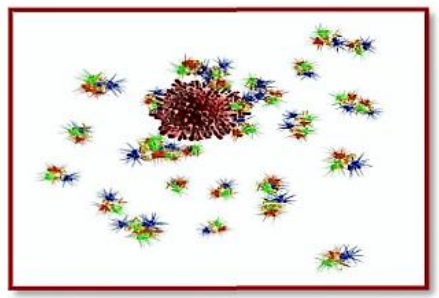
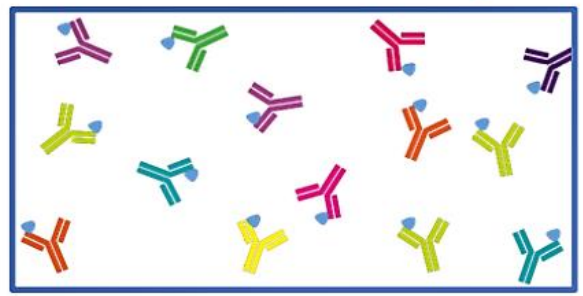
# Disclosures

**Speaker: DR. NINA G. GLORIANI**

- **I have no financial disclosure or conflicts of interest with regard to the subject matter of this presentation**
- This presentation is based on current available data and may change

# COVID Vaccines: Immunogenicity and Efficacy (Adult and Pediatrics)

*Nina G. Gloriani, MD, PhD*

**Dost Vaccine Expert Panel Chair (March 2020-2022)**
**Member, WHO Scientific Steering Committee for Solidarity Vaccines Trials**

**Asian Pacific Vaccinology Meeting * Philippines Edition**
**Mérieux Foundation & the Paediatric Infectious Disease Society of the Philippines (PIDSP)**
**November 30-December 2, 2022, Sofitel Hotel**

# TOPICS

- Immunogenicity and Efficacy of COVID-19 Vaccines (RCT)
  - General Population: (18 – 55 years)
  - Elderly >55 years old
  - Adolescents, Children, Infants (6 months to < 17)

- Real World Vaccine Effectiveness Studies
- Take Home Messages

# Considerations for Immunogenicity and Efficacy Data of vaccines: Original vaccines- administered via intramuscular route

**Head to head, direct comparisons could not be made for these COVID-19 vaccines as they differ/ vary in:**

- Platform/ type of vaccines
- Vaccine antigen content: whole virus or subunit (spike, RBD, etc)
- Dose –antigen concentration/ Number of Doses/ Interval between doses
- Primary series ( 1 or 2 or 3 ? ), vs Booster Doses
- Population:
  - Age group: General population, elderly/ older adults, Adolescents, children, Infants
  - Health status: healthy, immunocompromised, with co-morbidities
- **Immune response measurements used different methods * Need Biological standards to compare vaccine performance**
- Correlates of Protection
- Primary and secondary endpoints for effect measures: Laboratory confirmed COVID-19, Symptomatic vs Severe/critical COVID, serological testing
- Effects of waning immunity and emergence of variants of concern ➔ how these translate to Real World Effectiveness / Clinical Protection

# Considerations for Immunogenicity and Efficacy Data of vaccines: Original vaccines- administered via intramuscular route

WHO Collaboration Center for **Biological Standardization** and the National Institute for Biological Standards and Control **(NIBSC)** recently organized and completed the collaborative calibration of mRNA and antibody standards

- The First **WHO International Standard for SARS-CoV-2 RNA** for nucleic acid amplification techniques (NAT) based assays was established by the Committee with assigned **unitage of 7.40 log10 IU/ampoule.** The NAT-based assay is considered the gold standard for accurate diagnosis of infection

- The First **WHO International Standard for anti-SARS-CoV-2 immunoglobulin** was established with an assigned **unitage of 250 IU/ampoule (neutralizing antibody activity).** Previously, China's NIFDC had established the first COVID-19 national standard for neutralizing antibody using convalescent serum, which can be used for vaccine evaluation

- The **WHO International Reference Panel of anti-SARS-CoV2 immunoglobulin** was also established with no assigned units.

- The establishment of nucleic acid standard is of great significance not only for the facilitation of accurate diagnosis but also for the comparability of clinical trial data.
- The availability of an International Standard for antibodies to SARS-CoV-2 would facilitate the standardization of SARS-CoV-2 serological methods and allow for comparison and harmonization of datasets across laboratories.

# Immunogenicity and Efficacy of COVID-19 Vaccines in: General adult healthy population

# COVID-19 Vaccines: Current Understanding on Immunogenicity, Safety, and Further Considerations (He et al. 2021. Frontiers of Immunology. Volume 12 Article 669339)

- This paper reviewed and analyzed the clinical reports of different COVID-19 vaccines and found that the currently developed COVID-19 vaccines differ significantly in their effectiveness and safety.

| Platforms | Vaccines (Developers) | Phase | Regimen | Efficacy (%) | Immunogenicity | |
|---|---|---|---|---|---|---|
| | | | | | NtAb | T cell:IFN-γ (SFUs/1×10$^5$) |
| mRNA | mRNA -1273 (Moderna) (50, 78) | 3 | Day 0 + 28 100μg | 94.1 | 654.3 (PRNT80) | 0.1% (flowcytometry) |
| | BNT162b2 (BioNTech) (51, 79) | 3 | Day 0 + 28 30μg | 95.0 | 361 (mNG-NT50) | 1000 |
| Adenovirus vectored | AZD1222 (AstraZeneca) (30, 53) | 3 | Day 0 + 28 5×10$^{10}$vp | 70.4 (Total) 90 (LD/SD) 60.3 (SD/SD) | 161-193 ($MNT_{50}$) | 797-1187 |
| | Ad5-nCoV (CanSino) (32, 83) | 3 | Day 0 5×10$^{10}$vp | 65.7 | 18.3 ($MNT_{50}$) | 100 |
| | Sputnik V (Gamaleya) (33) | 3 | Day 0 + 21 1×10$^{11}$vp | 91.6 | 49.25 ($MNT_{50}$) | 1.3% (flowcytometry) |
| | Ad26.COV2.S (Janssen Pharm) (34) | 3 | Day 0 + 56 5×10$^{10}$vp | 66 | 1st: 277-321 2nd: 827 ($MNT_{50}$) | 0.08%-0.09% |
| Inactivated | BBIBP-CorV (Beijing, Sinopharm) (80) | 3 | Day 0 + 21 4μg | 79.34 | 282.7 ($MNT_{50}$) | — |
| | CoronaVac (Sinovac) (82) | 3 | Day 0 + 14 Day 0 + 28 3μg | 91.25 (Turkey) 86 (UAE) 50.38 (Brazil) | 65.4 ($MNT_{50}$) | 55 |
| | Inactivated (Wuhan, Sinopharm) (81) | 3 | Day 0 + 21 5μg | 72.51 | 247 ($PRNT_{50}$) | — |
| | BBV152 (Bharat Biotech) (39) | 3 | Day 0 + 14 6μg | — | 66.4($MNA_{50}$) ~120($PRNT_{50}$) | 55 |
| Recombinant subunit | NVX-CoV2373 (Novavax) (76) | 3 | Day 0 + 21 5μg | 89.3 | 3906 ($MNT_{90}$) | ≈0%-1.5% (flowcytometry) |
| | ZF2001 (Zhifei Longcom) (84) | 3 | Day 0 + 28+56 25μg | — | 102.5 ($MNT_{50}$) | ≈8 |
| | SCB-2019 (Clover) (77) | 2/3 | Day 0 + 21 9μg | — | 1810-3320 ($MNT_{50}$) | ≈0.1% (flowcytometry) |
| DNA | INO-4800 (Inovio) (27) | 2/3 | Day 0 + 28 1mg | — | 102.3 ($PRNT_{50}$) | 46 |

