Expert Report for the UK Covid-19 Public Inquiry

Module 4 – vaccines and therapeutics

Expert report on the development and trials of new and repurposed therapeutics

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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.

Nicholas White

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Preamble

I am Professor of Tropical Medicine at Oxford University and Mahidol University, Bangkok, and I am an active Consultant Physician at the John Radcliffe Hospital, Oxford. I chair the Wellcome South East Asian Research Units based in Thailand and Vietnam. I live mainly in Thailand. I am one of the top 200 most highly cited scientists. Most of my research has been on infectious diseases, and in particular the assessment of therapeutic responses. In Covid-19 our research team conducted the world's largest chemoprophylaxis study, and we have also conducted the largest pharmacometric assessments. I have never received funding from pharmaceutical companies or other organisations with commercial interests in pharmaceuticals. I chair the scientific advisory committee of the Drugs for Neglected Diseases Initiative which tried to develop affordable new Covid-19 medicines, and I chair the Coalition for Equitable Research in Low Resource settings. I have no conflicts of interest. I was peripherally involved in the RECOVERY trial evaluation of hydroxychloroquine (designing the dose regimen) but otherwise I was not involved directly with the UK research response to Covid-19 (as I live and work mainly in Asia). I interacted from the outside with the UK health and regulatory authorities through trying to conduct chemoprevention studies (the COPCOV trial) and assess antiviral treatments in the UK as part of multinational clinical trials (PLATCOV trial).

1. What are therapeutics?

1.1. Therapeutics are medicines used to treat diseases. They are given by mouth (tablets, liquid formulations), by injection, and sometimes by other routes. Most medicines in the past, and most used today are "small molecule" drugs, usually taken by mouth, sometimes by injection, and sometimes by inhalation (like asthma medicines). However, increasingly, monoclonal antibodies (mAbs) are given by injection to prevent or treat diseases. These are engineered antibodies. They are protein molecules which are much larger than small molecule drugs (see figure 1). They harness the natural immune response to bind to various drug targets.

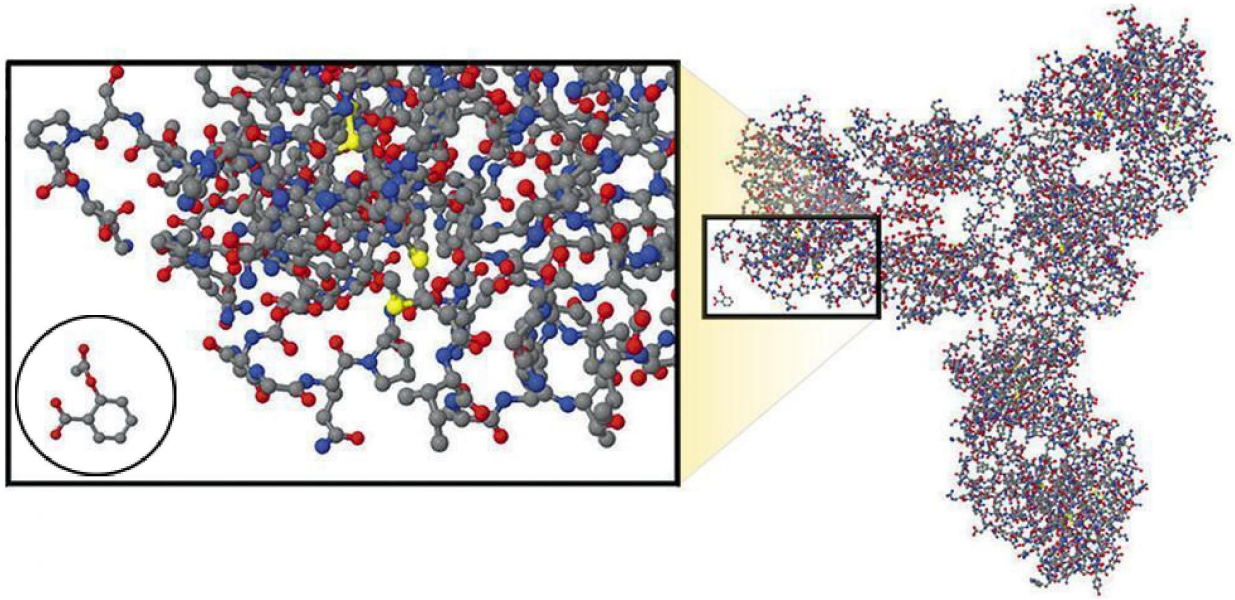

Figure 1: Size comparison of the typical small molecule drug aspirin (lower left encircled in the magnified box). It is approximately 800 times smaller than the monoclonal antibody on the right (99)

1.2. Infectious diseases are caused by microorganisms. In most infectious diseases, therapeutics such as antibiotics are used to clear the microorganisms causing the infection as quickly as possible from the body (cure), thereby reducing the illness and accelerating recovery. This may also reduce the chance the person infects someone else, conferring an additional public health benefit. Therapeutics usually work

alongside the body's immune system. The body's immune system can often eliminate a pathogenic infection itself without needing drugs, but sometimes this response is too slow, and sometimes the infection overwhelms the body's defences. Some chronic infections cannot be cured with drugs or cleared by the immune system, but can be suppressed indefinitely (e.g. HIV). Depending on the type of infection, some patients become very ill before reaching medical attention, in which case the first priority is to save life and, after that, it is to cure the infection. Anti-infective drugs are widely used and they have had a major beneficial impact on health and life expectancy over the past century.

1.3. Vaccines are given to everyone (usually in childhood) to protect against several dangerous infectious diseases. Vaccines can also be deployed to protect the population from outbreaks or epidemics. However, the process of discovering, developing, testing, manufacturing and distributing vaccines takes time and, if the outbreak is serious, many people may die before they can receive an effective vaccine even if one is available. In addition, there are sometimes people who do not want to receive a vaccine, who cannot receive a vaccine for medical reasons, or who could receive a vaccine but would not mount a sufficiently protective response, often because their immune system is being suppressed by other drugs they are taking or other medical conditions they have. Thus, even when we have vaccines that are working well, we still need drugs to treat infections as an important public health insurance policy. These drugs can prevent and treat those people who are not protected by, or did not receive a vaccine.

1.4. Related to therapeutics are **prophylactics** (also known as "chemoprevention"). These are medicines given to prevent development of a disease in someone who currently does not have it. In the case of an infectious disease, prophylactics are used to reduce the risk of a person developing the infection (**pre-exposure prophylaxis**), or to try and prevent illness if they have been exposed to an infectious contact and may have already caught it (**post-exposure prophylaxis**). Prophylactics can also come in the

form of either small molecules or monoclonal antibodies. They may be the same medicines used to treat the infection.[1]

1.5. Prophylactics are used to prevent certain infections in vulnerable people. In outbreaks they can play an important role in protecting high risk individuals (the elderly, the frail, the immunocompromised, or those with serious underlying respiratory disease) or sometimes, when outbreak contacts have been identified, to stop them becoming ill, particularly in care homes or other institutional settings where lots of vulnerable people are in close proximity.

General categories during Covid-19

1.6. Covid-19 is caused by a virus (SARS-CoV-2). In the context of **Covid-19** there were four main categories of medicines shown to be effective:

1.6.1. ***Small molecule antivirals***: these are drugs which stop the virus multiplying. If they are effective, they halt progression of the disease. Most can be given by mouth but some do need to be given by injections.

1.6.2. ***Neutralising monoclonal[2] antibodies*** (NmAbs): these are antibodies engineered and manufactured to be of one type and directed against the SARS-CoV-2 virus, so they are occasionally also described as "antivirals". They block the ability of the viruses to invade cells and they help the body to recognise and destroy infected cells. NmAbs should be stored in refrigerators and they need to be given by injection.

1.6.3. ***Anti-inflammatories*** (also known as "immunomodulators"): these are drugs which are used generally in diseases caused by too much inflammation, but

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[1]Vaccines are technically prophylactics, but this report will cover **non-vaccine prophylactics**. Unlike vaccines, which rely on triggering the immune system to remember and recognise the virus if exposed at a later date, prophylactic drugs provide what is known as "passive" protection, and need to be administered regularly to be present in the body and have an effect.

[2] "Polyclonal" antibodies, a mixture of different antibodies, can also sometimes be used to treat infections. They can either be produced from someone who has previously had the infection and recovered ("convalescent plasma"), or, less often in the modern era, from immunised animals such as horses. Monoclonal antibodies are generally safer, more specific, and easier to standardise than polyclonal antibodies but sometimes they are less potent. To increase potency monoclonal antibodies are often combined in mixtures or "cocktails".

some of these medicines can also treat the inflammatory complications of some infections such as Covid-19 (Figure 2). Some anti-inflammatories are given as tablets, others by injection, and some can be inhaled. Anti-inflammatories can either come in the form of small molecules or monoclonal antibodies, as for the antivirals, but, instead of targeting the virus, they target parts of the patient's immune system.

1.6.4 ***Treatments for complications***. Covid-19 was associated with an increased risk of blood clotting, so drugs to reduce this risk were sometimes needed (anticoagulants). Although many medical conditions do lead to an increased risk of blood clotting, this was an unexpected complication for a new infectious disease, and trials were needed to determine how best to prevent and treat it. In addition, patients with Covid-19 sometimes developed secondary bacterial infections needing treatment with antibacterial drugs, but this is outside the scope of this report.

1.7. Neither **symptomatic** treatments (such as paracetamol, taken to reduce fever) or **supportive** treatments (such as oxygen or intravenous fluids, used for organ support rather than direct treatment of disease) change the underlying disease process, although they do improve outcomes. They are outside the scope of this report.

1.8. The most important life-threatening complication of Covid-19 is inflammation in the lungs (pneumonitis). This usually follows the acute illness (i.e. the onset of fever) by about one week. It was the main cause of hospitalisation and death. Fortunately, now it is uncommon.

1.9. In Covid-19, once the inflammatory stage of the illness manifests itself (usually about a week after the patient first feels unwell), the first clinical sign is usually a low blood oxygen (which usually causes breathlessness). This is the stage of illness when the anti-inflammatory drugs are effective by reducing the immune system's excessive response to the preceding viral infection.

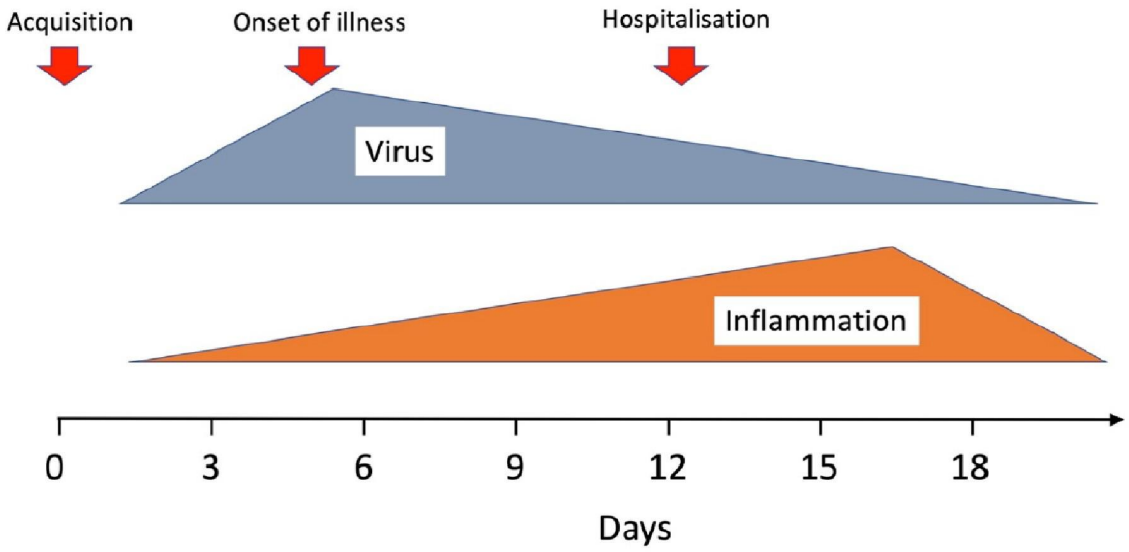


Figure 2. The two different but overlapping stages of Covid-19 illness require different treatments. This shows progression of Covid-19 over time from acute illness to severe disease (3). By the time the severe inflammation in the lungs is occurring the amount of virus in the body has declined substantially. Effective antiviral drugs work well in the first virus multiplication phase (blue) but they are less beneficial during the resulting inflammatory phase (orange). In the latter phase some anti-inflammatory drugs (notably corticosteroids and IL-6 receptor antagonists) reduce the risk of dying.

1.10. Antivirals (both small molecule drugs and NmAbs) are much less effective later on in the course of the infection i.e. approximately one week after first developing symptoms when severe complications may develop (particularly low blood oxygen resulting from lung inflammation) requiring hospitalisation (2,3) (Figure 2).

1.11. Antivirals work best when they are given early in the course of the infection, preferably as soon as the patient feels ill. Effective NmAbs and antivirals accelerate the clearance of the virus from the sites of infection. As a consequence, they accelerate clinical recovery and they prevent progression to severe illness. The Covid-19 antiviral drugs have been used, and are still used, in the community to treat people who are vulnerable to developing severe infections (the elderly, immunocompromised, and unvaccinated). For those who do become or may become seriously ill, Covid-19 antiviral drugs are also needed in hospital as they may still provide some benefit later

in the course of infection, in addition to the main benefit provided by the anti-inflammatory drugs.

1.12. Antivirals and NmAbs can also be used as prophylactics to prevent disease, and sometimes the same compound can be used for prevention and for treatment. In relation to prevention, the NmAbs have the advantage that they can be engineered to provide a protracted period (months) of protection, but they have the disadvantage that their efficacy[3] has waned or been lost altogether as new viral variants emerged.

Drug resistance

1.13. Antimicrobial resistance is a familiar and increasing problem with antibacterial drugs, and it can also happen with antiviral drugs. In order to survive and spread, pathogenic microorganisms commonly evolve mechanisms to avoid drugs or our immune responses (including escaping the immune responses from vaccines). This is why it is important to keep checking the efficacy (i.e. whether they still work well) of the drugs and looking for genetic changes in the viruses which may indicate resistance. One strategy to reduce the risk of resistance emerging is to attack parts of the virus which are less likely to evolve and become resistant. Another is to use drug combinations, making it more difficult for viruses to evolve two different resistance mechanisms at the same time. These predictions all need to be tested experimentally and can differ widely between pathogen species.

2. Preclinical evaluation of therapeutics

2.1. Therapeutics for an infectious disease are selected first based on their activities against the causative microorganism in the laboratory, provided that it can be cultured (i.e. grown in the lab) satisfactorily (9). Viruses must be grown inside cells. Potential antiviral drugs are screened for inhibitory activity against the cultured virus. Such lab

[3] Although often used interchangeably, strictly speaking, "efficacy" refers to a drug's effect in a controlled research setting where its correct dosing and administration can be assured, and "effectiveness" refers to how a prescribed medicine performs in routine use in healthcare settings, including if there are any issues with patient adherence to a prescription or incorrect dosing.

tests ("in-vitro" assays) are a guide to activity, and they are generally good for rejecting inactive candidates. However, before the drug has been tested in humans, direct extrapolation from the in-vitro test to "in-vivo" activity, that is, how well it will work in people with the illness, is uncertain.

2.2. If there is a satisfactory animal model of the infection (i.e. an experimental animal such as a mouse which can be infected, and has a similar disease to the human disease) (10), then the activities of the potential compounds are tested in these experimental infections. The concentrations of the drugs or NmAbs that inhibit the microbe, and the concentrations achieved in the blood or sometimes other body fluids of the animals are compared to try and predict whether effective concentrations of the drug will be achieved safely in humans. Characterising this relationship between drug concentrations in the experimental animal (or human) and the microbe killing effect is called "**pharmacometric** assessment" - see paragraph 3.3 for further explanation. It is necessary to guide optimum dosing in the clinical trials.

2.3. Sometimes the animal infection may differ significantly to that in humans and so the animal model may only have limited predictivity. Calibrating the animal model against the human infection to find out how good the model is takes time, and this is a challenge early in the outbreak of a new pathogen.

2.4. If the medicine is new (i.e. it has not been used before) then extensive safety evaluations in the lab and in animals will be needed before it is tested and used in humans. Reproductive toxicity and drug interaction risks need special assessment if the drug is to be used generally.

2.5. "**Repurposing**" means taking a drug which is already in use for one disease and then using it in another. If the compound is a repurposed drug then its safety profile will already be known, but a pharmacometric assessment will still be needed to determine whether the doses which have been used before (in its current use) are enough for the new indication. If higher doses are needed then further safety assessment is required.

2.6. Overall, this preclinical assessment often gives only a rough indication how the drug will perform in prevention and treatment. Clinical trials are essential to determine if a new medicine is safe and effective, and how best to use it.

3. Clinical evaluation of therapeutics

Clinical trial phases

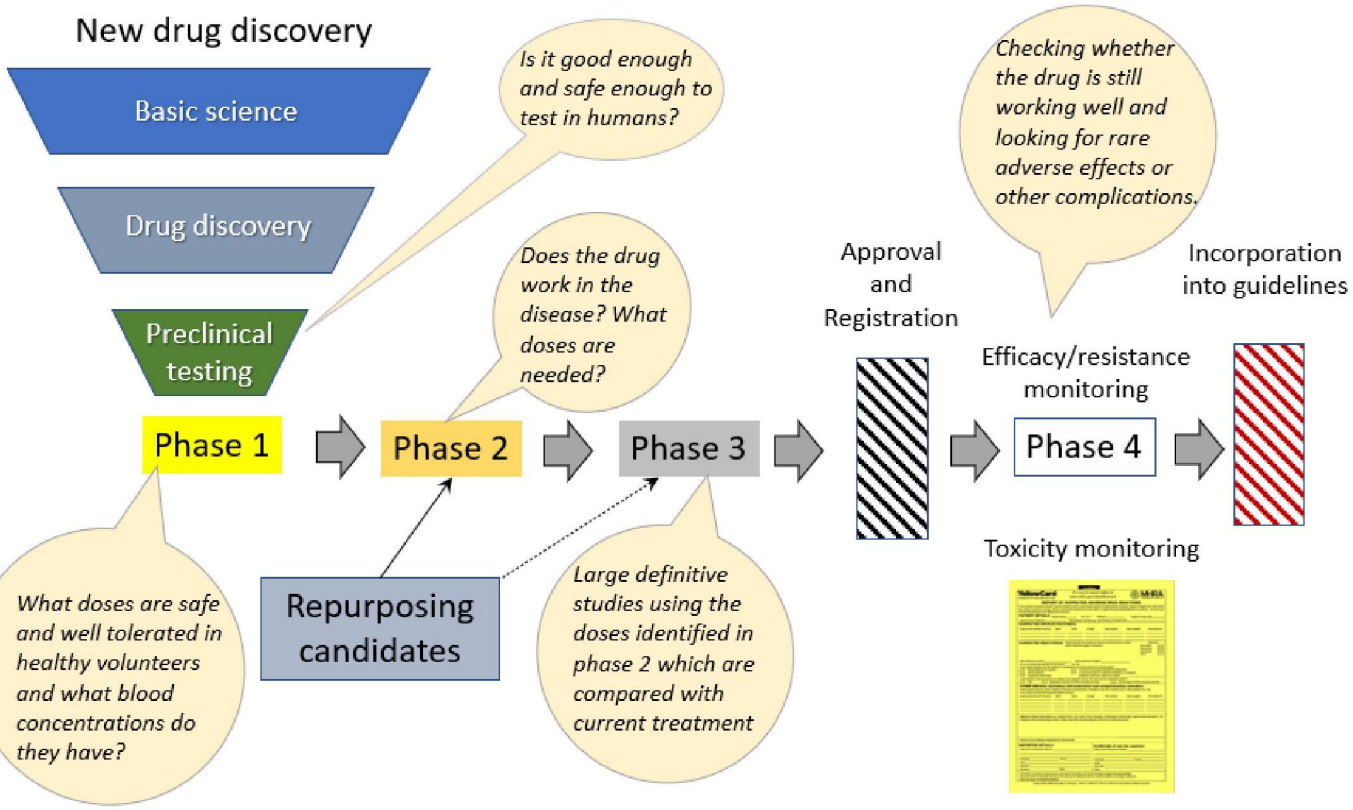


Figure 3. Clinical evaluation of new drugs: an outline of the different stages of drug development for newly discovered drugs, the questions being asked at each stage, and how repurposed drugs could enter this evaluation pathway are shown. If repurposed drugs are already registered and used then there should be good information on tolerability and toxicity, but their efficacy for the new indication will still need to be evaluated properly. If the repurposing requires higher doses than used in their original indication for safety assessments will also be needed

Phase 1

3.1. When a new medicine has completed preclinical testing, it is trialled first in a small number of closely observed healthy adult volunteers to assess tolerability and safety and to measure the blood or plasma drug concentrations ("pharmacokinetics") (Figure 3). This *phase 1* or "first in human" trial is conducted to see if the new medicine is well

tolerated and the drug levels predicted from the preclinical studies are in the right range. Usually, a single dose is tested first, then "multiple ascending doses" are evaluated to find the dose of the new medicine that is no longer well tolerated. This sets the ceiling for the dosing in treatment, or the "therapeutic range". For repurposed drugs the toxicity threshold will already have been established, and there will be clinical experience, so there is usually no need for a repeat of phase 1 testing.

Phase 2

3.2. The next stage of drug development is evaluation of the potential medicine in people with the disease. This is needed for new drugs, and should also be done for repurposed drugs. The objective of phase 2 trials is to establish the optimum dose regimen for definitive phase 3 evaluation, or if the drug does not work well enough, to stop its development.

3.3. Phase 2 has several aims. The first is to establish the relationship between the drug dose as taken by the patient and the consequent drug concentrations over time in the patient's body, which is usually measured in plasma or blood samples. This is known as **pharmacokinetics,** or PK for short. The second is to measure the desired response in relation to the drug concentrations. This is known as **pharmacodynamics,** or PD for short. The combined study of pharmacokinetics and pharmacodynamics (PK-PD) is called **pharmacometrics**. In Covid-19, the phase 2 studies measured how quickly the infection resolved. This was a) how quickly the patient's fever and illness resolved, and b) how quickly the virus went from the nose of throat. The two measures are related (as they are for most pathogens). The third aim is to measure any side-effects that might occur, which is known as "toxicity". The phase 2 assessment can either be done in the treatment of natural infections or, for some infectious diseases which are not very serious and resolve naturally or are readily treated, phase 2 testing can be conducted in a controlled human infection model (CHIM; also known as a "challenge" trial) (11). In a CHIM, a single strain of the pathogen is given to healthy, non-pregnant, adult volunteers and the drug under

evaluation is either given beforehand (if testing prevention), or when the infection is established (if testing treatment).

