# In-Depth Science Review

## February 14, 2022 Annex

CONTENTS

This science review is a snapshot of the new and emerging scientific evidence related to COVID-19 during the period specified. It is a review of important topics and articles, not a guide for policy or program implementation. **The findings captured are subject to change as new information is made available**. We welcome comments and feedback at **covid19-eiu@vitalstrategies.org**.

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**This annex is an accompaniment to the In-Depth Science Review released on February 14, 2022. It provides further details on the studies that informed the review. These studies cover three topics:**

1) Omicron severity assessed through patterns in health care resource utilization,

2) Risk of severe outcomes including hospitalization associated with Omicron, and

3) COVID-19 vaccine effectiveness against Omicron.

This annex includes reports from public health agencies, peer-reviewed studies and pre-print manuscripts that represent our current understanding of these topics. This is not a systematic or exhaustive review, and our knowledge continues to evolve as data and evidence accumulate.

First, a note on some of the limitations that are common to studies on the severity of Omicron and on vaccine effectiveness (VE) against it. To interpret and apply study findings, it is critical to be aware of these potential limitations and of researchers' attempts to address them. Some limitations stem from the very nature of COVID-19 (e.g. the high proportion of cases that are asymptomatic). Others arise from the challenges of comparing disease severity across time points and populations. Others result from the need for timely analyses to inform our understanding of Omicron as quickly as possible. Potential limitations include but are not limited to:

- Variant determination – In lieu of sequencing all virus isolates, many studies use proxies to differentiate between variants. One common proxy is S-gene target failure (SGTF), a gene detection pattern on some PCR tests that can distinguish between Delta and some sub-lineages of Omicron. Another common proxy is date of diagnosis. This may be less accurate if there was significant variant co-circulation during the study. Some studies

assess proxy accuracy by sequencing a subset of isolates.

- Severity assessment subjectivity – Although some COVID-19 severity parameters are measured objectively (e.g., blood oxygen saturation), others are largely based on clinical judgment. Thus, severity designations may differ between settings and over time.
- Changes in access to and quality of health care – Access to health care and the availability of health care resources — including effective COVID-19 treatments — can differ between settings and over time, and this can affect COVID-19 outcomes.
- Case detection rates – Changes in the proportion of total cases that are diagnosed can affect per-case severity estimates. Under-reporting is more likely if a variant causes milder disease, there is limited access to testing or more people test themselves at home.
- Study period duration – A short study period can yield small sample sizes and inconclusive analyses. Outcome data may also be skewed if follow up is truncated, as reporting of severe outcomes – especially deaths – can lag weeks or even months behind case detection.
- Incidental COVID-19 – People who are **hospitalized for reasons other than COVID-19 may incidentally test positive for SARS-CoV-2**. This is more likely to occur when a variant is highly transmissible and less severe. Some studies attempt to exclude incidentally positive patients by only including those who were diagnosed in the community prior to admission or who have COVID-19-compatible symptoms.
- Outcome definitions – The interpretation of VE estimates depends not only on the outcome of interest but also on how that outcome was defined. For example, studies that include asymptomatic infections as COVID-19 cases may yield lower VE estimates than studies in which all cases have symptoms.
- Differences between vaccine product and schedules – Some analyses group vaccine products together. Analyses may not stratify by the number of doses received or by the duration of follow up after the final dose. Estimates of VE can be more meaningful if they are product-, dose- and timing-specific, but robust data are needed to generate such estimates. Data on the long-term protection offered by boosters are particularly limited.

**1) Studies on severity trends and health care resource utilization during Omicron**

A. **Clinical severity of COVID-19 patients admitted to hospitals in Gauteng, South Africa, during the Omicron-dominant fourth wave**

Authors analyzed national South Africa data on COVID-19 cases diagnosed in Gauteng Province during the first four weeks of the Beta (end of 2020), Delta (May 2021) and Omicron (end of 2021) waves. The proportion of COVID-19 cases that required hospitalization and the proportion that died were substantially lower during the Omicron wave than during the Beta or Delta waves. Severe disease was defined as a hospitalized patient with at least one of: acute respiratory distress, need for oxygen or mechanical ventilation, admission to intensive care or death. Patients hospitalized during the Omicron wave were 73% less likely to have severe disease than those hospitalized during the Delta wave.

