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 a 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 M *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).

Current 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*	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 https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/deathsinvolvingcovid9inthecaresectorenglandandwales/deathsoccuringupto12June2020andregisteredupto20June2020provisional. Total deaths in care home residents up to 17 July 2020 were obtained from https://www.ons.gov.uk/peoplepopulationandcommunity/birthdeathsandmarriages/deaths/datasets/numberofdeathsincarehomesnotifiedtothecarequalitycommissionengland. 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 J *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

Evidence to date regarding the risk to pregnant women and neonates following SARS-CoV-2 is conflicting; early studies did not suggest increased intrauterine transmission (Karimi-Zarchi *et al*, 2020) nor any worsening of clinical presentation compared to non-pregnant adults (Elshafeey *et al*, 2020). A more recent systematic review suggested that pregnant women are less likely to manifest standard SARS-CoV-2 symptoms such as fever and cough but may require support in intensive care (Allotey *et al*, 2020). Severe infection in pregnancy was associated with increased maternal age, high-body mass index, pre-existing diabetes and chronic hypertension.

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 RBM and the host cell ACE2 are expected to be protective (Addetia *et al*, 2020, Thompson *et al*, 2020).

In the UK, two vaccines targeting the S protein have been authorised for supply first; one uses an mRNA platform (Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2) and the second an adenovirus vector (AstraZeneca COVID-19 vaccine).

Pfizer BioNTech COVID-19 vaccine is a nucleoside-modified messenger RNA vaccine (mRNA) vaccine. 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. Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 has been generated entirely in vitro and is formulated in lipid nanoparticles which are taken up by the host cells (Vogel *et al*, 2020). The 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).

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, and 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

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 65 and 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 the 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 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 in early December 2020.

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 boost 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 booster 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% (95·8% 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 in late December 2020.

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 5 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.

Presentation

Each pack of the Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 contains 195 vials with a minimum of 5 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.

Dosing and schedule

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 five or six doses of 0.3ml.

The vaccine should be administered in 2 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 2 doses, a minimum of 28 days apart.

Operationally, it is recommended that the second dose of both vaccines should be routinely scheduled between four and 12 weeks after the first dose. This will allow more people to benefit from the protection provided from the first dose during the roll out phase. Longer term protection will then be provided by the second dose.

If an interval longer than the recommended interval is left between doses, the second dose should still be given (preferably using the same vaccine as was given for the first dose if possible). The course does not need to be restarted.

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 administered as an intramuscular injection into the deltoid. 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. 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.

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

Provisional recommendations for the use of the vaccine

The objectives 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) have 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 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 pregnant women and 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 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 also 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. There are two key exceptions to this, pregnant women with heart disease and children under 16 years of age. Advice on vaccination in pregnancy and in children is set out below.

All CEV patients are also expected to also be included in the definitions in table 3. Therefore, any patients who change status with respect to their CEV classification during the roll out of the programme should also be called in their appropriate age cohort, or in priority group 6.

Evidence suggests that risk of serious COVID-19 disease is strongly related to age, and risk of COVID-19 mortality is low in those aged under 40 years, even for individuals with clinical risk factors. The lower age for vaccination of these groups has therefore been aligned with the terms of the approval for the supply of the Pfizer-BioNTech COVID-19 mRNA Vaccine BNT162b2, reflecting the available safety data for this particular vaccine.

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

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 disease (e.g. polio syndrome sufferers). This includes individuals with cerebral palsy, severe or profound learning disabilities, 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	Any diabetes, including diet-controlled diabetes.

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 (any age). 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. Some immunosuppressed patients may have a suboptimal immunological response to the vaccine.
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 ≥40 kg/m².
Severe mental illness	Individuals with schizophrenia or bipolar disorder, or any mental illness that causes severe functional impairment.
Adult carers	Those who are in receipt of a carer's allowance, or those who are the main carer of an elderly or disabled person whose welfare may be at risk if the carer falls ill.
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.

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.

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 provide care to vulnerable individuals. Although there is yet no evidence on whether vaccination leads to a reduction in transmission, a small effect may 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. Guidance on COVID-19 immunisation that may be appropriate 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 drivers, 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. Temporary staff, including those working in the COVID-19 vaccination programme, 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.

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.

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. 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.

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. There is no evidence on the interchangeability of the COVID-19 vaccines although studies are underway. 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. In these circumstances, as both the vaccines are based on the spike protein, it is likely the second dose will help to boost the response to the first dose. For this reason, until additional information becomes available, further doses would not then be required.

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.

Reinforcing immunisation

Booster doses of COVID-19 vaccine are not yet recommended because the need for, and timing of, boosters has not yet been determined.

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.

Because of the absence of data on co-administration with COVID-19 vaccines, it should not be routine to offer appointments to give this vaccine at the same time as other vaccines. Based on current information about the first COVID-19 vaccines being deployed, scheduling should ideally be separated by an interval of at least 7 days to avoid incorrect attribution of potential adverse events.

As both of the early COVID-19 vaccines are considered inactivated (including the non-replicating adenovirus vaccine), where individuals in an eligible cohort present having received another inactivated or live vaccine, COVID-19 vaccination should still be considered. The same applies for other live and inactivated vaccines where COVID-19 vaccination has been received first or where a patient presents requiring two vaccines. In most cases, vaccination should proceed to avoid any further delay in protection and to avoid the risk of the patient not returning for a later appointment. In such circumstances, patients should be informed about the likely timing of potential adverse events relating to each vaccine.

