Prevention of SARS CoV-2 Infection: Vaccine Development in Japan

Chairman, Biopharmaceutical Committee, Vaccine Subcommittee, Japan Pharmaceutical and Manufacturers Association (JPMA)

Akihisa Fukushima, Ph.D.

Disclaimer

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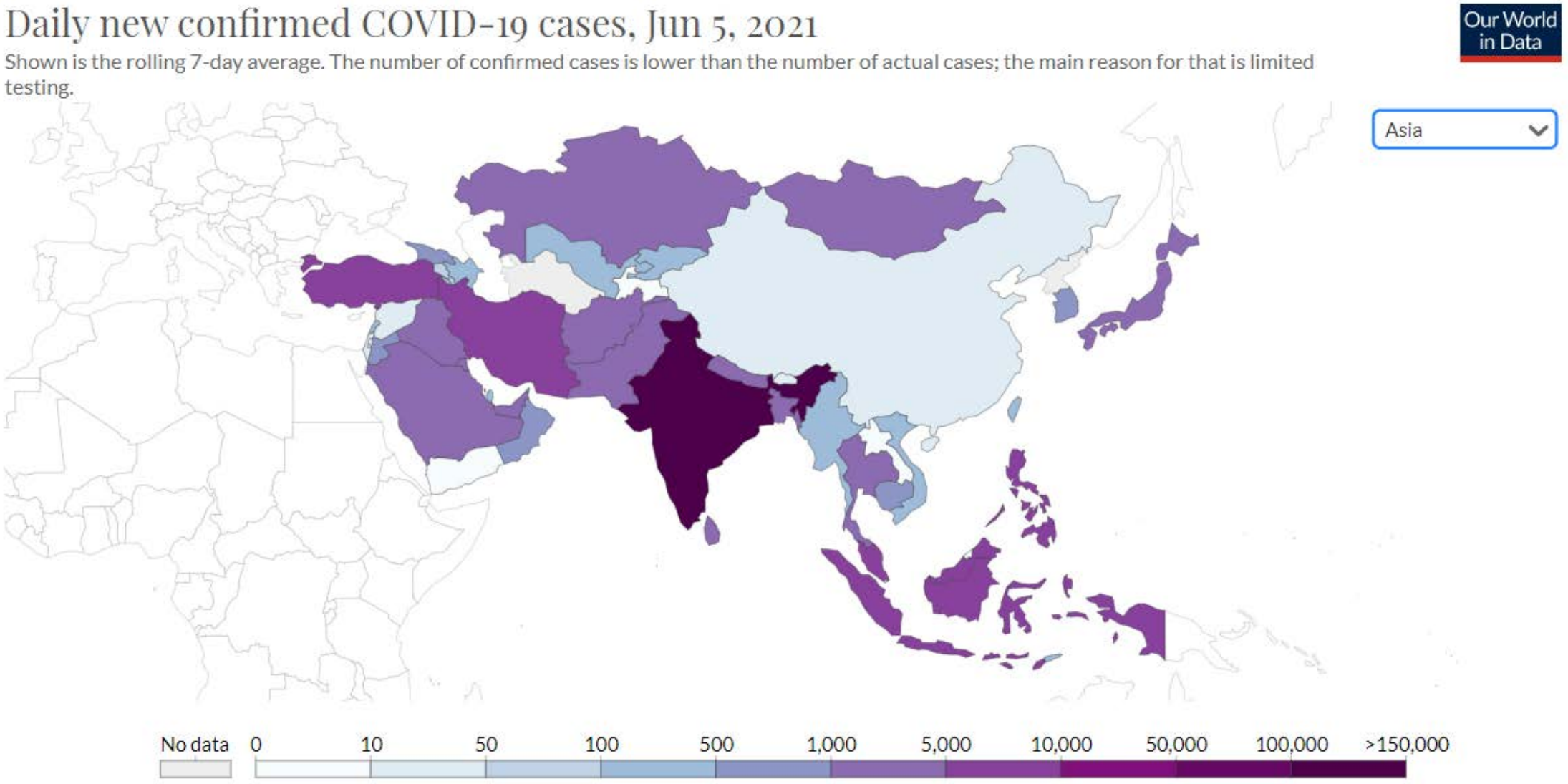
Agenda

