Evidence note

COVID-19 Vaccine update

Government of Nepal
Ministry of Health and Population
Policy, Planning and Monitoring Division

As a part of sharing evidence to support the health sector response to COVID-19 pandemic, the Ministry of Health and Population (MoHP) through the knowledge café secretariat at the Policy, Planning and Monitoring Division (PPMD) organised a mixed modality (physical + virtual) Knowledge Café – a platform for promoting the use of evidence - on 2 Mar 2021. The meeting was attended by senior Government officials, health external development partners, experts and other stakeholders. This evidence note is a product of the knowledge café discussion and presentation, with a rapid evidence synthesis.

Earlier Epidemics and pandemics and their impacts

The amount of a disease that is usually present in a community is referred to as the baseline or **endemic** level of the disease. A disease **outbreak** is when cases of a disease are in excess of what we would normally expect to see (WHO, 2021a). An **epidemic** is defined as "the occurrence in a community or region of cases of an illness, specific health-related behaviour, or other health-related events clearly in excess of normal expectancy"(ReliefWeb Project, 2008). Similarly, a **pandemic** is defined as a "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people"(Kelly, 2011).

Intermittent outbreaks of infectious diseases have had important and lasting effects on societies and thus, have strongly shaped the various aspects of societies including economic, political, and social. Epidemic outbreaks have forced the scientific community in advancing the principles of epidemiology, disease prevention, immunization, and treatments. Some of the major epidemic and pandemics in the human history are listed in the table 1.

Table 1: Epidemics and pandemics (Pitlik, 2020)

Time	Name	Microbe	Death Toll	R_0	Vaccine(s)
1520 onwards	New world Smallpox	Variola (Smallpox)	300M*(WHO, 2011)	3.5-6	Y
1800s	Yellow fever	Yellow fever	100–150K	-	-
1817–1923	Cholera pandemics	Vibrio cholera (Gram-negative bacteria)	>1M	-	-
1885	Third plague	Yersinia pestis	12M	-	Y
1889–1890	Russian flu	Influenza H2N2	1M	1.5	Y
1918–1919	Spanish flu	Influenza H1N1	40–50M	1.4-2.8	Y
1957–1958	Asian flu	Influenza H2N2	1.1M	1.5	Y
1968–1970	Hong Kong flu	Influenza H3N2	1M	1.5	Y
1981–present	AIDS	HIV (RNA virus)	25–35M		None
2002–2003	SARS	SARS-CoV-1 (RNA virus)	0.8K	0.19-1.08	None
2009–2010	Swine flu	Influenza H1N1	200K	-	Y
2014–2016	Ebola	Ebola virus (RNA virus)	11K	1.5-1.9	Y
2015–present	MERS	MERS-CoV (RNA virus)	0.8K	0.3-0.8	None
2019–present	COVID-19	SARS-CoV-2 (RNA virus)	>0.5M*	2.5	Y

For prevention and control of infectious-disease outbreaks, epidemics and pandemics, vaccines are critical. Vaccines boost body's immune system to reduce the risks of getting a disease. There are vaccines that prevent more than 20 life-threatening diseases, and thus, avoid 2-3 million deaths every year from those diseases such as diphtheria, tetanus, influenza, measles. Consequently, immunization has emerged as a global health and development success story (WHO, 2021g). Likewise, safe and effective vaccines are crucial for prevention and control of COVID-19 pandemic.

Vaccines

Vaccines contain weakened or inactive parts of a particular organism (antigen) or the "blueprints" for producing antigens that triggers an immune response within the body. This weakened version will not cause the disease but train the immune system to create antibodies (WHO, 2020).

It is important to understand efficacy and effectiveness when it comes to vaccines. They are defined as follows (Weinberg & Szilagyi, 2010):

- **Efficacy** of a vaccine can be defined as its performance under ideal and controlled circumstances
    - Percentage reduction in disease incidence in a vaccinated group compared to an unvaccinated group under optimal conditions
- **Effectiveness** of a vaccine refers to its performance, i.e., ability to prevent outcomes of interest under 'real-world' conditions.

Vaccine Development process

Traditionally, vaccine development is a long and expensive process, and comprises of following stages (Pfizer, 2020) :

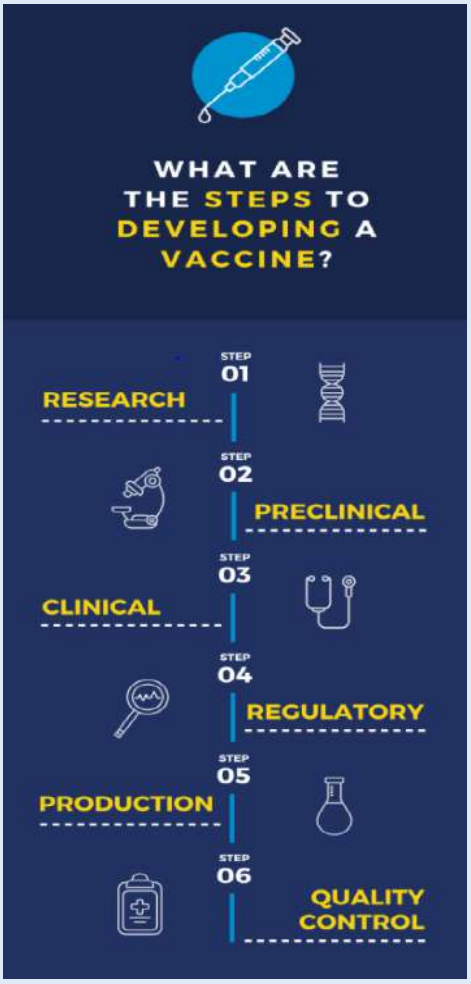


Figure 1: Vaccine Development process (Pfizer, 2020)

Discovery research (up to 2-5 years) / pre-clinical stage (up to 2 years)
Antigen discovery and development of vaccine formulation
Testing of dose, safety, immunogenicity, and efficacy in animal models

Phase I clinical stage (up to 2 years)
Testing of vaccine in a small number of healthy volunteers (10 – 100)
Primary questions: Is the vaccine safe? Does the vaccine induce a strong immune response? What is the optimal dose?

Phase II clinical stage (2-3 years)
Testing of vaccine in a moderate number of healthy volunteers (100 – 1000)
Primary questions: Is the vaccine safe? Does the vaccine induce a strong immune response?

Phase III clinical stage (5 - 10 years)
Testing of vaccine in a large number of healthy volunteers (1000 – 10,000+)
Primary questions: Is the vaccine effective (efficacy) in preventing disease? Is the vaccine safe in a larger, more varied population?

Implementation
Licensure / Regulatory approval (may take up to 2 years)

Production
Large scale manufacture: require specialist facilities that are highly regulated and expensive to set up.

Quality control
Post-licensure monitoring of safety and effectiveness.

COVID-19 vaccine update

The COVID-19 vaccine development process is taking an unprecedented speed and is challenging the traditional paradigm. Defendi, et al. (2021) identified technology-base and research and development (R&D) strategy as the two major contributing factors. The development in the field of biotechnology and molecular biology including new technological platforms as well as the parallelism of phases and adaptive clinical trials in agreement with the regulatory agencies are the strategies that stood out the most for the rapid vaccine development for COVID-19 (Defendi et al., 2021) . The COVID-19 vaccine development timelines have been accelerated at an extraordinary speed in all areas of development. Yet, all scientific and regulatory standards established for vaccines have been followed (Lupo & Pfleiderer, 2020; Wellcome, 2021).