3.4. One of the main difficulties with phase 2 assessments in infectious diseases is quantifying the therapeutic response (PD). This measurement of how the infection is cleared depends on the nature of the infection and how the therapeutic response can be characterised and measured. Ideally the amount of infection is quantified and then the speed and efficiency of clearing it can be measured. If the infection cannot be quantified then the assessment must rely on the less precise clinical and laboratory measures, e.g. in a febrile illness how quickly the fever declined, the heart rate fell and the patient felt better, and how quickly the abnormal blood tests went back to normal.

3.5. Phase 2 assessments often require thoughtful and sometimes innovative design, and dedicated investigators and study teams, particularly in relation to new infections. Although contract research organisations are usually hired by pharmaceutical companies to conduct their clinical drug developments, these commercial organisations follow established development pathways and are not well constituted to innovate in trial design or adapt to novel approaches or new challenges (such as an outbreak of a new infection).

3.6. Phase 2 assessments of drugs for severe illness are usually carried out in less severely ill hospitalised patients. This is an obvious bias which may result in an incorrect prediction of the optimum dose.

Measuring the microbes

3.7. In general, the more infecting microbes there are in an infection, the worse is the disease, so getting rid of them quickly and effectively is very important. If we can estimate how many microbes there are, then we can compare drugs to see how quickly and effectively the drugs get rid of them.

3.8. Where possible the concentrations of microbes should be measured in or near the site of infection and the decline in their numbers correlated with the blood concentrations of the tested drug (pharmacometrics) (15). The objective of this pharmacometric

assessment is to try and gauge how much drug is needed to clear the microbes as rapidly as possible without producing too much drug toxicity. If we know how much the drug levels vary between individuals, and the factors which affect these levels (pharmacokinetics), then this is a very efficient way of understanding what doses to give in the treatment of an infection, and for how long to give them. We can then test the best dose predicted from the phase 2 studies in the larger definitive phase 3 trials.

3.9. For some infectious diseases, the concentrations of microbes, or their contents or products, can be measured in blood (e.g. HIV). For other infections, we can measure the concentrations of microbes in relevant body fluids. In Covid-19 and other viral respiratory diseases the virus can be measured in pharyngeal swab samples. Oropharyngeal swabbing (swabbing from the back of the throat) is much more tolerable for patients than nasopharyngeal (swabbing from inside the nose), and this allows for daily sampling.

3.10. For some viral infections, the antiviral response is measured based on clinical recovery (which is usually assessed by measuring the time to fever resolution, and how quickly symptoms resolve) and "time to virus clearance" i.e. the interval from the start of treatment until the virus is no longer detectable. As described above, the clinical responses usually vary a lot, and measuring "time to virus clearance" is also an imprecise (and therefore inefficient) measure. It depends very much on how high the viral densities were before starting treatment (the higher they were, the longer they take to reach undetectable levels), the frequency of measurement, and the accuracy of the detection method (9). The pharmacometric approach, in which the rate of pathogen clearance (rather than time to clearance) is measured in relation to the drug levels, is a much better approach to phase 2 assessment.

3.11. Although in respiratory virus infections measuring how quickly the viruses are cleared (i.e. rate of clearance) provides a more precise measure of the antiviral response than the clinical recovery, this does assume that the amount of virus in the pharynx is proportional to the amount in the body. Viral clearance rates (measured from the nose or throat) in Covid-19, influenza and respiratory syncytial virus infections (the three

most important respiratory virus infections of humans) correlate with clinical benefit (51-53).

3.12. For disease complications, such as excessive inflammation in the lungs following Covid-19, the viral load *at the time* of hospitalisation may not correlate with the level of illness and the success of treatment (Figure 2). Other methods are therefore needed to help guide drug choice. If immunology investigations do reveal a clear immunopathological pathway (i.e. indicating that the body's immune reaction to the infection is damaging) then blood tests of specific immune system responses, such as high levels of chemical messengers, can be used as pharmacodynamic measurements in the phase 2 and phase 3 studies.

3.13. Sometimes, particularly when a disease is rare (i.e. phase 3 would take too long, or be impossible), or in an emergency, the phase 2 can be extended and provide sufficient evidence for a regulatory authority to approve the drug.

3.14. All clinical trials must have the appropriate ethics committee or review board approvals, should be monitored appropriately, and all must be registered on open access websites (e.g.(161), (162)).

Phase 3

3.15. These are the definitive large trials which lead to registration by a regulatory authority. Registration or approval by the regulators is necessary in most countries for doctors to prescribe the drugs. Phase 2 shows that the drug works, whereas phase 3 finds out how well it works, what side effects it has, and whether it is better than current treatment. The doses chosen for phase 3 trials are informed by the phase 2 assessment and should be the best estimated balance between safety, tolerability and efficacy. The phase 3 trials are usually large randomised comparisons with the current standard of care or a placebo. The patient population in the trial should be as representative as possible of the target population for the medicine in clinical use. This can be assisted by actions such as making trials as easy to enter patients to as possible, including many recruiting sites over a wide geographic area, informing

communities known to be at greater risk of the opportunity to participate, and having as few exclusion criteria as possible (for example, not excluding patients over an arbitrary age limit).

3.16. The phase 3 trial examines acceptability, safety and therapeutic benefit but it is usually "powered" by the effect size. This means that for infections the number of patients to be studied (the sample size) is usually calculated based upon how much better the new drug needs to be in preventing or curing the infection compared with the comparator) and the level of confidence required in identifying that difference. Sometimes, the phase 2 and phase 3 studies are merged together in one continuous trial.

3.17. Traditional clinical trials have a prespecified sample size (i.e. they state the number of patients they aim to recruit in order to detect a stated effect size or difference with the comparator with a stated level of statistical confidence). This results in a certain statistical "power" to detect a difference. For example, it might require several hundred enrolled patients to detect a 30% advantage reliably, but several thousand to detect a 10% advantage reliably. For a common, potentially lethal, infection even a small difference can save a lot of lives. If there is no effective treatment already, then the trial comparison is with no treatment, but if there is already a recommended treatment then the comparison is with that, as it would not usually be acceptable to withhold it.

3.18. There may be good information previously from which to calculate the sample size, but sometimes (as in the early days of the Covid-19 pandemic) there is no previous information and the treatment effect and thus the proposed sample size is more speculative. The final choice of sample size is influenced by many factors which include variation in the outcomes, patient and societal value of the outcome, feasibility, cost of the trial, and likelihood of regulatory approval. It is generally decided on by the Principal Investigators and trial statisticians.

3.19. Although extended phase 2 studies are large (hundreds of patients enrolled), phase 3 trials are larger (many hundreds or thousands). Despite this, phase 3 trials are still often not large enough to be very sure of the generalisability of the results. To try and

address this, the trial population should be representative of the target population in terms of disease severity, pathogen type, age range, gender balance, and ethnicity.

3.20. Overall, clinical trials are often underpowered (i.e. too small), sometimes because of optimistic assumptions about how easy it will be to recruit participants and sometimes because of their high cost, which means they can only detect large differences. They may therefore miss smaller but still valuable advantages. For new drugs the sample size must be large enough to provide enough information for the regulatory authority to approve the drug if the outcome is satisfactory.

3.21. In assessing a new or repurposed medicine it is very important to try and obtain an objective assessment of how effective and safe it is. Those who develop or propose the medicine are naturally inclined to take a positive view of it (i.e. to be biased). **Randomisation** is critical to avoid bias (i.e. to make the comparisons as fair as possible). Randomly allocating patients to different treatment groups, usually with a virtual coin flip simulated in a computer program, means that apart from the treatment given, there should be no systematic differences between the groups. Ensuring randomisation is done properly is critical. Thus, if there are differences between the groups in outcomes, they can be attributed fairly to the treatments given, and to the play of chance, but not to other factors. But if the trial is not properly randomised or is too small then, by chance, there may be important differences between the groups which are attributed incorrectly to the treatments. This is another reason why clinical trials in phase 3 and after registration should be as large as possible.

3.22. Unfortunately, throughout the history of medicine, there are often claims for benefit from interventions which later are found not to be as effective as asserted originally. These claims often originate from a retrospective observation that the intervention was associated with a good outcome. In an observational study, although an association between an intervention and an outcome may be observed, it is often unclear if the intervention actually caused that outcome. For example, sick patients are often given oxygen, and so in an observational study, receiving oxygen would be associated with an increased risk of death. But oxygen does not cause death – it is beneficial. The

association is observed because the medical team diagnosed the patient as being very sick and needing oxygen. This example is obvious, but sometimes the associations are not so obvious, and they are confused with causal relationships. In clinical research it is very important to try and understand causation, and to distinguish causal relationships from associations which are not causal. In observational studies differences can be adjusted for statistically but, usually, relevant factors are unknown or not recorded or are poorly characterised, and biases cannot be excluded reliably. The well-known phrase "correlation does not imply causation" reflects this problem. While observational studies may be very useful in identifying potential benefits and harms that need further investigation, particularly if there is a plausible mechanism based on known biology, they are often unreliable for the assessment of medicines. Randomisation in prospective trials is designed to counter this by equalising known and unknown factors between the groups. Randomisation allows causality to be ascribed, and so is critical in drug trials to assess benefits and harms reliably.

3.23. Observational studies are, by definition, not randomised, and some interventional studies of therapeutics are also not randomised. Because it is so difficult to exclude bias, non-randomised studies are not usually accepted by regulators as sufficient evidence for approval of a therapeutic.

3.24. Where possible in prospective studies, **blinding** also reduces bias. Blinding means that the investigators do not know what treatment the patient received. If the patient also does not know (e.g. if all the tablets look and taste the same) then this is called "double-blind".[4] Provided that the randomization and blinding are done properly in clinical trials this provides an unbiased estimate of the acceptability, safety and efficacy of a medicine.

3.25. In preparing a clinical trial it is very important to specify and define clearly the primary outcome, or "end-point". This is the main measurement answering the question the trial aims to answer. It should assess a genuinely important effect. The primary

[4] It can be quite difficult to make the placebo (if there is no current treatment) or the comparator drugs very similar - so "double blinding" is often not possible. However, it is often possible to separate the investigators from the measured end-point of the trial (e.g. a lab measurement) which reduces bias in the way outcomes are recorded. This is called "single-blinding".

outcome must be specified before the trial starts to avoid bias and ensure credibility. The primary end-point in phase 3 *treatment* trials depends on the disease. In infectious disease the primary end-point is usually the speed of clinical recovery (i.e., resolution of symptoms, variably defined) or microbiological "cures" in uncomplicated infections, and in life-threatening infections the reduction in rates of death or admission to intensive care units. In acute infections it is usual to specify a time limit such as one week or one month for these end-points to be measured in (i.e. what proportion of patients were cured within that interval or survived for that time). Times to recovery, rates of recovery, or proportion with recurrences are usually secondary end-points in these severe disease trials.

3.26. In *chemoprevention* trials people who may become ill with an infection are randomised to receive the test drug or the comparator (if there is an accepted and recommended standard chemoprevention), or to no drug. The double-blind placebo-controlled trial is the best way to assess chemoprevention, and is particularly valuable for assessing the side effect profile. The primary end point of the trial is usually the incidence of the infection. For example, in Covid-19 this was usually the number of participants who developed illness associated with a positive PCR test.[5]

3.27. It is very important to measure adverse effects, and particularly serious adverse events, in phase 3 trials, although these may overlap with those of the illness. Careful assessment of whether these "adverse events" can be attributed to the treatment is therefore required.

3.28. "**Meta-analysis**" is an important tool to synthesise the evidence from multiple phase 3 or post registration trials. It can help to understand differences between studies, and to combine multiple small underpowered studies (i.e. studies with too few subjects to be sure of the drug effect) in order to generate sufficient statistical power and therefore generate a more certain conclusion. Meta-analysis is only possible if the end-points being evaluated are consistent and measured in a similar way between studies.

[5] Sometimes such a test is not possible and instead the development of antibodies against the organism is detected in blood tests (seroconversion), usually in association with an illness. This indicates that the subject was infected. The proportion of subjects who seroconvert in the different study arms is then compared.

Phase 4

3.29. Once a new drug is registered and used there still needs to be continued vigilance with regard to safety, and for anti-infective and anti-cancer drugs, the emergence of resistance. Rare (e.g. <0.1%) but serious adverse events may only be observed when large numbers of patients are treated, so post-registration mechanisms to capture these must be supported (pharmacovigilance). The outcome of pregnancies exposed to the new medicine should be recorded in pregnancy registries. There are various approaches to this, including the long-standing yellow card passive reporting system to the Medicines & Healthcare products Regulatory Agency (MHRA), and there are more active programmes. For example, OpenSAFELY is a highly secure, transparent, open-source software platform for the analysis of electronic health records data which collaborates with NHS England (17).

3.30. Post registration observational studies of therapeutics are useful for characterising routine use, for identifying rare adverse effects and for assessing whether the drug still works in a different population or a different time-frame, especially where there is a risk of drug resistance. The results can be adjusted to account for known biases, but generally, randomised controlled trials are still needed to provide causal estimates (i.e. the drug caused the effect rather than being associated with the effect).

Conducting effective trials in a pandemic

Severe disease

3.31. Some drugs and NmAbs are developed specifically to treat severely ill patients. The initial therapeutic assessments in hospitalised patients also require dedicated clinical investigators and study teams. Conducting such studies may be operationally difficult, particularly in the midst of a pandemic when hospitals risk being overwhelmed (18). Disease severity is likely to affect both the "drug disposition", which describes the factors which determine what concentrations of drug occur in the body after it is given (PK), and the therapeutic outcomes (PD). Drug levels may be higher or lower than in

patients with less serious infections, and recovery times are usually slower in more seriously ill patients. Where hospitals are overstretched, designing studies of interventions for severe disease requires careful planning and consideration to ensure the studies are feasible, that key outcomes are recorded accurately, but that the study does not interfere with the care of sick patients. For the large phase 3 trials in severe disease where mortality is the primary end-point, it may be possible to simplify the study and incorporate assessments into busy routine hospital practice, as in the excellent "RECOVERY" trial in which it was easier for the admitting doctor to include a patient into the study than not to include the patient (1,18). When possible, the initial therapeutic assessments (phase 2) are best performed in a dedicated ward or unit or an intensive care unit, as frequent detailed measurement will be required. If there are clear correlates ('biomarkers") of life saving benefit these should be measured in addition to careful clinical and laboratory monitoring.

Adaptive platform trials

3.32. The fixed sample size approach described above is not the only way of conducting randomised trials. In modern "adaptive" trials the number of patients to be enrolled in a particular treatment arm is not prespecified as it depends on the outcomes. The results are monitored and analysed continually and the statistical criteria for stopping arms are prespecified. This allows several drugs to be compared at the same time (a "platform" trial) and for drugs to enter and leave the study at different times. This method is not used usually in pre-registration trials, but it is used in assessing or comparing registered medicines (as it was successfully in Covid-19 trials (1)). The adaptive platform trial is a new approach in the study of infectious disease therapeutics. Because it is efficient, and accommodates the different timing of drug availability (as new drugs are introduced), and it gives real time information as the pandemic evolves, it should be considered as the default for future pandemics. It is particularly valuable if there are several treatment options available, or likely to become available soon, and it is uncertain which is best.

Who should be included in the trials?

3.33. The patients enrolled in clinical trials should be as representative as possible of the overall patient population, but this may not always be possible, and it may be necessary to extrapolate the results from one patient group to another. For example, chest infections are a particular problem of the elderly and frail, but the results of treating younger patients with chest infections can often be applied to older patients.

3.34. To assess antiviral activity in respiratory virus infections adult patients with uncomplicated infections usually provide the necessary information on viral clearance. For many infections background immunity is an important determinant of outcomes so it may be necessary to stratify (i.e. adjust) for this, for example, by measuring antibody levels, and noting whether and when an effective vaccine has been received.

3.35. As described above, vulnerable groups (the elderly, frail, immune compromised, those with underlying chronic diseases etc.) have been the main recipients of antiviral drugs to treat Covid-19 (and also influenza), as they had a higher risk of progressing to severe disease and dying. However, it is not necessary to evaluate the drugs initially in this vulnerable target population as antiviral activity is unlikely to be very different in previously healthy adults. However, immunocompromised patients may not be able to clear some infectious pathogens effectively. Vulnerable people may have multiple other health conditions and be taking other medications, so interactions with other drugs are likely, and dose adjustments or different drug choices may be necessary for some patients. Drug interactions can often be predicted from preclinical assessments, but they may require separate drug-drug interaction studies in healthy volunteers.

3.36. Testing the efficacy of different interventions in severe disease is important, particularly if severe illness results from an immune reaction to the infection, rather than a direct consequence of the infection process, as was the case in Covid-19. In most (but not all) infections younger previously fit patients are less likely to develop severe disease. If patients become very sick or die early in the evaluation of a new drug because of the severity of their infections and their underlying conditions (and not because of drug toxicity or lack of efficacy), confidence may be lost and this may jeopardise the trial

and the subsequent drug development. Yet recruiting only patients with a likely good outcome may create biases in the drug assessment. This is why understanding the disease pathogenesis (how it makes you ill) and the context of treatment is very important in designing, analysing and interpreting the trials in order that the results are as generalisable, and as useful as possible.

3.37. Some ethnicities handle drugs differently, because they have inherited slightly different capacity to break down and eliminate the drugs from the body (pharmacogenetics), or they have different rates of drug reactions, but there is no need to recruit a range of different ethnicities specifically at the *early* phase of drug testing because the differences are usually small. If the drugs advance to a later clinical trial phase, then a closer focus on ethnic differences in therapeutic responses may be required. Drugs may also behave slightly differently in men and women so, in general, it is good practice to aim for approximately similar numbers of men and non-pregnant women in trials, including in early phase assessments.

3.38. Issues with drug trials recruiting patients who are not representative of the populations of patients the drugs will be used in predated the pandemic. For example, there have been lower proportions of South Asian participants in diabetes drug trials than those treated for diabetes in the community 100). Patients aged over 75, especially those with more comorbidities are generally underrepresented in clinical trials (101). There have been significant efforts to tackle this issue in recent years (102). Overall, the degree to which clinical trials must recruit particular participant or patient subgroups specifically depends on the likelihood that and the extent to which therapeutic responses and toxicity differ in those groups. There may already be information which informs this assessment before the clinical trial. Where obtaining clinical trial information rapidly is critical (as in a lethal pandemic such as Covid-19 in 2020) speed and simplicity of recruitment is paramount. There is an important trade-off between managing recruitment to ensure that a trial is as representative as possible and rapidly recruiting participants to obtain a sufficient sample size and an early result. Ensuring representativeness by selective recruiting to cover all demographic groups could risk

slowing down a trial, and hence the results needed to inform prescription of effective treatments, to the detriment of all.

Special groups - children and pregnancy

3.39. Antiviral drugs need to benefit everyone who needs active treatment, but drug development historically has tended to avoid evaluations in children and pregnancy. This has been acknowledged by regulatory agencies which now actively encourage early evaluation in these important patient groups. So, while a drug is being evaluated satisfactorily in non-pregnant adults the strategy for evaluation in children and in pregnancy should be developed.

3.40. While it may be reasonable to extrapolate responses in older children and adults to infants and young children initially, tolerability and safety does need to be assessed specifically in children. Children, particularly in the first year of life, may metabolise (process and break down) and distribute drugs around the body differently. Important adverse effects such as vomiting, which may lead to undertreatment with oral medicines, are often more common in children, and the assessment of nervous system toxicity may require different measures.

3.41. Some drugs give reproductive toxicity signals in pre-clinical testing and so should be avoided in women of child-bearing potential or in pregnancy (unless there is life saving benefit and no alternative). Pregnancy testing will therefore be required before entry into the clinical trials. If there are no reproductive toxicity concerns and the drugs are needed then pregnant women should be included in studies and pharmacokinetic assessments conducted, and pregnancy outcomes monitored. Once a new medicine is registered, pregnancy registries should be instituted to document the outcomes of all pregnancies exposed to the new drugs. Excretion of the drugs in breast milk should also be studied to assess infant exposures. If there are concerns over infant exposure, breast feeding may need to be interrupted while the mother receives drug treatment.

How long should early phase trials take?

3.42. In general, trials of new anti-infective drugs take at least 1-2 years to complete but, in an emergency, early phase trials could be completed within months (17). To achieve this would require coordination, very effective trial management and consensus on phase 2 design, accelerated ethics review, removal of bureaucratic obstructions, institutional approvals, rapid drug level measurement, statistical analysis in real time, effective public engagement (particularly with the health workers), and rapid recruitment. The obstacles are mainly bureaucratic rather than logistic. It would need high level authority to accelerate approvals and dedicated trial teams but it could be done. Rapid completion requires that disruption to health and research structures and society is not extreme. In my own, rather different, experience (in a tropical setting studying severe malaria) small single centre teams have completed detailed pharmacometric studies successfully recruiting up to four severely ill patients per day. In less severe but highly prevalent infections even higher recruitment rates may be possible. Safety assessments can be done in real time. Drug measurement capability in the public sector is unfortunately limited but high throughput drug level measurement is possible with modern laboratory equipment, and pharmacodynamic measures (e.g. PCR assessment of viral densities) can usually be processed within two weeks of sample receipt.

Obtaining results promptly before an epidemic wave is over

3.43. The normal pace of reporting the results of clinical trials is very slow and, unfortunately, reports often do not appear for years in the final published results. However, a well-organised, well-planned and well-supported trial can report very quickly - within months, and possibly within weeks of completion if the slowest elements (laboratory measures, data checking) are done in parallel and the statistical analysis plan is well prepared (18). Results can be posted immediately on websites or preprint servers before or at the time of submission to a peer-review journal.

4. Looking back: Preparedness of the UK

Preparedness for clinical therapeutics research and development

4.1. My view from the outside, as an academic disease clinician working on Covid-, is that in 2019 the UK was somewhat prepared for a bad influenza epidemic, although the serious concerns around H5N1, which peaked around 2005 (94, 95), and the interest in 'flu counter strategies had waned substantially over the following 14 years. Interest in Covid-19 has also declined precipitously over the past two years. The UK has a stockpile of drugs to treat influenza (which is the most likely next pandemic), reportedly enough to treat half the population, but I do not know exactly how large it is. It is also noteworthy that there have been very few studies to compare the efficacy and effectiveness of the different anti-influenza drugs (as was the case in Covid-19) so, as influenza is likely to be the next pandemic, it is unclear to me whether the UK is best prepared or not.

