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Invited Article

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COVID-19 Vaccines and Dentistry

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ABSTRACT

Transplant pioneer, Peter Medawar, once said that a virus is 'simply a piece of bad news wrapped in protein'. One could opine then, that the new COVID-19 vaccines are 'Bits of corona viral proteins in gift wrapping.' For, most of the COVID-19 vaccines are based on the principle that pre-exposure of the vaccinee's host immune system to the spike proteins of SARS-CoV-2, the first part of the viral anatomy that touches the vulnerable host cells, will elicit an effective antibody response to curb potential future infections. COVID-19 vaccines come in many sizes and shapes, and clearly, a return to normal, post-COVID dental practice entails protecting all members of the dental team with an appropriate vaccine, as and when available. We provide a thumbnail sketch of the COVID-19 vaccines currently in the offing, which we hope will be helpful for decision-making for choice of vaccine. The commentary ends with a discussion of the impact of COVID-19 vaccines on dentistry, in general.

1 INTRODUCTION

The genetic sequence of severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) was published approximately a year ago in January 2020, triggering an intense global competition to develop a vaccine against the lethal infection it causes, the coronavirus disease 2019 (COVID-19). Vaccine developers the world over are currently using next-generation vaccine platforms and novel paradigms to accelerate their production. Some of these, such as the mRNA vaccines, have been highly successful, reaching the arms of millions of recipients, at the time of writing. Indeed, the first COVID-19 vaccine, which entered the first human, clinical (Phase I) trials in March 2020, was approved in the US for emergency use in December 2020. This unprecedented rapidity of conducting vaccine trials, and approval by authorities, is a singular tribute to new technology as well as human ingenuity in the face of adversity.

Astonishingly, there are 233 vaccine candidates (61 in clinical appraisal and 172 in preclinical development phase) in development for COVID-19, a number of which, are already approved for emergency use in various jurisdictions.[(1)] A number of other vaccines in the pipeline should see the light of day in 2021 once they complete their, final (Phase II/III) human trials, and their proven safety and efficacy approved by the regulatory authorities. The account below is a sketch of the ideal properties essential for a vaccine, and the major COVID-19 vaccine platforms (highly simplified) used for their production.

In brief, the aim of a vaccine is to stimulate the body's

own protective immune responses so that, if an individual encounters the specific viral pathogen, then the immune system can quickly recognize the foe, jump into action, and prevent the spread of infection and terminate the disease process.[2] In the case of vaccines against SARS-CoV-2,the basic premise, in essence, is to produce antibodies against the spike protein or the proteins on the receptor binding domain (RBD) on the viral surface.[3] It is well recognized that the numerous spikes on the virus surface initiate its attachment to susceptible human cells, allowing viral entry to the cell and causing infection. Hence, blocking this all-important critical step with the help of either the naturally produced (infection) or the artificially produced (vaccine) antibody prevents the infection.

2 IDEAL PROPERTIES OF A SUCCESSFUL VACCINE

In general, there are a number of critical parameters to be fulfilled by an ideal vaccine.[4,5] Hence a vaccine targeting SARS- CoV-2 should fit the following profile of an ideal vaccine:

- Be safe, with only mild, transient side effects, if any (the usual transient effects of traditional vaccines include soreness of the vaccine focus, mild low- grade fever for up to 2 days, tiredness);
- Efficacious protection of the vaccinee against the specific disease (a vaccine efficacy of 70% or above is deemed highly satisfactory, and 90% excellent);
- Prevent transmission of infection to others, as a 'silent carrier', while immune due to the vaccination procedure;
- Easy to administer, even by novices, through a simple training procedure;
- Confer protection for a relatively long period (at least 1 year) in the healthy as well as in vulnerable populations (eg those with comorbidities and older adults);
- Ability to be administered as a single dose;
- Amenable to simple and safe large- scale production;
- Easy to store at room temperature, or moderate low temperatures such as in ordinary domestic (4°C) refrigerators (eg not at ultra-low temperatures, such as -70°C);
- Easy transportation and shipping (eg outside the cold-chain, or even by mail at ambient temperatures).