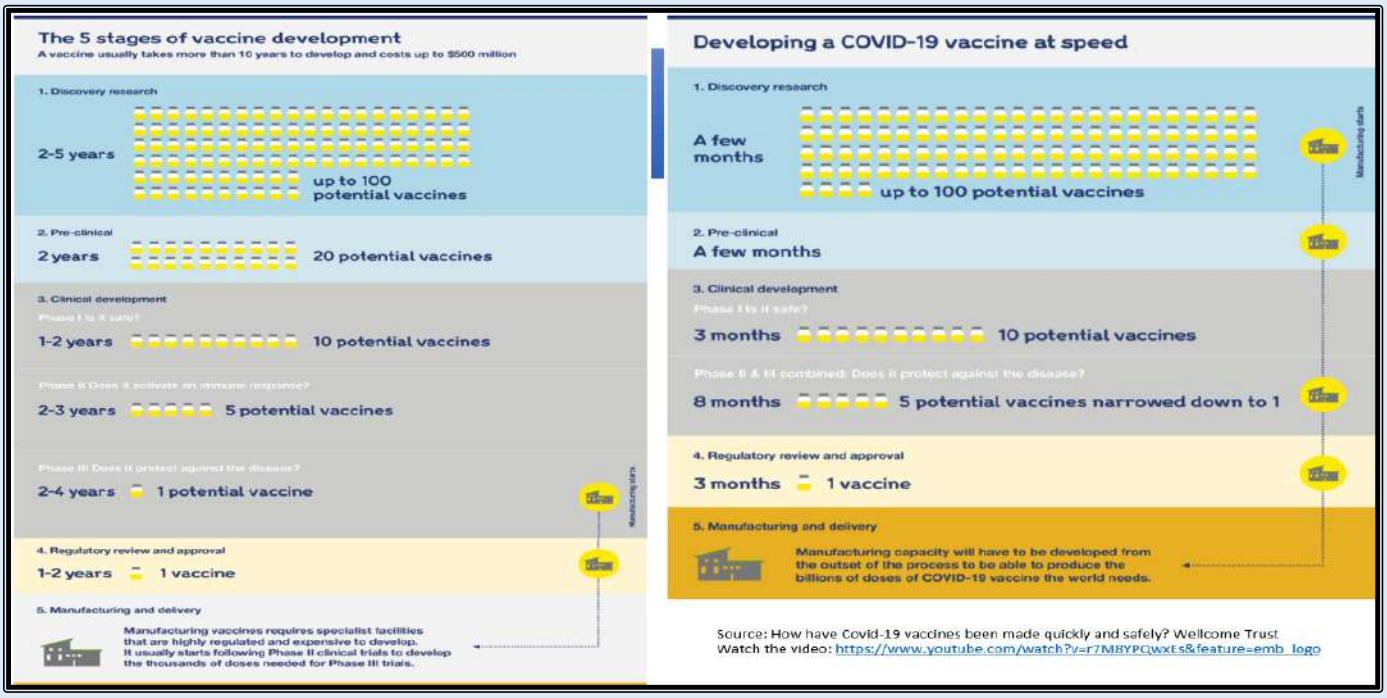


Figure 2: Vaccine development: Regular Vs COVID-19 (Wellcome, 2021)

COVID-19 vaccine types

There are three main approaches to developing a vaccine, based on whether they use i. a whole virus or bacterium, ii. sub-unit or just parts of a germ that prompts immune response or iii. genetic material that encodes instructions to make specific proteins and not the whole virus (WHO, 2021e) .

1. The whole microbe approach:

Vaccines using whole microbe approach may be live attenuated, inactivated, or viral vector.

Viral vector vaccines can further be of two types: those that can still replicate within cells (replicating) and those that cannot because key genes have been disabled (non-replicating).

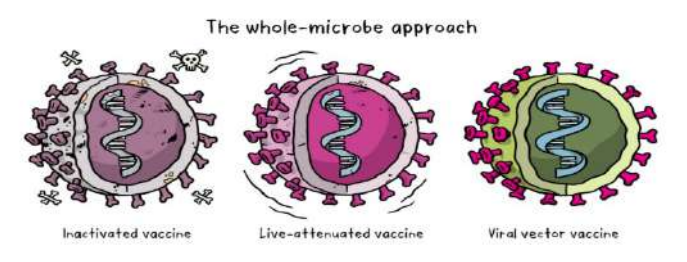


Figure 3: Types of vaccines using whole microbe approach (WHO, 2021e)

Table 2: Types of whole microbe vaccines (WHO, 2021e)

Inactivated vaccine	Live attenuated vaccine	Viral vector vaccine
• The disease-causing virus or bacterium is inactivated or killed using chemicals, heat or radiation. • Requires special laboratory facilities to grow the virus or bacterium safely, • Relatively long production time, • Likely requires 2-3 doses to be administered.	• A living but weakened version of the virus or one that is very similar is used • Uses similar technology to the inactivated vaccine and can be manufactured at scale. • May not be suitable for people with compromised immune systems.	• A safe/weakened virus is used to deliver specific sub-parts (specifically proteins) of the germ of interest so that it can prompt an immune response without causing the disease. • The safe virus serves as a platform or vector to deliver the protein into the host body, which then triggers the immune response.
Examples: Hepatitis A, influenza, rabies, IPV, whole cell pertussis vaccines	Examples: measles, mumps and rubella (MMR) vaccine, OPV, rotavirus, BCG, JE (SA-14-14-2), varicella, yellow fever, chickenpox and shingles vaccines	Examples: Ebola, ChAdOx1-S ([recombinant]

2. Sub-unit approach

A subunit vaccine is one that only uses the very specific parts (the subunits) of a virus or bacterium that the immune system needs to recognize. The subunits may be proteins or sugars or virus like particles (WHO, 2021e). Corona virus proteins or fragments of proteins or protein shells that mimic the coronavirus's outer coat are being tested to be used in COVID-19 vaccines (Callaway, 2020).

Many of the vaccines designed on sub-unit approach are using virus spike protein or a key part of it called as the receptor binding domain. These vaccines possibly require adjuvants. Few of the vaccines are also using the virus like particles as an approach of vaccine design. They are expected to trigger strong immune response, however they may be difficult to manufacture (Callaway, 2020).

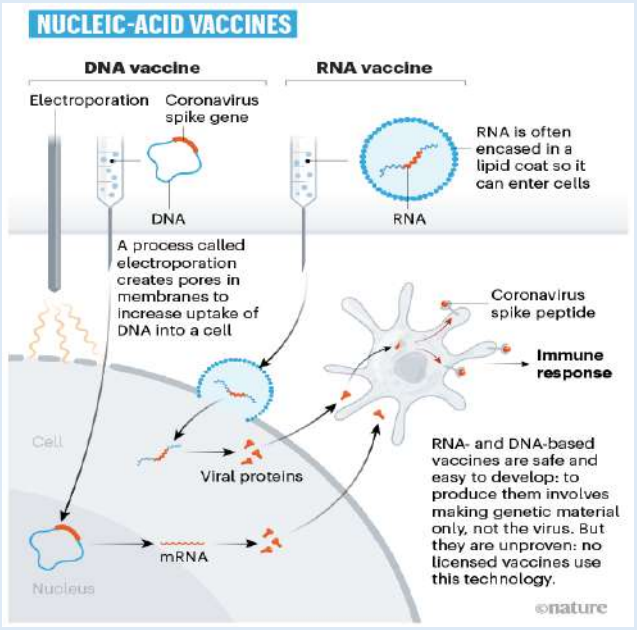


Figure 4: Nucleic acid vaccines (Callaway, 2020)

3. Genetic approach

A nucleic acid vaccine uses a section of genetic material that provides instructions for *making* specific proteins, not the whole microbe.
These vaccines can be either DNA or RNA vaccines.
They deliver a specific set of instructions to our cells, either as DNA or mRNA.

In the cells, DNA is first turned into messenger RNA, which is then used as the blueprint to make specific proteins, which trigger the immune response.

The nucleic acid approach is a new approach for vaccines. Before the COVID-19 pandemic, none had yet been through the full approvals process for use in humans (WHO, 2021e).

COVID-19 vaccines

As of 28 Jun 2021, 99 vaccines were being tested clinically and 18 are already in use (LSHTM, 2021). Majority of these vaccines are designed to be administered via injection, a large proportion of them through intra-muscular route. Likewise, a major number of these vaccines are double dose vaccines (WHO, 2021b).