*1. NtAb, Neutralizing Antibody; SFUs, Spot Forming Units; MNT, Micro-neutralization Test; PRNT, Plaque Reduction Neutralization Test.*

MNT: Microneutralization test or Plaque reduction neutralization test

# Immunogenicity * Neutralizing Antibody

**(He et al. 2021. Frontiers of Immunology. Vol 12 Article 669339) )**

- Neutralizing antibody (NtAb) titer is the most common correlate of protection against viral vaccines, highly correlated with protective effect and the durability of the protection.
- Results of previous studies on monoclonal antibodies and convalescent sera, as well as the tests conducted in animal models, have all confirmed the role of neutralizing antibodies in conferring protection against COVID-19
- According to the results of clinical trials, the **Geometric Mean Titer (GMT) of NtAb vary for different vaccine candidates.**

- The **recombinant protein vaccines** induced the highest neutralizing antibody GMTs, attributed to novel adjuvants:

  **Clover** GMT = 3320

  **Novavax** GMT = 3906,

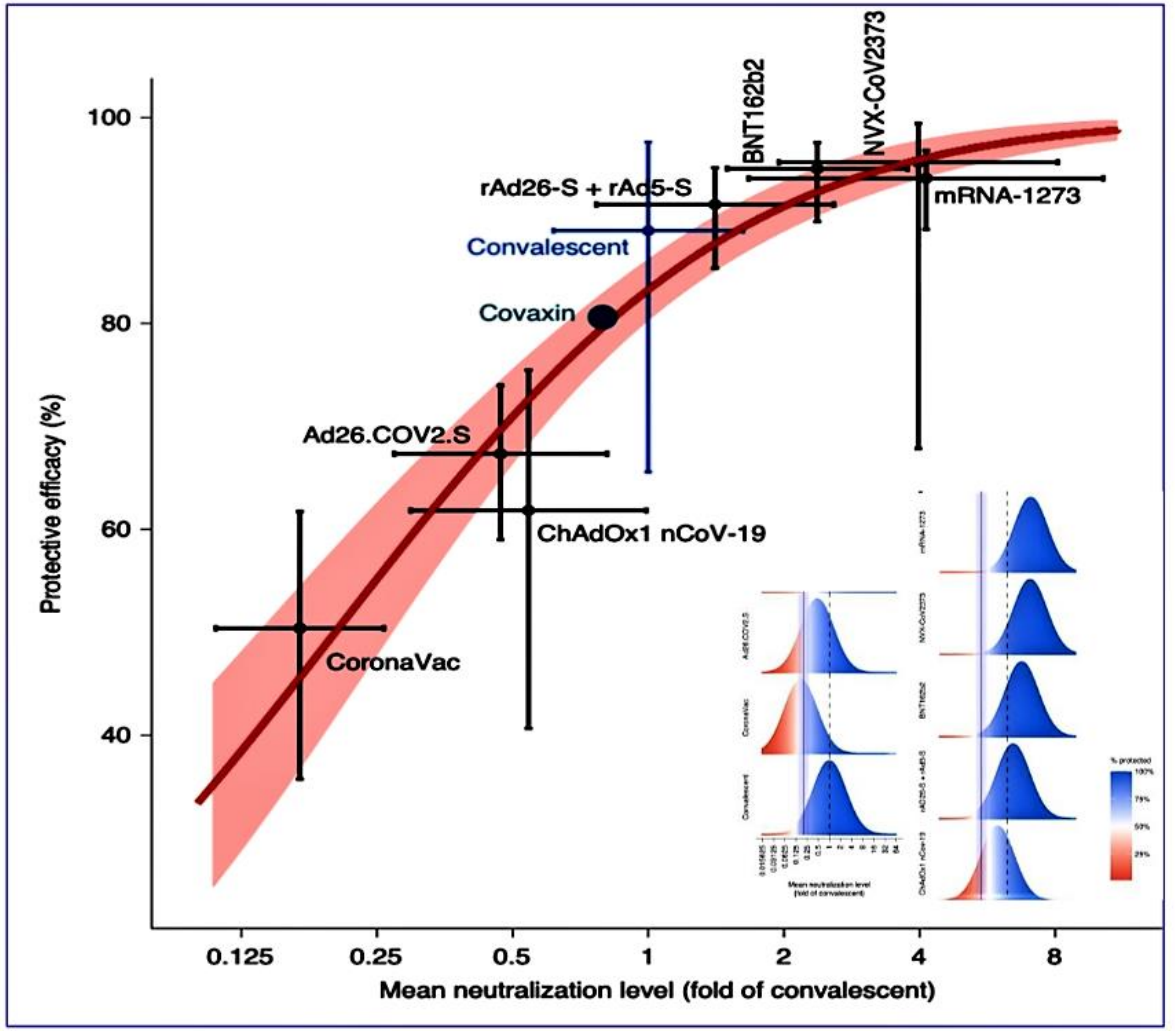
- Comparatively, the GMTs of **mRNA vaccines** were:

  **Moderna** GMT = 654.3

  **Pfizer GMT** = 361

- Various **inactivated vaccines** GMT = 50-300

# Neutralizing Antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection (Khoury et al. Nature Medicine | VOL 27 | July 2021 | 1205–1211 )



# COVID-19 Vaccines: Current Understanding on Immunogenicity, Safety, and Further Considerations (He et al. 2021. Frontiers of Immunology. Volume 12 Article 669339)

- **Highlights from published Vaccine Efficacies (VEs):**

1) All reported VEs are higher than the 50% criterion required by WHO, FDA and EMA, indicating that the currently developed COVID-19 vaccines are efficacious against symptomatic COVID-19 in early stage (about 2-3 months) after vaccination
2) The VE reported for elderly population is relatively lower. They are more susceptible to SARS-CoV-2 and show a higher death rate
3) The evidences for VE can be unreliable due to complicated demographic characteristics, such as population and geography; VE generalized from diverse settings with the dose and dosage influence the efficacy of the vaccine: single dose vs 2 doses and with different interval between doses

?????? Locally circulating variants combined with geography factor greatly affect the calculated VE of vaccine candidates: Beta variant in South Africa, Gamma variant in Brazil, Delta in India, Omicron in many parts of the world

# Immunogenicity and Efficacy of COVID-19 Vaccines in Older Adults

# Immunogenicity and Efficacy of COVID-19 Vaccines in: The Elderly * Older Adults >55 years (Li et al. 2022. Frontiers in Immunology. 13:965971)

- RCT from inception to April 9, 2022 systematically searched in Pubmed, EMBASE, Cochrane Library, Web of Science: 9 studies analyzed for efficacy and 21 for immunogenicity. (14-28 days after last vaccine administration across at least 7 vaccines)
- **Vaccine efficacy (VE)** vs COVID-19 in older adults = **79.49%** (95% CI: 60.55–89.34)
- **Seroconversion rate** = **92.64%** (95% CI: 86.77–96.91)
- **Geometric mean titer (GMT) =** SMD **3.56** (95% CI: 2.80–4.31) of **neutralizing antibodies**
- **Protection** rate against **severe disease = 87.01%** (95% CI 50.80–96.57)

- **mRNA vaccines showed:**
  - Best efficacy = **90.72%** (95% CI: 86.82–93.46)
  - Highest seroconversion rate = **98.52%** (95% CI: 93.45–99.98)
  - GMT = **SMD 6.20** (95% CI: 2.02 –10.39)

- **Overall Conclusion:** Acceptable efficacy and Immunogenicity in older people, providing high protection rate against severe disease.

