Title Page:

Article Title:

An exploration of the Covid-19 Vaccines and the training recommendations for vaccinators

Abstract: 100 words

This article provides an overview of current COVID-19 (C-19) vaccines available within the UK and provides insight into the training recommendations for vaccinators.

Keywords (x5) COVID-19, Vaccines, Mass Vaccination, Safety, Training

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Introduction

As C-19 vaccine development is a fast-paced arena, the reader should continue to refer to national guidelines and publications which are subject to updates, based on latest research findings. The 'Green Book' – chapter 14a contains up to date guidance on C-19 vaccines, the dose and schedule for the UK and recommendations for use of the vaccine (PHE, 2021a).

Background

COVID-19 is an infectious respiratory disease caused by novel coronavirus, severe acute respiratory syndrome 2 (SARS-CoV-2). Transmission is primarily via respiratory (droplet and aerosol) and contact routes. Transmission risk is highest where people are in close proximity of one another (within 2 meters). Airborne transmission may also occur in health and care settings where aerosol generating procedures are performed (PHE, 2020a).

Specific pre-existing comorbidities present an increased risk of severe infection and hospitalization, including dementia, type 2 diabetes, COPD and pneumonia (Atkins *et al* 2020); increasing age and male gender also places individuals at higher risk of morbidity and mortality (Xiaochen *et al* 2020).

Emerging data suggests BAME individuals are at increased risk of infection with increased incidence of morbidity, ITU admission and mortality in comparison to white individuals (Pan *et al* 2020).

In the UK, the likelihood of a front-line health care worker reporting a positive C-19 test is increased in comparison with the general community alongside associated factors of supply of PPE, clinical setting and ethnic background (Nguyen *et al* 2020).

The high number of cases and related morbidity and mortality have laid bare the far-reaching impact of pandemic infection across the globe. As of mid-February 2021, there have been over 100 million confirmed cases globally, including over 2.3 million deaths (representing a global mortality of 2.2%). Europe and the Americas have been particularly affected and within the UK the current incidence of

confirmed cases is almost 4 million with over 115,000 associated deaths, representing UK based mortality of 2.9% (WHO, 2021a).

The far-reaching impact of C-19 has demanded the development of safe and effective prophylactic vaccines, resulting in novel techniques for vaccine development, global collaboration and large cohort clinical trials, at a scale and pace not seen before. These developments will change the face of approaches to vaccination for years to come and will serve to contain the pandemic and limit the associated health, economic and social consequences of the disease.

In the UK, 3 vaccines have been authorised for supply; two use an mRNA platform (Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 and Moderna mRNA-1273 COVID-19 vaccine) and the third uses an adenovirus vector (AstraZeneca COVID-19 vaccine) (PHE, 2021a).

mRNA vaccines

The potential of mRNA vaccines has been acknowledged for some time, with the first invitro success in the 1990's; mRNA vaccines present a number of advantages over subunit, live attenuated, killed and DNA-based vaccines. There is no risk of infection or mutagenesis; mRNA is degraded by normal cellular processes; its half-life and immunogenicity can be regulated, which in turn increases the safety profile. Furthermore, the use of carrier molecules in contrast to the use of a viral vector, means anti-vector immunity is avoided, meaning the vaccine can be administered repeatedly. Importantly, mRNA vaccines have the potential for fast, scalable production and modification (Pardi, 2018), essential in response to new virus variants.

