14a

COVID-19 - SARS-CoV-2

NOTIFIABLE

The virus

COVID-19 disease first emerged as a presentation of severe respiratory infection in Wuhan, China in late 2019 (WHO, 2020). By January 2020, lower respiratory samples taken from affected patients were sequenced and demonstrated a novel coronavirus (SARS-CoV-2) (Huang *et al*, 2020). The first two cases in the UK were seen in late January (Lillie *et al*, 2020). In March 2020, the WHO declared a SARS-CoV-2 pandemic (WHO Director-General, 2020).

SARS-CoV-2 is a member of the family of Coronaviridae and genus Betacoronavirus (Zhu *et al*, 2020). Phylogenetic analysis of SARS-CoV-2 has shown that it is genetically distinct from the SARS coronavirus (Dhama, *et al*. 2020), but appears to share strong sequence similarity to bat coronaviruses in China (Lam *et al*, 2020).

As with other coronaviruses, SARS-CoV-2 is an RNA virus which encodes four major structural proteins, spike (S), membrane (M), envelope (E) and a helical nucleocapsid (N) (Dhama *et al*, 2020) The S glycoprotein is considered the main antigenic target and consists of an S1 and S2 subunit (Kaur *et al* 2020). The S1 subunit has two functional domains: the N terminal domain (NTD) and receptor binding domain (RBD) which contains the receptor binding motif (RBM) (Kaur *et al*, 2020). The RBM binds to angiotensin converting enzyme 2 (ACE2) on host cells and is endocytosed with subsequent release of the viral genome into the cytoplasm (Amanat *et al*, 2020).

SARS-CoV-2 is primarily transmitted by person to person spread through respiratory aerosols, direct human contact and fomites (Kaur *et al*, 2020). Estimates of the basic reproduction number [R] were initially between 2 and 3 although a recent estimate was as high as 5.7 (Sanche *et al*, 2020). This high transmissibility indicates that stringent control measures, such as active surveillance, physical distancing, early quarantine and contact tracing, are needed in order to control viral spread. Perinatal transmission has been reported although the exact transmission route has not been elucidated (ECDCa, 2020).

After the initial exposure, patients typically develop symptoms within 5-6 days (incubation period) although about 20% of patients remain asymptomatic throughout infection (Cevik *et al*, 2020). Polymerase chain reaction (PCR) tests can detect viral SARS-CoV-2 RNA in the upper respiratory tract for a mean of 17 days, although transmission is maximal in the first week of illness. Symptomatic and pre-symptomatic transmission (1-2 days before symptom onset), is thought to play a greater role in the spread of SARS-CoV-2 than asymptomatic transmission.

The disease

In adults, the clinical picture varies widely. A significant proportion of individuals are likely to have mild symptoms and may be asymptomatic at the time of diagnosis.

Symptoms are commonly reported as a new onset of cough and fever (Grant *et al*, 2020), but may include headache, loss of smell, nasal obstruction, lethargy, myalgia (aching muscles), rhinorrhea (runny nose), taste dysfunction, sore throat, diarrhoea, vomiting and confusion; fever may not be reported in all symptomatic individuals. Patients may also be asymptomatic (He *et al*, 2020).

Progression of disease, multiple organ failure and death will occur in some individuals (Pachetti *et al*, 2020).

Currently available data suggest that increasing age and male gender are significant risk factors for severe infection. However, there are also groups of patients with underlying comorbidities, where infection may result in increased risk of serious disease (Docherty *et al*, 2020). In a large review of primary care records pseudonymously linked with SARS-CoV-2 status, comorbidities including diabetes, cancer and severe asthma were associated with increased risk of death (Williamson *et al*, 2020).

Infection fatality ratios (IFR) for COVID-19, derived from combining mortality data with infection rates in seroprevalence studies, show a marked increase in IFR in the oldest age groups (Table 1) (Ward *et al*, 2020).

Table 1: Infection fatality ratio and estimated total numbers of deaths (February to July 2020)

Category	Population Size	SARS-CoV-2 antibody prevalence% (95% CI)[1]	Confirmed COVID-19 deaths[2]	Infection fatality ratio % (95% CI)[2]	Estimated number of infections (95% CI)
Total	56,286,961	6.0 (5.7, 6.8)	30180	0.9 (0.9, 0.9)	3,362,037 (3,216,816; 3,507,258)
Sex					
Male	27,827,831	6.5 (5.8, 6.6)	18575	1.1 (1.0, 1.2)	1,729,675 (1,614,585; 1,844,766)
Female	28,459,130	5.8 (5.4, 6.1)	11600	0.7 (0.7, 0.8)	1,633,785 1,539,821; 1,727,749)
Age (years)					
15-44	21,335,397	7.2 (6.7,7.7)	524	0.0 (0.0, 0.0)	1,535,884 (1,436,941; (1,634,826)
45-64	14,405,759	6.2 (5.8, 6.6)	4657	0.5 (0.5, 0.5)	895,238 (837,231; 953,244)
65-74	5,576,066	3.2 (2.7, 3.7)	5663	3.1 (2.6, 3.6)	181,044 (153,426; 208,661)
75+	4,777,650	3.3 (2.5, 4.1)	19330	11.6 (9.2, 14.1)	166,077 (131,059; 200,646)

1 All estimates of prevalence adjusted for imperfect test sensitivity and specificity (see text for details). Responses have been re-weighted to account for differential sampling (geographic) and for variation in response rate (age, gender, ethnicity and deprivation) in final column to be representative of the England population (18+).

2 Infection fatality ratios were calculated excluding care home residents. Confirmed COVID-19 death counts were obtained from https://fingertips.phe.org.uk/static-reports/mortality-surveillance/excess-mortality-in-England-week-ending-17-jul-2020.html. Deaths in care homes by age on 12 June 2020 were obtained from www.ons.gov.uk. Total deaths in care home residents up to 17 July 2020 were obtained from www.ons.gov.uk. The age stratified estimates of COVID-19 deaths were then estimated using the total deaths from 17 July and the age distribution from 12 June. We assumed that age distribution of deaths did not change between 12 June and 17 July 2020.

In Europe and the UK, deaths attributed to SARS-CoV-2 have been reported disproportionately from residential care homes (ECDCb, 2020, Graham *et al* 2020). Other notable risk groups include healthcare workers (Nguyen *et al*, 2020) who may acquire infection both in the hospital or within the community setting (Bielicki *et al*, 2020). Current evidence suggests that deprivation and being from black and asian minority ethnic groups results in a higher risk for death from SARS-CoV-2 infection (Williamson *et al*, 2020), although the factors that contribute to this are not yet clear.

Children

Fewer than 5% of COVID-19 cases are amongst children and in general they appear to exhibit mild disease. Although cough and fever are the main symptoms in children (Ladhani *et al*, 2020), a UK study tracking children of healthcare workers has recently shown that of those who were seropositive, gastrointestinal symptoms were also commonplace (Waterfield *et al*, 2020). Preliminary evidence suggested that not only do children have a lower susceptibility to SARS-CoV-2 infection, but they are also unlikely to be key drivers of transmission at a population level (Viner *et al*, 2020). However, a recent prospective study found higher secondary attack rates where the household index case was a child (Lopez-Bernal *et al*, 2020).

A spectrum of multi system inflammatory disease similar to Kawasaki disease (KD) was recently described in children admitted during the SARS-CoV-2 pandemic, temporally associated with severe acute respiratory syndrome attributed to SARS-CoV-2 (Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS)) (Whittaker *et al*, 2020). This severe presentation in children is extremely rare, but appears to encompass a wide range of features, including fever, gastrointestinal symptoms, rash, myocardial injury and shock (Swann *et al*, 2020).

Pregnant women and neonates

The risk to pregnant women and neonates following COVID-19 infection is generally low: more than half of pregnant women who test positive for SARS-CoV-2 are asymptomatic, and there is no increase in stillbirth or neonatal death rates associated with COVID-19 in pregnancy [Allotey *et al*, 2020]. It is still unclear whether SARS-CoV-2 can be transmitted vertically, and only about 2% of neonates born to COVID-positive mothers in the UK test positive for SARS-CoV-2 in the first 12 hours of life (Vousden *et al*, 2021). However, the risk of preterm birth is increased two to threefold for women with symptomatic COVID-19 (Vousden *et al*, 2021), usually as a result of a medical recommendation to deliver early to improve maternal oxygenation [NICE Guideline 25, 2019 https://www.nice.org.uk/guidance/ng25]. Furthermore, a small proportion of pregnant women can have severe or fatal COVID-19. The largest global systematic review indicates that pregnant women are more likely to be admitted to the intensive care unit (ICU) with COVID-19 than age-matched non-pregnant women, (Mullins *et al*, 2021) and there is a signal that this is true in the UK as well (https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports).