# Immunogenicity and Efficacy of COVID-19 Vaccines in: The Elderly * Older Adults >55 years (Li et al. 2022. Frontiers in Immunology. 13:965971)

## Characteristics of included selected studies on EFFICACY of COVID-19 Vaccines

| Study | Vaccine | Admin(#doses, intervals, dosage | Age range | # participants (vacc/control) | Country | Study types (phase, # centers, blinding) | VE (95% CI) |
|---|---|---|---|---|---|---|---|
| Falsey (2021) | **ChAdOx1-S (AZD1222)** | 2, 28 days 5x10(10) VP | > 65 | 3696/1812 | US, Chile, Peru | III, 88 double blind | **83.%** (54.2,94.1) |
| Halperin (2022) | **Ad5-nCoV (Cansino)** | 1, 5x10(10) VP | > 60 | 1323/1347 | Pakistan, Mexico, Russia, Chile, Argentina | III, 66 double blind | **53.3%** (0.9, 78) |
| Heath (2021) | **NVX-CoV 2373 (Novavax)** | 2,21 days 5 ug | > 65 | 1953/1957 | The UK | III, 33 Observer blinded | **88.9%** (12.8, 98.6) |
| Logunov (2021 | **Gam- Covid-Vac (Sputnik)** | 2,21 days 1 x10(11) | > 60 | 1611/533 | Russia | III, 25 double blind | **91.8%** (67.1, 98.3) |
| Sadoff | **Ad26.COV2.S (JNJ)** | 1 5x10(10) | > 60 | 6735/6724 | Latin America, Argentina,Brazil, Chile, Colombia, Mexico, Peru, South Africa, United States | III, 8 double blind | **55.0%** (42.9,64.7) |
| Sahly (2021) | **mRNA-1273 (Moderna)** | 2, 28 days 100 ug | > 65 | 3626/3595 | United States | III, 99 Observer blinded | **91.5%** (83.2, 95.7) |
| Thomas (2021) | **BNT162b2 (Pfizer)** | 2, 21 days 30ug | >55 | 8194/8208 | United States, Argentina, Brazil, Germany, South Africa, Turkey | II/III,152 Observer blinded | **90.9%** (86.3, 94.2) |

**Seroconversion Rates for selected vaccines**: **AZD1222**= 56.9%; Moderna **mRNA**=99.82%; **NVX-CoV2373**= 97.25%
**Gam-Covid-Vac**= 96.77%; **Ad26.COV2.S**= 91.59%; **Coronavac**= 98.16%; **Ad5-nCoV**= 92.21%

# Immunogenicity and Efficacy of COVID-19 Vaccines in Adolescents, Children and Infants

# Immunogenicity and Efficacy of COVID-19 Vaccines in: Adolescents, Children, Infants

Tian, Yang and Cheng. 2022. J Med Virol. 94:4644–4653

**A systematic review of RCT in children and adolescents:**

- COVID-19 vaccines were evaluated in a total of 10 950 children and adolescents in seven published studies and over 49 530 participants in 26 ongoing randomized controlled trials. Descriptive findings of the included published studies were reported stratified by vaccine type.
- In terms of efficacy, the investigated messenger RNA (mRNA) vaccine was found to be **90.7%–100%** efficacious in preventing COVID-19 among **children and adolescents**, revealing good efficacy profiles in this age group
- Studies suggested that mRNA vaccines can provide high protection against COVID-19 infection in pediatric age groups.
- In this review, RNA vaccines exhibited over ***90% efficacy after the second dose*** **in clinical trials** of young people **aged 5–17 years**, demonstrating that the policy of mass vaccination of children and adolescents is reasonable and feasible.
- Additionally, the Pfizer BNT162b vaccine was found among people aged **12–18 years** based on data from **real-world conditions** to have VE against:
  - SARS-CoV-2 Infection = 92%,
  - COVID-19 hospitalization = 93%,
  - Multisystem inflammatory syndrome = 91%

# Immunogenicity and Efficacy of COVID-19 Vaccines in: Adolescents, Children, Infants

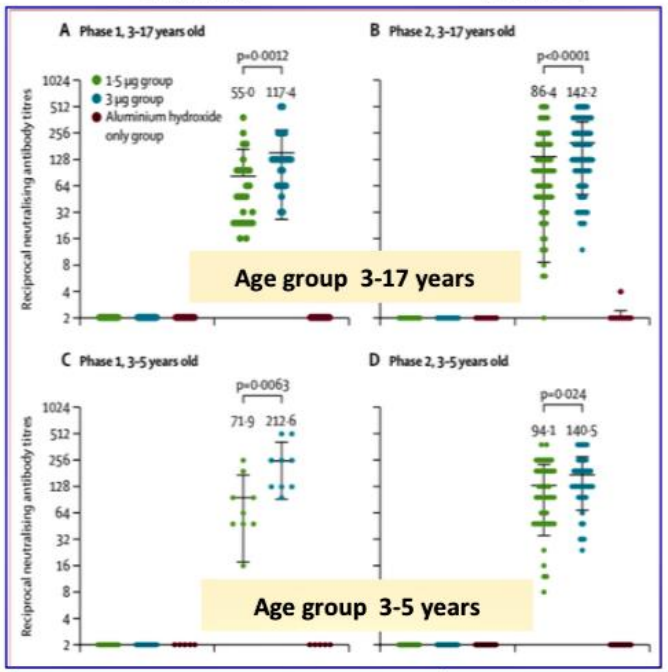
Sinovac (Coronavac) * Han et al Lancet Infect Dis 2021; 21: 1645–53

## Seroconversion rates of Neutralizing Antibody responses to live SARS-CoV-2 at 28 days after 2nd dose

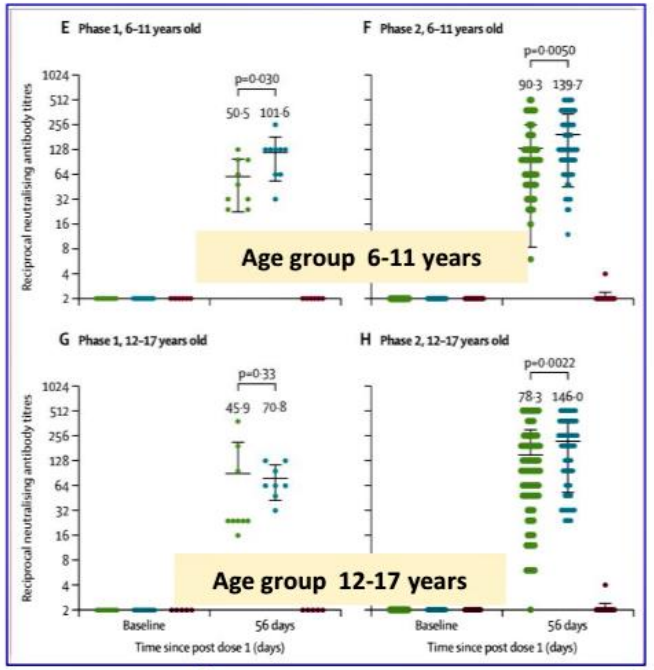
| | 1·5 µg group | | 3·0 µg group | | Aluminium hydroxide only group | | p value | |
|---|---|---|---|---|---|---|---|---|
| | Rate | % (95% CI) | Rate | % (95% CI) | Rate | % (95% CI) | Three groups | 1·5-µg vs 3·0-µg group |
| **Phase 1** | **Seroconversion rates 93-100%** | | | | | | | |
| Total | 27/27 | 100·0% (87·2-100·0) | 26/26 | 100·0% (86·8-100·0) | 0/16 | 0·0% (0·0-20·6) | <0·0001 | 1·0 |
| 3-5 years | 9/9 | 100·0% (66·4-100·0) | 9/9 | 100·0% (66·4-100·0) | 0/5 | 0·0% (0·0-52·2) | <0·0001 | 1·0 |
| 6-11 years | 9/9 | 100·0% (66·4-100·0) | 9/9 | 100·0% (66·4-100·0) | 0/6 | 0·0% (0·0-45·9) | <0·0001 | 1·0 |
| 12-17 years | 9/9 | 100·0% (66·4-100·0) | 8/8 | 100·0% (63·1-100·0) | 0/5 | 0·0% (0·0-52·2) | <0·0001 | 1·0 |
| **Phase 2** | | | | | | | | |
| Total | 180/186 | 96·8% (93·1-98·8) | 180/180 | 100·0% (98·0-100·0) | 0/94 | 0·0% (0·0-3·9) | <0·0001 | 0·030 |
| 3-5 years | 46/46 | 100·0% (92·3-100·0) | 45/45 | 100·0% (92·1-100·0) | 0/24 | 0·0% (0·0-14·2) | <0·0001 | 1·0 |
| 6-11 years | 68/69 | 98·6% (92·2-100·0) | 68/68 | 100·0% (94·7-100·0) | 0/35 | 0·0% (0·0-10·0) | <0·0001 | 1·0 |
| 12-17 years | 66/71 | 93·0% (84·3-97·7) | 67/67 | 100·0% (94·6-100·0) | 0/35 | 0·0% (0·0-10·0) | <0·0001 | 0·059 |

Data are n/N (% [95% CI]).