Clearly, none of the vaccines available today, for any disease, possesses all of the above characteristics, nor is 100% efficacious. In reality, the goal of vaccine manufacturers is to produce a vaccine that has most of these attributes. This said, the top two attributes of a good vaccine are its safety and efficacy. Hence, a successful COVID-19 vaccine should be safe, with long-lasting immunity developing shortly after vaccination, and protect the overwhelming majority, if not all, of vaccinees against moderate to severe disease, particularly those in the most vulnerable groups.

The next section, outlines the principles, advantages and disadvantages of five major vaccine platforms. Some of these vaccines have already undergone appropriate clinical trials and received approval, while others are in the pipeline and are currently undergoing Phase I/II/III trials.

3 MAJOR COVID-19 VACCINE PLATFORMS AND THEIR ADVANTAGES AND DISADVANTAGES (TABLE 1)

3.1 mRNA vaccines (Table 1, Figure 1)

- **Examples:** Moderna, Pfizer BioNTec, CureVac and Imperial College London.
- **Principle:** This is one of the newest, yet simplest and most elegant

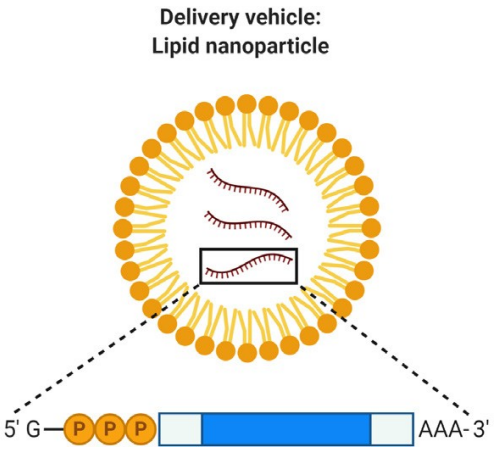

Fig. 1: mRNA vaccine platform. Example of a lipid nanoparticle encapsulated mRNA vaccine. The mRNA hasthe code for either the spike proteinor the receptor-binding domain (RBD) proteins. Once injected, the lipiddroplets are 'ingested' by a vaccinee's cells. The protein- making machinery in these cellsis now instructed to produce viralproteins (i.e. S or RBD antigens),that are displyedon the cell surface. The immunesystem produces antibodies to these, andis then primed to attack the invadingvirus, as antibodies can be produced to inactivate the invader. (Figure produced using biorender.com)

methods available to insert specific viral genes, such as the spike protein gene of SARS-CoV-2 to human cells. The technology is based on mRNA ingestion by immune cells, but it is not integrated into the nucleus, which tricks the body into producing viral S proteins that induce an immune response without a natural infection. As the method does not entail the use of either live or attenuated viral vectors, they are simpler to develop and manufacture. Hence, the reason they won SARS-CoV-2 vaccine race. Nevertheless, no mRNA vaccine has previously been approved for human viral infections, and prior experience with this technology

has been in cancer therapeutics.

- **Advantages:** Rapid design and production that does not entail handling of highly infectious material; strong and quick humoral and cell- mediated antiviral responses (over 90%); no potential for insertional mutagenesis; large scale production is feasible and relatively easy.
- **Disadvantages:** Most formulations require ultra-cold chain requirements (-70°C) for longevity and stability; require careful design with substituted nucleosides and skilled formulation of lipid nanoparticle carriers for effective delivery; boosting may be necessary to achieve robust and lasting immunity, as duration of protection will not be known for some time.

