COVID-19 Vaccines: Current Status and Implication for Use in Indonesia

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ABSTRAK

Coronavirus disease 2019 (COVID-19) telah membawa dampak bencana global dalam bidang kesehatan, ekonomi dan sosial. Indonesia memikul beban yang berat, di mana angka kejadian infeksi dan mortalitas akibat COVID-19 merupakan yang tertinggi di Asia Tenggara. Salah satu harapan terbesar untuk menghentikan pandemi COVID-19 adalah vaksin. Upaya pengembangan vaksin terhadap virus etiologi SARS-CoV-2 sejauh ini menjadi kesuksesan yang luar biasa, menghasilkan berbagai modalitas vaksin dalam waktu yang sangat singkat. Kandidat yang terdekat menyelesaikan uji klinis fase 3 adalah model vaksin mRNA (buatan BioNTech/ Pfizer, Moderna), virus inaktif (Sinovac, Sinopharm), vektor virus (Oxford/ AstraZeneca, Gamaleya, Janssen/ Johnson&Johnson, CanSino) dan subunit protein (Novavax). Vaksin yang diproduksi oleh BioNTech/ Pfizer sudah mulai digunakan secara luas sebagai vaksin COVID-19 pertama yang dilisensi. Dalam artikel ini, akan dibahas mengenai keempat modalitas vaksin ini, serta keamanan dan imunogenisitas dari setiap kandidat vaksin. Berikutnya akan dibahas hasil uji klinis fase 2/3 dari Sembilan kandidat vaksin dan kondisi terakhir sampai 29 Desember 2020, serta implikasi terhadap penggunaan dan distribusi vaksin di Indonesia. Situasi vaksin COVID-19 berjalan sangat cepat dengan perkembangan baru dalam hitungan hari, sehingga diharapkan tulisan ini dapat diperbaharui kembali pada awal 2021.

Kata kunci: *vaksin, COVID-19, Indonesia.*

ABSTRACT

The coronavirus disease 2019 (COVID-19) has inflicted catastrophic damages in public health, economic and social stability—putting life globally on hold in 2020 and presumably a year more. Indonesia bears a heavy burden of the pandemic, counting the highest case prevalence and fatality rate in all of Southeast Asia. One hope remains in the groundbreaking universal effort in search of a vaccine against the causative virus SARS-CoV-2, which has shown success unparalleled in human vaccine development thus far. An array of modalities including novel techniques are being utilized as vaccine platforms, with the closest to phase III clinical trial completion

being mRNA (manufactured by Moderna and BioNTech/Pfizer), inactivated virus (Sinovac, Sinopharm), viral vector (Oxford/AstraZeneca, Gamaleya, Janssen/Johnson&Johnson, CanSino), and protein subunit (Novavax). The vaccine produced by BioNTech/Pfizer has been deployed to the public as the first ever licensed COVID-19 vaccine. In this review, we will review all of these modalities on their safety and immunogenicity, phase II/III trial results of the nine vaccine candidates and current situation as of 29 December 2020, as well as the implication for use and distribution in Indonesia. COVID-19 vaccine progress, however, is moving exceedingly fast and new advances are unfolding on a daily basis, to which we hope an update to this review can be published in early 2021.

Keywords: *vaccine, COVID-19, Indonesia.*

INTRODUCTION

The world changed on the eve of the new year—a cluster of pneumonia cases of unknown origin was reported out of a street market on 31 December 2019 in Wuhan, China.[1] Nine days later, the causative agent was identified as a coronavirus subsequently named SARS-CoV-2, and the clinical spectrum as the coronavirus disease 2019 (COVID-19).[2] The virus is airborne, highly transmissible between humans with a long and insidious incubation period, and outbreaks rapidly escalated out of China to the world, pushing the World Health Organization (WHO) to declare a pandemic on 11 March 2020.[3] As of 20 December 2020, the number of COVID-19 cases has reached more than 75 million people with over 1.6 million deaths globally. In Indonesia, total cases are reaching 650 thousand with active cases of almost 100 thousand—the most in Southeast Asia—with 19,390 total deaths or case fatality rate (CFR) of 3.0%.[4] At least 100 doctors died, making the death toll of health care workers in Indonesia as one of the highest in the world.[5,6] The national index case was announced on 2 March, traced from a restaurant in South Jakarta.[7] Nine months later, over 7,000 new cases and over 150 daily deaths are reported as a seven days rolling average in the country, without once having any signs of slowing down or bending the curve.[4]

As a novel zoonotic pathogen that recently crosses the interspecies barrier, humans have no reliable pre-existing immunity against SARS-CoV-2. Prior infection of human coronaviruses (hCoVs)—particularly the four ubiquitous, common cold hCoVs—has been proposed to induce cross-reactive immunity in humoral[8,9] and CD4+ T cell responses,[10–14] but their specificity to SARS-CoV-2 is poorly defined. Non-neutralizing immunity may instead create an erroneous primary immune response.[15,16] Indeed, inept and faulty coordination between adaptive immune cells and innate response, as typified by the devastating cytokine storm,[17,18] is the main pathogenesis that leads to severe disease.[19,20] Defective innate (type I interferon)[21] and cellular (T cells) immunity[20,22] are the hallmarks of COVID-19, and both have been suggested as the culprit for severity among the elderly,[23] people with comorbidities,[24] and men.[25]

Studies, however, have shown that people that survived SARS-CoV-2 infection can achieve enduring immunity, in the form of sufficiently high titer of neutralizing immunoglobulin G (IgG). Antibody titer in the plasma has been found to be stable until at least five[26] to eight months[27] after infection, albeit with marked variation between persons (as discussed later). More recently, infection has also been found to induce SARS-CoV-2-specific long-lived memory CD4+ and CD8+ T cells,[28] memory B cells,[29] and mucosal-homing IgA plasmablasts.[30] This suggests the presence of strongly immunogenic antigen held by the virus, that can be exploited as an epitope to elicit neutralizing antibodies (NAbs). These NAbs can both bind the virion and physically block viral fusion to target cells, and interact with immune components to unleash effector actions leading to antibody-mediated pathogen clearance.[31,32] In SARS-CoV-2, these NAb epitopes are all parts of the Spike (S) protein: the receptor binding domain (RBD),[33] the N-terminal domain (NTD),[34] and the conserved parts of S2 subunit.[29]

Studies in SARS-CoV[31] and MERS-CoV[35] have pinpointed the highly neutralizing epitopes

of the S glycoprotein—the outermost crown-like projections that mediates viral attachment to the human receptor ACE2.[36] This was confirmed to be true as well for SARS-CoV-2 early on in the pandemic,[33,37,38] allowing for a head start in COVID-19 vaccine production. The first genetic sequence of the virus (Wuhan-Hu-1 isolate) was posted to virological.org on 10 January[39], and vaccine-makers the world over started to work on the S epitope on the very next day. The presence of furin-cleavage site (FCS)—a tiny stretch of four amino acids RRAR—in between the S1 and S2 subunits of SARS-CoV-2 S protein was discovered as the unique yet determining factor of its greater infectivity, compared to previous coronaviruses.[40–42] Fortunately, the strongest neutralizing epitope, i.e. the RBD of S, is relatively highly conserved and vaccine directed towards this epitope may cover all circulating SARS-CoV-2 strains.[38,43] Thus, the Achilles heel was located and vaccine construction commenced using the S epitope blueprint. This is a galvanized global effort; COVID-19 vaccine development has set a record speed in the history of human vaccines. As of 28 December 2020, WHO has listed 222 vaccine candidates in development, 56 of them in clinical trials and most of which are protein subunit designs.[44] Vaccine development was further accelerated by overlapping clinical trial phases (1/2 or 2/3) and running several phase 3 trials in parallel, without sacrificing methodological integrity.[45]

RATIONALE FOR VACCINE-INDUCED IMMUNITY

The adage that 'natural infection gives better immunity than vaccination' have been held as a long-standing belief, including among health professionals. Nevertheless, vaccine technology has progressed so much in the last two decades that this outcome should be the exception rather than the norm. Recent vaccines for human papillomavirus[46] and varicella zoster virus[47] are two examples where vaccine-induced immunity is vastly superior to primary infection. As for SARS-CoV-2, the superiority of vaccine-based immunity has been proven in immunogenicity studies of frontier vaccine candidates: post-vaccination antibody assays showed higher neutralizing anti-S-IgG compared to that of convalescent plasma (will be discussed more later).[48] Analyzing the mean IgG titer revealed how vaccines triggered consistently high levels of NAb across subjects, while natural infection brought about a widely varied immune response.[49–51]

The divergence in immune response corresponds to the multifaceted clinical picture of COVID-19. Up to 45% infections were asymptomatic[52] yet 20% of older people were hospitalized,[53] and two-thirds of people aged >70 were at risk of respiratory distress and multi-organ failure.[54] The host-virus interplay is exceedingly complex for SARS-CoV-2. The virus itself is capable to evade immune detection (see bulleted points below) and attack multiple organs (e.g. heart,[55] kidney,[56] and gut[57]) through the ubiquitous ACE-2 receptor,[58] with added tropism via coreceptors such as neuropilin[59] to attack neurons.[60] As for host, genome-wide association studies (GWAS) have uncovered subtle genetic nuances affecting COVID-19 severity such as the ABO blood type (higher risk in non-O)[61], viral coreceptor TMPRSS2,[62] gene relating to intracellular viral detection (*OAS1/2/3*). innate response (interferon receptor gene, *IFNAR*, tyrosine kinase *TYK2*),[63] and trafficking of immune cells (*CCR2, CXCR6*).[64] The sheer amount of determinants to the arms race between host and the virus therefore implies the unreliability of immune response toward natural infection, and the peril of depending on it to achieve herd immunity in the population.[65]

Another proof is reinfection cases. As of 28 December 2020, 30 reinfection cases have been reported worldwide, with one death and mostly mild first infection.[66] This number is severely underreported—because the second infection can be mild,[67] and whole genome sequencing is necessary to distinguish reinfection from persistent non-infectious viral shedding, which can last for 80 days.[68] Antibodies naturally wane over time[69] and people with weak initial response may eventually seroreverted, especially in mild symptoms—US Centers for Disease Control and Prevention (CDC) reported 28% IgG seroreversion after two months among people with mild COVID-19.[70,71] While the durability

of vaccine-induced antibodies is not known yet, most vaccine candidates have shown strong initial IgG induction from the first dose.[49–51]

Early functional antibody response within 14 days of symptoms correlates with disease severity and chance of recovery,[72] and delayed humoral immunity is evident in lethal COVID-19[73], highlighting the importance of achieving strong pre-immunity via vaccine priming. Two-dose vaccination also presents a higher chance to develop enduring immune memory via memory T and B cells as well as long-lived plasma cells, as compared to one-time exposure to the pathogen (**Figure 1**).[74] Other immunological reasonings in support of vaccines over naturally induced immunity are given as follows:

- Whole virus particle presents a variety of multivalent antigens for B and T cell recognition. A wide breadth of antibodies is beneficial in some infections e.g. HIV-1,[75] but not necessarily in SARS-CoV-2—a virus with narrow diversity and an awfully slow mutational rate.[76,77] Antibodies against the nucleoprotein (N), open reading frame 3b (ORF3b) and ORF8 are dominantly produced after natural infection,[78] which is useful for diagnostic purposes but do not aid as much in viral neutralization.[79] ORF8 is specifically linked with non-neutralization and immune evasion via MHC I downregulation.[80] Conversely, vaccines with partial epitope design, e.g. protein subunit and nucleic acid, enable the introduction of specific and best selection of antigen to elicit immune response, which do exist in SARS-CoV-2: the S antigen.
- The S protein nonetheless has an element of plasticity that may modify recognition by the host immunity. The upper part of spike protein (S1) consists of three identical peptides that can exist in either "up" or "down" configuration, affecting its RBD area.[81] At least two of the three peptides need to be open for the RBD to fuse with the ACE2 receptor, and thus the "up" (or open) shape is preferred to infect the target cell. Coincidentally, this "up" shape also leaves the S1 vulnerable to antibody binding.[82] On the other hand, "down" (or closed) conformation may lessen the antibody detection of RBD, necessitating immune recognition via non-RBD sites, i.e. the NTD and S2 epitopes.[81,83] The D614G mutation—currently accounts for >99% of globally circulating SARS-CoV-2—loosens the connections between peptides and more functionally supports the "up" orientation.[84] In regard to vaccine design, studies in previous coronaviruses have discovered that the addition of two prolines (2P) in the central helix of S2 stabilizes the RBD in the "up" conformation.[35] Thus, introduction of this synthetic S-2P optimizes antibody response toward infectious virion, which may not be achieved via the natural structure of S. This S-2P motif is now used by BNT/Pfizer,[85] Moderna,[49] Novavax,[86] and Janssen/J&J.[87]
- Similarly, synthetic production may permit enhancing non-epitope modifications that support the longevity of the S protein, that otherwise do not exist in the natural antigen. For example, changing the FCS residues in the S1-S2 junction from RRAR to QQAQ renders the protein to become protease resistant. This 3Q motif is used by Novavax.[86]
- The flexibility of S protein also enables it to change shapes before and after fusion with its cognate target receptor.[88] The distinctive crown-like coronaviruses' spike is the pre-fusion S. The post-fusion S is needle-like, rigid and coated with glycans, which allow it to survive a harsher environment and also hide the RBD epitope, thus evading immune response by inducing non-neutralizing antibodies (non-NAb).[89] Therefore, the pre-fusion S—especially with "up" RBD—is the prime immunogen. While pre-fusion S construction is easily achieved in nucleic acid and subunit vaccine designs, chemical inactivation of virus may alter the S structure into the post-fusion shape. The electron immunograph of the pilot version of inactivated vaccine by Sinovac, for example, showed needle-like projections on the viral surface.[90]
- Coronaviruses naturally excel at evading innate detection by pattern recognition receptors (PRRs), especially Toll-like

receptors (TLRs)[91] and retinoid acid-inducible gene I (RIG-I) receptors,[92,93] by hiding their RNAs and pathogen-associated molecular patterns (PAMPs). Failed early detection by innate immunity leads to poor initiation of type I and type III interferon responses, which are the hallmarks of severe COVID-19. Innate immunity stimulation by several types of vaccine such as the immunogenic adenoviral vector,[94] as well as vaccine adjuvants,[95] facilitates strong induction of the more specific adaptive immune response. Adjuvants used in SARS-CoV-2 vaccines are CpG (TLR9 agonist)[96] by Sinovac, Matrix-M (saponin)[97] by Novavax, and Advax (delta inulin)[98] by Janssen/ Johnson & Johnson.[99]

