Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Future developments in the prevention, diagnosis and treatment of COVID-19

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A B S T R A C T

The impact of the coronavirus disease-2019 (COVID-19) pandemic has been profound and global. Mitigating future waves and overcoming the pandemic is a global public health priority. This review focuses on future developments in the prevention, diagnosis and treatment of COVID-19, which may help to address these challenges. The specific relevance to women's and maternal health, which address the vulnerabilities in this group, is considered. The remarkable scientific achievements that have been made with respect to the development and implementation of both vaccines and therapeutics for COVID-19 are highlighted. The speed and processes for the development, approval and implementation of interventions herald a new way forward in combating emerging infectious diseases. However, it is important to note that this is a rapidly changing field with a constantly evolving knowledge base.

Introduction

In December 2019, the first documented cases of an unknown disease were reported in Wuhan, China. However, reports now suggest that cases may have been present 6 months before the official documented case [1–4]. The causative organism was subsequently identified to be a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which results in a clinical disease called coronavirus disease 2019 (COVID-19). Cases quickly spread worldwide, and

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COVID-19 was classified by the World Health Organisation (WHO) as a global pandemic on 11 March 2020. As of 13 February 2020, there have been approximately 107.7 million reported cases and nearly 2.4 million deaths of COVID-19 in 214 countries [5]. In England, there have been just over 4 million confirmed cases and 102,562 deaths (116,287 deaths in the UK) [6]. The impact has been profound, both in England and globally.

This review focuses on future developments in the prevention, diagnosis and treatment of COVID-19. We detail both current practices as well as future developments, which include those of specific relevance to women's and maternal health. The UK has been lauded globally for its approach to COVID-19 research and has made substantial scientific contributions [7], particularly towards the fields of vaccines and therapeutics for COVID-19. These remarkable achievements are detailed and will likely play a substantial role in overcoming this pandemic and mitigating future waves, which are global public health priorities.

Much of the information in this article is generalisable and not specific to pregnant women, for example, preventative measures apply to all. However, there are specific circumstances that apply to obstetric patients as pregnancy is a time of vulnerability. The evidence base is still evolving with respect to the effect of COVID-19 infection in pregnancy [8,9], but to date pregnant women are not thought to be more susceptible to COVID-19 infection than the general population, despite the degree of immunosuppression associated with pregnancy, but they may be more vulnerable to severe infection and resultant medical complications, particularly in the third trimester [10]. There is no high quality evidence that compares the risk of severe COVID-19 infection in pregnant women and non-pregnant women of the same age [11], but there is some evidence that COVID-19 may lead to an increase in pre-term births [12,13]. Additionally, good antenatal care demands regular hospital antenatal appointments/scans, which may bring additional risks by increasing contacts and potential exposures. Thus, it is important to place additional emphasis on ensuring the safety of this patient population. This article aims to draw out factors relevant to women's health audience.

COVID-19 is still a relatively new disease, and it is a rapidly changing field with a constantly evolving knowledge base. Therefore, this paper presents the current evidence base at the time of submission (mid-February 2021), but will be superseded/outdated as science evolves, particularly with respect to therapeutics and vaccines, where new information is emerging on a regular basis.

Prevention

A variety of containment measures have been shown to control the virus and are recommended practice. Reducing disease spread is focussed on two main measures: limiting contacts of infected individuals and reducing the transmission probability per contact. Thus, key public health measures include physical distancing, restricting the number of contacts and hygiene measures (including simple respiratory hygiene measures and hand hygiene). These principles have formed the basis of the non-pharmaceutical prevention methods recommended by the UK government. Each measure is not recommended in isolation, but as part of a wider package of measures and there is currently limited evidence to confidently quantify the absolute risk reduction attributed to each mitigation method.

The recommendations are constantly changing as the pandemic and knowledge of the virus evolve. Therefore, this section is focused on the scientific evidence underlying some of the key preventative measures, rather than a review of current practices [14]. However, Box 1 gives an overview of the key

Box 1
Government COVID-19 slogans

- March 2020: 'Stay home, Protect the NHS, Save lives'
- May 2020: 'Stay alert, Control the virus, Save lives'
- July and September 2020: 'Hands, Face, Space: Wash your hands, Cover your face, Make space'

Box 2
Prevention advice and interventions

General infection prevention advice

- Hygiene measures:
  - o Frequently wash hands with soap and water for at least 20 seconds or use an alcohol-based sanitiser (with >60% alcohol content). This is particularly important after exposure to a public place, blowing nose and coughing/sneezing
  - o Avoid touching eyes, nose and mouth with unwashed hands
  - o Practice respiratory hygiene (i.e. cover mouth and nose when coughing or sneezing with a tissue, discard the tissue immediately in a closed rubbish bin and then wash your hands)
  - o Clean and disinfect frequently touched surfaces
- Social distancing/minimising contacts:
  - o Avoid close contact with people - aim to maintain a distance of at least 2 m
  - o Avoid shaking hands, particularly with those who are unwell with a fever, cough or are sneezing
  - o Avoid crowded and poorly ventilated places
  - o Aim to maximise ventilation where possible
  - o Restrict meeting members of other households according to current guidance e.g. Rule of six'
- Isolation:
  - o Follow local isolation procedures, for example stay at home and self-isolate if you have any symptoms (even if mild)
  - o Follow isolation procedures if you are a contact of a confirmed case
- Facial coverings:
  - o Wear a facial covering according to local guidance

Examples of non-pharmaceutical interventions implemented during local and national restrictions and lockdowns [15]

- Stay at home order
- Contact within other households (banned/limited): including The Rule of Six'
- Closure of schools (except for key workers and vulnerable children), childcare facilities, colleges and universities
- Closure of places of worship
- Restrictions on indoor/outdoor gatherings and prohibiting large events
- Encouragement to work from home wherever possible. Only essential workers permitted to attend workplace
- Closure of bars, pubs, cafes and restaurants
- Closure of leisure and hospitality sector, which includes gyms, sports centres, etc.
- Closure of community centres
- Closure of non-essential retail
- Closure of close-contact personal services (hairdressing, beauty therapy, etc.)

government preventative slogans used during the pandemic, and Box 2 outlines the general infection prevention advice measure and non-pharmaceutical interventions that have formed the basis of the UK prevention campaign.

Social distancing

Physical distancing is a key component in the control measures for COVID-19. However, the exact details of the distance and length of safe exposures in various settings remain unclear as multiple

factors combine to determine the distribution of viral particle spread and therefore, risk. The recommended distances differ between countries, with the UK and US recommending 2 m, but other countries recommending 1 m as sufficient [16]. The distance of 2 m is controversial [16]. It stems from historical studies from other pathogens dating back to 1897, which proposed 1–2 m as a safe distance from visible droplets containing pathogens [17]. Traditionally, respiratory infections are divided according to the size of the droplet, which will determine how far it will travel from an infected person: large droplets travel less far (1–2 m) i.e. droplet spread, whereas small droplets i.e. aerosol or airborne spread (typically invisible to the naked eye) can travel less far, but with airflow can spread greater distances [16]. This dichotomy misses the complexities of the continuum of viral partical size, respiratory exhalation factors and airflow, all of which can determine how far a particle will travel [16,18]. Research in 1948 on haemolytic *Streptococci* found that 65% of participants ($n = 48$) produced large droplets only and <10% travelled >1.7 m [19], which further reinforces the concept of droplet infections and the 1–2 m distance rule. However, recent systematic reviews show that respiratory droplets >60 μm (SARS-CoV-2 virion is approximately 50–200 μm in diameter) can travel beyond 2 m [20], sometimes over 6–8 m [18,21]. Thus suggesting SARS-CoV-2 could spread beyond 1–2 m, particularly following coughing or sneezing [16,18]. Reports from other recent viral outbreaks (SARS-CoV-1, MERS-CoV and Avian flu) have also shown suspected spread beyond 2 m [22,23]. Furthermore, hospital studies have suggested SARS-CoV-2 shows airborne spread [16].

