

Whole virion inactivated vaccine with adjuvant

EQUIVAX

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1. Describe and discuss the pro and cons of your vaccine construct, including cold-chain and cost issues.
 2. Describe and discuss the pro and cons of route of administration including vaccine delivery devices, if applicable.
 3. Briefly describe your proposed preclinical toxicology, immunology and pre-clinical efficacy studies
 4. Present your Target Product Profile
 5. Present an abbreviated Phase 3 trial design including the following elements:
 - a. Population to be enrolled with inclusion and exclusion criteria
 - b. Estimated duration of the trial
 - c. Immunization schedule
 - d. Primary outcome measure and how the outcome will be determined/measured
 - e. Secondary outcome measures (up to 3) and how they will be determined/measured
 - f. Briefly describe immunology studies and when samples will be collected
 - g. Briefly describe how you will determine sample sizes for primary efficacy and safety outcomes
 6. Present an abbreviated post-marketing phase 4 study design, proposing outcomes to be explored.
 7. After your vaccine is approved, assume you are members of the WHO committee that will determine who should first receive the vaccine when becomes available. Please describe and defend your top five populations in low- and middle-income countries (who, and in what situation).

Suggestions

- 35-50 slides, 45 min presentation, 15 min Q&A
- Topic 3 includes toxicology studies/plans to test on animals before clinical trials
- Can look up Phase 3 trials from Pfizer and Moderna on Internet
 - Can go to summary for similar info about phase 3 trial plan
 - Current adjuvant for Sinopharm is alum, but can use another one if we want
- Go to clinicaltrials.gov in the Covid vaccines section to find the trials going on worldwide
 - Filter them by the ones in phase 3 - use them for ideas
 - NYT Covid vaccine tracker also has concise updates on vaccines in trials
 - Several inactivated ones (two from China, one in early development in India)
- Phase 4:
 - Look at safety questions too infrequent to be answered in phase 3, and for groups not studied in phase 3 (e.g. pregnant women - and following outcomes on vaccinated pregnant women)
 - Ex: immunogenicity study of a specific group over 10 years to study if antibodies persist - but you have to justify why you are doing this

Disclosures

None

EQUIVAX Mission Statement

“At EQUIVAX, we believe the future of healthcare lives at the intersection of medicine and public health. Through a combination of education, research, and practice, EQUIVAX demonstrates its explicit commitment to understanding and eliminating health disparities worldwide through the development of cost-effective, quality, and equitable vaccinations.”

Target Audience

In line with the EQUIVAX mission statement, our target audience includes stakeholders, corporate investors, scientists, public health officials as well as the lay population

Whole virion inactivated vaccine with adjuvant

What is it?

- **Inactivated vaccine:** vaccine that uses the killed version of the germ that causes a disease.
 - Made by exposure of virulent virus to chemical or physical agents (i.e beta-propiolactone) in order to destroy infectivity while retaining immunogenicity.
- **Adjuvant:** adjuvants are ingredients added to vaccines to create a strong immune response (i.e aluminum salts)
 - More local and systemic responses than non-adjuvanted vaccines

WHAT IS AN ADJUVANT, AND WHY ARE THEY USED IN VACCINES?

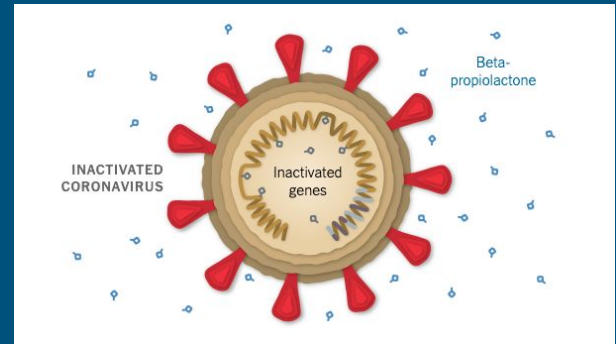


Talking about
Vaccines with
Dr. Stanley Plotkin

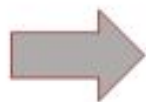


Pros

- Vaccine production is relatively straightforward to achieve
- Inactivated viral vaccines have a heightened safety aspect as compared to live attenuated viral vaccines.
 - The fact that the pathogen is completely inactivated directly negates reversion to a virulent phenotype within the vaccine recipient.
 - The improved safety profile of inactivated vaccines entails that they are also suitable for the rapidly increasing group of immunocompromised individuals
- Many are produced via virus growth on continuous cell lines
 - Infinite cell growth and division
 - Easy isolation of mutant cells
 - Reduced production costs
 - Straightforward upscaling
- Fewer regulatory hurdles for licensure