- Among 41,046 cases caused by Beta, 33,423 cases caused by Delta and 113,551 cases caused by Omicron, during the first four weeks of each wave:

    - 19%, 14% and 5% of cases were admitted to the hospital, respectively;
    - 20%, 26% and 7% of hospitalized patients were admitted to intensive care, respectively;
    - 24%, 24% and 6% of hospitalized patients died, respectively;
    - The median length of hospital stay was 7, 8 and 4 days, respectively.
- The number of hospitalized patients with severe disease during each surge: Beta – 1933/3500 (55%); Delta – 2346/3500 (67%); and Omicron – 932/3500 (27%).
    - Patients admitted during the Omicron wave had lower odds of severe disease than those hospitalized in earlier waves: adjusted odds ratio = 0.27 (95% CI 0.25-0.31).

B. **Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods — United States, December 2020–January 2022**

Authors used United States national surveillance and health care data to assess indicators of COVID-19 severity during three COVID-19 high transmission periods: Dec 1, 2020–Feb 28, 2021 (winter 2020–21); July 15–Oct 31, 2021 (Delta); and Dec 19, 2021–Jan 15, 2022 (Omicron). The Omicron-predominant period saw the highest reported numbers of COVID-19 cases and hospitalizations of the pandemic. However, disease severity indicators including ICU admission, mechanical ventilation and death, were lower during Omicron than previous waves.

- The maximum daily seven-day moving average number of cases (798,976), ED visits (48,238), admissions (21,586), and deaths (1,854) observed during the Omicron period compared with previous periods as follows:
    - Winter 2020-21: 219%, 137%, 31%, and -46%, respectively
    - Delta: 386%, 86%, 76%, and -4%, respectively
- Proportion of hospitalized adults with the following outcomes:
    - Omicron: mechanical ventilation = 3.5%; death = 7.1%.
    - Winter 2020-21: mechanical ventilation = 7.5%; death = 12.9%
    - Delta: mechanical ventilation = 6.6%; death = 12.3%
- Event-to-case ratios for ED visits, hospital admissions and deaths, per 1,000 cases:
    - Omicron: 87, 27, 9, respectively
    - Winter 2020-21: 92, 68, 16, respectively
    - Delta: 167, 78, 13, respectively

C. **Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves**

Authors compared outcomes during the early Omicron variant wave, defined as the time from an increase in cases until community test positivity reached 26% (Nov 15 – Dec 7, 2021), to similarly defined early waves of other variants (ancestral variant wave: June 14 – July 6, 2020; Beta variant wave:

December 1-23, 2020; Delta variant wave: June 1-23, 2021). During the Omicron wave, a lower proportion of outpatients with COVID-19 were hospitalized, and a lower proportion of hospitalized patients had severe outcomes, compared with previous surges.

- The median age of those with Omicron was 36 year; the median age of those infected during previous waves was 50-60 years. At least 24% of those hospitalized during Omicron were vaccinated; no vaccine was available during the first two waves; there were no vaccine data from the Delta wave.
- The number of patients hospitalized compared to those who presented to the emergency department: Omicron 971/2351 (41%), Delta 4400/6342 (69%), Beta 3198/4632 (69%), ancestral variant 2628/3875 (69%).
- Outcomes among patients hospitalized with COVID-19 during each wave:
    - Required O2 – Omicron 18%, Delta 74%, Beta 82%: ancestral 80%;
    - Admitted to ICU – Omicron 19%, Delta 30%, Beta 37%: ancestral 42%;
    - Median hospital length of stay in days – Omicron 3, Delta 9, Beta 8: ancestral 8;
    - Died – Omicron 3%, Delta 29%, Beta 26%: ancestral 20%.