When a national recommendation is implemented, it is very difficult to account for all eventualities; therefore, the decision should be practical, realistic and provide the best recommendation based on current knowledge. The Scientific Advisory Group for Emergencies (SAGE) reviewed the evidence and estimated that the risk of SARS-CoV-2 transmission at 1 m could be 2–10 times higher than at 2 m [24]. Therefore, UK guidance was based on 2 m initially. A WHO systematic review showed that a physical distancing of <1 m was reported to result in a transmission risk of 12.9%, as compared to 2.6% at distances ≥1 m, supporting a distancing rule of 1 m or more [25]. Other countries adopted this, and while current UK guidance retains the 2 m criteria, it now also allows for a 1 m distance with additional mitigations in some settings.

Facial coverings

Recommendations for facial covering for source control vary between countries [26]. The transmission route for COVID-19 is through respiratory droplet infection and facial coverings, fully covering the mouth and nose, are considered a public health measure by providing a physical barrier to contain respiratory droplets and reduce transmission [27]. The wearing of a facial covering does not primarily protect the wearer from others, but protects others from the wearer, provided the mask fits correctly and is made from appropriate material [28]. Facial coverings work best when used on a widespread scale with high compliance. In the UK, the recommendation is to wear a facial covering in specific indoor public situations and in all indoor places where social distancing may be difficult, unless one has an exemption. This is consistent with WHO's advice to use a non-medical mask in areas of known or suspected transmission [29]. Of note, face coverings are distinct from medical grade masks and are not classified as Personal Protective Equipment (PPE). Given the shortage of medical grade masks, their recommended use is limited to health and social care interactions.

The scientific evidence to support the widespread use of facial coverings (particularly cloth masks) is evolving rapidly [28,30]. However, the evidence base is lacking as the majority of studies have previously been conducted in healthcare settings with medical grade masks (FFP2/3) and focus on the protection of the wearer, with the consensus that the use of masks leads to reduction in virus transmission [31]. However, there are caveats in generalising these results directly to community settings, including the use of cloth coverings, poor technique, poor fitting and behavioural factors [28]. Furthermore, the evidence that does exist is based on a limited number of inconsistent observational studies [29] and those studies that did assess community mask use often did not distinguish between the different types of masks [28,32].

A Cochrane review determined that the use of a mask made little or no difference to the number of people who caught influenza-like illnesses, although the evidence base was of poor quality and did not include current studies from the COVID-19 pandemic [33]. A further meta-analysis concluded a slight

reduction in odds of respiratory infection [34]. The first randomised controlled trial to assess the efficacy of mask use in COVID-19 found that the use of a surgical mask outside the home did not reduce the incidence of SARS-CoV-2 infection as compared to the no mask recommendation [35]. In contrast, recent work is more favourable towards mask use. A recent review offers evidence in favour of widespread mask use as source control to reduce community transmission [36]. Recent research by the Centers for Disease Control (CDC) has suggested that double masking with a close fitting surgical mask worn under a cloth mask can significantly enhance protection against COVID-19 [37]. However, key questions remain on the effect of mask use on transmission and source control. Despite the lack of definitive evidence, there is potential benefit and no risks associated with mask use, plus clearer evidence of benefit in healthcare settings [30]. Thus, the consensus is to recommend the use of masks.

Isolation

Isolation of symptomatic cases, contact tracing and quarantining was used as early containment measures for COVID-19 in many countries [38]. These are old concepts that are used as standard public health containment measures for infectious disease outbreak from direct person-to-person transmission [38]. These interventions are designed to prevent those with the virus, or with a significant chance of having been infected, from transmitting the virus during the infectious period. However, not all cases will be detected as there are asymptomatic cases and false-negative test results. The success of these containment measures depends on the transmission dynamics of the infection and the proportion of asymptomatic transmission [39]. Evidence suggests that in SARS-CoV-2, self-isolation alone would need to be achieved in a high proportion of cases and contacts to successfully limit the effective reproduction number ($R < 1$) [38,40] and the proportion of asymptomatic cases reported in this pandemic is likely to hinder the success of self-isolation alone leading to successful reduction in cases [41]. If combined in a wider package of moderate social distancing measures, together with self-isolation and contact tracing, then control of SARS-CoV-2 transmission is more likely to be achieved [38].

Currently, in the UK, those with symptoms of coronavirus or positive test results for coronavirus are asked to immediately self-isolate for 10 days (previously 7 days), after which they will typically no longer be infectious. Their households and contacts are also asked to self-isolate for 10 days (previously 14 days). The isolation period for contacts was reduced as evidence suggested that the average incubation period was 5–6 days, with approximately 10% of cases developing illness after 10 days and 1%–2% after 14 days [42]. People are most infectious in the 48 h before developing symptoms and for approximately 5 days afterwards [41,43,44]. Thus, reduction in the isolation period may allow 10% of cases to leave isolation before symptom onset, but may increase compliance [42].

'COVID-safe' obstetric clinics

Obstetric patients present a unique challenge during this pandemic. Not only do they have specific vulnerabilities, but they have numerous interactions with healthcare providers. Recent evidence suggests that nosocomial infections may have played a substantial role in the first wave of the pandemic, accounting for 40% of COVID-19 infections in hospital patients [45]. Furthermore, a report from a New York City hospital at the peak of the pandemic showed that following universal testing of all pregnant patients, 15% were positive for COVID-19 and most were asymptomatic (87.9%) [46]. Thus, safe obstetric care is essential and services need to adapt practices to protect mothers, babies and healthcare workers during these challenging times. Many healthcare encounters have moved to telemedicine; however, this is not possible for many obstetric appointments that include scans. Therefore, other measures need to be considered and might include a universal testing programme with rapid point-of-care tests. Box 3 highlights some specific measures to ensure a 'COVID-safe' hospital environment.

Vaccination

The key pharmaceutical method for the prevention of COVID-19 infection and disease is vaccination. Vaccinations for COVID-19 have been developed more quickly than vaccination for any other

Box 3
Infection prevention and control (IPC) in healthcare settings to ensure a COVID-safe' environment

- Follow local IPC guidelines and basic principles
- Hand and respiratory hygiene
- Wearing appropriate PPE for droplet precautions or airborne precautions if performing an aerosol-generating procedure: follow local guidance but PPE will vary according to situation/location, but should include mask, gloves, gown and eye protection/face shield
  - o Specific local advice should be in place for precautions during labour when patients may be vocal, but it is difficult for them to wear masks
- Use of disposable equipment where possible
- Limit the number of contacts including those with healthcare providers, domestic and porter staff
- Consideration of universal testing/screening when community prevalence is high
- Isolation of suspected and confirmed cases
  - o Place patients in a well-ventilated single room when possible or cohort together in same bay/area with at least 1 m between patients [47]
  - o Patients to wear medical mask
  - o Safe waste management
  - o Appropriate cleaning procedures
- Telehealth consultations where possible and safe to do so

disease in history [48]. Just over 11 months passed between the first report of COVID-19 to the WHO [49] and a highly effective vaccine being authorised for use [50]. In comparison, the second fastest vaccine developed was mumps, which took approximately 4 years [51]. The speed of development was related to several factors: new technology, high prevalence of the disease, regulatory flexibility and the global importance of developing a vaccine, and the resource that went with that [52]. Box 4 outlines details of the UK's vaccine development. How best to maximise the impact of vaccines is the topic of considerable discussion, but their development and reported efficacy to date is a remarkable scientific achievement.