Virus SARS-CoV-2



Vaccines based on inactivated whole SARS-CoV-2 virus

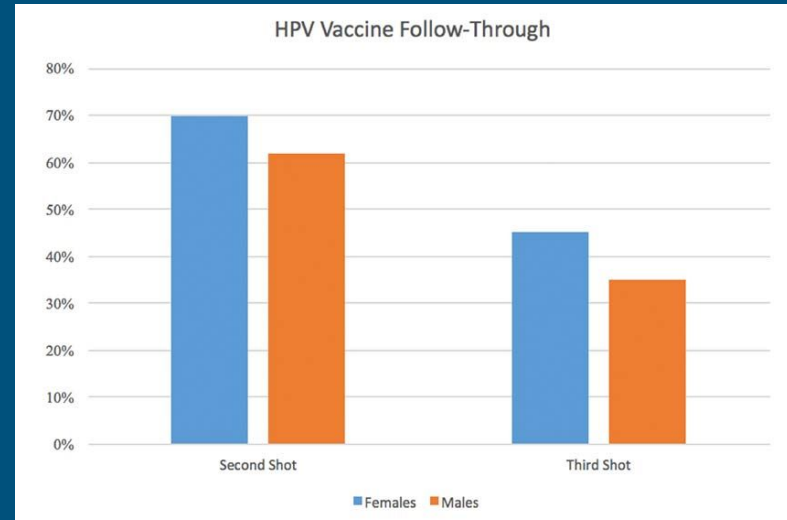
Company and country	Vaccine name	Number of doses	Approval and registration
Sinovac Biotech, China	---	2	Ahead of Phase II trial it is offered to essential workers and other high-risk people of the Chinese town of Jiaxing for about 30 €/dose
Beijing Institute of Biological Products and Sinopharm, China	BBIBP-CorV	2	Limited approval for Chinese health care workers and ahead of Phase III trial. This vaccine has been approved by United Arab Emirates on the basis of preliminary data showing that it is 86% effective.
Wuhan Institute of Biological Products, and Sinopharm, China	---	2	Limited approval for Chinese health care workers and soldiers ahead of Phase III trial.
Bharat Biotech, India	COVAXIN	2	The Phase III trial with 26 000 volunteers is expected to close in February 2021.

Pros

- No secondary mutations can lead to reversion to virulence so disease can't occur and the vaccine is not transmissible.
- Inactivated vaccines usually don't require refrigeration, and they can be easily stored and transported in a freeze-dried form, which makes them cheap and easily accessible to people in developing countries.
- BIBP-CorV can be transported and stored at normal refrigeration temperatures (2-8 degrees Celsius).
 - A large amount can be produced: Sinopharm said it may have the capacity to produce more than 1 billion doses in 2021

Cons

- These vaccines take longer to culture and produce than other vaccine types
 - Chemical treatment may reduce efficacy of the vaccine
- Protection from this vaccine type may be weaker, so a larger amount of antigen is needed to produce a satisfactory immune response
 - People may need multiple booster shots



