SARS-CoV-2 Inactivated Vaccines

A Review of Pertinent Drug Information for SARS-CoV-2

Caroline C. Jozefczyk, PharmD, BCIDP
Antimicrobial Stewardship Pharmacist, OhioHealth Mansfield and Shelby Hospitals
Caroline.Jozefczyk@OhioHealth.com
@ccjozefczyk

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Data as of January 27, 2021

SARS-CoV-2 Inactivated Vaccine Candidates

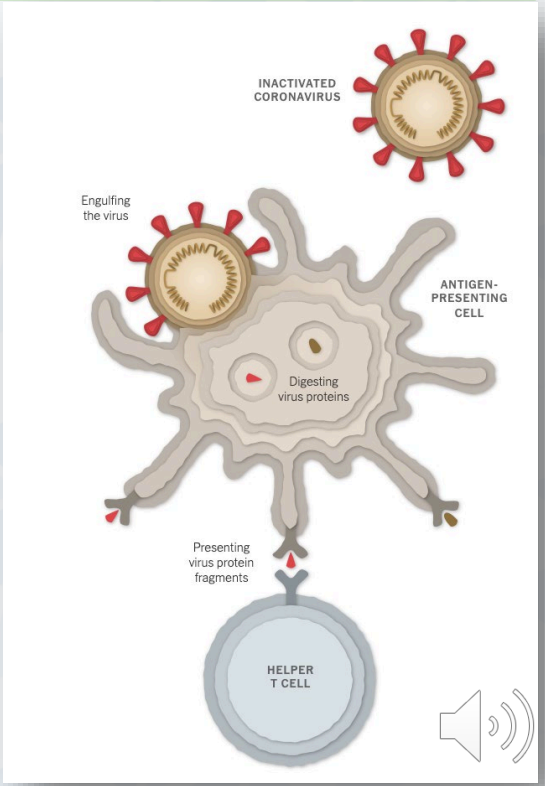
Candidate Name/Type	Sponsor	Clinical Trial Phase	Dosing	Clinical Trials
Covaxin (BBV152)	Bharat Biotech, Indian Council of Medical Research	Phase 3 *Approved in India*	2 doses (d0, d14)	NCT04471519 (Phase 1/2) CTRI/2020/09/027674 (Phase 1/2) NCT04641481 (Phase 3)
BBIBP-CorV	Sinopharm	Phase 3 *Approved in 8 countries*	2 doses (d0, d21)	ChiCTR2000032459 (Phase 1/2) ChiCTR2000034780 (Phase 3) NCT04612972 (Phase 3) NCT04510207 (Phase 3) NCT04560881 (Phase 3)
None	Sinopharm	Phase 3 *Approved in China and UAE*	2 doses (d0, d21)	ChiCTR2000031809 (Phase 1/2) ChiCTR2000034780 (Phase 3) NCT04612972 (Phase 3) ChiCTR2000039000 (Phase 3)
CoronaVac	Sinovac	Phase 3 *Approved in 5 countries*	2 doses (d0, d14)	NCT04352608 (Phase 1/2) NCT04383574 (Phase 1/2) NCT04551547 (Phase 1/2) NCT04651790 (Phase 3) NCT04456595 (Phase 3) NCT04508075 (Phase 3) NCT04582344 (Phase 3) NCT04617483 (Phase 3)

World Health Organization. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed Jan. 20, 2021

Mechanism of Action

Inactivated Vaccines

- Consist of entire pathogen that has been destroyed by heat, chemicals (usually formalin), or radiation
- Contain proteins that the immune system responds to
  - Spike protein, other viral proteins
- Cannot replicate = cannot cause disease
- Multiple vaccine doses
  - First dose, “primer”
  - Second or third dose, “protective immunity”
  - Periodic supplemental doses, “booster”
- Examples of other inactivated vaccines:
  - Hepatitis A
  - Influenza



SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Principles of Vaccination. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/prinvac.pdf
How the Sinopharm Vaccine Works. The New York Times. https://www.nytimes.com/interactive/2020/health/sinopharm-covid-19-vaccine.html