Phase 1 Phase 2




Phase 1 Phase 2




| Age in years: | Phase 1- NT Ab titer | | Phase 2- Nt Ab titer | |
|---|---|---|---|---|
| | 1.5ug dose | 3 ug dose | 1.5 ug dose | 3 ug dose |
| All ages: 3-17 | 55.0 | 117.4 | 86.4 | 142.2 |
| 3-5 years old | 71.9 | 212.6 | 94.1 | 140.5 |
| 6-11 years old | 50.5 | 101.6 | 90.3 | 139.7 |
| 12-17 years old | 45.9 | 70.8 | 78.3 | 146.0 |

# Immunogenicity and Efficacy of COVID-19 Vaccines in: Adolescents, Children, Infants

Adenov –spike vaccine (Cansino) * Zhu et al. Clinical Infectious Diseases 2022;75(1):e783–91

## SEROCONVERSION RATES of RBD-Binding ELISA Antibodies and Neutralizing Abs to Pseudovirus Post vaccination

| | 6-17 years (MIN Cohort) | | | 18-55 years (MID Cohort) | | > 56 years (OLD Cohort) | | |
|---|---|---|---|---|---|---|---|---|
| Time Point | Low-Dose Group (N = 100) | Placebo Group (N = 50) | | Low-Dose Group (N = 20) | Placebo Group (N = 10) | Middle-Dose Group (N = 100) | Low-Dose Group (N = 98) | Placebo Group (N = 50) |
| Receptor binding domain–binding enzyme-linked immunosorbent assay antibody | | | | RBD ELISA | | | | |
| Day 28 | 98.0% (93.0–99.5) | 0 | | 95.0% (76.4–99.1) | 0 | 79.0% (70.0–85.8) | 66.3% (56.5–74.9) | 0 |
| Day 56 | 97.0% (91.6–99.0) | 0 | | 95.0% (76.4–99.1) | 0 | 73.0% (63.6–80.7) | 50.0% (40.3–59.7) | 0 |
| Day 84 | 100.0% (96.3–100.0) | 0 | | 100.0% (83.9–100.0) | 0 | 89.0% (81.4–93.8) | 88.8% (81.0–93.6) | 0 |
| Neutralizing antibody to pseudovirus | | | | Pseudovirus Nt Ab test | | | | |
| Day 28 | 88.0% (80.2–93.0) | 6.0% (2.1–16.2) | | 75.0% (53.1–88.8) | 10.0% (1.8–40.4) | 83.0% (74.5–89.1) | 65.3% (55.5–74.0) | 0 |
| Day 56 | 85.0% (76.7–90.7) | 6.0% (2.1–16.2) | | 60.0% (38.7–78.1) | 0 | 65.0% (55.3–73.6) | 41.8% (32.6–51.7) | 4.0% (1.1–13.5) |
| Day 84 | 98.0% (93.0–99.5) | 4.0% (1.1–13.5) | | 95.0% (76.4–99.1) | 0 | 98.0% (93.0–99.4) | 86.7% (78.6–92.1) | 2.0% (0.4–10.5) |

Data are the percentage of participants with seroconversion (95% confidence interval). Seroconversion was defined as an increase in post-vaccination titer of at least 4 times baseline. Time point refers to the number of days since the prime vaccination. MIN cohort = 6–17 years cohort; MID cohort = 18–55 years cohort; OLD cohort = ≥56 years cohort.

- **Seroconversion rates** generally higher in younger age groups , decreasing with age using lower dose, but a little higher with middle dose
- **T cell responses TH1 skewed**, higher at day 28 post vaccination and sustained up to 84 days

**Specific T cell responses at Day 28 and 84 after prime vaccination – Spot forming cells secreting cytokines IFN-g, IL-2, Il-4, IL-5 and IL-13.**

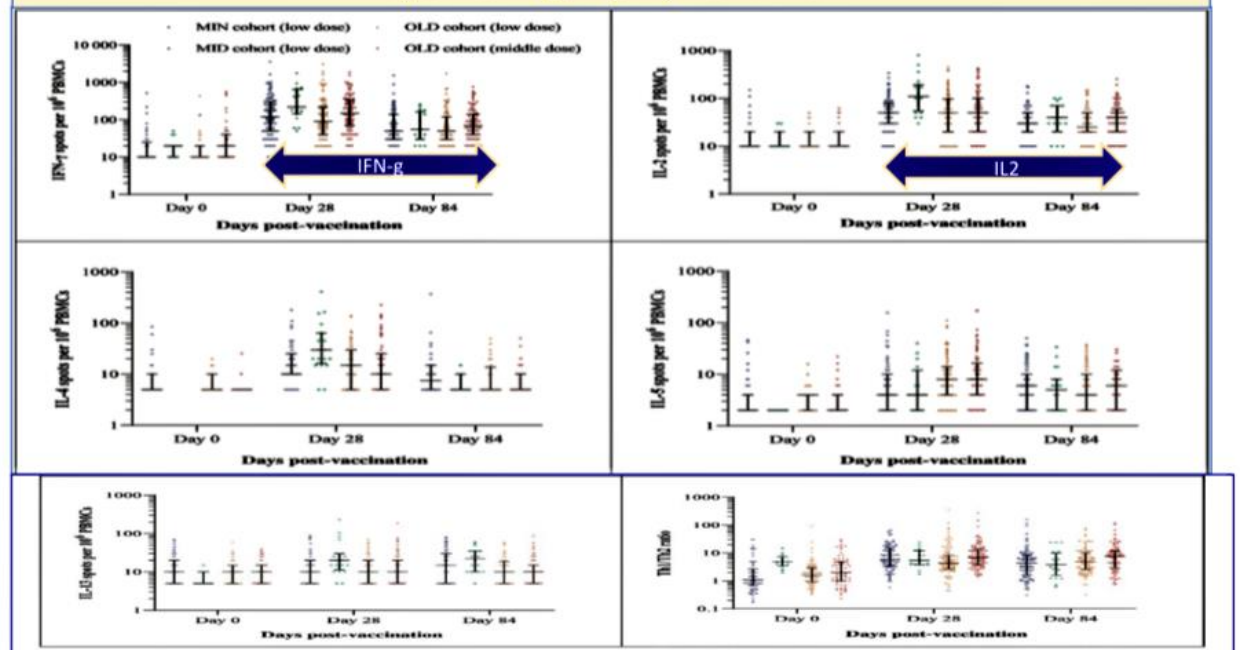



**Figure 4.** Specific T-cell response measured by enzyme-linked immunospot at baseline and at day 28 and day 84 after prime vaccination. Data are the spot-forming cells with secretion of cytokines per $1 \times 10^6$ PBMCs in participants who received vaccine, including IFN-γ, IL-2, IL-4, IL-5, and IL-13. The Th1/Th2 ratio was calculated by the sum of IFN-γ plus IL-2 cytokine levels divided by the sum of IL-4 and IL-5 plus IL-13 cytokine level. Horizontal bars show the median and error bars show the interquartile range. MIN cohort = 6–17 years cohort; MID cohort = 18–55 years cohort; OLD cohort = ≥56 years cohort. Abbreviations: IFN, interferon; IL, interleukin; PBMC, peripheral blood mononuclear cell.

