Prevent Future Deaths. Drug Saf. 2018;41:103-110.
[111] France HS *et al.* Preventable Deaths Involving Medicines: A Systematic Case Series of Coroners' Reports 2013–22. *Drug Saf* **46**, 335–342 (2023)
[112] Evans PM, Alberman E. Certified cause of death in children and young adults with cerebral palsy. Arch Dis Child. 1991;66:325-9.
[113] Hulscher N et al. Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis. ESC Heart Fail. 2024 Jan 14.

slightly delayed, assessments of those reports by the EU members states and the EMA. The MHRA clearly took a great deal of notice of what was happening globally and participated in ICMRA meetings, but direct access to EU data was, as far as I can tell, no longer possible. The reduced access following the UK's exit may (I cannot be sure) have slightly impaired our ability to report and evaluate possible new effects. The MHRA is unlikely to emphasise this. In my view it is an issue.

Were the data on safety signals analysed in as effective a way as possible?

6.37 As noted above, the sophisticated software used by the MHRA is as effective a tool as is available. New methods do go on being developed, but the MHRA uses good systems, and from the regulatory response, noting the comment from the Australian regulatory authority cited above, the UK analysis was effective.

The speed of the MHRA (compared to other national regulators) in reacting to safety issues with the AstraZeneca vaccine

6.38 Some of the actions taken by different countries were not taken by the regulators. As I understand it, in a few countries there are bodies that are responsible for delivering vaccines which also conduct safety monitoring. This is noted in regard to Denmark at para 457 of the MHRA statement. Some of these bodies in the past have been quick to take action that was not confirmed by the regulatory process which tends to require stronger evidence to take action. They are constrained by law and can be involved in litigation if their action is premature. This is a very difficult balance and on the whole the "precautionary principle" is followed. This is more difficult in a pandemic and getting the balance right in the middle of an emergency is not simple - it is much easier when looking back when one knows what is a real effect and what was spurious.

6.39 A notable problem is that with very rare adverse effects there can be other explanations. It is too easy retrospectively to say it was slow, without taking into account the "noise" in the system generated by many other possibly false "signals" that occurred at the same time. These take time in evaluation and the public will not be aware of them, unless a mistake is made, and a false signal is communicated when there is no causal effect. When the adverse effect can also be caused by another disease, especially Covid-19, this also makes careful assessment imperative.

6.40 In relation to thrombosis with thrombocytopenia syndrome (TTS), the MHRA consulted its advisory committees from 25 February 2021. They did not advise immediate action. It is also noted at para 458 that the MHRA were in touch with the Danish regulatory authority which had not itself taken regulatory action, and they noted the AZ vaccine was being used in younger people in Denmark than in the UK. This illustrates the general principle that risks are context dependent. There were early indications that platelet effects might be a problem, and these were followed up carefully. It should not be expected that all countries will act in the same way and at the same time. The balance of harm and benefit will depend on the vaccination policy (what ages are being vaccinated for example), and the prevalence of the circulating virus with its impact on the local population. A careful extensive evaluation is needed, taking all these factors into account.

6.41 The CHM witness statement (INQ000474336) at para 153 sets out the reasons why they did not advise restriction of use of the AZ vaccine to younger people at an earlier stage. The EMA itself was also slower than some of its member states in taking regulatory action.

6.42 When a condition that can occur with a viral disease that a vaccine will prevent and that the virus is still circulating in the population, it is very difficult indeed to be sure that there is a causal effect, and that even if causal, the harm outweighs the benefit. These are not simple decisions at the time.

Were key safety signals missed?

6.43 I am unaware of any. Some effects might be caused by background disease and they can easily be missed.

Were safety signals communicated that turned out to be 'false positives'?

6.44 Again, I am unaware of any; the concerns with the Pfizer vaccine around anaphylaxis were almost undoubtedly over-stated early on. Such things could occur although not at an importantly high rate. Concerns over enhanced disease were not communicated as a signal, and no such effect was seen. Vaccine-enhanced disease has been seen for four vaccines resulting in their not being licensed, withdrawn or usage restricted

(Dengue Fever).[114] It was listed among the "Adverse Events of Special Interest" (AESI) as a potential AE for Covid-19 vaccines. No cases were seen as far as I know, and the US Vaccine safety Datalink had strong evidence for a reduction in severity of disease associated with vaccination.[115]

Are the obligations on pharmaceutical companies to proactively collect long-term safety data and/or conduct post-authorisation trials effective?

6.45 As noted above, companies may be required to conduct post-authorisation safety or effectiveness studies. They can involve randomised ("interventional") or very much more likely, studies in EHR databases and sometimes specific observational studies to collect data not easily obtained from EHRs. There will be a need to obtain data on pre-specified outcomes where there is either a lack of information from the licensing trials or a signal about a possible rare adverse reaction. The companies almost invariably delegate the conduct of the studies to independent academic groups or "Contract Research Organisations". A review[116] from one of these organisations shows the lack of information about them and how they frequently had no comparison group.

6.46 These studies follow from the EU legislation of 2010 and they are not always easy to conduct. A review from a vaccine manufacturer sets out the challenges to getting valid data.[117]

6.47 As far as I can tell, most of the Covid-19 vaccine studies were done with academic collaborators, and these, together with those conducted independently of the companies, were the most useful for studying the effectiveness and safety of the vaccines.

6.48 More might be done to improve the system as a whole. In my view it would be better to have publicly funded studies using a system like OpenSAFELY conducting these studies. In a low-tax environment (that is a simplistic description I know), there have been pressures to reduce public expenditure, so the move to put the financial burden

[114] Jamrozik Enet al. Vaccine-enhanced disease: case studies and ethical implications for research and public health [version 1; peer review: 3 approved]. Wellcome Open Res 2021, 6:154
[115] Boyce TG et al (2024). Lack of Evidence for Vaccine-Associated Enhanced Disease From COVID-19 Vaccines Among Adults in the Vaccine Safety Datalink. *Pharmacoepidemiology and Drug Safety*, *33*(8), e5863.
[116] Engel P et al. Lessons learned on the design and the conduct of Post-Authorization Safety Studies: review of 3 years of PRAC oversight. Br J Clin Pharmacol. 2017;83:884-893.
[117] Cohet C et al. Challenges in conducting post-authorisation safety studies (PASS): A vaccine manufacturer's view. Vaccine. 2017;35(23):3041-3049.

onto industry has led to the model for post-authorisation studies that we have. In my view this is unsatisfactory. Randomised trials are not usually done, but could be when multiple vaccines are available and comparison could help inform selection of the best vaccines.

An explanation of the methods of calculating the number of excess deaths during and after a pandemic

6.49 This is not my main area of expertise. Excess deaths are the total number of deaths in a population during a specific period, minus the number of deaths expected in that population during that period.

6.50 The main issue is how the expected number of deaths is calculated. It may be some "baseline" value taken as an average over some previous period or may be calculated using some more complex formula. A good description of the basic issues is in a paper produced for use in humanitarian emergencies.[118]

6.51 Excess deaths are useful when causes of death are uncertain and diagnosis of Covid-caused deaths may be diagnostically difficult, especially in those at high risk of death and whose cause of death may be incorrectly recorded.

6.52 There are useful comments made in Professor Sir David Spiegelhalter's book, Covid by Numbers (Pelican, 2021):

> *"Excess mortality can be hard to interpret. Changes in deaths might be due to the virus, or critical care being overwhelmed, disruption to health services or the impact of anti-virus measures. All of these get combined into an overall count. There is no 'correct' way of calculating excess deaths."* [p133-4]

6.53 Understanding whether a vaccine causes an increase in mortality is achieved much more effectively by conducting an observational epidemiological study in which individuals are followed, and their vaccination status is known. Looking at total numbers of deaths, and total numbers of vaccinated, without knowing whether the individuals who died were vaccinated or not is at best a weak way of looking at causal

[118] Humanitarian Practice Network (2005) *Interpreting and using mortality data in humanitarian emergencies.* Available at: https://odihpn.org/publication/interpreting-and-using-mortality-data-in-humanitarian-emergencies/ (Accessed: 11 December 2024).

effects and at worst is totally misleading. It can be that the excess deaths are in those who are unvaccinated and might be caused by Covid or have other explanations.