Covaxin (BBV152) Pre-Clinical & Phase I

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

In Vivo Animal Data

Mice, rats, & rabbits

- BBV152: whole virion inactivated SARS-CoV-2 vaccine
  - Formulated with a new adjuvant – imidaquizoquinoline class toll-like receptor (TLR) 7/8 agonist adsorbed to Algel (Algel-IMDG)
    - Facilitate Th1 biased immunity
- High antigen binding and neutralizing antibody titers at both 3-µg and 6-µg doses in mice, rats, & rabbits
- Antigen formulated with Algel-IMDG skewed towards Th1 response
  - Elevated IgG2a/IgG1 ratio
  - Increased levels of SARS-CoV-2 specific IFN-γ+ CD4 T lymphocyte

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Ganneru et al. bioRxiv [Preprint]. 2020. doi: https://doi.org/10.1101/2020.09.09.285445

BBV152 Candidate

Safety and Immunogenicity

- Double blind, multi-center, randomized, controlled phase 1 trial
  - Age 18-55
    - Randomized
      - 1 of 3 vaccine groups
      - Control group – Algel only
    - 2 doses (d0, d14)

3-µg + Algel-IMDG	6-µg + Algel-IMDG	6-µg + Algel	Algel

- Primary Outcomes
  - Solicited local and systemic reactogenicity events at 2h and 7d post vaccine
- Secondary Outcome
  - Geometric mean titers (GMTs)
  - Seroconversion

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

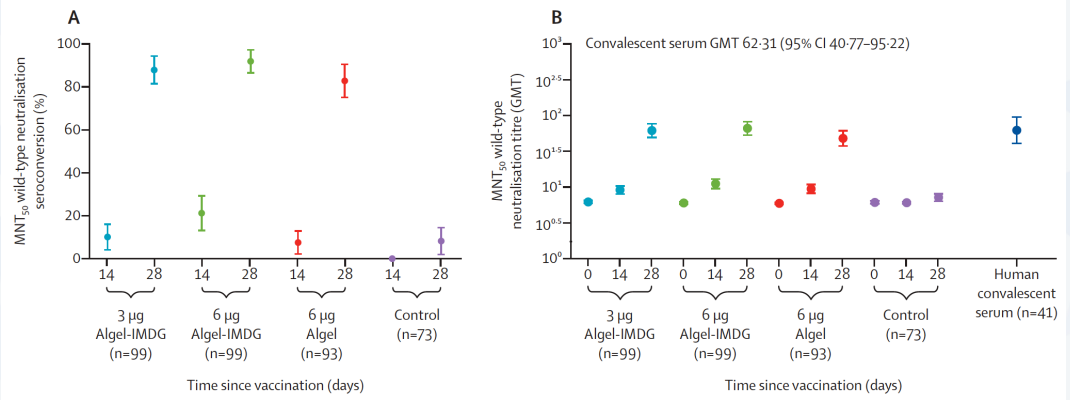
Algel-IMDG: toll-like receptor 7/8 agonist molecule adsorbed to alum
Algel: alum alone

Ella et al. Lancet Infect Dis 2021. https://doi.org/10.1016/ S1473-3099(20)30942-7

BBV152 Candidate

Safety and Immunogenicity

- Key Immunogenicity Findings
  - Seroconversion rates > 80% across all doses and formulations
    - 91.9% seroconversion in 6 µg Algel-IMDG group 28 days after vaccination
  - GMTs across all doses were similar to patients recovered from COVID-19



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Ella et al. Lancet Infect Dis 2021. https://doi.org/10.1016/ S1473-3099(20)30942-7

BBV152 Candidate

Safety and Immunogenicity

- Key Safety Findings
  - Most common adverse events:
    - Injection site pain
    - Headache
    - Fatigue
    - Fever
    - Nausea/vomiting
  - All adverse effects mild (69%) or moderate (31%)
  - Adverse effects were more frequent after first dose vs second