**2) Studies on the severity of COVID-19 caused by Omicron**

A. **Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study**

Authors analyzed national South Africa data on COVID-19 cases diagnosed from Oct 1 to Dec 6, 2021. Among those with Omicron, hospitalization was 80% less likely than among those with Delta. Two different severity analyses were performed; due to the discrepancy between results, the risk of severe disease associated with Omicron versus Delta could not be determined. There was no difference in the risk of severe disease among hospitalized patients diagnosed with Omicron versus Delta at the end of 2021. However, those hospitalized with Omicron were 70% less likely to have severe disease than patients hospitalized between April 1-Nov 9, 2021, who were likely infected with Delta.

- Between Oct 1 and Dec 6, 2021, there were 10,547 Omicron infections, of which 256 (2.4%) were hospitalized, and there were 948 Delta infections of which 121 (12.8%) were hospitalized. The chance of hospitalization with Omicron compared with Delta: aOR 0.2 (95% CI 0.1, 0.3).
- The odds of severe disease among patients hospitalized with Omicron:
    - Was not different from the odds of severe disease among patients hospitalized with Delta between Oct 1 – Nov 30: aOR 0.7 (95% CI 0.3, 1.4).
    - Was lower than the odds of severe disease among patients hospitalized between April 1-Nov 9, 2021 (likely with Delta): aOR 0.3 (95% CI 0.2, 0.5).

B. **SARS-CoV-2 variants of concern and variants under investigation in England: Update on hospitalization and vaccine effectiveness for Omicron, 31 Dec 2021**

This report included analyses of data on COVID-19 cases diagnosed in England between Nov 22 and Dec 26, 2021. This included 528,176 Omicron cases and 573,012 Delta cases, of which 3,019 Omicron cases and 13,579 Delta cases presented to an emergency department or were hospitalized. The risk of hospitalization among those with Omicron was approximately one-third the risk among those with Delta. The risk of hospitalization with Omicron was lower among those who had been vaccinated (65% lower after two doses, 80% lower after three doses).

- Compared to those with Delta, those with Omicron had a lower hazard of hospital admission from the emergency department: aHR 0.33 (95% CI 0.30, 0.37).
    - Among those with Omicron, compared to unvaccinated people:
    - The hazard of hospitalization after 2 vaccine doses: aHR 0.35 (95% CI 0.29, 0.43)
    - The hazard of hospitalization after 3 vaccine doses: aHR 0.19 (95% CI 0.15, 0.23)

C. **Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California** (preprint)

Authors analyzed data from a health care system in California to assess COVID-19 outcomes among those with Omicron and Delta diagnosed from Nov 30, 2021 to Jan 1, 2022. The analysis included outcomes that occurred between seven and 28 days after diagnosis, in order to exclude those who incidentally tested positive. Compared to those with Delta, those with Omicron were 52%, 74%, and 91% less likely to be hospitalized, admitted to the ICU or die, respectively. The average length of hospital stay was shorter for those with Omicron than with Delta. Those with Omicron had a lower risk of hospitalization regardless of prior infection or vaccination status.

Among 52,297 outpatients with COVID-19 caused Omicron and 16,982 with Delta:

- Hospital admission for symptomatic illness occurred among 84 patients with Omicron, and 184 patients with Delta: aHR 0.48 (95% CI 0.36, 0.64).
- ICU admission occurred among seven patients with Omicron and 23 patients with Delta: aHR 0.26 (95% CI 0.10, 0.73).
- Mechanical ventilation occurred among 0 patients with Omicron and 11 patients with Delta.
- Death occurred in one patient with Omicron and 14 patients with Delta: aHR 0.09 (95% CI 0.01, 0.75)

D. **Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of Omicron** (preprint)

Authors analyzed electronic health record data from 63 health care organizations across the U.S. to assess outcomes among persons diagnosed during the last two weeks of December 2021 (“Omicron cohort”) versus those diagnosed from September through early December (“Delta cohort”). Compared with the Delta cohort, those in the Omicron cohort had half the risk of hospitalization, one-third the risk of ICU admission and one-tenth the risk of receiving mechanical ventilation.

- The 3-day risks in the Omicron cohort (n=14,040) versus in the Delta cohort (n=14,040):

- Hospitalization: RR 0.44 (95% CI 0.38, 0.52);
- ICU admission: RR 0.33 (95% CI 0.23, 0.48);
- Mechanical ventilation: RR: 0.16 (95% CI 0.08, 0.32).