VACCINE MODALITIES AND THEIR COMPARISON

Inactivated Virus

Viral inactivation is one of the oldest, tried-and-true methods to create vaccines, and have been applied to various bacterial and viral diseases such as typhoid, influenza, and human papilloma virus.[100] Viruses are first grown in mammalian cell culture before inactivated with chemicals of either formaldehyde or β-propiolactone. The method is straightforward and relatively easy, but is time-consuming and the yield depends on

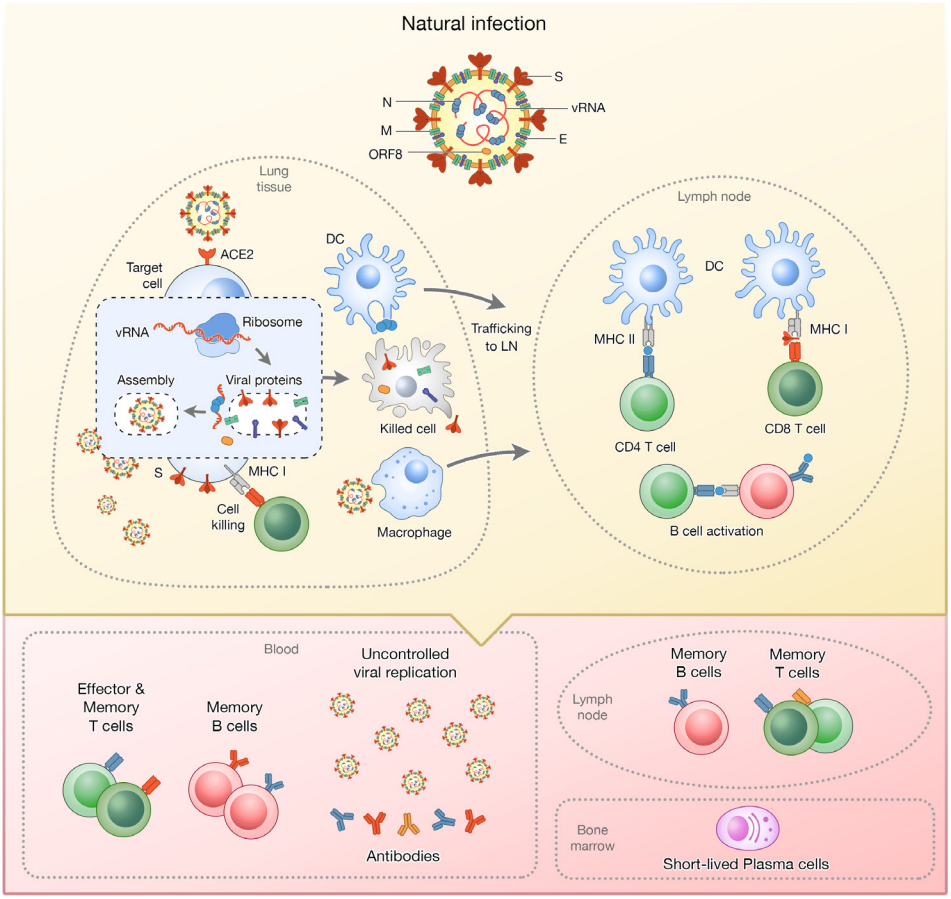

Figure 1. Immunogenesis in the natural infection of SARS-CoV-2. SARS-CoV-2 infects target cells in the lung tissue via ACE-2 receptor and coreceptors (not shown), where the virus hijacks host ribosomal process to transcribed its viral RNA (γRNA) into viral proteins, shown as spike (S, red), matrix (M, green), envelope (E, purple), nucleoprotein (N, blue) and one of the six non-structural proteins (ORF8, orange). Expression of viral proteins from infected cells leads to cell killing by cytotoxic T or natural killer cells. Antigen presenting cells (APC) such as dendritic cells (DC) and macrophages engulf either viral proteins from killed cells or the whole virion, before trafficking to the lymph node (LN). In the LN, viral antigens are presented by APC via the major histocompatibility complex (MHC) molecule class I and II to the T cell receptors of naive CD8 and CD4 T cells, respectively, to initiate activation and differentiation into effector or memory T cells. Naive B cells presenting viral antigens via MHC II are activated by CD4 T cells in the LN, initiating differentiation into memory B cells and antibody-producing plasma cells. Immune induction from a single infection also results in short-lived plasma cells in the bone marrow. Produced antibodies are multivalent and may be neutralizing, which is the anti-S antibody, or non-neutralizing to the virus. Disease outcome is determined by the arms race between viral replication against humoral and cellular immunity induction.

culture scale, viral replication in vitro, and the requirement of biosafety level 3 facilities.[101] The whole virion is presented, which might induce non-NAb (discussed above) and introduces risk of antibody-dependent enhancement (ADE).[102]

Inactivated viral vaccines manufactured by two companies in China, Sinovac and Sinopharm, have now reached phase 3 trials (**Table 1**).

CoronaVac (formerly PiCoVacc) by Sinovac is an inactivated viral vaccine with alum adjuvant. SARS-CoV-2 strain CN2 was extracted from bronchoalveolar lavage (BAL) of a hospitalized patient in Wuhan, cultured in Vero cells, harvested, inactivated using β-propiolactone, and purified before finally absorbed into aluminium hydroxide.[90] Phase 1 study involved 144 healthy adults aged 18-59 years old and yielded antibody seroconversion of slightly over 75% out of all subjects. Better purification improved the results in the phase 2 study, where seroconversion was achieved >95% out of 600 subjects.[117] While the highest antibody return resulted from 2 doses (day 0 and 28) of the 6 ug vaccine, the 3 ug was chosen for phase 3 study considering production capacity (seroconversion was 100% and 97%, respectively).

Concerns were raised, however, regarding the level of antibodies produced: geometric mean titer (GMT) of neutralizing S IgG were lower than that of human convalescent serum (HCS), i.e., antibodies resulting from natural infection (average GMT of 23.8-65.4 vs. 163.7). Meanwhile, results from other vaccine candidates showed superior GMT S IgG compared to HCS. CoronaVac's inferior immunogenicity might reflect the disadvantage of inactivated viral vaccine, such as antigen multivalency and alteration of S due to chemicals (as explained above). To address this, Sinovac referred to their immunogenicity results of their enterovirus 71 vaccine[118] also inactivated using similar processes—where vaccination was proven to be protective with GMT IgG levels of 8-24. Pre-clinical study on rhesus macaque also showed protective effect to SARS-CoV-2 infection with antibody titer of 1/24.[117]

The **BBIBP-CorV** by Sinopharm is almost a carbon copy: viruses cultured in Vero cells, inactivated with β-propiolactone and absorbed into alum. Virus strain used was HB02, obtained from a BAL sample of a hospitalized patient in Wuhan.[119] Phase 1 study recruited 192 subjects, including people over 60 years old, reporting no serious adverse effect. Phase 2 study showed a more promising immunogenicity compared to Sinovac, with 100% seroconversion achieved out of 448 subjects. NAb GMT was reported to be 282.7, but there was no comparison to that of HCS. Two doses (day 0 and 28) of the 4μg vaccine showed the highest NAb titer out of all dosing conditions tested,[120] but the clinical trial registry for phase 3 indicated 21 days interval between doses.[121]

Viral Vector

Viral vector, either replicating or non-replicating, can be used as a vehicle to introduce viral genes into cells, transcribed into viral proteins and presented to the immune system via MHC I (**Figure 2**).[122] Replicating vectors have been approved for widespread use for Ebola

Table 1. Basic Information of COVID-19 Vaccine Candidates Reaching Phase 3 Clinical Trials.

Manufacturer	Vaccine name	Antigen	Delivery platform	Ref.
BioNTech/Pfizer	BNT162b2	S	mRNA	50,103
Moderna	mRNA-1273	S	mRNA	49,104-106
University of Oxford/ Astra Zeneca	ChAdOx1 nCov-19 (AZD1222)	S	Chimpanzee adenoviral vector	107-111
Gamaleya	Sputnik V	S	Human adenoviral vector	112
Janssen/Johnson & Johnson	Ad26.COV2.S	S	Human adenoviral vector	87,113,114
CanSino	Ad5-nCoV	S	Human adenoviral vector	115,116
Sinovac	CoronaVac	S	Inactivated virus	90,117
Sinopharm	BBIBP-CorV	S	Inactivated virus	117
Novavax	NVX-CoV2373	S	Protein subunit	51,86

(rVSV-ZEBOV, a vesicular stomatitis virus)[123] and dengue virus (Dengvaxia, a chimeric yellow fever virus).[124] One non-replicating vector (Ad26)[125] is approved for Ebola virus in the European Union. Handling of live SARS-CoV-2 is not needed to assemble viral vectors, which may speed up the development process. The vast majority of vector vaccines in development for COVID-19 are non-replicating, with only one replicating vector design (using measles virus) has reached phase 1 study,[44] and thus non-replicating viral vectors are the focus in this review.

The non-replicating adenovirus (AdV) is a popular choice for vaccine design. AdV is easily grown, easily rendered replication-defective, non-pathogenic yet still causes mild inflammation necessary to generate immune response (unlike adeno-associated virus), has spacious gene capacity, broad tropism in even nondividing cells, good thermostability, and induces strong cellular immunity response. Human AdV consists of 59 serotypes and Ad5 is the first and most-widely studied for vaccine use.[94] However, AdV infection is widespread in humans, causing mild common cold at any age, and thus most people already have immunity toward the virus. Global seroprevalence of AdV antibodies is estimated to be 36-92%, with the highest in Africa (~70-100%).[126] Pre-existing immunity against the AdV vector is a major problem, as shown in the failed HIV-1 vaccine by Merck in 2008.[127] Some designs circumvent this by using the less common Ad26 or animal adenoviruses. Other issues with AdV include vector sequestering in the liver and spleen, and the dominance of vector genes over the actual antigenic genes.[128]

The four non-replicating vector vaccines reaching phase 3 are all adenoviral-based: Oxford/AstraZeneca (chimpanzee Ad), Gamaleya (Ad5/Ad26), Janssen/Johnson&Johnson (Ad26), and CanSino (Ad5). One vaccine in phase 1 uses gorilla Ad[129] and one in pre-clinical phase uses intranasal chimpanzee Ad.[130] Apart from adenoviruses, other non-replicating viral approaches for COVID-19 vaccine include modified vaccinia Ankara[131], influenza[132], human parainfluenza, adeno-associated, and Sendai virus.[44,45]

ChAdOx1 nCoV19 (or AZD1222) is an adenoviral vector-based vaccine developed by University of Oxford in the United Kingdom, in collaboration with the Sweden-based pharmaceutical company AstraZeneca. The design is based on their previous MERS-CoV vaccine[133]—the vector backbone is a replication-deficient chimpanzee adenovirus, which has human seroprevalence of 0-9%.[134] The vector contains genes encoding full length S protein with an adjuvant sequence (tissue plasminogen activator, tPA).[107] The phase 1/2 study recruited 1,077 participants aged 18-55, with a meningococcal vaccine as a control group to mask local injection reactions. Fever is more common in the ChAdOx1 group which was tolerated with prophylactic paracetamol, and no severe reactions were reported. Highest immunogenicity achieved in two-dose regimens, with anti-S IgG titer of up to median of 639 ELISA units (EU) at day 56 post-vaccination—it was not higher than HCS, however. S-specific effector T cell responses based on IFN-γ were strong, rising as early as day 7 and maintained until day 56, but not necessarily increased by the second dose.[109] The phase 2/3 study further recruited 240 people aged >70 years, which exhibited better toleration of side effects compared to younger subjects. Immunogenicity was consistent across all age groups after the second dose. The study, however, excluded people with comorbidities. Curiously, vector antibody anti-ChAdOx increases after the first dose but not the second. Two full-dose regimens were then decided for the next phase, but some implementation errors occurred (see phase 3 results below).