Cons

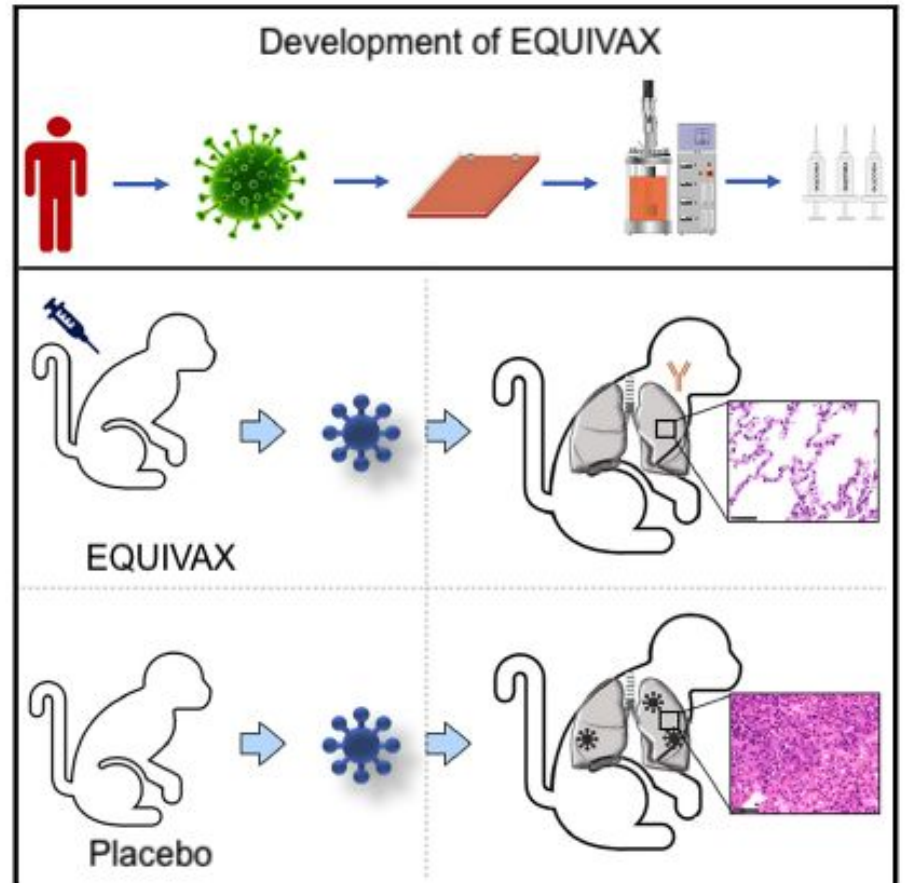
- Adding an adjuvant and the need for multiple doses raises production and vaccine cost
- Previous exposure could compromise the immune response
- Complete inactivation MUST be ensured
 - The Cutter Incident
 - RSV
- There is an increased risk of allergic reactions due to the presence of large amounts of unrelated structural antigens of microbes.

Pre-Clinical Studies

Highlights

- An inactivated SARS-CoV-2 vaccine candidate, EQUIVAX, is developed
- EQUIVAX induces high levels of neutralizing antibodies titers in animal models
- Two-dose immunization with 2 mg/dose EQUIVAX efficiently protects rhesus macaques
- EQUIVAX is efficiently produced, genetically stable, and seems to be safe in animals

Graphical Abstract



Immunogenicity of EQUIVAX

Initial immunogenicity studies evaluated EQUIVAX in mouse models

Mice received various doses (2, 4, or 8 mg/dose) of vaccine mixed with aluminum hydroxide adjuvant in a one, two or three dose series.

Serum neutralizing antibody levels were collected at predefined intervals to determine immunogenicity

We then expanded the evaluation to include different animal models including rabbits, guinea pigs, and rats.

The results demonstrated that EQUIVAX has good immunogenicity, and the seroconversion rate reached 100% at day 21 after immunization in all animal models.

Protection in a Nonhuman Primate Animal Model

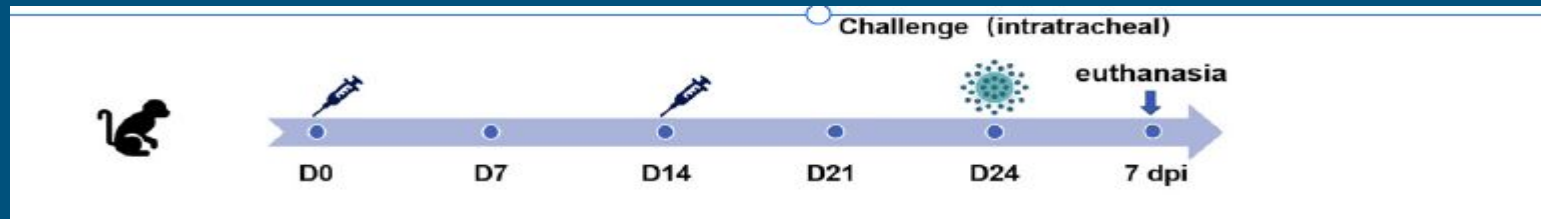
Recent studies have shown that SARS-CoV-2-infected rhesus macaques developed pulmonary infiltrates and histological lesions

We evaluated the immunogenicity and protective efficacy of EQUIVAX in rhesus macaques.