Pregnancy and breastfeeding

There is no known risk associated with giving inactivated, recombinant viral or bacterial vaccines or toxoids during pregnancy or whilst breast-feeding (Kroger A *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, specific clinical trials of COVID-19 vaccine in pregnancy have not been carried out.

Developmental and reproductivity testing of the Pfizer BioNTech 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 the available data do not indicate any harm to pregnancy, there is insufficient evidence to recommend routine use of COVID-19 vaccines during pregnancy. Routine questioning about last menstrual period and/or pregnancy testing is not required before offering the vaccine. If a woman finds out she is pregnant after she has started a course of vaccine, routine advice is to complete her pregnancy before finishing the recommended schedule. Women should be offered vaccine as soon as possible after pregnancy.

JCVI has advised that vaccination in pregnancy should be considered, however, where the risk of exposure to 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. In these circumstances, clinicians should discuss the risks and benefits of vaccination with the woman, who should be told about the absence of safety data for the vaccine in pregnancy.

Termination of pregnancy following inadvertent immunisation should not be recommended. Surveillance of administration in 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.

Breastfeeding

There is no known risk associated with giving non-live vaccines whilst breastfeeding. JCVI advises that breastfeeding women may be offered vaccination with the Pfizer-BioNTech or AstraZeneca COVID-19 vaccines.

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

Children

SARS-CoV-2 vaccine trials have only just begun in children and there are, therefore, very limited data on safety and immunogenicity in this group. 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.

There are currently very limited data on clinical risk factors in childhood, but children with neurological comorbidities are over-represented in those who develop severe COVID-19 requiring intensive care and those who die of COVID-19. Given the increased risk of exposure to infection and outbreaks in institutional settings, vaccination may be considered for children with serious neuro-disabilities (including cerebral palsy, severe autism and Down's syndrome) who spend regular time in specialised residential care settings for children with complex needs. As older children have higher risk of acquiring and becoming sick from infection and there are some safety data on the Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 in children aged 12 years and older, vaccination of older children in these settings should be considered using either vaccine. As this would be outside the terms of the MHRA approval, this would be considered unlicensed use. (https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials)

Recommendations on vaccinating children with other underlying conditions will be reviewed after the initial roll-out phase by which time additional data on use of the vaccines in adults should allow a better assessment of risks and benefits.

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 BioNTech COVID-19 mRNA Vaccine BNT162b2, 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 no evidence on response in immunosuppressed individuals there is also no evidence upon which to base advice on the optimal timing of delivery. 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. As two doses are required to make a full response, a decision to defer any possible benefit from vaccination or to suspend therapy should not be taken without due consideration of the risks from COVID-19 and from their underlying condition. Although the immune correlates of protection are currently unknown, post-vaccination testing may be considered. Until further information becomes available vaccinated patients with immunosuppression should continue to follow advice to reduce the chance of exposure.

Contraindications

There are very few individuals who cannot receive the Pfizer-BioNTech 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[1]
- any component (excipient) of the COVID-19 vaccine

The Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 contains polyethylene glycol (PEG), which is from a group of known allergens commonly found in medicines and also in household goods and cosmetics. Known allergy to PEG is extremely rare but would contraindicate receipt of this vaccine. (Sellaturay P *et al*, 2020). Patients with undiagnosed PEG allergy may have a history of unexplained anaphylaxis or of anaphylaxis to multiple classes of drugs (see precautions). The AstraZeneca vaccine does not contain PEG and is a suitable alternative.

1 Although not yet available yet in the UK, PEG is also an excipient in the Moderna mRNA COVID-19 vaccine; individuals who have a systemic allergic reaction to the Pfizer-BioNTech vaccine should not be given a dose of the Moderna vaccine, and vice versa.

Precautions

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.

A very small number of individuals have experienced anaphylaxis when vaccinated with the Pfizer BioNTech vaccine. Following close surveillance of the initial roll-out, the MHRA has advised that individuals with a history of anaphylaxis to food, an identified drug or vaccine, or an insect sting can receive any COVID-19 vaccine, as long as they are not known to be allergic to any component (excipient) of the vaccine. All recipients of the Pfizer BioNTech COVID-19 vaccine should 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).

The British Society for Allergy and Clinical Immunology (BSACI) has advised that:

- individuals with a history of immediate onset-anaphylaxis to multiple classes of drugs or an unexplained anaphylaxis should not be vaccinated with the Pfizer BioNTech vaccine. The AstraZeneca vaccine can be used as an alternative (if not otherwise contraindicated)
- individuals with a localised urticarial (itchy) skin reaction (without systemic symptoms) to the first dose of a COVID-19 vaccine should receive the second dose of vaccine with prolonged observation (30 minutes) in a setting with full resuscitation facilities (e.g. a hospital)
- 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

Adverse events

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 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).

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 and 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).

Vaccinated individuals should be advised that the COVID-19 vaccine may cause a mild fever which usually resolves within 48 hours. This is a common, expected reaction and isolation is not required unless there are epidemiological or other clinical reasons to suspect SARS-CoV-2 infection.

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

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