Sputnik V (previously Gam-COVID-Vac) was developed by Gamaleya, designed from 2 different adenoviral vectors: recombinant Ad26 and Ad5, both carrying the gene for S. Heterologous Ad vector system was chosen to circumvent the possibility of pre-existing immunity toward the vector from the first dose. In the phase 1/2 trial, 76 participants aged 18-60 years were enrolled. A single dose of rAd26-S was given on day 0 and one dose of rAd5-S was given on day 21. At day 42, NAb was 49,25 GMT with a seroconversion rate of 100%. All reported adverse reactions were mostly mild without any serious adverse events. The titres of

NAb were lower in comparison to those reported mRNA vaccines and Oxford/AstraZeneca, but the report stated that the NAb was the same as convalescent plasma from people recovered from COVID-19.[112]

Ad26.COV2.S is an Ad26-vector vaccine designed by the Belgian pharma Janssen under the American medical company Johnson & Johnson. The transgene contained in the vector encodes for full length S with addition of gene encoding tPA for adjuvant. Pre-clinical trials in mice and macaques showed robust immunogenicity in both humoral and cellular, particularly of the pre-fusion stabilized S immunogen (S-2P).[87,113] In the phase 1/2 trial, Ad26.COV2.S was administered at a dose level of $5x10^{10}$ or $1x10^{11}$ viral particles (vp) per vaccination, either as a single dose or as a two-dose schedule spaced by 56 days in healthy 18-55 years old and ≥ 65 years. There are 3 cohorts observed (1a, 1b for age 18-55 and 3 for ≥65 years). After only a single dose, seroconversion for anti-S was observed in 99% of cohort 1a participants (GMTs of 528 and 695, for the $5x10^{10}$ or $1x10^{11}$ vp dose level, respectively), and in 100% of cohort 3 (GMTs of 507 and 248), respectively. On day 14 post immunization, Th1 cytokine-producing, S-specific CD4+ T cell responses were measured in 80% and 83% in cohort 1a and 3, respectively. CD8+ T cell responses were also robust in both

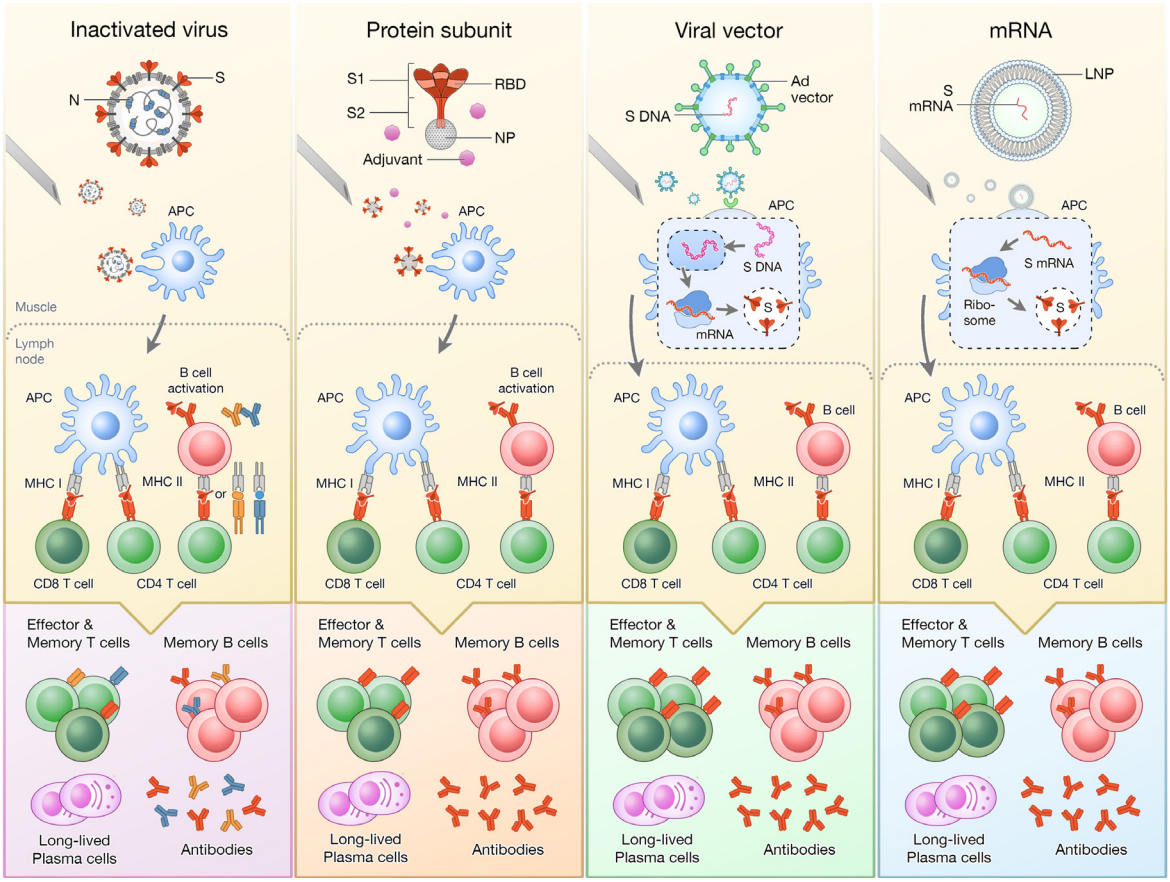

Figure 2. Comparison in immunogenesis of each vaccine platform. Natural infection, (shown in Figure 1), via ACE2-mediated cellular infection and APC presentation, produces wide variation of immunogenicity with multivalent antibodies—shown as red for anti-S, blue for anti-N, and yellow for anti-ORF8; the latter two are less neutralizing. Inactivated virus enters APC via phagocytosis, mostly utilizes MHC II presentation and also produces multivalent antibodies. Vaccine by Sinovac and Sinopharm uses alum adjuvant. While MHC I only presents small peptides of 8-9 amino acids, whole viral proteins are shown for simplicity. Protein subunit vaccine produces monovalent anti-S antibodies. Vaccine by Novavax uses saponin adjuvant to help recruit immune cells and stimulate innate pattern recognition receptors (PRR, not shown), and the S proteins are delivered embedded on nanoparticles. Adenoviral vector via episomal DNA expression and mRNA produced stronger cellular expression of S via MHC I presentation and may theoretically lead to more robust cellular immunity e.g. CD8 T cells. Vaccination with booster dose may better induce long-lived plasma cells (LLPC). Comparisons (e.g. number of antibodies, memory cells) are figurative and not quantitative. S, spike; N, nucleoprotein; ORF8, open reading frame 8; vRNA, viral RNA; RBD, receptor binding domain; MHC, major histocompatibility complex; APC, antigen presenting cells; NP, nanoparticle; Ad, adenovirus; mRNA, messenger RNA; LNP, lipid nanoparticle.

cohort 1a and 3, for both dose levels. The most frequent adverse event was local injection site pain.[114]

The Ad5-nCoV was developed by the Beijing Institute of Biotechnology and CanSino Biologics in China, where an Ad5 vector is used to express the full-length S DNA. In the phase 2 trial as published in the Lancet,[116] 603 participants aged 18 or older received either the vaccine—at a dose of 1×10^{11} or 5×10^{10} viral particles per mL—or a placebo. Vaccines were given in a single shot as a homologous booster was deemed non-beneficial for the A5 vector. Both doses of the vaccine induced significant NAb responses to authentic SARS-CoV-2, with GMTs of 19.5 (95% CI 16.8–22.7) and 18.3 (14.4–23.3) for respective doses. Seroconversion rates achieved 96% and 97%, respectively, on day 28. Robust T cell response is the best selling point of viral vector vaccine, and interferon-γ ELISA showed 90% and 88% positive responses for respective doses. Reactogenicity was mild to moderate. However, to circumvent pre-existing anti-Ad5 immunity, an additional dose was proposed to be given well after the first dose (between months 3 and 6) to boost immune endurance; similar to the previous experience with an Ad5 vector-based Ebola vaccine.

Nucleic Acid

In nucleic acid vaccine, the concept is to deliver genetic information instead of the antigen—host cellular transcriptional and translational machinery is used to construct the antigen intracellularly before expressed via the MHC I presentation. The technology is fairly recent, and no nucleic acid vaccines have been approved outside COVID-19. The nucleic acid can be DNA or RNA. DNA vaccines are similar to plasmids that are widely used for biomolecular works, which can be produced large scale in bacteria and are highly stable, but have to be administered via special devices, such as the electroporator.[135] DNA vaccines for COVID-19 have only reached phase 1 trial so far, while two RNA vaccine candidates have finished phase 3 study.[44] This review will focus only on these two RNA-based vaccines by BioNTech/Pfizer and Moderna.

The advantage of nucleic acid vaccine is that all assembly can be done in vitro without any living culture, and the freedom to construct the prime antigen expected to be the most immunogenic. The latter is similar to the benefit of recombinant protein vaccine, but oligonucleotides assembly is much faster and easier with much less cost. RNA, however, is prone to degradation to RNAse—which exists virtually everywhere—and thus RNA needs to be encapsulated with protective lipid nanoparticle (LNP). Its degradability, however, opens the possibility of fine dosing adjustment if toxicity occurs—this reason and the sheer simplicity of its structure elevates RNA vaccine as theoretically the safest method to introduce nucleic acid.[136] Further disadvantages are the need for frozen storage at -20°C, -80°C or liquid nitrogen to prevent degradation,[137] and can only be administered via injection.

The mRNA-1273 was manufactured by Moderna with support from the US National Institute of Allergy and Infectious Diseases (NIAID). The vaccine was completed within 45 days, with production starting one day after the first identification of SARS-CoV-2 sequence on 10 January. The mRNA encodes the full length S antigen, with a transmembrane anchor and an intact S1-S2 cleavage site, and two proline modification in the S2 (S-2P) stabilizes the produced S in its prefusion conformation. The latter is important to improve immunogenicity, as explained above. mRNA-1273 induces potent NAb and T cell responses in mice, including against both wild-type and the D614G mutant virus.[104] The phase 1 study was the first to put a COVID-19 vaccine into humans, which recruited 45 subjects aged 18-55 years, receiving two doses at 28 days apart. Excellent antibody response was evident after the second dose, with anti-S IgG GMT reaching 782,719 for 100 μg dose at day 57 post-vaccination. The vaccine also induced robust Th1-skewed CD4 T cell response and interferon-γ from CD8 T cells. No serious adverse event was noted, and the 100 μg is selected for phase 3 study.[49] The phase 1 study was later extended to recruit 40 older adults, stratified to age 56-70 and >70 years. Anti-S GMT was excellent in both subgroups (1,183,066

and 3,638,533, respectively), with strong CD4 Th1-skewed cytokine responses.[105]

BNT162b2 was manufactured by German biotech company BioNTech, in collaboration with the US-based pharmaceutical giant Pfizer. The mRNA encodes a pre-fusion membrane bound stabilized full-length S-2P encapsulated with LNP. A previous design, BNT162b1, encodes a secreted trimerized RBD, but the vaccine displayed higher reactogenicity in phase 1 trial and thus the b2 design was selected for later phases.[103] The b2 mRNA elicited exceedingly high neutralizing GMT in rhesus macaques, up to 18 times of that of HCS.[138] The phase 1/2 result that was published in Nature, however, was based on the b1 design. Phase 1 study recruited 45 subjects aged 18-55 years, who were randomized to receive 2 doses at 21 days apart. Local and systemic adverse events were dose-dependent, but no severe reactions were reported. As for immunogenicity, the 30 μg dose elicited excellent humoral immunity, with neutralizing GMT of 1.9-4.6-fold over that of HCS at day 28 post-vaccination. Similar to Moderna, strong Th1-skewed CD4 and CD8 T cell responses are confirmed as well at day 29.[50]

Protein Subunit

Recombinant protein vaccines can be produced from various expression systems using yeast, insect, or mammalian cells, without handling the actual pathogen. The flexibility of amino acid construction enables thorough modification of the peptide, and memory immunity induced depends on proper peptide selection and optimization, to ensure effective antigen presentation by MHC molecules across diverse demographics.[139] However, in case of SARS-CoV-2, the spike protein is relatively difficult to express in cellular expression system and may affect production yield and speed.[140] While the RBD is easier to express, full length S protein is preferred for its immunogenicity as multiple epitopes exist throughout the S1 and S2,[34] and design by BioNTech/Pfizer, for example, abandoned the RBD mRNA.[103] While subunit vaccines may elicit strong humoral immunity with the help of adjuvant, the durability and cellular-mediated immune memory is doubtful as in the case of hepatitis B,[141] thus necessitate booster doses.