Pregnant women are more likely to have severe COVID-19 infection if they are overweight or obese, are of black and asian minority ethnic background, have co-morbidities such as diabetes, hypertension and asthma, or are 35 years old or older (Vousden *et al*, 2021, Allotey *et al*, 2020).

COVID-19 vaccines

The recognition of the pandemic has accelerated the development and testing of several vaccines using platforms investigated during previous emergencies such as the SARS pandemic (Amanat *et al*, 2020) and Ebola in West Africa. Candidate vaccines include nucleic acid vaccines, inactivated virus vaccines, live attenuated vaccines, protein or peptide subunit vaccines, and viral-vectored vaccines.

Most vaccine candidates focus on immunisation with the spike (S) protein, which is the main target for neutralising antibodies. Neutralising antibodies that block viral entry into host cells through preventing the interaction between the spike protein Receptor Binding Motif (RBM) and the host cell Angiotensin-converting enzyme 2 (ACE2) are expected to be protective (Addetia *et al*, 2020, Thompson *et al*, 2020).

In the UK four vaccines targeting the S protein have been authorised for supply; two use an mRNA platform (Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 or Comirnaty® and Moderna mRNA-1273 COVID-19 vaccine or Spikevax®) and two use an adenovirus vector (AstraZeneca COVID-19 vaccine / Vaxzevria® and COVID-19 vaccine Janssen Ad26. COV2-S [recombinant]).

The Pfizer BioNTech and Moderna COVID-19 vaccines are nucleoside-modified messenger RNA (mRNA) vaccines. mRNA vaccines use the pathogen's genetic code as the vaccine; this then exploits the host cells to translate the code and then make the target spike protein. The protein then acts as an intracellular antigen to stimulate the immune response (Amanat *et al*, 2020). mRNA is then normally degraded within a few days. Both the Moderna mRNA-1273 and the Pfizer BioNTech COVID-19 BNT162b2 vaccines have been generated entirely in vitro and are formulated in lipid nanoparticles which are taken up by the host cells (Vogel *et al*, 2020, Jackson *et al*, 2020). The Pfizer vaccine was tested in healthy adults between the ages of 18-55 and 65-85 years in phase 1 studies and the BNT162b2 vaccine product at a 30 µg dose was chosen by Pfizer as the lead candidate in phase 2/3 trials (Walsh *et al*, 2020). The Moderna mRNA-1273 vaccine was tested at three dose levels in those aged 18-55 years and the 100µg dose chosen for phase 3 study (Jackson *et al*, 2020).

AstraZeneca COVID-19 vaccine uses a replication deficient chimpanzee adenovirus (ChAd) as a vector to deliver the full-length SARS-CoV2 spike protein genetic sequence into the host cell (Van Doremalen *et al*, 2020). The adenovirus vector is grown in a human cell-line (HEK293) (see chapter 1). ChAd is a non-enveloped virus; the glycoprotein antigen is not present in the vector, but is only expressed once the genetic code within the vector enters the target cells. The vector genes are also modified to render the virus replication incompetent, and to enhance immunogenicity (Garafalo *et al*, 2020). Once the vector is in the nucleus, mRNA encoding the spike protein is produced that then enters the cytoplasm. This then leads to translation of the target protein which acts as an intracellular antigen.

Vaccine effectiveness

Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2

Two doses of Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 successfully reduced the levels of detectable viral RNA in Rhesus macaques when followed by intra-nasal and intra-tracheal challenge with SARS-CoV-2 (Vogel *et al*, 2020). In phase 1/2 human trials, after prime and boost vaccination, neutralising antibodies were comparable or higher than in convalescent patients. Neutralising antibody responses were generally higher in the 18 to

55 year age group compared to the 65 to 85 year age group, but responses were comparable to levels in convalescent patients in both age groups.

A phase 3 study was conducted in around 44,000 individuals aged 12 years and above with a second dose delivered between 19 and 42 days. Initial analysis conducted as part of a phase 3 study demonstrated a two-dose vaccine efficacy of 95% (with credibility intervals from 90.3% to 97.6%) in those aged 16 years and above. Efficacy was consistent across age, gender, and ethnicity, and in the presence of co-morbidities (including asthma, obesity, diabetes, hypertension and lung disease). In naïve participants aged between 65 and 75 years, and in those aged 75 years and over, the efficacy was 94.7% (95% CI 66.7-99.9%) and 100% (95% CI 13.1-100%) respectively. Efficacy remained high when the analysis included those with evidence of prior immunity. Published efficacy between dose 1 and 2 of the Pfizer vaccine was 52.4% (95% CI 29.5-68.4%). Based on the timing of cases accrued in the phase 3 study, most vaccine failures in the period between doses occurred shortly after vaccination, suggesting that short term protection from dose 1 is very high from day 10 after vaccination (Polack *et al*, 2020). Using data for those cases observed between day 15 and 21, efficacy against symptomatic COVID-19 after the first dose was estimated at 89% (95% CI 52-97%). (https://www.fda.gov/media/144246/download)

The Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 received approval to supply in the UK from the MHRA on 2 December 2020.

Following an additional study in over 2000 children aged 12-15 years, which generated additional safety and efficacy data, the approval was extended to those in this age group in June 2021.

AstraZeneca COVID-19 vaccine

AstraZeneca COVID-19 vaccine elicited increased neutralisation antibodies in Rhesus macaques as well as a reduction in detectable virus in the lower respiratory tract following challenge with SARS-CoV-2 (Van Doremalen *et al*, 2020). In phase 1/2 human trials AstraZeneca COVID-19 vaccine was compared with a meningococcal conjugate vaccine (MenACWY) control in healthy adults aged between 18-55 years (Folegatti *et al*, 2020). Preliminary findings showed that neutralising antibodies were induced at day 14 and 28 after the first vaccination and titres increased after a second dose. Specific T cell responses were also induced after a single immunisation and were maintained after the second dose. Final data showed that IgG spike antibody responses and neutralising antibody 28 days after the second dose were similar across the three age cohorts (18–55 years, 56–69 years, and ≥70 years). More than 99% (208/209) of the participants had neutralising antibody responses two weeks after the second dose. Peak T-cell responses were seen 14 days after the first dose and were broadly equivalent in the three age groups (Ramasamy *et al*, 2020). In analysis of over 11,000 patients in the phase 3 study, overall vaccine efficacy against symptomatic disease was 70·4% (95% CI: 54·8–80·6%) (Voysey *et al*, 2020). There were ten cases hospitalised for COVID-19, of which two were severe, all in the control group, suggesting very high protection against severe disease. High protection against hospitalisation was seen from 21 days after dose 1 until two weeks after the second dose, suggesting that a single dose will provide high short term protection against severe disease (Voysey *et al*, 2020). An exploratory analysis of participants who had received one standard dose of the vaccine suggested that efficacy against symptomatic COVID-19 was 73.00% (95% CI: 48.79-85.76%).

The AstraZeneca COVID-19 vaccine received approval to supply in the UK from the MHRA on 30 December 2020.

Moderna COVID-19 vaccine

In phase 1 testing of the Moderna mRNA-1273 vaccine, all patients seroconverted to IgG by by Enzyme-Linked Immunosorbent Assay (ELISA) after the first dose of vaccine. Pseudo-neutralisation and wild virus neutralisation responses were detected in all participants after two 100µg doses of the Moderna mRNA-1273. Phase 3 placebo controlled testing in over 30,000 volunteers, showed a vaccine efficacy of 94.1% (95% CI: 89.3-96.8%). Efficacy was similar in those over 65 years. Vaccine efficacy against severe COVID-19 was 100% (95% CI: 87.0-100%) (Baden *et al*, 2020)

The cumulative case numbers in the phase 3 study showed a clear divergence between the vaccine and placebo groups from about 14 days after the first dose. Re-analysis of the phase 3 data from 15 days after the first dose to the time of the second dose, suggested that efficacy of a single dose was 92.1% (95% CI 68.8%-99.1%).

The Moderna vaccine was approved for use in the UK in January 2021.

Real world effectiveness

Vaccine effectiveness data from the UK are now emerging. A single dose of either the Pfizer-BioNTech or the AstraZeneca vaccines has been shown to provide around 60% protection against symptomatic disease; vaccinated cases are also around 40% less likely to require hospital admission or to die (LopezBernal *et al*, 2021 a). This is consistent with protection of around 80% against hospitalisation as seen in local studies (Vasileiou *et al* 2021, AvonCAP, 2021).