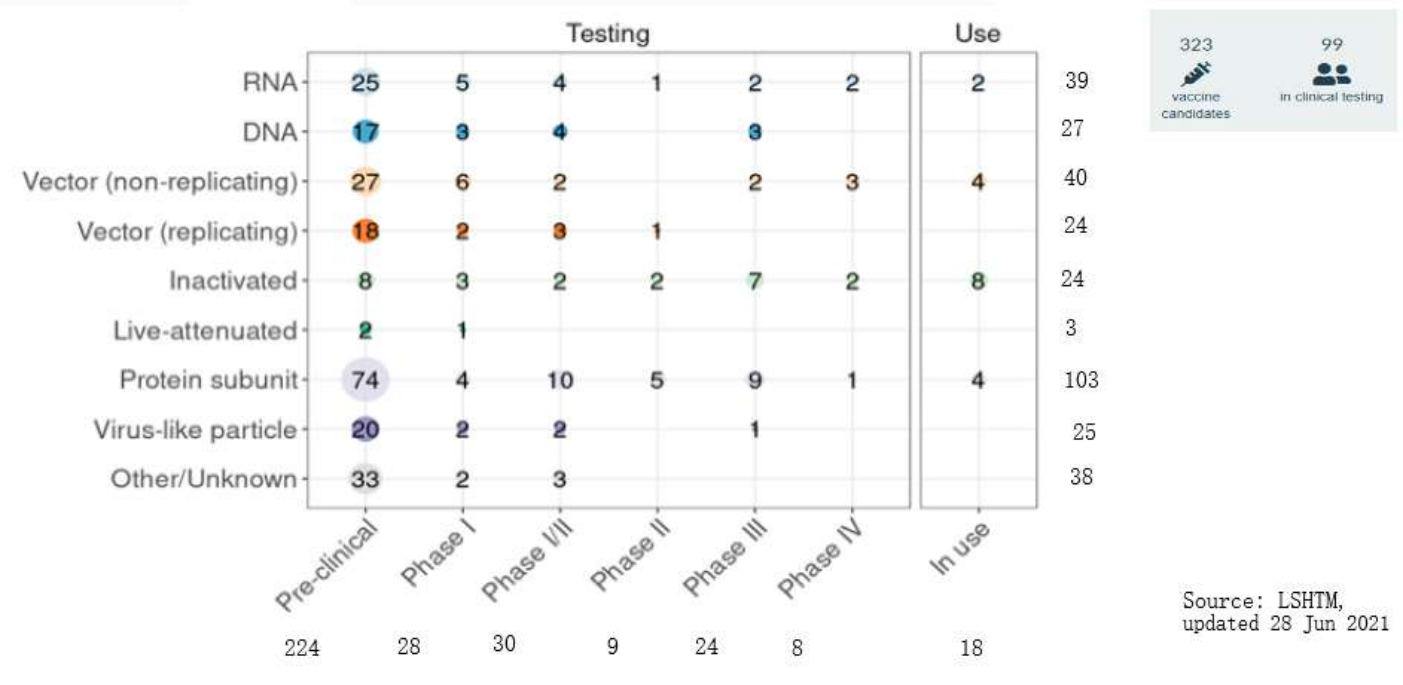
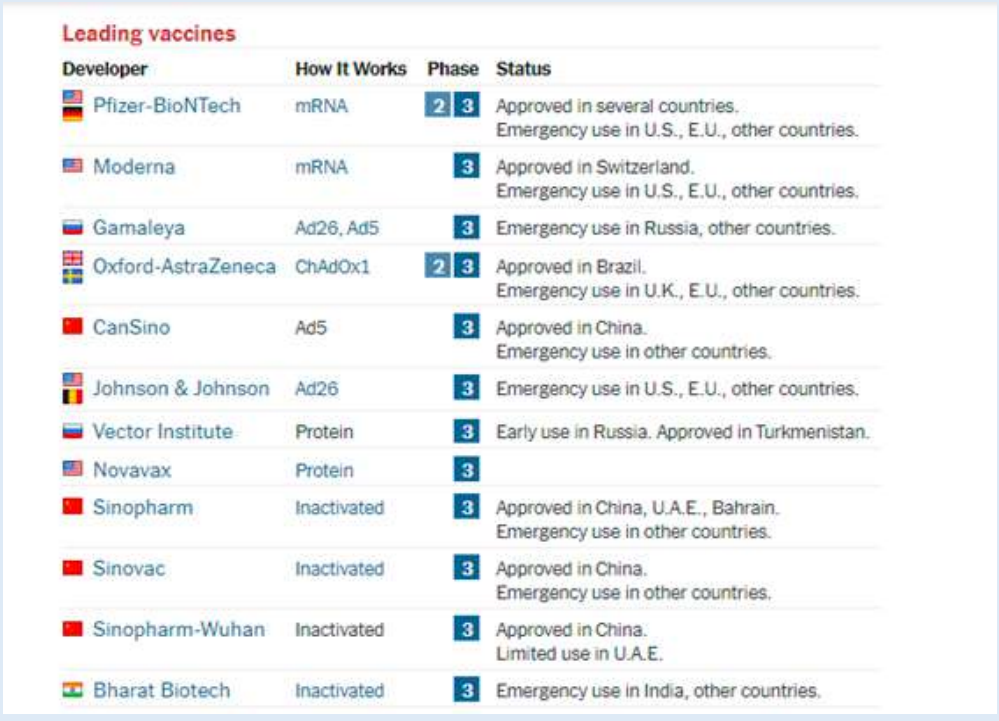


Figure 5: Vaccines at different stages of development (LSHTM, 2021)

Leading COVID-19 vaccines (The New York Times, 2021a) are presented in the figure 6. Among these leading vaccines, six has been approved for WHO's emergency use listing (EUL) as of 2 Jul 2021 (WHO, 2021d).



Leading vaccines

Developer	How It Works	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in several countries. Emergency use in U.S., E.U., other countries.
Moderna	mRNA	3	Approved in Switzerland. Emergency use in U.S., E.U., other countries.
Gamaleya	Ad26, Ad5	3	Emergency use in Russia, other countries.
Oxford-AstraZeneca	ChAdOx1	2 3	Approved in Brazil. Emergency use in U.K., E.U., other countries.
CanSino	Ad5	3	Approved in China. Emergency use in other countries.
Johnson & Johnson	Ad26	3	Emergency use in U.S., E.U., other countries.
Vector Institute	Protein	3	Early use in Russia. Approved in Turkmenistan.
Novavax	Protein	3	
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in other countries.
Sinovac	Inactivated	3	Approved in China. Emergency use in other countries.
Sinopharm-Wuhan	Inactivated	3	Approved in China. Limited use in U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India, other countries.

Figure 6: Leading COVID-19 vaccines as of 1 Jul 2021 (The New York Times, 2021a)

On 31 Dec 2020, BNT162b2 / COMIRNATY®, Pfizer/BioNTech became the first ever COVID-19 vaccine to be listed in WHO's EUL. After this, WHO has already listed Astrazeneca-SK Bio (15 Feb 2021), Serum Institute of India (15 Feb 2021), Astra Zeneca EU (15 Apr 2021), Janssen (12 Mar 2021), Moderna (30 Apr 2021), Sinopharm (7 May 2021) and Sinovac vaccines (1 Jun 2021) for emergency use (WHO, 2021d).

The following table provides information on the leading COVID-19 vaccines.