UK access to vaccines

There was a global race to develop COVID-19 vaccines. Several different vaccines were developed with varied mechanisms of action (Table 1). There are two vaccines that UK patients currently have

Box 4
Case study of UK Vaccine development

In 2015, the UK Vaccine Network (UKVN) was established to address the lack of incentive for the pharmaceutical industry to investigate the development of a vaccine for intermittent infectious disease outbreaks [53]. In 2016, the UKVN funded Oxford University to develop a vaccine for MERS. In February 2020, an early rapid research call into COVID-19 was launched by the National Institute for Health Research (NIHR) and UK Research and Innovation (UKRI) and funded Oxford University to reorientate the MERS vaccine technology to develop a COVID-19 vaccine [54–56]. In April 2020, the government announced £20 million of further funding for clinical trials of the Oxford vaccine and the NIHR prioritised these clinical trials. This approach of considerable state support, linkage with industry (AstraZeneca) and overlapping and heavily prioritised clinical trials brought this vaccine to use far earlier than would otherwise have been possible. The trials were targeted at high prevalence areas, for AstraZeneca (Oxford), this was in large part in the UK and in Brazil, which enabled an accelerated evidence base for the vaccine as it provided end-point events.

Table 1
Vaccine mechanisms of action.

Vaccine Type	Mechanism of action
mRNA [58,59]	An mRNA vaccine introduces an mRNA sequence that codes for a disease-specific antigen e.g. the spike protein for the COVID-19 vaccine. Once in the body, the human cell mechanisms use the mRNA to produce this antigen, which is recognised by the immune system to induce an immune response; therefore, it is primed to respond rapidly and effectively if exposed to this antigen in the future [59,60]. mRNA vaccines have been under development since the 1990s for infectious disease and cancer vaccines. They provide a promising, faster and cheaper alternative to conventional approaches. Furthermore, they are considered safe as they do not use or produce infectious elements. Both animal and human data have been promising. However, until recently, their implementation has been limited primarily due to vaccine instability and there are no widespread vaccines in use which use this technique. However, these challenges have now largely been overcome, although the storage and distribution requirements are often still significant (e.g. −70 °C for the Pfizer vaccine). Examples: Pfizer/BioNTech, Moderna, CureVac
Adenoviral Vector [61]	An unrelated and weakened virus vector is used (e.g. adenovirus) to deliver SARS-COV-2 genetic material. This is used by the body's cells to produce viral proteins that are recognised by the immune system to trigger an immune response and build immune memory for future encounters of the virus. There are several adenoviral vaccines in clinical and pre-clinical trials including for mycobacterium tuberculosis, HIV and Ebola vaccines. Examples: Oxford/AstraZeneca and Janssen
Protein Adjuvant [61]	Protein adjuvant vaccines contain SARS-CoV-2 proteins or protein fragments that are recognised by the immune system to induce an immune response and build immune memory. This is the technique used for the Hepatitis B vaccine. Examples: Novavax and GSK/Sanofi
Inactivated whole virus [61]	Inactivated/killed whole SARS-CoV-2 virus is used to elicit an immune response without causing illness. They are a proven technology already used in existing vaccines, including (most) influenza vaccines, Hepatitis A and rabies. Examples: Valneva, Sinovac and Sinopharm

access to: the Pfizer/BioNtech vaccine, an mRNA vaccine, and the AstraZeneca (Oxford) vaccine, a chimpanzee adenovirus vaccine.

The UK regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), authorised Pfizer, AstraZeneca and Moderna vaccines for use under their emergency use clause of the Human Medicines Regulations 2012 [57], which allows for authorisation by the licensing authority on a temporary basis in response to the suspected or confirmed spread of pathogenic agents that may cause harm to human beings. MHRA provided authorisation faster than usual by looking at the data in a rolling review, meaning it looked at the packages of data as they become available from ongoing studies on a staggered basis rather than waiting for one final large data package.

The UK met its initial target of vaccinating 15 million people with their first dose of the vaccine by 14 February 2021. There are a number of additional vaccines for which the UK, through the Vaccine Taskforce, has supply agreements in place (Table 2), which includes the Moderna vaccine, which has been authorised for use by the MHRA, but the UK has not yet received any supply.

Prioritisation

Currently, the data on the two vaccines in use are predominantly on their efficacy against symptomatic disease, which was the primary end point of all trials (Table 3). However, the criteria used to define symptomatic disease as the end point differs between trials (Table 3), which is one factor that makes comparison of headline efficacy difficult.

There are also data on the impact of disease severity, for example the AstraZeneca vaccine had no hospitalisation in its treatment arm 11 days after the first dose [68]. Although the data are currently limited, the consensus is that it is likely that the vaccines will be more effective against hospitalisations and deaths. However, the major area of uncertainty remains around the effect of the vaccines on transmission, which is a key question in terms of the public health impact. This is, in part, why the Joint Committee on Vaccination and Immunisation (JCVI) prioritisation focused on vaccination of those most

Table 2
Vaccine doses ordered and timeline for UK.

Vaccine Developer	Doses on order	Timeline
Oxford/AstraZeneca	100 million	Authorised and deployed
Janssen (Johnson & Johnson)	30 million	Phase 3 trial results
Pfizer/BioNTech	40 million	Authorised and deployed
Moderna	17 million	Authorised
GlaxoSmithKline/Sanofi Pasteur	60 million	Phase 1/2 trials
Novavax	60 million	Phase 3 trial results
Valneva	100 million	Phase 1/2 trials

Table 3
Phase 3 efficacy results for the UK-ordered vaccines.

Vaccine developer	Efficacy	Primary end point
Oxford/AstraZeneca	70·4% [62] 66.7% [63]	Symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test (NAAT) positive swab combined with at least one of four qualifying symptoms more than 14 days after a second dose of vaccine.
Janssen	66% [64]	Moderate to severe COVID-19, 28 days after vaccination. Moderate COVID-19 disease was defined as laboratory-confirmed SARS-CoV-2 and at least one of: evidence of pneumonia, deep vein thrombosis, shortness of breath or abnormal blood oxygen saturation <93%, abnormal respiratory rate (≥20) or two or more systemic symptoms suggestive of COVID-19. Severe COVID-19 was defined as laboratory-confirmed SARS-CoV-2 and at least one of: signs consistent with severe systemic illness, admission to an intensive care unit, respiratory failure, shock, organ failure or death.
Pfizer/BioNTech	95% [65]	Confirmed COVID-19 with onset at least 7 days after the second dose in participants who had been without serological or virological evidence of SARS-CoV-2 infection up to 7 days after the second dose. Confirmed COVID-19 defined as at least one of a list of nine qualifying symptoms, combined with a positive for SARS-CoV-2 by NAAT.
Moderna	94.1% [66]	Symptomatic COVID-19 in seronegative participants with a positive reverse transcription polymerase chain reaction (RT-PCR) test combined with at least two of six qualifying symptoms or one of three respiratory qualifying symptoms at least 14 days after the second dose.
Novavax	89.3 [67]	Occurrence of PCR-confirmed symptomatic COVID-19 with onset at least 7 days after second dose in serologically negative (to SARS-CoV-2) adult participants at baseline.