Protection against infection has also been seen in healthcare workers, where a single dose of Pfizer vaccine provided more than 70% protection against both symptomatic and asymptomatic infection (Hall *et al* 2021), and in care home residents where a single dose of either Pfizer or AstraZeneca vaccines reduced the risk of infection by around 60% (Shroti *et al*, 2021). The observed reduction in both symptomatic and asymptomatic infections suggests that vaccination has potential to reduce transmission; this was supported by a Scottish study that showed a 30% reduction in risk of infection in the household members of vaccinated compared to unvaccinated healthcare workers after a single dose of the Pfizer BioNTech vaccine. (Shah *et al*, 2021).

Higher levels of protection are observed after the second dose for both Pfizer BioNTech ((Lopez-Bernal J et al 2021) and AstraZeneca vaccines. A summary of the most recent data on real world effectiveness is now published on a weekly basis. https://www.gov.uk/government/publications/covid-19-vaccine-surveillance-report

Following the introduction of the Delta variant to the UK in April 2021, further updates to the analysis of real world effectiveness have been undertaken (LopezBernal *et al*, 2021 b). The latest data suggest that protection against Delta is slightly lower than against Alpha, particularly after a single dose. Protection against hospitalisation, however is maintained with two doses of the AstraZeneca and Pfizer BioNTech vaccines providing over 90% protection against this outcome. (Stowe J *et al*, 2021).

Safety

Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2

Local reactions at the injection site are fairly common after Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2, primarily pain at the injection site, usually without redness and swelling.

Systemic events reported were generally mild and short lived (Walsh *et al*, 2020). In the final safety analysis of over 21,000 participants 16 years and older, the most common events were injection site pain (>80%), fatigue (>60%), and headache (>50%). Myalgia, arthralgia and chills were also common with fever in 10-20%, mainly after the second dose. Most were classified as mild or moderate. Lymphadenopathy in the axillary, supraclavicular or cervical nodes on the same side as the injection was reported in less than 1% (Polack *et al*, 2020). Four cases of Bell's palsy were reported in vaccine recipients in the trial. Although within the expected background rate, this will be monitored closely post-implementation.

Side effects were less common in those aged over 55 than those aged 16 to 55 years. Severe systemic effects, defined as those that interfere with daily activity, included fatigue in 4% and headache in 2%. There was no signal to suggest that prior vaccination led to enhanced disease with only 1 case of severe COVID-19 in the 8 vaccine failures (Polack *et al*, 2020).

Recently a number of cases of myocarditis and pericarditis have been reported after Pfizer BioNTech vaccine. The reported rate appears to be highest in those under 25 years of age and in males, and after the second dose. Onset is within a few days of vaccination and most cases are mild and have recovered without any sequalae. The MHRA has advised the benefits of vaccination still outweigh any risk in most individuals.

A very small number of cases of Guillain-Barre Syndrome (GBS) have been reported after Pfizer-BioNTech vaccination but these reports have not reached the number expected to occur by chance in the immunised population.

Moderna COVID-19 vaccine

A high proportion (more than 75%) of vaccine recipients had localised pain at the injection site after both dose 1 and dose 2 of the Moderna mRNA-1273 vaccine. Redness and swelling were also seen after the second dose and local pain tended to last longer (around 3 days). Mild systemic effects were also common, including headache, fatigue, joint and muscle aches and chills. Systemic events were more severe after dose 2 and fever was only seen after dose 2, and both local and systemic reactions were less common in older participants (Baden *et al*, 2020). Adverse events were less common in those with pre-existing SARS-CoV-2 antibody. Axillary lymphadenopathy on the same side as the injection site was detected in more than one in ten recipients.

Bell's palsy was reported by three participants in the vaccine group and one participant in the placebo group. As for the Pfizer vaccine, this will be monitored closely post-implementation. There were no cases of severe COVID-19 disease in the vaccine group, and thus no signal for enhanced disease (Baden *et al*, 2020).

Recently a number of cases of myocarditis and pericarditis have been reported after Moderna vaccine. The reported rate appears to be highest in those under 25 years of age and in males, and after the second dose. Onset is within a few days of vaccination and most cases are mild and have recovered without any sequalae. The MHRA has advised the benefits of vaccination still outweigh any risk in most individuals.

A very small number of cases of GBS been reported after Moderna vaccination but these reports have not reached the number expected to occur by chance in the immunised population.

AstraZeneca COVID-19 vaccine

From early phase trials, mild pain and tenderness at the injection site was common with AstraZeneca COVID-19 vaccine occurring in 88% of 18-55 year olds, 73% of 56-69 year olds and 61% of people aged 70 years or over; similar levels were reported after each dose. Short lived systemic symptoms including fatigue and headache were also common but decreased with age, being reported in 86%, 77%, and 65% of those aged 18-55, 56-69 and 70 years or over respectively; most of these were classified as mild or moderate. These reactions were unusual after the second dose (Ramasamy *et al*, 2020). Mild fever (>38˚C) was recorded in the first 48 hours for around a quarter of younger participants but was not reported in those over 55 years of age or in any age group after the second dose (Ramasamy *et al*, 2020). Fever can be modified by the prophylactic use of paracetamol, which does not affect the immune response to this vaccine (Folegatti *et al*, 2020). In the phase 3 study, injection site reactions, mild fever, headache, myalgia and arthralgia occurred in more than 10% of vaccinees. Less than 1% reported lymphadenopathy or an itchy rash. Only one serious adverse event was reported as possibly linked to the vaccine; this was a case of transverse myelitis which occurred 14 days after dose 2. There was no signal to suggest that prior vaccination led to enhanced disease (Voysey *et al*, 2020).

A very rare condition involving serious thromboembolic events accompanied by thrombocytopaenia, has been reported after AstraZeneca vaccination. The condition presents with unusual venous thrombosis, including cerebral venous sinus thrombosis, portal vein thrombosis, and sometimes arterial thrombosis, with low platelet count and high D-dimer measurements. The condition has similarities to heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) and patients usually have positive antibody to platelet factor 4. The majority of the events occurred between 5 and 16 days following vaccination (Greinacher *et al*, 2021).

The current reported rate of this event in the UK around 15 cases per million after the first dose, although a higher incidence is seen in younger individuals. After the second dose the reported rate is much lower, particularly in younger individuals. Overall, the JCVI, MHRA and the WHO remain clear that the benefits of vaccination outweigh this small risk for adults aged 40 years and over, adults who are clinically extremely vulnerable and those with underlying clinical risks as defined in table 3.

GBS has been reported very rarely within six weeks of AstraZeneca vaccination, although it is not yet certain whether these are caused by the vaccine. The rare occurrence rates are broadly consistent with reports from previous viral mass vaccination campaigns. There was no evidence of a higher rate of reporting in individuals who had had a previous episode of GBS. A small number of cases of capillary leak syndrome have been reported across Europe within 4 days of AstraZeneca vaccination. Around half of those affected had a history of capillary leak syndrome.

Storage

The Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 should be stored in a freezer at -80°C to -60°C (-90°C to -60°C in the thermal container). Shelf life is 6 months at -80°C to -60°C. Frozen vials should be transferred to 2°C to 8°C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 25°C for immediate use.

After thawing, stability data have demonstrated that undiluted vaccine can be stored for up to 31 days at 2°C to 8°C. Once thawed, the vaccine cannot be re-frozen.

The AstraZeneca vaccine should be stored at 2°C to 8°C and has a shelf life of 6 months. The vaccine does not contain any preservative. After first opening the vial, it should be used within 6 hours. The vaccine may be stored between 2˚C and 25˚C during this period. After this time, the vial must be discarded.

Moderna COVID-19 vaccine vials should be stored frozen between -25° to -15°C and has a shelf life of 7 months at these temperatures. Once thawed, the vaccine may be stored refrigerated at 2°C to 8°C protected from light for up to 30 days if not punctured. The unopened vial is stable for 12 hours at 8° to 25°C.

Presentation

Each pack of the Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 contains 195 vials with a minimum of 6 doses per vial (975 doses per pack). It is supplied with 0.9% sodium chloride diluent for injection in plastic ampoules. After dilution, the vaccine should be kept at 2°C to 25°C and used within 6 hours. Any unused vaccine should be discarded.

The AstraZeneca vaccine is supplied in packs of 10 vials. Each vial contains 8 or 10 doses of vaccine, and is a colourless to slightly brown, clear to slightly opaque liquid.

Moderna COVID-19 vaccine is supplied in multidose vials containing 10 doses of 0.5ml.

Dosing and schedule

All COVID-19 vaccines

For both adenovirus vector and mRNA vaccines, there is evidence of better immune response and/or protection where longer intervals between doses in the primary schedule are used. (Amirthalingam G *et al* 2021, Payne RP *et al*, 2021, Voysey M *et al* 2021).