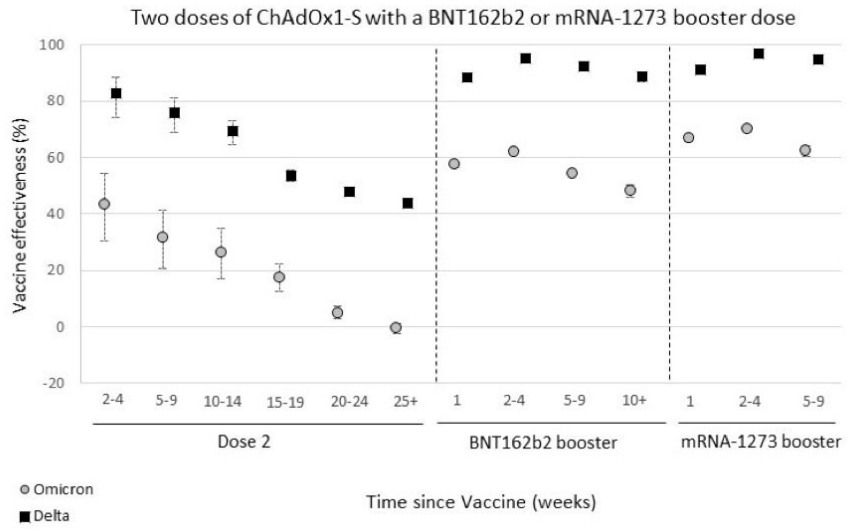
**3) Studies on vaccine effectiveness against Omicron**

A. **SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 34, 14 January 2022**

This report included estimates of vaccine effectiveness (VE) among COVID-19 cases diagnosed in England between Nov 7, 2021, and Jan 6, 2022. The VE analysis included symptomatic cases (236,023 caused by Delta and 760,647 by Omicron) that were tested in the community and presented for care up to 14 days later, in order to exclude incidentally positive hospitalizations. The effectiveness of a primary series against symptomatic disease caused by Omicron waned to essentially nothing 20 weeks after vaccination; VE against hospitalization caused by Omicron also waned but less dramatically. A booster dose bolstered protection against infection, and even more against hospitalization, with Omicron.

- VE against symptomatic COVID-19 caused by both variants are seen in Figure 3.
- VE against hospitalization caused by Omicron, by weeks after last dose:
  - 2 doses (all primary): VE 64% (2-24 weeks); 44% (25+ weeks);
  - 3 doses (any primary + any booster): VE 92% (2-4 weeks); 83% (10+ weeks).

(a)

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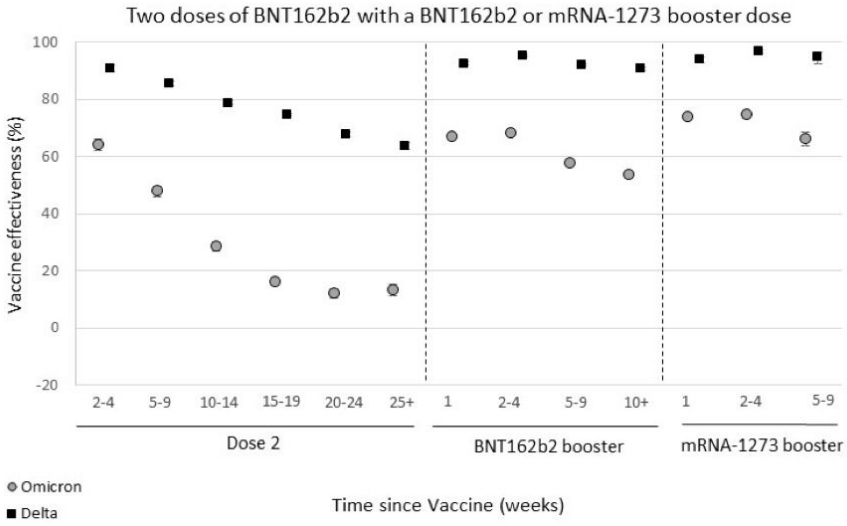