Immunogenicity and Protective Efficacy of EQUIVAX in Nonhuman Primates (NHPs)



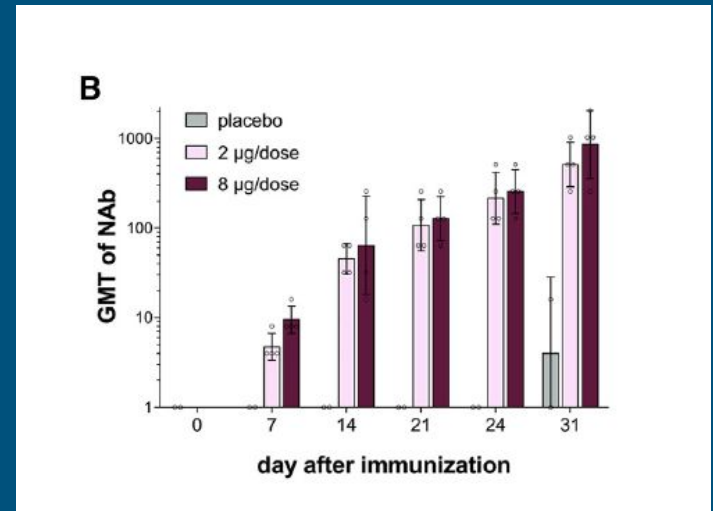
(A) Experimental strategy.



NHP Studies

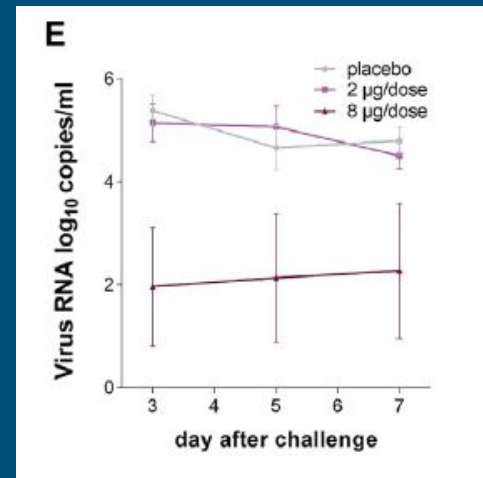
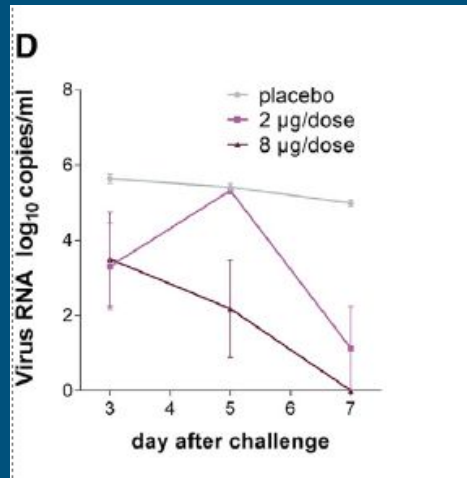
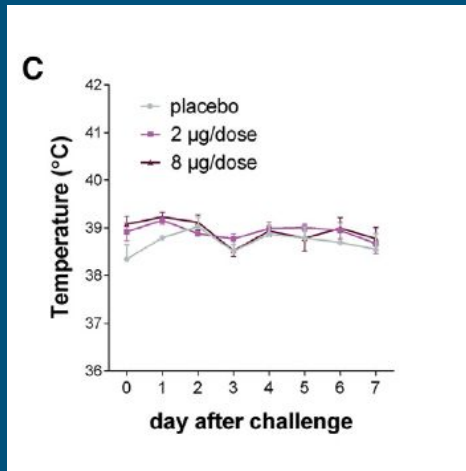
Macaques were immunized twice with 2 mg/dose (n = 4) or 8 mg/dose (n = 4) of EQUIVAX or placebo (n = 2). NAb titers were measured.

The protective efficacy of EQUIVAX against SARS-CoV-2 challenge at 10 days after second immunization was evaluated in macaques.



NHP Studies

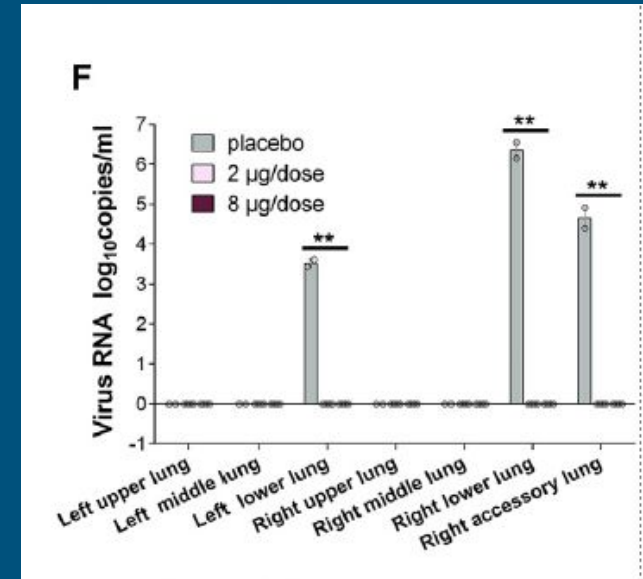
Changes in temperature (C) were recorded. Viral loads in throat (D) and anal swabs (E) obtained from macaques at 3, 5, and 7 days post inoculation.



NHP Studies

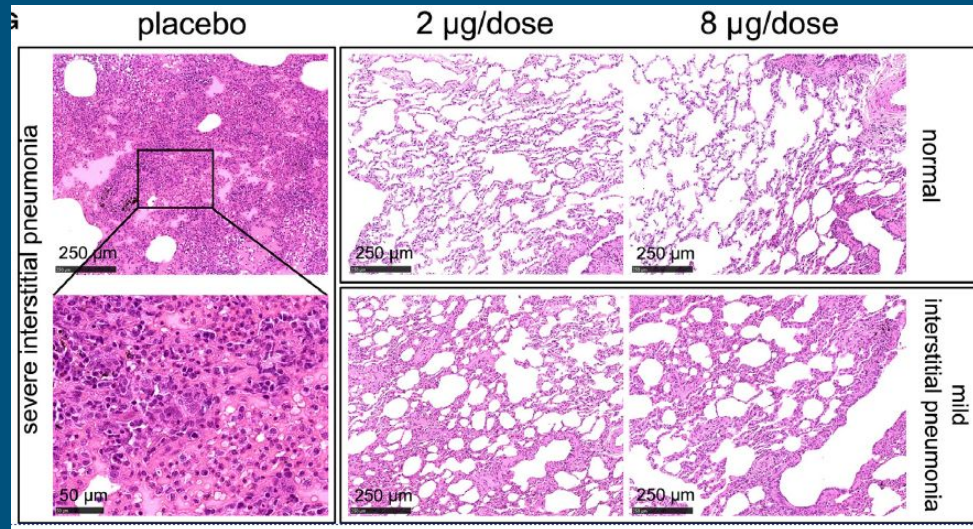
Viral loads in all seven lung lobes collected from all macaques at day 7 post inoculation were determined by real-time PCR.

- Data points represent individual macaques
- Asterisks indicate significance: $**p < 0.01$
- Dotted lines indicate the limit of detection



NHP Studies

Histopathological changes in lungs of macaques at day 7 post inoculation. All macaques received vaccination showed normal lung with focal mild interstitial pneumonia in few lobes.



NHP Studies: Results Summary

Dosage Range	4–8 µg (i.m.)
Neut. titre after prime	1:100 range ⁺
Neut. titre after boost	1:200 range ⁺
T Cell Response	Not Determined
Challenge Dose	10 ⁶ TCID ₅₀ (i.t.)
URT protection	partial ⁺⁺
LRT protection	complete ⁺⁺
Species	Cynomolgus macaques

Safety Data

We first performed a single intramuscular injection experiment in Sprague-Dawley rats to evaluate the acute toxicity of EQUIVAX

Systemic anaphylaxis due to EQUIVAX was subsequently evaluated by intramuscular and intravenous injections in guinea pigs.

The long-term toxicity of EQUIVAX was further evaluated in cynomolgus monkeys.

Summary

Initial studies demonstrate immunization with EQUIVAX promotes high levels of neutralizing antibody in six mammalian species, including rats, mice, guinea pigs, rabbits, cynomolgus monkeys, and rhesus macaques, protecting them against SARS-CoV-2 infection.

Study results demonstrated a two-dose immunization series using 2 mg/dose of EQUIVAX conferred highly efficient protection against SARS-CoV-2 in rhesus macaques without observable adverse effects or worsening immunopathological changes.

Target Product Profile

Elements of the TPP

1: Indications

2: Target population

3: Contraindications

4: Safety & Reactogenicity

5: Efficacy

6: Dose Regimen

7: Durability of Protection

8: Route of Administration

9: Coverage

10: Stability & Storage

11: Co-administration

12: Presentation

13: Production & Accessibility

14: Registration &
Prequalification

15: Post Marketing Surveillance

TPP#1: Indications

Preferred	Critical or Minimal
Prophylactic immunization protects against COVID-19 infection.	Immunization reduces the severity of COVID-19 disease

TPP#2: Target Population

Preferred	Critical or Minimal
All individuals 1-year and older	Adults including the elderly

TPP#3: Contraindications

Preferred	Critical or Minimal
None	<ul style="list-style-type: none"> ● Immunocompromised patients ● History of severe allergic reaction to inactivated COVID-19 vaccine or known allergy to any of its components

TPP#4: Safety & Reactogenicity

Preferred	Critical or Minimal
Mild, transient side effects No serious adverse effects	Safety and reactogenicity profile whereby vaccine benefits outweigh safety risks

TPP#5: Efficacy

Preferred	Critical or Minimal
<ul style="list-style-type: none"> ● General Population: > 70% efficacy ● Older Adults⁺/Elderly: > 70% efficacy 	<ul style="list-style-type: none"> ● General Population: > 70% efficacy ● Older Adults⁺/Elderly: >55% efficacy

**older adults includes individuals age 65 and older*

TPP#6: Dose Regimen

Preferred	Critical or Minimal
Single-dose regimen (use of time released injectable device acceptable)	Two dose regimen (administered 3-4 weeks apart)

TPP#7: Durability of Protection

Preferred	Critical or Minimal
<ul style="list-style-type: none"> ● Provides lifelong protection after single administration ● Booster dose not needed 	<ul style="list-style-type: none"> ● Confers protection for at least 12 months ● Annual boosters

TPP#8: Route of Administration

Preferred	Critical or Minimal
Simultaneous oral dose and parenteral administration of time released formulation	Any route of administration

TPP#9: Coverage

Preferred	Critical or Minimal
Multivalent	Monovalent

TPP#10: Stability & Storage

Preferred	Critical or Minimal
<p>Extreme Thermostability</p> <ul style="list-style-type: none"> ● Shelf life > 24 months at -20 °C ● Stability > 12 months at 2-8°C ● Stability > 12 months at 40-45°C ● Stability > 2 years at 20-22°C <p>Not light sensitive</p>	<p>Moderate Thermostability</p> <ul style="list-style-type: none"> ● Shelf life > 12 months at -20 °C ● Stability > 1 month at 2-8°C ● Stability > 12 months at 40-45°C ● Stability > 8 hours at 20-22°C

TPP#11: Co-administration

Preferred	Critical or Minimal
<p>Can be given with other vaccines without affecting immunogenicity, safety or efficacy of the vaccines.</p>	<p>Must be used as a stand alone product</p>

TPP#12: Presentation

Preferred	Critical or Minimal
<ul style="list-style-type: none"> ● Sterile liquid product for direct use ● Single dose vial or prefilled AD syringe ● Stored at room temperature, eliminating need for cold-chain requirement 	<ul style="list-style-type: none"> ● Sterile liquid for direct use <i>or</i> lyophilized product with simple reconstitution at point of use not requiring end-to-end cold chain ● Single-dose or multi-dose presentation

TPP#13: Production & Accessibility

Preferred	Critical or Minimal
<ul style="list-style-type: none"> ● 9 billion doses <i>or</i> ● Capability to rapidly scale up production (at cost/dose allowing for broad use) in LMIC ● Burden of cost to be covered collectively by upper & middle income countries 	<ul style="list-style-type: none"> ● 350 million doses <i>or</i> ● Availability of sufficient doses (at cost/dose) that allows for broad use in LMIC ● Burden of cost to be heavily subsidized by collective efforts of upper & middle income countries

TPP#14: Registration & Prequalification

Preferred	Critical or Minimal
<ul style="list-style-type: none"> ● WHO prequalified ● Meets criteria for Emergency Use Assessment & Listing (EUAL) Procedure 	<ul style="list-style-type: none"> ● Emergency Use Authorization (EUA) ● Expanded Access Program

TPP#15: Post Marketing Surveillance

Post Marketing Surveillance

- Implementing local, reliable vaccine safety monitoring systems in remote areas at the time of vaccine administration
- Assessment of serious adverse effects
- Monitoring vaccine effectiveness
- Emergence of vaccine resistant SARS COV-2 mutants

Phase 3 trial details

- Population to be enrolled with inclusion and exclusion criteria
- Estimated duration of the trial
- Immunization schedule
- Primary outcome measure and how the outcome will be determined/measured
- Secondary outcome measures (up to 3) and how they will be determined/measured
- Briefly describe immunology studies and when samples will be collected
- Briefly describe how you will determine sample sizes for primary efficacy and safety outcomes