NVX-CoV2372 produced by Novavax, a small US-based vaccine company,[142] contains recombinant SARS-CoV-2 S protein with matrix-M1 saponin adjuvant packaged in a nanoparticle. The protein was expressed using the Baculovirus system. In the pre-clinical trial, low-dose NVX-CoV2372 elicited excellent humoral and cellular immunity profile in mice and baboon.[143] Phase 1/2 clinical trial was conducted on 131 subjects aged 18-59 years and published in NEJM in December. Dosing was 2 injections of 3 weeks apart, which resulted in a robust humoral response as shown by the level of anti-S IgG. IgG GMT reached 3,906 after the second dose, exceeding the GMT of convalescent sera from symptomatic individuals (837) but not hospitalized patients (7,457). Th1 phenotype of CD4 T cellular response was detected as well. Adverse reactions were generally mild without any serious events.[51]

CURRENT STATUS OF VACCINE CANDIDATES AT PHASE III TRIAL, AS OF 20 DECEMBER 2020

SINOVAC (CoronaVac)

Sinovac is currently running phase 3 clinical trials in Indonesia, Turkey, Brazil, and Chile, with a target total of at least 30,000 participants (see **Table 2** for details on phase 3 trials). In Indonesia, Sinovac—in collaboration with state-owned pharmaceutical company Biofarma and Padjajaran University—has recruited 1,620 subjects aged 18-59 years in Bandung, West Java. Interim analysis may be done when a certain number of positive cases have arisen in the subject pool, which is estimated to be reached in January 2021.[144] Independent analysis is conducted by the Indonesian Food and Drug Monitoring Agency (Badan Pengawasan Obat dan Makanan, BPOM) and will grant the Emergency Use Authorization (EUA) if approved. The vaccine is administered in two doses at two weeks apart. Last blood tests to subjects are expected in December, but may be extended until March to review longer term efficacy and side effects.[145] According to interim data from the trial in Turkey, CoronaVac showed 91.25% efficacy, as only 3 of the 29 people who were infected during the trial were given the

vaccine as oppose to 26 in placebo group. This data must be interpreted with caution, however, due to the relatively small number of subjects included in interim analysis (n=1,322). The trial in Brazil reportedly reached a higher number of infected subjects (74 cases), giving an efficacy of "over 50%", but the detailed result was delayed at the company's request.[146]

Sinovac will be the main vaccine to be used by the Indonesian government, with the cost fully covered.[147] The first batch of 1.2 million doses of Sinovac vaccines has been delivered into Indonesia on 6 December, with the second batch of 1.8 million doses expected to arrive in early January.[148] The vaccine itself has been approved for limited use in China.[149] Similar to other inactivated vaccines, CoronaVac is stable at 4°C storage. The vaccine is slated to cost US$30 per dose (see **Table 3** for complete list of real-life efficiency characteristics).

SINOPHARM (BBIBP-CorV)

Phase 3 trials have included 31,000 volunteers across 125 nationalities in the UAE alone. In December, the UAE's Ministry of Health and Prevention reviewed Sinopharm interim analysis of the phase 3 trials, which shows Sinopharm inactivated vaccine to have 86% efficacy against COVID-19 infection. The analysis also shows the vaccine to have a 99% seroconversion rate of NAb and 100% effectiveness in preventing moderate and severe cases of the disease. No

Table 2. Efficacy Characteristic and Details on Phase 3 Trial of Each Vaccine Candidate.

Manufacturer	Current trial phase	Phase 3 trial location	Sample size	Subject age	Vaccine efficacy	Subgroup efficacy analysis	Safety concern
BioNTech/Pfizer	3 (completed)	US, Germany, Turkey, South Africa, Brazil, Argentina	43,548	16 years or older (including >55 years)	95% (all participants)	16-55 years:95,6% ≥ 55 years:93,7% ≥ 65 years: 94,7% ≥ 75 years: 100%	Anaphylactoid reaction (post-licensure)
Moderna	3 (completed)	US	>30,000	18 years or older (including >55 years)	94.5% (all participants)	18-<65: 93,4% ≥ 65 : 100%	ND
University of Oxford/ AstraZeneca	3 (interim)	UK, US, South Africa, Colombia, Peru, Argentina	40,000	18 years or older (including >55 years)	90.0% (LD/SD) 62.1% (SD/SD)	ND	Transverse myelitis (n=1)
Gamaleya	3 (interim)	Russia, UAE, Belarusia, India, Venezuela	>20,000	18-60 years	91.4%	N/A	ND
Novavax	3 (ongoing)	UK, India, South Africa, Mexico	15,000 (UK)	18-59 years*	ND	ND	ND
Janssen/ Johnson & Johnson	3 (ongoing)	US, Argentina, Chile, Colombia, Mexico, South Africa, Philippines	60,000	18 years or older (including >55 years)*	ND	ND	ND
Sinovac	3 (ongoing)	China, Indonesia, Brazil, Turkey, Chile	>30,000	18-59 years*	91.25% (Turkey)	N/A	ND
Sinopharm	3 (ongoing)	China, UAE, Morocco, Egypt, Bahrain, Jordan, Pakistan, Peru, Argentina	31,000	18-59 years*	86% (UAE)	N/A	ND
CanSino	3 (ongoing)	China, Pakistan, Argentina, Chile, Mexico, Russia	40,000	18 years or older (including >55 years)*	ND	ND	ND

* Based on phase 2 clinical trials; LD/SD, low dose/standard dose; SD/SD, standard dose/standard dose; N/A, not available; ND, no data.

serious safety concerns were reported. This vaccine was granted EUA in the UAE since September and Bahrain since November, to protect frontline healthcare workers at the most risk of infection.[150] Elsewhere, Sinopharm also started phase 3 testing in Morocco, Egypt, Bahrain, Jordan, Pakistan, Peru, and Argentina.[121]

Similar to the Sinovac vaccine, BBIBP-CorV can also be stored at 4°C. As for cost, the vaccine is priced at a staggering US$145 for two doses.[151]

MODERNA (mRNA-1273)

Moderna's phase 3 COVE trial, in collaboration with NIAID, enrolled more than 30,000 participants in the US. The first interim analysis was based on 95 cases, of which 90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 90-5/90 = 94.5%. A secondary endpoint analyzed severe cases of COVID-19 and included 11 severe cases in this first interim analysis. All 11 cases occurred in the placebo group and none in the mRNA-1273 vaccinated group, giving 100% efficacy in preventing severe disease. No significant safety concerns were reported as confirmed by the independent review board.[152] On 3 December, the durability of immune responses from the phase 1 trial was published in NEJM, where the neutralizing GMT at day 119 in vaccinated individuals exceeded the median GMT in convalescent sera, confirming more robust antibody longevity compared to natural infection.[106] Moderna has also registered a trial to test mRNA-1273 on adolescents aged 12-18 years.[153] Based on its excellent efficacy and safety profile, as outlined in the Vaccines and Related Biological Products Advisory Committee (VRBPAC) briefing, the US FDA authorized the EUA for the Moderna vaccine on 18 December.[154]

While mRNA generally is most stable at -80°C, the special concoction of mRNA-1273 and its LNP coating enable storage at -20°C, with possibility for -4°C for 30 days and at room temperature for 12 hours.[155] The vaccine, however, is one of the most expensive out of all with pricing at US$ 37 per dose. Moderna vaccine has been granted EUA by the US FDA on 18 December.[156] Moderna has also made deals to supply the vaccine to the European Union, Canada, Japan, and Qatar, while the Indonesian Ministry of Health granted the permission of use but any plan to purchase doses by the government is unclear.

BIONTECH/PFIZER (BNT162b2)

BioNTech/Pfizer has published their phase 3 trial in NEJM.[157] A total of 43,548 participants aged 16 years and older, including elderly aged >55 years, were assigned to receive injection

Table 3. Efficiency Characteristics of Each Vaccine Candidate.

Manufacturer	Doses	Storage	Dosing schedule	Price per dose	Global pre-order estimate (billions)	Production capacity target/year, by end of 2021 (billions)
BioNTech/Pfizer	30 ug	-70°C 2-8°C (5 days)	0.21 days	$19.5	1.1	1.3
Moderna	100 ug**	-20°C 2-8°C (1 month)	0.28 days**	$37	0.8	0.5
University of Oxford/ AstraZeneca	0.22 ml or 0.5 ml**	2-8°C	0.28 days**	$2-$5	3.2	3
Gamaleya	0.5 ml or 1.0 ml**	-18°C (frozen type); 2-8°C (lyophilized)	0.21 days**	$10	0.5	0.5
Novavax	5 ug or 25 ug*	2-8°C	0.21 days*	$16	1.4	2
Janssen/Johnson & Johnson	1 ml*	-20°C 2-8°C (3 months)	0 (single shot) or 0.56 days*	$10	1.3	1
Sinovac	3 ug or 6ug*	2-8°C	0.14 or 0.28*	$30	0.2	0.6
Sinopharm	4 ug or 8 ug*	2-8°C	0.21 days	$72.5	0.1	1
Cansino	1 ml*	ND	0 day (single shot)*	ND	ND	ND

* Based on phase 2 clinical trials. ** Based on phase 3 clinical trials interim report. ND, no data.

with 30 μg dose or placebo. Injections were given in two doses of 30 μg at day 0 and 21. Phase 3 was finished in late November—eight positive cases were observed in the vaccinated group and 162 cases in the placebo group, giving VE of 95.0% (95%CrI 90.3-97.6%), making it the first ever report on vaccine efficacy for COVID-19. Adverse events were reported more in the vaccine group than placebo (27% vs. 12%), but most were local and minimal reactions. Encouragingly, protection was consistent among all age groups including the elderly, across all racial groups and in people with comorbidities, such as obesity and diabetes, as shown in the FDA VRBPAC report.[158] The trial did not include subjects younger than 16 years, pregnant women, and the immunocompromised.

The vaccine storage requires a temperature of -70°C—which is regarded as the main drawback compared to the Moderna vaccine—but can last up to 5 days at 2-8°C. Pfizer has developed a special 10-inch cold box for thermal shipping.[159] As for pricing, the BNT162b2 was set at US$20.

BNT162b2 has now been fully approved in Canada, Bahrain, and Saudi Arabia. EUA approval was given in the UK on 2 December,[160] then the US on 11 December,[158] as well as in Singapore, Kuwait, Chile, Costa Rica, Ecuador, and Mexico. Pfizer has also made a deal with Japan and China, making it the first Western vaccine to be used in the latter. BNT162b2 was used as the first ever COVID-19 vaccination to the general public, delivered in the UK to a 91-year old female.[161] However, news of adverse effects came out soon after rollout two healthcare workers in UK—both with a history of anaphylaxis—reported anaphylactoid reaction soon after vaccine injection.[162] Three Alaskan healthcare workers without any known allergy also reported anaphylactoid reaction 10 minutes after injection, prompting epinephrine.[163] Polyethylene glycol (PEG2000) is one component in the vaccine assumed to be the allergen,[158] which may be not detected in phase 3 as the trial excluded volunteers with a history of anaphylaxis. Bell's palsy cases have also been reported but any link to the vaccine is inconclusive as the rare prevalence is similar to that of the general population.[164]

OXFORD/ASTRAZENECA (ChAdOx1 nCoV-19)

Phase 3 trials began initially in the UK and India, and soon followed by Brazil, South Africa, and the United States, totalling 23,848 participants. Interim analysis was conducted and published in November in The Lancet, when 131 COVID-19 cases were reached.[111] While the original plan was to administer two full doses in 28 days apart (standard doses, SD/SD), a subset of subjects in the UK received half dose as their first dose (low dose/standard dose, LD/SD) due to an error in the dose preparation. Surprisingly, the LD/SD dosing led to 90% VE, while the SD/SD only achieved 62%, thus averaging 70% for the two subgroups. Several hypotheses were given, including better mimicry of SARS-CoV-2 infection or the lower possibility of inciting anti-vector immunity in the LD group, but nothing was conclusive. This was regarded as good news nonetheless as lower dosing allows for more vaccine supplies, and the LD/SD dosing is expected for future rollout.

The phase 3 trial was temporarily halted twice due to the same adverse effects found in two subjects: transverse myelitis. The first one in July was concluded to be unrelated to the vaccine, while the other occurred 14 days after the second dose in a participant in the UK.[165] A transparency issue was raised as AstraZeneca failed to report the case to the US FDA.[166]

Owing to the thermostability of Ad vector, ChAdOx1 is stable at 4°C for at least six months. Astrazeneca also priced the vaccine at mere US$4, making it the cheapest vaccine announced to date. Such prospect of cost efficiency enticed global interest to the vaccine. Out of 10 billions global pre-order from 10 vaccine-makers (**Table 3**), AstraZeneca has received the most with over 3 billion doses.[167] British government ordered 100 million doses,[168] and the company joined the Operation Warp Speed in exchange for 300 million doses (covering ~60% of the US population). Outside analytics estimated that AstraZeneca is on track to account for 43% coverage in low- and middle-income countries (LMICs). The company itself has announced that the vaccines will be sold not-for-profit for until at least July 2021, and poorer countries indefinitely.