Table 3: Comparison between the leading COVID-19 vaccines

SN	Name	Manufacturer	Type	Efficacy	Dose, admin	Storage	Some countries, which approved the vaccines for use
1	Comirnaty (Tozinameran or BNT162b2)	Pfizer BioNTech	mRNA	95%	2 doses, 3 weeks apart: IM	–70°C	Norway, Singapore, UAE, UK, USA
2	mRNA-1273	Moderna	mRNA	94.5%	2 doses, 4 weeks apart; IM	30 days at 2-8°C, 6 months at –20°C	Switzerland, Canada, European Union, Norway, Singapore, UK, USA
3	AZD1222	Oxford / AstraZeneca	VVnr ChAdOx1	81% for 12 weeks schedule	2 doses, 8-12 weeks (WHO SAGE recommendation); IM	2-8°C (6 months)	Australia, Bangladesh, Bhutan, Brazil, India, Nepal, Norway, South Africa, UK
4	Sputnik V (Gam-Covid-Vac) (No WHO EUL)	Gamaleya	VVnr Ad 26, Ad 5	91.6%	2 doses, 3 weeks apart; IM	at –20°C; lyophilized form at 2-8°C	Russia, Argentina, Egypt, Ghana Hungary, Iran, Mexico, Mongolia, UAE
5	BBIBP-CorV	BIBP / Sinopharm	Inactivated	72.51 %	2 doses, 3 weeks apart; IM	2-8°C	Bahrain, China, UAE, Hungary, Iraq, Jordan, Nepal
6	CoronaVac	Sinovac Biotech	Inactivated	50.38 %	2 doses, 2 weeks apart; IM	2-8°C	China, Brazil, Chile, Turkey, Uruguay
7	Ad26.COV2.S	Johnson & Johnson	VVnr Ad26	66%	Single dose	2-8°C (3 months)	US, EU

Oxford AstraZeneca AZD1222 vaccine

Voysey et al (2021) found an acceptable safety profile for ChAdOx1 nCoV-19 and it was also found to be overall 70·4% (95·8% CI 54·8–80·6) efficacious against symptomatic COVID-19 in a pooled interim analysis of four clinical trials conducted across the UK, Brazil, and South Africa. However, this interim analysis does not clarify on the duration of protection (Voysey, Clemens, et al., 2021).

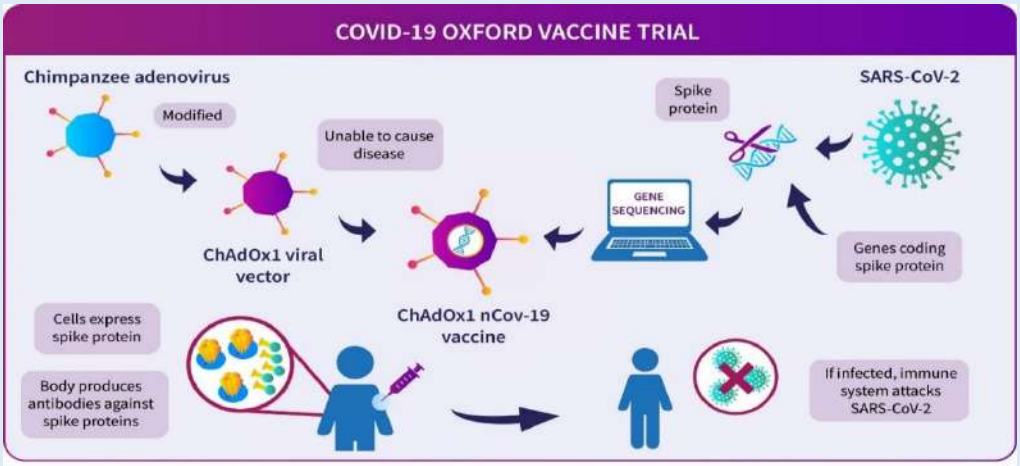


Figure 7: How COVID-19 Oxford vaccine works? (University of Oxford, 2020)

AZD1222 is a recombinant on-replicating (E1 and E3 gene-deleted)(Dicks et al., 2012) adenoviral vector vaccine, containing the genetic sequence of the surface spike protein of coronavirus as shown in figure 7. When the vaccine enters cells inside the body, it uses this genetic sequence to produce the surface spike protein of the

coronavirus, which triggers an immune response, priming the immune system to attack the coronavirus if it later infects the body (Dicks et al., 2012).

AZD122 uses ChAdOx1 vaccine technology has been used. The ChAdOx1 vaccine is a chimpanzee adenovirus vaccine vector. This adenovirus is a harmless virus that usually causes the common cold in chimpanzees. In ChAdOx1 vaccine technology, the adenovirus is genetically changed so that it is impossible for it to grow in humans[17]. ChAdOx1 has been shown to generate a strong immune response from one dose in other vaccines (Folegatti et al., 2020; University of Oxford, 2020).

Table 4: Vaccine efficacy according to WHO severity progression scale (Folegatti et al., 2020)

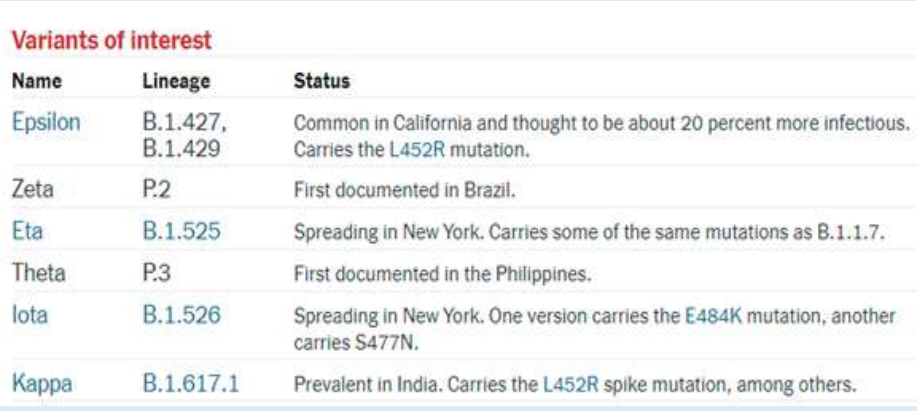
Analysis set Events	Participants with events		VE (%)	95% CI (%)
	AZD1222 n / N (%)	Control n / N (%)		
COVID-19 (WHO score ≥ 2)	**129 / 9335 (1.38)**	**331 / 9312 (3.55)**	**61.55**	**(52.91, 68.61)**
Hospitalisation (WHO score ≥4)	**0 / 9335 (0)**	**14 / 9312 (0.15)**	**100**	**(69.92, NE)**
Severe (WHO score ≥6)	**0 / 9335 (0)**	**2 / 9312 (0.02)**	–	–
Death (WHO score ≥10)	**0 / 9335 (0)**	**1 / 9312 (0.01)**	–	–

The vaccine was also found to have strong efficacy against COVID-19 hospitalization. Among participants with comorbidities, the vaccine efficacy was no different than among the observed in the general population. Even for elderly, though there were limited number of enrolled participants with shorter follow-up period and 4-8 weeks spacing between first and second doses, efficacy and immunogenicity trends indicate a favourable risk benefit balance (Vekemans, 2020).

A modelling analysis by Voysey, et al (2021) suggested that vaccine induced protection persisted during the initial 3-month period, post first dose. Correspondingly, there was only minimal waning in the antibody levels during this period. Among participants who received two standard doses, the efficacy was higher after the second dose, with a longer prime-boost interval (vaccine efficacy 81·3% [95% CI 60·3-91·2] at ≥12 weeks) than in those with a short interval (vaccine efficacy 55·1% [33·0-69·9] at <6 weeks). Immunogenicity data further showed that binding antibody responses were more than two-fold higher after an interval of 12 or more weeks compared with an interval of less than 6 weeks among 18-55 years participants (Voysey, Costa Clemens, et al., 2021).

Corona virus variants

Corona viruses, like any other viruses, keep changing or mutating in small ways as it passes from one person to another. Though these mutations are mostly inconsequential, some mutations trigger changes in the spike protein; such variants could potentially be more infectious or cause more severe disease. There are certain mutations that has given rise to variants of interest as shown in figure 8 and variants of concern as shown in table 5.



Variants of interest

Name	Lineage	Status
Epsilon	B.1.427, B.1.429	Common in California and thought to be about 20 percent more infectious. Carries the L452R mutation.
Zeta	P.2	First documented in Brazil.
Eta	B.1.525	Spreading in New York. Carries some of the same mutations as B.1.1.7.
Theta	P.3	First documented in the Philippines.
Iota	B.1.526	Spreading in New York. One version carries the E484K mutation, another carries S477N.
Kappa	B.1.617.1	Prevalent in India. Carries the L452R spike mutation, among others.