	Dose 1				Dose 2			
	3 µg with Algel-IMDG (n=100)	6 µg with Algel-IMDG (n=100)	6 µg with Algel (n=100)	Algel only (n=75)	3 µg with Algel-IMDG (n=100)	6 µg with Algel-IMDG (n=100)	6 µg with Algel (n=100)	Algel only (n=75)
Local reactions								
Pain at injection site								
Mild	4 (4%; 1·1–9·9)	4 (4%; 1·1–9·9)	1 (1%; 0·0–5·5)	2 (3%; 0·3–9·3)	2 (2%; 0·2–7·0)	1 (1%; 0·03–5·5)	1 (1%; 0·0–5·5)	0
Moderate	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	0	0	0	0	0
Swelling								
Mild	0	0	0	1 (1%; 0·0–7·2)	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Systemic reactions								
Fever								
Mild	0	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	2 (2%; 0·2–7·0)	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0
Moderate	0	1 (1%; 0·0–5·5)	2 (2%; 0·2–7·0)	0	0	0	0	0
Body ache								
Mild	0	1 (1%; 0·03–5·5)	0	0	0	0	0	0
Moderate	0	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	1 (1%; 0·0–5·5)	0	0	0
Fatigue								
Mild	1 (1%; 0·0–5·4)	0	0	0	1 (1%; 0·03–5·4)	0	3 (3%; 0·6–8·5)	0
Moderate	2 (2%; 0·2–7·0)	3 (3%; 0·6–8·5)	0	0	1 (1%; 0·0–5·5)	0	0	0
Headache								
Mild	1 (1%; 0·03–5·5)	2 (2%; 0·2–7·0)	0	5 (7%; 2·2–14·9)	0	0	0	0
Moderate	0	3 (3%; 0·6–8·5)	2 (2%; 0·2–7·0)	0	0	0	0	0
Nausea or vomiting								
Mild	1 (1%; 0·03–5·5)	2 (2%; 0·2–7·0)	2 (2%; 0·2–7·0)	2 (3%; 0·3–9·3)	0	0	0	0
Moderate	0	0	0	0	0	0	0	0

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Ella et al. Lancet Infect Dis 2021. https://doi.org/10.1016/ S1473-3099(20)30942-7

BBIBP-CorV Phase I/II

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

BBIBP-CorV Candidate

Safety and Immunogenicity

- Dose escalation, randomized, double-blind, placebo-controlled phase 1/2 trial

Phase 1	Phase 2
Age groups: 18-59 & ≥ 60-80 Randomized to vaccine or placebo 2-µg, 4-µg, or 8-µg (d0,28)	Adults 18-59 Randomized to vaccine or placebo 8-µg (d0), 4-µg (d0,14), 4-µg (d0,21), 4-µg (d0,28)

- Primary Outcomes
  - Occurrence of adverse reactions within 7 days after 1st and 2nd dose
- Secondary Outcomes
  - Immunogenicity – neutralizing antibody responses against SARS-CoV-2 and seroconversion

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

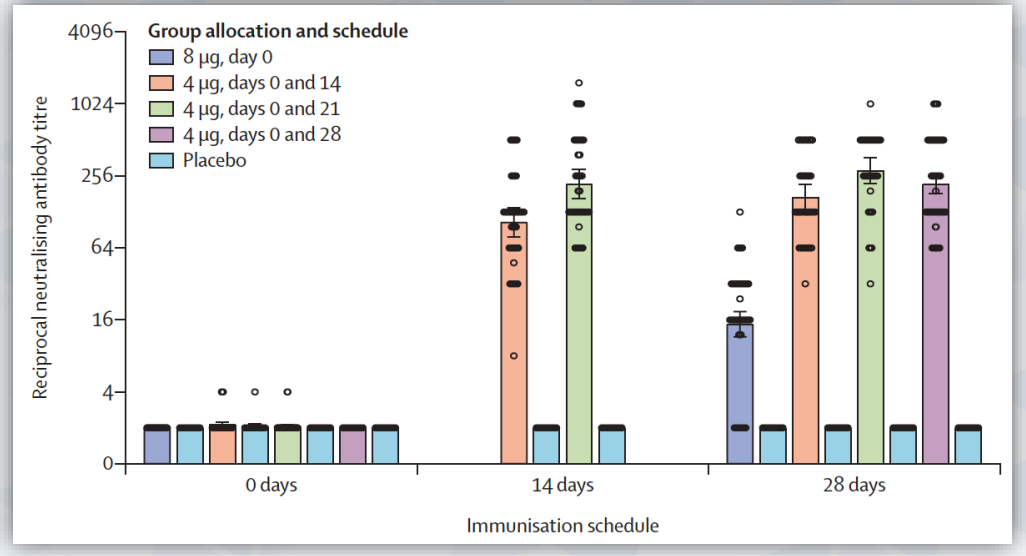
Xia et al. Lancet Infect Dis 2020; 21: 39–51. https://doi.org/10.1016/ S1473-3099(20)30831-8

BBIBP-CorV Candidate

Safety and Immunogenicity

- Key Immunogenicity Findings
  - Phase 1
    - By day 42, no significant difference in neutralizing antibodies titers between 4-µg and 8-µg dose
    - In both age groups, by day 42 the GMT in the 2-µg group was significantly lower than the 4-µg and 8-µg groups
  - Phase 2
    - By day 28 after the last inoculation, the 4-µg schedules persisted in neutralizing antibody titers compared to the single scheduled 8-µg dose