# Immunogenicity and Efficacy of COVID-19 Vaccines in: Adolescents, Children, Infants

**Gao et al. 2022. Vaccines 10:421**

**Results:** A total of 13 eligible studies were included for analysis (7 RCTs, 3 cohort studies, and 3 cross-sectional studies. Six articles for the effectiveness in children and adolescents. Four of those studies from the USA (207,859 participants) and two studies from multiple countries (3003 participants)

- For the **first dose**, the effectiveness of SARS-CoV-2 vaccines against:
  - SARS-CoV-2 infection was **88.5%** (95% CI:15.7–98.4%, p = 0.033)
  - pooled COVID-19 = **84.3%** (95% CI: 66.6–92.6%, p < 0.001)
- For the **second dose**, the effectiveness against
  - SARS-CoV-2 infection was **91.6%** (95% CI: 37.8–99.5%, p = 0.083)
  - pooled COVID-19 = **92.7** (95% CI: 82.2–97.0, p < 0.001)
- **Conclusion**:
  - SARS-CoV-2 vaccines can effectively prevent SARS-CoV-2 infection among children and adolescents.
  - Available data are still limited, and more basic research and clinical trials are still needed to explore vaccine effectiveness and immunogenicity in children

# SARS-CoV-2 Neutralizing Antibodies: A Network Meta-Analysis across Vaccines (Rogliani et al. 2021. Vaccines 9: 227)

**Methods:** A network meta-analysis performed to compare the peak levels of SARS-CoV-2 neutralizing antibodies across candidate vaccines. Data reported as standardized mean difference (**SMD**) since the outcome was assessed via different metrics and methods across the studies.

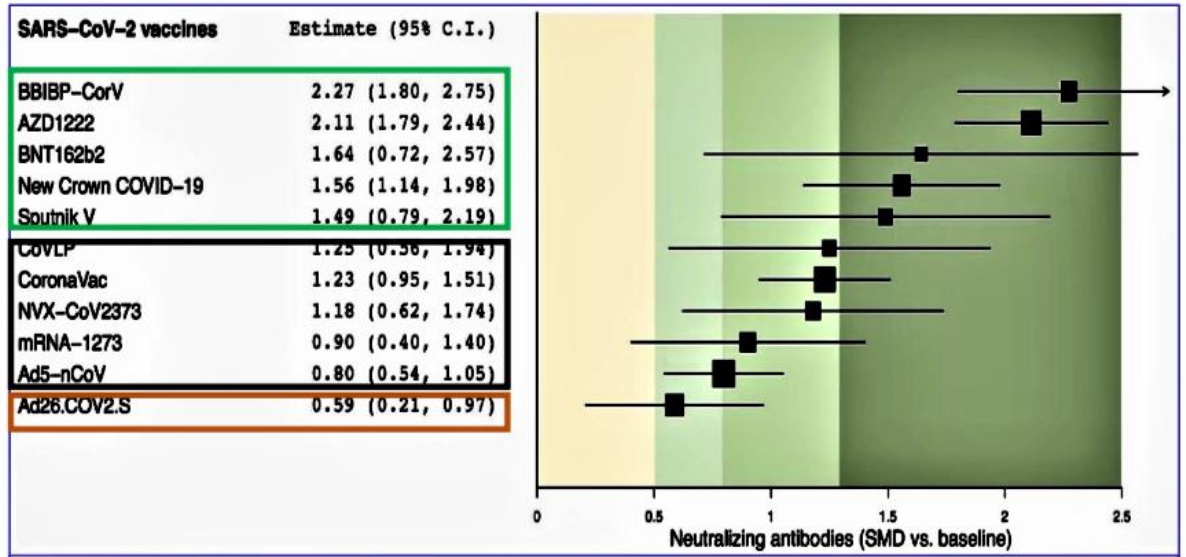
**Results: Data obtained from 836 healthy adult vaccine recipients extracted from 11 studies.**

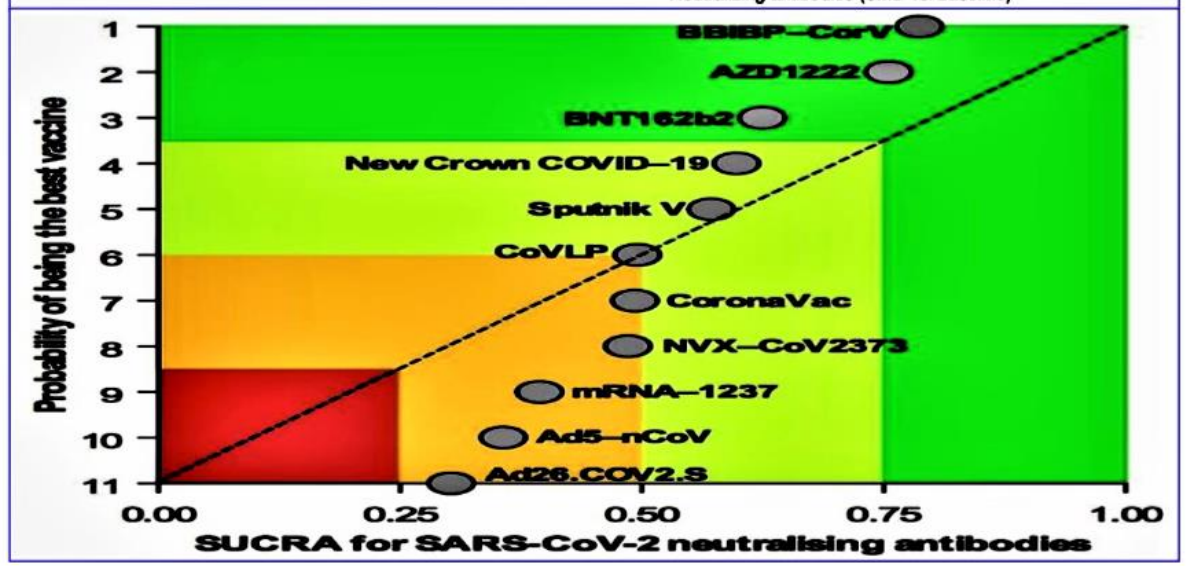
- BBIBP-CorV, AZD1222, BNT162b2, New Crown COVID-19, and Sputnik V induced a **very large effect on the level of neutralizing antibodies (SMD > 1.3);**
- CoVLP, CoronaVac, NVX-CoV2373, and Ad5-nCoV induced a **large effect (SMD > 0.8 to ≤1.3);**
- Ad26.COV2.S induced a **medium effect (SMD > 0.5 to ≤0.8).**

- **BBIBP-CorV and AZD122 were more effective** ($p < 0.05$) than Ad26.COV2.S, Ad5–nCoV, mRNA-1237, CoronaVac, NVX–CoV2373, CoVLP, and New Crown COVID-19; New Crown COVID-19 was more effective ($p < 0.05$) than Ad26.COV2.S, Ad5–nCoV, and mRNA-1237;
- **CoronaVac** was more effective ($p < 0.05$) than Ad26.COV2.S and Ad5–nCoV; and Sputnik V
- **BNT162b2** were more effective ($p < 0.05$) than Ad26.COV2.S.
- **In recipients aged ≤60 years, AZD1222, BBIBP-CorV, and mRNA-1237 were the most effective candidate vaccines.**

**Conclusion:**

All the candidate vaccines induced significant levels of SARS-CoV-2 neutralizing antibodies, but only AZD1222 and mRNA-1237 were tested in patients aged ≥70 years.