An overview of the data that exists on the number of deaths or other adverse reactions following the roll-out of the Covid-19 vaccines

6.54 There is always a need to balance benefits and risks. The studies involving individual follow-up are the most reliable source on this and simply looking at total deaths is not necessarily helpful and may be misleading. The "ecological fallacy" is very well-known and an example occurred in relation to Covid-19 with a paper published on places with "stay-at-home" policies that was retracted after critics showed clearly that the methodology did not allow for the interpretation the authors put on their data.[119]

6.55 One article that shows the problem of using aggregate data is also an example of "Simpson's paradox", where overall results can suggest treatment B is better than treatment A, but when the results are split by another variable the opposite is true.[120] In 1986 a paper was published showing that one form of surgery (B) was better than another (A) for kidney stones. In fact, when the results were split by size of stone A was better than B for small stones and also A was better than B for large stones. The problem was that there were many more patients with large stones who had treatment A and large stones had a lower rate of success. This is an example also of "confounding" at the individual level that may not be measured at the aggregate level.

6.56 There are multiple papers from around the world showing vaccine effectiveness against death. They consistently show high values of vaccine efficacy against death from Covid-19. The early vaccines were targeted at the so-called Wuhan variant of SARS-CoV-2, so that when other variants have appeared those early vaccines will have reduced efficacy in preventing infection and hence death from Covid-19. One UK example[121] showed that there was still high effectiveness for both AZ and Pfizer vaccines against death, even with the alpha and delta variants. There have been many studies on adverse effects of vaccines which are based on individual level data and

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[119] Savaris, R.F. *et al.* (2021) 'RETRACTED ARTICLE: Stay-at-home policy is a case of exception fallacy: an internet-based ecological study', *Scientific Reports*, 11(1), p. 5313. Available at: https://doi.org/10.1038/s41598-021-84092-1.
[120] Julious S A, Mullee M A. Confounding and Simpson's paradox BMJ 1994; 309 :1480
[121] Andrews, Nick, et al. "Duration of protection against mild and severe disease by Covid-19 vaccines." *New England Journal of Medicine* 386.4 (2022): 340-350.

these are the only sensible way of seeing whether a vaccine causes particular adverse reactions.

6.57 A study among younger people (aged 12-29) in England showed reductions in total (all-cause) mortality after all vaccinations.[122] There were slight excesses in cardiac death in women after a first dose of non mRNA vaccines, but overall deaths were reduced. The authors state, *"We found a significant decrease in the incidence of all-cause registered death, driven by the first two weeks after vaccination (any dose, week 1: IRR 0.47 [0.34, 0.64]; week 2: 0.77 [0.60, 0.99]."*

6.58 The study found much more dramatic effects after a positive SARS-CoV-2 test in unvaccinated people, with notable increases in all-cause mortality in the 5 weeks following a test. Cardiac deaths were very elevated in this group in the first week after a test. The excess was much less in those vaccinated who nevertheless had a positive test (about 1/5th of the risk in the unvaccinated).

6.59 A study from the USA[123] found a reduction in mortality among those hospitalised – "Statistically adjusted mortality rates for unvaccinated and vaccinated patients were 8.3% (95% CI, 8.1–8.5) and 5.1% (95% CI, 4.8–5.4)". Another study using a modified form of the SCCS design studied all-cause and non-Covid-19 causes of death and found substantial reductions for the vaccines in use in the US.[124]

6.60 Most studies look at death related to Covid-19 since it is that cause which is the target of the vaccines. Those that have looked at all-cause effects have not found excesses in total mortality and most have not found increases in even cardiac death. Carrying out a full review is a major undertaking, but others have reviewed the data.[125]

The systems and processes which were/are in place to detect whether the Covid-19 vaccines resulted in any increase in excess deaths and whether such systems and processes are effective

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[122] Nafilyan V et al. Risk of death following COVID-19 vaccination or positive SARS-CoV-2 test in young people in England. Nat Commun. 2023;14:1541.
[123] Baker TB et al. The Relationship of COVID-19 Vaccination with Mortality Among 86,732 Hospitalized Patients: Subpopulations, Patient Factors, and Changes over Time. J Gen Intern Med. 2023;38(5):1248-1255..
[124] Xu S et al. Mortality risk after COVID-19 vaccination: A self-controlled case series study. Vaccine. 2024;42(7):1731-1737.
[125] Global Vaccine Data Network (2024) 'Vaccine Victory: How COVID-19 shots slash all-cause mortality and outshine misinformation', 12 February. Available at: https://www.globalvaccinedatanetwork.org/news/Vaccine_Victory_How_COVID-19_shots_slash_all-cause_mortality_and_outshine_misinformation (Accessed: 11 December 2024).

6.61 As noted above, excess deaths are not the way to address this. There are many papers from the UK and elsewhere which track individuals who are vaccinated at various stages with primary and booster vaccines that show VE against death is substantial, even though the arrival of new variants means that the vaccines will not be as effective against them. PHE/UKHSA and others continually produced analyses of whether vaccines were providing protection against death.

Information provided about vaccine safety

Informing the public about safety issues in a timely fashion

6.62 In my view there was adequate information given regarding what was known at the time, but my expertise is not in risk communication. A prominent example of good risk communication with the public was the press conference on 7 April 2021, where a diagram produced by David Spiegelhalter and colleagues at the University of Cambridge's Winton Centre was used to explain the different risk benefit ratios of the AstraZeneca vaccine for different age groups (Figure 2).

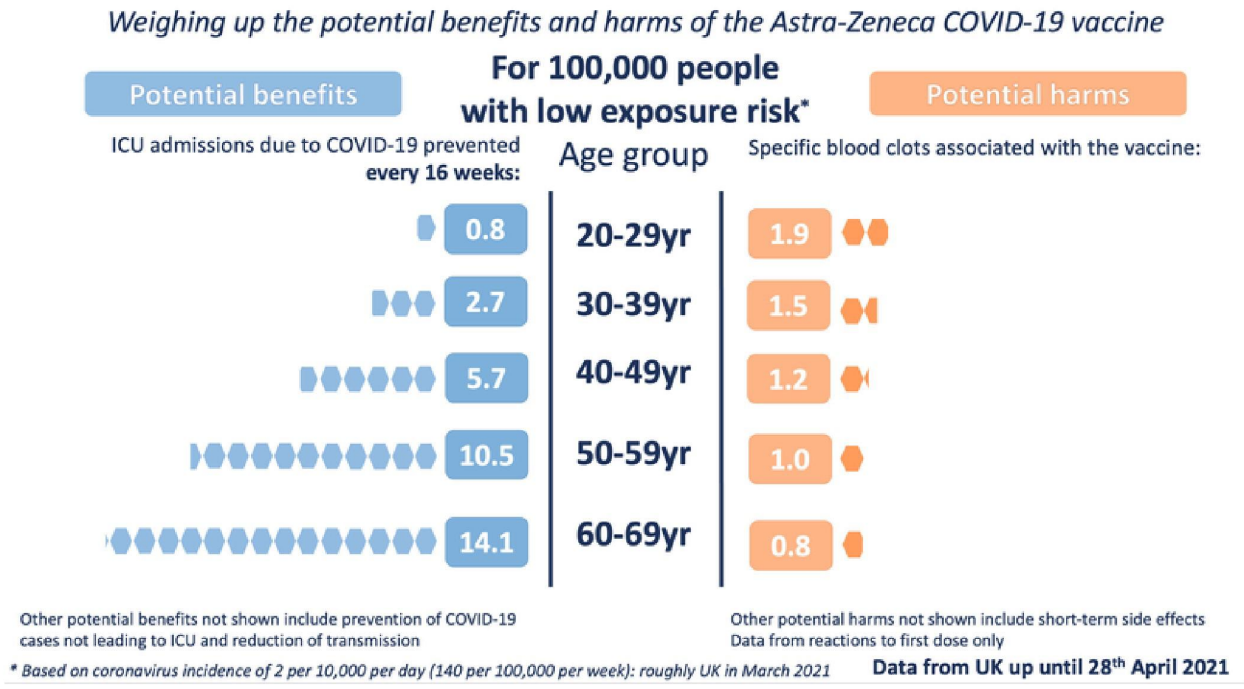


Figure 2: *Diagram from Winton Centre for Risk and Evidence Communication, communicating the balance of risks and benefits for different age groups from the AstraZeneca vaccine*