4.2. The 2003 SARS outbreak (caused by a previous coronavirus which originated in China) did not affect the UK significantly, with only four cases and no deaths. The Middle East respiratory syndrome (MERS), a viral respiratory disease caused by another zoonotic coronavirus MERS-CoV that was first identified in Saudi Arabia in 2012, raised interest but was considered unlikely to spread globally, and therefore not of wider public health concern. In 2019, I don't think anyone was prepared for "Disease X", a currently unknown pathogen that could emerge in future and cause a severe epidemic or pandemic (the last example of which was SARS). There was no evidence from the outside of preparedness (i.e. contingency provisions) by the UK Government for rapid drug evaluation – but I am not aware of all the information, and there may have been preparations taking place "behind the scenes".

4.3. From an external perspective (i.e. from someone who conducts clinical research mainly in low resource settings) my overall impression was that it had become

increasingly difficult and increasingly expensive to conduct clinical research in the UK. The UK has a good regulatory agency (MHRA) but the obstructive bureaucracy, the burdensome process requirements and regulations, the inappropriate imposition of "industry standard" ICH guidelines, the limited funding for clinical investigation, the general decline of bedside research in the academic sector, and the increasingly overstretched and under-resourced NHS had created an unfavourable milieu for clinical research, one where rapid action was difficult (25-27). On the other hand, the UK has a strong record in the science and the conduct of clinical investigation and clinical research, and this experience and knowledge could be mobilised rapidly and effectively. Thus, in spite of all these difficulties, the speed of the UK's Covid-19 clinical research response beginning in 2020 was admirable (discussed further below).

5. Looking back: Clinical research in Covid-19

5.1. The clinical therapeutics research in Covid-19 has to be assessed against the rapid acquisition of knowledge about a hitherto unknown infection, what was known about similar infections (e.g. SARS), heightened concerns and pressures on health care and medical research, general social and organisational disruption, and changes in incidence and severity as the pandemic evolved.

Timeliness and effectiveness of the clinical trials

The global picture

5.2. At the beginning of the pandemic there were no drugs and no vaccines. Patient management was symptomatic. The provision of oxygen and, if necessary, respiratory and other vital organ support in hospitals was the most important intervention. In the absence of conclusive evidence countries across the world made a wide variety of therapeutic recommendations. Even the guidelines for supplemental oxygen, which were based mainly on oxygen saturation in the blood and degree of respiratory

distress (dyspnoea), varied. In respect of drugs, medical attention initially focussed on potential antivirals, particularly those with proven benefit in other viral infections.

5.3. The early focus of clinical research was on the treatment of severe Covid-19. The question the research aimed to answer was *"what treatments could prevent disease progression and death?"*, and *"what were the **indications** for the medicine if it worked (i.e. who should receive it)?"*. Three large hospital based multicentre platform trials, which had all-cause mortality primary endpoints, provided convincing, complementary and definitive immediately actionable results. They were organised with commendable rapidity. These trials were RECOVERY (initially UK only, all hospitalised patients) (1, 27-29), REMAP-CAP (adaptive community acquired pneumonia study: multinational with significant UK component, largely critical care based) (30-31), and to a certain extent SOLIDARITY (WHO multinational, all hospitalised patients) (32-33). Together these trials enrolled over 70,000 hospitalised patients. DisCoVeRy was another large multicentre randomised adaptive trial based in Europe (44,78). In the USA the National Institutes of Health (NIH) initiated the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership which conducted large multicentre drug trials. These trials selected patients based on disease severity, so they were generally representative of the affected population in the trial locations.

5.4. The large randomised platform trials in hospitalised patients began to deliver clear results from mid-2020 onwards. They established the life-saving benefit of corticosteroids and other anti-inflammatories, and these drug treatments were adopted immediately. They also showed that repurposing candidates thought to have an antiviral effect against SARS-CoV-2 based on preclinical studies, such as lopinavir-ritonavir, azithromycin and hydroxychloroquine, did not reduce mortality in Covid-19 patients.

5.5. The clear and unequivocal results from the very large randomised trials in severe Covid-19 contrasted with the treatment of early disease where a large number of medicines were proposed, and often recommended by national authorities (77), and sometimes politicians, on the basis of small, often observational, often poorly

designed, and in some cases, suspect trials. Use of hydroxychloroquine (68) and ivermectin (80) became intensely politicised. This adversely impacted their objective evaluation, particularly for the role of hydroxychloroquine in chemoprevention (see paragraphs 5.60 to 5.61).

5.6. By October 2020, hundreds of small trials had been set up worldwide, but very few of them delivered meaningful results. This diverted resources, and created uncertainty.

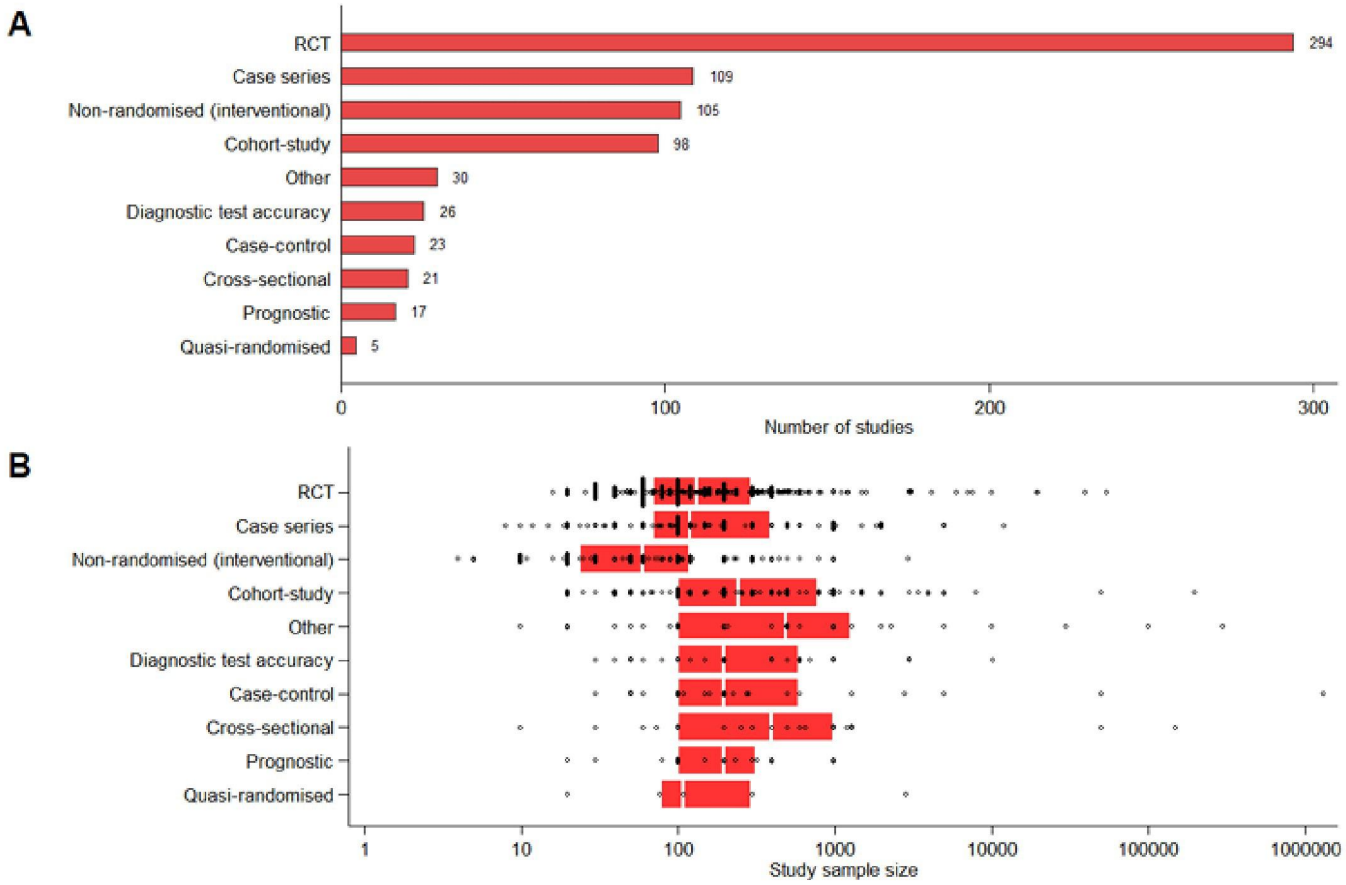


Figure 4A. Planned trials globally in Covid-19 as registered by October 2020. (A) Number of studies and (B) planned sample size by design type. Each black circle denotes one trial; red box denotes 25th and 75th percentiles; vertical white line indicates the median. Most of these trials were too small to show anything but very large differences (which, a-priori, were unlikely) (50).

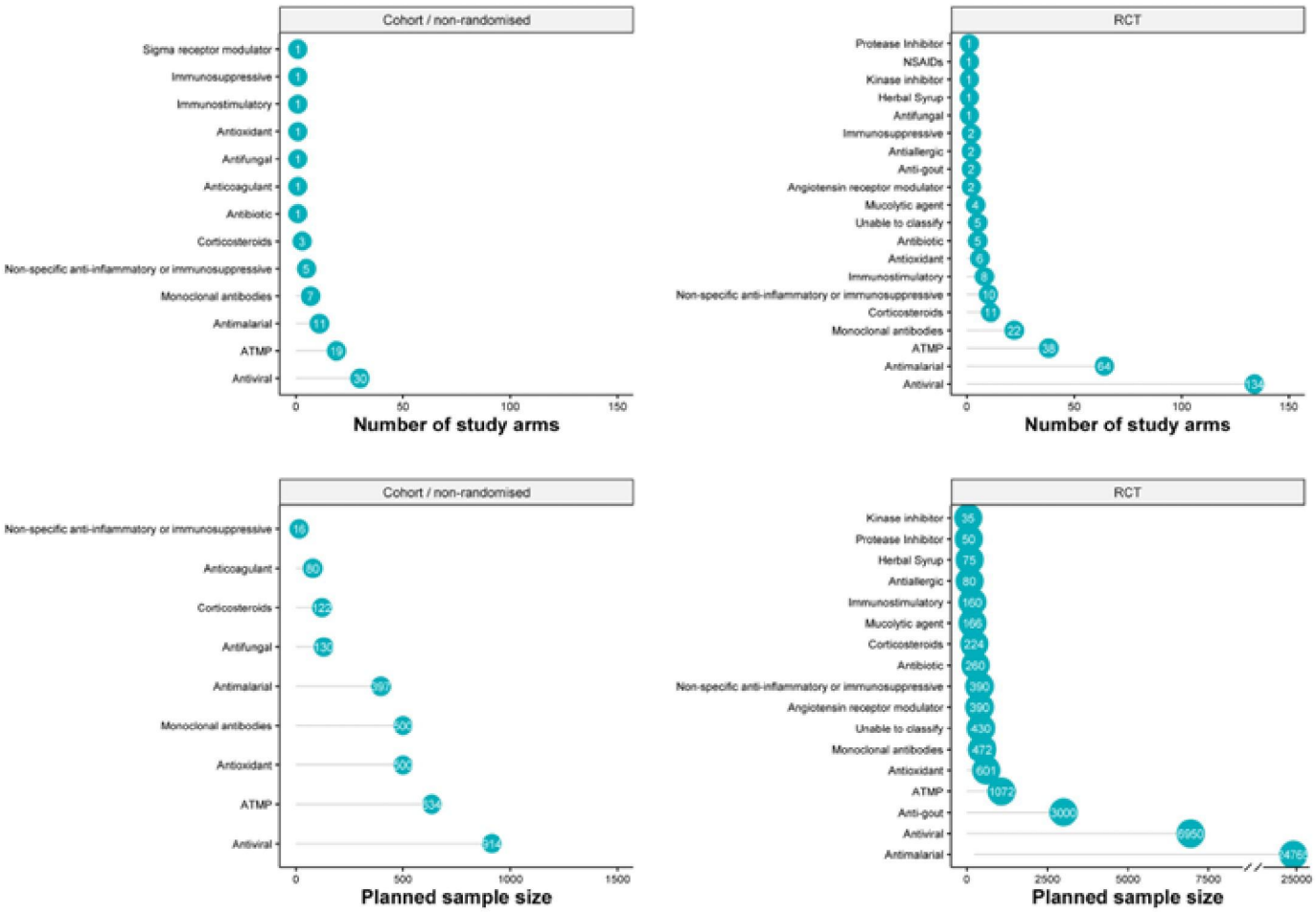


Figure 4B: Number of study arms and planned sample sizes in cohort/non-randomised, and randomised studies by October 2020. The number of study arms assessing each of the drug interventions is presented in upper panels and the planned sample sizes are presented in lower panels. ATMP = Advanced Therapy Medical Products; RCT = Randomised controlled trial (50).

Setting up trials in the UK at the start of the pandemic

5.7. This is a perspective of the UK trials from the outside in the context of trials conducted throughout the world. UK academic institutions, allied in the UK with the NHS, were the major contributor to information on the drug prevention and treatment of Covid-19 globally.

5.8. The bureaucratic processes that slow clinical research are substantial (24,25) and not to be underestimated, and they would need acceleration or circumvention in the event of a new pandemic. In the UK the "red tape" is formidable, but it can sometimes be overcome in emergencies. This is shown by the example of the RECOVERY trial below. Using the NHS as its clinical research platform the RECOVERY trial was able to report its first result within three months of starting recruitment (Figure 5) (18).

5.9. The UK Department of Health and Social Care, the National Institute for Health and Care Research (NIHR) (69), the pharmaceutical industry and academia in the UK all responded very rapidly to the Covid-19 threat. A series of committees were formed as the pandemic unfolded. According to the NIHR's account, in January 2020, as the first COVID-19 patients were identified in the UK, the NIHR enacted its Urgent Public Health (UPH) processes to collect as much clinical information as possible about the new infection. This was done using the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) protocol (69), which had been planned in advance for outbreaks by an international research group, and was ready to be pivoted to future epidemics and pandemics. In March 2020, the NIHR Clinical Research Network (CRN) was asked by the UK government to develop a review and prioritisation system for Covid-19 studies and funnel emergency resources from the CRN and the NHS based on expert review groups. These initially covered therapeutics, vaccines, diagnostics or collection of samples and data. Prophylactics was one of the categories added later. Studies approved through the UPH review process were then given final approval ("badging") by the Chief Medical Officer. Badging facilitated regulatory approval and access to CRN support. The CRN received 1,600 applications in total, 101 studies were UPH approved, and over 1.3 million participants were recruited across 8,773 sites. This was a substantial and timely national research effort. Not all these UPH badged studies reported results and, of those that did, only a few (such as RECOVERY) were valuable, but a high-risk approach was necessary to facilitate research progress during the unfolding emergency.

5.10. The largest trial (RECOVERY) recruited at 178 NHS trusts throughout the UK, eventually expanding to other countries as well. It was regarded by the NIHR, who partly funded it, as its "flagship Covid-19 treatment trial" and was able to report its first results within three months of starting recruitment, a remarkable achievement (Figure 5) (18).

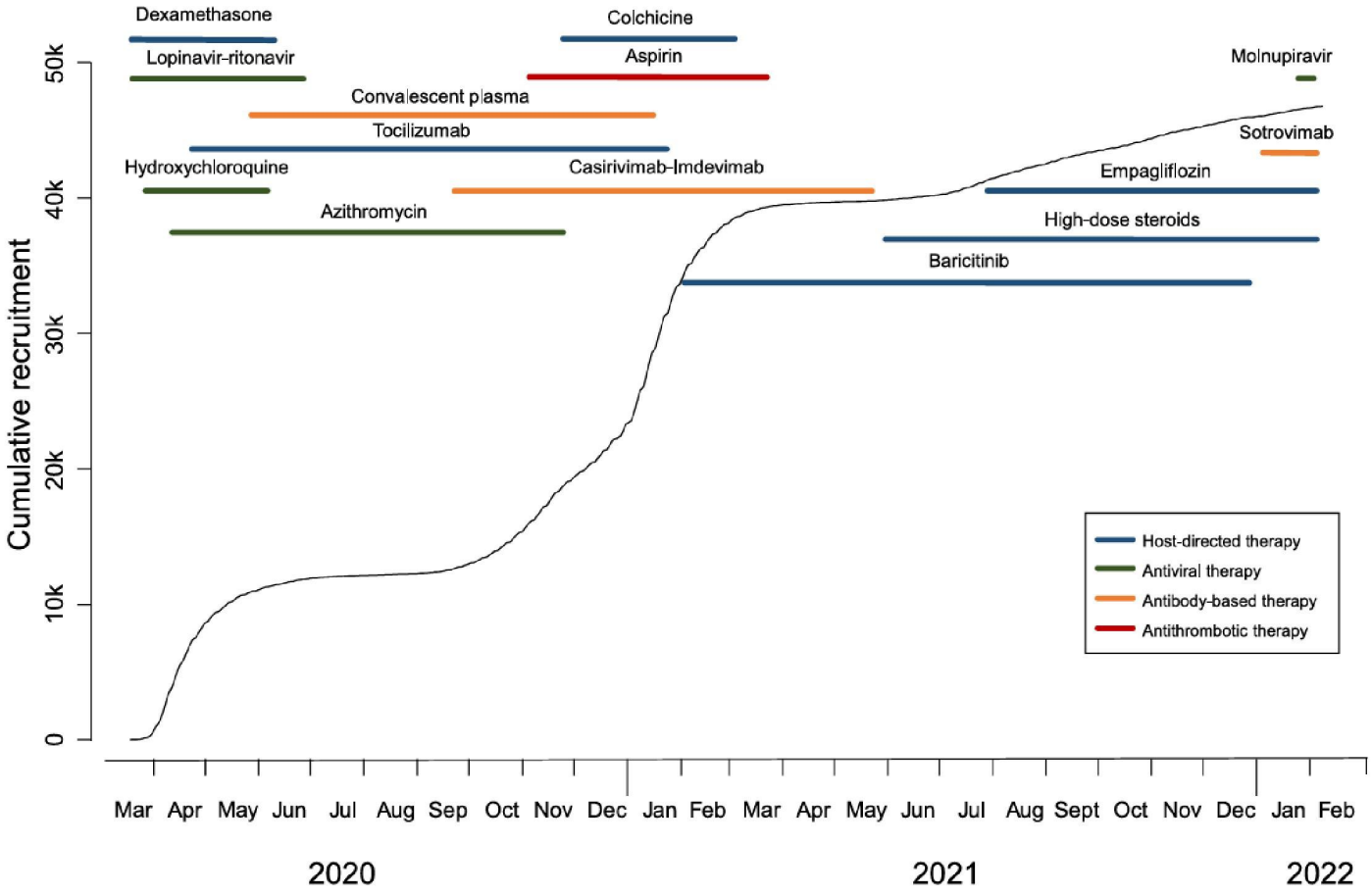


Figure 5: Recruitment to the hospital-based RECOVERY trial which had expedited MHRA and ethics approval, endorsement from the NHS and the UK Chief Medical Officers, financial support from the NIHR and the MRC and was designated as one of the two national Covid-19 treatment trials in hospitalised patients (18). It was an adaptive platform trial - shown by the multiple drugs trialled over time. Drugs were removed from the trial once they had a conclusive result of either being effective or ineffective. Further drugs with promising earlier phase data were added to the trial when this data became available.

Treatment of severe disease

5.11. As hospitals were overflowing with patients the initial therapeutic priority was to assess the treatment of severe Covid-19 (43). In the first few months of 2020 most experts thought that antivirals would be the most likely class of drug to be beneficial but, at that time, there were no specific anti-coronavirus drugs (although some were in the development pipeline), so a large number of repurposed candidates were evaluated. Most of the trials on these drugs were small, and thus underpowered, observational or randomised trials (see Figure 4 above). The medical priority was to reduce mortality and the initial focus was on patients hospitalised with respiratory compromise. Once patients were hospitalised (usually because of low blood oxygen, but the reasons varied), their oxygen levels were monitored, they were given oxygen, and, when needed and possible, they were ventilated (put on a breathing machine). The need for ventilation and death were therefore clear end-points for clinical trials to measure, although the thresholds for ventilation did vary between physicians and hospitals. Sometimes, neither ventilators nor sufficient numbers of specialist staff required to care for ventilated patients were available because of the overwhelming number of cases.

5.12. As mentioned in paragraphs 1.9 to 1.11 and figure 2, it soon became clear that, by the time people with Covid-19 reached hospital, their viral burdens had already decreased substantially (2,3). The results of the large trials then demonstrated that it was reactive immune processes rather than direct viral damage at the time that was causing the potentially lethal lung injury in hospitalised patients.

5.13. The first definitive results from RECOVERY very early on in the pandemic were that neither hydroxychloroquine (a drug used in rheumatic diseases) nor lopinavir-ritonavir (a drug to treat HIV/AIDS) were effective. Neither of these results was particularly surprising although both drugs had been recommended in some countries (on inadequate evidence) and hydroxychloroquine had become intensely politicised (103) (see paragraph 5.60 below)

5.14. RECOVERY then reported that dexamethasone saved lives when given at a moderately high dose to patients receiving respiratory support (1) (Figure 6). It also reduced disease progression and shortened hospital stay. Dexamethasone was not beneficial in patients who did not require respiratory support. This was the single most important therapeutics research result of the pandemic. Many had not anticipated these results. Indeed, beforehand some experts thought corticosteroids would be harmful in Covid-19 by encouraging virus multiplication.