The vaccine rollout will be started first in the UK on 4 January 2021.[169]

GAMALEYA (Sputnik V)

The efficacy of the Sputnik V vaccine was 91.4%, based on the second interim analysis of data obtained 28 days after administering the first dose. Calculation was based on the analysis of data on volunteers (n = 18,794) who received both doses of the Sputnik V vaccine or placebo at the second control point. In November, the interim result was announced with 39 confirmed cases, 8 cases in the vaccinated group and 38 cases in the placebo group. The efficacy result thus was criticized as only based on a small and unspecified group of volunteers. Some had short-term minor adverse events such as pain at the injection point and flu-like symptoms.[170]

Sputnik V can be stored at 4°C and priced relatively low, at US$10. On 11 August, the Russian regulator has conditionally approved the vaccine before phase 3 trials even begun, becoming the first country to approve a COVID-19 vaccine.[171] Gamaleya is now negotiating supplies to India and several South American countries, and also announced a plan to do a joint clinical trial with AstraZeneca to explore heterologous human-chimpanzee Ad-based vaccine regimen.[172]

JANSSEN/JOHNSON & JOHNSON

The Phase 3 ENSEMBLE clinical trial observed single dose vaccine versus placebo in up to 60,000 adults aged 18 years or older, including representation from those aged 60 or over. The trial will include those with and without comorbidities associated with an increased risk of severe COVID-19, and will aim to enroll participants in Argentina, Brazil, Chile, Colombia, Mexico, South Africa and The United States.[173] The trial was halted in October due to unexplained illness in one subject;[174] the trial continued 11 days later but the cause remains unannounced.[173]

CANSINO

CanSino's phase 3 trial is still ongoing with a total of 40,000 volunteers aged 18 years or older targeted, with around 10,000 of them from Pakistan. Other sites are Argentina, Chile, Mexico, and Russia.[175]

NOVAVAX (NVX-CoV2373)

Phase 2 trial was launched in South Africa in August. For the phase 3, Novavax completed enrollment of 15,000 participants in a pivotal trial in the UK. In the United States and Mexico, 100 trial sites have been selected to recruit 30,000 participants, and slated to start on 28 December.[176] Novavax said that over 25% of participants in this trial are over the age of 65, with a 'large proportion' of volunteers also having underlying medical conditions.[177,178] There are no details on storage temperature or pricing yet.

HURDLES FOR VACCINE DISTRIBUTION

Production deals between the original manufacturer and the local biopharma factory would determine an efficient distribution in said country. For example, India has secured 2 billion doses by leveraging the production at their institute in Pune, the world's largest vaccine factory. In Indonesia, Biofarma as the local vaccine manufacturer has set a target to have more than 250 millions doses production capacity in 2021, although this ultimately depends on material supply from Sinovac.[179] No other phase 3 manufacturers are tied in any production deal with Indonesian laboratory.

Equity in worldwide vaccine distribution remains a concern. Driven by high efficacy results in interim reports, most high-income countries have already pounced on a deal with multiple vaccine makers, potentially leaving LMICs with mere excess supply. Canada leads as the best supplied countries by having readied almost nine doses per person, followed by the US (seven per person) and UK (five). Indonesia sits at eleventh place by securing at least one dose per person—half of the necessities.[167] LMICs will most likely need to rely on COVAX, a joint initiative for equitable distribution of vaccines led by GAVI, CEPI and the WHO. COVAX offers doses for at least 20% of countries' populations, and has enrolled more than 189 countries with mostly LMICs, and has secured ~700 million doses and aiming of up to 2 billion by the end of 2021.[180,181]

Another important issue is thermostability. Cold chain distribution commonly used in Indonesia uses 2-8°C, which is in line with other commonly used inactivated vaccines

such as polio. As the government has endorsed inactivated viral vaccine as the main supply, then cold chain will not become a significant problem.[182] However, this will be a challenge to distribute vaccines that must be stored at -20°C (Moderna) or or -70°C (Pfizer). Pfizer has developed a special delivery coolbox but this will become added cost. It is possible that mRNA vaccines will become limited in places with the necessary infrastructures in the big cities in Indonesia, while inactivated viral and vector vaccines (especially AstraZeneca) will be sent to peripheral communities. It may also be worth learning from the experience of Sierra Leone, where rapid establishment of a -60° cold chain distribution needed for the Ebola viral vector vaccine (rVSV-ZEBOV) successfully controlled the Ebola epidemic in 2017.[183]

Lastly, public acceptance to the vaccine largely determines coverage—skepticism and the anti-vaccine movement remains a looming threat, especially in this internet age where misinformation spread faster than scientific articles. In Indonesia, a survey conducted by the Ministry of Health together with UNICEF on 115 thousands respondents from all provinces showed that around two-thirds of respondents are willing to vaccinate themselves, and around 35% are willing to pay if the price is around 50 thousands rupiah (US$3.5). However, if the price went up to 300 thousands rupiah (US$14), only about 6% were willing to pay. The main concerns among respondents who refused were vaccines safety, effectiveness, and whether the vaccines considered halal or not.[184] Another survey in Indonesia also reported 93.3% public acceptance if the vaccine has at least 95% VE, but this acceptance dropped to 67.0% if the vaccine only has 50% VE.[185] It is hoped that strengthening the bonds between science and society through better scientific mass communication, as well as transparent and scientific evidence-based government policies may help improve public trust in the vaccine.

VACCINE SUPPLIES IN INDONESIA

It is widely assumed that Indonesia needs to reach herd immunity of ~67% nationwide in order to stop the pandemic (as discussed next). This translates to 175 million people and a necessary supply of 350 million vaccines. The latest figure of vaccine pre-order done by the Indonesian government (as of 10 December 2020) is 271 million doses, with the following listing: 125.5 million from Sinovac, 50 million from Oxford/AstraZeneca, 50 million from BioNTech/Pfizer, 30 million from Novavax, and 16 million from the country's participation in the COVAX initiative—which brand of vaccine will be distributed by COVAX is still unannounced. It is reported that the Indonesian government will also make a deal with Moderna; the amount is undisclosed. The Minister of Research and Technology has galvanized the construction of the domestic-made 'Merah Putih' vaccine—a subunit S vaccine—involving Biofarma, Eijkman Institute, Indonesian Institute of Sciences (LIPI) and four major universities.[185] The vaccine is still in pre-clinical development; phase 3 target is far away in 2022 and how many domestic supplies can be prepared is still a blur.

The government will cover 30% of vaccination through the national vaccination program and make the vaccine (Sinovac) free for certain groups of people, while 70% is expected to be covered via independent vaccination programs by private sectors. This regulation, however, may change in the future as Indonesian government plans to cover 100% of the vaccination. Government-supported distribution will be facilitated by Biofarma and deployed to Provincial Health Offices (Dinas Kesehatan Provinsi) and then to District/City Health Offices (Dinas Kesehatan Kabupaten/Kota). Then, District/City Health Offices will distribute to primary health centers (Puskesmas) and government hospitals. As for independent vaccination programs, vaccines will be distributed through Biofarma corporation and handed over to distributors to be deployed to private parties—hospitals and clinics throughout Indonesia—while still coordinating with the Provincial and District/City Health Offices.[181] A rigorous post-licensure trial and surveillance should be maintained to examine long-term safety i.e. vaccine-related adverse events, including potential of disease enhancement, as well as efficacy as signified by duration of

protection.

REACHING THE HERD IMMUNITY WITH VACCINE

When an outbreak occurs in a defenseless population, the number of new cases increases exponentially until the trajectory hits an inflection point, where sufficient people have become immune. This point is called the herd immunity threshold (HIT). HIT is reached when an infected individual on average spreads the infection to fewer than one other person, or mathematically written as HIT=1-1/R0, where R0 is the basic reproduction number.[187,188]

Given that the estimate of COVID-19 R0 in Indonesia is 2 to 3.5,[189] nationwide herd immunity is regarded as ~50-70% or 135-175 million people. This HIT formula, however, rests on the assumption that immunity (and thus, infection) is distributed evenly among members of the population, that are also mixing at random.[190] Such homogenous example is in the sentinel population in the Brazilian Amazon, where unmitigated COVID-19 spread caused an attack rate of over 70% before hitting the inflection point.[191] Homogeneity is of course not expected in the Indonesian archipelago—outbreaks start and progress differently in each island, and the SIR model among others has largely failed to predict case trajectory in the country.[192,193] Most importantly, epidemiological data have unveiled the true nature of COVID-19 pandemic as a cluster spread, i.e. breaking in big bursts of stochastic superspreader events[194] especially via indoor airborne transmission.[195] This fact is best illustrated from the case of Patient 31 in South Korea, who initiated a mega-cluster event in a church, infected in downstream a total of over 5,000 people.[196]

While R0 is reliable to estimate average contagiousness in outbreaks with a deterministic pattern e.g. influenza, R0 varies wildly in COVID-19.[197] The overdispersion parameter K may be more relevant, where K<1 indicates overdispersion, i.e. one person infects many at a single time.[194] Early in the pandemic, K was estimated to be 0.06 in Jakarta and 0.2 in Batam, indicating that 10-15% of infected people are responsible for 80% of onward transmission.[198] Factoring in the stochastic nature of transmission and variation coefficients, HIT estimates may be reduced downward to 20-50%. Nevertheless, long-term protection must be taken into account, where heterogeneity in a population may in the end average out into a well-mixed model,[199] and antibody (particularly naturally-induced) wanes over time. More important factor that may affect HIT is the ongoing mitigation program. Inconsistencies in mitigation programs across provinces in Indonesia further introduces fluctuation in the effective reproduction number (Rt). Large-scale social restriction (PSBB), although once successful to suppress Rt for example in West Java[200] and Bali,[189] was lifted prematurely in many provinces, leading to rising infection cases. These factors again highlight the importance of reaching sufficiently high herd immunity via vaccination coverage.

WHO NEEDS TO BE VACCINATED?

The priority groups to be immunized, according to the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Roadmap, are as follows: (1) health care workers with high risk for infection and transmitting SARS-CoV-2 in community, (2) groups with high risk of death or serious disease, and (3) groups with high risk of contracting and transmitting SARS-CoV-2 because they are unable to effectively distance themselves, e.g. public service officers.[201] In terms of point (2), the elderly constitutes the highest risk of death followed by those with comorbidities. Vaccination program in the UK reflects this, where the highest priority is residents in elderly care homes and their carers, followed by age >80 and fronlinte health/social care workers, then continue to the next tier in descending order of age.[202]

In Indonesia, the groups that are targeted by the government vaccination program are: health workers, military/police officers and other public service officers; community leaders, central and local government officials, teachers; some groups who receive National Health Insurance (BPJS).[203] Number of the elderly in Indonesia is huge considering the nation's population, but it is unfortunate that the main vaccine candidate from Sinovac only recruited subjects aged 18-59 years

in their phase 3 trial, leaving the government with no choice but to deter vaccination to the elderly subgroup due to lack of evidence. The consequence is paramount; subpopulation at most risk is not protected and it will certainly undermine the effort to achieve herd immunity via vaccination.

Protection to Indonesia's healthcare workers is also urgently needed. The number of health workers in Indonesia is around 700 thousands, consisting of 164 thousands doctors, 36 thousands dentists, as well as 350 thousands nurses, midwives and community health workers.[204–206] As of December 2020, the number of infected health personnels reached more than 6,000 and 363 have died.[207] EUA grant for Sinovac vaccine will allow vaccination in healthcare workers. While being a healthcare worker was associated with higher vaccine acceptance,[185] actual reception from health workers to COVID-19 vaccines and specifically the Sinovac one is unknown. Since 24 November 2020, training for health workers have been promoted by the government to increase knowledge about vaccines and their deployment programs. Judging from the feedback out of this training, as well as realistic conditions in the healthcare services, the attitudes of healthcare workers are still divided—some of them want to undergo vaccination after EUA as per the government's recommendation, but some others are waiting for phase 3 trial completion and published, peer-reviewed data. At one side, the government is hopeful for healthcare workers to take advantage of the COVID-19 vaccination program following the EUA, but the acceptance of healthcare workers keeps changing based on the available data and news circulation. Better and transparent communication between policymakers and healthcare stakeholders is crucial, using the latest scientific data as evidence, to improve understanding and trust in the vaccination program.

CONCLUSION

The development of COVID-19 vaccines is moving at a warp speed. The sheer pace, the abundance of vaccine modalities, and the proven efficacy so far proved the scientific capability we have achieved to combat an infectious disease pandemic. We also have to take into account the real-world efficiency, especially in Indonesia with its enormous population and limited infrastructure. Logistic feasibility, distribution, cost, supply availability, and vaccine acceptance are the crucial factors for a successful rollout. Governing bodies also hold a massive responsibility to ensure protection to those at most risk, including the elderly and healthcare workers, and approach closer to vaccine-induced herd immunity.

An effective and efficient vaccine will surely be a silver bullet to end the pandemic. In the meantime, we need to maintain public health mitigation efforts: distancing, masks, avoiding indoor congregation, and prioritizing good air ventilation. Current trials were designed to measure disease prevention; whether vaccines are effective to prevent innocuous SARS-CoV-2 transmission is unknown. We have to keep vigilant until population immunity can be achieved.

ACKNOWLEDGMENTS

This work is supported by the Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia. The authors would like to thank Prof. Todd Allen for the support and Prof. Shiv Pillai for the discussion. We also thank PB PAPDI Adult Immunization Task Force team for their support.