6.63 National protocols were in place throughout the UK in relation to administering each individual vaccination. For example, the protocol for the Pfizer vaccine in England (INQ000486279). This contains the following: "As part of the consent process, healthcare professionals must inform the individual/parent/carer that this vaccine has been authorised for temporary supply in the UK by the regulator, MHRA, and that it is being offered in accordance with national guidance. The Regulation 174 Information for UK recipients for COVID-19 mRNA Vaccine BNT162b2 should be available to inform consent" (page 15). The protocol also contains a section on reporting adverse reactions via the Yellow Card scheme (page 16). Information leaflets, which summarised adverse effects and contained information on Yellow Card reporting, were also available (see, for example, INQ000477102). The reality is that patients may not read the PILs (see my other concerns about PILs noted above at paragraph 2.48), especially in relation to adverse effects, and in mass vaccination campaigns PILs are available but may not be given to every patient. They reflected, with an inevitable delay, what was known. In my view there needs to be a new approach to PILs based on restructuring the current information on the internet. This could be split into the following categories: 1) what you need to know about risks before you are given a medicine; 2) what you need to know about risks while taking the medicine; and 3) what you need to know in the event that an AE has occurred that might be a result of taking the medicine. This latter section should explain excess risks and background risks for the relevant AE. In my view, especially with a vaccination campaign, where vaccinees know that they are to be given a vaccine in the near future, it is better to be able to access the relevant information while at home or in a library rather than at the last minute in a busy clinic, pharmacy, vaccination centre or GP surgery. The problem is that the potential for inequity then becomes considerable for those without internet access. However, the PIL-type information should be available at the point of vaccination, and more time might be given to those who have not had the opportunity to read information about a vaccine beforehand. Similarly having information available in printed form after vaccination is also important.

Information given to the public about procedures for reporting side effects

6.64 The MHRA do attempt to inform, but most of the time people don't need the information and so they ignore it. At paragraph 6.63 above, I provide examples of what

the national vaccination protocols and information leaflets contained regarding the Yellow Card scheme. I think we need to focus on what will make a difference to public health and not simply increase reporting. Getting many more reports about the well-known features of reactogenicity (sore arm, rashes, etc.) do not contribute to public health. The reports that benefit public health are the ones that "signal" a previously unknown adverse reaction. The public needs to be most aware of this and to be encouraged to ensure that they, or their health professional, reports something new. This is not easy to communicate.

Updating people who have received a vaccine of subsequently discovered side effects

6.65 There is no such system but there is widespread media reporting. Health professionals are informed but I see no realistic way of informing individual patients in a non-pandemic environment, never mind in a pandemic situation. The GP record will have the vaccination status and the GP will therefore have access to any problems that result in medical attention being sought. It is unrealistic to think that any healthcare system could or should follow-up millions of patients for a very rare outcome that has not yet resulted in symptoms appearing in that patient. For most of those patients any follow-up is unnecessary.

Providing information to the public about relative risk and absolute risk statistics

6.66 This is a very general issue and should perhaps be taught in schools. Major efforts are made by epidemiologists to explain the difference, but drug and vaccine scares sell newspapers etc., and social media flourishes through such things, so relative risks are emphasised there. Many journalists are highly responsible, but the headline writers seem to have a different agenda. Major efforts were made, repeatedly, in the pandemic to explain absolute risks, contrasted with relative risks. The BBC had an excellent statistician (Robert Cuffe) who explained many numerical issues very clearly during the pandemic. The example from Sir David Spiegelhalter quoted above and Figure 2 is a clear example showing that absolute risks are vital when balancing benefits and harms.

7. Conclusions and recommendations for improvement of systems and processes concerning vaccine safety; aspects relevant to a future pandemic.

I summarise my key conclusions as follows:

7.1 The authorisation process used in relation to the Covid-19 vaccines in the UK was appropriate to the circumstances and was based on a large amount of data. While the authorisation process was expedited by way of, among other things, a 'rolling review' of trial data, this did not impact on the assessment of the safety of the vaccines. The basic principles of assuring efficacy, safety and quality which apply to medicine regulation outside of a pandemic were applied to the authorisations of the Covid-19 vaccines by the MHRA.

7.2 The oversight mechanisms for the Covid-19 vaccine clinical trials were robust and on a par with non-pandemic standards. There were large numbers of participants in the Covid-19 vaccine trials; however, the trials were never going to identify very rare adverse effects which only came to light when millions had been vaccinated.

7.3 The MHRA's 'four pillar' strategic approach to post-authorisation monitoring of the Covid-19 vaccines was reasonable and built upon tried and trusted methods of analysis.

7.4 The Yellow Card scheme's passive collection of spontaneous reports is only one part of the pharmacovigilance jigsaw and its greatest value is in identifying new safety signals. Observational studies, using electronic health records, provide a less biased and more detailed picture than spontaneous reports. Such studies are central to establishing whether signals are actually adverse reactions to the vaccines. The UK was at the forefront in relation to these; however, improvements could be made to ensure better access to more comprehensive healthcare data.

7.5 The UK regulatory system responded effectively to safety concerns, including those relating to Thrombosis with Thrombocytopenia Syndrome (TTS) and myo/pericarditis. Safety signals were examined by the MHRA in a timely and thorough manner with the assistance of expert working groups. It is easy, with hindsight, to say action should

have been taken sooner but this ignores the finely balanced nature of risk/benefit assessment in a pandemic.

7.6 Global information sharing and collaboration is key and to the extent that this was affected by the UK's departure from the EU this should be addressed. Consideration should be given to obtaining formal involvement with the EU processes and data on safety of medicines.

7.7 Steps taken to convey information to the public about the risks of the Covid-19 vaccines were adequate. In particular there was a great deal of transparency regarding Yellow Card reports. However, a new approach is needed to Patient Information Leaflets, with categories of information - what one needs to know and when - available online using a structure that is appropriate to the user's needs at different stages of their taking a medicine.

Recommendations

A. Authorisation of medicines

The basic systems of assuring efficacy, safety and quality must remain. The requirements for randomised trials to show benefits on clinical outcomes should be retained for all pandemic vaccines. Randomised trials with surrogate variables may be possible once correlates of protection are known. Trials should be powered to detect a doubling of risk for an adverse event that occurs in the background at 1 in 1,000 during two months, that is over 23,500 per group, in addition to any considerations around efficacy.

B. Process of authorisation

Rolling reviews can be utilised and should be in an emergency. They will not be necessary for routine authorisations. Authorisation of randomised trials should be done as simply and quickly as possible. Large trials should be facilitated. A key thing is to make initiation of randomised trials by respected and experienced investigators as easy as possible, and more randomised trials should be done.

C. Using roll out of vaccines to generate higher-quality evidence on adverse effects

It should be routine that all treatments are randomised wherever possible, unless there are strong reasons against, rather than at the moment putting heavy barriers against randomisation. Consideration should be given for all vaccines to be introduced using cluster randomised trials using EHRs for follow-up, so that genuine adverse effects are detected earlier, and spurious effects are reduced if not eliminated. The MHRA witness statement (INQ000474337 para 821) suggests that only a small proportion of RCTs in the pandemic led to "actionable data". This requires investigation so that useless trials are not initiated, though it is possible that the situation in the UK was better than elsewhere in the world. The use of "Cluster RCTs"[126] should be utilised during rollout of vaccines. These would allow for different vaccines to be randomly allocated to say clinics or GP surgeries rather than randomising individual participants. Individual consent to this should not be necessary. If a single vaccine only is available, then a variation of such trials, the "Stepped-Wedge" design[127] is appropriate. Here everyone eventually gets the vaccine but the time when it is given is randomised in groups. It is of considerable utility in a pandemic when the supply of a new vaccine is restricted in the early stages.