Phase 2 Neutralizing Antibody Titers



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Xia et al. Lancet Infect Dis 2020; 21: 39–51. https://doi.org/10.1016/ S1473-3099(20)30831-8

BBIBP-CorV Candidate

Safety and Immunogenicity

- Key Safety Findings
  - Phase 1
    - In 18-59 age group, the most significant local AE was **pain** at injection site (35%) compared to placebo (8%) (p=0.017)
    - No significant difference in overall AEs compared to placebo seen in either age group up to day 28 post vaccination
    - No serious AEs reported within 28 days post vaccination across all cohorts
  - Phase 2
    - More participants experienced any AE in 8 ug group (39%) vs placebo (11%) (p=0.0049)
    - Most common injection site reaction was **pain** in all cohorts compared to placebo (16% vs 4%, p=0.0008)
    - Most common systemic AEs in vaccination cohorts were **fatigue** (3%) and **fever** (2%)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Xia et al. Lancet Infect Dis 2020; 21: 39–51. https://doi.org/10.1016/ S1473-3099(20)30831-8

Sinopharm Inactivated COVID-19 Vaccine (Wuhan Institute) Phase I/II

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Sinopharm-Wuhan Institute Candidate

Safety and Immunogenicity

- Double-blind, randomized, placebo-controlled phase 1 and 2 trials
- Adults 18-59
  - Phase 1: low (2.5-µg), medium (5-µg), and high (10-µg) → d0,28,56
  - Phase 2: 5-µg → d0,14 and d0,21
  - Control group: Alum adjuvant only
- Primary Outcomes
  - Adverse reactions within 7 days of each injection
  - Neutralizing antibody response 14 days post-vaccination
- Secondary Outcomes
  - Adverse reactions during 28-day follow-up
  - Seroconversion rate

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

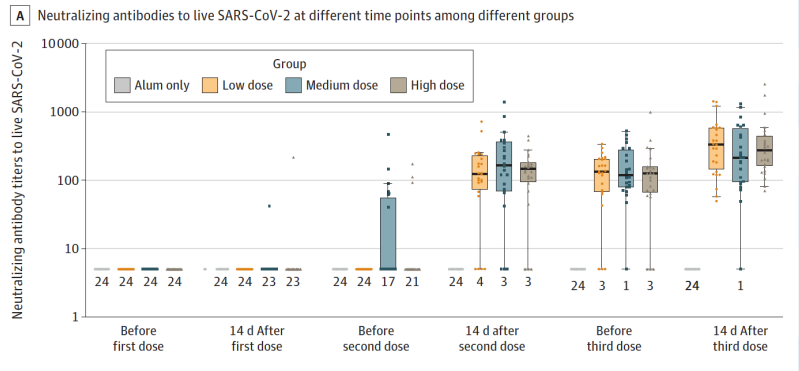
Xia et al. JAMA. 2020;324(10):951-960. doi:10.1001/jama.2020.15543

Sinopharm-Wuhan Institute Candidate

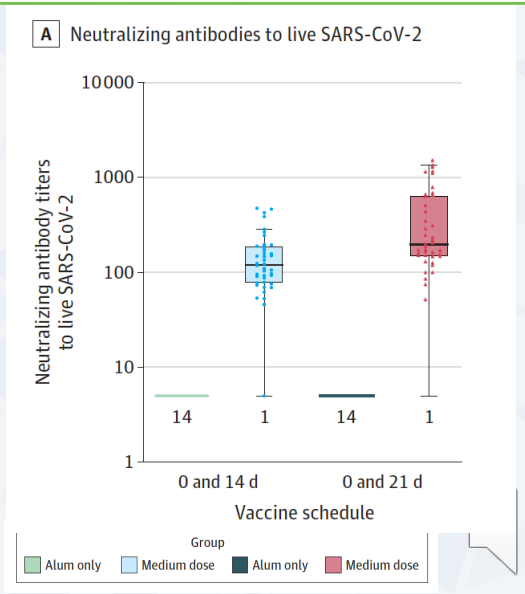
Safety and Immunogenicity

- Key Immunogenicity Findings
  - Longer intervals (21 and 28 days) produced higher antibody responses compared to a shorter interval (14 days)
  - Seroconversion seen in >97% of participants in phases 1 and 2