CONFLICT OF INTEREST

All authors declare no competing interests.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727–33.
2. WHO Statement regarding cluster of pneumonia cases in Wuhan, China [Internet]. [cited 2020 Dec 17]. Available from: https://www.who.int/china/news/detail/09-01-2020-who-statement-regarding-cluster-of-pneumonia-cases-in-wuhan-china.
3. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. [cited 2020 Dec 17]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-

covid-19---11-march-2020.
4. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Coronavirus pandemic (COVID-19). Our World in Data [Internet]. 2020 Mar 4 [cited 2020 Dec 17]; Available from: https://ourworldindata.org/coronavirus.
5. Setiati S, Azwar MK. Dilemma of prioritising health and the economy during COVID-19 pandemic in Indonesia. Acta Med Indones. 2020 Jul;52(3):196–8.
6. Erdem H, Lucey DR. Healthcare worker infections and deaths due to COVID-19: A survey from 37 nations and a call for WHO to post national data on their website. Int J Infect Dis. 2020 Oct 29;102:239–41.
7. Natalia DL. Presiden: Ibu-anak warga Indonesia positif COVID-19 [Internet]. Antara. 2020 [cited 2020 Dec 17]. Available from: https://www.antaranews.com/berita/1329602/presiden-ibu-anak-warga-indonesia-positif-covid-19.
8. Khan S, Nakajima R, Jain A, et al. Analysis of serologic cross-reactivity between common human coronaviruses and SARS-CoV-2 using coronavirus antigen microarray. bioRxiv [Internet]. 2020 Mar 25; Available from: http://dx.doi.org/10.1101/2020.03.24.006544.
9. To KK-W, Cheng VC-C, Cai J-P, et al. Seroprevalence of SARS-CoV-2 in Hong Kong and in residents evacuated from Hubei province, China: a multicohort study. Lancet Microbe. 2020 Jul;1(3):e111–8.
10. Le Bert N, Tan AT, Kunasegaran K, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature. 2020 Aug;584(7821):457–62.
11. Mateus J, Grifoni A, Tarke A, et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. Science. 2020 Oct 2;370(6512):89–94.
12. Weiskopf D, Schmitz KS, Raadsen MP, et al. Phenotype of SARS-CoV-2-specific T-cells in COVID-19 patients with acute respiratory distress syndrome [Internet]. medRxiv; 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.04.11.20062349v2.
13. Braun J, Loyal L, Frentsch M, et al. Presence of SARS-CoV-2-reactive T cells in COVID-19 patients and healthy donors [Internet]. medRxiv; 2020. p. 19. Available from: https://www.medrxiv.org/content/10.1101/2020.04.17.20061440v1.
14. Meckiff BJ, Ramírez-Suástegui C, Fajardo V, et al. Single-cell transcriptomic analysis of SARS-CoV-2 reactive CD4+ T cells [Internet]. bioRxiv; 2020. Available from: https://www.biorxiv.org/content/10.1101/2020.06.12.148916v1.
15. Beretta A, Cranage M, Zipeto D. Is cross-reactive immunity triggering COVID-19 immunopathogenesis? Front Immunol. 2020 Oct 15;11:567710.
16. Sette A, Crotty S. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns. Nat Rev Immunol. 2020 Aug;20(8):457–8.
17. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020 Dec 3;383(23):2255–73.
18. Rumende CM, Susanto EC, Sitorus TP. The management of cytokine storm in COVID-19. Acta Med Indones. 2020 Jul;52(3):306–13.
19. Blanco-Melo D, Nilsson-Payant BE, Liu W-C, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020 May 28;181(5):1036–45.e9.
20. Rydyznski-Moderbacher C, Ramirez SI, Dan JM, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell. 2020 Nov 12;183(4):996–1012.e19.
21. Wang Z, Pan H, Jiang B. Type I IFN deficiency: an immunological characteristic of severe COVID-19 patients. Signal Transduct Target Ther. 2020 Sep 14;5(1):198.
22. Yang L, Liu S, Liu J, et al. COVID-19: immunopathogenesis and immunotherapeutics. Signal Transduct Target Ther. 2020 Jul 25;5(1):128.
23. Pietrobon AJ, Teixeira FME, Sato MN. Immunosenescence and inflammaging: Risk factors of severe COVID-19 in older people. Front Immunol. 2020 Oct 27;11:579220.
24. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020 Aug 7;369(6504):718–24.
25. Takahashi T, Ellingson MK, Wong P, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature. 2020 Aug 26;588(7837):315–20.
26. Wajnberg A, Amanat F, Firpo A, et al. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. Science. 2020 Dec 4;370(6521):1227–30.
27. Dan JM, Mateus J, Kato Y, Hastie KM, Faliti C. Immunological memory to SARS-CoV-2 assessed for greater than six months after infection. bioRxiv [Internet]. 2020; Available from: https://www.biorxiv.org/content/10.1101/2020.11.15.383323v1.abstract.
28. Rodda LB, Netland J, Shehata L, et al. Functional SARS-CoV-2-specific immune memory persists after mild COVID-19. Cell. 2020 Nov 23;S0092-8674(20):31565–8.
29. Nguyen-Contant P, Embong AK, Kanagaiah P, et al. S protein-reactive IgG and memory B cell production after human SARS-CoV-2 infection includes broad reactivity to the S2 subunit. MBio. 2020 Sep 25;11(5):e01991–20.
30. Sterlin D, Mathian A, Miyara M, et al. IgA dominates the early neutralizing antibody response to SARS-CoV-2. Sci Transl Med. 2020 Dec 7;eabd2223.
31. Du L, He Y, Zhou Y, Liu S, Zheng B-J, Jiang S. The spike protein of SARS-CoV--a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009 Mar;7(3):226–36.
32. Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. Nat Rev Immunol. 2020 Jun;20(6):339–41.

33. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020 May;581(7807):215–20.
34. Chi X, Yan R, Zhang J, et al. A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. Science. 2020 Aug 7;369(6504):650–5.
35. Pallesen J, Wang N, Corbett KS, et al. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci U S A. 2017 Aug 29;114(35):E7348–57.
36. Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog. 2018 Aug;14(8):e1007236.
37. Shi R, Shan C, Duan X, et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. Nature. 2020 Aug;584(7819):120–4.
38. Yuan M, Wu NC, Zhu X, et al. A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV. Science. 2020 May 8;368(6491):630–3.
39. Novel 2019 coronavirus genome [Internet]. 2020 [cited 2020 Dec 17]. Available from: https://virological.org/t/novel-2019-coronavirus-genome/319.
40. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020 Mar 27;11(1):1620.
41. Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the Spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell. 2020 May 21;78(4):779–84.e5.
42. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 2020 Apr;176:104742.
43. Dearlove B, Lewitus E, Bai H, et al. A SARS-CoV-2 vaccine candidate would likely match all currently circulating variants. Proc Natl Acad Sci U S A. 2020 Sep 22;117(38):23652–62.
44. World Health Organization. Draft landscape of COVID-19 candidate vaccines [Internet]. WHO. [cited 2020 Dec 18]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
45. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020 Oct;586(7830):516–27.
46. Day PM, Kines RC, Thompson CD, et al. In vivo mechanisms of vaccine-induced protection against HPV infection. Cell Host Microbe. 2010 Sep 16;8(3):260–70.
47. Cunningham AL, Heineman TC, Lal H, et al. Immune responses to a recombinant glycoprotein E herpes zoster vaccine in adults aged 50 years or older. J Infect Dis. 2018 May 5;217(11):1750–60.
48. Burton DR, Topol EJ. Toward superhuman SARS-CoV-2 immunity? Nat Med. 2020 Nov 30;s41591.
49. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med. 2020 Nov 12;383(20):1920–31.
50. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020 Oct;586(7830):589–93.
51. Keech C, Albert G, Cho I, et al. Phase 1-2 trial of a SARS-CoV-2 recombinant Spike protein nanoparticle vaccine. N Engl J Med. 2020 Dec 10;383(24):2320–32.
52. Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: A narrative review. Ann Intern Med. 2020 Sep 1;173(5):362–7.
53. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020 Jun;20(6):669–77.
54. Clark A, Jit M, Warren-Gash C, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob Health. 2020 Aug;8(8):e1003–17.
55. Lindner D, Fitzek A, Bräuninger H, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol. 2020 Nov 1;5(11):1281–5.
56. Braun F, Lütgehetmann M, Pfefferle S, et al. SARS-CoV-2 renal tropism associates with acute kidney injury. Lancet. 2020 Aug 29;396(10251):597–8.
57. Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science. 2020 Jul 3;369(6499):50–4.
58. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020 Jul;26(7):1017–32.
59. Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science. 2020 Nov 13;370(6518):856–60.
60. Zhang B-Z, Chu H, Han S, et al. SARS-CoV-2 infects human neural progenitor cells and brain organoids. Cell Res. 2020 Oct;30(10):928–31.
61. Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, Bujanda L, et al. Genomewide association study of severe Covid-19 with respiratory failure. N Engl J Med. 2020 Oct 15;383(16):1522–34.
62. Russo R, Andolfo I, Lasorsa VA, Iolascon A, Capasso M. Genetic analysis of the coronavirus SARS-CoV-2 host protease TMPRSS2 in different populations. Front Genet. 2020 Aug 4;11:872.
63. Sa Ribero M, Jouvenet N, Dreux M, Nisole S. Interplay between SARS-CoV-2 and the type I interferon response. PLoSPathog. 2020 Jul;16(7):e1008737.
64. Pairo-Castineira E, Clohisey S, Klaric L, et al. Genetic mechanisms of critical illness in Covid-19. Nature. 2020 Dec 11;s41586.
65. Fontanet A, Cauchemez S. COVID-19 herd immunity: where are we? Nat Rev Immunol. 2020;20(10):583–4.

66. BNO News. COVID-19 reinfection tracker [Internet]. 2020 [cited 2020 Dec 19]. Available from: https://bnonews.com/index.php/2020/08/covid-19-reinfection-tracker/.
67. To KK-W, Hung IF-N, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis. 2020 Aug 25;ciaa1275.
68. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. The Lancet Microbe. 2020 Nov 19;0(0):s2666.
69. Iyer AS, Jones FK, Nodoushani A, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol. 2020 Oct 8;5(52):eabe0367.
70. Self WH, Tenforde MW, Stubblefield WB, et al. Decline in SARS-CoV-2 antibodies after mild infection among frontline health care personnel in a multistate hospital network - 12 states, April-August 2020. MMWR Morb Mortal Wkly Rep. 2020 Nov 27;69(47):1762–6.
71. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid decay of anti-SARS-CoV-2 antibodies in persons with mild Covid-19. N Engl J Med. 2020 Sep 10;383(11):1085–7.
72. Lucas C, Klein J, Sundaram M, Liu F, Wong P, Silva J, et al. Kinetics of antibody responses dictate COVID-19 outcome [Internet]. medRxiv. 2020. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.12.18.20248331
73. Zohar T, Loos C, Fischinger S, Atyeo C, Wang C, Slein MD, et al. Compromised humoral functional evolution tracks with SARS-CoV-2 mortality. Cell. 2020 Dec 10;183(6):1508–19.
74. Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol. 2020 Dec 22;s41577–020 – 00479–7.
75. Sok D, Burton DR. Recent progress in broadly neutralizing antibodies to HIV. Nat Immunol. 2018 Nov;19(11):1179–88.
76. Ophinni Y. SARS-CoV-2 mutation and dissemination in Southeast Asia: implications for a prospective vaccine. CSEAS Newsletter [Internet]. 2020 Jun 14 [cited 2020 Dec 17];(78). Available from: https://covid-19chronicles.cseas.kyoto-u.ac.jp/post-041-html/
77. Dilucca M, Forcelloni S, Georgakilas AG, Giansanti A, Pavlopoulou A. Codon usage and phenotypic divergences of SARS-CoV-2 genes. Viruses. 2020 Apr 30;12(5):498.
78. Hachim A, Kavian N, Cohen CA, et al. ORF8 and ORF3b antibodies are accurate serological markers of early and late SARS-CoV-2 infection. Nat Immunol. 2020 Oct;21(10):1293–301.
79. Park MD. Immune evasion via SARS-CoV-2 ORF8 protein? Nat Rev Immunol. 2020 Jul;20(7):408.
80. Zhang Y, Zhang J, Chen Y, et al. The ORF8 protein of SARS-CoV-2 mediates immune evasion through potently downregulating MHC-I [Internet]. bioRxiv; 2020. Available from: http://dx.doi.org/10.1101/2020.05.24.111823.
81. Henderson R, Edwards RJ, Mansouri K, Janowska K, Stalls V, Gobeil SMC, et al. Controlling the SARS-CoV-2 spike glycoprotein conformation. Nat Struct Mol Biol. 2020 Oct;27(10):925–33.
82. Lu M, Uchil PD, Li W, Zheng D, Terry DS, Gorman J, et al. Real-time conformational dynamics of SARS-CoV-2 spikes on virus particles. Cell Host Microbe. 2020 Dec 9;28(6):880–91.e8.
83. Barnes CO, Jette CA, Abernathy ME, Dam K-MA, Esswein SR, Gristick HB, et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature. 2020 Oct 12;s41586.
84. Callaway E. The coronavirus is mutating - does it matter? Nature. 2020 Sep;585(7824):174–7.
85. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med. 2020 Dec 17;383(25):2439–50.
86. Bangaru S, Ozorowski G, Turner HL, Antanasijevic A, Huang D, Wang X, et al. Structural analysis of full-length SARS-CoV-2 spike protein from an advanced vaccine candidate. Science. 2020 Nov 27;370(6520):1089–94.
87. Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature. 2020 Oct;586(7830):583–8.
88. Turoňová B, Sikora M, Schürmann C, Hagen WJH, Welsch S, Blanc FEC, et al. In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges. Science. 2020 Oct 9;370(6513):203–8.
89. Cai Y, Zhang J, Xiao T, Peng H, Sterling SM, Walsh RM Jr, et al. Distinct conformational states of SARS-CoV-2 spike protein. Science. 2020 Sep 25;369(6511):1586–92.
90. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020 Jul 3;369(6499):77–81.
91. Totura AL, Whitmore A, Agnihothram S, Schäfer A, Katze MG, Heise MT, et al. Toll-Like Receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. MBio. 2015 May 26;6(3):e00638–15.
92. Hu Y, Li W, Gao T, et al. The Severe Acute Respiratory Syndrome Coronavirus Nucleocapsid Inhibits Type I Interferon Production by Interfering with TRIM25-Mediated RIG-I Ubiquitination. J Virol [Internet]. 2017 Apr 15;91(8). Available from: http://dx.doi.org/10.1128/JVI.02143-16
93. Chang C-Y, Liu HM, Chang M-F, Chang SC. Middle

East respiratory syndrome coronavirus nucleocapsid protein suppresses type I and type III interferon induction by targeting RIG-I signaling. J Virol [Internet]. 2020 Jun 16;94(13). Available from: http://dx.doi.org/10.1128/JVI.00099-20
94. Tatsis N, Ertl HCJ. Adenoviruses as vaccine vectors. Mol Ther. 2004 Oct;10(4):616–29.
95. Iwasaki A, Omer SB. Why and how vaccines work. Cell. 2020 Oct 15;183(2):290–5.
96. Bode C, Zhao G, Steinhagen F, Kinjo T, Klinman DM. CpG DNA as a vaccine adjuvant. Expert Rev Vaccines. 2011 Apr;10(4):499–511.
97. Magnusson SE, Altenburg AF, Bengtsson KL, et al. Matrix-MTM adjuvant enhances immunogenicity of both protein- and modified vaccinia virus Ankara-based influenza vaccines in mice. Immunol Res. 2018 Apr;66(2):224–33.
98. Gordon D, Kelley P, Heinzel S, Cooper P, Petrovsky N. Immunogenicity and safety of AdvaxTM, a novel polysaccharide adjuvant based on delta inulin, when formulated with hepatitis B surface antigen: a randomized controlled Phase 1 study. Vaccine. 2014 Nov 12;32(48):6469–77.
99. Gupta T, Gupta SK. Potential adjuvants for the development of a SARS-CoV-2 vaccine based on experimental results from similar coronaviruses. Int Immunopharmacol. 2020 Sep;86:106717.
100 Rengganis I, Soegiarto G, Sinto R. Aspek imunologis imunisasi. In: Djauzi S, Rengganis I, Sundoro J, Koesnoe S, Soegiarto G, Maria S, editors. Pedoman imunisasi dewasa 2017. Jakarta: Interna Publishing; 2017. p. 37–54.
101. Sanders B, Koldijk M, Schuitemaker H. Inactivated viral vaccines. In: Nunnally BK, Turula VE, Sitrin RD, editors. Vaccine Analysis: Strategies, Principles, and Control. Berlin, Heidelberg: Springer Berlin Heidelberg; 2015. p. 45–80.
102. Lee WS, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. Nat Microbiol. 2020 Oct;5(10):1185–91.
103. Walsh EE, Frenck R, Falsey AR, et al. RNA-based COVID-19 vaccine BNT162b2 selected for a pivotal efficacy study. medRxiv [Internet]. 2020 Aug 20; Available from: http://dx.doi.org/10.1101/2020.08.17.20176651
104. Corbett KS, Edwards DK, Leist SR, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature. 2020 Oct;586(7830):567–71.
105. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020 Dec 17;383(25):2427–38.
106. Widge AT, Rouphael NG, Jackson LA, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. N Engl J Med. 2020 Dec 3;NEJMc2032195.
107. van Doremalen N, Lambe T, Spencer A, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature. 2020 Oct;586(7830):578–82.
108. Folegatti PM, Ewer KJ, Aley PK, et al. 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. Lancet. 2020 Aug 15;396(10249):467–78.
109. Barrett JR, Belij-Rammerstorfer S, Dold C, et al. Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. Nat Med. 2020 Dec 17;s41591.
110. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2020 Nov 18;396(10267):1979–93.
111. Voysey M, Clemens SAC, Madhi SA, et al. 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. Lancet. 2020 Dec 8;S0140–6736(20)32661–1.
112. Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet. 2020 Sep 26;396(10255):887–97.
113. Bos R, Rutten L, van der Lubbe JEM, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. NPJ Vaccines. 2020 Sep 28;5:91.
114. Sadoff J, Le Gars M, Shukarev G, et al. Safety and immunogenicity of the Ad26.COV2.S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial [Internet]. bioRxiv. medRxiv; 2020. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.09.23.20199604
115. Zhu F-C, Li Y-H, Guan X-H, Hou L-H, Wang W-J, Li J-X, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet. 2020 Jun 13;395(10240):1845–54.
116. Zhu F-C, Guan X-H, Li Y-H, Huang J-Y, Jiang T, Hou L-H, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020 Aug 15;396(10249):479–88.
117. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-

CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2020 Nov 17;S1473–3099(20)30843–4.
118. Li J-X, Song Y-F, Wang L, et al. Two-year efficacy and immunogenicity of Sinovac Enterovirus 71 vaccine against hand, foot and mouth disease in children. Expert Rev Vaccines. 2016;15(1):129–37.
119. Wang H, Zhang Y, Huang B, et al. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell. 2020 Aug 6;182(3):713–21.e9.
120. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2020 Oct 15;S1473-3099(20):30831–8.
122. Ura T, Okuda K, Shimada M. Developments in viral vector-based vaccines. Vaccines (Basel). 2014 Jul 29;2(3):624–41.
123. Gsell P-S, Camacho A, Kucharski AJ, et al. Ring vaccination with rVSV-ZEBOV under expanded access in response to an outbreak of Ebola virus disease in Guinea, 2016: an operational and vaccine safety report. Lancet Infect Dis. 2017 Dec;17(12):1276–84.
124. Thomas SJ, Yoon I-K. A review of Dengvaxia®: development to deployment. Hum Vaccin Immunother. 2019 Oct 7;15(10):2295–314.
125. Pollard AJ, Launay O, Lelievre J-D, et al. Safety and immunogenicity of a two-dose heterologous Ad26. ZEBOV and MVA-BN-Filo Ebola vaccine regimen in adults in Europe (EBOVAC2): a randomised, observer-blind, participant-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis. 2020 Nov 17;S1473–3099(20)30476 – X.
126. Mennechet FJD, Paris O, Ouoba AR, et al. A review of 65 years of human adenovirus seroprevalence. Expert Rev Vaccines. 2019 Jun;18(6):597–613.
127. Sekaly R-P. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? J Exp Med. 2008 Jan 21;205(1):7–12.
128. Singh S, Kumar R, Agrawal B. Adenoviral vector-based vaccines and gene therapies: Current status and future prospects. Adenoviruses. 2019;(Chapter 4):53–91.
129. Capone S, Raggioli A, Gentile M, et al. Immunogenicity of a new gorilla adenovirus vaccine candidate for COVID-19 [Internet]. bioRxiv; 2020 [cited 2020 Dec 19]. p. 2020.10.22.349951. Available from: https://www.biorxiv.org/content/10.1101/2020.10.22.349951v1.full-text.
130. Hassan AO, Kafai NM, Dmitriev IP, et al. A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2. Cell. 2020 Oct 1;183(1):169–84.e13.
131. Routhu NK, Gangadhara S, Cheedarla N, Shiferaw A. Modified vaccinia Ankara based SARS-CoV-2 vaccine expressing full-length spike induces strong neutralizing antibody response. BioRxiv [Internet]. 2020; Available from: https://www.biorxiv.org/content/10.1101/2020.06.27.175166v1.abstract.
132. Loes AN, Gentles LE, Greaney AJ, Crawford KHD, Bloom JD. Attenuated influenza virions expressing the SARS-CoV-2 receptor-binding domain induce neutralizing antibodies in mice. Viruses. 2020 Sep 5;12(9):987.
133. Folegatti PM, Bittaye M, Flaxman A, et al. Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. Lancet Infect Dis. 2020 Jul;20(7):816–26.
134. Dicks MDJ, Spencer AJ, Edwards NJ, et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. PLoS One. 2012 Jul 13;7(7):e40385.
135. Kutzler MA, Weiner DB. DNA vaccines: ready for prime time? Nat Rev Genet. 2008 Oct;9(10):776–88.
136. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov. 2018 Apr;17(4):261–79.
137. Fabre A-L, Colotte M, Luis A, Tuffet S, Bonnet J. An efficient method for long-term room temperature storage of RNA. Eur J Hum Genet. 2014 Mar;22(3):379–85.
138. Vogel AB, Kanevsky I, Che Y, et al. A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates [Internet]. bioRxiv; 2020 [cited 2020 Dec 19]. p. 2020.09.08.280818. Available from: https://www.biorxiv.org/content/10.1101/2020.09.08.280818v1.abstract.
139. Liu G, Carter B, Gifford DK. Predicted cellular immunity population coverage gaps for SARS-CoV-2 subunit vaccines and their augmentation by compact peptide sets. Cell Systems. 2020 Nov 27;S2405–4712(20)30460–1.
140. Amanat F, Stadlbauer D, Strohmeier S, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. medRxiv [Internet]. 2020 Apr 16; Available from: http://dx.doi.org/10.1101/2020.03.17.2003771.
141. Gara N, Abdalla A, Rivera E, et al. Durability of antibody response against hepatitis B virus in healthcare workers vaccinated as adults. Clin Infect Dis. 2015 Feb 15;60(4):505–13.
142. Wadman M. Will a small, long-shot U.S. company end up producing the best coronavirus vaccine? [Internet]. Science. 2020. Available from: http://dx.doi.org/10.1126/science.abf5474.
143. Tian J-H, Patel N, Haupt R, et al. SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 elicits immunogenicity in baboons and protection in mice [Internet]. bioRxiv; 2020 [cited 2020 Dec 19]. p. 2020.06.29.178509. Available from: https://www.

biorxiv.org/content/10.1101/2020.06.29.178509v1.abstract.
144. Anonymous. Bio Farma aims to submit interim review on Sinovac vaccine in January. {The Jakarta Post} [Internet]. 2020 Nov 21 [cited 2020 Dec 19]; Available from: https://www.thejakartapost.com/paper/2020/11/20/bio-farma-aims-to-submit-interim-review-on-sinovac-vaccine-in-january.html.
145. Anonymous. BPOM to extend monitoring stage of Sinovac vaccine trial for next three months. {The Jakarta Post} [Internet]. 2020 Dec 15 [cited 2020 Dec 19]; Available from: https://www.thejakartapost.com/news/2020/12/15/bpom-to-extend-monitoring-stage-of-sinovac-vaccine-trial-for-next-three-months.html.
146. Turkey says China's Sinovac COVID vaccine 91.25% effective in late trials. Reuters [Internet]. 2020 Dec 24 [cited 2020 Dec 28]; Available from: https://www.reuters.com/article/health-coronavirus-turkey-china-int-idUSKBN28Y1R3
147. Tani S. Jokowi pledges free COVID vaccinations for all Indonesians. Nikkei Asia [Internet]. 2020 Dec 16 [cited 2020 Dec 20]; Available from: https://asia.nikkei.com/Spotlight/Coronavirus/Jokowi-pledges-free-COVID-vaccinations-for-all-Indonesians.
148. Anonymous. 1.2M doses of China-made COVID vaccine arrive in Indonesia. Associated Press [Internet]. 2020 Dec 6 [cited 2020 Dec 8]; Available from: https://apnews.com/article/technology-indonesia-joko-widodo-coronavirus-pandemic-china-4e741b7b44447eee54bde32481418bf5.
149. Anonymous. Sinovac's coronavirus vaccine candidate approved for emergency use in China - source. Reuters [Internet]. 2020 Aug 28 [cited 2020 Dec 19]; Available from: https://www.reuters.com/article/us-health-coronavirus-china-vaccines-idUSKBN25O0Z3.
150. UAE Ministry of Health and Prevention. UAE Ministry of Health and Prevention announces official registration of inactivated COVID-19 vaccine used in #4Humanity Trials [Internet]. WAM. 2020 [cited 2020 Dec 19]. Available from: https://www.wam.ae/en/details/1395302893589.
151. Anonymous. China Sinopharm chief rules out high price for coronavirus vaccine. The Jakarta Post [Internet]. 2020 Aug 18 [cited 2020 Dec 20]; Available from: https://www.thejakartapost.com/news/2020/08/18/china-sinopharm-chief-rules-out-high-price-for-coronavirus-vaccine.html.
152. Moderna Therapeutics. Moderna's COVID-19 vaccine candidate meets its primary efficacy endpoint in the first interim analysis of the Phase 3 COVE study [Internet]. Moderna. 2020 [cited 2020 Dec 19]. Available from: https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy.
153. Moderna Therapeutics. Moderna announces first participants dosed in phase 2/3 study of COVID-19 vaccine candidate in adolescents [Internet]. Moderna. 2020 [cited 2020 Dec 19]. Available from: https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-first-participants-dosed-phase-23-study-covid.
154. Food and Drug Administration. VRBPAC December 17, 2020 Meeting Announcement [Internet]. FDA. 2020 [cited 2020 Dec 19]. Available from: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-17-2020-meeting-announcement.
155. Moderna Therapeutics. Moderna announces longer shelf life for its COVID-19 vaccine candidate at refrigerated temperatures [Internet]. Moderna. 2020 [cited 2020 Dec 20]. Available from: https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-longer-shelf-life-its-covid-19-vaccine.
156. U.S. Food and Drug Administration. FDA takes additional action in fight against COVID-19 by issuing emergency use authorization for second COVID-19 vaccine [Internet]. FDA; 2020 [cited 2020 Dec 29]. Available from: https://www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid
157. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 10;NEJMoa2034577.
158. Food and Drug Administration. VRBPAC December 10, 2020 Meeting Announcement [Internet]. FDA. 2020 [cited 2020 Dec 20]. Available from: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-10-2020-meeting-announcement.
159. Barston S. Cracking the cold case [Internet]. Walgreens Newsroom. [cited 2020 Dec 20]. Available from: https://news.walgreens.com/covid-19/stories/cracking-the-cold-case.htm.
160. Herper M, Goldhill O, Chakradhar S, Goshua A. U.K. approves Pfizer's Covid-19 vaccine, putting pressure on FDA [Internet]. STAT. 2020 [cited 2020 Dec 20]. Available from: https://www.statnews.com/2020/12/02/u-k-approves-pfizers-covid-19-vaccine-putting-pressure-on-fda/.
161. Triggle N. Covid-19 vaccine: First person receives Pfizer jab in UK. BBC [Internet]. 2020 Dec 8 [cited 2020 Dec 19]; Available from: https://www.bbc.com/news/uk-55227325.
162. Triggle N, Schraer R. Covid-19 vaccine: Allergy warning over new jab. BBC [Internet]. 2020 Dec 9 [cited 2020 Dec 19]; Available from: https://www.bbc.com/news/health-55244122.
163. Firger J, Caldwell T. Third Alaskan health care worker has allergic reaction to Covid-19 vaccine. CNN [Internet]. 2020 Dec 19 [cited 2020 Dec 19]; Available