D. Databases of Electronic Health Records

EHR use in a pandemic should be made dramatically easier with linkage to various different data sources. There was no linkage between GP health records and occupational records. If there had been, we might have learnt much earlier about the dangers faced by low-paid workers in jobs having close proximity to large numbers of members of the public. The current national database of Hospital Episode Statistics is a summary record with a notable delay before it is available for linkage to e.g. GP records. Better linkage to hospital data is required. Non-prescription medicines should be able to be linked to individual health records. Lack of knowledge of these can lead to biased estimates of effects in epidemiological studies. GP records contain only prescription records. The use of EHRs to assess medicines, both drugs and vaccines, was a major step forward and will be vital in the future. The terrible effects of the pandemic were turned into a major commitment by a wide range of people to do good quality research at high speed with very little funding. This could not be sustained, and delays in obtaining funding, especially for infrastructure, caused

[126] Patrick J. Heagerty (2023) 'Cluster Randomized Trials', *NIH Clinical Trials Collaboratory: Rethinking Clinical Trials.* Available at: https://rethinkingclinicaltrials.org/chapters/design/experimental-designs-and-randomization-schemes/cluster-randomized-trials/ (Accessed: 11 December 2024).

[127] LSHTM (2015) *Stepped-Wedge Trials | Quantifying impact | Centre for Evaluation.* Available at: https://www.lshtm.ac.uk/research/centres/centre-evaluation/stepped-wedge-trials (Accessed: 11 December 2024).

delays in research output. Key people in being able to do this are software developers who can make very high salaries in the financial world, so they make considerable sacrifices to work in health on relatively low salaries. They are needed, not for specific projects but for any project that is done using many millions of EHRs in a Trusted Research Environment.

E. Prizes to incentivise clinicians to recognise and report new potential side effects.

This idea is to encourage reporting of new suspected adverse reactions (as noted above at paragraph 6.34, which, for most health professionals, will not increase their workload notably, but will allow them to make an important contribution to public health as well as looking after their own patients. Recognition of such contributions by prizes will not be a major resource but utilises the ability of health professionals to be alert to something unusual. There will need to be national levels of publicity around this, and it should apply in all situations but especially in a pandemic.

8. Appendix 1 Numerical measures used in vaccine studies

The measures explained below are *"risk", "risk ratio", "odds", "odds ratio", "hazard", "hazard ratio", "vaccine efficacy"*, "*incidence rate*", "*incidence rate ratio*" *"relative risk"*, "*confidence intervals*", *"absolute risk"*, "*statistical power*", "*statistical significance*" and *"sample size calculations"*.

Events

8.1 Many studies, especially with vaccines, count the number of times an "event" occurs, rather than measuring something as a continuous number like blood pressure or weight.

8.2 An "event" is something that occurs or does not occur, often referred to as a binary outcome. It can be death, or a non-fatal event like a heart attack. With vaccine research it is often occurrence of an infection or clinical symptoms of a disease caused by an infection. Admission to hospital with disease caused by an infection (hospitalisation) is also a frequent binary outcome.

8.3 Taking an example of a clinical trial of a vaccine, after the vaccine being studied is given to the participants, they are followed up to take regular measurements assessing its effect in comparison with the control. As the key element of the follow-up in a trial with a clinical outcome (not a surrogate), the proportion of those who get the disease in the vaccinated group is compared with the proportion who get it in the control group.

8.4 The definition of "disease" could be "infected with the virus". This may include those *with* symptoms (clinical cases) and those *without* symptoms (asymptomatic cases) but is sometimes only clinical cases. These may also be graded as to their severity, and this requires careful pre-definition of the criteria to classify severity, and this should be done without knowledge of whether the participant was in the vaccine or the control group.

Risks

8.5 "Risk" has a technical statistical meaning that is more precise than its use in general English. In a trial both groups are followed up equally and identically, and the numbers who get the event of interest are counted and summarised possibly during the trial for a data monitoring committee, but certainly at the end of the trial. The "risk" is the numbers who get the event divided by the numbers who could have got the event. The latter are called those "at risk" of having the event. Those at risk are taken as the numbers in the vaccine or control groups at the start of the study. "Risk" is then a proportion (a number between 0 and 1), but for descriptive purposes is often given as a percentage.

Risk Ratio

8.6 To compare the groups, the ratio of the risk in each group is taken and the convention is that this "risk ratio" is the risk in the vaccine group divided by the risk in the control group.

8.7 If the vaccine makes no difference the risk on average will be 1, and if it is beneficial, the risk ratio will be less than 1, and if it is harmful, it will be greater than 1 (the risk in the vaccine group is greater than the risk in the control group.

8.8 As an example, if 100 people are in each of the two groups, vaccine and control, and at the end of the study 10 people in the vaccine group get the "event", say "symptomatic infection", and 20 people in the control group have the event.

8.9 Then the "risk" in the vaccine group is 10/100 = 0.1 (or 10%) and in the control group is 20/100=0.2 (or 20%). The ratio of these risks is 0.1/0.2 =0.5.

8.10 This risk ratio may also be expressed as a percentage 50%. The vaccine is preventing 50% of the events.

Vaccine Efficacy

8.11 "Vaccine efficacy" (VE) expresses the prevention of a specific adverse event in numerical terms as (100- "risk ratio expressed as a percentage"). In the fictitious example it is 50%.

8.12 VE may be estimated most reliably in a randomised trial but may also be estimated with greater uncertainty in non-randomised studies[128] [129]. The uncertainty is not generally fully captured in the confidence interval (see below) quoted. The confidence interval is calculated purely on the numbers involved and does not incorporate the uncertainty arising from bias or other forms of non-comparability between the vaccine and control groups.

8.13 VE is not a fixed number. It will have different values according to the outcome being studied. It will be different for infection (and possibly different between symptomatic and asymptomatic infection), hospitalisation for the infection and death from the infection. Usually, the more serious the outcome studied, the greater the VE. This is because a vaccine might not totally prevent infection but will usually reduce the severity of the infection.

8.14 It may also vary with the duration of follow-up and with the prevalence of the virus circulating in the population studied.

Real Example

8.15 For a genuine example, the table below shows the results for the Matisse trial of a vaccine against Respiratory syncytial virus (RSV)[130]. The groups were randomly allocated to vaccine or control and then they are followed up to see if they get symptoms of a lower respiratory tract infection likely to be caused by RSV. "Nasal swabs for reverse-transcriptase–polymerase chain-reaction (RT-PCR) assays were obtained at any medically attended visit for respiratory infection." If the swab test showed that their symptoms were caused by RSV then they were classified as a case of RSV disease that required medical attendance. An adjudication committee reviewed each case and classified them as "severe" or not. The primary endpoint was "severe RSV infection" within 90 days.

[128] Hulme WJ et al. Challenges in Estimating the Effectiveness of COVID-19 Vaccination Using Observational Data. Ann Intern Med. 2023;176(5):685-693.
[129] Evans SJW, Jewell NP. Vaccine Effectiveness Studies in the Field. N Engl J Med. 2021;385(7):650-651.
[130] Kampmann B et al. N Engl J Med 2023;388:1451-1464

	Vaccine	Control
Cases of severe RSV disease	6	33
Participants without disease	3489	3447
Total	3495	3480

8.16 In the vaccine group the risk was 6/3495 (0.0017 or 0.17%), while in the placebo group the risk was 33/3480 (0.0094 or 0.94%) got severe disease. The ratio of these (0.17/0.94), the risk ratio is 0.18. Then, the vaccine efficacy (VE as %) against medically attended severe disease is calculated as

100%-(0.18*100) =82%.