3.2 DNA vaccines (Table 1, Figure 2)

- **Examples:** INO-4800 Company, Inovio USA, BacTRL-Spike (a trivalent version) Company , Symvivo, Canada.
- **Principle:** DNA vaccine involves the direct introduction into appropriate tissues of a plasmid – a double- stranded DNA molecule that exists inside bacterial cells (also called 'jumping genes' as they are readily transmissible from one cell to another). A DNA plasmid found in *Bifidobacterium longum* expressing trimeric spike protein is delivered to colonic epithelial cells to prime an immune response via colonic lymphoid tissues. The advantage of this technique is that the plasmid-containing vector bacterium could be ingested as a probiotic. Nevertheless, DNA vaccines are not currently on the market for use in humans, and this particular strategy is untested.
- **Advantages:** Containment facilities for live virus handling are not required; easily administered through the oral route even as a probiotic (Symvivo); can be used in immunocompromised subjects; both humoral and cell-mediated immune response activated; easy boosting through repeat administration; rapid and scalable manufacturing; long-term stability possible, even at room temperature.
- **Disadvantages:** No DNA vaccines have been approved for infectious diseases, only veterinary applications thus far; variable mucosal immunity and other immune responses; early experimental trials are promising.

3.3 Viral vector vaccines (Table 1, Figure 3)

- **Examples:** AstraZeneca with the University of Oxford, Johnson & Johnson, CanSino Biologics, and the Gamaleya Research Institute, USSR Ministry of Health.
- **Principle:** These vaccines use another non-replicating vector virus (eg Vaccinia, adenoviruses and retroviruses) to deliver SARS- CoV-2 genes, in the form of DNA, into human cells where viral proteins are produced to induce a protective immune response. It is noteworthy, that the viral DNA is not integrated into the host genome, as falsely rumoured, but is copied into messenger RNA of the host cells, and directly translated into proteins. Of over 50 common adenoviruses that can cause cold-like symptoms, the weakened form of adenovirus 5 and 26 are used to produce the SARS-CoV-2 vaccine.
- **Advantages:** Years of proven experience in the gene therapy field; strong antibody and cellular responses; weakened vector vaccines are safe as they do not replicate (due to gene deletion); slim, if any, risk of chromosomal integration and resultant oncogenicity.
- **Disadvantages:** Cannot be used in immunocompromised subjects, as most have been exposed to multiple adenoviruses and hence have pre-existing immunity to the virus that may impede vector entry into host cells; to obviate this problem animal adenovirus vectors are used (eg AstraZeneca/Oxford University vaccine uses a chimpanzee adenovirus as a vector).

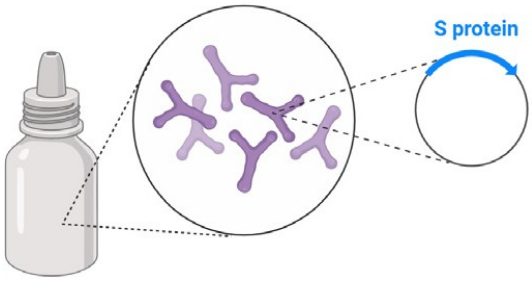

Fig. 2: DNA vaccineplatform. A synthetic plasmid (a 'jumping gene') encoding SARS-CoV-2spike protein is introduced to a bacterium, such as *Bifidobacterium longum* (usedas a probiotic). The innocuous bacterium can then be ingestedand the spike protein is integrated into gut lymphoid tissue, which producesantibodies. (Figure produced using biorender.com)

3.4 Protein-based/subunit vaccines (Table 1)

- **Examples:** Novavax, Sanofi and GlaxoSmithKline, SpyBiotech.
- **Principle:** Much like inactivated vaccines, protein-based, or subunit vaccines work by exposing the immune system to viral proteins to induce a protective immune response. For COVID-19 vaccine production, either the spike protein, or a portion of the spike protein, the receptor-binding domain, which is the first point of contact between the virus and the host cell surface, are used. Protein-based vaccines are already in wide use and have a long history of safety and efficacy (eg herpes zoster, pertussis and hepatitis B vaccines).