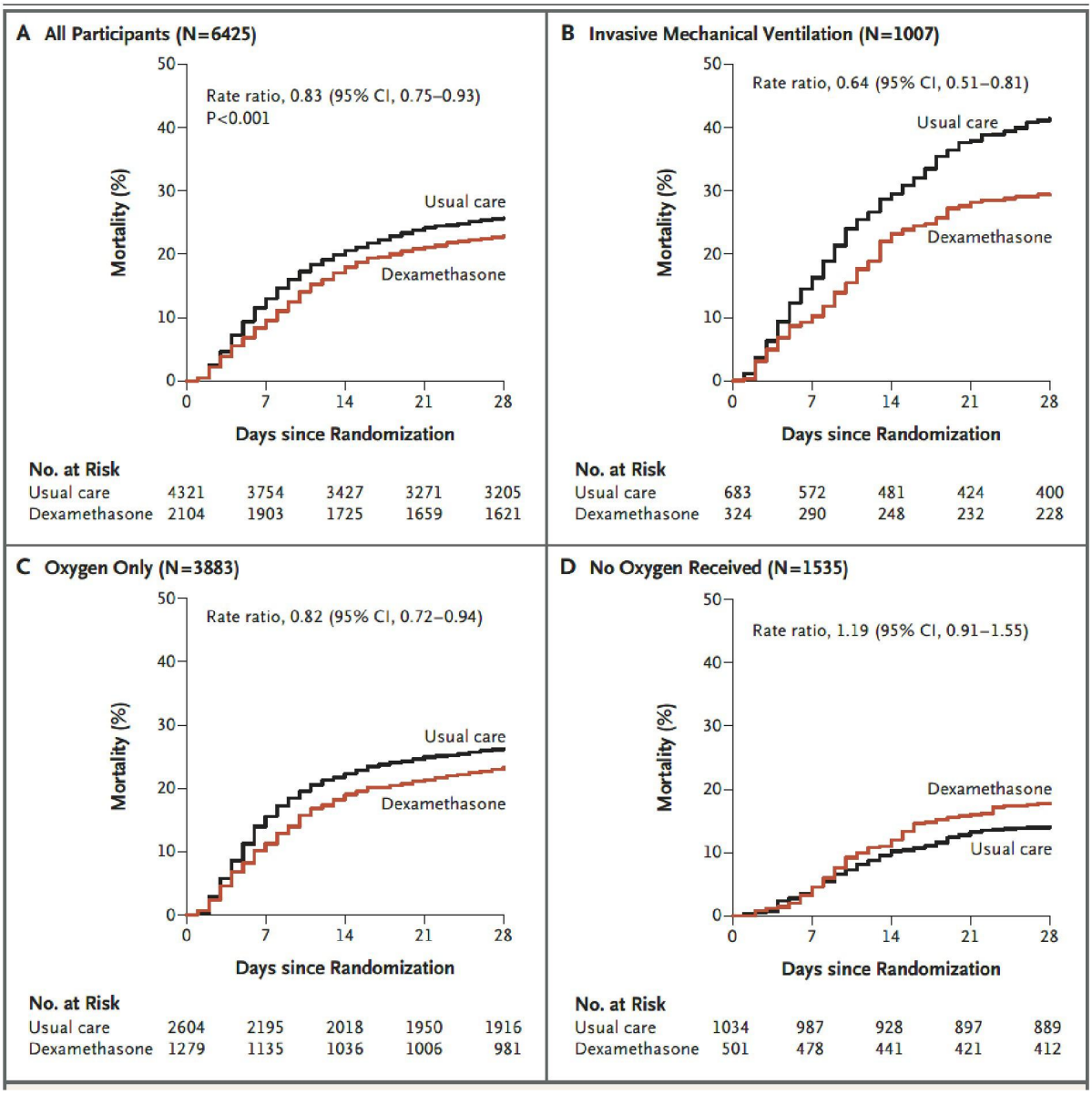
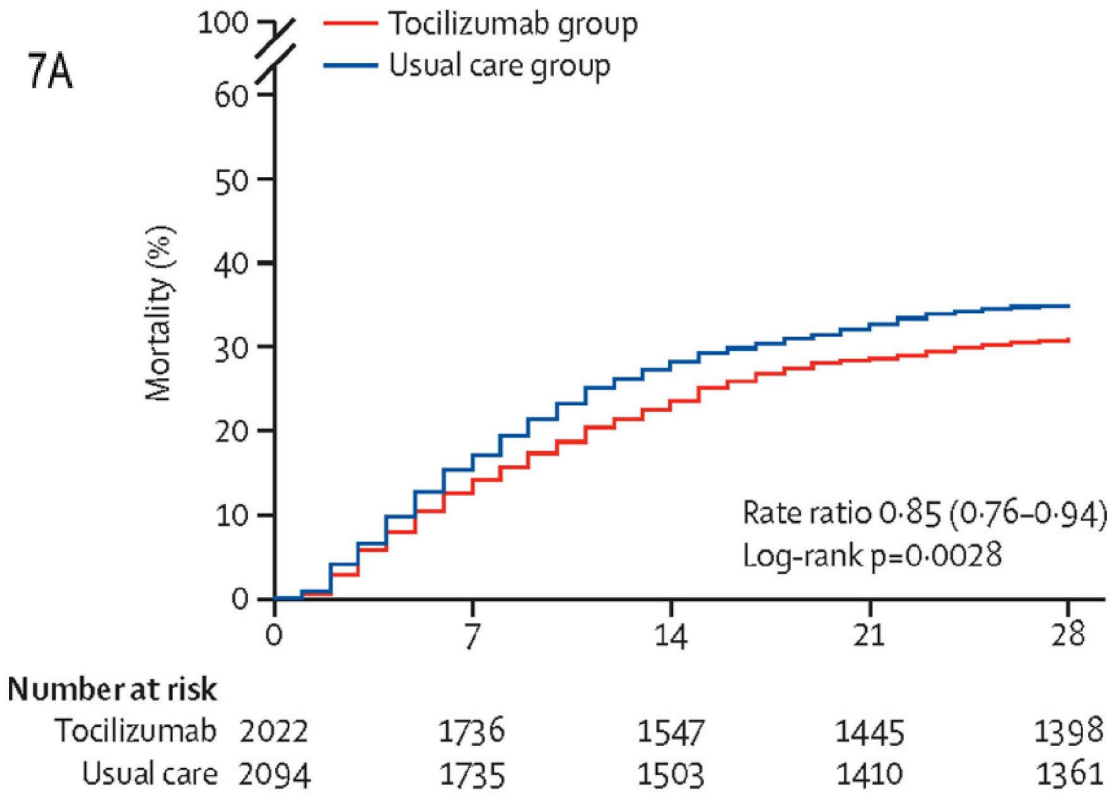


Figure 6: The most important clinical trial result for therapeutics in the Covid-19 pandemic was from the open randomised platform trial RECOVERY (see also Figure 5), conducted in hospitals throughout the UK, which showed that the corticosteroid dexamethasone (red lines) reduced mortality in patients receiving supplemental oxygen or being ventilated (1). Dexamethasone did not benefit the sub-group who were not receiving respiratory support (bottom right box).

5.15. The life-saving benefit of corticosteroids, shown first in the RECOVERY trial (Figure 6) and supported in part by the REMAP-CAP trial of hydrocortisone (a very similar drug) (1, 30) rapidly focussed attention on immunopathology (the damage caused to the body by the immune reaction to the virus rather than the virus itself), and the possibility that adding other anti-inflammatory drugs in severely ill patients could be beneficial. This provided an important insight into the pathological pathways in Covid-19 (i.e. how and what immune processes were causing harm) and how they might be blocked. There were many potential immune modulating treatments which had already been registered for other medical conditions. A lot was known about these medicines based on their use in autoimmune diseases like rheumatoid arthritis – other than dexamethasone, none of the anti-inflammatory drugs found to be effective for Covid-19 had previously been approved in the UK for other infectious diseases (104). Interleukin-6 receptor antagonists added to the life-saving benefit of dexamethasone (27,31) (Figure 7) by blocking a specific immune signalling pathway and, on top of these two interventions, baricitinib further reduced mortality by blocking a different immune signalling pathway (79). The choice of drugs tested in the large platform trials was reasonable, given the evolving information available at the time, although why anti-TNF antibodies were not evaluated is puzzling (105).

5.16. The large adaptive platform trials in Covid-19, which were recruiting very rapidly (Figure 5), provided the best method of finding out whether other anti-inflammatories provided additional benefit to the corticosteroids in severely ill patients. Meanwhile a variety of results were obtained with small trials (i.e. some showed benefit and others did not) which left therapeutic uncertainty initially. For example, small trials evaluating the IL-6 receptor antagonist tocilizumab gave inconclusive results (34-39) whereas the large RECOVERY trial (27) showed definitively its life-saving value (Figure 7).

Importantly, although severe disease became less common as the pandemic evolved, the pathological processes which caused severe disease did not change, so results with anti-inflammatory drugs at the beginning of the pandemic could be compared with more recent results. Whether the doses of these anti-inflammatory drugs were optimal was not assessed in detail, although very high doses of dexamethasone were evaluated subsequently in the RECOVERY trial and found to be harmful (16). Once corticosteroids had shown life-saving benefit in patients receiving respiratory support (oxygen, ventilation), it was no longer acceptable to omit them, so subsequent comparisons in trials in patients with severe disease requiring respiratory support have all been in patients being treated with corticosteroids. For hospitalised patients who did not require respiratory support there was, and still is, equipoise. This term refers to uncertainty about what the right treatment was. Equipoise is required for a trial to be deemed ethical. No new anti-inflammatory treatments were developed *specifically* for Covid-19.



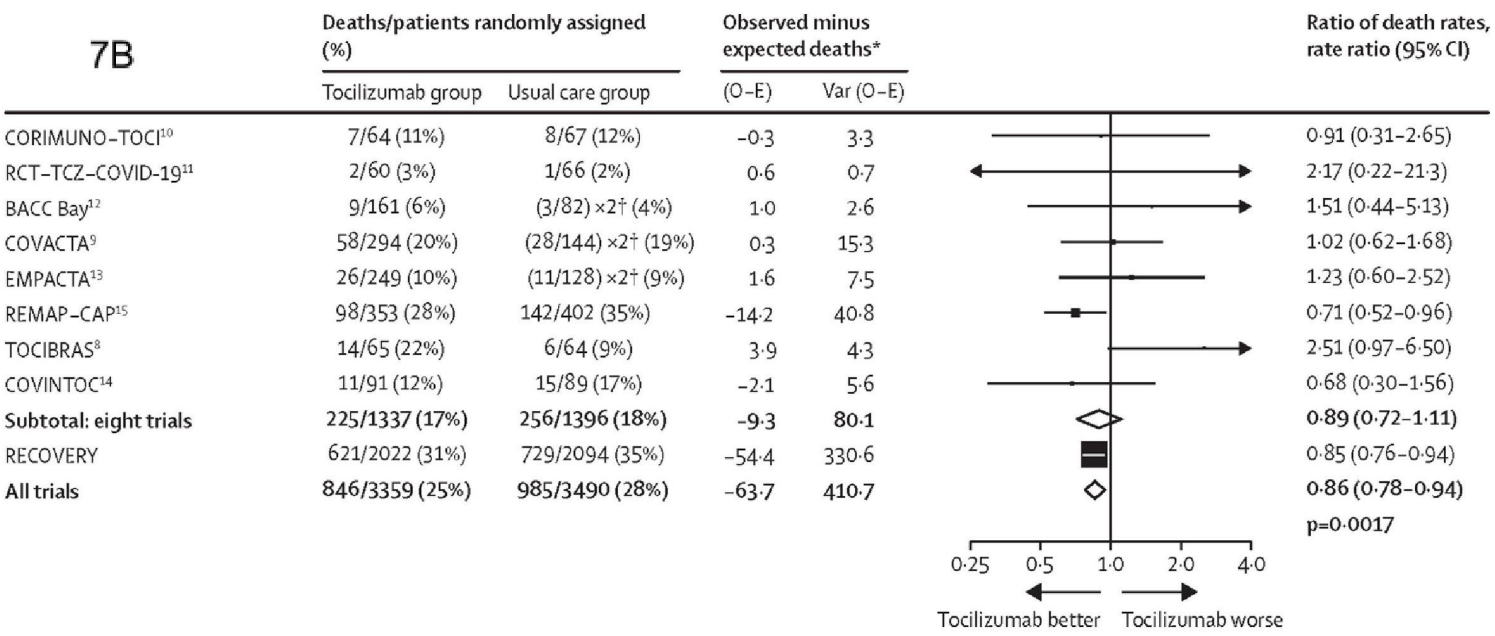


Figure 7. The IL-6 receptor antagonist tocilizumab reduced the mortality of hospitalised patients with Covid-19 who had low blood oxygen by about 15%. The results of the large RECOVERY trial (27) are shown in panel 7A (time in days along the horizontal axis) and all the randomised trials preceding and including the RECOVERY report (full peer-reviewed paper published in May 2021) are shown in panel 7B. This figure shows that the results of smaller trials were inconclusive, and it needed a very large trial to demonstrate the beneficial effect clearly.

5.17. In addition to anti-inflammatories, benefit was shown also in hospitalised patients in terms of mortality and need for ventilation for some antivirals. RECOVERY showed that Regen CoV® (a monoclonal antibody cocktail of casirivimab and imdevimab which gained international attention when it was used to treat President Trump) was shown to reduce mortality as well as disease progression in patients who did not have antibodies against SARS CoV-2 in their blood (28,40) (Figure 8). Remdesivir (an intravenous broad-spectrum antiviral developed originally for Ebola virus disease) had initially been shown in US National Institutes of Health sponsored trials to be beneficial in terms of accelerating clinical recovery (42,81) but, for a time, the World Health Organization recommended against remdesivir because of interim results of the SOLIDARITY trial [33]. Eventually the SOLIDARITY trial (but not the smaller DisCoVeRy trial) confirmed the modest benefit of remdesivir in those who were

hospitalised but not on mechanical ventilation (32,52). Remdesivir was used widely in hospitals in the UK.

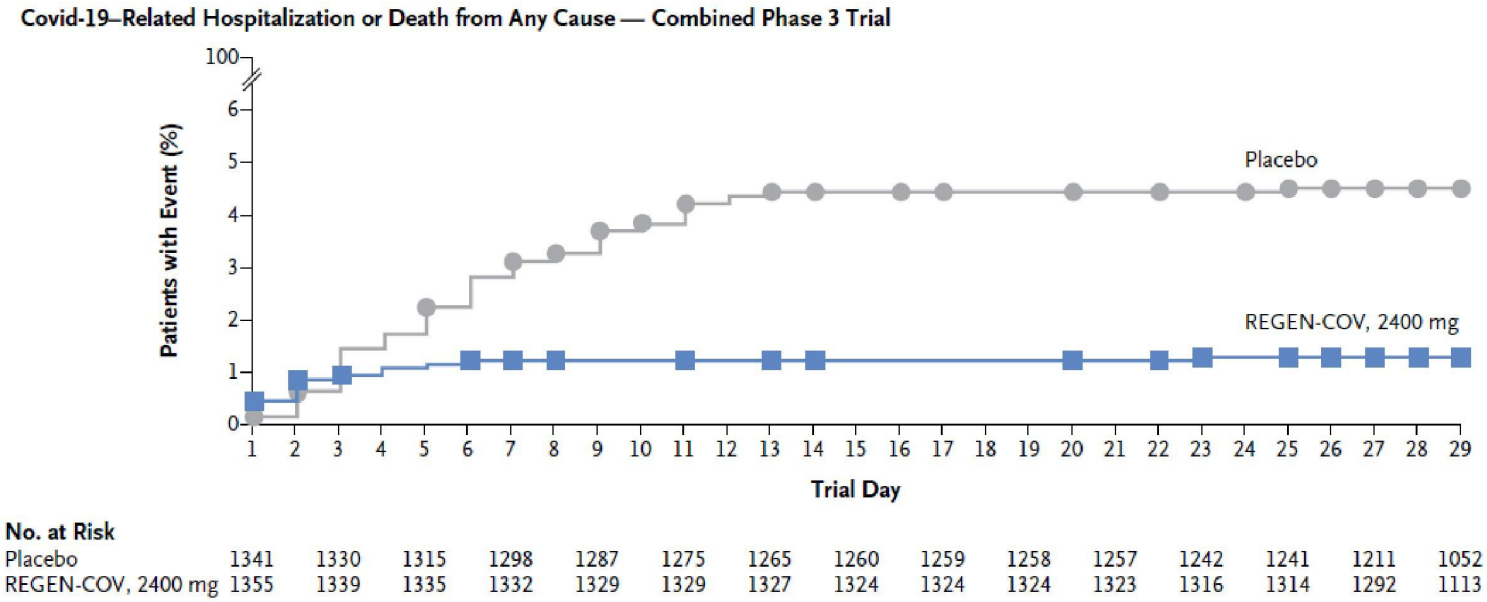


Figure 8. The first NmAb to show clear life-saving benefit in preventing progression of Covid -19 to severe disease and death was a cocktail of two NmAbs, casivirimab and imdevimab directed against the SARS CoV2 spike protein (40). Patients were enrolled in the phase 3 trials between September 24 and 2020, and January 17, 2021 but, by the time the peer reviewed publication appeared in December 2021, a new less susceptible SARS-CoV-2 variant (Omicron B.1.1.529) had started to spread rapidly across the world. The casivirimab and imdevimab cocktail was highly effective against the delta and all preceding variants, and although imdevimab retained antiviral activity against some early Omicron variants, it was withdrawn based on laboratory studies indicating reduced activity against the Omicron variants.

5.18. In addition to excessive immune responses, the platform trials also assessed drugs aimed at treating and preventing blood clotting complications. RECOVERY and REMAP-CAP found no effect from aspirin (which acts against blood clots and against inflammation). REMAP-CAP found a beneficial effect from high dose heparin in hospitalised patients who had not yet been admitted to critical care, but no effect in those who were in critical care receiving advanced organ support (such as a ventilator) (106, 107, 108).

5.19. RECOVERY also showed that, contrary to views at the beginning of the pandemic, giving natural antibodies obtained from the plasma of convalescent patients did not accelerate viral clearance.

5.20. By showing clearly what did and what did not work in hospitalised patients, clinical practices were improved, effective drugs were given, and use of ineffective drugs was discontinued (at least in the UK), and so many lives were saved. RECOVERY and REMAP-CAP continue. They are recruiting patients with influenza in separate study arms. SOLIDARITY stopped in 2022.

Treatment of early disease

5.21. Initially it was thought that antiviral drugs would be the best candidates to save lives in hospitalised patients, but it soon became clear that the benefits of effective antivirals would be greatest when they were given at the beginning of the illness in preventing progression to severe disease (2,3) (Figure 2). In other words, they were most effective as soon as people felt ill and were diagnosed with Covid-19 in the community. An early effective treatment could prevent severe illness and thus hospitalisation. This approach had the potential to save even more lives indirectly through reducing pressure on overwhelmed hospitals.

5.22. One of the problems confronting researchers was deciding exactly what to measure in the outpatient clinical trials to show if the medicines worked or not. Early in the pandemic, before the vaccine roll-out, many people were dying from Covid-19. Hospitalisation was the usual primary end-point of treatment trials (i.e. could the drug reduce the need for hospitalisation?), although this did depend upon the criteria for hospitalisation and their consistent application in the trials. The main serious complication of Covid was lung inflammation, and this could be checked by measuring the amount of oxygen in blood with a simple and inexpensive finger tip or ear lobe oximeter. This was moderately accurate, and it was objective. But, although low blood oxygen or difficulty breathing were common criteria for hospitalisation, the definitions of severe Covid-19 differed significantly which made it difficult to compare results from different trials (109).

5.23. There were high rates of asymptomatic and mildly symptomatic SARS-CoV-2 infection, especially in younger patients, so trials focussed mainly on people with a high

likelihood of needing hospitalisation (such as the elderly, or people with underlying conditions that made them more vulnerable. As the pandemic progressed and the disease became milder as a result of vaccine roll out and natural immunity, the size of the phase 3 trials required to show convincing benefit spiralled. Many of these later trials never finished..

5.24. There was little consensus on precise definitions of severity, so it was not clear what should be measured as the primary end-point of community based or smaller hospital studies which were unlikely to have sufficient statistical power to detect a difference in the increasingly rare outcome of mortality.

5.25. The lack of consensus on definitions and the large number of small heterogeneous trials contributed to substantial variation in the guidelines for the prevention and treatment of Covid-19 across the world. The interpretation of trial results also varied. For example, the WHO treatment guidelines extrapolated the negative findings from RCTs conducted in severely ill patients to patients with mild and/or early disease. This extrapolation was inappropriate as the pathological processes were different in early and late stage disease (22). All this was very confusing for practitioners.

Repurposed drugs

5.26. The initial clinical antiviral studies in 2020 and 2021 focussed on drugs with potential antiviral activity against SARS-CoV-2 that were already available and could be repurposing candidates. However, as explained above, the trials of repurposed drugs in early disease were initially smaller and the clinical end-points were not as clear, so the results were generally inconclusive.

5.27. Overall, a large variety of small molecule potential repurposing candidates, which had shown some antiviral activity in laboratory experiments, were tested in a range of small observational and randomised preventive and treatment trials (50) (see Figure 4B above) – to see if they could reduce progression to severe disease. None of these were conclusive. In hindsight the predictive value of the laboratory and animal experiments which led to the clinical evaluation of antiviral repurposing candidates was

not as good as hoped. It would have been better to measure antiviral responses in pharmacometric trials as these could show if drugs worked or not with relatively small numbers of patients recruited.

5.28. Although many small inconclusive trials were funded, the need for large, well-conducted randomised controlled trials to find out whether drugs worked (i.e. could prevent serious illness and accelerate recovery) and were well tolerated in outpatients was recognised from the beginning of the pandemic. In the UK the randomised phase 3 PRINCIPLE trial was the largest such study. It evaluated repurposed medicines that could be used in the community to treat early Covid-19. PRINCIPLE was funded by NIHR and started recruiting to its adaptive platform in April 2020 – this was not quite as quick to get going as RECOVERY, but was still impressively rapid by comparison with most other trials. From September 2020 the trial had two co-primary endpoints 1) time to first reported recovery, defined as the first instance that a participant reports feeling recovered, and 2) hospitalisation or death related to COVID-19.

5.29. PRINCIPLE eventually published results for six candidate drugs. This trial showed no benefits in terms of hospitalisation and death for azithromycin and doxycycline (press release January 2021), colchicine (preprint September 2021), ivermectin (a definitive negative in over 5,000 patients reported in March 2024), and favipiravir (110) (published August 2024) (87-90). Although these results were clear, it did show that both ivermectin and favipiravir were associated with small reductions in the time to first reported recovery (results which are not explained by antiviral activity). Whether this reflected an anti-inflammatory effect or a placebo response in the open label study is not clear. On the other hand the PRINCIPLE trial did show benefit for inhaled budesonide (a corticosteroid) in patients over 65 years of age (press release April 2021) (91). This result prompted an alert from the Chief Medical Officer via the NHS Central Alerting System in April 2021 recommending its use off-label for older vulnerable patients. This alert followed earlier results of the smaller STOIC phase II trial (111), which also showed positive results. In both studies, inhaled budesonide was associated with shorter times to recovery and a borderline reduced risk of

hospitalisation. Despite the CMO's recommendation, this intervention was not widely adopted in the UK. Following review by NICE and the lack of any further evidence, another CMO alert was issued in December 2021 (112) stating that budesonide should only be prescribed for Covid-19 patients in the context of a clinical trial.