8.17 If the clinical outcome were different, then different numbers would be counted. So, for any RSV disease the numbers of cases were 24 vs 56, leading to a VE of 57%. This difference is in the direction noted above; that is that the vaccine will usually be more effective at preventing severe disease.

8.18 If there were no difference in the proportions, then the risk ratio would be 1 and VE would be 0%.

Outcome event definition

8.19 The MATISSE trial illustrates that the definitions of the outcome must be done carefully and that pre-defining which outcome to be analysed is vital to avoid "cherry-picking" the result to suit the views of a commentator or investigator. In the MATISSE trial, "severe" disease gave convincing evidence of benefit, while for non-severe disease the evidence was weaker.

Odds vs proportions

8.20 Those who make bets regularly may be familiar with "odds". Instead of the proportion of those with the event the "odds" uses the ratio of the numbers of those with the event

to the numbers of those without the event. returning to the fictitious example, the odds of having the event in the vaccine group would be 10:90, 10/90 = 0.1111

8.21 In the control group it would be 20:80, 20/80 = 0.25.

8.22 These values are somewhat different to the proportions or risks calculated above. The odds will always be larger than the proportions because the denominator for proportions has those with the event included in it, while for odds it does not.

Odds ratios

8.23 These may be calculated like the risk ratio and are, conventionally, the ratio of the odds in the vaccine group divided by the odds in the control group. In the fictitious example above it is (0.11/0.25) = 0.44. Simply because of the mathematics, the odds ratio will be further from 1 than the risk ratio.

8.24 When the numbers of those with the event are small compared with those at risk, having them included or not in the denominator makes little difference. The odds ratio and risk ratio will be similar with rare events.

MATISSE example

8.25 The slightly different numerical calculation takes the ratio of cases to non-cases which from the table above is (6/3489) also, to two significant figures = 0.0017 - the "odds" of being a case of disease in the vaccine group to (33/3447) = 0.0096- the "odds" of being case of disease in the control (placebo) group. The ratio of these, the "odds ratio" is 0.1796. Here, cases are rare, and the odds ratio and risk ratio are approximately equal, with the odds ratio always being a little further away from 1.

"Hazard" and "Hazard Ratios"

8.26 In any trial in which people are followed up over time, the numbers of those "at risk" of having the event occur to them can vary over the follow-up time. Those who have already had the event are no longer "at risk"; there can be loss to follow-up or withdrawal from a trial, which, if the proportion being lost starts to reach 1% can affect the results of the trial, or if the proportion with the event becomes large similarly the

numbers "at risk" may be substantially different At any instant of time when at least one participant experiences the event, the ratio of the number experiencing the event to the number "at risk" is called the "Hazard". Dealing with follow-up over time, taking into account varying numbers at risk is called "survival analysis", as it was developed in the context of studying death as the event of interest, but the methods can be applied to any event. The "hazard" is then varying over time but may be cumulated or averaged to obtain the overall hazard for a group.

8.27 The most common measure is the "hazard ratio" which is the ratio of the hazards in the vaccine and control groups. This will be of a similar value to the odds ratio and hazard ratio but is often a better measure since it takes the follow-up time pattern into account.

8.28 Analysis of trials can be quite complex and there is a variety of validated and standard statistical software that is able to calculate all these different measures.

8.29 All these measures may be calculated in non-randomised studies but interpretation, especially of the confidence intervals, must be done in those studies.

"Incidence rate"

8.30 Incident cases are new cases of a disease in people who did not have that disease during some previous time (sometimes a lifetime), The incidence rate is the number of new cases in a specified population over some defined period of time, divided by the person-time at risk in that population. It is usually expressed as a rate per 1000 or 10,000 person years even though it may not be measured over even a full year. If you follow up 100 people for 1 year each, and 400 people for 3 months (1/4 of a year) each, the total person-time at risk would be 200 person-years. It is an absolute measure of risk. It effectively assumes the rate is constant over that time.

"Incidence rate ratio" (IRR)

8.31 This is the ratio of the incidence rates in a vaccine (or other exposure) to the incidence rate in a control group. In some studies where a person acts as their own control, it is the incidence rate in a defined period after vaccination, compared with the incidence

rate in control period(s) where the person is not exposed to the vaccine. The IRR is a relative measure of risk.

Relative risk

8.32 The term "Relative risk" can be loosely applied to the risk ratio, the odds ratio or other statistical measures such as those used in survival analysis, the "hazard ratio" described above or even incidence rate ratios. In the results of studies these ratios will be similar unless the proportions (or percentages) with the disease or infection become quite high, above 10%. So in the fictitious example we see a difference between the risk ratio of 0.5 and the odds ratio of 0.44. Using the term "relative risk" without it being clear to what it refers, is not good scientific usage, but is often found in the literature.

Uncertainty and confidence intervals

8.33 It is clear that with the fictitious example, if just one or two of the cases had been classified differently, the numerical effect on the risk ratio or odds ratio would change quite a bit because the numbers are small. It is intuitive that the uncertainty is dependent on the numbers of cases in the study and hence on the total sample size.

8.34 There are statistical formulae, derived from mathematical theory, that enable a range of uncertainty to be given to each of the numbers. These formulae can be found in statistical textbooks or on the Web. It is conventional to use a 95% range of uncertainty, which may be called a "confidence interval", or when using a Bayesian approach to statistics[131] it is called a "credibility interval". Sometimes 90%, 99% or other intervals may be used.

8.35 It is important to note that there are many assumptions baked into calculations of confidence intervals, so it is not simply an interval with a 95% probability of containing the true value. Professor David Spiegelhalter describes a 95% confidence interval as "the result of a procedure that, in 95% of cases in which its assumptions are correct, will contain the true parameter value".[132]

[131] Bayesian Approaches to Clinical Trials and Health-Care Evaluation. D.J. Spiegelhalter, K.R. Abrams and J.P. Miles. Wiley, Chichester, 2004
[132] Spiegelhalter, D.J. (2019) The art of statistics: learning from data. [London] UK: Pelican.

8.36 In the fictitious example the 95% confidence interval for the risk ratio of 0.5 is (0.25 to 1.01). For the odds ratio of 0.44 it is (0.2 to 0.99). There can be slightly different ways of calculating these intervals and again, it is vital to pre-specify in the study protocol how the intervals are calculated, and which % interval is used as well as what measure, odds ratio or risk ratio, is to be used. Bias can result from making post-hoc decisions.

8.37 As noted above, the interpretation of confidence intervals from randomised studies is fairly straightforward, but non-randomised studies may have non-random differences between the groups being compared and the confidence interval does not capture that uncertainty. It will typically require the injection of some expert opinion in order to estimate uncertainty arising from sources other than the sample size. Confidence intervals may be applied to all the relative and absolute measures of risk.

Absolute Risk

8.38 The measures that involve ratios are relative measures, but for clinical and public health purposes it is vital to understand what absolute risks apply.

8.39 In the fictitious example we had a comparison of 10/100 in the vaccine group with 20/100 in the control group.

8.40 The rate of events caused by a virus will depend on many factors, especially what proportion of the population currently are exposed to the virus. The relative measures are used because they are often not dependent on the so-called “background rate”. This is effectively the risk in the control group; 20/100 in our example. If the numbers instead were 1/100 compared with 2/100 or 1/10,000 compared with 2/10,000, the relative measures would be essentially the same, the risk ratio would still be 0.5. Alternatively, if they were 20/100 and 40/100, again the risk ratio would be 0.5.

8.41 However, the public health impact would be quite different. The absolute risk difference in the original fictitious example was 10/100 compared with 20/100 and the absolute risk difference is (10/100)-(20/100) = 10/100 (10%), a reduction of 10 cases per 100. The other two fictional scenarios had a reduction of 1 per 100, 1 per 10,000 and 20 per hundred. Very different results in public health terms.

8.42 When you think about risk in absolute terms, time needs to be taken into account. The two arms in the trial were each followed for the same time (it is assumed) but the public health impact would be quite different if the trial duration was 1 week, 1 month, 1 year or say 5 years.

8.43 Absolute risks should not be given as pure numbers but should say over what time period the cases were counted, and for this reason the word *'rate"* is generally used to show that time is involved.