# Real-world Effectiveness of COVID-19 Vaccines

# Real world effectiveness of COVID-19 Vaccines: A meta analysis.

Zheng et al. 2022. Intl J Infectious Diseases. 114: 252-260

**Methods:** Observational studies (39 Cohort, 4 case control, 8 test-negative case control) reporting COVID-19 VE from **August 6, 2020 to October 6, 2021** included. The summary VE (with 95% confidence intervals (95% CI)) against disease related to COVID-19 was estimated. The results were presented in forest plots. Predefined subgroup analyses and sensitivity analyses were also performed

**Overall Results:** A total of 51 records from 14 countries were included in this meta-analysis. VE estimates derived from effect measures: odds ratio, relative risk, hazard ratio, incidence rate ratio

- In fully vaccinated populations the VE reported as follows against:
  - SARS-CoV-2 infection = **89.1%** (95% CI 85.6–92.6%)
  - COVID-19-related hospitalization = **97.2%** (95% CI 96.1–98.3%)
  - Admission to the intensive care unit = **97.4%** (95% CI 96.0–98.8%)
  - Death = **99.0%** (95% CI 98.5–99.6%)
- **The VE against infection (age group and HCW)**
  - General population aged ≥16 years = **86.1%** (95% CI 77.8–94.4%)
  - Elderly = **83.8%** (95% CI 77.1–90.6%)
  - Healthcare workers = **95.3%** (95% CI 92.0–98.6%)
- **For fully vaccinated against infection (by vaccine type or brand)**
  - Pfizer-BioNTech vaccine (23 articles) = 91.2%
  - Moderna vaccine (5 articles) = 98.1%
  - CoronaVac vaccine (3 articles) = 65.7%; with Delta variant = VE= 59% after 2 doses
  - Astra Zeneca (India-1 article) = 88.6% fully vaccinated; (8 articles) Partially Vaccinated VE = 81.8%

**Conclusions:** The COVID-19 vaccines are **highly protective against SARS-CoV-2-related diseases in real-world settings**

# Real world effectiveness of COVID-19 Vaccines: A meta analysis.

Zheng et al. 2022. Intl J Infectious Diseases. 114: 252-260

## VE against infectiousness:

- ❑ Retrospective cohort study in USA = **80%** effectiveness after 2nd dose Pfizer BNT vaccine
- ❑ A single dose of Moderna vaccine could reduce potential transmission to others by **61%**
- ❑ A single dose of Ad26.COV2.S = **68.1%** VE vs gamma variant – moderate to severe COVID-19.

## General Conclusions on RWE studies:

- ❖ Consistent with the results of Phase III CT, the effectiveness of vaccines against confirmed COVOVID-19 infection in REAL-WORLD conditions varied.
- ❖ Overall, the results suggest that the available vaccines currently approved for use have a good protective effect against the major outcomes , especially, critical COVID-19.

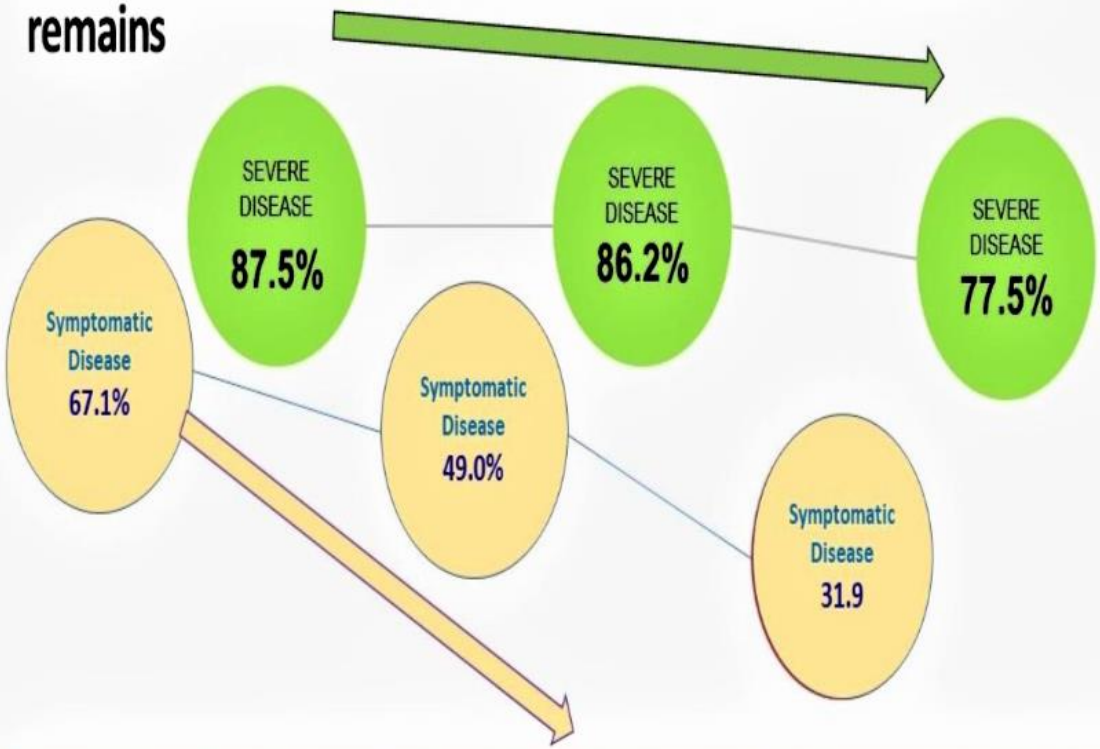
# Waning Immunity and emergence of SARS-CoV-2 variants which kept on producing immune evasive subvariants

## Summary of results of neutralization studies assessing primary series and booster vaccine performance against Omicron variant of concern (data updated as of 20 November 2022)