New antivirals specific to Covid-19

General issues with new antivirals

5.30. In the first two years of the pandemic several pharmaceutical companies discovered and developed several NmAbs and small molecule antiviral drugs specifically to treat Covid-19. The NmAbs were raised against the virus spike protein (the same target as the vaccines). The small molecule drugs were redirected from other antiviral development pathways.

5.31. There was a clear and persuasive rationale for developing these therapeutic antiviral NmAbs as well as the more traditional small molecule drugs. NmAbs are already used in some virus infections such as respiratory syncytial virus infection and Ebola virus disease. They can be directed against important parts of the virus which are known to be essential for cell invasion (such as the SARS-CoV-2 spike protein).

5.32. NmAbs can be designed and generated relatively quickly compared to small molecule drugs, but the clinical trial phases (described above, paragraphs 3.1 to 3.28 and figure 3) required once the molecule is ready can still take many months, as can the scale-up for mass manufacturing and then rollout. When the monoclonal antibodies and specific antivirals for Covid-19 eventually reached the phase 2 and phase 3 stages of development, they were all evaluated using similar clinical primary end-points: prevention of disease progression, times to recovery, and death. In contrast to the repurposing candidates, many of these new antivirals were effective. These drugs did not start becoming generally available until mid-2021 and into 2022, after the second wave in the UK had ended (43-49).

5.33. The pharmaceutical companies which developed new small molecule drugs and NmAbs early in the pandemic were able to recruit enough patients to show benefits

and obtain regulatory approvals (see below) but, until the PANORAMIC study began to compare the oral antivirals, no post-registration comparisons between the medicines were commissioned to guide policies and practices. PANORAMIC has not yet reported the final results (originally scheduled for early 2022). By 2022 the Covid-19 disease had become much milder. As a result, the usual end-point of early treatment trials, which was prevention of hospitalisation, was much rarer and so even very large trials such as PANORAMIC were insufficiently powered to show moderate benefits.

Neutralising monoclonal antibodies

5.34. The first NmAb shown to prevent disease progression (as well as reduce mortality - see above) was Regen CoV®, a "cocktail" of two NmAbs (see Figure 8 above) (28, 40). Large purchases were made by governments, including the UK.

5.35. Several other NmAbs soon followed (44-49), but these different NmAbs were not compared directly (i.e. head to head) in randomised trials. This meant that they could only be compared from their laboratory testing results. These tests showed whether a NmAb could reduce the invasion of cells by the SARS-CoV-2 virus but they did not provide accurate guidance on how good they would be in the treatment of patients. This is because the NmAb concentrations in patients' bodies were very much higher than in the laboratory tests, and the laboratory tests do not reflect all the complex processes in a patient with Covid-19 (68).

5.36. One unresolved question was whether NmAbs could be harmful in severe disease. The RECOVERY trial and two subsequent trials with different NmAbs did suggest a worse outcome in severely ill patients who were already sero-positive (i.e. already had antibodies against the virus in their blood when they were admitted to hospital). But the ACTIV-3 trial which evaluated Tixagevimab/cilgavimab (Evusheld®) and reported a 30% reduction in mortality, did not find this. The mortality reduction was similar in seropositive and seronegative patients (113).

5.37. Early in the pandemic the NmAbs, which had been developed against the original SARS-CoV-2 virus (the "Wuhan" strain) were generally very effective, particularly in

preventing progression to severe disease. But as the SARS-CoV-2 viruses, and particularly their spike protein, evolved and became less recognisable, these NmAbs began to lose activity. As time passed, and particularly with the abrupt advent of the Omicron variant in winter 2021/2022, the reduced virus neutralisation observed in the laboratory (70-74) and the consequent predicted reduced efficacy of NmAbs reduced enthusiasm for their use.

5.38. This loss of activity was predictable. However, observing some loss of activity in the laboratory was sometimes assumed to be definitive evidence that the NmAbs would not work in patients. It is not. For example, if the NmAb concentrations in blood are 100 times greater than those required for the maximum inhibitory effect, then with a reduction in potency by 99% against a new variant may still provide the maximum effect. Nevertheless important policy decisions were based on these uncalibrated in-vitro lab studies. For example, for the Omicron viruses it was assumed initially (incorrectly) that lack of activity of the stockpiled Regen CoV® NmAb against BA.1 applied to all the Omicron variants.[6] Use of Regen CoV® was discontinued in the UK and in the USA. While both antibodies in the cocktail were indeed ineffective against BA.1, one of the antibodies (imdevimab) regained partial activity against some of the later Omicron viruses. This was shown in patients in the PLATCOV viral clearance study I was involved in. This uncertainty was at the centre of the UK assessment of tixagevimab/cilgavimab (Evusheld®) for prevention of Covid19. The NmAb cocktail had shown excellent protective efficacy against severe disease and death in randomised controlled prevention trials, and also a 30% reduction in mortality in the treatment of disease in hospitalised patients (in addition to remdesivir and dexamethasone). But these trials had been conducted in the "pre-Omicron era" and in mainly unvaccinated individuals. There was some reduction in the antiviral activity of both NmAbs against the early Omicron variants (BA.1 and BA.2) in the lab tests and

[6] Approval for Regen CoV® (casirivimab/ imdevimab) was withdrawn in the USA and the UK when the Omicron variant arrived. The withdrawal decision was based mainly on initial in-vitro neutralization assays with the BA. 1 variant (70-73). But the NmAb concentrations achieved in vivo (in the body) are substantially higher than in the in-vitro tests (in the lab). The in-vitro results were not calibrated with in-vivo responses (74, 75). An inhibitory concentration estimated in the lab cannot be extrapolated directly to assume the same effect in humans. Such "validation" is very important in assessing the treatment of infectious diseases. While casivirimab was inactive against all Omicron variants, it was shown that imdevimab did retain significant clinical activity (i.e. accelerated viral clearance) against BA. 2 (except BA. 2.75), 4 and 5. (39).

so, based on this uncertain extrapolation, Evusheld® was not taken forward. The clinical antiviral efficacy of NmAbs could have been monitored and evaluated continuously in ongoing relatively small pharmacometric studies (see paragraphs 5.44 to 5.47 below). Overall, the activities of the different NmAbs and drugs should have been compared in clinical studies of viral clearance in patients rather than relying on uncalibrated lab tests. Much of the expensive purchased Regen CoV NmAb expired and was never used. Given that it had already been purchased, it could have been used (particularly in patients unable to receive nirmatrelvir-ritonavir because of its frequent interaction with other drugs) if guided by contemporaneous viral clearance evaluations.

Oral antivirals

5.39. In late 2021 and early 2022 the first specific oral antivirals arrived. Molnupiravir was the first to be approved (the UK led the world in approvals of these new oral antivirals). Molnupiravir acts by causing errors in copying of viral genetic material. Molnupiravir was developed before the pandemic (primarily for influenza treatment) and designed to be broadly effective across several types of RNA viruses (114). The pre-registration trials showed good evidence of efficacy of molnupiravir in preventing progression of Covid-19 disease and in accelerating viral clearance (83-84), although there was some debate about these results. Molnupiravir was followed closely by a new combination drug nirmatrelvir-ritonavir (also known as Paxlovid®). Nirmatrelvir had been developed for SARS-CoV-1. It inhibited an enzyme called the main protease (Mpro) which is found in both SARS-CoV-1 and SARS-CoV-2. Nirmatrelvir is eliminated very quickly from the body so, in order to slow down metabolism of nirmatrelvir in the liver and thereby boost the levels in the blood, a second drug, ritonavir, was added. This is a well-established drug which was developed originally to treat HIV infection. It does not act specifically on SARS-CoV-2, but it blocks the metabolism of nirmatrelvir, and that keeps the nirmatrelvir levels high enough so that it can work better (115). In a phase 2/3 study of 2,246 patients ritonavir-boosted nirmatrelvir showed clear evidence of efficacy in preventing progression of disease, preventing death and in accelerating viral clearance (85). Molnupiravir and nirmatrelvir-ritonavir could both be given as

tablets to outpatients. The PLATCOV randomised platform trial (see paragraphs 5.50 to 5.52) later showed that nirmatrelvir-ritonavir had much more potent antiviral activity in patients compared with molnupiravir.

5.40. Both drugs were made available to some patients on the NHS in winter 2021/2022 while clinical trials were ongoing but, by then, the severe Covid-19 waves were over and the UK population was well vaccinated. Although Covid-19 was still an important and very common disease in the winter of 2021/2022, and in vulnerable groups it continued to cause significant morbidity, but conducting the large clinical trials (such as PANORAMIC) became progressively harder. This was because as Covid-19 became less serious and hospitalization rarer, even for high risk groups, trials which aimed to show if hospitalisation could be prevented became prohibitively large (because large trials are needed to show small differences conclusively). That meant that it was not known how the two oral drugs compared (i.e. which was better, and by how much?).

5.41. The last and largest of the NIHR funded community-based trials (and the largest in the world) was the UK-based PANORAMIC study (92), which launched in December 2021 and closed recruitment by March 2024. It was a randomised open-label (i.e. not blinded) platform trial designed to assess the efficacy of the two new oral antivirals molnupiravir and ritonavir boosted nirmatrelvir compared with usual care (i.e. no specific antiviral). Plans and policies for later deployment of the oral antivirals in the UK were to be guided by its results. It was hoped that read-outs for both drugs would be available by the end of March 2022, but recruitment was less than expected. The PANORAMIC trial primary end-point was prevention of hospitalisation and/or death within 28 days of randomisation in patients with Covid-19 who were aged over 50, or were younger with underlying conditions that made severe Covid-19 more likely. The nirmatrelvir arm of the study has still not reported as of December 2024. In the molnupiravir comparison (published in January 2023), despite enrolling 25,786 patients, only 199 hospitalisations and 8 deaths were reported. Thus, less than 1% of patients met the primary end-point of the study which meant the trial was underpowered to identify moderate differences. This was in stark contrast to 2020, when hospitals were full of unvaccinated Covid-19 patients, and the virus was a

common cause of severe illness and death. By 2022, in a largely vaccinated and previously infected population, Covid-19 was no longer a major cause of mortality and other causes of illness and death were much more common. Although there was some evidence of benefit with more rapid recovery in molnupiravir recipients in the PANORAMIC trial, this was regarded generally as a "negative result", and enthusiasm for molnupiravir was dampened (92).

5.42. In contrast to the NmAbs, the small molecule drugs have not lost antiviral activity against the new SARS-CoV-2 variants. However, these new medicines were never compared with each other in randomised phase 3 trials before they were registered (which is not unreasonable), and apart from the PANORAMIC trial (which as of November 2024 has yet to report on nirmatrelvir versus molnupiravir) and the OpenSAFELY observational studies, were not compared after registration while they were being procured and used (which is more questionable), so relative antiviral efficacies were not known. The lack of comparative data, the differing guidelines and recommendations, even between hospitals, and the increasing mildness of the illness meant that these drugs were not used very widely in the general population. Even in higher risk groups and hospitalised patients use of these drugs in acute Covid-19 was inconsistent.

5.43. Once effective drugs became available, clearer evidence-based guidelines based on detailed pharmacometric comparisons could have informed the choice of NmAbs and small molecule drugs and thereby improved the early treatment of Covid-. It is now clear that nirmatrelvir is the most effective currently available antiviral drug against SARS-CoV-2 (56), although its use is still inconsistent. Drug development has slowed markedly over the past three years with few new SARS-CoV-2 treatments now in development (116).

Phase 2 studies

5.44. In an epidemic or pandemic where there is uncertainty, or no known therapies, it is essential to find out the best drug treatment as soon as possible. In a respiratory virus infection such as Covid-19 or influenza, measuring how quickly the drug clears the

virus in phase 2 studies in patients can be used to assess drugs (15). As virus burdens are usually highest early in the illness, these studies can be performed rapidly in previously healthy adults with mild disease. The more effective the drug, the faster the virus disappears from the respiratory tract.

Measuring viral clearance rate

5.45. Early in the Covid-19 pandemic, accurate measurement of the virological responses in phase 2 evaluations of the new or repurposed antivirals was not done. The antiviral drugs were evaluated mainly based on clinical recovery and, usually, time (i.e. interval) to nasopharyngeal viral clearance. This is the interval from the start of treatment until the virus is no longer detectable with swab testing, that is, the PCR test on the swab sample is negative. Although most studies reported it, "time to viral clearance" is an imprecise (and therefore inefficient) measure.[7] It depends on how high the viral densities were before treatment, how often the measurements are taken, and how sensitive the assay is. Measuring viral clearance rate (how fast the concentrations of virus declined) is much better (15).

5.46. In some of the early phase assessments of the new antivirals in Covid-19, viral densities in nasopharyngeal samples were measured at fixed intervals after starting treatment (on days 3 and 5, or on day 7) (40-43). This gave a crude estimate of the viral clearance rate, and it was a better measure than "time to clearance", but there were not enough measurements for it to provide an accurate measure of the rate. Despite these clear limitations the time to viral clearance was, and still is, widely reported as the primary pharmacodynamic end-point in clinical trials (including in other viral infections) (53).

5.47. The net result was that phase 2 studies in Covid-19 in the first 2-3 years of the pandemic needed to recruit more patients to determine if the medicine was effective or not, and were less efficient and less informative than if oropharyngeal virus densities had been measured daily.

[7] Time to viral clearance is a poor measure of viral clearance because it depends 1) on how high the viral density is before treatment, 2) how often viral densities are measured and 3) how sensitive and accurate the test is. A patient with a high viral density will take longer to clear the virus. Measuring the rate of viral clearance is much better.

Comparisons of antivirals

5.48. Apart from the PANORAMIC trial, which is yet to report on both arms, direct comparisons between antivirals with randomised trials were not done. In the pre-registration randomised trials of antiviral drugs in Covid-19 the comparison was invariably with "no drug" (often called "standard of care") or a placebo. There were no comparisons with other effective interventions initially because when these trials were started there were no clearly effective comparators. The NmAbs and small molecule drugs were purchased by Governments on the basis of the evidence from these pre-registration trials. This was understandable in the early days of the pandemic when the health burden was high, but not instituting methods to evaluate and compare them, and monitor their continuing efficacy, was puzzling. As described above, there were particular concerns over the efficacy of the NmAbs as the virus continued to evolve rapidly. These concerns were based on lab measurements not clinical evaluations. However, after the drugs had been purchased by the NHS and used widely, retrospective observational data was obtained. The large OpenSAFELY platform, (117) which was supported by the Wellcome Trust and funded by several agencies, analysed near real time data from NHS electronic health records. This provided valuable, albeit retrospective data. In a comparison of outcomes (hospitalisation and/or death) of over 6,000 patients who had been treated with either molnupiravir or the NmAb sotrovimab between December 2021 and 10 February 2022 outcomes were reportedly significantly better in the NmAb recipients. There was later observational evidence from this same source that sotrovimab was effective in Omicron BA.2 infections (partly allaying concern that these emerging variants were less susceptible). Later in 2022 the OpenSAFELY retrospective observational study compared sotrovimab with ritonavir-nirmatrelvir and concluded that the two interventions resulted in similar outcomes. This study covered the period when the BA.2, BA.5 and BQ.1 Omicron variants were prevalent, and so gave some further support for sotrovimab efficacy against these variants. The health service structure, the electronic records and the NHS strict criteria for prescribing make this approach powerful for evaluating medicines as outcomes can be compared knowing that the indications for treatment

were comparable. These results from very large numbers of treated patients provided support for the continued recommendation of both sotrovimab and nirmatrelvir-ritonavir, while holding molnupiravir as third line alternative (demoted because of the disappointing results of PANORAMIC). However, whereas susceptibility to nirmatrelvir did not change, susceptibility to sotrovimab was diminishing as viral evolution continued, so the confidence that sotrovimab was still working well was limited. Although sources of bias can be adjusted for in observational studies they cannot be excluded completely. After 2022 there has been no comparative information, despite increasing concerns over the continued efficacy of sotrovimab. This is part of the reason why prescribing practices and guidelines today still vary substantially.

5.49. By the time the effective antiviral drugs were introduced and pharmacometric methods had been developed for Covid-19 which could compare the drugs efficiently (see below), the vaccines had been rolled out and Covid-19 had become a milder (but still widely prevalent) illness. This coincided with a marked decline in public, academic, health sector and pharmaceutical sector interest. Therapeutics research and development slowed.

Pharmacometric assessment in PLATCOV

5.50. In September 2021 I helped start the multinational, phase 2, randomised, adaptive PLATCOV trial. This is the largest pharmacometric study in Covid-19. PLATCOV recruits previously healthy outpatients (aged <60 years) with early Covid-19 symptoms. The trial was based in Thailand but had recruiting sites in several other countries, not including the UK. This pharmacometric assessment method allows comparison with no treatment and between interventions with relatively small patient numbers. A highly effective intervention can be identified with as little as 10 treated patients. The assessment is based on well tolerated viral clearance measurement (measurement of daily oropharyngeal viral densities) (9, 54-56) (Figure 9).[8] The

[8] It is also important to note that natural viral clearance in Covid-19 is getting faster. Increasing natural rate of SARS-CoV-2 oropharyngeal clearance over the past two years has been shown in the PLATCOV trial (63), mainly in Thailand, but this is likely a general phenomenon as the populations immunity becomes more effective. This means it is necessary to adjust for time of study in historical comparisons of therapeutics in Covid-19.

PLATCOV platform trial has evaluated two therapeutic monoclonal antibodies, shown that ivermectin and favipiravir do not affect viral clearance, that fluoxetine does accelerate viral clearance by a small amount, that molnupiravir and remdesivir substantially accelerate viral clearance, and that ensitrelvir and ritonavir-boosted nirmatrelvir are the most potent antivirals tested (Figure 9)[1].

5.51. Rapid viral clearance correlates with rapid recovery from illness. There is still uncertainty over the relationship between viral loads and subsequent risk of inflammatory pneumonitis (i.e. were people with higher viral loads more likely to get sick?) but pharmacometric studies such as PLATCOV provide a relatively simple and rapid way of comparing small molecule drugs and monitoring the efficacy of NmAbs.

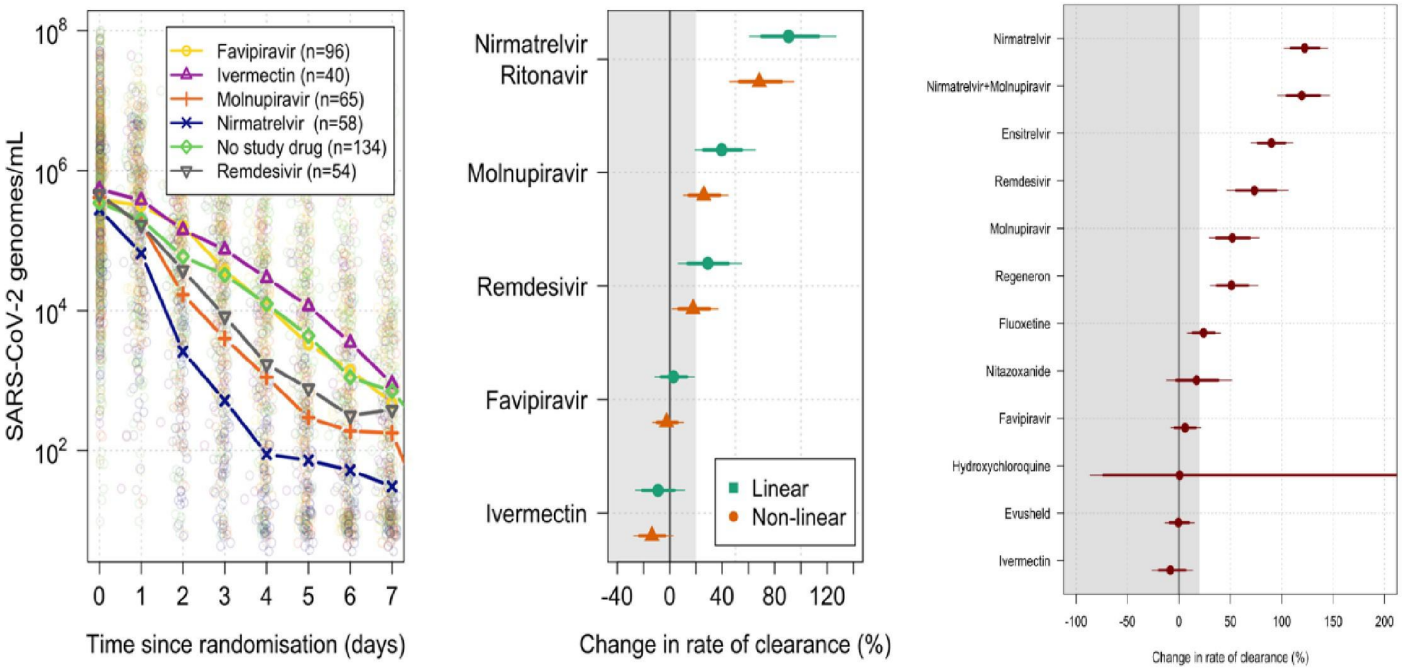


Figure 9. Measuring viral clearance and comparing antiviral drug effects in Covid-19. Outputs of the ongoing adaptive randomized platform pharmacometric comparison of potential drugs to treat Covid-19 (PLATCOV) (56). The left side shows the declining median daily oropharyngeal eluate viral densities (and individual values) with the different treatments against a background of the individual viral densities. The middle figure shows the corresponding estimated 95%

credible intervals for the population estimated viral clearance half-lives (shorter half-life means faster clearance). The two colours represent two different ways of modelling viral clearance. The right side shows all the completed studies (over 2100 enrolled patients, results not yet published). The change in rate of clearance compares the drug results with no drug results. Ritonavir boosted nirmatrelvir gives the greatest acceleration in viral clearance. It is currently the most potent antiviral treatment of Covid-19.

5.52. The adaptive platform trial approach used in PLATCOV in outpatients allows small molecule drugs or NmAbs or combinations to be evaluated as they become available. Now that effective drugs are available, new drugs must be at least as good and preferably better than those we already have. PLATCOV is now designed to detect at least a 20% acceleration in viral clearance compared to no treatment (9). If the effect is less than this, the test drug is dropped from the platform trial (as less effective drugs are no longer required). If the acceleration in viral clearance is more than this, the drug enters a second phase in which it is compared with the best current treatment (ritonavir boosted nirmatrelvir) (63).