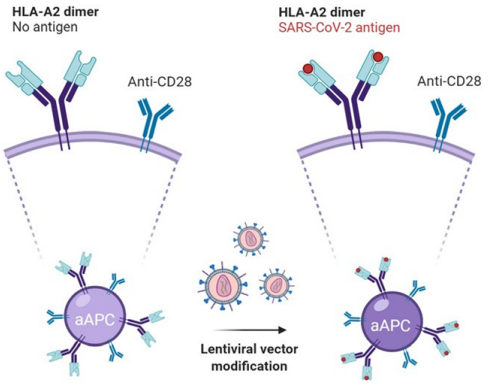

Fig. 3: Viral vector vaccineplatform. Artificial antigen presenting cells (aAAPC) transformed with a viral vector(in the case of AstraZeneca vaccine, chimpanzee adenovirus) to present the SARS-CoV-2 antigento a vaccinee's immune system to provoke an artificial antibodyresponse against spikeantigens. (Figure produced using biorender.com)

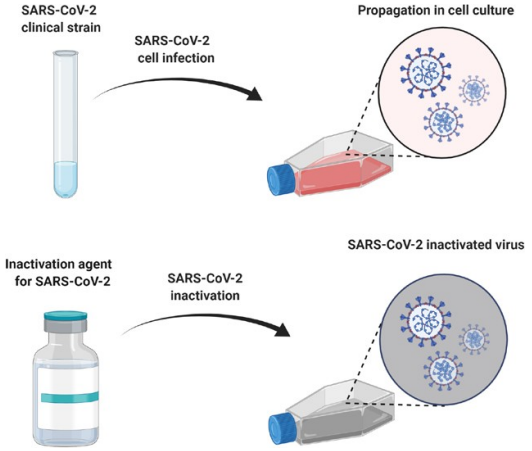

Fig. 4: Inactivated virusvaccine platform. First, theSARS-CoV-2 isolated from a clinical sample is propagated in laboratory tissueculture (upper panel),then live virusgrowth in cellsis inactivated by a suitable agent(lower panel).
The resultant SARS-CoV-2, which is the active ingredient of the inactivated virus vaccine, is non- vital, yet retains immunogenicity as the surface spike proteins are intact.(Figure produced using biorender.com)

- There are various ways of producing the (recombinant) viral proteins for the vaccine and these include their production in yeast or insect cell vectors. As protein-based vaccines may not induce strong CD8 T cell responses (the cells that destroy virus- infected cells) on occasions, chemical adjuvants are used to rectify this issue. Such adjuvants have been used in vaccines for decades, to stimulate a strong and robust immune response. The proteins have to be transported into the body by a carrier, and these include nanoparticles of cholesterol, phospholipid and saponins (from the soap bark tree).
- **Advantages:** Containment facilities for live virus handling not required; produces a strong antibody response; a proven, tested method; good precedents such as the current hepatitis B vaccines; can be administered even to individuals with weakened immune systems or comorbidities; induces strong and durable protection in older adults whose immune systems may be less responsive.
- **Disadvantages:** Vaccines with adjuvants can cause more injection- site reactions, such as redness, swelling and pain, and more systemic reactions such as fever, chills and body aches, than non- adjuvanted vaccines.

3.5 Inactivated or attenuated virus vaccines (Table 1, Figure 4)

- **Examples:** Sinovac Biotech, Sinopharm, Wuhan Institute of Biological Products, and Bharat Biotech.
- **Principle:** This is a well-established and time-tested method for vaccine production, and many inactivated viral vaccines ranging from influenza to hepatitis A are currently in use globally . The virus is inactivated by chemical means so that it is no longer infectious or able to replicate in human cells. Nevertheless, the viral antigens are intact and evoke a robust antibody response by the host antibody- producing B lymphocytes. When the vaccine is exposed to the natural virus, antibodies are called to action to fight the virus.
- **Advantages:** Proven technology with a robust and lasting immune response; simple formulation; does not require adjuvants.
- **Disadvantages:** Requires dedicated, high biosafety containment facilities for production of SARS-CoV-2 in cell cultures; virus inactivation has to be complete (with no residual infectious particles) yet adequate to maintain all the necessary viral antigens for provoking a successful antibody response; hence, scaling up the manufacturing process is difficult and complex; they may not induce the same degree of immunity as a live vaccine; frequent booster shots may be necessary to maintain immunity.