| | | Omicron Sub-Lineage | | | | | |
|---|---|---|---|---|---|---|---|
| | | BA.1 | BA.2 | BA.2.12.1 | BA.2.75 | BA.3 | BA.4/BA.5 |
| **Primary Series Vaccination** | | | | | | | |
| WHO Emergency Use Listing (EUL) Qualified Vaccines | AstraZeneca-Vaxzevria/SII-Covishield | $HNR_{15}$ | $HNR_{1}$ | $HNR_{1}$ | — | — | $HNR_{1}$ |
| | Beijing CNBG-BBIBP-CorV | $HNR_{9}$ | $HNR_{1}$ | $HNR_{2}$ | — | $HNR_{1}$ | $HNR_{2}$ |
| | Bharat-Covaxin | $\downarrow\downarrow_{1}$ | — | — | — | — | — |
| | Cansino-Convidecia | — | — | — | — | — | — |
| | Janssen-Ad26.COV2.S | $HNR_{10}$ | $HNR_{1}$ | $HNR_{1}$ | — | — | $HNR_{1}$ |
| | Moderna-Spikevax | $\downarrow\downarrow\downarrow_{11}$ | $\downarrow\downarrow$ to $\downarrow\downarrow\downarrow_{7}$ | $HNR_{1}$ | — | — | $HNR_{1}$ |
| | Novavax-Nuvaxovid/SII - Covavax | $HNR_{1}$ | $HNR_{1}$ | $HNR_{1}$ | — | — | $HNR_{1}$ |
| | Pfizer BioNTech-Comirnaty | $HNR_{17}$ | $HNR_{19}$ | $HNR_{1}$ | $HNR_{1}$ | $HNR_{1}$ | $HNR_{5}$ |
| | Sinovac-CoronaVac | $HNR_{11}$ | $HNR_{1}$ | $HNR_{1}$ | — | — | $HNR_{2}$ |
| Vaccines without WHO EUL | Anhui ZL-Recombinant | — | — | — | — | — | — |
| | Gamaleya-Sputnik V | $HNR_{1}$ | $HNR_{1}$ | $HNR_{1}$ | — | — | $HNR_{1}$ |
| | Chumakov-CoVi-Vac | $HNR_{1}$ | — | — | — | — | — |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First Booster Vaccination (Primary Series Vaccine + Booster Vaccine)** | | | | | | | |
| WHO Emergency Use Listing (EUL) Qualified Booster Vaccines | AstraZeneca-Vaxzevria/SII-Covishield + AstraZeneca-Vaxzevria/SII Covishield | $HNR_{1}$ | $HNR_{1}$ | — | — | $\downarrow\downarrow_{1}$ | $\downarrow\downarrow\downarrow_{1}$ |
| | AstraZeneca-Vaxzevria/SII-Covishield + Moderna-Spikevax | $\downarrow_{1}$ | — | — | — | — | — |
| | AstraZeneca-Vaxzevria/SII-Covishield + Pfizer BioNTech-Comirnaty | $\downarrow\downarrow$ to $\downarrow\downarrow\downarrow_{2}$ | $\downarrow\downarrow_{1}$ | — | — | $\downarrow\downarrow_{1}$ | — |
| | Beijing CNBG-BBIBP-CorV + Beijing CNBG-BBIBP-CorV | $\downarrow\downarrow$ to $\downarrow\downarrow\downarrow_{6}$ | $\downarrow_{4}$ | $HNR_{2}$ | $\downarrow_{1}$ | $\downarrow\downarrow_{2}$ | $\downarrow_{5}$ |
| | Cansino-Convidecia + Cansino-Convidecia | $\downarrow_{1}$ | — | — | — | — | — |
| | Janssen-Ad26.COV2.S + Janssen-Ad26.COV2.S | $HNR_{1}$ | — | — | — | — | — |
| | Janssen-Ad26.COV2.S + Moderna-Spikevax | $\downarrow\downarrow\downarrow_{1}$ | — | — | — | — | — |
| | Janssen-Ad26.COV2.S + Pfizer BioNTech-Comirnaty | $\downarrow$ to $\downarrow\downarrow\downarrow_{1}$ | — | — | — | — | — |
| | Moderna-Spikevax + Moderna-Spikevax | $\downarrow$ to $\downarrow\downarrow\downarrow_{11}$ | $\downarrow\downarrow$ to $\downarrow\downarrow\downarrow_{4}$ | $\downarrow\downarrow_{1}$ | $\downarrow_{2}$ | $\downarrow\downarrow_{1}$ | $\downarrow\downarrow\downarrow_{4}$ |
| | Moderna-Spikevax + Pfizer BioNTech-Comirnaty | $\downarrow\downarrow\downarrow_{1}$ | — | — | — | — | — |
| | Novavax-Nuvaxovid/SII – Covavax + Novavax-Nuvaxovid/SII - Covavax | $\downarrow\downarrow_{1}$ | — | — | — | — | — |
| | Pfizer BioNTech-Comirnaty + Pfizer BioNTech-Comirnaty | $\downarrow$ to $\downarrow\downarrow\downarrow_{12}$ | $\downarrow$ to $\downarrow\downarrow_{14}$ | $\downarrow$ to $\downarrow\downarrow_{4}$ | $\downarrow\downarrow_{3}$ | $\downarrow$ to $\downarrow\downarrow_{5}$ | $\downarrow\downarrow$ to $\downarrow\downarrow\downarrow_{15}$ |
| | Pfizer BioNTech-Comirnaty + Janssen-Ad26.COV2.S | $\downarrow_{2}$ | — | — | — | — | — |
| | Pfizer BioNTech-Comirnaty + Moderna-Spikevax | $\downarrow$ to $\downarrow\downarrow_{3}$ | $\downarrow\downarrow_{1}$ | — | $\downarrow\downarrow\downarrow_{3}$ | — | $\downarrow\downarrow\downarrow_{3}$ |
| | Sinovac-CoronaVac + Sinovac-CoronaVac | $HNR_{11}$ | $\downarrow\downarrow$ to $\downarrow\downarrow\downarrow_{6}$ | $HNR_{3}$ | $\downarrow\downarrow_{1}$ | $\downarrow\downarrow_{1}$ | $HNR_{5}$ |
| | Sinovac-CoronaVac + AstraZeneca-Vaxzevria | $\downarrow\downarrow_{1}$ | — | — | — | — | — |
| | Sinovac-CoronaVac + Pfizer BioNTech-Comirnaty | $\downarrow\downarrow_{5}$ | $\downarrow$ to $\downarrow\downarrow_{4}$ | $\downarrow$ to $\downarrow\downarrow_{3}$ | — | — | $\downarrow$ to $\downarrow\downarrow\downarrow_{3}$ |
| Booster Vaccines without WHO EUL | Anhui ZL-Recombinant + Anhui ZL-Recombinant | $\downarrow$ to $\downarrow\downarrow_{3}$ | $\downarrow\downarrow_{1}$ | $\downarrow\downarrow_{1}$ | — | $\downarrow\downarrow\downarrow_{1}$ | $\downarrow\downarrow\downarrow_{1}$ |
| | Beijing CNBG-BBIBP-CorV + Anhui ZL - Recombinant | $\downarrow\downarrow$ to $\downarrow\downarrow\downarrow_{5}$ | $\downarrow\downarrow$ to $\downarrow\downarrow\downarrow_{2}$ | $HNR_{2}$ | $\downarrow\downarrow\downarrow_{1}$ | $\downarrow\downarrow\downarrow_{2}$ | $HNR_{2}$ |
| | Cansino-Convidecia + Anhui ZL - Recombinant | $\downarrow_{1}$ | — | — | — | — | — |
| | Gamaleya-Sputnik V + Gamaleya Sputnik Light | $\downarrow\downarrow_{1}$ | — | — | — | — | — |
| | Sinovac-CoronaVac + Anhui ZL - Recombinant | $\downarrow$ to $\downarrow\downarrow_{2}$ | $\downarrow$ to $\downarrow\downarrow_{2}$ | $\downarrow$ to $\downarrow\downarrow\downarrow_{2}$ | — | $\downarrow$ to $\downarrow\downarrow\downarrow_{2}$ | $\downarrow\downarrow_{1}$ |
| | Sinovac-CoronaVac + Cansino-Ad5-nCoV-IH | $\downarrow\downarrow\downarrow_{1}$ | — | — | — | — | — |
| **Second Booster Vaccination (Primary Series + First Booster Vaccine + Second Booster Vaccine)** | | | | | | | |
| WHO Emergency Use Listing (EUL) Qualified Booster Vaccines | Moderna-Spikevax + Moderna-Spikevax + Moderna-Spikevax | $\downarrow_{1}$ | — | — | — | — | — |
| | Moderna-Spikevax + Moderna-Spikevax + Moderna-Spikevax Bivalent Original/Omicron BA.1 | $\downarrow_{1}$ | — | — | — | — | $\downarrow\downarrow_{1}$ |
| | Pfizer BioNTech-Comirnaty + Pfizer BioNTech-Comirnaty + Pfizer BioNTech-Comirnaty | $\downarrow\downarrow\downarrow_{1}$ | — | — | — | — | — |
| | Pfizer BioNTech-Comirnaty + Pfizer BioNTech-Comirnaty + Moderna-Spikevax | $\downarrow\downarrow\downarrow_{1}$ | — | — | — | — | — |

# Protection against symptomatic COVID-19 decreases over time, but even during Omicron, protection against severe disease remains