Antibody Responses at Different Time Points in Phase 1 Trial



Antibody Responses 14 days After the Second Dose in the Phase 2 Trial



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Xia et al. JAMA. 2020;324(10):951-960. doi:10.1001/jama.2020.15543

Sinopharm-Wuhan Institute Candidate

Safety and Immunogenicity

- Key Safety Findings
  - Most common adverse reaction was **injection site pain** and **fever**
  - Total adverse reactions were similar across the 3 vaccine groups in phase 1
  - More participants in the medium dose 0 and 21-d group experienced adverse reactions compared to the 0 and 14-d group
    - Injection site pain (14.3% vs 2.4%)
  - Incidence rate of adverse reactions = **15%** among all participants

Table 2. Adverse Reactions After 3 Doses in the Phase 1 Trial and 2 Doses in the Phase 2 Trial in the Safety Set[a]

	Phase 1 clinical trial; 0, 28, and 56-d group				Phase 2 clinical trial			
					0 and 14-d Group		0 and 21-d Group	
Adverse reaction	Low dose (n = 24)	Medium dose (n = 24)	High dose (n = 24)	Alum only (n = 24)	Medium dose (n = 84)	Alum only (n = 28)	Medium dose (n = 84)	Alum only (n = 28)
0-7 d								
Total adverse reactions	5 (20.8)	4 (16.7)	6 (25.0)	3 (12.5)	5 (6.0)	4 (14.3)	16 (19.0)	5 (17.9)
Systemic reactions	0	3 (12.5)	1 (4.2)	1 (4.2)	4 (4.8)	2 (7.1)	4 (4.8)	2 (7.1)
Coughing	0	0	0	0	1 (1.2)	0	0	0
Diarrhea	0	0	0	0	0	0	1 (1.2)	0
Fatigue	0	1 (4.2)	0	0	1 (1.2)	0	0	0
Fever	0	1 (4.2)	1 (4.2)	0	4 (4.8)	1 (3.6)	2 (2.4)	1 (3.6)
Headache	0	0	0	0	1 (1.2)	1 (3.6)	0	1 (3.6)
Nausea and vomiting	0	1 (4.2)	0	1 (4.2)	0	0	1 (1.2)	1 (3.6)
Pruritus (noninoculated site)	0	0	0	0	0	0	0	1 (3.6)
Local reactions	5 (20.8)	1 (4.2)	6 (25.0)	2 (8.3)	2 (2.4)	3 (10.7)	13 (15.5)	4 (14.3)
Itching	0	0	0	0	0	0	1 (1.2)	1 (3.6)
Pain	5 (20.8)	1 (4.2)	6 (25.0)	2 (8.3)	2 (2.4)	3 (10.7)	12 (14.3)	4 (14.3)
Redness	0	0	1 (4.2)	0	0	0	0	1 (3.6)
Swelling	1 (4.2)	0	1 (4.2)	0	0	0	1 (1.2)	1 (3.6)
Other reactions	0	0	0	0	0	0	0	0
0-28 d								
Total adverse reactions	5 (20.8)	4 (16.7)	6 (25.0)	3 (12.5)	5 (6.0)	4 (14.3)	16 (19.0)	5 (17.9)

Xia et al. JAMA. 2020;324(10):951-960. doi:10.1001/jama.2020.15543

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

CoronaVac Phase I/II

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

CoronaVac Candidate

Safety and Immunogenicity

- Single-center, randomized, double-blind, placebo-controlled, phase 1 and 2 trial
  - Adults 18-59
  - Vaccine doses: 3-µg (d0,14), 6-µg (d0,14), 3-µg (d0,28), 6-µg (d0,28)
- Primary Safety Endpoint
  - Adverse reactions within 28 days after injection
- Primary Immunogenic Outcome
  - Seroconversion rates of neutralizing antibodies to SARS-CoV-2 at day 14 after the last dose in the days 0 and 14 vaccination cohort, or day 28 after the last dose in the days 0 and 28 vaccination cohort.

