Delaware Health Advisory #492: Bivalent mRNA Effectiveness in Preventing Symptomatic SARS-CoV-2 Infection

Note: Tables and references can be viewed at the original version of the MMWR at https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e1.htm?s_cid=mm7148e1_w.

The Delaware Division of Public Health (DPH) is issuing this health advisory to Delaware health care providers on the effectiveness of bivalent mRNA vaccines in preventing symptomatic SARS-CoV-2 infection.

Summary

Monovalent mRNA COVID-19 vaccines were less effective against symptomatic infection during the period of SARS-CoV-2 Omicron variant predominance.

In this study of vaccine effectiveness of the U.S.-authorized bivalent mRNA booster formulations, bivalent boosters provided significant additional protection against symptomatic SARS-CoV-2 infection in persons who had previously received two, three, or four monovalent vaccine doses. Due to waning immunity of monovalent doses, the benefit of the bivalent booster increased with time since receipt of the most recent monovalent vaccine dose.

All persons should stay up to date with recommended COVID-19 vaccinations, including bivalent booster doses for eligible persons.

Background

On 9/1/22, bivalent COVID-19 mRNA vaccines, composed of components from the SARS-CoV-2 ancestral and Omicron BA.4/BA.5 strains, were recommended by the Advisory Committee on Immunization Practices (ACIP) to address reduced effectiveness of COVID-19 monovalent vaccines during SARS-CoV-2 Omicron variant predominance (*1*). Initial recommendations included persons aged ≥12 years (Pfizer-BioNTech) and ≥18 years (Moderna) who had completed at least a primary series of any Food and Drug Administration–authorized or –approved monovalent vaccine ≥2 months earlier (*1*). On October 12, 2022, the recommendation was expanded to include children aged 5 to 11 years. At the time of recommendation, immunogenicity data were available from clinical trials of bivalent vaccines composed of ancestral and Omicron BA.1 strains; however, no clinical efficacy data were available. In this study, effectiveness of the bivalent (Omicron BA.4/BA.5–containing) booster formulation against symptomatic SARS-CoV-2 infection was examined using data from the Increasing Community Access to Testing (ICATT) national SARS-CoV-2 testing program.* During September 14 to November 11, 2022, a total of 360,626 nucleic acid amplification tests (NAATs) performed at 9,995 retail pharmacies for adults aged ≥18 years, who reported symptoms consistent with COVID-19 at the time of testing and no immunocompromising conditions, were included in the analysis. Relative vaccine effectiveness (rVE) of a bivalent booster dose compared with that of ≥2 monovalent vaccine doses among persons for whom 2 to 3 months and ≥8 months had elapsed since last monovalent dose was 30% and 56% among persons aged 18–49 years, 31% and 48% among persons aged 50 to 64 years, and 28% and 43% among persons aged ≥65 years, respectively. Bivalent mRNA booster doses provide additional protection against symptomatic SARS-CoV-2 in immunocompetent persons who previously received monovalent vaccine only, with relative benefits increasing with time since receipt of the most recent monovalent vaccine dose. Staying up to date with COVID-19 vaccination, including getting a bivalent booster dose when eligible, is critical to maximizing protection against COVID-19 (*1*).

The ICATT program was designed to increase access to COVID-19 testing in areas with high social vulnerability† through contracts with retail pharmacy chains to provide SARS-CoV-2 testing at no cost to

the recipient at selected sites nationwide (*2*). ICATT vaccine effectiveness (VE) methods have been described previously (*3*). Briefly, at test registration, adults report their vaccination history[§] and information on current COVID-19 symptoms, previous SARS-CoV-2 infection, and underlying medical conditions. Adults receiving testing at participating sites during 9/14 to 11/11/22, (when Omicron variant BA.4/BA.5 lineages and their sublineages predominated[¶]) who reported one or more COVID-19–compatible symptoms were included; case-patients were persons who received a positive rapid or laboratory-based NAAT result; control-patients were those who received a negative NAAT result. Tests from persons who reported an immunocompromising condition (*4*), who received non-mRNA COVID-19 vaccines, who had received only a single monovalent mRNA vaccine dose or >4 monovalent mRNA doses, or who had received their last monovalent dose <2 months before the SARS-CoV-2 test were excluded from analyses.** In addition, tests from persons who reported a positive result during the preceding 90 days[††] were excluded to avoid analyzing repeated tests for the same illness episode or reinfections within a relatively short time frame. Absolute VE (aVE) was calculated by comparing the odds of receipt of a bivalent booster dose (after two, three, or four monovalent vaccine doses) to being unvaccinated (zero doses of any COVID-19 vaccine) among case- and control-patients. rVE was calculated by comparing the odds of receiving a bivalent booster dose (after two, three, or four monovalent doses) versus not receiving a bivalent booster dose (but receiving two, three, or four monovalent doses). To explore how waning of protection after receipt of the most recent monovalent vaccine dose influenced the measured relative effectiveness of a subsequent bivalent booster dose, rVE of a bivalent booster dose was calculated by interval since receipt of the most recent monovalent vaccine dose among those who had not received a bivalent booster (2 to 3 months, 4 to 5 months, 6 to 7 months, and ≥8 months). Odds ratios (ORs) were calculated using multivariable logistic regression[§§]; VE was calculated as (1 − OR) x 100. Analyses were conducted using R software (version 4.1.2; R Foundation). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[¶¶]