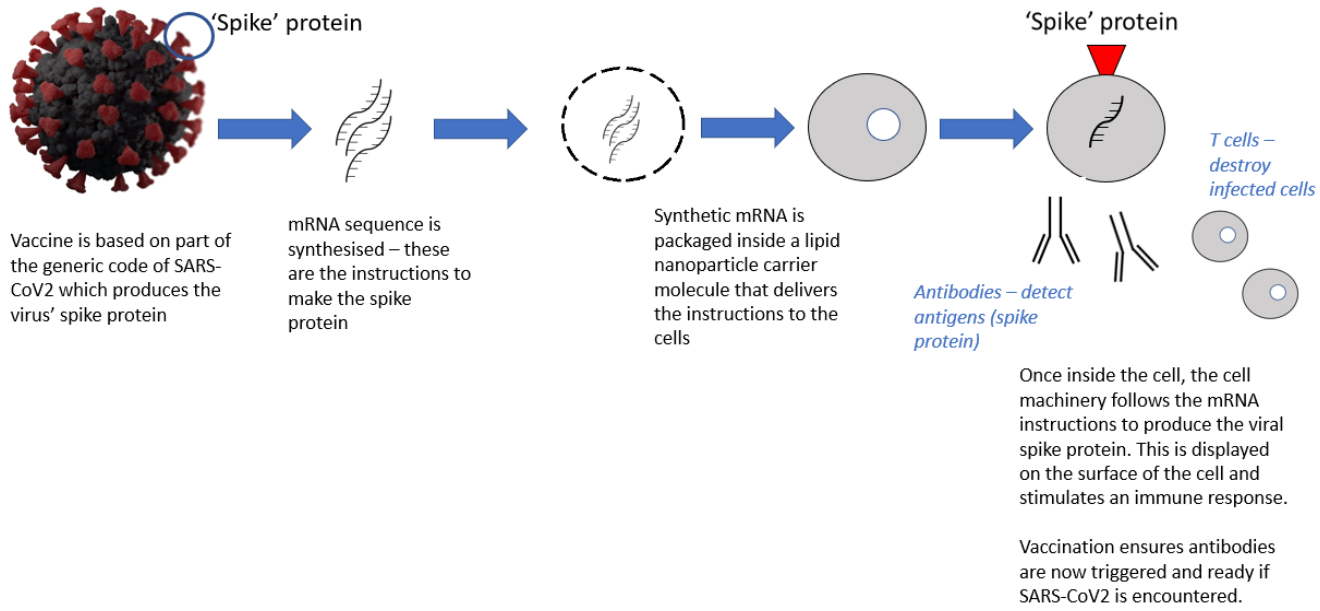
Pfizer BioNTech - BNT162b2 and Moderna mRNA-1273 COVID-19 vaccines

Approved for emergency use in the UK in December 2020 and January 2021 respectively, the Pfizer BNT162b2 and Moderna mRNA-1273 COVID-19 vaccine candidates are lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that encode for a full-length SARS-CoV2 spike protein (Polack *et al*, 2020; Baden *et al* 2021). Essentially, a piece of genetic code, isolated from the

sequenced DNA of the virus, is encased within a fat molecule which instructs the cell to make the spike protein displayed on the surface of COVID-19 cells (antigen), thus initiating an immune response resulting in antibody production and mobilisation of T cells, conferring protection against further exposure to SARs-CoV2.

A summary of the mode of action of mRNA vaccines is provided in figure 1.

Figure 1 – Mode of action of mRNA vaccines



Adenoviral vector vaccines

Adenoviruses are a group of common and diverse DNA viruses which cause non-life-threatening infection in a diverse range of hosts (Singh *et al* 2020). Adenovirus vectors have been developed to be used as gene delivery systems, or 'platforms' for recombinant DNA vaccines; vector-based vaccines can be produced at relatively low cost in a short space of time (Sayedahmed *et al,* 2020). Some studies have highlighted draw backs to the use of this vaccine technology with focus on pre-existing or the development of immunity, meaning a range of viral vector candidates may be

required over time as more individuals are exposed to the adenoviral vector-based vaccine (Singh, 2020).

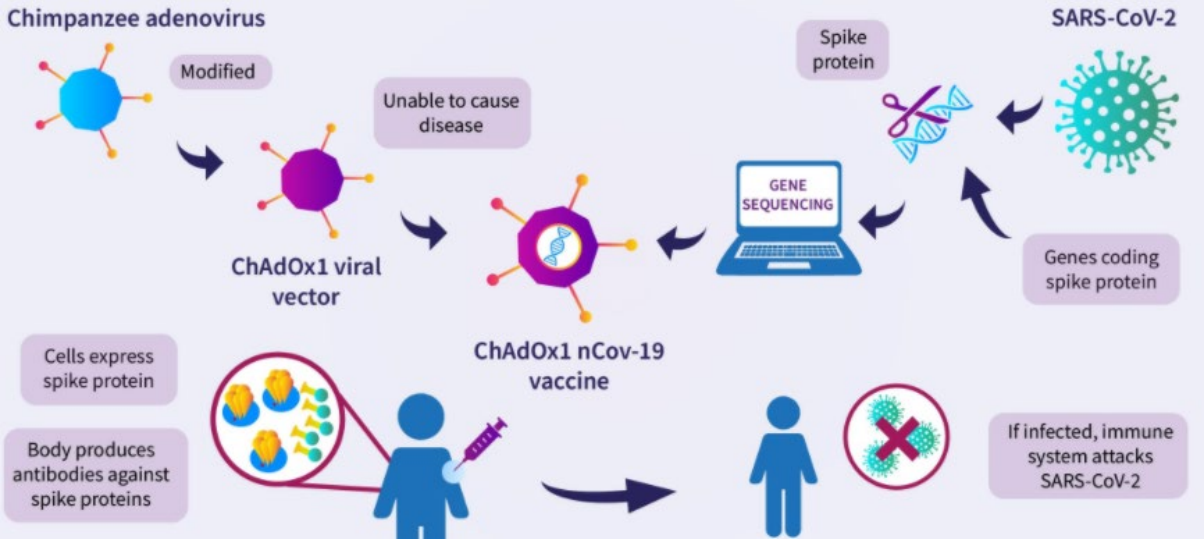
Astra Zeneca – ChAdOx1 nCoV-19 (AZD1222) vaccine