Based on this evidence, longer intervals are likely to provide more durable protection. JCVI is currently recommending a minimum interval of eight weeks between doses of all the available COVID-19 vaccines where a two-dose primary schedule is used. Operationally, this consistent interval should be used for all vaccines with a two-dose primary schedule to avoid confusion and simplify booking, and will help to ensure a good balance between achieving rapid and long-lasting protection.

The main exception to the eight week lower interval would be those about to commence immunosuppressive treatment. In these individuals, the minimal intervals outlined below may be followed to enable the vaccine to be given whilst their immune system is better able to respond.

Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2

The dose of Pfizer BioNTech COVID-19 vaccine is 30µg contained in 0.3ml of the diluted vaccine. After dilution each multidose vial can be used to deliver six doses of 0.3ml.

The vaccine should be administered in two doses, a minimum of 21 days apart.

AstraZeneca COVID-19 vaccine

The dose of AstraZeneca COVID-19 vaccine is 0.5ml.

The vaccine should be administered in two doses, a minimum of 4 weeks apart.

Moderna COVID-19 vaccine

The dose of Moderna COVID-19 vaccine is 0.5ml.

The vaccine should be administered in two doses, a minimum of 28 days apart.

Administration

Vaccines are routinely given intramuscularly into the upper arm or anterolateral thigh. This is to reduce the risk of localised reactions, which are more common when vaccines are given subcutaneously (Mark *et al*., 1999; Zuckerman, 2000; Diggle and Deeks, 2000).

Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 should be administered as an intramuscular injection into the deltoid muscle. A 1ml syringe with a 23g x 25mm needle will be provided for administration. The vial should be discarded if the solution is discoloured or visible particles are observed.

AstraZeneca COVID-19 vaccine is administered as a single dose of 0.5ml intramuscular injection into the deltoid muscle. A 1ml syringe with a 23g/25g x 25mm needle will be provided for administration. The vaccine should be inspected visually for particulate matter and discolouration prior to administration. The vial should be discarded if the solution is discoloured or visible particles are observed. The vial should not be shaken. A separate needle and syringe should be used for each individual. It is normal for liquid to remain in the vial after withdrawing the final dose.

Moderna COVID-19 vaccine should be administered as an intramuscular injection into the deltoid muscle. A 1ml syringe with a 23g x 25mm needle will be provided for administration. A separate needle and syringe should be used for each individual. It is normal for liquid to remain in the vial after withdrawing the final dose.

Individuals with bleeding disorders may be vaccinated intramuscularly if, in the opinion of a doctor familiar with the individual's bleeding risk, vaccines or similar small volume intramuscular injections can be administered with reasonable safety by this route. If the individual receives medication/treatment to reduce bleeding, for example treatment for haemophilia, intramuscular vaccination can be scheduled shortly after such medication/ treatment is administered. Individuals on stable anticoagulation therapy, including individuals on warfarin who are up-to-date with their scheduled INR testing and whose latest INR is below the upper level of the therapeutic range, can receive intramuscular vaccination. A fine needle (23 or 25 gauge) should be used for the vaccination, followed by firm pressure applied to the site without rubbing for at least 2 minutes (ACIP 2019). The individual/parent/ carer should be informed about the risk of haematoma from the injection.

Disposal

Equipment used for vaccination, including used vials, ampoules or syringes, should be disposed of by placing them in a proper, puncture-resistant 'sharps box' according to local authority regulations and guidance in Health Technical Memorandum 07-01: Safe management of healthcare waste (Department of Health, 2013).

AstraZeneca COVID-19 vaccine contains genetically modified organisms (GMOs). Sharps waste and empty vials should be placed into yellow lidded waste bins and sent for incineration; there is no need for specific designation as GMO waste. An appropriate virucidal disinfectant should be available for managing spills in all settings where vaccination is administered. Potentially contaminated gloves and aprons can be disposed in yellow/black striped offensive waste bags.

The COVID-19 immunisation programme

Phase 1 recommendations for the use of the vaccine

The objectives of first phase of the COVID-19 immunisation programme is to protect those who are at highest risk from serious illness or death. The Joint Committee of Vaccination and Immunisation (JCVI) has set out a prioritisation for persons at risk. JCVI ranked the eligible groups according to risk, largely based on prevention of COVID-19-specific mortality.

Evidence from the UK indicates that the risk of poorer outcomes from COVID-19 infection increases dramatically with age in both healthy adults and in adults with underlying health conditions. Those over the age of 65 years have by far the highest risk, and the risk increases with age. Residents in care homes for older adults have been disproportionately affected by the COVID-19 pandemic. Table 2 sets out JCVI advice on priority groups for COVID-19 vaccination. Table 3 sets out JCVI advice on clinical and other risk groups for COVID-19 vaccination.

Table 2 – Priority groups for vaccination advised by the Joint Committee on Vaccination and Immunisation

Priority group	Risk group
1	Residents in a care home for older adults Staff working in care homes for older adults
2	All those 80 years of age and over Frontline health and social care workers
3	All those 75 years of age and over
4	All those 70 years of age and over Clinically extremely vulnerable individuals (not including those under 16 years of age)
5	All those 65 years of age and over
6	Adults aged 16 to 65 years in an at-risk group (Table 3)
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

Clinically extremely vulnerable (group 4) and adults in priority group 6

People who are defined as clinically extremely vulnerable (CEV) are considered to be at high risk of severe illness from COVID-19 (https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#cev); these patients should be flagged on the GP system. A hospital clinician or GP can also add a patient to the list, based on their clinical judgement, because they consider them to be at very high risk of serious illness from COVID-19.

Many individuals considered CEV are in the oldest age groups and will be among the first to receive vaccine. Given the level of risk seen in this group as a whole, the remainder of the CEV group should be offered vaccine alongside those 70-74 years of age.

Children who are on the CEV list are not generally recommended for vaccination unless they have serious neurodisabilities (see section on children).

All patients on the CEV list will also fall into the broader disease categories outlined in table 3, but are in priority group 4 because of more recent treatment, more advanced condition or co-morbidities. Other patients in the same clinical risk group, but not on the CEV list at the time group 4 is called, should be called in priority group 6, or with their appropriate age cohort.

Table 3 Clinical and other risk groups 16 years of age and over who should receive COVID-19 immunisation.

Clinical risk groups	
Chronic respiratory disease	Individuals with a severe lung condition, including those with asthma that requires continuous or repeated use of systemic steroids or with previous exacerbations requiring hospital admission, and chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD).
Chronic heart disease and vascular disease	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease. This includes individuals with atrial fibrillation, peripheral vascular disease or a history of venous thromboembolism.
Chronic kidney disease	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis.
Chronic neurological disease	Stroke, transient ischaemic attack (TIA). Conditions in which respiratory function may be compromised due to neurological or neuromuscular disease (e.g. polio syndrome sufferers). This group also includes individuals with cerebral palsy, severe or profound and multiple learning disabilities (PMLD), Down's syndrome, multiple sclerosis, epilepsy, dementia, Parkinson's disease, motor neurone disease and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological disability.
Diabetes mellitus and other endocrine disorders	Any diabetes, including diet-controlled diabetes, current gestational diabetes, and Addison's disease.

Immunosuppression	Immunosuppression due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, patients undergoing radical radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients, HIV infection at all stages, multiple myeloma or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement disorder, SCID). Individuals who are receiving immunosuppressive or immunomodulating biological therapy including, but not limited to, anti-TNF, alemtuzumab, ofatumumab, rituximab, patients receiving protein kinase inhibitors or PARP inhibitors, and individuals treated with steroid sparing agents such as cyclophosphamide and mycophenolate mofetil. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day for adults. Anyone with a history of haematological malignancy, including leukaemia, lymphoma, and myeloma and those with systemic lupus erythematosus and rheumatoid arthritis, and psoriasis who may require long term immunosuppressive treatments. Most of the more severely immunosuppressed individuals in this group should already be flagged as CEV. Individuals who are not yet on the CEV list but who are about to receive highly immunosuppressive interventions or those whose level of immunosuppression is about to increase may be therefore be offered vaccine alongside the CEV group, if therapy can be safely delayed or there is sufficient time (ideally two weeks) before therapy commences. Some immunosuppressed patients may have a suboptimal immunological response to the vaccine (see Immunosuppression and HIV).
Asplenia or dysfunction of the spleen	This also includes conditions that may lead to splenic dysfunction, such as homozygous sickle cell disease, thalassemia major and coeliac syndrome.
Morbid obesity	Adults with a Body Mass Index (BMI) ≥40 kg/m².
Severe mental illness	Individuals with schizophrenia or bipolar disorder, or any mental illness that causes severe functional impairment.
Younger adults in long-stay nursing and residential care settings	Many younger adults in residential care settings will be eligible for vaccination because they fall into one of the clinical risk groups above (for example learning disabilities). Given the likely high risk of exposure in these settings, where a high proportion of the population would be considered eligible, vaccination of the whole resident population is recommended. Younger residents in care homes for the elderly will be at high risk of exposure, and although they may be at lower risk of mortality than older residents should not be excluded from vaccination programmes (see priority 1 above). For consideration of children under 16 see below.