4 THE LOOMING IMPACT OF COVID-19 VACCINES ON DENTISTRY

The dental team is exposed to an incessant array of emerging and re-emerging microbial threats throughout a lifetime of clinical practice. SARS-CoV-2 is the latest addition to this list, and it is likely that this pervasive disease will be entrenched in the global community for many a decade, probably in many guises. Indeed, barely a year has passed since the first signs of infection, and we are already

Table 1: Manufacturing platforms, immunization attributes and examples of different COVID-19 vaccine categories (either currently available or in developmental pipeline).

Reference type	Vaccine platform	Mode of action	Examples of SARS-CoV-2 vaccine (currently available, and developmental)	Immunization attributes*	Currently available for these infections (not an exhaustive list)	Viral vaccines currently prescribed for dental healthcare workers
1	mRNA vaccines (Figure 1)	Delivers one or more of SARS-CoV-2 RNA genes into cells to provoke an immune response	Moderna, Pfizer/ BioNTec, CureVac, Imperial	Expresses spike protein	COVID-19 (Moderna and Pfizer/BionTech approved in USA; Pfizer/ BionTech in UK)	–
2	DNA vaccine (Figure 2)	Delivers SARS-CoV-2 DNA genes into cells, with the help of a plasmid (a 'jumping gene' found in bacteria) to provoke an immune response	INO-4800 Company, Inovioa USA BacTRL-Spike (a trivalent version) Company, Symvivo, Canada	Expresses spike protein	Veterinary infections	–
3	Viral vector (replicating/ non-replicating) (Figure 3)	Viruses engineered to carry coronavirus genes (Trojan horse principle), but non-replicating, enters receptive cells and instructs them to make viral proteins or slowly replicate, carrying coronavirus proteins on their surface. Vector examples: chimpanzee adenovirus, Vaccinia	AstraZeneca with the University of Oxford, Johnson & Johnson, CanSino Biologics, Gamaleya Research Institute, part of Russia's Ministry of Health	Expresses spike protein	COVID-19 (AstraZeneca approved in UK in December 2020; Ebola infections	–
4	Protein based/ subunit	Vaccines that contain SARS-CoV-2 proteins only, either whole protein, or fragmented, subunits. Some pack many of these molecules into nanoparticles	Novavax, Sanofi and GlaxoSmithKline, SpyBiotech	Recombinant spike or receptor- binding domain proteins	Hepatitis B, acellular whooping cough (Pertussis)	Hepatitis B
5	Inactivated or attenuated virus (Figure 4)	Vaccines created from weakened SARS-CoV-2 or those attenuated with chemicals	Sinovac Biotech, Sinopharm, the Wuhan Institute of Biological Products, Bharat Biotech, India	Expresses multiple viral antigens	Measles, mumps, and rubella (MMR), Varicella (chickenpox), whooping cough (pertussis), hepatitis A, polio (Sabine variant)	MMR, Varicella, influenza

The last columnshows the categorization of viral vaccinescurrently prescribed for dental healthcare workers. *All vaccines essentially need two repeateddoses to achieveoptimal seroconversion and are injectedintramuscularly (usually the arm). Note:other major platforms based on virus-like particles, and repurposed vaccines(e.g. BCG vaccine) are not shown.

witnessing a more infectious variant of SARS-CoV-2 (variant VUI 202012/01) in the UK and elsewhere.

The bulwark against such viral threats is the stringent, standard infection control measures routinely enforced in dentistry, and incorporated therein is the vaccination routine for the team members. In addition, it is obligatory that the principal employer considers measures to reduce risks to employees from all workplace biological hazards, including infections, as per the Control of Substances Hazardous to Health Regulations (COSHH) regulations in the UK.[6] Further, the UK Department of Health stipulates that all healthcare workers in general practice, including dental practice staff, be immunized against a range of preventable, occupationally acquired infections including hepatitis B, influenza, varicella and rubella.[7] Clearly, it is a matter of time until COVID-19 is incorporated into this extensive list (Table 1).

In these circumstances, the principal employer in a dental practice setting will have to face COVID-19 infection as a lasting threat, and be prepared to overcome the various logistical issues arising from such a new provision that will benefit all stakeholders. These include dentists, paradental personnel, such as dental assistants and hygienists, dental technicians and administrative staff working in the premises, and above all, the patients attending the clinic.