Approved for emergency use in the UK in December 2020, the ChAdOx1 nCoV-19 vaccine (AZD1222) consists of a replication deficient chimpanzee adenovirus vector ChAdOx1, containing SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene (Voysey *et al* 2021).

Put simply, this is a chimpanzee adenovirus vaccine vector – a platform to deliver the modified spike protein genetic sequence, into the target cells. The is a harmless, weakened virus that usually causes the common cold in Chimpanzees. It has been altered to ensure it cannot replicate in humans making it safer for older persons and those with pre-existing conditions. Humans have had minimal exposure to it; therefore this vector has been shown to generate a strong immune response (University of Oxford, 2020).

When the adenovirus vaccine enters the cells of the body, it utilises the cell machinery to produce the surface spike protein, inducing an immune response as shown in figure 2.

Figure 2: Mode of action of ChAdOx1 nCoV-19 vaccine (AZD1222) – courtesy of University of Oxford (2020)



Eligibility for vaccination

The objective of the vaccination programme is to protect those most at risk of serious illness and death (PHE, 2021a). The Joint Committee for Vaccination and Immunisation (JCVI) have set out priority groups for those at risk (table 1 and box 1) linked to COVID-19 specific mortality (JCVI, 2020). Risk due to increasing age, pre-existing conditions and residence in a care home setting inform the priority of vaccination.

Table 1 - priority groups for vaccination advised by the JCVI

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 2)
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

Box 1: Clinical risk groups 16 years of age and over who should receive C-19 immunisation

- Chronic respiratory disease
- Chronic heart disease and vascular disease
- Chronic kidney disease
- Chronic liver disease
- Chronic neurological disease
- Diabetes mellitus - any type
- Immunosuppression
- Asplenia or dysfunction of the spleen
- Morbid obesity - Body Mass Index ≥40 kg/m^2.
- Severe mental illness
- Adult carers
- Younger adults in long-stay nursing and residential care settings

Alongside those at clinical risk, the occupational immunisation programme seeks to protect health and social care staff at high risk of exposure who provide care to vulnerable individuals. The following occupational groups are prioritised:

- Staff involved in direct patient care – this includes student nurses
- Non- clinical staff in secondary or primary care /community healthcare settings
- Laboratory and pathology staff
- Frontline social care workers (PHE, 2021a)

Safety and Efficacy

It is key that COVID-19 vaccines are safely and effectively delivered to as many of those eligible as possible. This will require knowledgeable, confident and competent vaccinators who have undertaken the appropriate training and that they are supported and supervised in practice. To date there are a minority of individuals who cannot receive the Pfizer BioNTech, Moderna or AstraZeneca COVID-19 vaccines. Vaccinators as part of the consent process, will identify any patients who may be at risk and appropriate advice sought. 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 or any component (excipient) of the COVID-19 vaccine e.g., polyethylene glycol (Polack *et al*, 2020a). 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 allergy) can now have the vaccine.

Contraindications, pregnancy, and breastfeeding

Pregnant women are at higher risk of severe C-19 disease with an associated risk of pre-term birth. Clinical trial data is insufficient currently to assess safety and efficacy of C-19 vaccinations in pregnant women, or indeed to recommend routine use in pregnancy (PHE, 2021b), however, clinical trials are ongoing. Pregnant women should receive vaccination if the benefit outweighs the risk, for example, for those women with comorbidities or health care workers (JCVI, 2020; RCOG, 2020). If pregnancy is apparent after vaccination, she should complete the pregnancy before finishing the recommended vaccine schedule. Routine pregnancy testing or delaying pregnancy prior to vaccination is not recommended (JCVI 2020, WHO, 2021b).

Within the UK, the UK vaccine in pregnancy surveillance programme seeks to compile additional information about women who are immunised with specified vaccines whilst pregnant to monitor the outcome of such exposures. This data being utilised to gain further information to guide practice and provide information. All COVID-19 vaccines given from the first day of last menstrual period to any time in pregnancy should be reported to the UK vaccine in pregnancy surveillance programme (PHE, 2021b).

As both Pfizer, Moderna and Astra Zeneca vaccines are non-live, JCVI (2020) advise that breastfeeding women may be offered vaccination with either of the approved vaccines within the

Vaccines are administered by a range of healthcare professionals and other non-registered staff and volunteers. To facilitate this the UK government introduced changes to The Human Medicines Regulations 2012 to allow an unlicensed medicine to be administered via a Patient Group Direction (UK Statutory Instrument 1125, 2020). In cases where vaccines are administered by non-healthcare professionals there is a separation between the task of vaccination and the clinical assessment and decision making. With the registered healthcare professionals being responsible for the later and the non-registered volunteer carrying out the physical task of administering the vaccine. Irrespective of whether the vaccinator is a volunteer or a health professional either the NHS Resolution indemnity

or General Practice / Community Pharmacy third party liability insurance (NHS England, DHSC and NHS Resolution, 2020) has provided indemnity to all individuals involved in helping deliver the vaccination programme including volunteers.

Training is dependent on the individual employer and the current experience of the practitioner, but as a minimum staff are required to have specific training in the storage, dilution (where appropriate) and administration of each individual vaccine together with anaphylaxis training. Other statutory and mandatory training around information governance, basic life support and safeguarding may also be required (Public Health England, 2020a). Health Education England (2021) have developed a detailed e-learning package which supports staff with the theory side of training. In addition, individual competence assessment tools have been developed to allow for clinical assessment of vaccinators (Public Health England, 2020b).

Storage, transit and handling of vaccines.

At the time of writing the Medicines and Healthcare Regulatory Authority (MHRA) have approved three Covid-19 vaccines for use. All three vaccines require two doses. Each vaccine has its own storage and administration requirements. As vaccines are biological products, they are temperature sensitive and must be stored and transported within the recommended temperature range (NHS England Midlands and East, 2015).

Pfizer BioNTech Vaccine

The Pfizer BioNTech vaccine is stored at a temperature of minus 70 degrees centigrade and the vaccine must be thawed for before administration. There are two permitted ways of thawing the vaccine either by allowing vial(s) to thaw in the refrigerator (2°C to 8°C) or by thawing at room temperature (up to 25 degrees centigrade) for 2 hours. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours). Once thawed

the vaccine must be used within 5 days (120 hours) and it must be stored in a medical refrigerator at a temperature of between 2 and 8 degrees. Once removed from the refrigerator and diluted the vaccine must be used within 6 hours (MHRA, 2020a). Care must be taken with the distribution of vaccines to clinics and other locations to maintain the vaccine cold chain. The vaccine once thawed must be stored in a medical grade refrigerator or if transported (prior to dilution) it should be in a medical grade cool bag with minimum and maximum temperature monitoring. Prior to administration the Pfizer BioNTech vaccine must be diluted with 1.8 ml of Sterile unpreserved Sodium Chloride 9 mg/ml (0.9%) for injection prior to administration – the procedure for the dilution of the Pfizer BioNTech vaccine is shown in Box 1.

[place Box 1 near here]

Once diluted the vial contains 5 or 6 doses, depending on syringe type used, with each dose being 0.3 ml. To maximise vaccine from each vial low dead volume syringes should be used.

AstraZeneca Vaccine

The AstraZeneca vaccine is stored in a medical refrigerator at between 2 and 25 degree centigrade. The vaccine comes in two presentations; either a 5 ml (10 dose) multi-dose vial or a 4 ml (8 dose vial) – where low dead volume syringes are used it is possible to obtain an additional dose from each vial. The dose per patient is 0.5 ml. The vaccine does not require dilution and the vial should be visually inspected (the vaccine is a colourless to slightly brown, clear to slightly opaque solution). Care should be taken not to shake the vial (MHRA, 2020b).

The ease of storage of the AstraZeneca vaccine makes it ideal for community administration. Care must be taken to maintain the vaccine cold chain including transfer of the vaccine to clinic locations and to care homes and patient's homes. Vaccines that are to be used during home visits or community vaccination sessions where there are no refrigeration facilities must be transported and stored in a medical grade cool box or bag and the box or bag should then be packed following the

manufacturer's instructions and avoiding overfilling. All vaccines should be kept in their original packaging until use and the minimum and maximum temperatures should be recorded whilst vaccines are stored in the cool box or bag.

Once removed from the refrigerator the vial, which contains either 10 or 11 doses or 8 or 9 doses depending on size, must be used within 6 hours. Once the vial bung is punctured the date and time should be noted on the label to ensure it is used within the time limit.

Moderna Vaccine

The Moderna vaccine is stored frozen between minus 25 degrees centigrade to minus 15 degrees and must be thawed prior to administration. The vaccine can be thawed in a medical refrigerator for 2.5 hours and then stored between 2 and 8 degrees centigrade for up to 30 days. The vaccine should be protected from the light and retained in its original packaging throughout. One removed from the refrigerator it can be stored between 8 and 25 degrees centigrade for up to 12 hours. Prior to use every vial must be brought to room temperature for 15 minutes. Each vial contains 10 doses of vaccine with 0.5 ml being administered to each patient. The vaccine requires no dilution, and the vial should be inspected prior to use (the normal appearance being is a white to off-white dispersion. It may contain white or translucent product-related particulates). Once punctured the vial should be discarded if not used within 6 hours. The date and time should be noted on each vial after the first dose is drawn.

Patient Assessment and Consent

Prior to vaccine administration the patient should be assessed to identify any contra-indications or cautions in relation to the vaccine. This includes identifying if the patient has had a previous allergic reaction or anaphylaxis, whether they are on anti-coagulants, whether they are pregnant or breastfeeding, whether they have had a previous vaccination and whether they are febrile or have symptoms of Covid-19.

If the patient is on anti-coagulants, they need to be advised of the risk of haematoma and the vaccinator should take care to apply pressure after vaccination. Previous allergic reactions including anaphylaxis may result in a different vaccine being selected or the administration being delayed.

Before giving a COVID-19 vaccine, vaccinators must ensure that they have obtained informed consent from the patient or that a best interest decision has been made if the patient does not have mental capacity at the time of vaccination. To be able to consent to vaccination, the vaccinee should receive an explanation of the treatment and its benefits and risks, ideally verbally from a clinician (Department of Health, Scottish Executive, Welsh Assembly and Department of Health Social Services and Public Safety, 2006). There is no need to obtain written consent if consent is valid following appropriate disclosure, an opportunity to ask questions and the patient verbally agrees to proceed.

Vaccine Administration

All three vaccines are administered via the same intra-muscular route. The vaccine should be drawn using a low dead volume syringe (different syringes should be used for different vaccine doses e.g., 1ml syringe for the Pfizer vaccine to allow 0.3 ml to be accurately drawn. Aseptic technique should be observed for vaccination. Once the correct dose is drawn it is administered by injection into the deltoid muscle in the upper arm or, if there is insufficient muscle mass in the area of the deltoid or a particular reason the deltoid muscle is otherwise unsuitable, into the vastus lateralis muscle in the anterolateral aspect of the thigh. Skin cleaning prior to administration is not required and adhesive plasters are not usually required post administration.

Following administration, the patient should be given advice about common side effects e.g., sore arm, feeling unwell for a day and regarding the need for a second dose which should be administered within 12 weeks (Department of Health and Social Care, 2020). If the second dose is

delayed longer than 12 weeks the second dose should still be given and there is no need to restart the vaccination programme (Department of Health and Social Care, 2021). Patients should be advised to continue to take precautions around social distancing, hand washing, face coverings etc. A vaccination card is usually provided together with a patient information leaflet. Details of clinical assessment, consent, and the vaccine (vaccine name, batch number, expiry date, administration site, name of vaccinator) is also recorded in the clinical system. The MHRA have instigated enhanced monitoring for the approved vaccines and adverse events should be reported via the Yellow Card scheme.

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Box 01: Procedure for the dilution of the Pfizer BioNTech Vaccine

Step 1 The vials of the Covid-19 Pfizer BioNTech vaccine must be brought up to room temperature before dilution and dilution must occur within 2 hours. Clean hands- and put-on gloves.

Step 2 Before dilution invert vaccine vial gently 10 times. Taking care not to shake the vial. Inspect the liquid in the vial (the liquid should be a white to off-white suspension and may contain white to off-white opaque amorphous particles). Do not use if liquid is discoloured or if other particles are observed.

Step 3 Obtain sterile 0.9% Sodium Chloride Injection, USP which is supplied with the vaccine. Use only this as the diluent. Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). Cleanse the vaccine vial stopper with a single-use antiseptic swab and allow to dry. Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

Step 4 Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL of air into the empty diluent syringe.

Step 5 Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix it taking care not to shake the vial. The inspect the vaccine in the vial (the vaccine should be an off-white suspension). Do not use if vaccine is discoloured or contains particulate matter.

Step 6 Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. During use store between 2°C to 25°C. Discard any unused vaccine 6 hours after dilution.

Note following dilution the vaccine should not be transported.