Next Generation COVID-19 Vaccines

KEY FACTS

The first vaccines produced for COVID-19 used novel technologies like mRNA (Pfizer, Moderna) and viral vector-based platforms (AstraZeneca and Janssen).

Next-generation or second-generation vaccines are vaccines that are beginning to be available now that **may offer improvements** on the first wave of COVID-19 vaccines in several areas:

Providing better and longer lasting protection against COVID-19, especially **against new variants**

Fewer side effects, for example by giving smaller doses

Easier to give to people, such as with **needle-free vaccines**

Less expensive, achieved with new low-cost manufacturing

These advantages are not just great for preventing COVID-19, but also for responding more quickly to future pandemics, and may apply to vaccines for other pathogens.

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Why Do We Need Next Generation COVID-19 Vaccines?

In response to COVID-19, fast-track vaccine development led to regulatory approval of multiple candidates within a year.

Large-scale real-world studies have reported substantial protection conferred by first generation vaccines against symptomatic disease and severe outcomes in addition to being safe and tolerable.

However, next-generation COVID-19 vaccines can offer an improvement on the first wave of COVID-19 vaccines.

Waning of Vaccine Effectiveness: Evidence for 1st generation vaccines shows that their effectiveness against symptomatic disease and infection declines over time. New vaccines that provide longer lasting protection are needed.

Efficacy against variants: Mutations in SARS-CoV-2 have reduced the efficacy of existing COVID-19 vaccines. Vaccines designed to target currently circulating variants can provide better protection.

Prevention of transmission: Reducing onward transmission of SARS-COV-2 by infected individuals is an important goal. Intranasal and oral vaccines can induce immunity in the mucosal lining of the respiratory pathway and may play an important role in reducing transmission.

Easier logistics: Next generation vaccines may help address current challenges including storage requirements, affordability and/or programmatic feasibility.

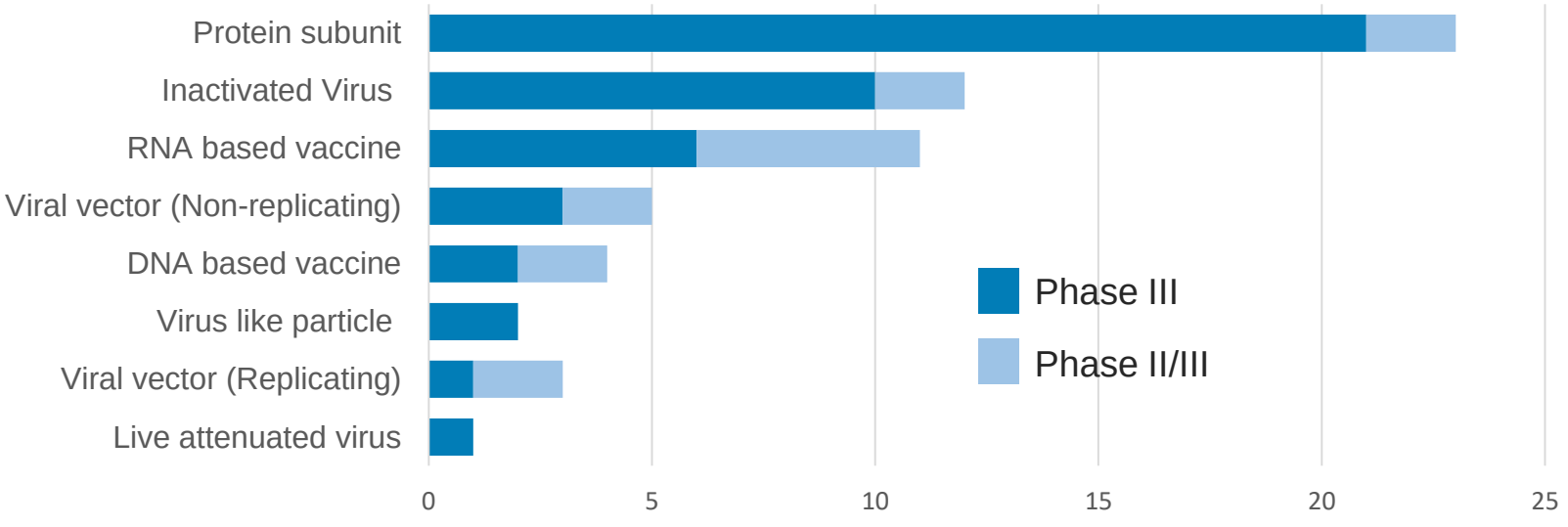
Where Do We Stand with COVID-19 Vaccine Development?