Other risk groups	
Adult household contacts of people with immunosuppression	Individuals who expect to share living accommodation on most days (and therefore for whom continuing close contact is unavoidable) with individuals who are immunosuppressed (defined as above).
Adult carers	Those who are eligible for a carer's allowance, or those who are the sole or primary carer of an elderly or disabled person who is at increased risk of COVID-19 mortality and therefore clinically vulnerable.[1]

The examples above are not exhaustive, and, within these groups, the prescriber should apply clinical judgment to take into account the risk of COVID-19 exacerbating any underlying disease that a patient may have, as well as the risk of serious illness from COVID-19 itself.

A list of eligible diagnoses, and the appropriate clinical codes, can be found in the link at the end of the chapter.

Recommendations by staff groups

The objective of occupational immunisation of health and social care staff is to protect workers at high risk of exposure who may also expose vulnerable individuals whilst providing care. There is increasing evidence that vaccination will lead to a reduction in transmission, and even a small effect will have major additional benefit for staff who could expose multiple vulnerable patients and other staff members. Potential exposure to COVID-19, and therefore the priority for vaccination, may vary from workplace to workplace. Therefore, it is recommended that these staff groups are vaccinated against COVID-19 as follows.

Frontline healthcare staff

This includes the following groups:

Staff involved in direct patient care

This includes staff who have frequent face-to-face clinical contact with patients and who are directly involved in patient care in either secondary or primary care/community settings. This includes doctors, dentists, midwives and nurses, paramedics and ambulance staff, pharmacists, optometrists, occupational therapists, physiotherapists and radiographers. It should also include those working in independent, voluntary and non-standard healthcare settings such as hospices, and community-based mental health or addiction services. Staff working on the COVID-19 vaccination programme, temporary staff, students, trainees and volunteers who are working with patients must also be included.

Non-clinical staff in secondary or primary care/community healthcare settings

This includes non-clinical ancillary staff who may have social contact with patients but are not directly involved in patient care. This group includes receptionists, ward clerks, porters and cleaners.

1 Those clinically vulnerable to COVID-19 include children with severe neuro-disabilities, those who are designated Clinically Extremely vulnerable (CEV), adults who have underlying health conditions (as defined in table 3), and those who need care because of advanced age. Eligible carers should be vaccinated in priority group 6.

Laboratory and pathology staff

Hospital-based laboratory and mortuary staff who frequently handle SARS-CoV-2 or collect or handle potentially infected specimens, including respiratory, gastrointestinal and blood specimens should be eligible as they may also have social contact with patients. This may also include cleaners, porters, secretaries and receptionists in laboratories. Frontline funeral operatives and mortuary technicians/embalmers are both at risk of exposure and likely to spend a considerable amount of time in care homes and hospital settings where they may also expose multiple patients.

Staff working in non-hospital-based laboratories and those academic or commercial research laboratories who handle clinical specimens or potentially infected samples will be able to use effective protective equipment in their work and should be at low risk of exposure, and of exposing vulnerable patients.

Frontline social care workers

This would include:

- those working in long-stay residential and nursing care homes or other long-stay care facilities where rapid spread is likely to follow introduction of infection and cause high morbidity and mortality
- social care staff directly involved in the care of their patients or clients
- others involved directly in delivering social care such that they and vulnerable patients/clients are at increased risk of exposure

Young people age 16-18 years, who are employed in, studying or in training for health and social care work should be offered vaccination alongside their colleagues, if a suitable vaccine is available (see section on age specific recommendations). Younger people who are taking part in health and social care work as volunteers, interns or for the purposes of work experience, should make all efforts to avoid exposure to infection; vaccination would not normally be required.

Phase 2 advice

The objectives of the second phase of the COVID-19 immunisation programme is to continue to protect those who are at highest risk from serious illness or death, but also to protect the NHS by reducing the risks of hospitalisation and critical care admission. Phase 2 of the programme should therefore be accompanied by continued efforts to maximise coverage amongst those prioritised in Phase 1 but who remain unvaccinated, and to complete delivery of second doses to all those given first doses in Phase 1.

There is good evidence that the risks of hospitalisation and critical care admission from COVID-19 increase with age. **JCVI has therefore advised that the offer of vaccination during Phase 2 is age-based starting with the oldest adults first.** As there is an increased risk of hospitalisation in males, those from certain ethnic minority backgrounds, those who are obese or morbidly obese, and those from socio-economically deprived areas, JCVI advises that specific focus should be used to promote and deliver vaccination to the following groups:

All those aged 40-49 years

All those aged 30-39 years

All those aged 18-29 years

This includes those turning 18 years of age in the next three months.

Individuals aged 12 years or above at higher risk of severe COVID-19 infection.
This includes those with:

- severe neuro-disability and/or neuromuscular conditions that compromise respiratory function. This includes conditions (such as cerebral palsy, autism and muscular dystrophy) that may affect swallowing and protection of the upper airways, leading to aspiration, and reduce the ability to cough and resulting overall in increased susceptibility to respiratory infections
- children and young adults with learning disability (LD), including:
  - individuals with Down's syndrome
  - those who are on the learning disability register
  - those with profound and multiple learning disabilities (PMLD) or severe LD
- immunosuppression due to disease or treatment, including:
  - patients undergoing chemotherapy leading to immunosuppression, patients undergoing radical radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients, HIV infection at all stages or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement disorder, SCID)
  - individuals who are receiving immunosuppressive or immunomodulating biological therapy including, but not limited to, anti-TNF, alemtuzumab, ofatumumab, rituximab, patients receiving protein kinase inhibitors or PARP inhibitors, and individuals treated with steroid sparing agents such as cyclophosphamide and mycophenolate mofetil
  - individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg per day (or for children under 20kg body weight a dose of 1mg/kg or more per day).
  - anyone with a history of haematological malignancy, including leukaemia, lymphoma, and myeloma and those with auto-immune diseases who may require long term immunosuppressive treatments

Individuals aged over 12 years who are contacts of immunosuppressed individuals

Those aged 12 years and above who expect to share living accommodation on most days (and therefore for whom continuing close contact is unavoidable) with individuals **of any age** who are immunosuppressed (defined in table 3).

Age specific recommendations on vaccine type

Children under 16 and young adults aged 16-18 years

The Pfizer BioNTech vaccine has approval for use from 12 years old and currently has the most extensive safety data in those aged 12-15 years. This vaccine is therefore the preferred vaccine in this age group. Young people who have had a first dose of AstraZeneca vaccine, however, should complete with the same vaccine (see contraindications and precautions).

Healthy adults aged 18-39 years

Evidence suggests that the risk of serious COVID-19 disease is strongly related to age, and the risk of COVID-19 mortality, hospitalisation and ICU admission is lower in younger adults. Based on the current epidemiological situation, and taking into account projected vaccine supply, JCVI are advising a preference for a vaccine other than AstraZeneca to be offered to healthy people under 40 years of age, including health and social care workers, unpaid carers and household contacts of immunosuppressed

individuals. This advice may change if there is a change in the epidemiology or an interruption in the supply of the alternative vaccines. Within this age group, those who are are older (over 30 years of age), male, from certain minority ethnic backgrounds, in certain occupations at high risk of exposure, and those who are obese, remain at high risk of COVID-19. In the absence of a suitable alternative these individuals should still be offered the AstraZeneca vaccine, and may choose to receive the vaccine, provided they have been informed and understand the relative risks and benefits. They should be given the latest version of the COVID-19 vaccination and blood clotting leaflet (https://www.gov.uk/government/publications/covid-19-vaccination-and-blood-clotting). Those who have already received a dose of AstraZeneca vaccine should complete with the same vaccine (see contraindications and precautions).

Aged 40 years and over or in high risk groups

Individuals aged 40 years and over, those who are clinically extremely vulnerable and those in clinical risk groups (see table 3) are at high risk of the complications of COVID-19. The JCVI, MHRA and WHO consider that any risk from the rare side effects seen after AstraZeneca vaccine are outweighed by the benefits of vaccination. These individuals can therefore be offered vaccination with any of the available products, unless otherwise contra-indicated.