8.44 If the difference in risk is 10 per hundred participants and it is a trial of one year duration, the difference is 10 per hundred person years. If it is over 5 years and still 10 per 100 participants and they are all followed for 5 years, then it is (10/500 person years) 2 per hundred person years. A major problem is that absolute risks may vary widely with another factor such as age, and so the ages concerned must be defined carefully. Relative risks tend to be more stable with such factors but are not always exactly the same and can have important differences.

8.45 In practice, the usual denominator is per 1000 person years but sometimes 10,000 or even larger denominators may be used in population studies.

Benefit-risk balance

8.46 If a trial of a vaccine shows an absolute reduction of, let's say, clinically severe disease of 50 per 1000 person years exposed to the virus, and a separate observational study of 100,000 people followed for a year has a risk ratio of 4 for some adverse event, it is vital that the absolute rate of occurrence of this adverse event is reported and not just a relative measure. If the "background" or control group rate is 1 per 10,000 person

years then the vaccine rate is 4 per 10,000 person years for that adverse event. The absolute risk difference per 1,000 is an increase of 0.4-0.1 = 0.3 per 1000 person years. This needs to be set against the benefit of 50 per 1,000 patient years. Now the severity of the disease prevented and its sequelae must be balanced against the harm and its consequences. It is not the different relative measures that should be used in balancing benefit and harm.

8.47 The process of regulatory decision-making is (or should be) always a careful balancing of benefits and harms. The problem is that the absolute risk can vary with, for example, calendar time, age, gender, economic status and other factors. This can make such decision making very difficult when the data are not fully characterised by age etc. In the absence of good data expert opinion may have to be relied upon.

Statistical Power

8.48 Statistical power relates to statistical hypothesis testing and refers to the probability that a test will correctly reject a null hypothesis that is assumed to be false. It is the likelihood that a study will detect an effect when there is one to be detected. This effect can be a benefit or a harm.

- Null Hypothesis (H_0): This is an assumption that there is no effect or difference. It may be expressed as an odds or risk ratio of 1.
- Alternative Hypothesis (H_1): This is the hypothesis that there is an effect or difference. The magnitude of this difference will need to be defined and can vary.
- Type I Error (α): The probability of rejecting the null hypothesis when it is true (a false positive). In most hypothesis testing a value of α of 0.05 is conventionally taken as the largest probability that is used. Sometimes a value of 0.01 may be used.
- Type II Error (β): The probability of not rejecting the null hypothesis when it is false (a false negative). In statistical power calculations it is this value which is calculated.

8.49 So, a formal statistical definition of Statistical Power of a test is expressed as $(1 - \beta)$. It is the probability that it will reject a false null hypothesis (i.e., detect an effect if there is

one of a specified magnitude). A powerful test is one that is good at detecting differences when they exist.

8.50 In general, the larger the sample is, the greater the statistical power. When dealing with "events" (like "infection with a virus", or "hospitalisation") it will depend even more crucially on the number of events. So a trial can have tens of thousands of participants, and if it has as the outcome "symptomatic infection with SARS-CoV-2", but only a small number, say less than 5, such outcomes actually occur, it will still have low power to detect a reduction in the outcome using the vaccine. Similarly, if a harm is very rare, then the power to detect it will be low.

8.51 There are statistical calculations that can precisely obtain the power, given various assumptions, particularly those at 2 (H_1) & 3 (α) above. The magnitude of the difference needs to be set out (and often power is calculated for various possible differences).

8.52 The key things that affect power can be set out as-

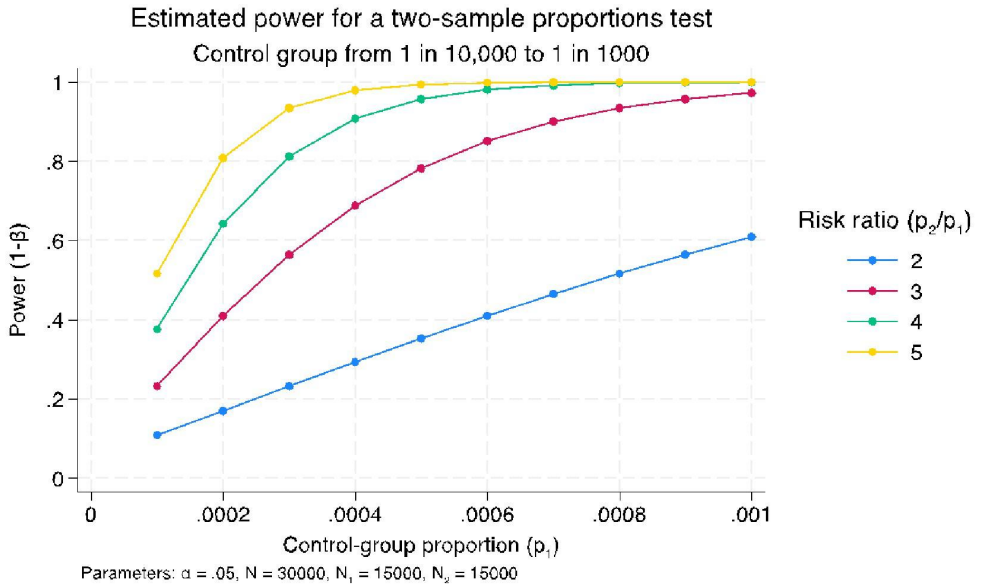
- Sample Size: Larger samples tend to provide more information and thus increase power, with the caveat noted above related to numbers of events.
- Effect Size: Larger effects are easier to detect, so power increases with effect size. It is easier to detect a risk ratio <0.2 than a risk ratio<0.5 (or equivalently a risk of 5 than one of 2.
- Significance Level (α): A higher significance level (e.g., 0.05 vs. 0.01) increases power but also increases the risk of a Type I error.
- Variability in Data for a continuous outcome: Less variability in the measured data increases power because the effect becomes more distinguishable from random variation. For binary outcomes, the variability is determined by the risk in the comparison group. With very low risks (and so very rare events) the power is lower than for higher risks.

Statistical significance

8.53 When hypothesis tests are carried out, a probability value "The P value" is calculated and if this is less than the pre-defined chosen value of α, then the result is called "*statistically significant*". It is written as P<0.05. It is better practice to give the exact P value, and even better to calculate a confidence interval. It is often written with a lower-case p, but this is better reserved to refer to a proportion.

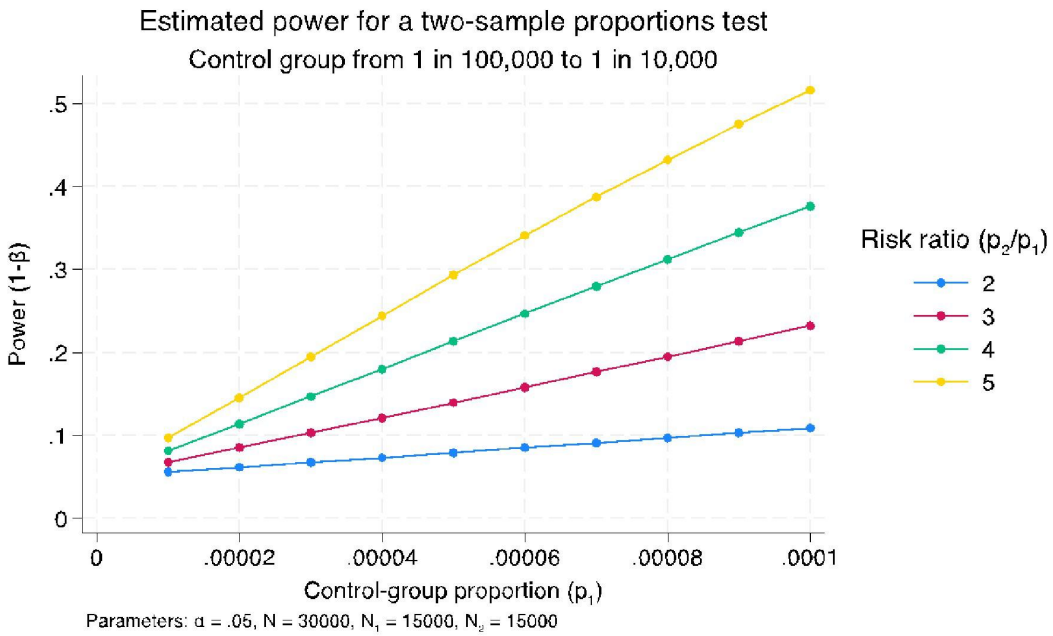
8.54 It must be realised that statistical significance does not mean "clinically important". This is one of the reasons why confidence intervals are better, because the likely range of an estimate can be used with clinical judgement to see whether the results may be clinically meaningful. A very large sample size can result in a finding to be statistically significant, but of little or no clinical relevance. A very large trial can find a difference in blood pressure between two treatments of 0.1mm Hg, which has no clinical relevance. On the other hand, a study that finds the results to be "*not statistically significant*", does not mean "*no difference*". The study may be too small to detect what might be of clinical or public health importance. If the 95% confidence interval for the risk ratio of a serious adverse event is from 0.9 to 3.0, the null hypothesis value of 1 is within that interval, and P >0.05 so the result is "not statistically significant, but if the true risk ratio is even 2, a doubling of risk could be important. The absolute risk difference will determine whether it is or not.