5.53. In the UK, the University of Liverpool based AGILE adaptive platform for the pharmacometric evaluation of new drugs (phase 1 and phase 2) was set up (described in more depth in the statement of Professor Saye Khoo, INQ000474449 (86) (Figure 10). It merged with the University of Southampton based ACCORD (phase 2) trial. For the phase 2 part, AGILE relied primarily on time to negative PCR test, i.e. the time until the virus was completely cleared, though more detailed measurements of the changes in amount of virus were also performed as an exploratory endpoint (118).

Figure 10 - Introduction to the AGILE platform trial https://www.agiletrial.net/ accessed 15 July 2024

5.54. This trial was not initially supported by the UK Government, having Urgent Public Health status turned down in April 2020 because, as an earlier phase trial, it was deemed unlikely to change practice within 12 months.[9] But for the determination of the investigators and local support, it could well have stopped altogether as a consequence. However, UPH status was eventually awarded in April 2021.

5.55. Professor Khoo highlights important issues with earlier phase pharmacometric platforms from his experience on the AGILE trial, three of which I will highlight here.

- He states that "*by far the most important rate-limiting step was enrolment*".[10] Challenges are posed by having to screen many people for inclusion as some will decline to take part or be ineligible. It is important to take advantage of the surges of patients when and where they take place.

- He also suggests that early phase trials should not be only the responsibility of the drug industry and they should be publicly funded. For pandemic preparedness especially, industry does not have a good enough incentive to

[9] INQ000474449_0013 paragraph 49
[10] INQ000474449_0014 paragraph 53

invest in candidate drug development against a pathogen that has not yet emerged, and might never spread. I whole heartedly agree with this.

- Finally, I also agree that single "broad spectrum" antivirals usually face a trade-off between breadth of coverage and potency, that "broad spectrum" combinations of drugs may be more achievable, and that structures to trial them should be enabled.

Chemoprevention trials

5.56. From a disease prevention standpoint, the initial research was on understanding (and therefore hopefully reducing) Covid-19 transmission and accelerating vaccine development. Before the vaccine rollout began in December 2020 attempts were also made to study if repurposed drugs could prevent Covid-19. The focus initially was on trying to protect healthcare workers to reduce sickness absence from Covid-19 and improve health system resilience.

5.57. The possibility of using drugs to prevent Covid-19 in 2020 focussed mainly on hydroxychloroquine.

5.58. Hydroxychloroquine, along with ivermectin, were the most contentious drugs in Covid-19 (68). Both were endorsed by leading politicians in early 2020 without evidence, and both polarised public and medical opinion. This interfered with objective scientific evaluation in prophylaxis as well as treatment.[11]

5.59. I was the co-principal investigator for the largest chemoprevention study COPCOV, a multinational study which started recruiting in the UK April 2020. On 22 May 2020 a description of an observational study was published in the Lancet, which claimed that use of hydroxychloroquine in Covid-19 treatment was associated with ventricular arrhythmias (dangerously fast and weak heart beat) and an increased risk of death. The large multinational study was reportedly coordinated by a very small USA based company called Surgisphere.

[11] Many of these drugs were recommended in guidelines and used in other countries without sufficient evidence (77).

5.60. On the day of publication, the MHRA immediately withdrew its approvals for trials testing hydroxychloroquine, including COPCOV (except for the RECOVERY trial assessment of hydroxychloroquine as a treatment rather than prophylactic in hospitalised patients, which was nearing its completion (65)).

5.61. The Lancet paper was criticised in an open letter composed by our group and signed by over 120 international scientists on 28 May 2020 (119). The letter highlighted multiple serious methodological and data integrity concerns and called for independent validation. Several journalists then investigated. The Guardian published an article on 3 June 2020 that found several concerning details about Surgisphere, casting doubt on whether the company had indeed collected the data claimed in the Lancet paper (120). On 5 June 2020, the Lancet retracted the paper on the basis that the authors could not verify primary data sources, and in a 14 June 2020 article in the New York Times, the editor of the Lancet, Richard Horton, called the paper a "fabrication" and "a monumental fraud" (121). An earlier paper on Covid-19 in the New England Journal (a leading medical journal), also coordinated by Surgisphere, was also retracted for the same reasons (122). After the retractions the MHRA was slow to allow trials to restart. By the time the MHRA finally permitted continuation of the studies on 26 June (123) the first wave of infections had receded further. In addition, public opinion was still negative towards hydroxychloroquine, and recruitment to the trials had become difficult. By February 2021 the British Government had placed orders for 457 million vaccine doses and vaccine rollout had begun. Most chemoprevention trials in the UK then stopped.

5.62. The confusion on this topic also further affected the WHO guidelines (see paragraph 5.25) (Figure 11), which extrapolated incorrectly from available evidence. They considered that there was strong evidence that hydroxychloroquine chemoprevention did not prevent death, when there had been no deaths in any of the pre-exposure chemoprevention randomised controlled trials (i.e. it was obviously not possible to say whether or not hydroxychloroquine chemoprevention prevented death). In my opinion the toxic atmosphere generated by the politicisation of hydroxychloroquine and false claims of toxicity clouded judgement at this stage of the pandemic.

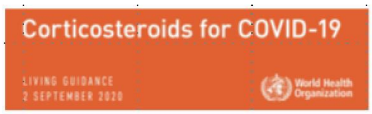
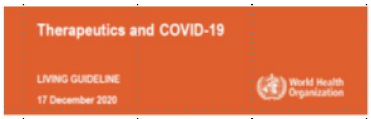
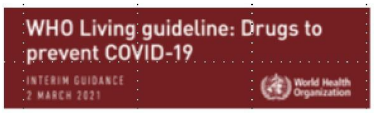
Treatment & patient group	Endpoint	Underlying data	Evidence appraisal	
Dexamethasone for severe COVID-19 (on respiratory support)	Mortality	1 multicentre randomised open label trial: • RECOVERY: 980 deaths/3883 [OR: 0.82 (0.72-0.94)]	**Benefit; Moderate certainty:** *the authors believe that the true effect is probably close to the estimated effect* Risk of bias: **Serious**	
Hydroxychloroquine to treat confirmed COVID-19	Mortality	10859 patients from 7 trials, of which 60% are from: • RECOVERY: 1211 deaths/4716 [OR: 1.09 (0.97-1.23)] • SOLIDARITY: 188 deaths/1853 [OR: 1.19 (0.89-1.59)]	**No benefit: Moderate certainty:** *the authors believe that the true effect is probably close to the estimated effect* Risk of bias: **Serious**	
Hydroxychloroquine to prevent COVID-19	Mortality	1 cluster randomised open label PEP trial. There were no deaths in the PrEP trials • Mitjà *et al.*: 13 deaths/2314 contacts of COVID-19 cases [OR: 0.67 (0.22-2.05)]	**No benefit: High certainty:** *the authors have a lot of confidence that the true effect is similar to the estimated effect* Risk of bias: **No serious concerns**	

Figure 11: A comparison (76) of WHO guidelines for dexamethasone and hydroxychloroquine in hospitalised patients based on the mortality endpoints in very large randomised controlled trials which were regarded as conclusions of moderate certainty with serious risk of bias. In contrast, the much smaller studies of hydroxychloroquine in prevention were regarded as having no serious concerns of bias and providing a high degree of certainty that hydroxychloroquine did not prevent death despite there being no deaths in any of the pre-exposure prevention trials. These assessments of certainty and bias are clearly inconsistent and, in the case of hydroxychloroquine chemoprevention, illogical.

5.63. The COPCOV study, which enrolled 4,652 people in 26 centres in 11 countries (including the UK), did ultimately provide evidence that hydroxychloroquine and the closely related chloroquine were moderately protective against symptomatic Covid-19 when given daily over three months (66). Pooling all the chemoprevention studies evaluating these drugs in a meta-analysis suggests that they provide about 20% protection against symptomatic Covid-19 illness (Figure 12). Furthermore, at the doses used in chemoprevention, which were similar to those used in the treatment of rheumatoid arthritis, hydroxychloroquine and chloroquine were safe and well tolerated. The cardiovascular safety of hydroxychloroquine and chloroquine in the Covid-19 chemoprevention and treatment studies was predicted from earlier studies of self-poisoning with these drugs which had established the relationship between dose and toxicity and determined their margin of safety (124). When high doses of

chloroquine (over 60% higher than used in RECOVERY) were evaluated in a study conducted in Brazil, there was predictable cardiovascular toxicity. The safety and moderate efficacy of hydroxychloroquine for Covid-19 chemoprevention might have warranted widespread deployment had the information been available in 2020 and 2021 before the vaccines arrived. For comparison, before the effective vaccines were developed, WHO felt a vaccine with 30% preventive efficacy would be acceptable (125, pg 6). However, once the excellent protective efficacy of the vaccines was demonstrated and the effective vaccine roll-out was under way, there was no longer a need for moderately effective chemoprevention. This reduced the pressure to evaluate chemoprevention, although there was still a need to protect vulnerable groups who could not receive or benefit from the vaccine.

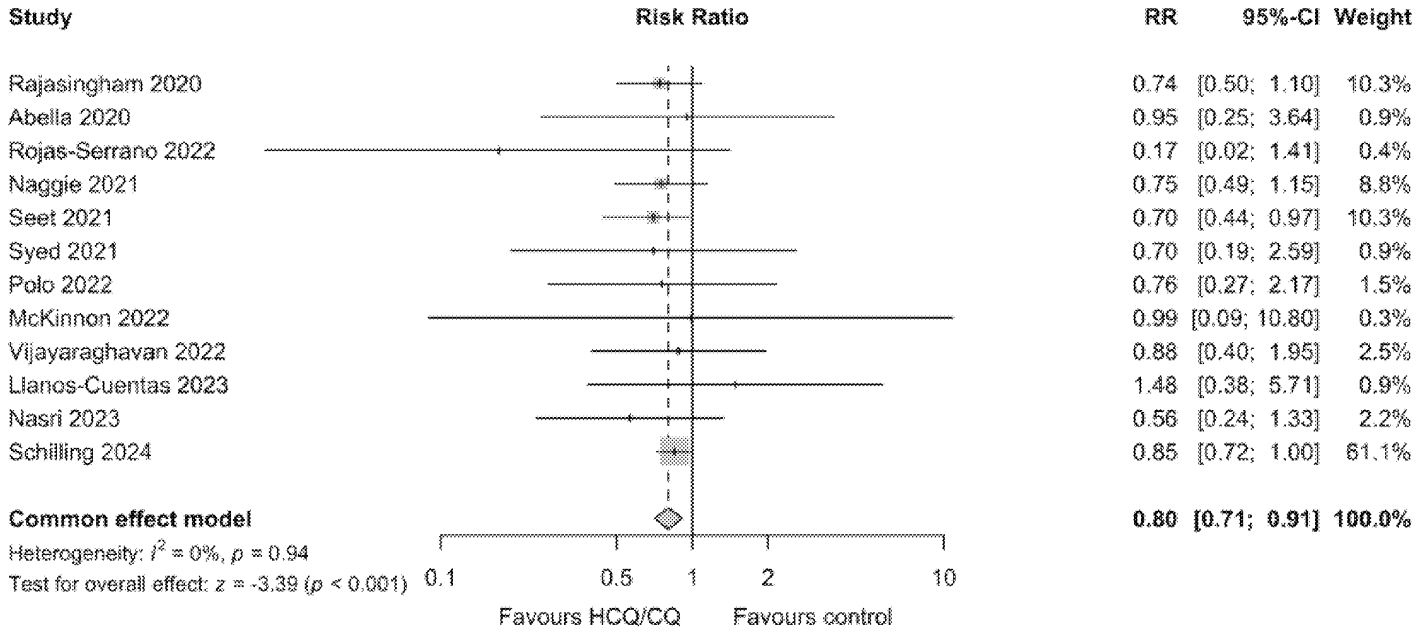


Figure 12. Hydroxychloroquine provided a moderate protective benefit as a prophylactic drug (66). This forest plot in the prespecified meta-analysis from the multinational COPCOV study published in September 2024 shows the results of all the randomised chemoprevention trials (66). It suggests that hydroxychloroquine (HCQ) and chloroquine (CQ) provide about 20% protection against Covid-19 illness, shown by the summary diamond at the bottom of the figure.

5.64. Another study conducted in the UK was PROTECT-V, a prevention trial in immunocompromised individuals which evaluated the NmAb Sotrovimab and

intranasal niclosamide (126). It began in February 2021, and closed in May 2024 (127). PROTECT-V has not reported a final result. PROTECT-CH was another prevention trial designed to evaluate protection of care home residents but, because severe end-points had become so infrequent, it was deemed to be not feasible and did not start.

5.65. Several factors combined to prevent early completion of the chemoprevention trials. For hydroxychloroquine chemoprevention trials across the world, the intense politicisation and then the negative publicity arising from the Surgisphere study reduced enrolment in trials in 2020 when the incidence of disease was high and the need was greatest. The "better than predicted" vaccine protective efficacy correctly changed the focus to rapid vaccine deployment for disease protection. Then the development of specific NmAbs, which provided protection for at least a month after injection, gave a more attractive prophylactic option for use in care homes or in high-risk individuals.

5.66. It is unclear why there were not more newly developed candidates for Covid-19 prophylaxis. Most NmAbs were developed as therapeutics. Tixagevimab/cilgavimab, otherwise known as Evusheld®, was one of the exceptions. It was developed by AstraZeneca and comprised two NmAbs directed against the spike protein. They were engineered to have an antibody stem (the part of the antibody that does not bind to the target) that allows them to last longer in the body than normal antibodies. This created a convenient pre-exposure prophylactic that only needed to be injected once every six months. A press release was published announcing the initial results of the industry-funded PROVENT trial in August 2021, (128) reporting a 77% reduction in the risk of developing symptomatic Covid-19 in the six months after a single injected dose. The final report of two studies was published in May 2024. In a large study of Covid-19 prevention which enrolled over 5,000 subjects, protection over 6 months was estimated at 83%, and at one year as 46%. Severe or critical Covid-19 was reduced by 91.4% (129). The UK TACKLE tixagevimab/cilgavimab early treatment study in acute uncomplicated Covid-19 also showed an approximate halving of severe Covid-19 or mortality (130). Both studies were conducted in the "pre-Omicron" era in subjects who

were unvaccinated. In a much smaller study of post-exposure prophylaxis protection over 6 months was estimated at 43%, and at one year as 3.6%. The approval processes and evolution of resistance to this drug are covered further in paragraphs 6.8 to 6.16.

Diversity of trial participants

5.67. General principles around diversity of trial participants are covered in paragraphs 3.33 to 3.41.

5.68. In the UK it was found that patients of black or Asian ethnicity had an increased risk of severe Covid-19 and death, so it was important to try and understand why this was, and in particular whether drug responses would be different in the different ethnicities.

5.69. With regard to the UK's Covid-19 therapeutics trials, although not perfectly matched to the population, the representation was generally better than many other trials. Whilst the RECOVERY trial did not report a detailed breakdown of ethnicities, the proportion of its participants who were non-white was similar to the UK population in the 2021 census, (131) reflecting broad recruitment across many different hospitals. Age was a major risk factor for death from Covid-19. Approximately 22% of patients enrolled in the inpatient RECOVERY dexamethasone study were over 80 years old (132). The large outpatient PRINCIPLE trial reported a detailed ethnic minority breakdown. The proportion of Black participants was lower than in the general population at a similar age, but the proportion of Asian participants was higher (133). PRINCIPLE also had a very large number of sites (pharmacies and GP surgeries) covering many parts of the country. They reported using outreach materials in multiple languages. A systematic review of Covid-19 studies in the UK found that reporting was inconsistent. Where data were available, underrepresentation was most marked in Black groups, but this did improve significantly over time (134).

5.70. Overall, given the difficult trade-off between representativeness and speed of recruitment (see paragraph 3.38), my view is that investigator teams for the main Covid-19 therapeutics trials in the UK did well in ensuring the trials were diverse

enough. In a rapidly unfolding pandemic speed in identifying effective drugs is paramount. There are similar themes in vaccines as well as therapeutics, outlined in paragraphs 4.17 to 4.24 of Professor Prieto-Alhambra's report on vaccine safety.

A perspective on conducting clinical trials during Covid-19

5.71. I was not in the UK during the pandemic. My direct experience with the UK response was through setting up COPCOV (the double-blind hydroxychloroquine/chloroquine chemoprevention trial). In the UK clinical trials conducted in the NHS were supported through UK Clinical Research Collaboration registered clinical trials units. Operating through these requires a substantial administration. After NIHR Urgent Public Health Group study review and some negotiation the COPCOV chemoprevention study was badged as "Urgent Public Health" and therefore was considered eligible for NIHR CRN support (69). The main obstacle for our chemoprevention study, namely the impact of the Surgisphere paper published in the Lancet, could not have been foreseen. Later the NIHR "badging" for chemoprevention studies was restratified to level 1b, below the vaccine studies and platform treatment studies, although by then recruitment in the UK had already declined. As NIHR had not provided any support for the trial, beyond allowing it to be conducted, this did not affect the study in the UK.

5.72. Our research team and I personally interacted with the relevant UK authorities throughout this period. We initiated all interactions. Throughout we were given the strong impression that "everything was in hand". Attention was clearly focussed on the NIHR sponsored studies. As a result, when we began pharmacometric trials in 2021 we did not try and conduct the trials in the UK. However, we knew that comparative data on antiviral efficacy had not been obtained in the UK or anywhere else, and would be useful in guiding policies and practices, so we informed the UK Covid-19 Antivirals and Therapeutics Taskforce (ATTF) of our ongoing pharmacometric studies and we asked for help in obtaining drugs to test. They were unable to help us.

5.73. After some delays, we were able to purchase elsewhere most of the drugs and NmAbs for comparative evaluation in the pharmacometric platform study. We were particularly

interested to evaluate Sotrovimab as it was used extensively, and there were concerns over its continued efficacy against the evolving Omicron variants. However, despite repeated attempts, we were unable to obtain Sotrovimab (Xevudy® GSK). We engaged in extensive correspondence and on-line discussions with GSK in 2021/2022 seeking to obtain Sotrovimab in our trials but the company stated it was unable to supply it, referring to the need to balance global treatment demand with existing or planned studies.

5.74. We also wrote to the UK Covid-19 Antivirals and Therapeutics Taskforce in early 2022 in order to try and obtain the NmAb Sotrovimab for pharmacometric evaluation. We explained that we had a method that could ascertain whether a NmAb was an effective antiviral with as few as ten treated patients. However, this request was unsuccessful. The ATTF stated that it was not in a position to support the request on the basis that DHSC had procured sotrovimab solely for NHS use. We also had discussions with Dr Cliff Lane (deputy to Dr Antony Fauci) of the National Institutes of Health in the US who, in sympathising with our difficulties in obtaining medicines for independent evaluation, stated that US-purchased supplies also could not be used for clinical trials without permission of the companies. In 2023, while I was on duty as a consultant general physician in Oxford, I found out that a significant stock of Sotrovimab was in the hospital pharmacy and was about to expire. Knowing that Sotrovimab was still being prescribed widely in UK hospitals and that much of the Sotrovimab stocks in the UK were about to expire, we thought that would be a good opportunity to try again to obtain the NmAb for independent evaluation. In May 2023, I wrote to the ATTF to try and obtain Sotrovimab but the ATTF had been stood down and I did not receive a response. We then wrote to DHSC but this too was unresponsive. I was given to believe the reason for this was because the purchase agreement prevented further trial comparison. My personal view is that this prevented a proper pharmacometric (and comparative) study which could have informed therapeutic guidelines

5.75. Very substantial purchases of NmAbs for the NHS were made and, as far as I know, much of the purchases were never used. This was particularly unfortunate for Sotrovimab which is still being recommended in the UK at the time of writing in

December 2024, but its clinical antiviral activity has not been monitored or evaluated as SARS CoV2 has evolved . As set out above, the large observational study OpenSAFELY provided reassuring albeit retrospective information that Sotrovimab was effective in treating early Omicron variants, but whether this NmAb still works against current variants is not known.

Concluding remarks on clinical research

5.76. The main problem with clinical trials in Covid-19 globally was the lack of coordination which resulted in academic groups and clinical teams conducting a very large number of underpowered and ultimately inconsequential trials. Trial quality, analysis and reporting was often poor. Guidelines from countries and WHO were also unclear and sometimes contradictory. WHO guidelines initially extrapolated from severe disease to uncomplicated disease despite the different pathological processes and therapeutic responses. The intense journalistic and public interest, combined with unusual politicisation compromised the conduct of good clinical trials. Although several underpowered and ultimately inconsequential trials were also conducted in the UK, overall the country stood out in the pandemic for conducting generally high quality and impactful therapeutic studies which have benefitted the whole world and saved many thousands of lives.

5.77. From the outside, the UK is considered to have "done well" in Covid-19 research largely because of the rapid and successful development and production of the Oxford AstraZeneca vaccine and because the RECOVERY trial was the most important therapeutics research output during the entire pandemic. The under-resourced and over-stretched NHS performed magnificently. The RECOVERY trial drew on the strong structure and commitment of the NHS, the support of the Department of Health and the NIHR, the experience and wisdom of the University of Oxford clinical trials experts, and importantly - the willingness to sacrifice inessential detail for simplicity and thus "doability" and speed. Overstretched clinicians cannot deal adequately with complex research protocols.

5.78. Overall, the design and implementation of the large adaptive platform studies was appropriate for the urgency of the therapeutic questions being asked. The use of the NHS both as a base for trials, for delivery of medicines, and as a source of retrospective information (e.g. from electronic health records) was exemplary. Laboratory based studies such as viral genetic sequencing were also very strong in the UK, contributing importantly to global surveillance. The clinical and pathological investigations of Covid-19 and its sequelae have also been of very high quality and impact. Perhaps the weakest part of therapeutic research in the UK and elsewhere was the assessment and monitoring of clinical antiviral activity, and thus the comparative evaluation of medicines -particularly NmAbs.

6. Looking back: Enabling the use of therapeutics in the UK

The authorisation of major therapeutics in the UK

6.1. Once clinical research had been published providing the scientific rationale for using a therapeutic, several further steps were needed before it could be used to treat patients. My expertise and experience is mainly in conducting research and treating patients in hospital and in the community, rather than the regulatory systems and processes for the approval and use of therapeutics, but I have been asked to provide an overview for the Inquiry.