Figure 8: Variants of interest (The New York Times, 2021b)

Variants of interest are those may evade antibodies or bind more tightly to human cells but are not yet shown to be more infectious. On the other hand, variants of concern are those that appear to be more infectious or cause more severe disease

than other variants. These have already been identified in UK, South Africa, Brazil and India, and have now spread to dozens of countries (The New York Times, 2021b). WHO has named these variants with Greek names.

Table 5: Variants of concern (The New York Times, 2021b)

Alpha: B.1.1.7 pango lineage	Beta: B.1.351 pango lineage	Gamma: P.1 pango lineage	Delta: B.1.617.2 pango lineage
Mutations in the spike protein include: — N501Y, which helps the virus latch on more tightly to human cells. But the mutation is not likely to help the virus evade current vaccines. — P681H, which may help infected cells create new spike proteins more efficiently. — The H69-V70 and Y144/145 deletions, which alter the shape of the spike and may help it evade some antibodies.	**Mutations near the tip of the spike protein include:** — N501Y, which helps the virus latch on more tightly to human cells. This mutation also appears in the B.1.1.7 and P.1 lineages. — K417N, which also helps the virus bind more tightly to human cells. — E484K, which may help the virus evade some kinds of antibodies.	**Key mutations in the spike protein** are similar to those in the B.1.351 lineage, although they arose independently: — N501Y, which helps the virus latch on more tightly to human cells. This mutation also appears in the B.1.1.7 and B.1.351 lineages. — K417T, which is the same site as the K417N mutation in the B.1.351 lineage. It may also help the virus latch on tighter. — E484K, which may help the virus evade some kinds of antibodies.	**Key mutations include** T19R, G142D, 156del, 157del, R158G, L452R, T478K, D614G, P681R, D681R, D950N **in the spike protein** (Davis et al., 2021; Global Virus Network, 2021) **.** The Delta variant contains multiple mutations in the spike protein. At least four mutations are important. -L452R, P681R, D614G have been associated with increased transmissibility (Deng et al., 2021; Frazier et al., 2021; Zhou et al., 2021). L452R has also been associated with reduced antibody efficacy (Deng et al., 2021). -T478K is associated with increased infectivity (di Giacomo et al., 2021).
Earliest documented samples: Sep 2020, UK (WHO, 2021f)	**Earliest documented samples: May 2020, South Africa** (WHO, 2021f)	**Earliest documented samples: Nov 2020, Brazil** (WHO, 2021f)	**Earliest documented samples: Oct 2020, India** (WHO, 2021f)

Vaccine response to the variants

This first national population level study, led by the University of Edinburgh together with Public Health Scotland, assessed the effect of currently licensed COVID-19 vaccines on a serious COVID-19 outcome in 5.4 million people in Scotland, UK, including adults aged 65 years and older. The effects of the vaccine were seen to be comparable across all age groups. The results, also available as a preprint, showed that four weeks after the first doses of the Pfizer BioNTech and Oxford AstraZeneca vaccines were administered, the risk of hospitalisation from COVID-19 fell by up to 85% (95% CI 76 to 91) and 94% (95% CI 73 to 99), respectively (Vasileiou et al., 2021).

However, Wang et al (2021) suggested that the neutralizing activity of mRNA vaccines decreased by few folds against the variants. Thus, to avoid potential loss of clinical efficacy, mRNA vaccines need to be periodically updated (Wang et al., 2021). After the second dose, Pfizer vaccine has been shown to effectively neutralize the B.1.1.7 variant, whereas the neutralization of the B.1.351 variant was reduced by five-folds. Nonetheless, neutralizing antibodies were developed against the B.1.351 variant showing at least some degree of protection (Jalkanen et al., 2021).

A slight reduction in vaccine effectiveness of AZD1222 against B.1.1.7 in the United Kingdom was shown by preliminary analysis. Another preliminary analysis from the Phase 1/2a trial in South Africa indicated a marked reduction in vaccine effectiveness against mild and moderate disease due to B 1.351 based on a small sample size and substantial loss of neutralizing antibody activity (WHO, 2021c).

A recently published study from Scotland (Jun 2021) suggested that 14 days post second dose, Pfizer was 92 per cent effective against the Alpha variant, B.1.1.7 and 79 per cent effective against the Delta variant (B.1.617.2) while the AstraZeneca vaccine

provided 73 per cent protection against the Alpha variant and 60 per cent against the Delta variant (Sheikh et al., 2021). A similar results of reduced vaccine effectiveness against both these variants with Pfizer and AstraZeneca vaccine were also reported by a study conducted in England. Yet, protection provided by Pfizer was higher than by AstraZeneca vaccine (Bernal et al., 2021).

COVID-19 immunization strategies in Nepal

For developing effective COVID-19 immunization strategies, four dimensions need to be considered (Wouters et al., 2021) as shown in figure 9.

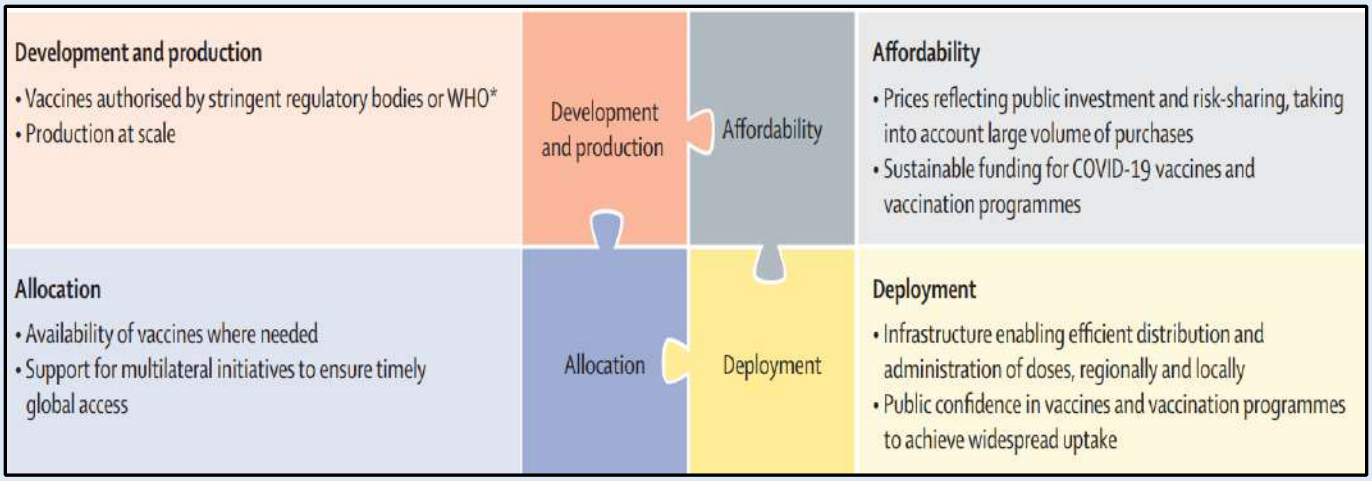


Figure 9: Four dimensions of effective immunization strategies (Wouters et al., 2021)

While production of COVID-19 vaccines is limited by the highly concentrated state of global vaccine manufacturing capacity, scaling up production to meet global demand is a monumental challenge. A possible solution to this crisis would probably require widespread technology transfer to aid in the expansion of manufacturing capacity. Existing examples are collaboration agreements between AstraZeneca and the Serum Institute of India, Fiocruz in Brazil, mAbxience Buenos Aires in Argentina, and Siam Bioscience in Thailand; between Johnson & Johnson and Aspen Pharmacare in South Africa; and between Novavax and the Serum Institute of India (Wouters et al., 2021).

Other challenges include ensuring affordability and sustainable financing of COVID-19 vaccines in low-income and middle-income countries as well as safeguarding global availability of adequate doses to prevent uneven access to vaccines and ensuring smooth deployment of COVID-19 vaccines. Thus, a pooled procurement initiative, COVAX, has been established to secure low prices and it aims to provide all countries with access to a diversified portfolio of vaccines during the acute phase of the pandemic in 2021. According to the COVAX model, all participating countries would initially receive enough stock for 20% of their populations, after which distribution would adhere to the WHO framework for allocating COVID-19 vaccines internationally on a need-based approach (Wouters et al., 2021).

Bubar et al (2020), in a mathematical model comparing five age-stratified prioritization strategies (<20, 20+, 20-49, 60+, all ages), showed that highly effective transmission-blocking vaccine prioritized to adults aged 20-49 years minimized cumulative incidence. However, mortality and years of life lost were minimized in most scenarios when the vaccine was prioritized to adults over 60 years old (Bubar et al., 2021). Thus, vaccine prioritization is not only a question of science but also a question of ethics. Besides, there can be other challenges in vaccine distribution, such as ensuring equitable distribution of vaccine, establishing and strengthening the infrastructure for mass immunization campaigns, overcoming vaccine hesitancy, cost of vaccines, cold chain maintenance and so on (Burki, 2021).

COVID-19 immunization activities in Nepal

Nepal is also eligible to receive COVID-19 vaccines through COVAX facility. In addition, the Government of Nepal is negotiating directly with different vaccine manufacturers, and other governments, to procure vaccines for the citizens. Some of the milestones and guiding documents for COVID-19 vaccination in Nepal are as follows (Family Welfare Division, 2021):

- National Regulatory Authority (NRA) of Nepal is the Department of Drug Administration (DDA). In normal cases, it follows the procedures to register new medicines as per the Drug regulation and directives. Drugs (Third Amendment) Ordinance, 2077 (2020) has been issued in November 2020 to amend the Drug Act 1978, (2037 BS) which allows for emergency use authorization of vaccines and drugs in the context of the COVID-19 pandemic.
- Decisions of the Cabinet of Ministers (4 Jan 2021/20 Poush 2077) for:
    - Formation of coordination and monitoring committee at all levels
    - Resource allocation
    - Indemnification to manufacturer, distributor, and donor in case of occurrence of adverse event following immunization for COVID-19 vaccination.
- Technical proposal on COVID-19 vaccine introduction in Nepal
- National Deployment and Vaccination Plan (NDVP) for COVID-19 vaccine 2021
- COVID-19 Vaccination Operational Guideline and Training Package
- Application to COVAX Facility
- The priority groups for vaccination have been listed as follows:

Table 6: Vaccination priority groups in Nepal as per NDVP (MoHP, 2021)

First priority	Second priority	Third priority
• Frontline Health Workers, FCHVs • Cleaner and Janitor staff • Ambulance/mortuary van Driver • Security staff managing dead body • People in Geriatric Home and caretaker • Prisoners & Jail security staff • Staff working in int'l border post • UN Staff & Diplomats • Journalist, Bankers • Elected representatives • Employ of government offices • Police, Armed Police force, Nepal Army • Staff of Corporation and Authority • Employee of judicial offices	• ≥55 years old age group • Faculties, teachers and other staff of university and schools • Drivers/conductors of public transportation • 40 to 54 years old population with defined co-morbidity • Refugees and returnee Nepalese from foreign employment with defined co-morbidities	• Remaining 40 to 54 years old population • 15 to 39 years old population

Nepal granted emergency use authorization (EUA) to Oxford AstraZeneca's COVID-19 vaccine, which is locally manufactured by Serum Institute of India by the name COVISHIELD on 15 Jan 2021 (Department of Drug Administration, 2021b). A month later, Nepal also granted EUA to the vaccine manufactured by the Beijing Institute of Biological Products Co, Ltd (BIBP), China under Sinopharm on 16 Feb 2021 (Department of Drug Administration, 2021c) . As of Jun 2021, additional three vaccines have been provided EUA in Nepal: COVAXIN manufactured by Bharat Biotech International, India on 19 Mar 2021 (Department of Drug Administration, 2021d), Gam-COVID-Vac (Sputnik) manufactured by FSBI N.F. Gamaleya National Research Center of Epidemiology and Microbiology, Ministry of Health, Russia on 20 Apr 2021 (Department of Drug Administration, 2021a) and Vero Cell, inactivated CoronaVac manufactured by Sinovac Life sciences, China on 4 Jun 2021 (Department of Drug Administration, 2021e).

Figure 10 shows the vaccine transport plan for COVID-19 vaccination campaigns in Nepal.

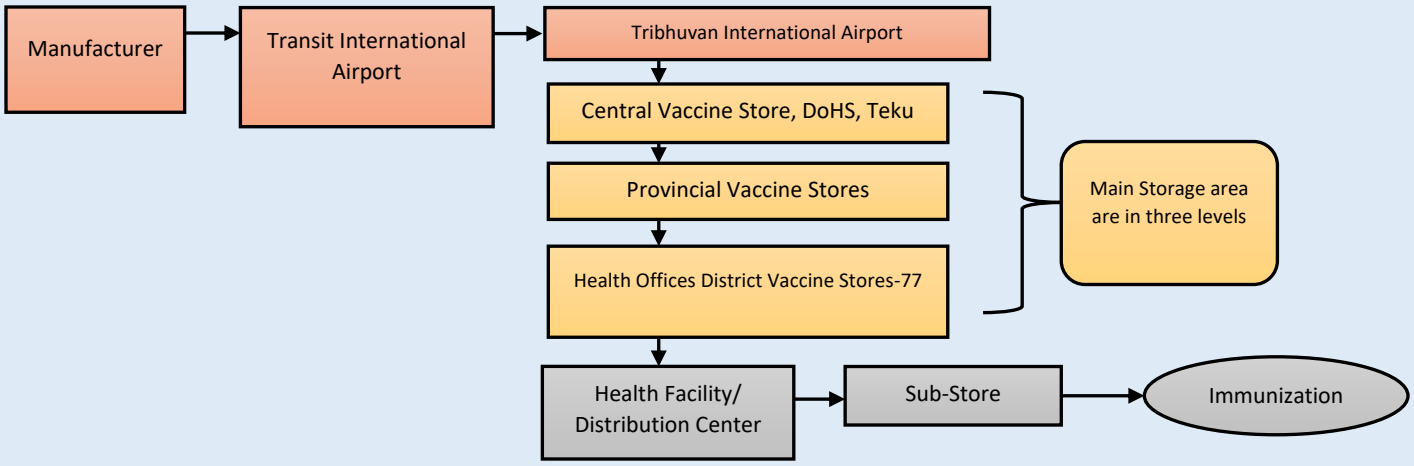


Figure 10: COVID-19 Vaccine Transport Plan, Nepal (source: NDVP)

Major activities and timeline for COVID-19 vaccination implementation in Nepal during the early phases

- Full political commitment at all levels
- Nepal received 1 million doses of COVISHIELD, manufactured locally by Serum Institute of India (SII) as grant-in-aid from Govt. of India on 21 Jan 2021
- Trainings (in-person for Kathmandu Valley and virtual for nation-wide) from central level was conducted on 25 Jan 2021
- Nation-wide virtual training from central level to AEFI focal persons was conducted on 26 Jan 2021
- Trainings conducted by provinces/districts at sub-national level and AEFI management team is formed in districts.
- A provision has been established to provide the Immunization card to all the vaccinated individuals which will also facilitate in the follow-up for second dose. Budget, vaccines, and logistics supplied to and received by all provinces and districts (including adrenaline)
- 1st phase of vaccination campaign launched on 27 Jan 2021 in all the provinces and districts with COVISHIELD vaccine (Family Welfare Division, 2021).

During the first phase of vaccination campaign, frontline workers including the health professionals, government employees, sanitation workers and security personnel were administered the COVISHIELD vaccine, followed by people of different age groups and profession as per NDVP in subsequent phases. In addition to the grant-in-aid from Indian government, Nepal also procured 2 million doses of COVISHIELD vaccine from the Serum Institute of India (SII) with full payment. However, Nepal received only 1 million vaccines as India put a ban on vaccine export (Business Standard, 2021). Nearly 1.4 million people including the senior citizens, aged over 65 have been waiting for the booster dose of the COVISHIELD vaccine as the Serum Institute of India Pvt Ltd- halted the supply (myRepublica, 2021). Meanwhile the government of Nepal received COVID-19 vaccines from China as grant-in-aid, after which vaccination campaign was re-initiated. Nepal further plans to procure Vero Cell vaccines as well as Johnson and Johnson vaccines (Business Standard, 2021). As of 18 Jun 2021, 1,828,484 people have received first dose and 411,373 people have received both doses of COVISHIELD vaccine whereas 671,712 people have received first dose and 291,035 people have received both doses of Vero Cell vaccine. (WHO country office Nepal, 2021).

Regardless of vaccination, social distancing, mask use and hand hygiene continue to be important measures for COVID-19 prevention (Silberner, 2021; Su et al., 2021), as vaccines are not the magical medicine for the COVID-19 pandemic control and containment. Besides, everyone cannot get vaccinated immediately and for herd immunity, more than 60% of population will need to be vaccinated. Furthermore, it is yet to be ascertained whether vaccinated people can transmit the virus or not. Additional concern is that the severity of variants is still unknown.

References

Bernal, J. L., Andrews, N., Gower, C., Gallagher, E., Simmons, R., Thelwall, S., Stowe, J., Tessier, E., Groves, N., Dabrera, G., Myers, R., Campbell, C., Amirthalingam, G., Edmunds, M., Zambon, M., Brown, K., Hopkins, S., Chand, M., & Ramsay, M. (2021). Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. *MedRxiv*, 2021.05.22.21257658. https://doi.org/10.1101/2021.05.22.21257658

Bubar, K. M., Reinholt, K., Kissler, S. M., Lipsitch, M., Cobey, S., Grad, Y. H., & Larremore, D. B. (2021). Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. *Science*, *371*(6532). https://doi.org/10.1126/science.abe6959

Burki, T. (2021). Equitable distribution of COVID-19 vaccines. *The Lancet Infectious Diseases*, *21*(1). https://doi.org/10.1016/S1473-3099(20)30949-X

Business Standard. (2021). *Nepal to procure 4 mn Covid vaccines from China under non-disclosure deal*. Business Standard. https://www.business-standard.com/article/current-affairs/nepal-to-procure-4-mn-covid-vaccines-from-china-under-non-disclosure-deal-121061700560_1.html

Callaway, E. (2020). *The race for coronavirus vaccines: a graphical guide*. Nature. https://www.nature.com/articles/d41586-020-01221-y

Davis, C., Logan, N., Tyson, G., Orton, R., Harvey, W., Haughney, J., Perkins, J., The COVID-19 Genomics UK (COG-UK) Consortium, Peacock, T. P., Barclay, W. S., Cherepanov, P., Palmarini, M., Murcia, P. R., Patel, A. H., Robertson, D. L., Thomson, E. C., & Willett, B. J. (2021). Reduced neutralisation of the Delta (B.1.617.2) SARS-CoV-2 variant of concern following vaccination. *MedRxiv* . https://www.medrxiv.org/content/10.1101/2021.06.23.21259327v1

Defendi, H. G. T., da Silva Madeira, L., & Borschiver, S. (2021). Analysis of the COVID-19 Vaccine Development Process: an Exploratory Study of Accelerating Factors and Innovative Environments. *Journal of Pharmaceutical Innovation*. https://doi.org/10.1007/s12247-021-09535-8

Deng, X., Garcia-Knight, M. A., Khalid, M. M., Servellita, V., Wang, C., Morris, M. K., Sotomayor-González, A., Glasner, D. R., Reyes, K. R., Gliwa, A. S., Reddy, N. P., Sanchez San Martin, C., Federman, S., Cheng, J., Balcerek, J., Taylor, J., Streithorst, J. A., Miller, S., Kumar, G. R., … Chiu, C. Y. (2021). Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. *MedRxiv*, 2021.03.07.21252647. https://doi.org/10.1101/2021.03.07.21252647

Department of Drug Administration. (2021a). *EUA (Emergency Use Authorization) for SPUTNIK-V - COVID-19 Vaccine*. Ministry of Health and Population, Government of Nepal. https://www.dda.gov.np/events/eua-emergency-use-authorization-for-sputnik-v-covid-19-vaccine

Department of Drug Administration. (2021b). *EUA of covid 19 vaccine (COVISHIELD)*. Ministry of Health and Population, Government of Nepal. https://tinyurl.com/7vd4kjan

Department of Drug Administration. (2021c). *EUA of covid 19 vaccine (Vero cell)*. Ministry of Health and Population, Governemnt of Nepal.

Department of Drug Administration. (2021d). *Regarding the permission for Emergency Use Authorization of Covid-19 Vaccine*. Ministry of Health and Population, Government of Nepal. https://www.dda.gov.np/events/regarding-the-permission-for-emergency-use-authorization-of-covid-19-vaccine

Department of Drug Administration. (2021e). *Regarding the permission for Emergency Use Authorization of Covid-19 Vaccine (2078/02/21)*. Ministry of Health and Population, Government of Nepal. https://www.dda.gov.np/events/regarding-the-permission-for-emergency-use-authorization-of-covid-19-vaccine-2078-02-21

di Giacomo, S., Mercatelli, D., Rakhimov, A., & Giorgi, F. M. (2021). Preliminary report on SARS-CoV-2 Spike mutation T478K. *BioRxiv*, 2021.03.28.437369. https://doi.org/10.1101/2021.03.28.437369

Dicks, M. D. J., Spencer, A. J., Edwards, N. J., Wadell, G., Bojang, K., Gilbert, S. C., Hill, A. V. S., & Cottingham, M. G. (2012). A Novel Chimpanzee Adenovirus Vector with Low Human Seroprevalence: Improved Systems for Vector Derivation and Comparative Immunogenicity. *PLoS ONE*, *7*(7). https://doi.org/10.1371/journal.pone.0040385

Family Welfare Division. (2021). COVID-19 Vaccination in Nepal. In *Department of Health Services, Ministry of Health and Population, Nepal*.

Folegatti, P. M., Ewer, K. J., Aley, P. K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E. A., Dold, C., Faust, S. N., Finn, A., Flaxman, A. L., Hallis, B., Heath, P., Jenkin, D., Lazarus, R., Makinson, R., … Yau, Y. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *The Lancet*, *396*(10249). https://doi.org/10.1016/S0140-6736(20)31604-4

Frazier, L. E., Lubinski, B., Tang, T., Daniel, S., Jaimes, J. A., & Whittaker, G. R. (2021). Spike protein cleavage-activation mediated by the SARS-CoV-2 P681R mutation: a case-study from its first appearance in variant of interest (VOI) A.23.1 identified in Uganda. *BioRxiv*, 2021.06.30.450632. https://doi.org/10.1101/2021.06.30.450632

Global Virus Network. (2021). *Delta (B.1.617.2)*. Global Virus Network. https://gvn.org/covid-19/delta-b-1-617-2/

Jalkanen, P., Kolehmainen, P., Häkkinen, H. K., Huttunen, M., Tähtinen, P. A., Lundberg, R., Maljanen, S., Reinholm, A., Tauriainen, S., Pakkanen, S. H., Levonen, I., Nousiainen, A., Miller, T., Välimaa, H., Ivaska, L., Pasternack, A., Naves, R., Ritvos, O., Österlund, P., … Julkunen, I. (2021). COVID-19 mRNA vaccine induced antibody responses against three SARS-CoV-2 variants. *Nature Communications*, *12*(1). https://doi.org/10.1038/s41467-021-24285-4