8.55 The graphs below illustrate the general principles:



8.56 The graph above shows that with a total trial size of 30,000 participants and a control or background rate of an event being 1 in 10,000, even a 5 times increase in risk has a low power of having convincing evidence of that increase (the yellow curve at a control group proportion of 0.0001 (1 in 10,000) has a power of 0.5). For a doubling of risk the power is below 0.6 even for a control group rate of 1 in 1000 (the blue line does not go above 0.6).

8.57 For the graph below the control group rate is reduced by a factor of 10, and it can be seen that for all comparisons up to an increase of 5 times in the risk, power remains very low.



"Sample size calculations"

8.58 When a study, especially a randomised trial, is being designed, very careful consideration is paid to the number of subjects required- the "sample size". In nearly every situation, this is based on the benefit that is expected to be clinically meaningful. The power calculations will be varied to set out the various assumptions around type I and type II errors and the intended "power" of the study is set. The control group proportion of events is set out, based on what is known at the time, and the risk ratio or vaccine efficacy that is desired to be detected is also set out. For vaccine trials this will result in the number of events that need to be seen to achieve the objectives. This will also be dependent on the duration of the trial. Safety is considered when specifying the duration. There will need to be a certain period of follow-up so that adverse events that do not appear immediately are able to be seen.

8.59 The Pfizer trial of the original vaccine against Covid was requiring a total of 164 events, which were test-confirmed cases of infection with SARS-CoV-2 having clinical symptoms.

9. Appendix 2 - an overview of the US's FDA Regulatory process for the Pfizer Covid vaccine

Context and Background for the USA

9.1 There has always been pressure on medicine regulators to speed up the approval process. The US Congress introduced legislation in 1992 to allow the FDA to collect fees from industry (previously it was essentially supported by central taxation). According to the US organisation representing the pharmaceutical industry, the Prescription Drug User Fee Act (PDUFA) was "*created in response to a bottleneck of new medicine approvals that left patients waiting for years for an under-staffed and under-funded FDA to review new drug applications. Before PDUFA, it often took the FDA more than two years to review new medicines, and more than 70% of medicines were first approved outside of the United States*" [133].

9.2 They go on to state that, having passed the act in 1992, *"30 years later, the average approval time for a new medicine is 10 months for standard applications and eight months for priority review applications, and in 2021 alone, approximately 76% of novel drugs were approved in the United States before any other country. PDUFA has played an essential role in strengthening FDA's ability to support innovation while maintaining the Agency's high standards for scientific rigor and patient safety".*

9.3 The act requires renewal every 5 years. The fees for assessment of studies that required clinical data having been $100,000 in 1992 had reached $2.87M[134] in 2021 and $4M in 2024[135]

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[133] https://phrma.org/en/policy-issues/Research-and-Development/PDUFA (Accessed 11/12/2024)
[134] Mitchell AP et al. The Prescription Drug User Fee Act: Much More Than User Fees. Med Care. 2022;60(4):287-293.
[135] https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments (Accessed 11/12/2024)

9.4 Following these increases in fees, the FDA started to offer "Fast Track" assessment where there is "*the potential to address an unmet medical need*", which means the medicine may be eligible for[136]:

- *"More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval*
- *More frequent written communication from FDA about such things as the design of the proposed clinical trials and use of biomarkers*
- *Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met*
- *Rolling Review, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed. BLA or NDA review usually does not begin until the drug company has submitted the entire application to the FDA*
- *Fast Track designation must be requested by the drug company.*"

9.5 "Priority Review" refers to the timescale of the review with 60 days being the target; it does not affect the requirement for full data for an approval.

9.6 "Accelerated Approval" does affect the data required to be submitted and will allow for a surrogate variable to be used as the primary outcome and not a "clinical endpoint" (see the main document for more details". This means the randomised trials can be of shorter duration and smaller sample size so that they take less time. The FDA will require that a surrogate endpoint has been shown to correlate with a clinical endpoint, and will also require further studies to confirm this in practice. The use of only a single "pivotal" trial has increased since 1992, though they did occur prior to then[137].

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[136] https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track (Accessed 11/12/2024)

[137] Darrow JJ et al. FDA Approval and Regulation of Pharmaceuticals, 1983-2018. JAMA. 2020;323:164-176.

9.7 In 2020 , as the structure and genetics of the SARS-CoV-2 virus became known, the potential for a vaccine to be developed was of major interest.

9.8 The potential for Emergency Use Authorisation (EUA) existed long before the 2019 pandemic and was brought up to date in 2013 after the 2008-10 H1N1 flu pandemic. It requires that the United States secretary of health and human services declares that an EUA is appropriate, which is beyond declaring a public health emergency, and this happened in February 2020. It applies to drugs as well as vaccines and the first EUAs were approved before any vaccines were available[138].

Submission to FDA by Pfizer/BioNTech for an EUA for their vaccine

9.9 This occurred in November 2020[139]. The FDA's "Vaccines and Related Biological Products Advisory Committee" (VRBPAC) had a meeting on 10th December 2020 and links may be followed from the meeting announcement to all documents[140]. While this document written by SJWE refers to the FDA process, with the exception of being done in public and with public comment, a similar process goes on at the MHRA with the CHM as advisory committee and at the EMA with the CHMP as advisory committee[141].

9.10 There is a full transcript of the meeting which runs to 400 pages, and this includes the individual votes.

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138 https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#abouteuas (Accessed 11/12/2024)

139 https://www.fda.gov/media/144246/download (Accessed 11/12/2024)

140 https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-10-2020-meeting-announcement (Accessed 11/12/2024)

141 It should be noted that with a very few exceptions nearly all the members of the CHMP are employees of the relevant member state's medicines regulatory authority or within other government agencies. In theory they are appointed as expert scientists by their government, but they are rarely at the forefront of any medical or scientific field but are experts in regulatory matters. They will generally have taken advice from their national advisory committees who will have leading experts in relevant clinical fields.

9.11 There are links there, which is the meeting announcement, firstly to the live meeting, and notes of how the public (or for example, interested academics) could send questions or documents to the committee. Secondly there are links to all relevant documents. Key documents would be available two days before the meeting. A session of the meeting allows for comments from the public.

9.12 The FDA themselves have a briefing document which is essentially their assessment of the data and information submitted by the company. The FDA present their view of the background and after some other presentations, the company present their view of the data and their briefing document is also available. Then the FDA present their technical view of the submission. All the slides from the meeting are also available from links followed from the meeting announcement.

9.13 There is a list of voting members (that includes people from the pharma industry, though not from the companies making the submission) with knowledge of vaccines. Most of the members are from infectious disease, paediatric (most vaccines are given to children) and other clinical specialties. There are statisticians, a lawyer/consumer representative. Most are from academia though some are from the National Institutes of Health (NIH) or Centers for Disease Control (CDC).