likely to die (Box 5), rather than vaccination to prevent transmission. The JCVI statement states that 'it is estimated that taken together, these groups represent around 99% of preventable mortality from COVID-19'. It is unlikely that vaccines will have no impact on transmission, but we cannot yet be certain and we do not yet know what degree of transmission they will prevent. Initial data from the Oxford

Box 5
The Joint Committee on Vaccination and Immunisation (JCVI) vaccine priority list to protect those most likely to die from COVID-19

1. Residents in a care home for older adults and their carers
2. All those 80 years of age and over and frontline health and social care workers
3. All those 75 years of age and over
4. All those 70 years of age and over and clinically extremely vulnerable individuals
5. All those 65 years of age and over
6. All individuals aged from 16 years to 64 years with underlying health conditions which put them at higher risk of serious disease and mortality
7. All those 60 years of age and over
8. All those 55 years of age and over
9. All those 50 years of age and over

trial are promising, showing a 67% reduction in PCR positive readings after a single dose [63]. As the vaccine is rolled out in large numbers, data will start to accumulate to allow us to understand the impact. Of note, care home workers for older adults and frontline health and social care workers are included in the priority list despite not having the same level of personal risk of death as others on the list. This is based on the assumption that the vaccines will have some impact on transmission, and therefore, vaccinating them also protects those people vulnerable to death from COVID-19, for whom they care. The rationale is that these workers have high exposures and interact with a high number of those who are likely to die from COVID-19; hence, even a modest impact on transmission could have a significant impact on mortality.

The JCVI prioritisation is supported by the COVID-19 Actuaries Response Group who explore the rationale for the priority order by exploring the deaths in each group and estimating the number of vaccinations required to prevent one COVID death per group (Table 4) [69]. This is based on mortality data up to 20 November 2020 and assumes that the vaccine is 100% effective in the prevention of death. It shows the significant differences in vulnerability between the groups, with the number of vaccinations required to save one life increasing rapidly going down the priority groups [69]. Thus, supporting the prioritisation, particularly in a situation of limited supply.

Exceptions to use: pregnancy and breast feeding

When the first tranche of JCVI advice was published, there were two clear exceptions to the priority list: children and pregnant/breastfeeding women. Children were not recommended for vaccination as there are limited data [70]. The Oxford Vaccines Group have recently announced a trial of their vaccine in children aged 6–17 years, looking at immune response [71]. Pfizer and Moderna also have ongoing trials in children over 12 years [72,73].

The initial advice on vaccination in pregnancy (3 December 2020) stated:

> *Given the lack of evidence, JCVI favours a precautionary approach, and does not currently advise COVID-19 vaccination in pregnancy. Women should be advised not to come forward for vaccination if they may be pregnant or are planning a pregnancy within 3 months of the first dose.*

However, this changed on 30th December when it became more permissive, although it continued not to recommend the routine use of COVID-19 vaccines during pregnancy:

> *'vaccination in pregnancy should be considered where the risk of exposure to Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV2) infection is high and cannot be avoided, or where the woman has underlying conditions that put them at very high risk of serious complications of COVID-19'.* [74].

Table 4
Overview of the number needed to vaccinate to prevent one death, per priority vaccine group.

Vaccination group	Number of COVID deaths[a]	Approximate population number (million)	No. needed to vaccinate to prevent one COVID death
1. Care home residents	22,800	0.5 m	20
2. ≥80 years old	18,900	3.0 m	160
3. ≥75 years old	6300	2.2 m	350
4. ≥70 years old	5600	3.3 m	600
5. ≥65 years old	3100	3.3 m	1000
7. ≥60 years old	2000	3.8 m	2000
8. ≥55 years old	900	4.4 m	4000
9. ≥50 years old	500	4.7 m	8000
10. Everyone else	600	37.0 m	47,000

Adapted from Gong et al., 2020 [69].
Groups with COVID-19 deaths ≤1000 not included because of limited data e.g. care home residents carers, frontline health and social care workers, clinically extremely vulnerable, 16-64-year-old with underlying health conditions.
[a] COVID-19 deaths as of 20/11/2020.

Given the potential risks of disease in pregnancy [10–13], there is a case to consider vaccination in this group despite the absence of specific data on vaccination in pregnancy. Thus, in these circumstances, a discussion should be had with regard to risk (including the lack of safety data) and benefits to allow an informed decision to be made. The initial non-clinical data from Pfizer BioNTech showed no concerns about safety in pregnancy [74]. Furthermore, the vaccines do not include any infectious agent that could cause harm to the foetus. Those trying to conceive can be vaccinated, if eligible, and the initial recommendation to delay conception after vaccination has been withdrawn [74].

A change in recommendation also happened for breastfeeding women. The initial advice, based on the original MHRA regulation, was that Pfizer/BioNTech should not be used while breastfeeding [75]. This was revised by the MHRA and the JCVI advice (at the time of submission) for authorised vaccinations, which is that: '*breastfeeding women may be offered vaccination… and the woman should be informed about the absence of safety data for the vaccine in breastfeeding women'.* [74].

Given the lack of data on the vaccine in pregnant and breastfeeding populations, it will be important to ensure that vaccine monitoring captures data on these groups such that its impact can be monitored. Any trial into vaccines in pregnancy would likely need to be international to secure a sufficient sample size.

Vaccination risks and side effects

At the initial roll out of the Pfizer/BioNTech vaccine, there were preliminary concerns around anaphylaxis reactions in a small number of people. Clinical trials are to a degree exclusionary; therefore, it will always be at the start of roll out that a degree of caution is needed in assessing and monitoring any adverse events that occur as the general population starts to take the vaccine. The Pfizer/BioNTech vaccination reported two cases of anaphylactic events during the first few days of population vaccination (in people with severe allergies and pre-existing conditions) [76]. The MHRA tightened its advice as a result of this, although as more data have been accumulated, the advice was relaxed as the extent of the risk became clearer. Following this, the precautionary roll out of the AstraZeneca vaccine was initially undertaken in hospital settings, for a few days, before being rolled out more widely.

Both vaccines in use in the UK appear to be tolerated well. Box 6 details the most frequent adverse reactions documented in the clinical trials. The MHRA data up to 31 January 2021 shows that the vast majority of reported side effects during the deployment have been mild and short lasting. Most reports relate to injection-site reactions and generalised symptoms: 'flu-like' illness, headache, chills, fatigue, nausea, fever, dizziness, weakness, aching muscles, and rapid heartbeat. The MHRA conclude that 'the number and nature of suspected adverse reactions reported so far are not unusual in comparison to other types of routinely used vaccines' and 'the overall safety experience with both vaccines is so far as expected from the clinical trials' [77].

Extended interval for second dose

On 30 December 2020, the JCVI gave advice on extending the interval between the first and second dose stating that the delivery of the first dose should be initially prioritised over the delivery of a second vaccine dose. Previously for Pfizer/BioNTech, it had been a 3-week and for AstraZeneca a 4-

Box 6
Most frequent vaccination adverse reactions reported from clinical trials [68,78].