So, what are the provisional, logistical issues that may be entailed in a newly mandated provision of COVID-19 vaccination for all healthcare workers? Although not an exhaustive list, these provisions are likely to include the following:

- In consultation with a local medical care provider, an offer of an appropriate, current COVID-19 vaccine for all staff members of the dental practice, and provision of information on the offered vaccine type, side effects and other relevant details.
- Once a staff member consents to have the vaccine, the immune status of the staff member should be established by checking antibody levels prior to vaccination, and immunizing those with uncertain immune status. This should be performed even if the staff member has contracted the infection previously, as antibody levels may have waned or be suboptimal.
- Once a usual two-dose vaccine has been given, sero conversion status should be established by measuring the antibody titre approximately 1 month after the second dose.
- Depending on the vaccine type administered, a minority (10–20%) may not seroconvert (Table 2). The usual practice in such situations is to offer a third dose (eg as in the case of hepatitis B vaccine recipients who do not seroconvert).[8]

- If the vaccine recipient does not seroconvert even after a third dose, then it may be obligatory for the

Table 2: Vaccines currentlyapproved in the UK and USA and their major attributes

Property	Pfizer–BioNTech	Moderna	AstraZeneca–Oxford
Type	mRNA-based	mRNA-based	Adenovirus vector
Country of approval	Both UK and USA	USA	UK
Efficacy (in Phase III clinical trials)	95.0%	94.1%	70.0%
Administration	Deltoid muscle (upper arm) Two doses, 3 weeks apart	Deltoid muscle (upper arm) Two doses, 4 weeks apart	Deltoid muscle (upper arm) Two doses, 1 month apart
Reported minor side effects	Fatigue, headache and chills (worse after second dose)	Fever, muscle ache, headaches lasting a few days (worse after second dose)	Not known, as yet
Reported significant side effects	Six cases of anaphylaxis; four cases of Bell's palsy (similar to general population)	Four cases of Bell's palsy (similar to general population)	Not known, as yet
Contra indications	Those with serious allergies	Not yet known	Not yet known
Shelf life	>Dry-ice: (-70° C); up to 30 days > Ultra-cold freezer: (-70° C); up to 6 months	> Standard freezer: (-20° C); up to 6 months	> Standard (home) refrigerator; up to 6 months
Predicted production capacity	Up to 50 million vaccine doses by the end of 2020, and up to 1.3 billion doses globally in 2021	Up to 20 million doses ready for the US by end of 2020, and up to 500 million–1 billion doses globally in 2021	Up to 3 billion doses of the vaccine in 2021

NB: differentvaccine types are not interchangeable; the same vaccine must be used for a second dose.

dentist to discontinue the unresponsive vaccinee from the practice. Whether a different type of COVID-19 vaccine (ie manufactured on a different platform) could be given for an unresponsive vaccinee needs to be resolved in due course, when more information is available. Alternatively, the principal employer needs to obtain a written, and signed, non-liability statement from the unresponsive vaccine, in the rare event that they develop COVID-19 through exposure to a patient/attendee at the clinic. Such written records must be properly stored and retained for retrieval and future use, if necessary.

- It is not known, as yet, whether booster doses are necessary for the COVID-19 vaccines after a specific period, and if so how often these should be administered. A good example is the influenza vaccine, which requires annual boosting to maintain seropositivity for the prevalent virus type. It may be that the regularity and frequency of the antigenic shifts we are witnessing in SARS-CoV-2, will result in a situation leading to the necessity of an annual vaccine boost either for the old strain of the virus or a newly circulating virus variant.

Clearly, some of the above are conjectural scenarios owing to the sparsity of data on the subject, and the rapidly shifting landscape of COVID-19. The eventual impact of this dreaded disease on dentistry is incomprehensible, as yet. Nevertheless, the foregoing should serve as a preparatory primer for the profession on COVID-19 vaccines. Finally, Table 2 provides detailed attributes of the vaccines that are currently approved in the UK and USA, which should be helpful in decision- making when choosing a vaccine.

4.1 Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Informed Consent: Informed consent was obtained from all individual participants included in the article.

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