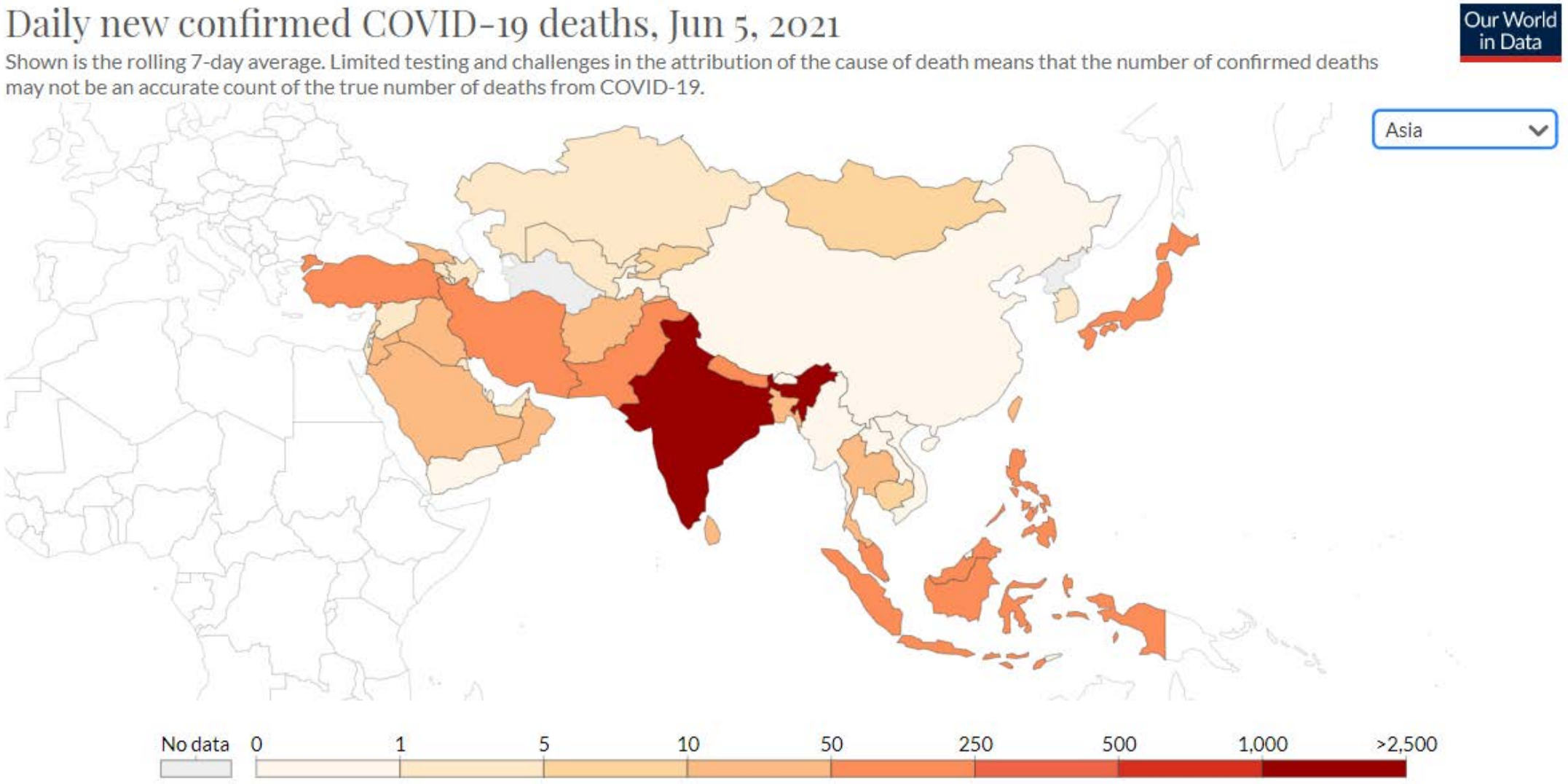
1. Current COVID Situation in Asia and Japan
2. COVID-19 Vaccines and Candidates
3. Challenges in Japan COVID-19 Vaccine Development
4. Pandemic Preparedness
5. Reshaping Vaccine Ecosystem