from: https://www.cnn.com/2020/12/18/health/alaska-third-allergic-reaction-vaccine/index.html.
164. Higgins-Dunn N. FDA staff recommends watching for Bell's palsy in Moderna and Pfizer vaccine recipients [Internet]. CNBC. 2020 [cited 2020 Dec 20]. Available from: https://www.cnbc.com/2020/12/15/fda-staff-recommends-watching-for-bells-palsy-in-moderna-and-pfizer-vaccine-recipients.html.
165. Knoll MD, Wonodi C. Oxford-Astra Zeneca COVID-19 vaccine efficacy. Lancet. 2020 Dec 8;S0140–6736(20)32623–4.
166. Mahase E. Covid-19: Vaccine trials need more transparency to enable scrutiny and earn public trust, say experts. BMJ. 2020 Oct 22;371:m4042.
167. Mullard A. How COVID vaccines are being divvied up around the world. Nature. 2020 Nov 30;d41586–020 – 03370–6.
168. Department for Business, Energy & Industrial Strategy. Funding and manufacturing boost for UK vaccine programme [Internet]. gov.uk. 2020 [cited 2020 Dec 8]. Available from: https://www.gov.uk/government/news/funding-and-manufacturing-boost-for-uk-vaccine-programme.
169. Yorke H, Rudgard O, Sheridan D, et al. Millions to receive Oxford coronavirus vaccine from Jan 4. The Daily Telegraph [Internet]. 2020 Dec 26 [cited 2020 Dec 28]; Available from: https://www.telegraph.co.uk/news/2020/12/26/millions-receive-oxford-jab-jan-4/
170. Gamaleya Institute. Second interim analysis of clinical trial data showed a 91.4% efficacy for the Sputnik V vaccine on day 28 after the first dose; vaccine efficacy is over 95% 42 days after the first dose [Internet]. Sputnik V. 2020 [cited 2020 Dec 20]. Available from: https://sputnikvaccine.com/newsroom/pressreleases/second-interim-analysis-of-clinical-trial-data-showed-a-91-4-efficacy-for-the-sputnik-v-vaccine-on-d/
171. Burki TK. The Russian vaccine for COVID-19. Lancet Respir Med. 2020 Nov;8(11):e85–6.
172. Gamaleya Institute. Astra Zeneca will test using component of Russia's Sputnik V in clinical trials of its own vaccine against coronavirus [Internet]. Sputnik V. 2020 [cited 2020 Dec 20]. Available from: https://sputnikvaccine.com/newsroom/pressreleases/astrazeneca-will-test-using-component-of-russia-s-sputnik-v-in-clinical-trials-of-its-own-vaccine-ag/.
173. Johnson & Johnson. Johnson & Johnson prepares to resume phase 3 ENSEMBLE trial of its Janssen COVID-19 vaccine candidate in the U.s [Internet]. Johnson & Johnson. 2020 [cited 2020 Dec 19]. Available from: https://www.jnj.com/our-company/johnson-johnson-prepares-to-resume-phase-3-ensemble-trial-of-its-janssen-covid-19-vaccine-candidate-in-the-us.
174. Herper M, Goldhill O, Florko N, Facher L, Brodwin E. Johnson & Johnson Covid-19 vaccine study paused due to illness. STAT [Internet]. 2020 Oct 13 [cited 2020 Dec 19]; Available from: https://www.statnews.com/2020/10/12/johnson-johnson-covid-19-vaccine-study-paused-due-to-unexplained-illness-in-participant/.
175. ICH GCP Clinical Trials Registry. Clinical trial on COVID-19: Recombinant novel coronavirus vaccine (adenovirus type 5 vector), placebo [Internet]. ICH GCP. 2020 [cited 2020 Dec 20]. Available from: https://ichgcp.net/clinical-trials-registry/NCT04526990.
176. National Institute of Health. Phase 3 trial of Novavax investigational COVID-19 vaccine opens [Internet]. NIH; 2020 Dec [cited 2020 Dec 29]. Available from: https://www.nih.gov/news-events/news-releases/phase-3-trial-novavax-investigational-covid-19-vaccine-opens
177. Novavax. Novavax announces COVID-19 vaccine clinical development progress [Internet]. Novavax. 2020 [cited 2020 Dec 20]. Available from: https://ir.novavax.com/news-releases/news-release-details/novavax-announces-covid-19-vaccine-clinical-development-progress.
178. Parsons L. Novavax moves closer toward launch of US phase 3 COVID-19 vaccine trial. PMLive [Internet]. 2020 Dec 2 [cited 2020 Dec 20]; Available from: https://www.pmlive.com/pharma_news/novavax_moves_closer_toward_launch_of_us_phase_3_covid-19_vaccine_trial_1358854.
179. Anonymous. Bio Farma to produce more than 16 million doses of COVID-19 vaccine per month. The Jakarta Post [Internet]. 2020 Oct 20 [cited 2020 Dec 20]; Available from: https://www.thejakartapost.com/news/2020/10/20/bio-farma-to-produce-more-than-16-million-doses-of-covid-19-vaccine-per-month.html.
180. Berkley S. COVAX explained [Internet]. GAVI. 2020 [cited 2020 Dec 8]. Available from: https://www.gavi.org/vaccineswork/covax-explained.
181. World Health Organization. Global equitable access to COVID-19 vaccines estimated to generate economic benefits of at least US 153 billion in 2020–21, and US 466 billion by 2025, in 10 major economies, according to new report by the Eurasia Group [Internet]. WHO. 2020 [cited 2020 Dec 8]. Available from: https://www.who.int/news/item/03-12-2020-global-access-to-covid-19-vaccines-estimated-to-generate-economic-benefits-of-at-least-153-billion-in-2020-21.
182. Kementerian Kesehatan Republik Indonesia, editor. Perencanaan vaksinasi COVID-19. In: Juknis Pelayanan Vaksin COVID-19. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020. p. 20–3.
183. Jusu MO, Glauser G, Seward JF, et al. Rapid establishment of a cold chain capacity of -60°C or colder for the STRIVE Ebola vaccine trial during the Ebola outbreak in Sierra Leone. J Infect Dis. 2018 May 18;217(suppl_1):S48–55.
184. Satgas Penanganan Covid. Hasil Kajian [Internet]. covid19.go.id. 2020 [cited 2020 Dec 19]. Available

from: https://covid19.go.id/p/hasil-kajian/covid-19-vaccine-acceptance-survey-indonesia.
185. Harapan H, Wagner AL, Yufika A, et al. Acceptance of a COVID-19 vaccine in Southeast Asia: A cross-sectional study in Indonesia. Front Public Health. 2020 Jul 14;8:381.
186. Adelayanti N. Minister of Research and Technology Builds "Merah Putih" Vaccine Acceleration Team [Internet]. Universitas Gadjah Mada. 2020 [cited 2020 Dec 20]. Available from: https://ugm.ac.id/en/news/20429-minister-of-research-and-technology-builds-merah-putih-vaccine-acceleration-team.
187. Fox JP, Elveback L, Scott W, Gatewood L, Ackerman E. Herd immunity: basic concept and relevance to public health immunization practices. Am J Epidemiol. 1971 Sep;94(3):179–89.
188. Ma J, Earn DJD. Generality of the final size formula for an epidemic of a newly invading infectious disease. Bull Math Biol. 2006 Apr;68(3):679–702.
189. Wirawan IMA, Januraga PP. Forecasting COVID-19 transmission and healthcare capacity in Bali, Indonesia. J Prev Med Public Health. 2020 May;53(3):158–63.
190. Fine P, Eames K, Heymann DL. "Herd immunity": A rough guide. Clin Infect Dis. 2011 Apr 1;52(7):911–6.
191. Buss LF, Prete CA Jr, Abrahim CMM, et al. Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic. Science. 2020 Dec 8;eabe9728.
192. Sulaiman A. On dynamical analysis of the data-driven SIR model (COVID-19 outbreak in Indonesia) [Internet]. medRxiv; 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.06.22.20137810v1.abstract.
193. Nuraini N, Khairudin K, Apri M. Modeling simulation of COVID-19 in Indonesia based on early endemic data. Communication in Biomathematical Sciences. 2020 Apr 17;3(1):1–8.
194. Endo A, Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Abbott S, Kucharski AJ, Funk S. Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. Wellcome Open Res. 2020 Jul 10;5:67.
195. Morawska L, Milton DK, Others. It is time to address airborne transmission of COVID-19. Clin Infect Dis. 2020;6:ciaa939.
196. Choi S, Ki M. Estimating the reproductive number and the outbreak size of COVID-19 in Korea. Epidemiol Health. 2020 Mar 12;42:e2020011.
197. Mohd MH, Sulayman F. Unravelling the myths of R0 in controlling the dynamics of COVID-19 outbreak: A modelling perspective. Chaos Solitons Fractals. 2020 Sep;138:109943.
198. Hasan A, Susanto H, Kasim M, Nuraini N, Triany D, Lestari B. Superspreading in early transmissions of COVID-19 in Indonesia. medRxiv [Internet]. 2020; Available from: https://www.medrxiv.org/content/medrxiv/early/2020/07/24/2020.06.28.20142133.full.pdf.
199. Tkachenko AV, Maslov S, Elbanna A, Wong GN, Weiner ZJ, Goldenfeld N. Persistent heterogeneity not short-term overdispersion determines herd immunity to COVID-19 [Internet]. arXiv [q-bio.PE]. arXiv; 2020. Available from: http://arxiv.org/abs/2008.08142
200. Hasan A, Nasution Y. A compartmental epidemic model incorporating probable cases to model COVID-19 outbreak in regions with limited testing capacity. medRxiv [Internet]. 2020; Available from: https://www.medrxiv.org/content/10.1101/2020.07.30.20165282v1.abstract.
201. World Health Organization. WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply [Internet]. WHO. 2020 [cited 2020 Dec 20]. Available from: https://www.who.int/publications/m/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply.
202. Department of Health and Social Care. Priority groups for coronavirus (COVID-19) vaccination: advice from the JCVI, 2 December 2020 [Internet]. gov.uk. 2020 [cited 2020 Dec 20]. Available from: https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-2-december-2020/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-2-december-2020.
203. Kementerian Kesehatan Republik Indonesia, editor. Perencanaan vaksinasi COVID-19. In: Juknis Pelayanan Vaksin COVID-19. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020. p. 20–3.
204. Ikatan Dokter Indonesia. Statistik anggota [Internet]. IDI. [cited 2020 Dec 20]. Available from: http://www.idionline.org/statistik/.
205. PB PDGI [Internet]. [cited 2020 Dec 20]. Available from: http://pdgi.or.id/halaman/statistik.
206. Badan Pusat Statistik. Persebaran perawat di Indonesia 2019 [Internet]. BPS. 2020 [cited 2020 Dec 20]. Available from: https://databoks.katadata.co.id/datapublish/2020/03/26/persebaran-perawat-di-indonesia-2019.
207. Anonymous. 363 tenaga medis meninggal karena Covid-19, ini 3 saran dari IDI. Kompas.com [Internet]. 2020 Dec 16 [cited 2020 Dec 20]; Available from: https://www.kompas.com/sains/read/2020/12/16/070200323/363-tenaga-medis-meninggal-karena-covid-19-ini-3-saran-dari-idi?page=all.