Phase 3 trial design

Overview and objectives

- **Randomized, double-blinded, multinational trial** conducted across low- and middle-income countries (LMICs)
- Enrollment of subjects from **diverse socioeconomic backgrounds**, collaborating with healthcare and community centers
- Enrollment of subjects with **common underlying conditions**
- **Regular monitoring** of symptoms, SARS-CoV-2 infection status, and additional outcome measures
- **Regular monitoring** of overall health status

Inclusion criteria

- Healthy subjects (age 18+)
- Female subjects of childbearing age who are not nursing/pregnant and have no family planning within first 3 months of enrollment
- Ability to understand study procedures, informed consent, and comply with study protocols

Exclusion criteria

- Confirmed/suspected SARS-CoV-2 infection
- History of SARS/MERS infection
- Associated symptoms within 14 days before vaccination (e.g. fever, dry cough, dyspnea, sore throat, diarrhea)
- Pregnancy or upcoming family planning within 3 months
- Previous severe allergic responses to vaccination or known ingredients
- Severe disease (e.g. uncontrollable hypertension, malignant tumors)
- Immunodeficiency (e.g. HIV, lymphoma, autoimmune diseases)
- Patients receiving immunotherapy
- Recent vaccinations (within 14 days, or 1 month for live-attenuated)
- Received other research drugs within 6 months

Duration and schedule

Duration

- 12 months after enrollment of last subject
- Allows effective monitoring of all subjects up to 12 months
- Weekly PCR testing, symptom check-ins, health check-ins after first dose up to 6 months
- Biweekly testing and check-ins up to 12 months

Schedule

- Two identical doses
- 21 days apart

Primary outcome measure

Incidence of COVID-19 cases after two doses of vaccination

- Comparison of COVID-19 case numbers between intervention and placebo arms
- Between 14 days and 12 months after 2nd dose
- PCR tests being administered every week, performed at a central laboratory in a blinded fashion

Secondary outcome measures

Severe COVID-19 cases and deaths

- Monitoring for severe cases and deaths due to COVID-19
- Between 14 days and 12 months after 2nd dose

Incidence of short-term adverse events (AEs)

- Monitoring subjects through self-reporting
- Up to 12 months after each dose

Secondary outcome measures

Incidence of long-term serious adverse events (SAEs)

- Monitoring subjects through self-reporting
- Up to 12 months after each dose

Antibody levels against SARS-CoV-19

- Blood samples for serum antibody analysis (**immunological studies**)
- Various time points after vaccination course

Immunological studies

Geometric mean titer (GMT) of anti-SARS-CoV-2 antibodies

- Geometric mean of antibody titer

Geometric mean fold rise (GMFR) of anti-SARS-CoV-2 antibodies

- Geometric mean of ratio of post-vaccination titer to pre-vaccination titer

Four-fold increase rate of anti-SARS-CoV-2 antibodies

- Rate of four-fold increase in titer (seroconversion)

Time points: 14 days, 28 days, 3 months, 6 months, 9 months, 12 months after 2nd dose

Sample size

- Our sample size is based on our
 - Desired power (80%)
 - Desired confidence (95%)
 - 1:1 vaccine : placebo allocation
- Our target sample size for Phase 3 is 30,000 participants
- Increasing sample size allows us to have a representative and replicative trial

Phase 4 trial

- Phase 4 will begin after the drug is approved
- Phase 4 will including continuous surveillance and measuring different outcomes of interest
- Looking at vaccine outcomes in populations of interest that were not included in phase 3 clinical trials

Phase 4 trial: Outcomes of interest

- Long-term side effects and adverse events
- Long-term vaccine efficacy
- Long-term vaccine safety
- Monitoring of severe adverse effects
- Effectiveness against different strains