Daily new confirmed COVID-19 cases



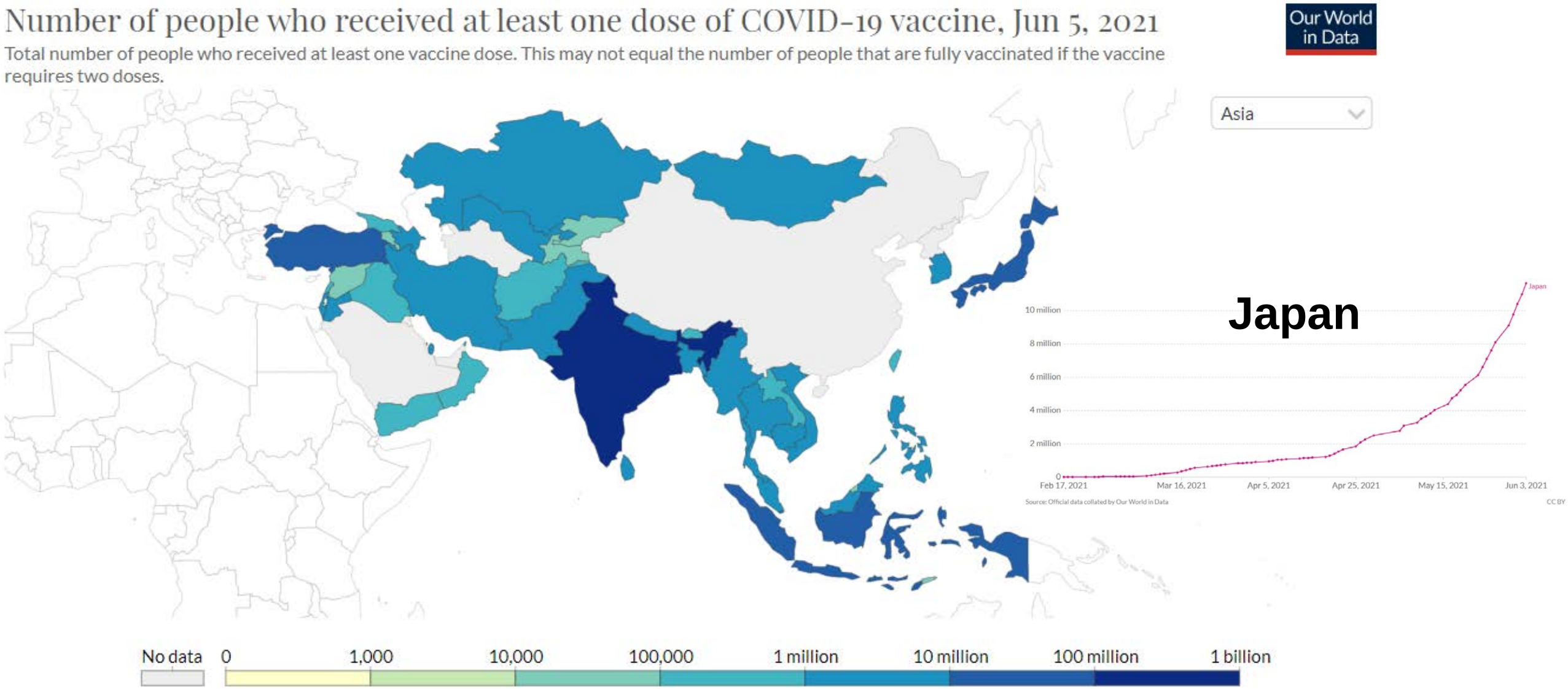
Source: https://ourworldindata.org/ CC BY

Daily new confirmed COVID-19 deaths



Source: https://ourworldindata.org/

People COVID-19 Vaccinated



Source: https://ourworldindata.org/covid-vaccinations,

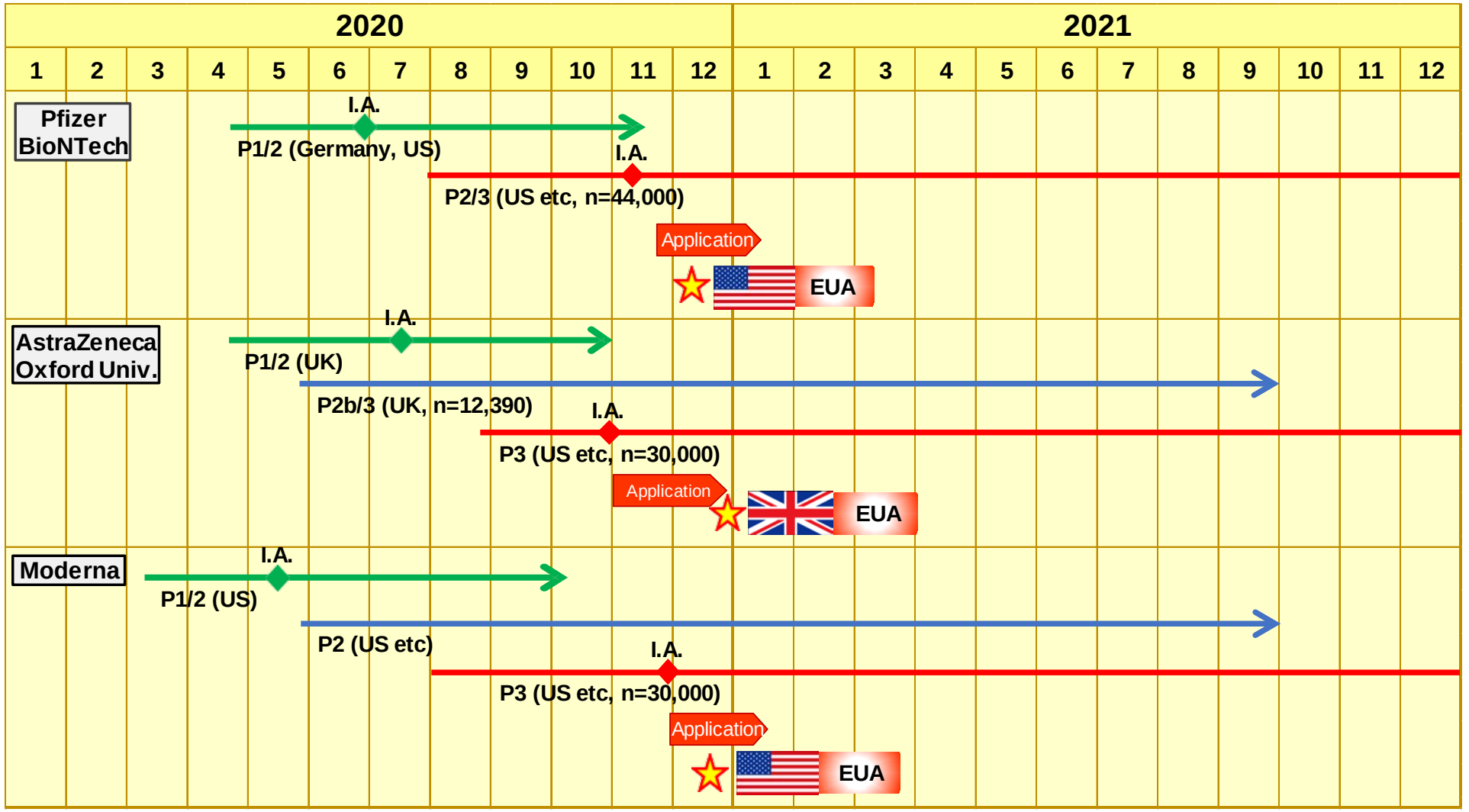
Type of COVID-19 Vaccines

	Annotation	Key Features	Developers e.g.
Conventional	A vaccine that uses the pathogen itself as an antigen. A vaccine that uses an attenuated pathogen is called a "live vaccine", and a vaccine that uses a part of bacteria or viruses that have lost their pathogenicity is called an "inactivated vaccine".	• The production method differs depending on the vaccine type, and a dedicated production line is required. • Difficult to control production volume and quality.	KM Biologics, Sinovac, Sinopharm
Subunit, Recombinant	No pathogens are used. Proteins, which are components of pathogens, are created by genetically modified technology.	• A variety of vaccines can be produced in one production line. • Stable production and quality. • Refrigeration can be stored and distributed.	Shionogi Pharm. / UMN Pharm., Novabax GSK / Sanofi
DNA	No pathogens are used. DNA, which is a blueprint for creating proteins in the body, is called DNA vaccine. DNA is converted into mRNA in the body, and proteins are biosynthesized based on the sequence of mRNA.	• A variety of vaccines can be produced in one production line. • Stable production and quality. • Storage and distribution at low temperatures (-20 to 30 ° C) are required.	Angers / Osaka Univ. Inovio Pharmamaticals
mRNA	No pathogens are used mRNA, which is a blueprint for creating proteins in the body, is enclosed in lipid particles and administered is called an "mRNA vaccine". Proteins are biosynthesized based on the sequence of mRNA administered.	• A variety of vaccines can be produced in one production line. • Stable production and quality. • Storage and distribution at ultra-low temperatures (-20 to -70 ° C) are required.	Daiichi Sankyo / Tokyo Univ., Pfizer / Biontec, Modelna CureBack
Viral Vector	Vaccines with non-toxic or weakly toxic viruses against humans. Inserted DNA in a virus, a blueprint for creating proteins in the body, is called a "virus vector vaccine."	• Mass production is possible at low cost. • Can be stored and distributed in refrigerators (2-8 ° C).	AstraZeneca / Ox ford University, J.J., Russia Gamalya Institute

Status: Global COVID-19 Vaccine Development

Developer	Status overseas	Production/Supply prospect	Status in JP
Pfizer (US) mRNA vaccine UK: 02Dec20 US: 11Dec20 EU: 21Dec20	Since July 2020, P3 trials (44K people) has started in the US and other countries. Vaccinated has started in the UK, US and EU.	Expected to produce up to 50M vaccines by the end of 2020 and up to 2B by the end of 2021.	If the vaccine is successfully developed, a contract will be signed with Japan to receive 144M within 2021. Approved in Japan (2021/2/14).
AZ, Oxford Univ. (UK) Viral vector vaccine UK: 30Dec20 EU: 29Jan21	P2/3 trials have been underway in the UK since May 2020. P3 trial (10K people) is underway in Brazil since Jun 2020. A P3 study (40K people) has been conducted in the US since Aug 2020. Vaccination started in the UK.	Production plans for 2B people worldwide. Plan to supply 300M people to the US, 100M people to the UK, 400M people to EU, and 1B people to emerging countries.	If the vaccine is successfully developed, a contract will be signed with Japan to receive 120M doses, of which 30M doses by Mar 2021. In addition to supplying APIs from overseas, JCR Pharma will manufacture APIs in Japan. Partnered with 4 domestic companies for filling, etc. The MHLW subsidizes 16.23B yen for the establishment of a system for manufacturing and formulation of APIs in Japan (emergency maintenance project for production system, etc.). Approved in Japan (2021/5/21).
Moderna (US) mRNA vaccine US: 18Dec20 EU: 06Jan21 UK: 08Jan21	P3 trials in the US from Jul 2020 (30K people) is being underway. Vaccination started in the US.	Plans to supply 500M to 1B doses / year to the world. Plans to supply 20M times in the US by the end of Dec 2020.	Under domestic distribution by Takeda, a contract was signed to receive 40M supplies in the first half of 2021 and 10M supplies in the 3Q2021. Takeda was adopted for AMED research funding. Approved in Japan (2021/5/21).
J&J(Janssen)(US) Viral vector vaccine US: 27Feb21 EU: 11Mar21	Since Sep 2020, P3 trials (60K people) have been conducted in the US and other countries. Since Nov 2020, P3 trials (30K people) have been conducted in the UK and other countries.	Aim for mass supply from 2021 (sequentially, 1B people a year in the world).	Domestic clinical trials have been conducted since Sep 2020.
Sanofi (FR) Recombinant protein vaccine, mRNA vaccine	P2b trials have been underway in the US and other countries since Feb 2021. P1/2 trials of the mRNA vaccine have been underway since March 2021.	Announced that the vaccine is expected to be put into practical use in the 4Q2021, if it goes well. (Adjuvant AS03 Supplied by GSK.)	
Novavax (US) Recombinant protein vaccine	P3 trials in the UK from Sep 2020 (15K people) is being implemented. Since Dec 2020, P3 trials (30K people) have been conducted in the US and other countries.	Overseas, the target is to produce 100M doses / year in late 2020.	Takeda plans to manufacture and sell from the drug substance. Announced that it will build a production capacity of over 250M times a year. The MHLW subsidizes Takeda for 30.14B yen for the production system (emergency maintenance project for the production system, etc.). Takeda was adopted for AMED research funding (second public offering in 2020). A domestic clinical trial has been underway since Feb 2021.

Global COVID-19 Vaccine Development Timeline



I.A.: Interim Analysis
EUA : Emergency Use Authorization

COVID-19 vaccine procurement scheme in Japan

1. Purchase contracts with individual companies

Formal contract signed-off

- **Moderna (US) / Takeda Pharm. (JP) (29 Oct 20)**
  40M doses of COVID-19 vaccine will be supplied by Takeda. in the first half of 2021 and 10M doses in the 3Q 2021 if developed successfully.
- **AZ (UK) (10 Dec 20)**
  120M doses of COVID-19 vaccine will be supplied from the beginning of 2021 if developed successfully. (Of which, about 30M will be supplied during the 1Q2021).
- **Pfizer (US) (20 Jan 21)**
  144M doses of COVID-19 vaccine will be supplied by end of 2021 if developed successfully.

Additional contract signed-off

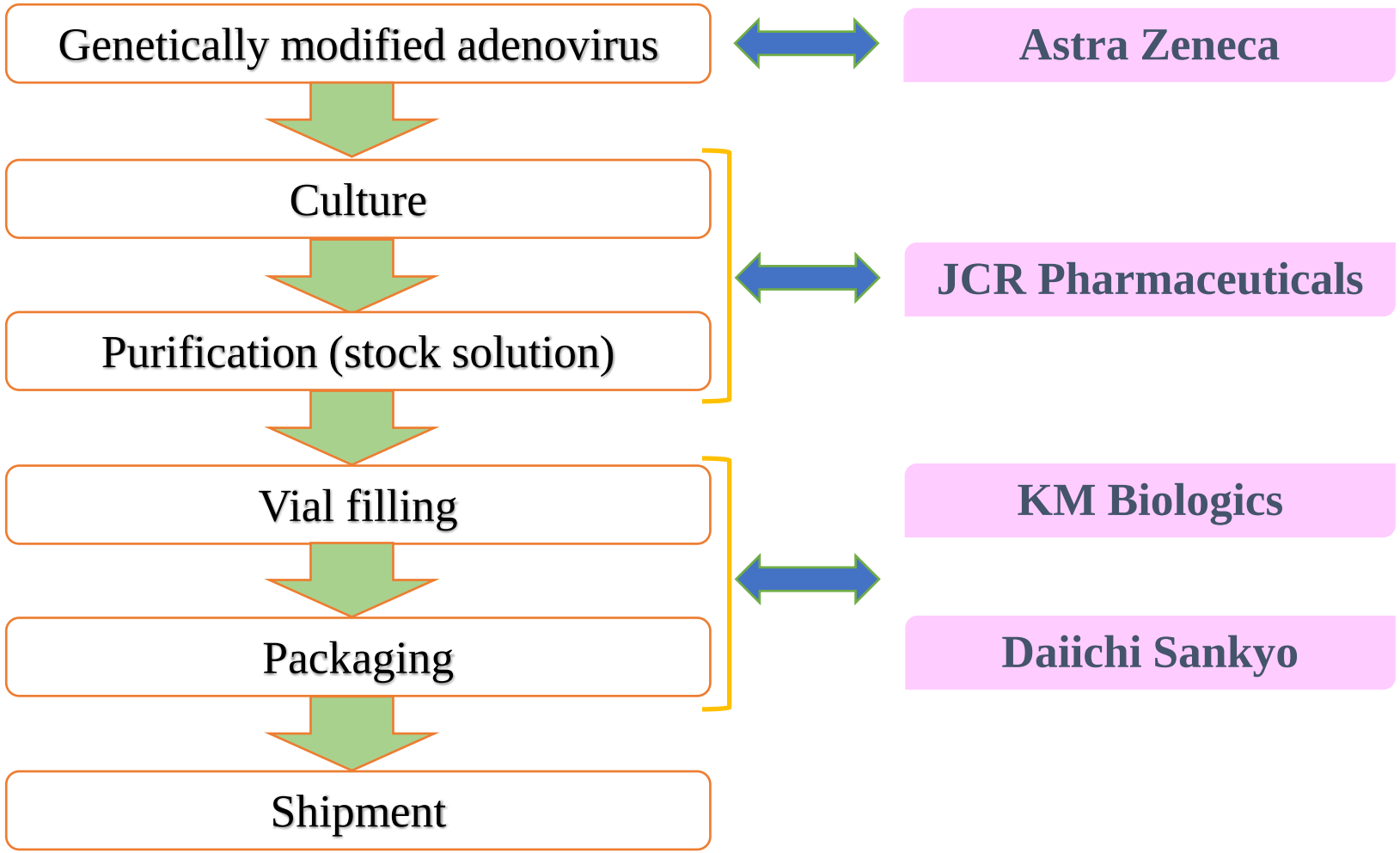
- **Pfizer (US) (20 Jan 21)**
  50M doses of COVID-19 vaccine will be supplied in the 3Q 2021 in addition to current supply above.

Contract under negotiation

- **Moderna (US) / Takeda (JP)**
  In addition to the existing contract, 50M doses is under discussion to supply them from the beginning of next year (2022).
- **Novavax (US) / Takeda (JP)**
  150M doses of COVID-19 vaccine will be supplied by Takeda Pharma. From the beginning of 2022 if developed successfully.

2. Participation in COVAX Facility

e.g.) COVID-19 Vaccine Cross-company Collaboration in Japan



Status: JP COVID-19 Vaccine Development

	Basic info	Phase	Prospect of production	Funding
Shionogi /NIID/UMN	Recombinant viral protein (antigen)	P1/2 trial started (Dec 2020)	30M people by the end of 2021. Aim to build a production system for minutes. Emergency maintenance business such as production system Subsidized 22.3B yen	• AMED (2019) 100M yen NIID • AMED (1st open offering in 2020) 1,309M yen Shionogi • AMED (2020 secondary open call)
Daiichi Sankyo/IMSUT	mRNA vaccine	P1/2 trial started (Mar 2021)	Emergency maintenance business such as production system Subsidized 6.03B yen	• AMED (2019) 150M yen Institute of Medical Science, University of Tokyo • AMED (2020 year secondary open offering)
AnGes/Osaka Univ./Takara Bio	DNA vaccine	P1/2 trial started (Osaka City Univ., Osaka Univ.) P2/3 trial started (8 institutes in Tokyo and Osaka)	Manufactured by Takara Bio, AGC, Kaneka, etc. and subsidized 9.38B yen for the production system (emergency maintenance project for the production system, etc.)	• MHLW (2019) 10M yen Osaka Univ. • AMED (1st open offering in 2020) 2,000M yen AnGes • AMED (2020 secondary open offering)
KM Biologics/IMSUT/NIID/NIBIOHN	Inactivated vaccine	P1/2 trial started (Mar 2021)	Subsidized 6.09B yen (emergency maintenance project for the production system, etc.)	• AMED (1st open call in 2020) 1,061M yen KM Biologics • AMED (2020 secondary open offering)

JP EUA system and immediate response to current issues

1. Development of legal framework (continuous)

JP EUA legislation

- Implement optimal measures appropriately and promptly in response to the "emergency situation" in which JP is placed

2. Dealing with the current system (immediate)

Flexible early approval system

- Expanded application to COVID-19 related medicines, etc. from the viewpoint of responding immediately to current emergencies

Challenges in JP COVID-19 vaccine development (1)

Approved vaccines might make it difficult to conduct placebo-controlled onset prevention studies in near future.

- **(Alternative 1) Verification trial with neutralization activity as surrogate endpoint**
  - Neutralization activity of domestic clinical trial specimens, measurement by the standardized method (NIID)
  - Necessary to compare neutralization activity data among different methods
  - Based on above, by comparing with the neutralization activity data of the vaccine of which onset preventive effect has confirmed
- **(Alternative 2) Human challenge study**
  - Currently being considered for safe human challenge study in Europe, including the UK, and investigating existing vaccines in this year

Challenges in JP COVID-19 vaccine development (2)

Being supplied in countries where clinical trials have been conducted, the scalable vaccine manufacture is required.

- **To ensure the security of supply including those for non-Japanese citizens, as JP vaccines would be required and supplied in countries where the clinical trials have been conducted.**
  - National support is needed to increase production capacity for overseas supply
  - To secure its own vaccines in Japan, and also could contribute to international cooperation

Challenges in JP COVID-19 vaccine development (3)

Necessary to establish a Japanese manufacturing systems to secure vaccines in Japan

- **To secure raw materials and materials for the production of JP vaccines due to increase of demand**
  - In the US, the Defense Production Act was enforced to restrict exports of related materials and accelerate the production of US domestic vaccines. In the EU, vaccine exports will be restricted, and in India, the preferential supply of manufactured vaccines to the domestic market. It will lead to delay the supply of vaccines overseas.
  - Harder to obtain related materials necessary for vaccine production in Japan.
  - Necessary to support the securing of vaccine raw materials by government, and to improve production systems in Japan in future

Challenges in JP COVID-19 vaccine development (4)

Early approval of JP vaccine is essential for national security because new variants occur in near future

- **Required reasonable and agile regulation application for JP vaccines**
  - —Neutralizing antibodies induced by currently available vaccines have been reported to be slightly less active against South African and Brazilian strains
  - —In the US, immunogenicity data (neutralizing activity) in clinical trial is acceptable for an additional emergency use authorization (EUA) against new mutant strains without new clinical trials which vaccine has been authorized by EUA
  - —Risks of new variants occur in Japan and spread out, possibility that vaccines against the Japanese mutant strain might not be supplied by overseas companies
  - —Essential to approve the JP vaccines earlier through agile regulatory operation and prepare for prompt response in the home country

Background: JP COVID-19 Vaccine Development Delay

- **Insufficient preparedness against emergencies such as pandemics**
  - Huge and continuous R&D supports: e.g., DARPA * under the direct control of the President and Secretary of Defense within the U.S. Department of Defense in 2013
  - Many vaccine developers receive development and supply support from US BARDA **
  - In Japan, the government lacks investment and support for innovation of vaccines and infectious disease therapeutics in academia, companies, etc., and shrinking activities of research, clinical study, and technology platform development
- **Safety issue concerns and strict regulations at the cost of speed**
  - The US Food and Drug Administration (FDA) is proactive in supporting companies in clinical trial procedures, patient registration, data analysis, etc. (Published COVID-19 vaccine development guidelines ahead of Japan, etc.)
- **High risk in business**
  - Litigation risk
  - Loss of business opportunities after outbreak
- **Lack of public awareness of vaccinations**

*DARPA: Defense Advanced Research Projects Agency
**BARDA: The Biomedical Advanced Research and Development Authority

Pandemic Preparedness: Needed Countermeasures

- In the US, DARPA * and BARDA ** have been established under the Department of Defense and the Department of Health and Human Services, respectively, and from the perspective of national security, actively support research and development, including in the field of infectious diseases in normal conditions.
- In Europe, based on the lessons learned from the COVID-19 pandemic, EU are considering establishing HERA***, a central element for strengthening the European Health Union with better EU preparedness and response to serious cross-border health threats, by enabling rapid availability, access and distribution of needed countermeasures.
- Currently, COVID-19 response is an urgent issue in Japan as well, but need organization and systems to prepare for future pandemics in normal conditions.
  - ➢ Promoting and Encouraging Collaborative Innovation

*DARPA: Defense Advanced Research Projects Agency
**BARDA: The Biomedical Advanced Research and Development Authority
***HERA: Health emergency preparedness and response authority

Reshaping Vaccine Ecosystem

Long-term Key Priorities in Japan

1. Greater predictability of inclusion into the National Immunization Program
2. Promotion of development, etc. of vaccines with a high development priority
3. Enhancement of the database and monitoring system
4. Strengthening of information dissemination and improvement of discussion and process transparency
5. Securing stable supply