6.2. For new Covid-19 therapeutics, pharmaceutical companies interacted directly with the MHRA to obtain a "marketing authorisation". The process is very similar to that for vaccines, explained in detail in Professor Stephen Evans' expert report on vaccine safety systems.[12] Overall, I think the MHRA got the balance right between speeding up the process and maintaining standards for therapeutics. The UK benefitted from carefully considered rapid regulatory approvals. The level of public concern around side effects of therapeutics used in treatment was understandably lower than it was for vaccines or prophylactics. People who are ill with Covid-19, their loved ones, and the clinical team are all willing to accept a higher risk of side effects given the clear and present danger of their current infection. Furthermore, side effects of drugs may not be distinguishable from the symptoms of illness. In contrast people who are well do not want to experience any adverse effects. Examples of proposed drugs that did not receive this marketing authorisation for Covid-19 include ivermectin and hydroxychloroquine. Evusheld® did receive a conditional marketing authorisation, but did not receive approval in later steps and was ultimately not made available on the NHS (see paragraphs 6.8 to 6.14).

[12] INQ000474707 paragraphs 2.33 – 2.51

6.3. Alongside the marketing authorisation, a "summary of product characteristics" (SmPC) is written, which includes the detailed information a clinician needs to prescribe the medicine, including the indication (the disease it can be used to treat), recommended dose, types and frequency of side-effects, "contraindications" (health conditions that mean one should not take that specific medicine), and any other warnings.

6.4. "Off-label" prescription is a term used to describe where a clinician prescribes a drug outside the terms of its marketing authorisation. For example, the anti-inflammatory baricitinib is licensed in adults for eczema, alopecia (an autoimmune hair loss disorder) and some forms of inflammatory arthritis. It was used off-label to treat patients with severe Covid-19. Inhaled budesonide was also used off-label for early Covid-19 disease. There was some scientific evidence of effectiveness supporting these decisions (see paragraphs 5.15 and 5.28), but the drugs' licences had not changed. Prescribing clinicians take on more responsibility in this scenario because the pharmaceutical company is not responsible for any harm or damage incurred from side effects in off-label prescribing. The objective is to benefit the patient and any potential risks are managed by the clinician's training, knowledge and experience, guided by their professional ethical codes (such as the General Medical Council's Good Medical Practice standards for doctors), and the prescribing policies of their employers (135).

6.5. In some cases, there is insufficient or poor quality direct clinical evidence to support use of a drug in a particular circumstance yet there is a clinical need and there is indirect evidence that would support clinicians' prescribing decisions. Sometimes medicines are prescribed off-label on the basis of indirect evidence, clinical judgement and experience. Outside of a pandemic, this often applies to the use of drugs in children, pregnant women, or those with rare diseases, where there is usually less published direct evidence. At the beginning of the Covid-19 pandemic, large numbers of people were being admitted to hospitals and deaths were rising but there was no vaccine and no specific treatment. The pressure on clinicians to "just do something" by prescribing some kind of treatment for severely unwell patients was intense. This was

noted in the technical report on the UK COVID-19 pandemic in the UK.[13] However, if there is a randomised trial accepting new participants, which can generate information to treat future patients with more effective drugs, off-label prescription of drugs of uncertain efficacy without entering the patient to a trial is widely regarded in the medical community as unethical. The four UK CMOs and the National Medical Director of NHS England stated in a letter to all UK clinicians in April 2020 (137) that they *"strongly discourage"* off-label prescription of drugs of uncertain efficacy, and instead urged clinicians to enter their patients with Covid-19 to trials wherever possible. This was very wise advice.

RAPID C-19 process for making drugs available for patient use

6.6. For a newly licensed drug to be used widely in the UK, it will need to be paid for by NHS commissioners, and included in clinical guidelines to encourage clinicians to change their practice and start prescribing it. The National Institute for Health and Care Excellence, also known as NICE, is central in this process in England and Wales (in Scotland, the Scottish Medicines Consortium fulfils this role. In Northern Ireland, in practice, the Department of Health usually adopts NICE decisions). This arm's-length body of the Department for Health and Social Care scrutinises research published by drug companies and academics and assesses the clinical and cost-effectiveness of a drug in a process known as "Technology Appraisal". If a new drug compares well against the typical cost-effectiveness threshold of £20,000 to £30,000 per quality-adjusted life year, then it will usually be recommended by NICE. Broader "Guidelines" are also produced by NICE, which usually cover diagnosis, advice to give to patients, and other information as well as a list of recommended treatments. Rarely, NICE will include an off-label drug in a guideline (such as baricitinib for Covid-19) based on a simpler evidence review rather than a full technology appraisal. Drugs will

[13] The authors of this report included the CMOs and deputy CMOs across the UK, the Government Chief Scientific Adviser, and National Medical Director of NHS England. (136) Page 335

only receive a technology appraisal where a new licence or an extension of an existing licence is being sought by the drug company.[14]

6.7. The RAPID C-19 committee was newly set up during the pandemic to monitor the output of clinical research on therapeutics, reporting to the CMO through the DHSC Antivirals and Therapeutics Task Force. It was a collaboration between NICE, NHSE, MHRA and NIHR with involvement of several other organisations including devolved nation representatives. It essentially replaced part of NICE's role, providing commissioning policies to facilitate patient access, though without the usual assessment of cost-effectiveness and with a radically streamlined process (full assessments were performed at a later date).[15] It did not produce guidelines or other advice for clinicians. Further details on its role and chronology can be found in the witness statement of Helen Knight (INQ000474611). I was unaware of the RAPID C-19 process during the pandemic, working outside the UK and only interacting with the NIHR and ATTF. Clearly the typically slow process of assessment of clinical trial results and development of guidelines needed to be accelerated during the pandemic. On balance, based on the reported descriptions, the process RAPID C-19 used to assess therapeutic drugs appears to have been comprehensive and well-infomred but the exact details of how individual decisions were reached was not always clear (from the reports).

Prophylactics and Evusheld®

6.8. The systems and processes for regulating prophylactic drugs for viral infections in the UK were generally similar to those for regulating therapeutics before the Covid-19 pandemic. During the pandemic several new committees were involved in assessing new prophylactic drugs. I have been asked to comment on the decision-making processes surrounding approval of prophylactics, and refer to the reports on the drug

[14] INQ000474611 states that NICE can only produce technology appraisals for drugs with a licence
[15] INQ000474611 para 35, INQ000474611, para 34

sent by RAPID C-19 to the CMO, and statements from Helen Knight[16], James Palmer[17] and David Lalloo.[18]

6.9. Initially there was a good rationale for evaluating prophylactic drugs as an alternative to vaccines, as it was not known how rapidly vaccines would be developed, nor how effective they would be. Initially many prophylaxis trials (including the large COPCOV hydroxychloroquine/chloroquine trial) focused on healthcare professionals as a group who were critical for health system resilience in the face of the Covid-19 threat, and were particularly likely to be infected. It was also known that there are many people who have impaired immune systems and would be unlikely to mount an effective immune response to vaccines when they were developed.

6.10. On 8 December 2021 RAPID C-19 had received a confidential manuscript from AstraZeneca reporting promising data on Evusheld. The committee proposed to the CMO that the new prophylactic drug should be rolled out to patients, subject first to the marketing authorisation being granted and to confirmation from UKHSA that the drug still neutralised the Omicron variant in laboratory tests. It was to be used mainly as a pre-exposure prophylactic, but had also been tested as a therapeutic and as a post-exposure prophylactic.

6.11. The drug was granted conditional marketing authorisation by the MHRA in March 2022, but the results of the in vitro testing in May 2022 showed some effect against early Omicron variants but less effect on more recent variants. The Prophylaxis Oversight Group, chaired by David Lalloo, assisted RAPID C-19 with interpretation. The reduced neutralisation of recent Omicron variants in the lab tests was extrapolated to mean that Evusheld would have reduced clinical efficacy. The group also felt there was a risk of encouraging the evolution of resistance from a partially effective antibody. However, the relationship between the lab tests and clinical effect was not established. This critical knowledge gap is described Helen Knight[19]. Why pharmacometric testing was not encouraged or commissioned is not clear to me. Perhaps the various bodies

[16] INQ000474611_0047-57
[17] INQ000474312
[18] INQ000474625_14-16
[19] INQ000474611_0047-57

advising on therapeutics were not aware this could be done? It is not mentioned in any of the statements. I do not think the resistance risk was substantial. Overall this was a cautious judgement that would have been strengthened substantially by pharmacometric evaluation.

6.12. The PROVENT trial showing good preventive efficacy of tixagevimab and cilgavimab was first published in the New England Journal of Medicine in April 2022. These studies were conducted between November 21, 2020, and March 22, 2021 i.e. before the advent of the Omicron variants. The high protective efficacy of the Covid-19 vaccines reduced substantially the pressure to develop and evaluate prophylactic NmAbs and small molecule drugs.

6.13. RAPID C-19 assessed recently published observational studies in August 2022 to investigate whether tixagevimab and cilgavimab may have performed better in patients in the real world than in the laboratory. RAPID C-19 deemed that there was still remaining uncertainty whether Evusheld would protect patients from the current Omicron variants, and noted that NICE was due to conduct a full technology appraisal to be published in April 2023 (after this Inquiry's relevant period). That technology appraisal reached a similar conclusion, and was also highly uncertain about its cost-effectiveness (138).

6.14. At paragraph 136 of the NICE statement from Helen Knight, she states that *"with the benefit of hindsight, the UK public health and regulatory system could have looked more intensively at whether or not Evusheld was effective against SARS-CoV-2 variants"*, perhaps referring to the time between UKHSA starting work on assessing in vitro activity against Omicron in December 2021 and reporting in May 2022 – she ends the paragraph by stating that *"whilst NICE were aware of the progress of variants, UKHSA was responsible for providing that information".*

6.15. Overall while it is certain that Evusheld® would not have been as effective against Omicron variants as it had been against earlier variants, the extent to which it would have been less effective was not assessed in pharmacometric or clinical outcome studies. For example, a 5% loss of virological activity (measured as reduced viral

clearance) in patients would not have had a significant clinical effect whereas a 95% loss would have. In my view the questions over the efficacy of Evusheld® remained unanswered, but could have been answered rapidly by contemporary pharmacometric studies.

6.16. From my reading of the reports including those of Helen Knight and Prof. David Lalloo it appears that the various committees were generally passive, in that they reviewed all available information in a rigorous and informed way and gave wise advice, but they did not direct or initiate necessary research. I may be wrong, but amongst the various bodies, advisories and committees the mandate of the Task Forces was described as *identifying potential COVID-19 therapeutics,* ***trialling these****, and making effective treatments available to UK patients* but it seems it was up to academics and industry to initiate and conduct the necessary research to develop and evaluate interventions. Clearly candidate prioritisation was discussed, but it is unclear to me who made the decisions on what and how to test and why those decisions were made. Important questions, such as determining the clinical correlates of the lab assessments of the NmAbs, or comparing the antiviral effects of the small molecule drugs, were probably identified but they were left unanswered – or retrospectively addressed in large observational studies such as OpenSAFELY. Had there been ongoing pharmacometric evaluation this would have informed the policy decisions in real time. This would have been particularly valuable for the contentious decisions over Evusheld®.

Eligibility for therapeutics

6.17. When medicines are in limited supply, or are expensive, or have significant adverse effects it is important to try and balance the risks (and the costs) against the benefits for the individual patients. This is a normal clinical decision made (implicitly or explicitly) every time a patient is prescribed a treatment. It is often also appropriate for national health authorities to prioritise some groups of patients for receiving treatment first, or to set out clear eligibility criteria or guidelines for who can and who cannot receive publicly-funded treatment, where sufficient evidence exists to guide these policies. This removes some of the discretion that individual clinicians have, but it can

help to maximise the benefit for the whole population and avoid wasting resources.[20] Health authorities and the medical profession need to prepare for these difficult decisions in advance, explain them, and constantly re-examine them. This is especially important, but also even more challenging, in the midst of a major epidemic.

Understanding risk factors for severe disease to inform eligibility criteria

6.18. At the beginning of the Covid-19 pandemic, risk stratification was extrapolated from previous experience with other respiratory virus infections (mainly seasonal influenza). Very soon it was evident that the patient risk profile for Covid-19 was similar. At that time a larger proportion of the population was vulnerable to developing severe infections and hence could have been helped the most by therapeutics, although we did not have drugs of proven benefit. Today, Covid-19 is a much less severe disease on average and drug treatment in the community is used only in high-risk patients. This is a perfectly reasonable approach to deploying and using a limited resource. Such cost-effectiveness and cost-benefit assessments form the basis for current NICE guidelines and NHS provision. This applies equally to therapeutics and prophylactics, so pre- or post-exposure prophylaxis might also only be given to people with risk factors for severe disease and/or in a vulnerable setting like a care home (8).

6.19. Age is a major risk factor for severe or fatal Covid-19. The risk of death rises exponentially with increasing age. Data from the Office for National Statistics shows that the age-specific Covid-19 death rate (per 100,000 population) for those aged 90 years and older was over 10,000 times that of the death rate in those aged 5 to 9 years old.[21] There are many other risk factors for severe disease. Our scientific understanding of these has evolved over time. It is challenging to tease out the causal effect of specific risk factors when many of them may overlap in one individual. The

[20] For example, at the beginning of the pandemic preventing health care workers from becoming ill was a priority in order to keep the health service running. Another example is that patients with terminal diseases may be at very high risk but the additional benefit from a protective intervention may be less than in someone who has a greater life expectancy with a higher quality of life.
[21] INQ000271436_0016, not adjusted for sex, comorbidities or any other factor.

risk of getting infected, often increased due to occupational risk factors or housing, should be separated from the risk of developing severe disease once infected.

6.20. Detailed observational studies that measure many factors and adjust statistically for each of them have consistently identified several risk factors for severe disease and death from Covid-19. In addition to age, these include diabetes, obesity, male sex, blood cancer, Down's syndrome, chronic respiratory disease, immunosuppression, and receiving an organ transplant (139). For other risk factors, findings have been more controversial. Initial studies found, for example, that high blood pressure may be a risk factor for higher risk of severe Covid-19 (140), and that smoking (141) was associated with lower risk, but both findings were contested by later studies (142, 143).

6.21. Some of these risk factors were used to determine eligibility for Covid-19 therapeutics, but also the shielding list, covered in module 3 of the Covid-19 Inquiry on the healthcare system, and vaccine prioritisation, covered in this module's expert report on vaccine rollout from Dr Chantler and Dr Kasstan-Dabush (INQ000474623, paragraphs 34-35).

6.22. The risk factors and/or lists of pre-existing medical conditions that were used to designate someone as clinically vulnerable or clinically extremely vulnerable were influenced by the evolving scientific research, the availability of data in individual-level health records, and policy decisions setting the scope within which expert committees could select high-risk conditions (see paragraph 6.31).

6.23. Policies setting eligibility criteria should be informed by science, but must also take other factors into account. There would be little point adding groups to the list if they were found to be at high risk in a scientific study but they could not be readily identified in clinical practice, for example if blood tests are required that are more often used in research than routine practice (e.g. complex 'multi-omics' studies (163)). There could also be public controversy if demographic factors that do predict risk but may be perceived as unfair are used in eligibility criteria, such as sex or ethnicity.

Trial evidence to inform eligibility criteria

6.24. It is important to note that risk factors for mortality or severe disease are not necessarily the same as those that predict a good response to treatment. Ideally, prospectively designated subgroup analyses would be used in the randomised trials to determine the groups most likely to benefit. For example, this directly informed the decision to restrict eligibility for dexamethasone to only those patients who required oxygen, even though the drug was effective on average when patients on oxygen and not on oxygen were analysed together (1). However, for most risk factors, the randomised trials are not large enough to rule in or out statistically significant effects in small subgroups, such as those with specific types of cancer, so an understanding of the disease and treatment responses, and indirect evidence from observational studies assessing risk of mortality need to be used to guide eligibility criteria instead. It would have been very challenging or impossible to recruit large enough numbers of participants to assess precisely the effectiveness and safety in all clinically vulnerable subgroups. Clinical trials experts are justifiably suspicious of multiple sub-group analyses as they increase the risk of false conclusions. In my view, the balance struck here was reasonable, and sufficient consideration was given in phase III trials to including clinically vulnerable subgroups (diversity in Covid-19 clinical trials is covered further in paragraphs 5.67 to 5.70).

6.25. In 2020 and 2021, the drugs recommended in the UK to treat Covid-19 were typically given in hospital settings, because they had only been found to be effective in patients with more severe disease (e.g. dexamethasone) or they needed to be given by injection (e.g. the casirivimab / imdevimab (Regen CoV®) NmAb cocktail). Strict eligibility criteria for most of these drugs were generally not used in the UK beyond those criteria that had already been shown in the clinical trials.

6.26. The PANORAMIC trial was used prospectively during the pandemic to guide policies and practices and help inform later changes to eligibility criteria.[22] Given the relatively limited evidence available at that time, in my view it was a reasonable strategy to use a

[22] INQ000067958 - COVID-19 oral antivirals deployment plan update v0.3 12/01/22 – page 1

large-scale trial as part of the rollout plan. The problem for PANORAMIC was the low event rate for the primary outcome (hospitalisation and death) so it was not as timely or useful as hoped. However, many other countries did not take such an approach and decided to roll out new drugs more widely on the basis of one phase 3 trial (144), despite the concerns about generalisability.

Systems and processes established for determining eligibility for oral antivirals

6.27. There were several new expert groups on therapeutics set up during the pandemic, in addition to those mentioned in previous sections of this report. They were often called on to assess questions of eligibility for treatments that had been approved for rollout (unlike Evusheld). Eligibility criteria had to be pragmatic, and often where trial evidence was not definitive, expert opinion was used to set clear guidance and reduce unwarranted variation. There is a complex pattern of timeframes, responsibilities and scope of these expert groups, some of which seem to overlap. As with RAPID C-19, I was not aware of them during the pandemic as my work was mainly outside the UK. However, I have reviewed the material given to me by the Inquiry and present an overview here. I focus on oral antivirals, as these had a greater degree of controversy highlighted by some of the core participant groups to the Inquiry.

6.28. Eligibility criteria for antiviral drugs in the community seem to have been scoped out for modelling purposes by the Antiviral Use Case Expert Panel in June 2021 (known as the "Mike Jacobs Group" after its chair Sir Michael Jacobs).[23] The COVID-19 Neutralising Monoclonal Antibodies (nMABs) Access and Policy National Expert Group, and a smaller clinical subgroup, both chaired by Prof. Anthony Kessel, looked in more detail at potential eligible groups, this time for NmABs, in June and July 2021.[24] However, the even more detailed list of conditions that was ultimately most influential in policy decisions on access outside a clinical trial (i.e., led to the widest

[23] Eddie Gray statement INQ000474342 paragraph 27.2
[24] James Palmer exhibit INQ000479899 "Process for Developing Priority Patient Cohorts for Access to Neutralising Monoclonal Antibodies (nMABs) in the Community Setting", undated

rollout of medicines) was determined by a different set of groups after this, addressed in the following paragraphs.

6.29. The Deputy Chief Medical Officer Sir Jonathan Nguyen-Van-Tam set up the COVID-19 Neutralising Monoclonal Antibodies and Antivirals Access Independent Advisory Group ("the Advisory Group", chaired by Prof Iain McInnes) in October 2021,[25] followed by the Department of Health and Social Care setting up the Covid-19 Therapeutics Clinical Review Panel ("the Review Panel", chaired by James Palmer) to oversee the Advisory Group's work in December 2021.[26] These committees were tasked with prioritising patients who should receive the new oral antiviral drugs that could be taken at home. In contrast to hospitalised patients, the vast majority of Covid-19 patients in the community got better with no treatment, especially if vaccinated, so giving all of them expensive new drugs would pose significant costs for potentially little gain. On the other hand, as mentioned previously, treatments for patients early in the course of disease can prevent hospitalisation and reduce pressure on hospitals. The cost-effectiveness assessment depended on cost of goods, degree of benefit (prevention of hospitalisation and death, shorter times to recovery), tolerability and safety. Deployment also depended on availability. It was recognised that these decisions were *"less straightforward"* (see paragraph 34 of James Palmer statement, INQ000474312_0013) than the decisions on earlier treatments (see paragraph 6.24 of this report), leading to the establishment by the DCMO of this Review Panel, and the Advisory Group that reported to it.

6.30. Prof McInnes' Advisory group produced an interim report in November 2021,[27] which was not made publicly available but largely replicated the vulnerable cohorts in the later published list (see following paragraph). It seems to have been used to inform the opening of the Covid Medicines Delivery Units (CMDUs) who started providing treatments (initially mainly molnupiravir and sotrovimab (145)) to eligible groups from December 2021.[28]

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[25] INQ000479904 pages 13 to 15
[26] INQ000474312_0012 James Palmer statement paragraphs 33-38
[27] INQ000067910
[28] INQ000474335 paragraph 179

6.31. The Advisory Group published their first full report on 30 May 2022 (INQ000479904). It was a publicly-available and comprehensive piece of work from a large team of eminent experts, who interacted with patient groups and charities and considered the data they provided. They had reference to the QCOVID3 and ISARIC risk prediction scores (though these were not used in the list itself), other published studies and their expert opinions to draw up a list of conditions which should confer eligibility for antivirals. They considered the use of blood tests to check for antibodies and help identify those who were not protected, but the evidence to enable this was not sufficient at that time. They also considered evidence for young people aged 12-18. They were *"not tasked with estimating the separate impact of older age in addition to underlying conditions rendering individuals vulnerable"* but recognised *"that this should be a factor in policy evaluation".* It is my view that this process did give sufficient consideration to protecting immunocompromised groups. It is not clear, however, why they were not also tasked with considering the risk conferred by older age and comorbidities. The witness statement of James Palmer states that "*age is a complex factor to account for because of the co-morbidities that accompany it".*

6.32. In March 2023 (after this inquiry's relevant period) another subgroup of the Review Panel focusing on statistical modelling of the risk of deterioration published a report, led by Prof John Edmunds at LSHTM (151).[29] According to James Palmer's statement, they were established in March 2022, but the report was not commissioned until October 2022 as they were waiting for data from the PANORAMIC, OpenSAFELY and QCovid studies.[30] Of those, the final report only refers to OpenSAFELY and QCovid, with an additional large observational study that used patient records from across the four nations of UK from Utkarsh Agrawal, Prof Sir Aziz Sheikh and colleagues (148). It does not refer to the PANORAMIC study, perhaps because the slower than expected recruitment resulting from milder illness associated with Omicron variant infections meant that results were not available. The modelling subgroup reported that people who are obese, some classes of diabetes patients, and dementia patients (none of whom were eligible for antivirals in the community at the time) were all at greater

[29] INQ000479902
[30] James Palmer statement INQ000474312_0014-0015 paragraph 36c

relative risk of severe disease than those with rheumatoid arthritis (who were eligible). They also reported that the absolute risk of death from Covid-19 in individuals who were over 70 years of age was significantly higher than that of a typical (age-standardised) patient with rheumatoid arthritis. Taking multiple factors (eg including age, sex and comorbidities) into account requires an individual risk prediction tool, which was available using QCovid. They cautioned that further investigation was needed on these and the many other factors that had some evidence of being associated with increased risk, and whether the risk was ameliorated by improved access to antivirals. It is notable that James Palmer's statement ends the section on eligibility (pg.17 paragraph 38) with: *"As the digitisation of healthcare records develops I expect in future scenarios the NHS might be able to deploy a risk assessment tool at scale alongside the Advisory Group approach",* also mentioning that some factors like ethnicity and obesity are currently not complete in health records.

6.33. As of January 2024, NICE changed its recommendations for nirmatrelvir/ritonavir (Paxlovid®) to include some other groups such as people aged 85 years and over, those on the organ transplant waiting list, and care home residents or hospital inpatients over 70 who also have obesity, diabetes or heart failure (150). The PANORAMIC trial results for nirmatrelvir/ritonavir had still not been published by that time, so the decision (152) was rested in large part on the results of the original industry-funded randomised trial (EPIC-HR, press release December 2021 (149), full paper published in February 2022(147)) and OpenSAFELY (general risk factor studies were available from 2020, but their first nirmatrelvir comparison study was published in October 2023(146)). These extra groups could possibly have been identified sooner, though it is unclear who would have been responsible at which times given the shift back from pandemic-era decision-making to routine drug approval processes.

Rollout of therapeutics in England

6.34. Between October and December 2021 the UK purchased 5 million patient courses of the oral antiviral drugs molnupiravir and ritonavir boosted nirmatrelvir. Data on the speed of rollout of various therapeutics in community settings is available open access

from NHS England (figure 13) (153). Note also that previous observational studies of community antiviral and NmAb use in England and Scotland have found that although the risk of side effects appears to be minimal (154), uptake as a proportion of those eligible is relatively low (155) (156), with evidence of inequalities, including by ethnicity (157) (158). The authors of these descriptive studies did not investigate the cause of these inequalities. Whatever the reason, given the increased risk that some ethnic groups face of severe Covid-19 disease, an unequal rollout risks exacerbating pre-existing health inequalities, and policymakers need to try and tackle this.

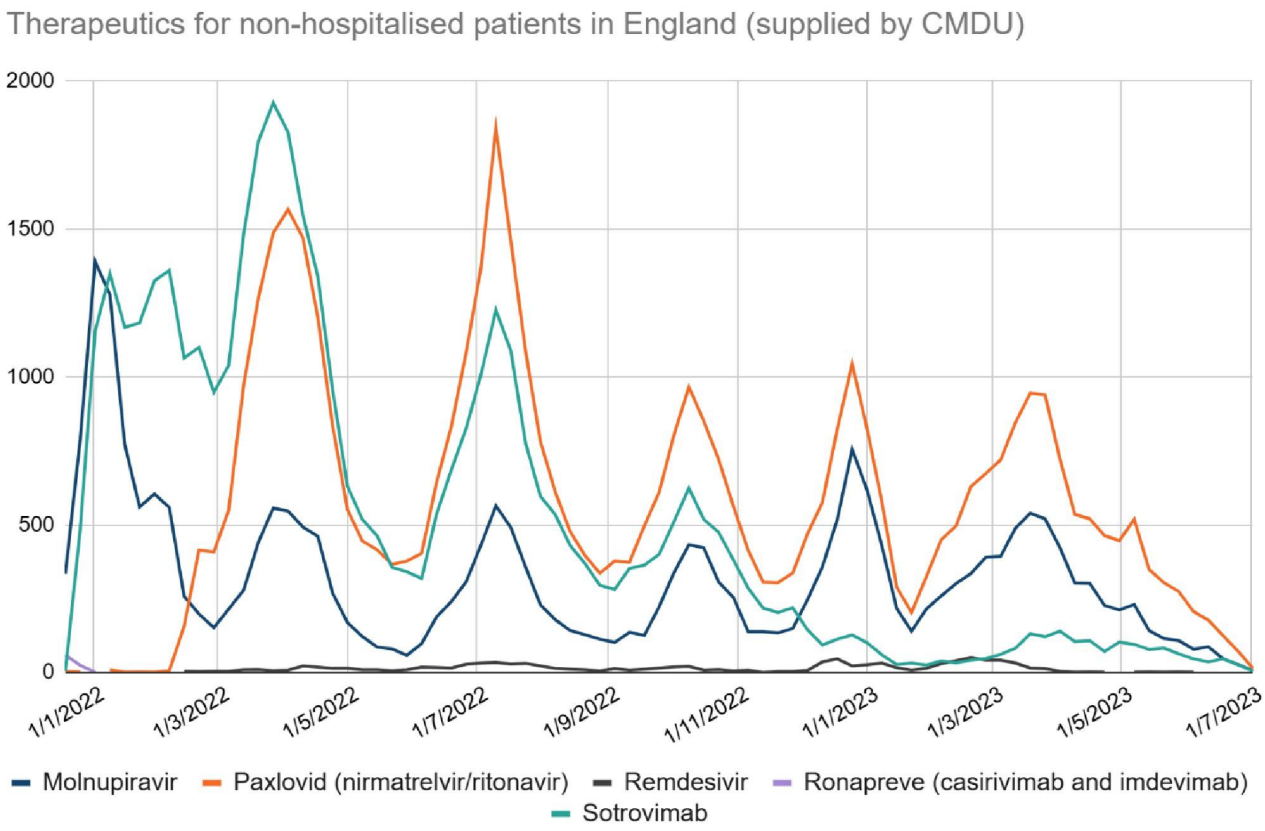

Figure 13 Therapeutics for non-hospitalised patients in England (supplied by Covid Medicines Delivery Units). Data before 1 January 2022 are not available. Paxlovid and sotrovimab were most widely used overall. Molnupiravir was widely prescribed initially. Remdesivir and Ronapreve were less frequently used in the community than in hospitals.

6.35. Similar open access data is also available from Stats Wales (159), and Scottish data has been compiled and published by Tibble and colleagues in the Lancet in 2022 (160). I was not able to locate any open access data for Covid-19 therapeutics rollout in Northern Ireland.

6.36. Today the NmAbs are less likely than before to play either a prevention or a treatment role because they were developed to neutralise previous viruses (i.e. the original Wuhan strain that emerged in 2019), and they often do not recognise the new circulating virus variants. The efficacy of Sotrovimab (the only NmAb currently being recommended) is uncertain as its antiviral efficacy in patients with the Omicron variant

viruses has not been assessed directly. Overall the evidence base for current antiviral guidelines is rather outdated.

6.37. In general, both the oral antiviral drugs were well tolerated and effective. The combined evidence from the effect sizes observed in the non-comparative pre-registration trials, the direct comparative pharmacometric study (PLATCOV) and indirect evidence from retrospective studies strongly indicates that nirmatrelvir-ritonavir is superior to molnupiravir. These oral drugs have probably been underused. For nirmatrelvir-ritonavir the many potential drug interactions from the ritonavir component prevented its use in some high-risk patients, and nearly everybody who received it had an unpleasant metallic taste in the mouth (from the ritonavir). There were some concerns that molnupiravir might select for drug resistance in SARS-CoV-2 but there is no evidence that the virus mutations that result from molnupiravir have led either to drug resistance or increased virulence. Nevertheless, this would need continuous monitoring if the drug was to be used widely.

7. Looking forward: Facing a future pandemic

7.1. In a future viral pandemic, we would probably be in a much better situation than before the Covid-19 pandemic because of the substantially faster mRNA vaccine development capability. Organisational lessons have also been learned and more rapid approaches to drug development and evaluation can be taken (98). If the important features of the new virus were well characterised and it was known what components ("antigens") the vaccine should be developed against, then rapid vaccine development should be relatively straightforward for Covid-19 or a related virus. However, for some other viruses this is not a straightforward process because the induced immune responses are not sufficiently protective, and vaccine development has so far been unsuccessful, such as for HIV. The safety of new vaccines does need to be established, and this also takes time. The design of the clinical studies and the differences sought in trials will depend on the available medicines and the disease severity. Small benefits may still be valued if there are no effective drugs and the disease is potentially severe (as it was for Covid-19 in 2020), whereas if there are already good treatments for the infection then a new drug will need to outperform them to be worth using. Drugs play an important role in prevention and treatment while waiting for an effective vaccine to be deployed, and afterwards, in treating vaccine breakthrough infections or the unvaccinated in vulnerable groups.

The need for different types of drugs in epidemic virus infections

7.2. The more severe the illness is, the broader the potential use of antiviral medicines. Antiviral activity can be assessed rapidly in pharmacometric studies measuring viral clearance. Whereas (repurposed) available drugs can be deployed immediately after positive trial results if there are sufficient stocks and manufacturing capacity, new drug development is generally slower than vaccine development, so for a new and unexpected virus, an effective early therapeutics response would depend initially on repurposed drugs having efficacy against the new disease. We have learned a lot

about SARS-CoV-2 therapeutics and we know what targets to aim at, what might work from available compounds, and how to measure antiviral activity rapidly in patients. Some of this knowledge will be applicable to other coronaviruses, including species that have not yet emerged. NmAbs can be developed rapidly and could probably be developed and deployed more quickly than new classes of small molecule drugs, although they are vulnerable to antigenic changes in the viruses.

7.3. The development of anti-inflammatory therapeutics continues rapidly as there is a need for new drugs in common conditions such as rheumatoid arthritis and other diseases of the immune system. We do not know enough about the importance of immunopathology in other severe respiratory infections, so more basic science research is needed before embarking on later phase trials. Based on current understanding, my opinion is that there is no need for specific development or stockpiling of anti-inflammatory drugs generally as a pandemic preparedness measure (in contrast to anti-influenza and anti-coronavirus drugs - see below), though there will be a need to understand immune system dysfunction rapidly and the pathology of complications at the onset of the next pandemic to inform the repurposing efforts. Covid-19 has demonstrated that therapeutics acting on the host (the infected person) can save lives in pandemic infections and should not be neglected by focusing *only* on specific antivirals and vaccines. It is also likely that some form of drug treatment and/or organ support will be required to treat the complications of severe disease.

7.4. There remains a strong rationale for non-vaccine prophylactics to be used alongside vaccines and therapeutics in a future pandemic, as is it very likely that there will again be a significant proportion of the population who do not respond as well to vaccines, and vaccines may take a long time to develop.

Therapeutics stockpiling as a pandemic preparedness strategy

7.5. If a substantial infectious disease threat is identified and drugs are known to be effective then strategic stockpiling is essential for rapidity of response (and responses

may need to be very rapid for a virulent airborne respiratory infection). With the exception of a large-scale drinking water contamination, it is unlikely that serious food, water or vector borne infections would require such speedy emergency responses. That narrows the range of potential therapies. For each decade of the twentieth century influenza was the main threat, and it seems very likely that 'flu will be the next pandemic. We are in the midst of the largest recorded H5N1 influenza pandemic in birds (95). The threat is significant. There are several different deployable anti-influenza drugs, but curiously there have been few good head to head comparisons, no detailed pharmacometric comparisons and no clear guidance from the World Health Organisation outside of the management of severe illness (96). I think it would be sensible to reflect on the lessons learned from Covid-19 and to maintain an emergency anti-influenza and anti-coronavirus stockpile.

Development of new drugs

7.6. If there are no existing drugs which are sufficiently active then drug discovery research is needed to try and find effective drugs. The process of discovering new compounds, making them as safe and effective as possible and checking that they are not toxic in animals typically takes more than a year. It is also very expensive, and the pharmaceutical industry is unlikely to invest in developing drugs which may never be used. This requires that incentives for pharmaceutical research on potential epidemic pathogens are provided.

Clinical trials and research in a future pandemic

Organisation of therapeutics research

7.7. Coordinating a complicated research and implementation system speedily to provide effective therapeutics to patients in a pandemic requires many of the same organisational approaches as other parts of pandemic response:

7.7.1. Governmental bodies, health services, academic experts, regulators and the pharmaceutical industry must work together. The system will need to take on a "war footing", focusing on the same ultimate goals, and recognising the central importance of research on therapeutics as well as vaccines as the ultimate way out of the crisis. Innovation may be required and should be nurtured.

7.7.2. Speed is essential at every step of the research, approval and rollout process to outpace the epidemic wave. Mistakes may be made as a result but this should be recognised, accepted, and explained.

7.7.3. Advisory groups are essential to guide policy-makers in a very technical area. They should be multidisciplinary but not overlapping. They must be inclusive and transparent to maintain the trust of the medical profession and outside experts. The choice of which drugs to study must be unbiased and independent.

7.7.4. Executive authority and understanding is needed to reduce the bureaucratic and process hurdles obstructing clinical research, including a lack of coordinated funding.

7.7.5. At the same time good science needs protection, particularly in emergencies. Political and social influence can disrupt objective evaluation, so policymakers should allow and protect space for science. Purchases of drugs and vaccines must include the option for independent testing, comparison and efficacy monitoring.

7.7.6. The public must be kept "on side" through clear communication. They will also need to be involved as research participants, so their trust is essential. Policymakers, media representatives, lobby groups, and the public need to understand uncertainty and the scientific process. Investment in public understanding and engagement is critical.

7.7.7. The NHS provides a unique large-scale research platform to help answer important research questions as well as providing clinical care.

Adaptive platform trials in different groups of patients

7.8. We do not know with any certainty what the infectious disease will look like in a future pandemic. However, it is likely that the clinical illness will have several stages, similar to Covid-19:

- an early stage, when the person is infected and probably infectious, but not unwell enough to be admitted to hospital;
- a middle stage in some people when they become more unwell and are likely to be admitted to hospital
- a late stage, in some of those who progressed to the middle stage, when they are very unwell, and may develop complications leading to multiple organ failure; and
- a recovery stage, possibly with lasting symptoms similar to Long Covid.

The more serious the infection, the more patients progress through these stages, and the more rapidly the disease progresses.

7.9. High-quality trials of therapeutics will likely be needed at all these stages to evaluate and optimise treatment. The large RECOVERY and REMAP-CAP studies in hospitalised patients succeeded at producing timely results that saved lives from the second wave of the Covid-19 pandemic onwards. Unfortunately, despite significant efforts, there were few positive findings that substantially changed treatment in the early and recovery stages of the illness before vaccines were made available and turned Covid-19 into a far less severe disease.

Phase 2 studies

7.10. The capability and expertise in conducting phase 1 and phase 2 trials rapidly must be supported. Publicly funded platforms should be maintained. Critically the phase 2

assessment process should be much more efficient than it was in Covid-19. Investment in good pharmacometric assessment to guide choice of drugs, doses and duration of therapy accelerates and improves the efficiency of developing effective treatments, and allows their efficacy to be monitored and resistance to be evaluated. This is particularly important for developing therapeutics to treat early disease in order to prevent disease progression.

Monitoring drug resistance

7.11. In the pandemic the NmAbs were initially very effective, but later they were much less effective against the new viral variants. Importantly, small molecule drugs still work well against these new viruses. Although resistance to small molecule drugs can develop, unlike the NmAbs, fortunately this has not been a problem to date in Covid-19. If resistance arises readily then combinations of drugs are usually less vulnerable. Resistance to any kind of pathogen-directed drug (antivirals and vaccines) may be a problem in future pandemics. It is therefore essential to monitor the pathogen genetic sequences for signs that resistance is developing and to consider the need for monitoring and the methods of assessment of efficacy and, if necessary, adaptation (eg NmAb reformulation).

Eligibility

7.12. Who needs treatment depends on the severity of the illness at presentation and the risk of progression to severe disease. Informed treatment policies and practices require an assessment of benefits, risks and cost. Methods of determining eligibility require a strong and sound research evidence base. For a very severe illness, such as H5N1 influenza, (which until recently had a consistent case fatality rate over 50%) every ill person needs anti-influenza drug treatment. But for infections with much lower mortalities and morbidities drug treatment is usually reserved for vulnerable individuals (such as in Covid-19 now). Minor benefits may still justify treatment if that treatment is simple, effective, safe and affordable, and is an improvement on existing options. In

future pandemics, health authorities will likely once again face hard choices about who should be eligible for treatment, so this should be considered in their preparations.

8. Recommendations

8.1. Drugs (both small molecule and NmAbs) are very important in reducing the morbidity and mortality of an epidemic infection.

8.2. Therapeutics research must be coordinated and well informed. Inessential bureaucratic obstacles to the rapid conduct of clinical trials should be minimised and, in an emergency, circumvented.

8.3. An open forum for exchange of information in the relevant scientific community should be created, but with clear and capable leadership.

8.4. Methods of quantitating the therapeutic response in patients should be developed ("phase 2" for new drugs) and supported in an open publicly funded platform. This will accelerate drug evaluation and inform the therapeutic comparisons which provide the evidence base for policies, and also for continued efficacy monitoring.

8.5. Large definitive randomised and, where appropriate, adaptive controlled trials both in hospital and in the community should be supported through the NHS. Small underpowered trials should be avoided. Consideration should be given to standing platforms (i.e. continued inter-pandemic infrastructure support).

8.6. The larger trials must aim to recruit participants who are representative of those who will receive the drugs in routine practice, and in an emergency, balance the need for speed against any delays incurred in ensuring representativeness.

8.7. New drug candidate selection for clinical trials must be independent and unbiased. The choice of drugs and their doses in the larger trials should be informed by earlier pharmacometric evaluation.

8.8. As medical treatments become available and are deployed widely they should be compared in the publicly funded platform trials to provide a health-economic

justification for their procurement and continued use. The procurement deals must not prevent this.

8.9. Drug resistance and its effect on prevention and treatment efficacy should be studied, molecular markers identified, and the effect on therapeutic efficacy should be monitored.

9. Glossary

Adaptive platform trial: A trial in which medicines are entered and tested and later leave at different times. The results are continually compared and a treatment arm is stopped when a prespecified target is reached - indicating either that the drug works well enough or not well enough.

Antibody: When the body is attacked by a pathogen it defends by mounting an immune response. There are two arms to the response; a "humoral" arm and a "cellular" arm. The humoral arm comprises making complex proteins called antibodies, which bind to pathogens, blocking their function and making them easy for the body's cells to recognize and destroy. The cellular arm is complex and involves white blood cells which kill the pathogens and others which help in this process and have a long term-memory for previous infections.

Open label randomized controlled trial: A trial comparing two or more treatments in which patients who give informed consent to joining the trial are allocated at random ("randomized") to receive one of the two treatments. One arm of the trial can be "no treatment" other than supportive care if there is no accepted treatment or if there is a treatment but most patients do not receive it (such as Covid-19 now).

Double blind randomized controlled trial: A randomized comparison in which neither the patients nor the trial investigators (except for the trial statistician) know which medicine has been received. Sometimes when no-drug is the comparator, or medicines cannot be made similar enough, placebos are given used. These are made to look identical to the active medicine, but contain no active drug

Pharmacokinetics: characterizing mathematically the changes in the blood concentrations of a drug and the factors which affect these changes. This is often divided into absorption, distribution, metabolism and elimination.

Pharmacodynamics: characterizing mathematically the responses of the body, or for infectious pathogens, the numbers or effects of the infectious pathogens. Examples include the cure rate, mortality, the rate of clinical improvement, the time to fever resolution, the rate of decline in pathogen numbers, and side effects.

Pharmacometrics: The relationship between pharmacokinetics and pharmacodynamics

PCR: The polymerase chain reaction is a laboratory method of amplifying specific sequences in the nucleic acid of cells (in this case pathogens) so that small quantities can be detected. This can be quantified (qPCR) by counting the number of amplification cycles (Ct value) required to reach a calibrated value. This provides an estimate of the density of cells or viruses in the sample.

10. Inquiry Documents

INQ000474449	Witness Statement of Professor Saye H Khoo. Dated 18/10/2024.
INQ000474707	Report from Professor Stephen Evans titled Expert Report for the UK Covid-19 Inquiry Module 4 - Vaccines and Therapeutics, Hurdles and Nets: Authorising and Monitoring Vaccines, dated 06/11/2024.
INQ000474611	Witness statement of Helen Knight on behalf of the National Institute for Health and Care Excellence, dated 18/11/2024.
INQ000474312	Witness Statement of Professor James Palmer, National Medical Director for Specialised Services, NHS England, dated 27/08/2024.
INQ000474625	Witness Statement of Professor David Lalloo, Vice Chancellor and Professor of Tropical Medicine at the Liverpool School of Tropical Medicine, dated 28/11/2024
INQ000271436	Additional Witness Statement of Sir Ian Diamond, Chief Executive of the UK Statistics Authority and National Statistician, dated 11/09/2023.

INQ000474623	Expert Report for the UK Covid-19 Public Inquiry, Module 4 - Vaccines and Therapeutics, Vaccine Delivery and Disparities in Coverage by Dr Ben Kasstan-Dabush and Dr Tracey Chantler, dated 15/11/2024.
INQ000067958	Paper titled COVID-19 oral antivirals deployment plan, dated 12/01/2022.
INQ000474342	Witness Statement of Eddie Gray, Chair of Antivirals Taskforce (DHSC), dated 20/08/2024.
INQ000479899	Paper titled Process for Developing Priority Patient Cohorts for Access to Neutralising Monoclonal Antibodies in the Community Setting, undated
INQ000479904	Report from GOV.UK titled Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group, dated 30/05/2022. [Publicly Available]
INQ000479904	Report from GOV.UK titled Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group, dated 30/05/2022. [Publicly Available]
INQ000067910	Report from Professor Ian McInnes, titled 'Independent Advisory Group concerning use of Neutralising Monoclonal Antibodies (nMABS) and anti-viral drugs in highest risk clinical subgroups upon community infection with SARS-CoV-2', dated 19/11/2021.
INQ000474335	Seventh Witness Statement of Clara Swinson (Part B) on behalf of the Department of Health and Social Care, dated 06/09/2024.
INQ000479902	Report from GOV.UK titled TCRP modelling group findings: risk of severe COVID-19 outcomes, dated 31/03/2023. [Publicly Available]

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