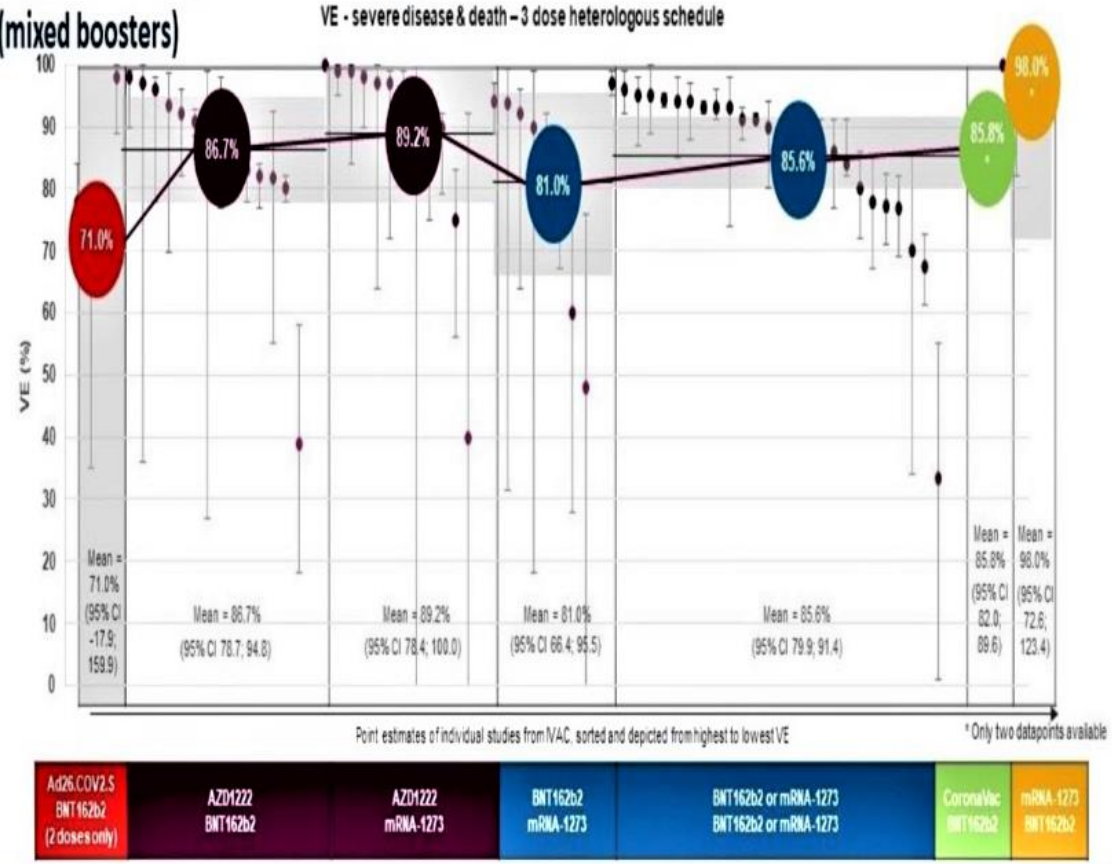

| 14 days after a booster | 14-90 days after a booster | 90+ days after a booster |
|---|---|---|

Solante R, Alvarez-Moreno C, Burhan E et al. Expert Review of Global Real-World Data on COVID-19 Vaccine Booster Effectiveness & Safety During the Omicron-dominant Phase of the Pandemic. 6 September 2022, PREPRINT (Version 1) available at Research Square https://www.researchsquare.com/article/rs-2015733/v1 [Accessed September 2022]

Understanding COVID-19 Vaccine Effectiveness

# Equivalent protection against severe disease and death

## (mixed boosters)




**Boosting after any two dose schedule provides equivalent protection against Omicron-related severe disease and death**

**Protection against severe disease and death is no different with a mixed or a homologous booster schedule**

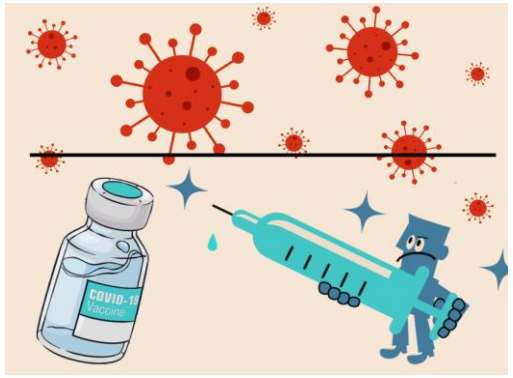
Solante R, Alvarez-Moreno C, Burhan E et al. Expert Review of Global Real-World Data on COVID-19 Vaccine Booster Effectiveness & Safety during the Omicron-dominant phase of the pandemic. XX September 2022, PREPRINT (Version 1) available at Research Square [link]

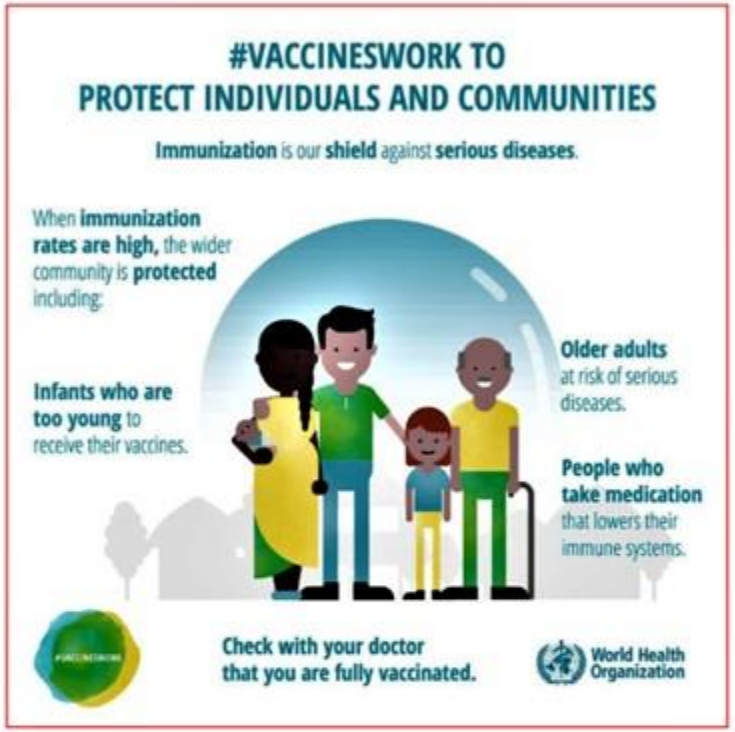
# KEY Take home messages:

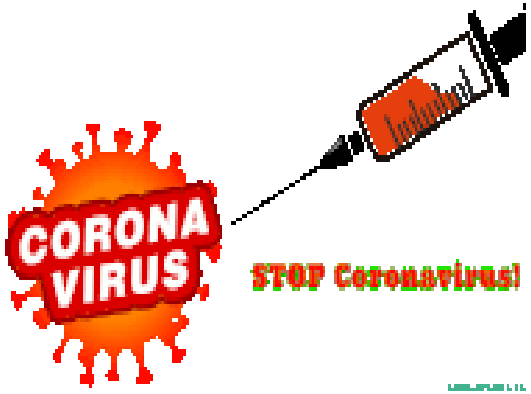
- Varying Vaccine Platforms, antigen content, number of doses, interval between doses, RCT conducted at different times (early surges, circulating variants of concern), different population groups (ages, geography, health status, etc)
- **Head to head, direct comparisons could not be made for these COVID-19 vaccines**
- Immunogenicity measurements and Efficacy end points vary

- General observations so far:
  - Current COVID-19 vaccines less effective at blocking infection or transmission (i.e., Omicron variants)
  - BUT, Protection against severe/ critical COVID-19 disease remains largely preserved or sustained
  - Real world effectiveness so far good, with higher protection vs severe COVID, across ages, consistent with RCT data

- Way forward: Waning immunity and emergence of variants require that COVID-19 vaccines and Boosters be continuously evaluated for:
  - ➔ Short term neutralizing antibody titers
  - ➔ Durability of antibody responses vs T cell responses
  - ➔ Memory B and T cell responses
  - ➔ Updating vaccines to be more inclusive* broader more lasting protection vs current or future variants




# Thank you for your attention !