Among persons aged ≥18 years reporting COVID-19–compatible symptoms, 360,626 tests were included; of these, 121,687 (34%) persons received positive test results (Table 1). Among these case-patients, 28,874 (24%) reported being unvaccinated, 87,013 (72%) had received 2, 3, or 4 monovalent vaccine doses but no bivalent booster dose, and 5,800 (5%) had received a bivalent booster dose. Among 238,939 control-patients who received negative test results, 72,010 (30%) reported being unvaccinated, 150,455 (63%) had received two, three, or four monovalent vaccine doses but no bivalent booster dose, and 16,474 (7%) had received a bivalent booster dose. Median interval between receipt of the bivalent booster dose and SARS-CoV-2 testing was 1 month (range = 0–2 months) and did not vary by case status. Self-reported infection >90 days before the current test was more common among persons who received a negative test result (43%) than among those who received a positive test result (22%).

aVE of a bivalent booster dose received after ≥2 monovalent doses (compared with being unvaccinated) was similar among persons aged 50 to 64 years (28%) and ≥65 years (22%) but varied somewhat by number of previous monovalent vaccine doses (Table 2). Among adults aged 18 to 49 years, aVE after ≥2 monovalent doses (43%) was higher than that for older age groups and did not vary among those who received two or three previous monovalent vaccine doses.

Among persons who received ≥2 monovalent vaccine doses, rVE increased with time since the most recent monovalent vaccine dose in all age groups (Table 3). At 2 to 3 months and ≥8 months after receipt of the most recent monovalent dose, rVE of a bivalent mRNA COVID-19 vaccine dose was 30% and 56% among persons aged 18 to 49 years, 31% and 48% among persons aged 50 to 64 years, and 28% and 43% among persons aged ≥65 years, respectively.

Discussion

Among symptomatic adults who received testing for SARS-CoV-2 infection at pharmacies nationwide during 9/14 to 11/11/22, bivalent mRNA vaccines provided additional protection against infection compared with previous vaccination with two, three, or four monovalent vaccines alone. These are the

first published estimates of VE for newly authorized bivalent mRNA booster vaccines. In this study, relative benefits of a bivalent booster compared with monovalent vaccine doses alone increased with time since receipt of last monovalent dose.

Postauthorization immunogenicity studies have shown similar neutralizing antibody titers to BA.4/BA.5 after receipt of either a monovalent or BA.4/BA.5–containing bivalent vaccine as a fourth dose (*5*,*6*); however, immunogenicity studies are not generally designed to measure clinical impact. Findings from this real-world VE study indicate that the bivalent formulations authorized in the United States provide additional protection when administered to persons who previously received two, three, or four doses of monovalent mRNA vaccines.

Waning VE with time since monovalent vaccine receipt has been observed during the Omicron-predominant period, with more rapid waning during the period when Omicron BA.4/BA.5 lineages predominated.*** Results from this study show that bivalent boosters provide protection against symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages and restore protection observed to wane after monovalent vaccine receipt, as demonstrated by increased rVE with longer time since the most recent monovalent dose. Most tests (81%) in this study were conducted during a period of BA.4/BA.5 predominance. Results limited to the period of BA.4/BA.5 predominance were not meaningfully different from the results shown, which include data from the period when BA.4/BA.5 sublineages (including BA.4.6, BA.5.2.6, BF.7, BQ.1, and BQ.1.1) predominated.

This study evaluated aVE and rVE by number of previous monovalent doses received and generally found similar additional benefit of the bivalent vaccine regardless of the number of previous monovalent vaccine doses received, when controlling for time since receipt of the last monovalent dose. These findings support the current COVID-19 vaccination policy recommending a bivalent booster dose for adults who have completed at least a primary mRNA vaccination series, irrespective of the number of monovalent doses previously received.

In the United States, >90% of adults have received ≥1 COVID-19 vaccine dose.††† Therefore, aVE should be interpreted with caution because unvaccinated persons might have different behaviors or a fundamentally different risk for acquiring COVID-19 compared with vaccinated persons. aVE in this study appeared lower in persons aged ≥50 years who received three or four monovalent doses before a bivalent booster dose compared with those who received only two monovalent doses before a bivalent booster dose; this might be because of differential rates of previous infection or differences in behaviors in those who had not previously received a booster dose compared with those who remained up to date with previous booster dose recommendations.

The findings in this study are subject to at least six limitations. First, vaccination status, previous infection history, and underlying medical conditions were self-reported and might be subject to recall bias. In particular, if previous infection provides protection against repeat infection, then VE estimates in this study would likely be biased toward the null, because self-reported previous infection differed by vaccination status, and statistical power was not sufficient to stratify VE estimates by presence of previous infection. In addition, previous infection might have been underreported (*7*). Second, acceptance of bivalent booster doses to date has been low (approximately 10% of persons aged ≥5 years as of November 15, 2022),§§§ which could bias the results if persons getting vaccinated early are systematically different from those vaccinated later. Third, important data including SARS-CoV-2 exposure risk and mask use were not collected, which might result in residual confounding. Fourth, the circulating variants in the United States continue to change, and results of this study might not be generalizable to future variants. Fifth, tests used in this study were collected predominantly (although not exclusively) in areas with higher social vulnerability; therefore, data might not be fully representative of the broader U.S. population. Finally, these results might be susceptible to bias because of differences in testing behaviors between vaccinated and unvaccinated persons.

In this study of immunocompetent persons tested at ICATT locations, bivalent booster doses provided significant additional protection against symptomatic SARS-CoV-2 infection during a period when

Omicron variant BA.4/BA.5 lineages and their sublineages predominated. All persons should stay up to date with recommended COVID-19 vaccines, including bivalent booster doses, if it has been ≥2 months since their last monovalent vaccine dose (*1*).