Number of COVID-19 vaccines in each stage of development

Pre-clinical **199** → Phase I or II **105** → Phase II/III **16** → Phase III **50** → **13** WHO Emergency Use Listing; **49** Regional or Country Approval

67% of vaccines in Phase II/III and Phase III trials are protein subunit and inactivated vaccines which are based on more traditional vaccine technologies and are easier to manufacture and distribute. This may improve access to COVID-19 vaccines regardless of where people live.

Vaccine Platforms in Phase II/III & Phase III Clinical Trials



How Can New COVID-19 Vaccines Improve Upon Current Ones?

Number of vaccines in Phase III trials with novel attributes

**In addition to the new Moderna and Pfizer BioNTech bivalent Omicron vaccines currently in use*

Considerations for Next Generation Vaccine Development

Scalability: The feasibility to rapidly manufacture next-generation platforms on a large scale is currently unclear.

Vaccine effectiveness: Data on vaccine efficacy and real-world effectiveness against emerging variants is sparse and mostly from high-income nations.

SARS-CoV-2 genome: A key bottleneck is the rapidly evolving mutational change in the SARS-CoV-2 structure which raises concerns about vaccine efficacy.

Cost of advanced technologies: Some vaccine platforms like DNA-based vaccines use special delivery devices or require adjuvants and delivery molecules which will need to be manufactured on a mass scale as well. This may not be feasible for small-scale pharmaceutical companies and new vaccine producing countries.

Willingness to vaccinate: Vaccines that are locally produced may not be trusted as well as better known vaccines and could adversely impact vaccine uptake.

Manufacturing capacity: Manufacturing supply chains designed to produce vaccines for clinical studies may struggle to meet the increased volume requirements of a vaccination program once emergency use or market authorization has been granted.

Uniform Packaging: Country-specific packaging and labeling that deviates from WHO recommended standards for COVID-19 vaccines may limit the number of countries that can use them.

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Some Next Generation COVID-19 Vaccines Use New Platforms

This section highlights a few vaccines employing platforms that, while new for COVID-19, include some that have been in use for other diseases for years. These COVID-19 vaccines using **DNA**, **virus-like particles** and **replicating viral vector** platforms have received country/regional approval for use or are in Phase III development.

DNA Vaccines

DNA-based vaccines work by inserting a genetically engineered blueprint of viral gene(s) into small DNA molecules (called plasmids).

Licensed vaccines that use this strategy: None

Advantages

- Easily adaptable technology
- Manufacturing process is relatively rapid
- Non-infectious
- Induction of T and B cell immune responses
- Thermostable and less refrigeration requirements

Disadvantages

- May require special techniques to administer
- Potential integration into human genome
- May produce a mild immune response and require subsequent boosting
- High production costs

Plant-based Virus-like Particle

Virus-like particle (VLP) vaccines closely resemble viruses but are non-infectious because they contain no viral genetic material. Since VLPs cannot replicate, they provide a safer alternative to attenuated viruses.

Licensed vaccines that use this strategy: HPV, Hep B

- Non- infectious
- Highly immunogenic
- Safe for immunocompromised individuals
- Faster manufacturing process
- Stability
- No risk of mutation
- No allergens

- Assembly of the particles may be challenging
- Lower yield than mammalian cells
- Requires specialized technology

Replicating Viral Vector Vaccines

This involves putting a gene for a viral protein into a different virus. Replication of the viral vector also produces copies of the viral protein, which triggers an immune response to that protein.

Licensed vaccines that use this strategy: Recombinant vesicular stomatitis virus (rVSV)-Zaire Ebola virus vaccine and live attenuated tetravalent Dengue vaccine

- Well established technology
- Elicits broad immune response
- Can be engineered to deliver vaccine antigens to specific cells or tissues

- Assembling the vaccine requires multiple steps, which may increase chances of contamination
- May impair response to other strains of target pathogen
- Concerns about safety in immunocompromised patients
- Scalability can be an issue

DNA Vaccines

Product: ZyCoV-D - *Authorized for use*

- **Manufactured by**: Zydus Cadila
- **Number of doses**: 3
- **Route of administration**: Intra-dermal using needle free Tropis ID jet injector system
- **Efficacy**: A three-dose regimen of ZyCoV-D, was found to be 67% effective against symptomatic COVID-19 during a Delta-predominant period.
- **Storage**: ZyCoV-D is stored at 2-8°C but has shown good stability at temperatures of 25ºC for at least three months.
- **Authorization by**: Drug Controller General of India (DCGI)
- **Countries of use**: India- Two dose vaccine regimen for children above 12 years of age

Plant-based Virus Like Particle

Why do we use plants? 1) Ability to produce large quantities of recombinant protein at low-cost, 2) Do not require expensive fermentation facilities for biomass generation, 3) Low-risk of introducing human pathogens.

Product: Medicago Covifenz - *Authorized for use*

- **Manufactured by:** Medicago Inc.
- **Number of doses**: 2
- **Route of administration**: Intra-muscular (IM)
- **Efficacy**: Phase III vaccine efficacy was 70% against symptomatic COVID-19 disease and 79% against moderate-to-severe disease during Delta and Gamma circulation.
- **Storage**: Unopened vials must be stored in a refrigerator (2-8°C). Once the antigen and adjuvant components are mixed, the vaccine must be used within 6 hours, handled, and stored at room temperature (20-30°C).
- **Authorization by**: Approved by Health Canada
- **Countries of use**: Canada for age groups 18 to 64 years.

Replicating Viral Vector Vaccines

Product: Wantai Biopharm - *In the pipeline*

- **Manufactured by:** University of Hong Kong, Xiamen University, and Beijing Wantai Biological Pharmacy.
- **Number of doses**: 2
- **Route of administration**: Intranasal
- **Efficacy**: The results of phase I on 60 healthy subjects and phase II on 720 healthy subjects indicated that the vaccine is well- tolerated and immunogenic. Phase III trial is under investigation in the Philippines, and no data have been reported on therapeutic efficacy, on adjuvant used, and treatment-related SAE. So far, 5 trials in 3 countries have been conducted to assess their safety and efficacy.
- **Authorization by**: Awaiting approval
- **Countries of use**: Awaiting approval

Next Generation Oral and Intranasal Vaccines

Although most COVID-19 vaccines are delivered using needles, oral and intranasal vaccines have been used to protect children against other diseases such as polio and influenza.

Despite limited success of intranasal vaccines in the past (e.g. flu), they may offer some key advantages. These include induction of strong mucosal immune response to prevent infection, elimination of needle-associated injuries, less training and faster to administer, and less expensive.

There has been steady, substantive progress with multiple oral and intranasal COVID-19 candidates. Three oral vaccines are in phase I or II clinical trials, and at least 12 intranasal vaccines are in clinical development**. Five intranasal vaccines are in late stage evaluation:** the four described below and Beijing Wantal Biological described on the previous page.

Viral Vector (Non-replicating): Currently in Phase III and Authorized for Use

Product: Ad5-nCoV

- **Manufactured by:** CanSino
- **Manufactured in:** China
- **Number of doses**: 1
- **Route of administration**: Intra-nasal (inhaled through nose and mouth)
- **Efficacy**: Safe and more immunogenic following two-dose priming with CoronaVac compared to three doses, although immune responses waned over time.
- **Storage**: 2-8°C
- **Authorization by**: National Medical Products Administration of China
- **Countries of use**: China- To be used as a booster dose

Protein Subunit: Authorized for Use

Product: RAZI-COV PARS

- **Manufactured by:** Razi Vaccine and Serum Research Institute
- **Manufactured in:** Iran
- **Number of doses**: 2
- **Route of administration**: Intra-nasal (spray)
- **Efficacy**: : In phase III trial (status unknown). No published results of vaccine efficacy. In phase I/II trials, the vaccine was reported to be safe and immunogenic
- **Storage:** 2-8°C
- **Authorization by**: Received emergency authorization in Iran in October 2021
- **Countries of use**: Iran

Viral Vector (Non-replicating): Currently in Phase III and Authorized for Use

Product: BBV154

- **Manufactured by:** Bharat Biotech and Washington University
- **Manufactured in:** India
- **Number of doses**: 2
- **Route of administration**: Intra-nasal (drops)
- **Efficacy**: Unpublished preliminary findings indicated that the vaccine is safe and effective at eliciting a strong immune response when used either as a primary vaccine or as a booster.
- **Storage**: 2-8°C
- **Authorization by**: Drug Controller General of India (DCGI)
- **Countries of use**: India- Two dose vaccine regimen for adults above 18 years of age

Live Attenuated: In the Pipeline

Product: COVI-VAC

- **Manufactured by:** Codagenix Inc. and Serum Institute of India
- **Manufactured in:** India
- **Number of doses**: 1
- **Route of administration**: Intra-nasal (drops)
- **Efficacy**: Phase I unpublished data reported robust serum antibody response as well as mucosal immune response. Currently, phase I trial using COVI-VAC as a heterologous booster in individuals previously immunized is underway.
- **Storage**: Stable outside ultra-low temperature freezers.
- **Authorization by**: Pending authorization
- **Countries of use**: None

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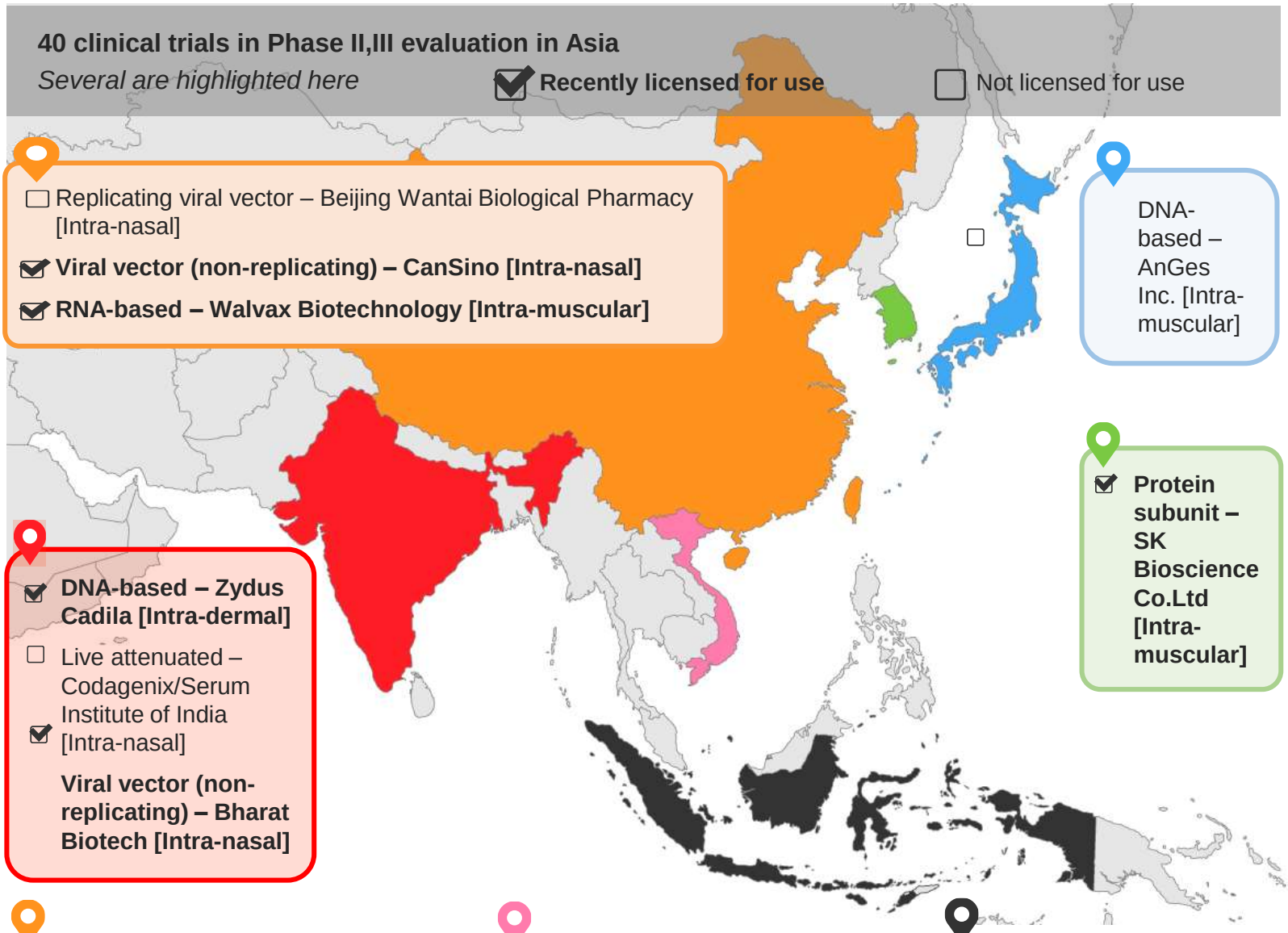
New COVID-19 Vaccines in Use or in Clinical Development (Phase II/III) in Asia

Asian countries have taken various initiatives for the development and manufacturing of COVID-19 vaccines. The map highlights a few of the vaccines that have recently been or soon will be approved in Asian countries not already described in previous sections.

In addition to vaccines already in use, there are **40 Phase II/III or III clinical trials in Asia:** 9 in China, 7 in India, 6 in Philippines, 5 in Japan, 5 in Indonesia, 4 in Russia, 3 in Thailand, and 1 in Singapore.



RNA-Based Vaccine

Walvax COVID-19 (ARCoV)

Approved for Use

- **Manufactured by:** Walvax Biotechnology
- **Manufactured in:** China
- **Number of doses**: 2
- **Route of administration**: Intra-muscular
- **Efficacy**: No published findings from Phase III trials. Reported efficacy of 71% against moderate disease by the Omicron variant.
- **Storage: thermostable at room temperature for at least 1 week. Can be stored at (2–8 °C)** for six months
- **Authorization by**: Approval by Indonesia's food and drug agency
- **Country of use**: Indonesia

Protein Subunit

Nanocovax

- **Manufactured by:** Nanogen Pharmaceutical Biotechnology
- **Manufactured in:** Vietnam
- **Number of doses**: 2
- **Route of administration**: Intra-muscular
- **Efficacy**: In phase III trial , the vaccine's protective efficacy was 52% against symptomatic infections by the Delta variant and 93% against hospitalisation/death.
- **Storage:** 2°C to 8°C
- **Authorization by**: Pending emergency use approval
- **Low cost: Currently priced at USD 5 a dose.**

Protein Subunit

Indovac

Approved for Use

- **Manufactured by:** PT Bio Farma and Texas Children's Hospital Center for Vaccine Development
- **Manufactured in:** Indonesia
- **Number of doses**: 2
- **Route of administration**: Intra-muscular
- **Efficacy**: against hospitalisation/death.
- **Storage:** 2°C to 8°C
- **Authorization by**: Authorised by Indonesia Ministry of Health

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New Omicron Vaccines

There are 4 new Omicron vaccines in phase III trials:

Sponsor (Vaccine Platform)	Variants/Sub-Variants Targeted	Location
Novavax (Protein subunit)	Bivalent - Subvariant BA.4, BA.5	Australia
Sinovac (Inactivated vaccine)	Monovalent - Omicron (BA.1)	China
Sinovac (Inactivated vaccine)	Trivalent - Prototype, Delta and Omicron (BA.1)	Columbia
Beijing Institute of Biological products (Inactivated vaccine)	Monovalent - Omicron variant (BA.1)	Hong Kong

What We Don't Know About the New COVID-19 Vaccines

Challenges with assessing new vaccines: The Efficacy of new COVID-19 vaccines against current and future variants is not easily measured since finding an unvaccinated comparison group with no prior immunity is difficult. Immunogenicity studies and vaccine effectiveness studies will need to account for pre-existing immunity.

Length of immunity: We don't know how long protection of the new vaccines lasts for all outcomes.

On the Horizon

Adjuvants may play an important role in improving immunity conferred by inactivated vaccines.

Novel **needle-free technologies** like:

- High density microarray patch (HD-MAP) currently under evaluation by Vaxxas and researchers in Australia.
- Oral recombinant COVID-19 vaccine, currently in Phase II trials by Vaxart.

Vaccines designed to **provide broad protection** against SARS-like betacoronaviruses using a mosaic approach.

- 'Mosaic-8' vaccine showed an effective immune response against multiple SARS-like betacoronavirus strains in mice and non-human primates.

mRNA vaccines that **do not require ultra-cold chain** (or can be stored at 2-8^{o}C)

- Chula Cov-19 (currently in Phase II trials in Thailand) and Walvax COVID-19 vaccine (currently approved for use in Indonesia) are also thermostable at room temperature for at least 1 week.

Smaller doses using self-amplifying (saRNA) technologies that may cause fewer side-effects.