Pregnant women in eligible groups

Pfizer and Moderna vaccines are the preferred vaccines for eligible pregnant women of any age, because of more extensive experience of their use in pregnancy. Pregnant women who commenced vaccination with AstraZeneca, however, are advised to complete with the same vaccine (see section on pregnancy).

Previous incomplete vaccination

If the course is interrupted or delayed, it should be resumed using the same vaccine but the first dose should not be repeated. Evidence from trials of co-administration suggest that those who receive mixed schedules, including mRNA and adenovirus vectored vaccines make a good immune response, (Liu X *et al*, 2021) although rates of side effects at the second dose are higher. (Shaw R *et al*, 2021). Therefore, every effort should be made to determine which vaccine the individual received and to complete with the same vaccine. For individuals who started the schedule and who attend for vaccination at a site where the same vaccine is not available, or if the first product received is unknown, it is reasonable to offer one dose of the locally available product to complete the schedule. This option is preferred if the individual is likely to be at immediate high risk or is considered unlikely to attend again. Further doses would not then be required.

Individuals who experience severe expected reactions after a first dose of AstraZeneca or Pfizer vaccines appear to have a higher rate of such reactions when they receive a second dose of the alternate vaccine. (Powell A *et al*, 2021). Therefore, individuals who have received a first dose of the AstraZeneca vaccine should complete the course with the same vaccine, with the exception of those who experience anaphylaxis or an episode of thrombosis combined with thrombocytopaenia (see contraindications and precautions).

Individuals who are participating in a clinical trial of COVID-19 vaccines who present for vaccination should be referred back to the investigators. Eligible persons who are enrolled in vaccine trials should then be provided with written advice on whether and when they can be safely vaccinated in the routine programme.

Individuals who have been vaccinated abroad are likely to have received an mRNA or vector vaccine based on the spike protein, or an inactivated whole viral vaccine. Specific advice on completing vaccination in these individuals is available from Public Health England. https://www.gov.uk/government/publications/covid-19-vaccination-programme-guidance-for-healthcare-practitioners

Reinforcing immunisation

Interim advice on a potential COVID-19 booster programme has been issued by JCVI.

https://www.gov.uk/government/publications/jcvi-interim-advice-on-a-potential-coronavirus-covid-19-booster-vaccine-programme-for-winter-2021-to-2022

Co-administration with other vaccines

Although no data for co-administration of COVID-19 vaccine with other vaccines exists, in the absence of such data first principles would suggest that interference between inactivated vaccines with different antigenic content is likely to be limited (see Chapter 11). Based on experience with other vaccines any potential interference is most likely to result in a slightly attenuated immune response to one of the vaccines. There is no evidence of any safety concerns, although it may make the attribution of any adverse events more difficult.

As all of the early COVID-19 vaccines are considered inactivated (including the non-replicating adenovirus vaccine), where individuals in an eligible cohort present having recently received another inactivated or live vaccine, COVID-19 vaccination should still be given. The same applies for most other live and inactivated vaccines where COVID-19 vaccination has been received first or where a patient presents requiring two vaccines. It is generally better for vaccination to proceed to avoid any further delay in protection and to avoid the risk of the patient not returning for a later appointment. An exception to this is shingles vaccination, where a seven day interval should ideally be observed given the potential for an inflammatory response to COVID-19 vaccine to reduce the response to the live virus.

Studies are on-going to support co-administration of COVID-19 vaccines with influenza in the 2021-2022 season. Where co-administration does occur, patients should be informed about the likely timing of potential adverse events relating to each vaccine.

Pregnancy

There is no known risk associated with giving inactivated, recombinant viral or bacterial vaccines or toxoids during pregnancy or whilst breast-feeding (Kroger *et al.*, 2013). Since inactivated vaccines cannot replicate, they cannot cause infection in either the mother or the fetus. Although AstraZeneca COVID-19 vaccine contains a live adenovirus vector, this virus is not replicating so will not cause infection in the mother or the fetus. As with most pharmaceutical products, large clinical trials of COVID-19 vaccine in pregnancy have not been carried out.

Developmental and reproductivity testing of the Pfizer BioNTech, Moderna and AstraZeneca vaccines in animals have not raised any concerns. Adenovirus vectors, similar to those used in the AstraZeneca COVID-19 vaccine, have been widely used to vaccinate women against Ebola without raising any concern; formal trials of these vaccines in pregnancy are due to proceed.

Although clinical trials on the use of COVID-19 vaccines during pregnancy are not advanced, the available data do not indicate any harm to pregnancy. JCVI has therefore advised that women who are pregnant should be offered vaccination at the same time as non-pregnant women, based on their age and clinical risk group. There is extensive post-marketing experience of the use of the Pfizer BioNTech and Moderna vaccines in the USA with no safety

signals so far (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafepregnancyregistry.html). Over 50,000 women now report having been vaccinated whilst pregnant or when they might be pregnant in England. Because of wider experience with mRNA vaccines, these are currently the preferred vaccines to offer to pregnant women. Clinicians should discuss the risks and benefits of vaccination with the woman, who should be told about the limited evidence of safety for the vaccine in pregnancy.

Routine questioning about last menstrual period and/or pregnancy testing is not required before offering the vaccine. Women who are planning pregnancy or in the immediate postpartum should be vaccinated with a suitable product for their age and clinical risk group.

If a woman finds out she is pregnant after she has started a course of vaccine, she should complete vaccination during pregnancy using the same vaccine product (unless contra-indicated).

Termination of pregnancy following inadvertent immunisation should not be recommended. Surveillance of the inadvertant administration of COVID-19 vaccines in early pregnancy is being conducted for the UK by the PHE Immunisation Department, to whom such cases should be reported https://www.gov.uk/guidance/vaccination-in-pregnancy-vip. As above, women who are inadvertantly vaccinated in early pregnancy should be offered the second dose of the same product.

Breastfeeding

There is no known risk associated with being given a non-live vaccine whilst breastfeeding. JCVI advises that breastfeeding women may be offered any suitable COVID-19 vaccine.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for immunisation against COVID-19; at the same time, women should be informed about the absence of full safety data for the vaccine in breastfeeding.

Children

SARS-CoV-2 vaccine trials have been conducted in those aged 12-15 years for both Pfizer and Moderna vaccines, and more safety and immunogenicity data is emerging. Children and young people have a very low risk of COVID-19, severe disease or death due to SARS-CoV-2 compared to adults and so COVID-19 vaccines are not routinely recommended for children and young people under 16 years of age.

Children under 16 year of age, even if they are CEV, are at low risk of serious morbidity and mortality, and, given the absence of safety and efficacy data on the vaccine, are not recommended for vaccination. Recent analysis confirms that some children, such as those with profound and multiple LD (PMLD) and severe LD, and including children with Down's syndrome and cerebral palsy are at higher risk of hospitalisation for COVID-19 (Williamson E *et al*, 2021).

Recommendations on vaccinating children with other underlying conditions will be reviewed based on analysis currently being undertaken by an expert group commissioned by the Deputy Chief Medical Officer.

Immunosuppression and HIV

Individuals who have immunosuppression and HIV infection (regardless of CD4 count) should be given COVID-19 vaccine in accordance with the recommendations and contraindications above. Although AstraZeneca COVID-19 vaccine contains a live adenovirus vector, this virus is

not replicating and is considered safe in immunosuppressed people. Other adenovirus vector vaccines have been trialled in populations with high prevalence of HIV and shown no serious adverse events (Kennedy *et al*, 2017). Although individuals with stable treated HIV infection were not excluded from the phase 3 trial of the Pfizer and Moderna mRNA vaccines, data on safety and effectiveness in this group have not been presented. A study of the AstraZeneca vaccines in people living with HIV infection is underway.

Individuals with immunosuppression may not make a full immune response to vaccination. As there is limited evidence on response in immunosuppressed individuals there is also very little evidence upon which to base advice on the optimal timing of delivery. A recent study suggested immune responses were better, however, in patients with cancer who received their chemotherapy at least two weeks earlier (Monin-Aldama *et al*, 2021). Specialists may advise their patients based on their knowledge and understanding of their immune status and likely immune response to vaccination, but should also consider the risk from COVID-19 and the patient's likelihood of exposure. The small number of patients who are about to receive planned immunosuppressive therapy should be considered for vaccination prior to commencing therapy (ideally at least two weeks before), when their immune system is better able to make a response. Where possible, it would also be preferable for the 2-dose schedule to be completed prior to commencing immunosuppression. This would entail offering the second dose at the recommended minimum for that vaccine (three or four weeks from the first dose) to provide maximum benefit that may not be received if the second dose was given during the period of immunosuppression. Any decision to defer immunosuppressive therapy or to delay possible benefit from vaccination until after therapy should not be taken without due consideration of the risks from COVID-19 and from their underlying condition.