- Pfizer/BioNTech: pain at the injection site, fatigue, headache, myalgia (muscle pains), chills, arthralgia (joint pains) and fever. Adverse reactions were reported less frequently in older adults (over 55 years) than in younger people.
- AstraZeneca (Oxford) vaccine: injection-site tenderness, injection-site pain, headache, fatigue, myalgia, malaise, pyrexia (fever), chills, arthralgia and nausea. Adverse reactions were generally milder and reported less frequently in older adults (65 years and older) than in younger people.

week dosing interval. However, this advice allowed the second dose to be given up to 12 weeks after the first. This advice came after the MHRA changed its advice to be permissive of this approach. The UK CMOs set out the rationale in a joint letter explaining that the great majority of the initial protection from clinical disease came after the first dose of vaccine and that '*in terms of protecting priority groups, a model where we can vaccinate twice the number of people in the next 2 to* 3 months *is obviously much more preferable in public health terms than one where we vaccinate half the number but with only slightly greater protection*'. [79].

The JCVI released a document setting out the science underlying an extended interval, which considered the first dose efficacy for AstraZeneca to be around 70%, with high protection against severe disease [80]. The MHRA state that the vaccine efficacy of the AstraZeneca vaccine at 22 days post dose one was 73%, with a longer dose interval that potentially leads to a stronger immune response [68]. The JCVI consider the short-term vaccine efficacy from the first dose of Pfizer-BioNTech to be around 90%. This differs from the Pfizer data, which states that after one dose their vaccine is 52.4% effective [65,81]. The difference is due to the time point when the data were analysed, with Pfizer using the time of vaccination as the cut-off as compared to the cut-off of day 15 for the JCVI data. The Pfizer approach is very conservative and would mean someone getting COVID-19 the day after the vaccination would count against the efficacy, although it is not biological plausible that they would have mounted an effective immune response at this stage. Therefore, after one dose, the efficacy is highly likely to be higher than 52.4%, likely in the high 80s, and thus the logic in the policy to delay the second dose, particularly in the situation of constrained supply. This is even clearer in the case of AstraZeneca, where the delay may be beneficial. The latest data from Oxford support this, finding vaccine efficacy after a single standard dose of vaccine from day 22 to day 90 post-vaccination was 76% with modelled analysis indicating that protection did not wane during this initial 3-month period [63]. The JCVI and UK government position remains that the second dose of vaccine is important for longer-term protection. This was not a move to a single-dose regimen.

The Royal College of General Practitioners [82], the Royal Pharmaceutical Society [83] and the British Society on Immunology [84] have supported the 12-week extended interval, while the Food and Drug Administration (FDA) has ruled against extending the interval at all for Pfizer, saying '*we have committed time and time again to make decisions based on data and science*'. The WHO advice was that countries with exceptional epidemiology can consider delaying the second dose to maximise the number of people receiving vaccine. Their recommendation did not extend to 12 weeks, instead going to 6 weeks [88]. However, they recently changed this advice for AstraZeneca (Oxford), which recommended an interval of 8–12 weeks [89]. Debate regarding delaying the second dose will continue until the evidence emerges to determine which regimens are effective. The evidence will be very significant as use of an extended interval would be of benefit to many countries, given the shortage of supply.

New variants

The current major concern for vaccination programmes around the world is that a variant will emerge that reduces significantly the protection afforded by the vaccine. There are four variants of concern detailed in a recent Public Health England (PHE) report [91]:

- VOC 202012/01 (B.1.1.7), first detected in Kent England.
- VOC 202102/02 (B.1.1.7 cluster with E484K mutation), first detected in South West England.
- VOC 202012/02 (B.1.351), first detected in South Africa.
- VOC 202101/02 (P.1), first detected in Brazil.

Oxford trials found that a two-dose regimen of their vaccine provided minimal protection against mild-moderate COVID-19 infection from the B.1.351 variant [92]. The trial could not assess moderate or severe disease, and the hope remains that this and other vaccines will remain effective in the prevention of hospitalisation and deaths. The Novavax phase 2b trial in South Africa showed 60% efficacy in the HIV-negative population against symptomatic COVID-19 infection, and the majority of events were the B.1351 variant [67].

However, manufacturers, including Oxford and Moderna, are already starting to produce vaccines targeted at certain variants. The UK has recently announced a partnership with CureVac to develop potential vaccine candidates against SARS-CoV-2 variants, including an initial supply of 50 million doses of variant vaccines to the UK [93].

Diagnostics

The UK has approved three main types of diagnostic tests for COVID-19: the PCR test, the antibody (serology) test and the lateral flow assay devices.

PCR testing

Initially, the UK testing strategy was limited to quantitative real-time reverse transcriptase PCR (RT-PCR) testing, and this remains the most widely used test and the current gold standard. This is usually done on a swab taken from the nose and/or throat and is used to detect viral genetic material, if present, in those who are currently infected and 'shedding' the virus (both symptomatic and asymptomatic people). Of note, other sample types have also been evaluated and a recent meta-analysis of the accuracy of diagnostic tests for COVID-19 showed that PCR testing on sputum and saliva is also sensitive to detecting the virus [94].

PCR tests have a theoretical assay sensitivity and specificity that approaches 100%. However, in operational use, the sensitivity is lower, 73.3% using nasopharyngeal swabs in a recent meta-analysis [94]. This may be due to many reasons, including: a false-negative test, timing of sampling, poor sampling technique, and technical/operational issues such as labelling errors and degradation of the samples/swabs or transport medium if not processed in a timely manner. The timing of the swab test in relation to symptoms is likely to be the biggest factor impacting the test result and potentially leading to a false-negative result [95]. Thus, recommendations (government and NHS) are to take a swab test as early as possible after symptom onset, ideally within 24–48 h to obtain an accurate result. This fits with documented patterns of viral shedding, peaking just before or at the onset of symptoms, although further work is needed to fully understand the exact time course and length of viral shedding and its relationship to infectiousness [43,44]. Later in the disease course, the virus may only be detectable in the lower respiratory tract.

As with any diagnostic test, COVID-19 laboratory tests, both positive and negative, should be interpreted in the context of the clinical picture. A single positive PCR test effectively confirms the diagnosis, although there is a very small false-positive rate. PCR testing is sometimes said to be 'overly sensitive' as it can detect viral shedding and dead virus particles after the infectious period (usually approximately 9 days) with people testing positive for a mean of 17 days [43,44,96,97]. False-negative tests are more common, although when the background prevalence is low, they have little impact on the reliability of a negative result. Where the prior probability of having the virus is high, a negative test may need to be repeated to help exclude the presence of the virus. The false-negative results may paradoxically increase transmission risk with a potential increase in risky behaviours following a negative test [98].

Of note, point-of-care rapid PCR tests for use as near patient-testing devices (e.g. on arrival in Emergency departments to ensure appropriate isolation/cohorting) or in mobile laboratories have also been developed. This can be almost as sensitive as quantitative PCR [97].

Serology

Serology tests detect those who have had an antibody response from previous infection with SARS-CoV-2; therefore, they need to be taken after a time lag of at least 2–3 weeks to allow for the development of a sufficient detectable immune response. A range of commercially available SARS-CoV-2 antibody immunoassays exist using enzyme-linked immunosorbent assays or chemiluminescence immunoassays on venous blood. The main tests currently used in UK laboratories are the Abbott SARS-CoV-2 assay that detects IgG and the Roche Elecsys assay that detects both IgM and IgG, although there are several other tests, which have been approved.

Evaluation by Public Health England reports that the serology tests (in widespread use in England) have a sensitivity of 83.9%–92.7% with a specificity of 100% (dependent on the test) in laboratory conditions [99]. A recent Cochrane review of SARS-CoV-2 antibody tests (across 25 assays, 54 studies and 15,976 samples of which 8,526 were confirmed infections) showed a maximum sensitivity for combined IgG or IgM tests at 96% at 22–35 days after symptom onset. For IgG tests alone, the sensitivity was 88.2% at 15–21 days after symptom onset [100]. The overall specificity was 98% (reported in 35 of the 54 studies) [100]. However, the accuracy of a serology test is determined by comparing the result with a gold standard (in this case PCR testing normally), which itself may be limited by its own sensitivity [101]. Therefore, the results should be interpreted with caution.

Recent evidence suggests that past infection confers a robust cellular immunity, which persists for at least 6 months post-infection, even in mild or asymptomatic disease [102]. However, the immune response against SARS-CoV-2 at 6 months was 50% greater in those who had symptomatic disease [102]. It is still unclear how long an immune response may persist post-infection and previous infection does not mean that people cannot be re-infected [103]. This is an active area of research and further work is needed to understand this field, particularly the interaction between an antibody response and T-cell immunity on further transmission potential of an individual.

Lateral flow

Lateral flow testing assays detect viral antigens and commercially available assays have been validated and incorporated into the NHS Test and Trace programme alongside lab-based PCR tests. Many governments are now purchasing them in large quantities [97]. They are easy to use, much like a sophisticated pregnancy test and relatively cheap.

Lateral flow devices (LFDs) are thought to be useful in the detection of infectious cases, not infections *per se* [97,104]. They are less sensitive than PCR testing, thus generating more false-negative results [97,105]. This is particularly true if used during the incubation period (5–7 days following the infectious exposure) before the viral antigen can be detected through shedding in the nose and throat, which is normally possible approximately 1–2 days before symptom onset [43,44]. The difference in sensitivity between lateral flow assays and PCR testing is, in part, due to the threshold of detection of virus between the two methods. However, in theory, due to the rapid increase in viral shedding after the incubation period, the difference between the two thresholds (PCR versus LFD) translates to only a short period of time where the two tests may practically differ [106,107]. The false-positive rate for LFDs is low, and this can be overcome by using confirmatory PCR testing (in a low prevalence setting). They are particularly sensitive to the sampling quality and the ideal window of use is narrow [108].

Their main benefit is the ability to rapidly scale up decentralised testing with quick results. They are appropriate for widespread community testing to reduce transmission or to limit the time spent in isolation and enable 'normal' social and economic activities to resume. They are most useful in the setting of frequent use to detect infectious cases with high viral shedding immediately before and after symptom onset. This allows the timely isolation of the most infectious cases and appropriate management of their contacts, and prevents transmission events associated with the time delay in awaiting PCR results [109]. Modelling suggests that frequent testing with a lower sensitivity test can achieve the same probability of case detection as a higher sensitivity test with less frequent testing [110,111]. Additionally, further data suggest that rapid and frequent testing can reduce transmission [110,112]. Recent modelling studies suggest that the best lateral flow tests can detect 91% of cases that lead to onward transmission (under laboratory conditions and with the implicit uncertainty and assumptions of the modelling) [104]. However, real-world data suggest that lateral flow tests missed less than a third of people likely to be infectious, but 60% of PCR-positive cases (half of whom are likely to be post-infectious shedders, therefore not infectious) [104,113]. LFDs may be less likely (than PCR tests) to detect post-infectious continuous shedders [97], i.e. people who are no longer infectious.

In the UK, a pilot study in Liverpool evaluated the use of LFDs in three main domains: test-to-protect, test-to-release and test-to-enable regimens [113]. Real-world evaluations are needed to assess how these strategies and technologies work across different regimens, populations, settings and behaviours. However, there is consensus that they may provide the potential to interrupt transmission

while allowing restrictions to be eased, thereby minimising the psychological, physical and economic harms from these restrictions [97]. LFDs are due for wider roll-out as part of the UK national response for both specific situations and subsequently for wider population availability.

Rapid testing technologies

In the UK, initially, the testing capacity was limited as quantitative PCR diagnostics require a molecular laboratory with specialised technical equipment and fully trained staff. Additionally, there is a time lag between test and result, which means that infections can spread before the result is known. Testing technologies that shorten this interval and allow decentralised local testing could play a key role in minimising onward transmission. Thus, the identification of rapid testing technologies became a major area or research and development, particularly those that could be undertaken as near-patient testing requiring little or no technical expertise to successfully undertake the test. The main rapid technologies developed include LFDs (outlined above), Loop-mediated isothermal amplification (LAMP), and Next generation sequencing (LamPORE - a diagnostic platform combining LAMP with nanopore sequencing) testing. The first two are already in use as part of the wider testing strategy. Table 5 outlines LAMP and LamPORE. Point-of-care PCR testing has also been used as detailed above.

Numerous tests are currently in different stages of development, validation, MHRA approval and roll out. The performance characteristics of each test is different, and each test may be useful in different settings, for example, rapid point-of-care tests for universal screening for O&G patients according to local policies. Understanding the utility of each type of test (and each specific brand) is essential to ensure they are optimal and effective, particularly in a time of urgent need and limited resources.

Table 5
Novel rapid testing technologies.

Loop mediated isothermal amplification (LAMP)	LAMP is a technology which enables rapid nucleic acid amplification using primers and DNA polymerase with chain/strand displacement. This method bypasses the need to denature the DNA by heat (as in PCR reactions) and can therefore be undertaken at one constant temperature (usually 65 °C). Thus, the devices to run the test can be simpler, cheaper and smaller than the conventional PCR machines that require thermal cycling. This may make them more mobile and appropriate for use in communities. Evaluation carried out by NHS trusts and universities has found OptiGene RT-LAMP tests (validated by MHRA) to be accurate and sensitive for COVID-19 testing, including in asymptomatic patients (overall sensitivity 79% on saliva specimens and 70% on nasopharyngeal swab specimens, specificity 100%). This was higher in samples with higher viral load and when RNA extraction was undertaken (sensitivity 95% on swabs and 80% on saliva) [114].
Next generation sequencing (LamPORE)	Next generation sequencing (LamPORE) is a novel diagnostic platform combining LAMP with nanopore sequencing (direct, real-time analysis, which detects changes to an electrical current as the nucleic acids are passed through a protein nanopore, to allow real-time genotyping). This technology can be used with nasopharyngeal swabs and salvia samples. It offers rapid, mobile testing at a relatively low-cost. This technology has been trialled by the University of Oxford as a high-throughput platform [115]. Pop-up LamPORE laboratories have been piloted in Aberdeen, Telford, Brent and Newbury [116]. Clinical evaluation in these mobile laboratories has confirmed LamPORE testing to be highly accurate [116,117]. In symptomatic patients, the LamPORE assay (with RNA extraction) showed a sensitivity and specificity of 100%. In asymptomatic patients, the sensitivity was 99.6% and specificity 99.4%. On saliva samples from asymptomatic patients, the sensitivity was 98.9% and specificity 99/4% [117].

Testing strategies

Testing strategies have formed a crucial role in the government's COVID-19 plan. However, they are only one part of a comprehensive response. Rapid tests provide new opportunities to overcome the COVID-19 pandemic, they are associated with their own strengths and weaknesses. Further pilot data and evaluation are needed to assess the practicalities, utility and implementation of these tests. Table 6 outlines some potential testing strategies where rapid diagnostics could be useful.

Table 6
Possible testing strategies.

Testing strategy	Explanation
Mass testing	This involves testing on a large scale in the community to enable early case finding of those that would otherwise have gone undetected. Mass testing requires substantial resources and logistical capabilities. The ethics and benefits of implementing these programmes are controversial [97]. Leaked government documents suggested that the UK government considered a mass population testing programme for COVID-19 called 'Operation Moonshot' [118]. The aim was to test the whole UK population each week by '*utilising the full range of testing approaches and technologies to help reduce the R rate, keep the economy open and enable a return to normal life*'. This testing strategy moved away from the current testing strategy that primarily tests those with symptoms, to testing the whole population, which includes asymptomatic people [118]. The SAGE advice was cautionary saying '*careful consideration should be given to ensure that any mass testing programme provides additional benefit over investing equivalent resources into improving the speed and coverage of NHS Test and Trace for symptomatic cases … and the rate of self-isolation and quarantine for those that test positive*' [119]. However, '*mass testing can only lead to decreased transmission if individuals with a positive test rapidly undertake effective isolation*' [119]. The UK government did not take forward this testing strategy further [120]. Forms of mass testing for SARS-CoV-2 have been done in other countries including China, Vietnam, South Korea, USA, Netherlands, France, India and Iceland [118]. However, none rolled out mass testing on the whole population. In France, this broader testing strategy allowed use by the 'worried well' leading to queues and delays in results [118].
Test to protect and cluster identification	Given the time lag between developing symptoms, getting a PCR result, to test and trace management of contacts, substantial onward transmission can occur and clusters of cases can develop into larger outbreaks. This is particularly true in high-risk settings for outbreaks e.g. care homes, schools, universities, hospitals, and prisons. Thus, LFDs could be deployed to rapidly identify clusters, cut the delay, and limit transmission. This could be used to protect those who are vulnerable (either clinically vulnerable or vulnerable to infection or transmission) and protect essential services e.g. keyworkers. Furthermore, to reduce the risk of false-negative results, people with symptoms could additionally have a parallel PCR test. This strategy has been adopted in some settings in the UK with NHS staff being able to access bi-weekly lateral flow testing [121].
Test to release	Frequent testing to reduce unnecessary quarantine of non-infectious individuals. This bases isolation decisions on infectivity rather than infections. This has been deployed for use at international arrivals to shorten the duration of isolation (and hopefully increase compliance) [122] e.g. Germany and Netherlands.
Test to enable	Testing to minimise risk-allowing activities that are currently restricted and to open society and the economy. Examples include testing to enable care home visiting, or post-natal ward visiting or to allow workplaces to operate with risk mitigation (particularly to fragile businesses). Regular testing strategies in these scenarios are thought to be more logical than single tests for entry, which are unlikely to lead to a population benefit [98]. However, allowing additional activities would increase risk, even with testing in place.

Treatment

Development of therapeutic agents for COVID-19

The UK has been lauded globally for its approach to COVID-19 treatment research [9]. The UK treated research as a crucial component of the COVID-19 response, and a priority, at the start of the pandemic. Thus, the UK was at the forefront of research to investigate potential treatments for COVID-19 with the NIHR and UKRI launching a rapid response research call very early in the pandemic (February 2020). This funding enabled the UK's flagship COVID-19 treatments trial, the RECOVERY trial, which remains the largest COVID-19 treatment trial in the world. As of 13 February 2021, it had over 36,300 participants. Another large treatment trial is the WHO SOLIDARITY trial which, at last report, has enrolled 12,000 participants across 30 countries [123].

The NIHR set up a priority process, trials were designated 'Urgent Public Health badged' by an independent panel [124]. This focused the research workforce on a smaller number of trials that resulted in larger recruitment across a narrower remit; therefore, trials were able to achieve end points. There was an early emphasis on confining treatments to clinical trials, rather than going to emergency use [125]. The current national priority trials, as designated by the Therapeutics Taskforce, are listed in Table 7 alongside the treatments they are trialling or have results for.

Initially, the focus was on therapeutics already in use that could be repurposed for COVID-19. The New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) compiled an initial list of promising candidates, which included the corticosteroid dexamethasone [126]. An independent COVID-19 Therapeutics Advisory Panel (UK-CTAP), advises on which treatments should be proposed for testing through the nationally prioritised trials [127]. Subsequent additions to the national trials have included novel treatments such as REGN COV2, a monoclonal antibody cocktail.

There are still a very limited set of therapeutics that have been shown to be effective against COVID-19. The RECOVERY trial proved that dexamethasone reduced deaths in patients on oxygen or ventilation [128]. A total of 2,104 patients were randomised to receive 6 mg of dexamethasone per day for 10 days and were compared with 4,321 patients randomised to standard care alone. Dexamethasone reduced deaths by approximately one-third in ventilated patients (rate ratio 0.64 (95% CI 0.51–0.81) and by approximately one fifth among those receiving oxygen without invasive mechanical ventilation (rate ratio, 0.82 (CI 0.72–0.94)). There was no benefit among those patients who did not require respiratory support. RECOVERY reported that one death would be prevented by the treatment of approximately 8 ventilated patients or approximately 25 patients requiring oxygen alone [129]. Thus, it is estimated that dexamethasone treatment may have saved 12,000 lives in the UK and 650,000 globally by January 2021 [130]. This was supported by REMAP-CAP trial, which did not reach its end point but did find a 93% probability of superiority for hydrocortisone with regard to the odds of improvement in organ support–free days within 21 days. NHS guidance now advises the use of corticosteroids in patients with severe or critical COVID-19 [131]. However, many questions remain, including the optimal steroid dosing and timing. Other key positive results from the nationally prioritised trials are presented in Table 8.

The therapeutic agent not studied by the UK national trials, but widely used, is remdesivir, originally designed for the treatment of Ebola. On 22 May 2020, the ACTT-1 trial showed that patients in the

Table 7
COVID-19 therapeutic trials.

Trial	Participants recruited (as of 13/02/2021)	Treatments trialling currently	Treatments with results from trial
PRINCIPLE	4,182	Inhaled budesonide	Azithromycin and doxycycline
RECOVERY	36,333	Colchicine, REGN-COV2, aspirin and baricitinib	Dexamethasone, lopinavir/ritonavir, hydroxychloroquine, azithromycin, convalescent plasma and tocilizumab
REMAP-CAP	4,123	Simvastin, anti-platelets, anakinra and interferon-beta	Tocilizumab and sarilumab

Table 8
Summary of key results from nationally prioritised trials.

Treatment	Effective or not	Trial	Detail
Interleukin-6 inhibitors (Tocilizumab and Sarilumab) [132]	Effective	REMAP-CAP	Effective in the reduction of the risk of mortality when administered to patients within first 24 h of starting organ support. Hospital mortality was 28% for tocilizumab group, 22% for sarilumab group and 36% for control group. A combined reduction in the risk of death of 24% [133]. This improvement appears to be on top of corticosteroids as most patients in the trial also received corticosteroids. Thus it should be used early in critical illness [133].
Tocilizumab [134]	Effective	RECOVERY	Reduces the relative risk of death by 14% and absolute risk by 4% for hospitalised patients with severe COVID-19. This effect is in addition to the benefit from dexamethasone. For every 25 patients treated with tocilizumab, one additional life would be saved. Tocilizumab also shortens the time until patients are successfully discharged from hospital and reduces the need for a mechanical ventilator.
Hydroxychloroquine [87]	Ineffective	RECOVERY	Ineffective in hospitalised patients
Lopinavir/ritonavir [135]	Ineffective	RECOVERY	Ineffective in hospitalised patients
Azithromycin [136]	Ineffective	RECOVERY	Ineffective in hospitalised patients
Convalescent Plasma [137]	Ineffective	REMAP-CAP	No evidence of improved survival rate in intensive care patients or reduction in number of days in ICU.
Convalescent Plasma [138]	Ineffective	RECOVERY	No benefit in hospitalised patients[a]
Azithromycin [139]	Ineffective	PRINCIPLE	Ineffective in early stage of disease
Doxycycline [139]	Ineffective	PRINCIPLE	Ineffective in early stage of disease

[a] Of note, standalone trials have showed: i) PLACID trial showed faster clearance of the virus, but no effect on disease progression or mortality [140]; ii) Early administration of high-titre convalescent plasma against SARS-CoV-2 to mildly ill, infected older adults reduced the progression of COVID-19 [141].

remdesivir group had a shorter time to recovery than patients in the placebo group (10 days as compared with 15 days), but had no impact on mortality [142]. Remdesivir was widely considered the first drug shown to work against COVID-19, however, there remains uncertainty [143]. The WHO SOLIDARITY trial, a larger trial than ACTT-1, found that remdesivir had no impact on hospitalisation duration or death [144]. Thus, the WHO have issued a conditional recommendation against the use of remdesivir, stating that there is not enough evidence to support its use, although it is the best directly acting antiviral we have to date [145].

Treatments to date are mainly focused on the acute and severe phases of illness. However, there are other treatments that have an increasing evidence base suggesting that they may have value in the treatment of early COVID-19, but are not included in the trials to date, e.g. ivermectin that may have a role in the inhibition of viral replication [146,147].

The approach to find proven therapeutics has been damaged throughout the pandemic by an understandable, but unhelpful desire to act immediately, without the data. Claims were widely made, with politicians, the public and scientists who advocated for their own preferred drug, with hydroxychloroquine an example of this. The negative results out of trials are, therefore, very important, in addition to the more heralded positive results.

Prophylactic agents

At present, there are no medications that have been shown to be effective in the prevention of infection or transmission of COVID-19. There has been limited progress in prophylactic treatments, with a lack of clear candidates for trials. Prophylaxis can be divided into preventing people developing

COVID-19 'pre-exposure prophylaxis' and reducing the severity of disease if they have already been infected 'post-exposure prophylaxis'. The PRINCIPLE trial, as listed above, is trialling the latter and has had recent results, which show that azithromycin and doxycycline are ineffective. These are particularly useful results given the antimicrobial resistance implications of using antibiotics more widely than needed.

Vitamin D is another treatment, which has not yet been included in formal clinical trials, but with a growing evidence base for benefit in COVID-19 infection. Evidence suggests that supplementation can offer preventative effects against acute respiratory infections and COVID-19 specifically [150–153]. Furthermore, two studies suggest that treatment with vitamin D may reduce adverse outcomes in hospitalised patients by the reduction of ICU admission and mortality [154,155]. However, the studies contributing to this evidence are heterogeneous, based on different dosing regimens and individually of weak quality, but cumulatively provide some evidence advocating for vitamin D supplementation [156].

Many people in the UK have low vitamin D levels, particularly in the winter and spring, which coincides with the peak time for respiratory infection transmission, including COVID-19 [157]. The UK government's recommendation is that everyone should take low-dose vitamin D during the winter months [158]. Vitamin D is cheap and the side effects of administration in moderate doses are minimal and, therefore, it may provide a low cost, low-risk strategy with the potential to make a difference at a population level. The key question is approximately what dosing is optimal for the prevention of COVID-19 and much of the evidence is based on higher dosing than the standard supplementation dose. However, in the interim, enthusiastic reinforcement to women to encourage the vitamin D supplementation may have additional benefits related to COVID-19 infection.

The UK has a COVID-19 Prophylaxis Oversight Group to guide prophylaxis options for the disease and the NIHR is funding the PROTECT trial to investigate how to reduce the transmission of COVID-19 and its severity in care homes. There remains a question about the importance of prophylaxis treatment given vaccine deployment. For a limited subset of immunosupressed people, there may still be a case for use. But if vaccines succeed in reducing the level of COVID-19 in circulation, the number needed to treat to prevent infection would likely be very high, which may exclude high-cost treatments such as monoclonal antibodies.

Conclusion

The impact of the COVID-19 pandemic has been profound globally. This outbreak has tested the limits of medical knowledge and the international global health response. However, the response has been unprecedented in many ways, particularly with respect to the remarkable scientific achievements in the fields of vaccines and therapeutics. The rapidity of, and pipelines for, development, approval and implementation herald a new way forward for combating future emerging infectious diseases.

We have highlighted that while traditional public health measures remain the mainstay of preventative measures, including the principles of limiting contacts of infected individuals and reducing the transmission probability per contact, novel scientific discoveries and technologies play a crucial role. Rapid diagnostics such as LFDs, LAMP and LamPORE platforms may have a key role in rapidly identifing new cases to prevent small clusters that result in larger outbreaks. In addition, testing strategies to maximise the potential of the available diagnostics will be crucial. Vaccination will also play a vital role to overcome this pandemic. We are at the early stages of implementation of vaccine strategies globally, but we have seen remarkable achievements to date and important lessons have been learnt. There is an international precedent now for vaccine development and therapeutic trials that can be called upon if needed in the future.

In conclusion, considering women's health in particular, the best practice guidance for the prevention and management of COVID-19 applies to the entire population with no specific changes required for this population. However, meticulous attention should be paid to prevention methods in obstetric units and for patients to reduce transmission during pregnancy. Furthermore, this review highlights the need for further research in the pregnant and breastfeeding population to ensure that appropriate, effective and safe vaccines and treatments are available.

Finally, it is important to note that the COVID-19 evidence base is a rapidly changing field with a constantly evolving knowledge base. Many major research questions remain. The hope is that the scientific progress trajectory seen to date will continue and limit the devastating losses recorded, both for COVID-19 and other emerging infectious diseases in the future. Mitigating future waves and overcoming this pandemic is a global public health priority.

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Practice points

- Barriers have been broken down in terms of validating and approving diagnostics and therapeutics at speed during public health emergencies
- It is possible to develop, approve and implement vaccines at speed, heralding a new era for combating emerging infectious diseases
- Best practice guidance for the prevention and management of COVID-19 applies to the entire population with no specific changes required for women's health population. However, meticulous attention should be paid to prevention methods in obstetric units and for patients to reduce transmission during pregnancy.

Research agenda

- Immunity is incompletely studied; more research is needed to elucidate the relationship between past infection, vaccination, immunity, reinfection and onward transmission
- Given the expedient roll out of vaccines, vaccine efficacy trials will be crucial. Key questions include:
  - o Clinical end-point comparisons of extended interval regimen versus clinical trial interval regimen
  - o Safety data in pregnant women (and breastfeeding)
  - o Vaccine trials in children
  - o Vaccine efficacy to prevent transmission
  - o Immunogenicity and reactogenicity studies of possible booster vaccination or revaccination due to waning protection or variant vaccine escape
- The continuation of current treatment trials, including trials of emerging therapeutics.

Declaration of competing interest

LCF works for the Department of Health and Social Care.

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