9.14 After the presentations there is an extended time for discussion by the advisory committee followed by votes on the question asked by the FDA. The votes are not binding on the FDA, it is after all an "Advisory" committee, but the FDA almost always follows the general advice though there are a few occasions when they approve a drug a committee has advised against and not approved a drug a committee has voted for.[142] There are details around what exactly goes

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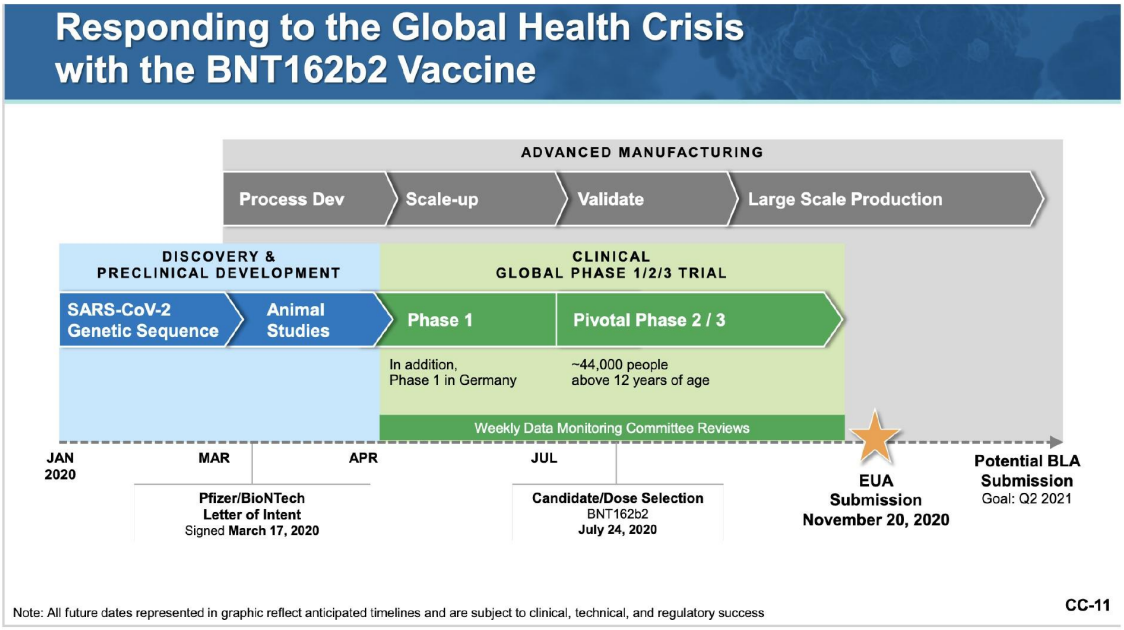
142 https://pink.citeline.com/PS147536/Advisory-Committee-Disagreement-With-US-FDA-On-Approval-Decisions-An-Increasingly-Rare-Event#:~:text=The%20study%20found%20only%20six,advisory%20committee%20had%20recommended%20approval. (Accessed 11/12/2024)

onto the "label" ("Summary of Product Characteristics in the EU) which are decided by the FDA.

Key aspects of the Advisory Committee's deliberations

Overall process

9.15 A useful part of the Pfizer presentation was this slide[143]



9.16 It shows the development process, which in spite of being shortened compared with the usual timescale (immense resources were devoted to the program), there was more than six months from early production of the vaccine to be used in lab and animal studies to the point where the phase 2/3 studies had accumulated sufficient data to be submitted for an EUA.

9.17 Following slides show the key preclinical data; then the phase 1 data with neutralizing antibody and cellular responses from German and US studies.

[143] https://www.fda.gov/media/144325/download (Accessed 11/12/2024)

9.18 A summary of the planned pivotal trial is given which intended to recruit 44,000 participants with a substantial number of older patients than are usually included in randomised trials. For context, it may be noted that the median number of patients included in drug trials used for approvals at the EM was found to be <2000[144]. Vaccine trials tend to be larger, but this was definitely a very large trial.

9.19 A great deal of attention is paid to clinical safety with the anticipated adverse events being ascertained (solicited), together with unexpected adverse events which are also recorded and documented. It may be noted that there were only 6 deaths, 2 on vaccine and 4 on placebo, so with such low numbers almost nothing can be said about VE for death.

9.20 There is then a major discussion on efficacy, and what was at the time, completely unexpectedly high rates of VE across all groups.

FDA presentation

9.21 For both the Pfizer and the FDA presentations the briefing documents contained many more details than the presentations. The advisory committee members will have read the briefing documents, especially the one from the FDA.

9.22 The FDA presentation emphasises the legal basis for an EUA and notes the requirements on both efficacy and safety issues. It also discusses the follow-up for rarer adverse events when the vaccine is rolled out (there was a separate presentation on this from CDC which also describes plans to monitor VE in sub-groups).

[144] Duijnhoven RG et al. Number of patients studied prior to approval of new medicines: a database analysis. PLoS Med. 2013;10(3):e1001407

9.23 The transcript shows that there was a great deal of scrutiny, though much of the detailed assessment was done by the FDA well before the VRBPAC meeting and put into their briefing document.

Conclusion

9.24 The notion that the standards were notably lowered to obtain the EUA cannot be sustained.

9.25 The UK CHM and its vaccine sub-committee(s) will have received from Pfizer essentially the same data as the FDA and came to the same conclusion. Since the pivotal trial was ongoing, there are minor differences in some numbers. While the MHRA staffing levels are much lower than the FDA, as pointed out elsewhere this particular period was one where MHRA staff had availability to work on the assessments. Their public reports, particularly the assessment report from December 2020 had much less detail than the FDA reports but showed that they had seen the same key data[145]. The MHRA report was a total of 74 pages.

9.26 The EMA was intermediate between the FDA and the MHRA in its length of report[146] (140 pages). The index on pages 2/3 gives a useful overview of the topics which go into an assessment. The timetable in section 1.2, pages 9-11 of this public assessment report also gives a clear picture of the rolling review.

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https://assets.publishing.service.gov.uk/media/63529601e90e07768265c115/COVID-19_mRNA_Vaccine_BNT162b2__UKPAR___PFIZER_BIONTECH_ext_of_indication_11.6.2021.pdf (Accessed 11/12/2024)

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https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf (Accessed 11/12/2024)

Appendix 3 - Documents disclosed by the UK Covid-19 Inquiry

INQ000474337	Witness Statement provided by Dame June Munro Raine on behalf of Medicines and Healthcare products Regulatory Agency, dated 11/09/2024.
INQ000474703	Report of Professor Daniel Prieto Alhambra
INQ000274036 (P.32, 3.18)	Report from Medicines & Healthcare products Regulatory Agency, titled Report of the Commission on Human Medicines Expert Working Group on COVID-19 vaccine safety surveillance, dated 05/02/2021. [Publicly Available]
INQ000486279 (P. 73, 6.63)	Document from UK Health Security Agency titled National protocol for Comirnaty Covid-19 mRNA vaccine, dated 20/11/2021.
INQ000477102 (P. 73, 6.63)	Leaflet from UK Health Security Agency, titled What to expect after your COVID-19 vaccination - Information for people who just had a COVID-19 vaccination, dated March 2023. [Publicly Available]
INQ000474336 (P. 67, 6.14)	Witness Statement provided by Professor Sir Munir Pirmohamed on behalf of the Commission on Human Medicines, dated 05/09/2024.
INQ000507357 (P. 59, 6.16)	Decision from MHRA (GOV.UK Website) titled ARCHIVE: Information for Healthcare Professionals on COVID-19 Vaccine Pfizer/BioNTech (Regulation 174), dated 08/08/2024. [Publicly Available]
INQ000508000 (P. 30, FN 41)	Report from MHRA titled Summary of the Public Assessment Report for COVID-19 Vaccine Pfizer/BioNTech, dated 21/03/2024.