Kelly, H. (2011). The classical definition of a pandemic is not elusive. *Bulletin of the World Health Organization*, *89*(7), 540–541. https://doi.org/10.2471/BLT.11.088815

LSHTM. (2021). *COVID-19 vaccine tracker*. London School of Hygiene and Tropical Medicine. https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

Lupo, N., & Pfleiderer, M. (2020). *How far are we with the accelerated development of SARS-COV-2 vaccines- a review and outlook*. Biopharma Excellence. https://www.biopharma-excellence.com/news/2020/8/20/how-far-are-we-with-the-accelerated-development-of-sars-cov-2-vaccines-a-review-and-outlook

MoHP. (2021). *National deployment and vaccination plan (ndvp) for covid-19 vaccine 2021*. Kathmandu: Government of Nepal, Ministry of Health and Population

myRepublica. (2021). *COVID-19 vaccination in Nepal: 757,962 receive both doses, 2,604,866 only first*. MyRepublica. https://myrepublica.nagariknetwork.com/news/covid-19-vaccination-in-nepal-757-962-receive-both-doses-2-604-866-only-first/

Pfizer. (2020). *How are vaccines developed?* Pfizer. https://www.pfizer.com/news/hot-topics/how_are_vaccines_developed

Pitlik, S. D. (2020). COVID-19 Compared to Other Pandemic Diseases. *Rambam Maimonides Medical Journal*, *11*(3). https://doi.org/10.5041/RMMJ.10418

ReliefWeb Project. (2008). *Glossary of Humanitarian terms*. WHO. https://www.who.int/hac/about/reliefweb-aug2008.pdf?ua=1

Sheikh, A., McMenamin, J., Taylor, B., & Robertson, C. (2021). SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *The Lancet*, *397*(10293). https://doi.org/10.1016/S0140-6736(21)01358-1

Silberner, J. (2021). *Why You Should Still Wear A Mask And Avoid Crowds After Getting The COVID-19 Vaccine*. NPR. https://www.npr.org/sections/health-shots/2021/01/12/956051995/why-you-should-still-wear-a-mask-and-avoid-crowds-after-getting-the-covid-19-vac

Su, Z., Wen, J., McDonnell, D., Goh, E., Li, X., Šegalo, S., Ahmad, J., Cheshmehzangi, A., & Xiang, Y.-T. (2021). Vaccines are not yet a silver bullet: The imperative of continued communication about the importance of COVID-19 safety measures. *Brain, Behavior, & Immunity - Health*, *12*. https://doi.org/10.1016/j.bbih.2021.100204

The New York Times. (2021a). *Coronavirus Vaccine Tracker*. https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

The New York Times. (2021b). *Coronavirus Variants and Mutations*. https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html

University of Oxford. (2020). *About the Oxford COVID-19 vaccine*. https://www.research.ox.ac.uk/Article/2020-07-19-the-oxford-covid-19-vaccine

Vasileiou, E., Simpson, C. R., Robertson, C., Shi, T., Kerr, S., Agrawal, U., Akbari, A., Bedston, S., Beggs, J., Bradley, D., Chuter, A., Lusignan, S. de, Docherty, A. B., Ford, D., Hobbs, R., Joy, M., Katikireddi, S. V., Marple, J., McCowan, C., … Sheikh, A. (2021). Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people . *Preprint, The University of Edinburgh*. https://www.ed.ac.uk/files/atoms/files/scotland_firstvaccinedata_preprint.pdf

Vekemans, J. (2020). *AstraZeneca COVID-19 Vaccine Update*. . WHO.

Voysey, M., Clemens, S. A. C., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Aley, P. K., Angus, B., Baillie, V. L., Barnabas, S. L., Bhorat, Q. E., Bibi, S., Briner, C., Cicconi, P., Collins, A. M., Colin-Jones, R., Cutland, C. L., Darton, T. C., Dheda, K., Duncan, C. J. A., … Zuidewind, P. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet*, *397*(10269). https://doi.org/10.1016/S0140-6736(20)32661-1

Voysey, M., Costa Clemens, S. A., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Aley, P. K., Angus, B., Baillie, V. L., Barnabas, S. L., Bhorat, Q. E., Bibi, S., Briner, C., Cicconi, P., Clutterbuck, E. A., Collins, A. M., Cutland, C. L., Darton, T. C., Dheda, K., Dold, C., … Zuidewind, P. (2021). Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *The Lancet*, *397*(10277). https://doi.org/10.1016/S0140-6736(21)00432-3

Wang, Z., Schmidt, F., Weisblum, Y., Muecksch, F., Barnes, C. O., Finkin, S., Schaefer-Babajew, D., Cipolla, M., Gaebler, C., Lieberman, J. A., Oliveira, T. Y., Yang, Z., Abernathy, M. E., Huey-Tubman, K. E., Hurley, A., Turroja, M., West, K. A., Gordon, K., Millard, K. G., … Nussenzweig, M. C. (2021). mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. *Nature*. https://doi.org/10.1038/s41586-021-03324-6

Weinberg, G. A., & Szilagyi, P. G. (2010). Vaccine Epidemiology: Efficacy, Effectiveness, and the Translational Research Roadmap. *The Journal of Infectious Diseases*, *201*(11). https://doi.org/10.1086/652404

Wellcome. (2021). *How have Covid-19 vaccines been made quickly and safely?* Originally Published by Wellcome, Derived from Gavi, The Vaccine Alliance. https://www.gavi.org/vaccineswork/how-have-covid-19-vaccines-been-made-quickly-and-safely

WHO. (2011). Smallpox, eradicating an ancient scourge. In *Bugs, drugs & smoke* (pp. 1–21). WHO. https://www.who.int/about/bugs_drugs_smoke_chapter_1_smallpox.pdf

WHO. (2020). *How do vaccines work?* https://www.who.int/news-room/feature-stories/detail/how-do-vaccines-work

WHO. (2021a). *Disease outbreaks*. https://www.emro.who.int/health-topics/disease-outbreaks/index.html#:~:text=Outbreaks%20are%20urgent%20emergencies%20accompanied,community%2C%20geographical%20area%20or%20season

WHO. (2021b). *Draft landscape and tracker of COVID-19 candidate vaccines*. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

WHO. (2021c). *Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID19 developed by Oxford University and AstraZeneca: interim guidance. Updated 10 February 2021 (No. WHO/2019-nCoV/vaccines/SAGE_recommendation/AZD1222/2021.1)*. . https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

WHO. (2021d). *Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process*. Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process

WHO. (2021e). *The different types of COVID-19 vaccines*. https://www.who.int/news-room/feature-stories/detail/the-race-for-a-covid-19-vaccine-explained

WHO. (2021f). *Tracking SARS-CoV-2 variants*. World Health Organisation. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

WHO. (2021g). *Vaccines and immunization*. https://www.who.int/health-topics/vaccines-and-immunization#tab=tab_1

WHO country office Nepal. (2021). *Situation Update #62- Coronavirus Disease 2019 (COVID-19) WHO Country Office for Nepal*. https://cdn.who.int/media/docs/default-source/nepal-documents/novel-coronavirus/who-nepal-sitrep/-62_weekly-who-nepal-situation-updates.pdf?sfvrsn=b6856bc7_5

Wouters, O. J., Shadlen, K. C., Salcher-Konrad, M., Pollard, A. J., Larson, H. J., Teerawattananon, Y., & Jit, M. (2021). Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *The Lancet*, *397*(10278). https://doi.org/10.1016/S0140-6736(21)00306-8

Zhou, B., Thao, T. T. N., Hoffmann, D., Taddeo, A., Ebert, N., Labroussaa, F., Pohlmann, A., King, J., Steiner, S., Kelly, J. N., Portmann, J., Halwe, N. J., Ulrich, L., Trüeb, B. S., Fan, X., Hoffmann, B., Wang, L., Thomann, L., Lin, X., … Beer, M. (2021). SARS-CoV-2 spike D614G change enhances replication and transmission. *Nature*, *592*(7852). https://doi.org/10.1038/s41586-021-03361-1

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