Emerging evidence suggests that many patients with immunosuppression are protected after two doses of vaccination. (Whitaker H *et al*, 2021). Individuals aged 12 years or over who are household contacts of immunosuppressed patients of any age should be offered vaccine to reduce the risks of exposure.

Despite the overall reassuring evidence, some individuals with more severe immunosuppression do not make a good immune response to a complete course of vaccine and may therefore remain at high risk. This includes, but is not limited to, individuals on immunosuppression for solid organ transplants (Prendecki M *et al* 2021), those with haematological cancers who are within six months of completing curative therapy (Lim SH *et al*, 2021), and those on certain monoclonal antibody therapies (Mahil SK *et al*, 2021). Post-vaccination testing for spike antibody may therefore be considered by specialists managing individuals with severe immunosuppression. Individuals can then be advised whether to take precautions to reduce their chance of exposure, taking into account their underlying immune defect and any test results. Although the immune correlates of protection are currently unknown, antibody levels taken 28-42 days after the second dose may be reassuring if positive and/or with antibody levels similar to those seen with the same assay used in immunocompetent older individuals. Low levels of detectable antibody may indicate poor protection against mild infection, although protection against severe disease may still be present due to T and B cell immunological memory.

Individuals who have received a bone marrow transplant after vaccination should be considered for a re-immunisation programme for all routine vaccinations and for COVID-19 (see chapter 7).

Contraindications and precautions

There are very few individuals who cannot receive the Pfizer BioNTech, Moderna or AstraZeneca COVID-19 vaccines. Where there is doubt, rather than withholding vaccination, appropriate advice should be sought from the relevant specialist, or from the local immunisation or health protection team.

The vaccine should not be given to those who have had a previous systemic allergic reaction (including immediate-onset anaphylaxis) to:

- a previous dose of the same COVID-19 vaccine
- any component (excipient) of the COVID-19 vaccine e.g. polyethylene glycol (PEG)

Further advice on anaphylaxis and on the thrombosis and thrombocytopaenia syndrome are outlined below.

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness (including COVID-19) by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

There is no evidence of any safety concerns from vaccinating individuals with a past history of COVID-19 infection, or with detectable COVID-19 antibody.

Vaccination of individuals who may be infected or asymptomatic or incubating COVID-19 infection is unlikely to have a detrimental effect on the illness. Vaccination should be deferred in those with confirmed infection to avoid confusing the differential diagnosis. As clinical deterioration can occur up to two weeks after infection, ideally vaccination should be deferred until clinical recovery to around four weeks after onset of symptoms or four weeks from the first confirmed positive specimen in those who are asymptomatic.

Having prolonged COVID-19 symptoms is not a contraindication to receiving COVID-19 vaccine but if the patient is seriously debilitated, still under active investigation, or has evidence of recent deterioration, deferral of vaccination may be considered to avoid incorrect attribution of any change in the person's underlying condition to the vaccine.

Very rare reports have been received of GBS following COVID-19 vaccination, so healthcare professionals should be alert to the signs and symptoms of GBS to ensure correct diagnosis and to rule out other causes, in order to initiate adequate supportive care and treatment.

Individuals who have a history of GBS should be vaccinated as recommended for their age and underlying risk status. Cases of GBS that occur following vaccination may occur by chance (the rate of GBS is 2 per 100000 per year in the population); no causal link with vaccination has been proven. As there is no evidence to suggest that having had a prior diagnosis of GBS predisposes an individual to further episodes, in those who are diagnosed with GBS after the first dose of vaccine, the balance of risk benefit is in favour of completing a full COVID-19 vaccination schedule. Based on an understanding of the natural history of GBS, the same vaccine product may be used to complete the course; using an alternative product may increase the chance of experiencing known side effects.

Extremely rare reports of capillary leak syndrome have been reported after AstraZeneca vaccine in individuals with a prior history of this condition. These individuals may be offered vaccination with an alternative COVID-19 vaccine.

Anaphylaxis following COVID-19 vaccination

A very small number of individuals have experienced anaphylaxis when vaccinated with the Pfizer BioNTech vaccine. Following close national surveillance, the MHRA is **no longer** advising that individuals with a history of anaphylaxis to any vaccine, medicine or food do not get the vaccine. Anyone with a previous history of allergic reactions to the ingredients of the vaccine should not receive it, but those **with any other allergies** (such as a food or penicillin allergy) **can have the vaccine**.

The Pfizer BioNTech and Moderna mRNA vaccines contain polyethylene glycol (PEG). PEGs (also known as macrogols) are a group of known allergens commonly found in medicines, many household products and cosmetics. Medicines containing PEG include some tablets, laxatives, depot steroid injections, and some bowel preparations used for colonoscopy. Known allergy to PEG is rare but would contraindicate receipt of this vaccine (Sellaturay *et al*, 2020). It is unclear whether PEG is the only cause of allergic reactions in patients with systemic allergic symptoms after the first dose of Pfizer-BioNTech vaccine.

The rate of anaphylaxis reported to date to the AstraZeneca vaccine is in line with the expected rate of anaphylaxis to non-COVID vaccines. The AstraZeneca vaccine does not contain PEG but does contain a related compound called polysorbate 80. Some people with PEG allergy may also be allergic to polysorbate 80. However, polysorbate 80 is widely used in medicines and foods, and is present in many medicines including monoclonal antibody preparations. Some injected influenza vaccines (including the main vaccine used in over 65 year olds) contain polysorbate 80. Individuals who have tolerated injections that contain polysorbate 80 (such as certain influenza vaccines) are likely to tolerate the AstraZeneca vaccine. This is summarised in table 4.

Table 4: Management of patients with a history of allergy

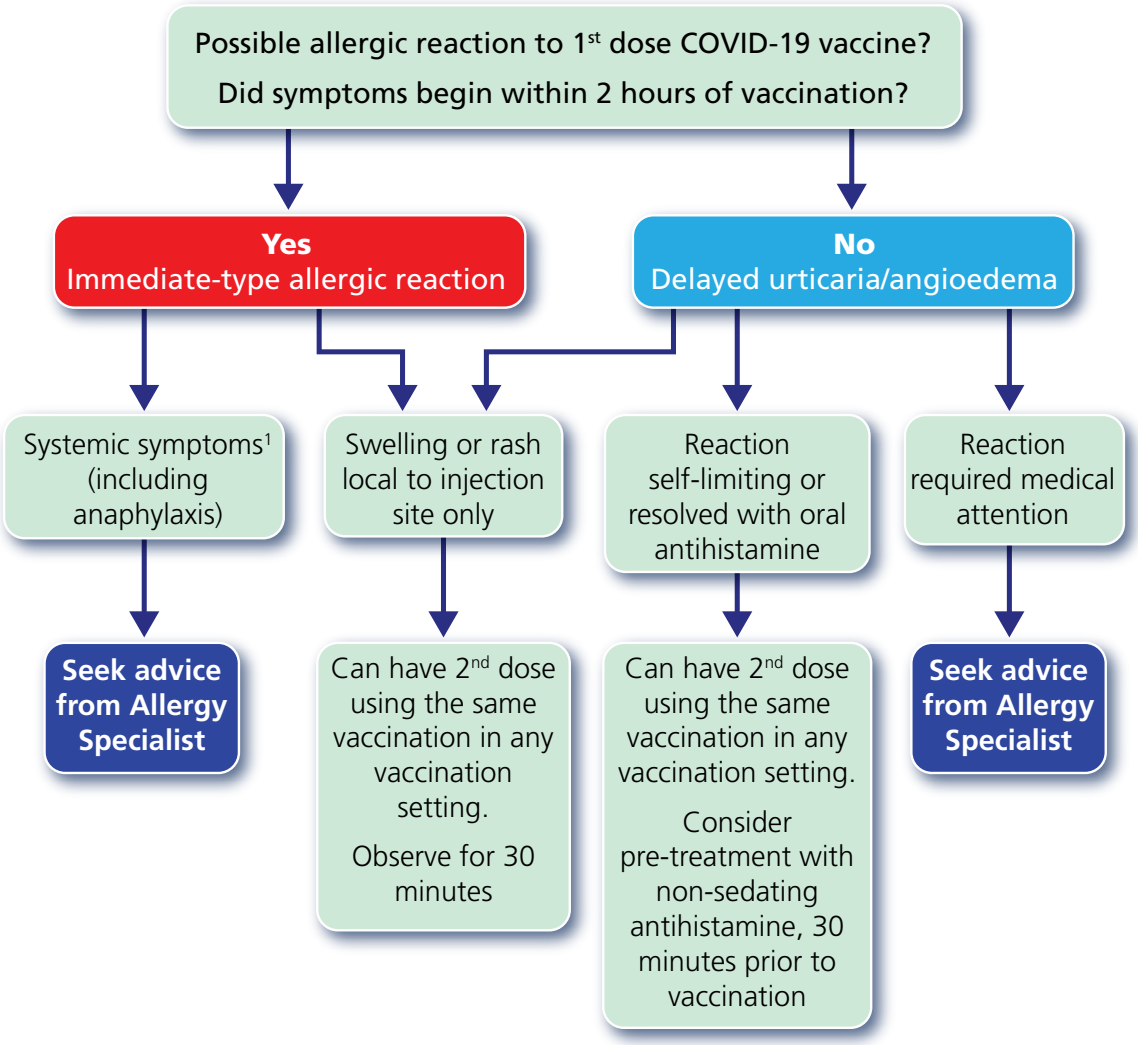
	Proceed with vaccination	Special precautions	Vaccination contra-indicated
PATIENT CHARACTERISTICS	• previous allergic reaction (including anaphylaxis) to a food, insect sting and most medicines (where trigger has been identified) • family history of allergies • previous non-systemic reaction to a vaccine • hypersensitivity to non-steroidal anti-inflammatory drugs e.g. aspirin, ibuprofen • mastocytosis	• history of immediate anaphylaxis to multiple, different drug classes, with the trigger unidentified (this may indicate PEG allergy) • history of anaphylaxis to a vaccine, injected antibody preparation or a medicine likely to contain PEG (e.g. depot steroid injection, laxative) • history of idiopathic anaphylaxis	• prior systemic allergic reaction to the COVID-19 vaccine • for an mRNA-based COVID-19 vaccine, prior allergic reaction to another mRNA vaccine • prior allergic reaction to a component of the vaccine, including PEG
ACTIONS	• proceed with vaccination as normal, according to local guidelines	• discuss with allergy specialist and consider possibility of PEG-allergy • consider observation for 30 minutes if vaccination proceeds (see precautions) • some patients may benefit from pretreatment with antihistamine, however this may mask initial symptoms of a reaction	• do not give vaccine in question • refer to allergist