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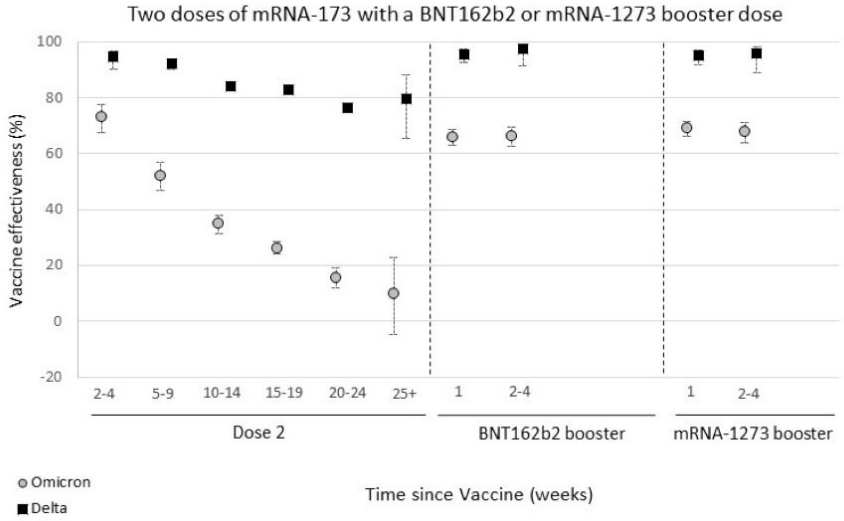


**Vaccine effectiveness against symptomatic COVID-19, by period after dose, for Delta and Omicron.**

*Legend: (a) Recipients of AstraZeneca (ChAdOx1-S) as the primary series and Pfizer (BNT162b2) or Moderna (mRNA-1273) as a booster; (b) Recipients of Pfizer as the primary series and Pfizer or Moderna as a booster; (c) Recipients of Moderna as the primary series (insufficient data for boosters after Moderna). Source:* ***UK Health Security Agency***

B. COVID-19 vaccine surveillance report, 27 January 2022.

This report includes a summary of studies on vaccine effectiveness against Delta and Omicron from the United Kingdom. Findings are summarized in the table below. The report includes a list of source studies.

| | | Two doses | | | Three doses | |
|---|---|---|---|---|---|---|
| | | 0-3 months | 4-6 months | 6+ months | 0-3 months | 4-6 months |
| Symptomatic disease | Omicron | 25-70% | 5-30% | 0-10% | 50-75% | 40-50% |
| | Delta | 65-90% | 45-65% | 40-60% | 90-99% | 90-95% |
| Hospitalization | Omicron | 65-85% | 55-65% | 30-35% | 80-95% | 75-85% |
| | Delta | 95-99% | 80-90% | 70-85% | 95-99% | Insufficient data |
| Death | Omicron | Insufficient data | Insufficient data | 40-70% | 85-99% | Insufficient data |
| | Delta | 95-99% | 90-95% | 80-99% | 95-99% | Insufficient data |

**Summary of select vaccine effectiveness estimates from the United Kingdom, stratified by variant, outcome, number of vaccine doses, and time since last dose.**

*Gray shading - Little evidence is available; analyses are inconclusive. Adapted from:* ***UK Health Security Agency***

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C. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants (preprint)

Authors assessed the effectiveness of the Moderna vaccine among 6,657 persons infected with SARS-CoV-2 (56% with Omicron, 44% with Delta) diagnosed within a large health care network in California between Dec 6-23, 2021. Primary series VE against Omicron infection started lower and waned more rapidly than primary series VE against Delta. A booster provided higher, more durable protection.

- Primary series VE against Delta vs Omicron infection by time since last dose (excluded 95% CIs for brevity):
  - 80% vs 43% at 14-90 days;
  - 66% vs 23% at 91-180 days;
  - 61% vs 16% at 181–270 days;
  - 58% vs 9% at >270 days.
- Primary series + booster VE against Delta vs Omicron infection by time since last dose:
  - 93% vs 68% if boosted an average of 1-2 months before;
  - 88% vs 50% if boosted an average of 3-4 months before.

D. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa

Researchers used data from a managed care organization in South Africa to estimate the effectiveness of the Pfizer primary series against COVID-19 hospitalization during Nov 15-Dec 7 (considered the Omicron period) versus during Sept 1-Oct 30 (considered the Delta period), 2021.

During the Omicron period, VE against hospitalization ranged from 50% (against any hospitalization) to 70% (against symptomatic hospitalization). VE against hospitalization was high during the Delta period (>90%).

- During the Delta period, 8,569 people tested positive for SARS-CoV-2 and 925 were hospitalized.
  - VE against hospitalization with Delta was 93% (95% CI 90%, 94%).
- During the Omicron period, 19,070 tested positive and 220 were hospitalized.
  - VE against hospitalization with Omicron was 70% (95% CI 62%, 76%);
  - VE against hospitalization with symptoms consistent with COVID-19: 50% (35%, 62%).

E. Vaccine effectiveness against hospital admission in South African health care workers who received a homologous booster of Ad26.COV2 during an Omicron COVID19 wave: Preliminary Results of the Sisonke 2 Study.

This analysis included health care workers in South Africa who received a J&J booster 6-9 months after a primary J&J dose, matched with unvaccinated individuals enrolled in the same managed care organization. A J&J booster was highly effective in preventing COVID-19 hospitalizations during Nov 15 – Dec 20, 2021, the period of Omicron emergence. Protection did not wane for up to two months after boosting.

- 2,514 health care workers received a booster 14-27 days, and 823 health workers received a booster 1-2 months, prior to infection.
- Among 734 COVID-19 admissions, 713 were unvaccinated and 10 were vaccinated less than 2 weeks prior. VE against hospitalization:
  - 14-27 days after booster = 84% (95% CI 67%, 92%);
  - 1-2 months after booster = 85% (95% CI: 54%, 95%).

F. COVID-19 Incidence and Death Rates Among Unvaccinated and Fully Vaccinated Adults with and Without Booster Doses During Periods of Delta and Omicron Variant Emergence — 25 U.S. Jurisdictions, April 4–December 25, 2021

This analysis included data from 25 state and local health departments covering over 60% of the U.S. population. Decreasing case incidence rate ratios for unvaccinated versus fully vaccinated persons over time suggested both time and variant effects on vaccine effectiveness against infection. VE against death remained stable while Delta predominated; there were not enough deaths in December to estimate VE against death with Omicron. Those who received boosters had better protection against both variants than those with primary series alone.

- Primary series:
  - VE against infection: 93% pre-Delta, 89% during Delta emergence, 80% during Delta predominance, and 68% during Omicron emergence.

    - VE against death: 95% pre-Delta, 94% during Delta emergence, and 94% during Delta predominance.
- Primary series + booster:
    - VE against infection: 93% during October 2021, 80% during December 2021.
    - VE death: 98% during October-November 2021.

G. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022

Authors studied the effectiveness of mRNA vaccines to prevent COVID-19 emergency department and urgent care (ED/UC) encounters and hospitalizations among adults with COVID-19-like illness during Aug 26, 2021–Jan 22, 2022. VE was generally lower against Omicron than Delta. VE was higher after a third dose than after 2 doses but waned over time since vaccination. Protection against hospitalizations was higher than protection against ED/UC encounters.

- The median interval between receipt of the most recent vaccine dose and either ED/UC encounter or hospitalization was 214-216 days among those who had received 2 doses and 46-49 days among those who had received 3 doses.
- VE against ED/UC (time since most recent vaccine dose):
    - Omicron:
        - Two vaccine doses: 69% (<2 months), 37% (≥5 months);
        - Three vaccine doses: 87% (<2 months); 66% (4-5 months), 31% (≥5 months);
    - Delta: Three vaccine doses: 97% (<2 months), 89% (≥4 months).
- VE against hospitalization (time since most recent vaccine dose):
    - Omicron:
        - Two vaccine doses: 71% (<2 months), 54% (≥5 months);
        - Three vaccine doses: 91% (<2 months), 78% (≥4 months);
    - Delta: Three vaccine doses: 96% (<2 months), 76% (≥4 months).

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