Vaccine distribution in LMICs

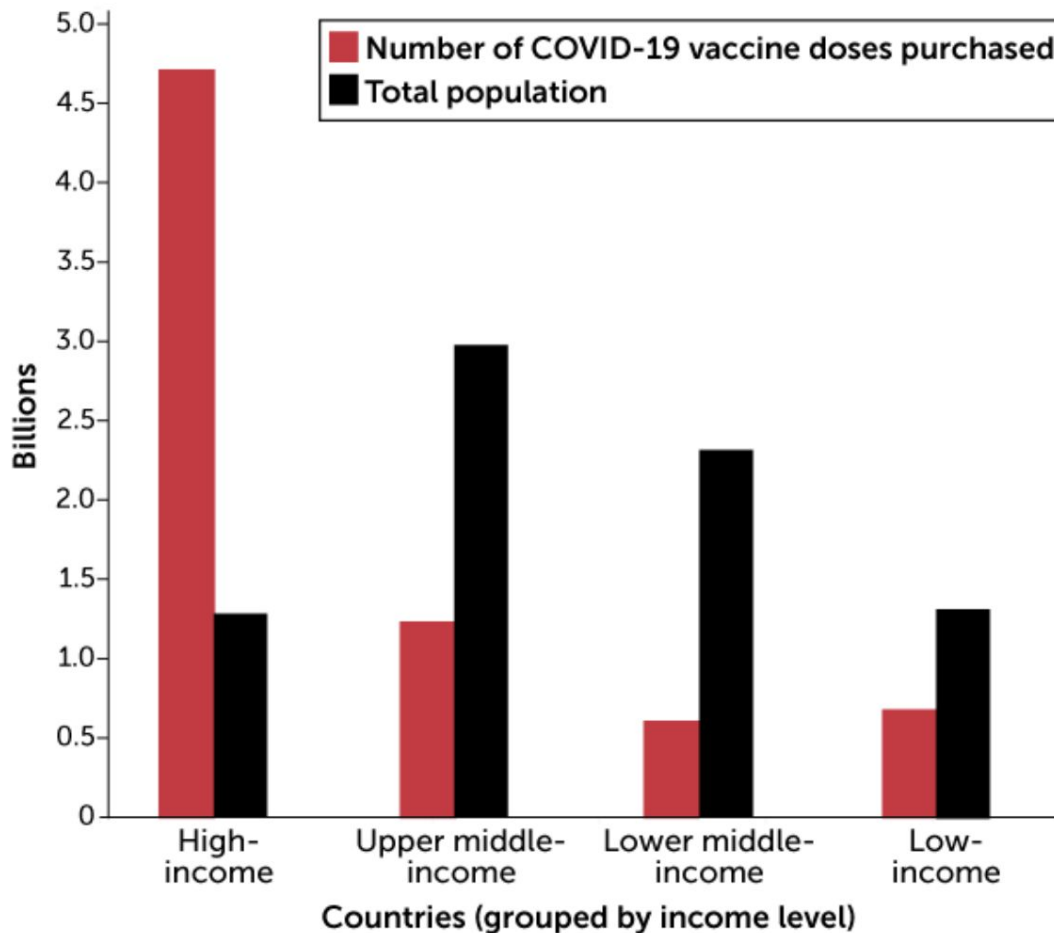
- Healthcare workers at risk of being exposed to COVID-19
- People over 75 years of age
- Other frontline/essential workers (e.g. law enforcement, firefighters, public transit workers)
- People over 65
- People under 65 with 2 or more comorbidities

Current status

- Ongoing phase 3 trials conducted for the **Sinopharm** vaccine in Bahrain, Egypt, Jordan, UAE, Peru, Argentina, etc.
- Approved and being used in China, UAE, Bahrain, Peru, Jordan, etc., among other countries in Europe, Africa, South America, Asia

- UAE government reports 86% efficacy
- Chinese government reports 79.34% efficacy

COVID-19 vaccine doses purchased by countries, grouped by income



Current status

With the tailoring of our Phase 3 and 4 trials geared toward LMICs, we strive to fulfill our mission to play our part in fighting the global pandemic by vaccinating both with efficacy and equity.

EQU
VAX



Sources

- <https://www.fiercebiotech.com/research/inactivated-covid-19-vaccine-by-china-s-sinopharm-clears-animal-tests>
- <https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html>
- <https://www.sciencedirect.com/science/article/pii/B9780123751560000114>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7189890/>
- <https://www.nytimes.com/interactive/2020/health/sinopharm-covid-19-vaccine.html>
- <http://www.chictr.org.cn/showprojen.aspx?proj=56651>
- <https://clinicaltrials.gov/ct2/show/NCT04510207>
- <https://covid19.trackvaccines.org/vaccines/5/>
- https://www.who.int/biologicals/expert_committee/Clinical_changes_IK_final.pdf
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- <https://clinicaltrials.gov/ct2/show/NCT04612972>
- <https://clinicaltrials.gov/ct2/show/NCT04560881>