All recipients of the Pfizer BioNTech and Moderna vaccines should be kept for observation and monitored for a minimum of 15 minutes. Facilities for management of anaphylaxis should be available at all vaccination sites (see chapter 8). Advice has also been issued by the Resuscitation Council.[1]

Patients with undiagnosed PEG allergy often have a history of immediate onset-unexplained anaphylaxis or anaphylaxis to multiple classes of drugs or an unexplained anaphylaxis. Such individuals should not be vaccinated with the Pfizer BioNTech or Moderna vaccines, except on the expert advice of an allergy specialist. The AstraZeneca vaccine can be used as an alternative (unless otherwise contraindicated), particularly if they previously tolerated an injected influenza vaccine. The vaccine should be administered in a setting with full resuscitation facilities (e.g. a hospital), and a 30 minute observation period is recommended.

The British Society for Allergy and Clinical Immunology (BSACI) has advised that individuals who have a reaction to the first dose of a COVID-19 vaccine may be able to receive a second dose of vaccine, as in the flowchart (figure).

Figure: Flowchart for managing patients who have allergic reactions to the first dose of COVID-19 vaccine



1 www.resus.org.uk/about-us/news-and-events/rcuk-publishes-anaphylaxis-guidance-vaccination-settings

Individuals with non-allergic reactions (vasovagal episodes, non-urticarial skin reaction or non-specific symptoms) to the first dose of a COVID-19 vaccine can receive the second dose of vaccine in any vaccination setting.

Thrombosis and thrombocytopenia occurring after COVID-19 vaccination

A recently recognised condition involving serious thromboembolic events accompanied by thrombocytopaenia, has been reported after AstraZeneca vaccination.

There is no evidence of any underlying risk factors in the individuals affected by this condition who have mainly been previously healthy. The condition is rare, tends to present with unusual forms of clotting and the mechanism is believed to be an idiosyncratic reaction related to an immune response to the AstraZeneca vaccine. This may be related to the recipient's polymorphisms in genes encoding Fc receptors in the immune system and is an area of active research. Because of this likely immune mechanism, there is no reason to believe that individuals with a past history of clots or of certain thrombophilic conditions would be at increased risk of this very rare condition. Similarly, although pregnancy increases the risk of clotting conditions, there is no evidence that pregnant women, those in the post-partum or women on the contraceptive pill are at higher risk of the specific condition of thrombosis in combination with thrombocytopaenia after the AstraZeneca vaccine. There have been no confirmed cases reported in pregnant women to date. Caution should be used, however, when vaccinating individuals who have a history of a previous episode of heparin induced thrombocytopenia and thrombosis (HITT or HIT type 2).

Individuals who experience a clotting episode with concomitant thrombocytopaenia following the first dose of AstraZeneca vaccine should be properly assessed. If they are considered to have the reported condition, further vaccination should be deferred until their clotting has completely stabilised, and they should then be considered for a second dose of an alternative product. Based on the analogy of HITT, antibodies to platelet factor 4 may persist for around six months.

Individuals who have received the first dose of AstraZeneca vaccine without developing this rare condition are advised to receive the second dose of the same vaccine at the currently recommended. To date, there is no signal of an increased risk of this condition after the second dose and the rate of other reactions is lower at the second dose than after the first dose of this vaccine. Using an alternative product for the second dose is more likely to lead to common side effects.

Based on current evidence JCVI is advising a preference for an alternative vaccine for healthy people under 40 years of age, including health and social care workers, unpaid carers and household contacts of immunosuppressed individuals.

Individuals with past clotting episodes and those diagnosed with thrombophilia, whether or not they are on long term anti-coagulation, remain at risk of COVID-19 disease. There is no evidence that those with a prior history of thrombosis or known risk factors for thrombosis are more at risk of developing this immune-mediated condition of thrombosis in combination with thrombocytopaenia after the AstraZeneca vaccine. For most of these individuals, the risk of recurrent thrombosis due to COVID-19 infection, remains far greater than the risk of this syndrome. Therefore individuals aged 40 years and over with such a history should be vaccinated with any of the available vaccines (provided they are not otherwise contra-indicated).The same consideration applies to those who experience common clotting episodes after the first dose of AstraZeneca vaccine but without concomitant thrombocytopaenia.

Reporting anaphylaxis and other allergic reactions

Anaphylaxis is a very rare, recognised side effect of most vaccines and suspected cases should be reported via the Coronavirus Yellow Card Scheme (www.coronavirus-yellowcard.mhra.gov.uk). Chapter 8 of the Green Book gives detailed guidance on distinguishing between faints, panic attacks and the signs and symptoms of anaphylaxis. If a case of suspected anaphylaxis meets the clinical features described in Chapter 8, this should be reported via the Yellow Card Scheme as a case of 'anaphylaxis'. Cases of less severe allergic reactions (i.e. not including the clinical features of anaphylaxis) should not be reported as anaphylaxis but as 'allergic reaction'.

As these vaccines are labelled with a black triangle, all adverse reactions occurring in individuals of any age after vaccination should be reported to the MHRA using the Yellow Card Scheme. Anyone can report a suspected adverse reaction to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme (www.yellowcard.gov.uk). Any adverse reaction should also be documented in accordance with local procedures.

Management of suspected cases and contacts

There is currently limited evidence to support the use of COVID-19 vaccines as post-exposure prophylaxis or to interrupt transmission during outbreaks. The use of vaccine to provide direct protection to vulnerable individuals in prolonged community outbreaks should be discussed with the local health protection teams.

Current recommendations for testing and contact tracing and guidance on infection control is regularly updated can be found in the following links:

https://www.gov.uk/coronavirus

https://www.gov.scot/collections/coronavirus-covid-19-guidance/

https://www.hps.scot.nhs.uk/a-to-z-of-topics/covid-19/

https://phw.nhs.wales/topics/latest-information-on-novel-coronavirus-covid-19/

https://www.publichealth.hscni.net/covid-19-coronavirus/guidance-hsc-staff-healthcare-workers-and-care-providers

Supplies

COVID-19 vaccines for those authorised by the NHS to deliver the programme will be made available for ordering on the ImmForm website https://portal.immform.phe.gov.uk/ telephone 0207 183 8580.

Arrangements in Scotland, Wales and Northern Ireland may be different, please contact Public Health Agencies in each respective administration for local details.

Key links

The full specification for those diagnoses, and associated clinical codes, eligible for COVID-19 vaccination has been developed and is available on the PRIMIS website https://www.nottingham.ac.uk/primis/covid-19/covid-19.aspx. Access to the link is available to NHS professionals and requires online registration.

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