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Zhang et al. Lancet Infect Dis 2020. https://doi.org/10.1016/ S1473-3099(20)30843-4

CoronaVac Candidate

Safety and Immunogenicity

- Key Immunogenicity Findings
  - Change in manufacturer prior to phase 2 led to higher intact spike protein content
  - Longer schedules produced higher antibody responses regardless of dose in phase 2

	3 μg group	6 μg group	Placebo group	p value*
Phase 1				
Days 0 and 14 vaccination cohort				
Neutralising antibodies to live SARS-CoV-2				
Day 14	11/24 (45·8%; 25·6–67·2)	12/24 (50·0%; 29·1–70·9)	0/24 (0·0%; 0·0–14·3)	0·77
Day 28	6/24 (25·0%; 9·8–46·7)	20/24 (83·3%; 62·6–95·3)	0/24 (0·0%; 0·0–14·3)	<0·0001
Days 0 and 28 vaccination cohort				
Neutralising antibodies to live SARS-CoV-2				
Day 14	19/24 (79·2%; 57·9–92·9)	20/24 (83·3%; 62·6–95·3)	0/23 (0·0%; 0·0–14·8)	1·00
Day 28	20/24 (83·3%; 62·6–95·3)	19/24 (79·2%; 57·9–92·9)	1/23 (4·4%; 0·1–22·0)	1·00

	3 μg group	6 μg group	Placebo group	p value*
Phase 2				
Days 0 and 14 vaccination cohort				
Neutralising antibodies to live SARS-CoV-2				
Day 14	109/118 (92·4%; 86·0–96·5)	117/119 (98·3%; 94·1–99·8)	2/60 (3·3%; 0·4–11·5)	0·030
Day 28	111/118 (94·1%; 88·2–97·6)	117/118 (99·2%; 95·4–100)	0/60 (0·0%; 0·0–6·0)	0·066
Days 0 and 28 vaccination cohort				
Neutralising antibodies to live SARS-CoV-2				
Day 28	114/117 (97·4%; 92·7–99·5)	118/118 (100%; 96·9–100)	0/59 (0·0%; 0·0–6·1)	0·12

Time points refer to the number of days after the second dose of vaccine in the schedule

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Zhang et al. Lancet Infect Dis 2020. https://doi.org/10.1016/ S1473-3099(20)30843-4

CoronaVac Candidate

Safety and Immunogenicity

- Key Safety Findings
  - No significant difference in adverse events among the different doses and schedules
    - Overall incidence of adverse events
      - Phase 1: 20%
      - Phase 2: 25%
  - Most common adverse event was injection site pain
    - Phase 1: 13%
    - Phase 2: 15%
  - One case of hypersensitivity with urticaria 48 hours after the first dose (6 ug)
    - Possibly related to the vaccine
    - No similar reaction seen after 2nd dose
  - No serious adverse events reported within 28 days of vaccination

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

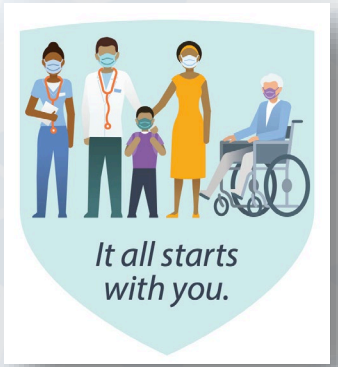
Zhang et al. Lancet Infect Dis 2020. https://doi.org/10.1016/ S1473-3099(20)30843-4

Summary

- Currently no inactivated COVID-19 vaccines available in the U.S.
- Potential for decreased local and systemic reactogenicity compared to mRNA vaccines
- Historically suitable for immune-compromised populations
- Theoretical concern for antibody-dependent development of infection if a person is infected
  - Importance of determining Th1 response during Phase I/II trials
- Inactivated vaccines will all likely require multiple doses for efficacy

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Useful Links



- CDC Website
  - https://www.cdc.gov/vaccines/covid-19/index.html
- CDC Vaccine Communication Toolkit
  - https://www.cdc.gov/vaccines/covid-19/health-systems-communication-toolkit.html
- CDC Guidance for Infection Prevention Considerations Post Vaccination
  - https://www.cdc.gov/coronavirus/2019-ncov/hcp/post-vaccine-considerations-healthcare-personnel.html
- COVID-19 Real-Time Learning Network (CDC and IDSA)
  - https://www.idsociety.org/covid-19-real-time-learning-network/

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

1. Get Vaccinated
2. Tell Others Why
3. Build the Confidence

SARS-CoV-2 Inactivated Vaccines

A Review of Pertinent Drug Information for SARS-CoV-2

Caroline C. Jozefczyk, PharmD, BCIDP
Antimicrobial Stewardship Pharmacist, OhioHealth Mansfield and Shelby Hospitals
Caroline.Jozefczyk@OhioHealth.com
@ccjozefczyk

Data as of January 27, 2021

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS