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Building the U.S. COVID-19 vaccine effectiveness program: Past successes and future directions

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Abstract

COVID-19 vaccines were originally authorized in the United States in December 2020 on the basis of safety, immunogenicity, and clinical efficacy data from randomized controlled trials (RCTs). However, real-world vaccine effectiveness (VE) data are necessary to provide information on how the vaccines work in populations not included in the RCTs (e.g., nursing home residents), against new SARS-CoV-2 variants, with increasing time since vaccination, and in populations with increasing levels of prior infection. The goal of CDC's COVID-19 VE program is to provide timely and robust data to support ongoing policy decisions and implementation of vaccination and includes VE platforms to study the spectrum of illness, from infection to critical illness. Challenges to estimating VE include accurate ascertainment of vaccination history, outcome status, changing rates of prior infection, emergence of new variants, and appropriate interpretation of absolute and relative VE measures. CDC COVID-19 VE platforms have played a pivotal role

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Data Statement

Building the U.S. COVID-19 Vaccine Effectiveness Program: Past Successes and Future Directions.

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Ruth Link-Gelles: Conceptualization, Writing – original draft. **Amadea Britton:** Writing – review & editing. **Katherine Fleming-Dutra:** Writing – review & editing.

Declaration of Competing Interest

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in numerous vaccine policy decisions since 2021 and will continue to play a key role in future decisions as the vaccine program moves from an emergency response to a routine schedule.

Keywords

Vaccine effectiveness; COVID-19; Moderna; Pfizer-BioNTech

1. Background

The COVID-19 pandemic ushered in a period of rapid development and evaluation of vaccines not previously observed in U.S. history. As SARS-CoV-2 spread worldwide during Spring 2020, the US government allocated funding via Operation Warp Speed (OWS), a public–private partnership with a goal to rapidly develop, manufacture, and distribute COVID-19 vaccines. Randomized controlled trials (RCT) completed in Fall 2020 showed two mRNA vaccines, manufactured by Pfizer- BioNTech and Moderna, were safe and highly efficacious in healthy adults [1,2]. The vaccines were authorized by Food and Drug Administration (FDA) under an emergency use authorization in December 2020 for individuals ≥16 years of age (Pfizer-BioNTech) and ≥18 years of age (Moderna) [3,4]. Additional COVID-19 vaccines were authorized in February 2021 (Johnson and Johnson/Janssen) and October 2022 (Novavax) [5,6]. However, RCTs generally did not include important populations at high risk for severe COVID-19 disease and death (e.g., individuals living in long-term care facilities, individuals with immunocompromising conditions), were not powered to assess efficacy against more severe outcomes such as hospitalization and death, had limited follow-up time, were conducted prior to the emergence of SARS-CoV-2 variants of concern (e.g. Alpha, Delta, Omicron), and were conducted in a population with almost no immunity to SARS-CoV-2 infection [1,2]. Real-world data are therefore necessary to monitor the postlicensure performance of the vaccines (known as vaccine effectiveness [VE]). These data in turn serve as the foundation for updates to vaccine policy in the context of ever-changing population immunity, and virus and pandemic characteristics. To date, VE data have contributed extensively to policy decisions, discussed elsewhere in this supplement [7], including booster recommendations in the context of new variants, expansion of recommendations to include children, and the need for new vaccine formulations [8–14].

CDC's COVID-19 VE program initially leveraged existing platforms used to monitor influenza VE, as well as rapidly designed and implemented COVID-19-specific platforms. Each VE platform had strengths, including larger platforms to rapidly assess VE, smaller platforms that allowed more detailed data collection, and platforms that focus on individual populations of interest, such as residents of long-term care facilities and healthcare workers. This paper summarizes CDC's COVID-19 VE program, including a framework for developing studies, methodological considerations, and a summary of CDC's COVID-19 VE platforms with context around strengths and limitations of different platforms.

2. CDC COVID-19 vaccine effectiveness framework

The goal of the US COVID-19 Program is to prevent severe disease, including hospitalization and death in the American public [15]; the goal of the VE program then

is to provide timely and robust data to support this goal, i.e. to inform policy decisions and public communications to prevent severe disease. Guiding principles of the CDC COVID-19 VE framework include:

1. Ensure existing VE platforms and data sources align and have statistical power to evaluate COVID-19 VE in key populations, against outcomes that inform vaccine policy decisions and non-vaccine prevention measures related to COVID-19 control;
2. Provide timely data to evaluate effectiveness of new vaccine recommendations (e.g., new products, age groups, and dosing regimens);
3. Include populations at high risk for severe COVID-19, including persons with immunocompromising conditions, elderly, and residents of long-term care facilities;
4. Ensure data sources are sensitive and robust enough to allow for monitoring and detection of changes in VE due to emerging new variants or waning of vaccine-induced immunity;
5. Generate high quality and scientifically sound vaccine effectiveness evaluations to inform national policy decisions;
6. Monitor vaccine effectiveness data generated by outside partners (domestic or global) as part of the evidence contributing to vaccine policy decisions.

3. COVID-19 vaccine effectiveness study design considerations

3.1. Vaccine effectiveness methods

VE is generally measured in observational studies by either 1) comparing rates of disease in vaccinated individuals to rates in unvaccinated individuals via a cohort study, or 2) comparing the odds of vaccination among persons with and without disease (cases and controls) via a case-control study. Benefits of cohort studies, particularly prospective cohort studies, in the context of COVID-19 include the potential to better ascertain and control for prior infection(s) if swabbing or blood collection are included, and ongoing assessment of non-vaccine mitigation factors and risk factors for COVID-19, including masking, school/work attendance, and social distancing. However, cohort studies are far more resource intensive than case-control studies, often making them prohibitively expensive to initiate or maintain and leaving them underpowered, especially during periods of low disease incidence. The test negative design (TND), a modified case-control study design in which cases and controls are both drawn from a population of persons undergoing testing for a specific clinical presentation is a second study type which has been extensively used in VE studies for other vaccines, including influenza. The TND methodology provides important benefits compared to a traditional case-control study, including better controlling for testing practices and healthcare access by enrolling both cases and controls with COVID-19-like-illness (CLI) and test results for SARS-CoV-2 [16]. Case-control VE studies are more efficient study designs, enabling increased statistical power with smaller sample sizes to

estimate VE although the ability to control for potentially important confounders may be diminished.

3.2. Ascertainment of vaccination status

Accurate ascertainment of vaccination status is a crucial component of VE studies; failing to capture vaccine doses can substantively impact VE estimates. In the U.S., routine vaccine administration data are reported to the 64 independent jurisdictional immunization information systems (IIS). However, completeness of these data is limited by varied reporting requirements by jurisdiction, minimal enforcement for non-reporting providers, and lack of a national system to combine data across jurisdictions or link with case data. For COVID-19 vaccines, concerted federal and jurisdictional efforts were made to improve vaccine reporting. The declaration of a Public Health Emergency (PHE) for COVID-19 and the federal provider agreement, which allowed vaccine providers to administer COVID-19 vaccines, gave jurisdictions new abilities to require reporting of COVID-19 vaccinations. This included an enforcement mechanism that allowed jurisdictions and the Federal Government to discontinue providing COVID-19 vaccine doses to providers who did not report doses to IIS. These policy changes were also accompanied by an increase in automated reporting of administered vaccine doses by many healthcare and electronic health records (EHR) providers. The increase in IIS completeness allowed streamlined VE studies beyond what has historically been possible in the US. However, with the end of some data reporting requirements, the impact of the expiration of the PHE on May 11, 2023, on IIS COVID-19 vaccine data quality remains to be seen and will likely vary by jurisdiction.

3.3. Outcomes

CDC VE platforms are designed to measure VE against key outcomes and in populations at varying risk of severe COVID-19 disease. Outcomes of interest span the spectrum of illness, from infection to critical illness. Evaluation of severe outcomes, including emergency department and urgent care visits, hospitalizations, and critical illness (e.g., requiring intensive care unit [ICU]-level care) provide important insight into impact on the healthcare system, provide inputs for vaccine risk–benefit analyses, and inform policy decisions. Protection against infection, although not the goal of the U.S. COVID-19 program, can also provide a useful early signal into vaccine protection against emerging variants or in populations where vaccine coverage or case counts are too low to estimate VE against more severe outcomes. For specific populations, other outcomes have included post-COVID conditions, multisystem inflammatory syndrome in children (MIS-C), and infant hospitalization after maternal vaccination.

Although many prioritized outcomes for COVID-19 VE mirror outcomes in other respiratory virus VE programs [17], estimation of VE against COVID-19 outcomes poses some unique challenges. One important consideration is whether a patient hospitalized with a positive SARS-CoV-2 test was hospitalized for COVID-19 (i.e., severe respiratory complications due to SARS-CoV-2 infection) or with incidental SARS-CoV-2 infection (i.e., hospitalized due to other reasons, especially in the context of widespread testing among hospitalized patients at many points in the pandemic). Inclusion of patients hospitalized for

other reasons can dilute VE, yielding estimates for VE against hospitalization that are more similar to those for VE against infection.

3.4. Additional methodologic considerations for estimating COVID-19 VE

Aside from overall study design, there are a number of specific methodological considerations for COVID-19 VE. First, obtaining accurate estimates in the context of increasing population-level immunity due to prior infection(s) is challenging. When COVID-19 vaccines were initially authorized and recommended, only a small percentage of the population had infection-induced immunity. However, over time, the high incidence of COVID-19 has made prior infection increasingly common. For those individuals who survive an initial infection, some level of protection is afforded against future infection and disease [18]. Since vaccination provides some protection against infection, unvaccinated individuals may be more likely to have prior infection(s), which may blunt measured VE by reducing risk of disease in the unvaccinated group, even when vaccination continues to provide substantial protection. However, to appropriately control for prior infection in VE studies, access to individual-level data on number of prior infection(s), time since most recent infection, and SARS-CoV-2 variant(s) of prior infection (s) are needed. In most studies, these data are not feasible to obtain given that many individuals may not be aware of asymptomatic or mildly symptomatic infections or may be diagnosed via home testing which is not reported in medical records. VE estimates have important implications for public perception of vaccination, as well as impact on policy decisions, so careful consideration of bias inherent in unmeasured prior infection is necessary, as is appropriate context for interpretation of VE estimates.

Second, in addition to changing patterns of infection-induced immunity, SARS-CoV-2 testing patterns have changed substantially due to changing perceptions of risk, at-home testing availability, and healthcare systems' testing policies. A central assumption of the TND is that vaccination does not impact likelihood of testing or seeking healthcare; however, this assumption may not be met as individuals who are higher risk for severe outcomes of COVID-19 may be both more likely to get tested and seek healthcare and more likely to get vaccinated. [19] Understanding these potential biases and exploring ways to mitigate them in VE studies is important for ensuring valid estimates and interpretations.

Third, SARS-CoV-2 has mutated much more quickly than many other common respiratory viruses, necessitating disentangling waning of VE (decreased protection with more time since vaccination) from reduced VE against variants other than those used in the vaccine formulations. Time is inextricably linked to both waning effectiveness and emergence of new variants, resulting in reduced clarity around the drivers of declining VE during the emergence of the Delta variant (and subsequent recommendation for a first booster dose), the initial Omicron variant (and additional booster dose recommendations for older adults and those with immunocompromise), and the XBB sublineages of Omicron (and bivalent booster VE assessment).

Finally, the number of booster doses recommended over such a limited period between 2020 and 2023 led to a particular challenge in estimation and appropriate interpretation of absolute VE (effectiveness compared to an unvaccinated population) and relative VE

(effectiveness compared to a differently vaccinated population, such as those with booster doses compared to those with only a primary series). Although absolute VE is generally easier to interpret and explain in public communications, it may be biased due to meaningful differences between individuals who did and did not get at least one dose of COVID-19 vaccine, and it is therefore important to estimate both absolute and relative VE whenever possible to ensure conclusions align. In addition, due to high rates of prior infection in the general population by 2022, even absolute VE must now be interpreted as an incremental or relative benefit beyond what individuals may have from prior infection(s), vaccination(s), or both (hybrid immunity).

4. CDC COVID-19 vaccine effectiveness study platforms

To meet the challenges of providing timely and robust data on COVID-19 VE for policy decisions, CDC designed and implemented numerous VE study platforms during late 2020 and early 2021. These platforms provide both depth and breadth in COVID-19 VE estimation and represent existing CDC platforms that rapidly pivoted from other pathogens to assess COVID-19, new platforms stood up to address specific needs, and leveraging of non-traditional data sources to meet the emergency nature of the pandemic (Table 1).

4.1. VE against severe outcomes

The *Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION)* is an electronic-healthcare record (EHR)-based network originally designed to measure VE for influenza vaccines. VISION measures VE against emergency department and urgent care visits and hospitalization, generally using a TND (although a subset of sites contributes denominator data allowing cohort analyses) and is designed as a partnership between CDC and healthcare systems in 10 states, including > 250 hospitals and > 400 emergency department and urgent care facilities. Because VISION is EHR-based, it can rapidly assess VE against multiple endpoints and by different strata of interest (e.g., age groups, underlying condition categories, number of doses). Key accomplishments of VISION have included rapid estimates of VE in children and adolescents, adults with immunocompromising conditions, and early, robust estimates of bivalent VE against hospitalization [20–22].

The *Investigating Respiratory Viruses in the Acutely Ill (IVY)* and *Overcoming COVID-19* platforms use a case-control design with active enrollment and interviews with patients, parents, or proxies for most cases and controls. IVY, also originally designed to investigate influenza VE, includes 25 adult hospitals across 20 states and conducts in-depth chart reviews to ascertain data on critical COVID-19 disease (e.g., mechanical ventilation and death). Overcoming COVID-19, which currently includes 33 hospitals in 27 states was originally designed to conduct surveillance for multisystem inflammatory syndrome in children (MIS-C) and expanded to conduct VE studies for MIS-C and acute COVID-19 hospitalization in children aged < 19 years, including assessing effectiveness of maternal vaccination for protection of young infants. IVY accomplishments have included early bivalent VE estimates against hospitalization and estimates of durability of protection from critical illness and death from monovalent vaccines lasting longer than a full year [23,24].

Overcoming COVID-19 has been one of the few platforms globally to publish estimates of maternal vaccination for infant protection and VE against MIS-C [25,26].

The *New Vaccine Surveillance Network (NVSN)* was originally designed to study vaccines for respiratory syncytial virus (RSV) and includes population-based surveillance for hospitalizations and outpatient visits associated with acute gastroenteritis and acute respiratory illness among children at seven medical centers. VE analyses within NVSN use a TND; COVID-19 VE analyses are ongoing [27].

4.2. VE against infection and transmission

HEROES-RECOVER (HR) was a network of longitudinal adult cohorts in six states that shared a common protocol and methods and began enrolling essential workers (including healthcare personnel, first responders, and frontline workers) in July 2020 with collection of weekly nasal swabs regardless of symptoms to accurately assess VE against all infection, including asymptomatic infection. *PROTECT*, a pediatric counterpart to HR added in July 2021, included children of HR participants or community residents in 4 states. Cohort members also routinely submitted information on vaccination status, completed questionnaires on behavior and COVID-19 exposures, and had blood drawn for SARS-CoV-2 antibody testing. The routine testing for SARS-CoV-2 combined with antibody testing allowed for complete capture of all SARS-CoV-2 infections and estimation of VE by prior infection status. HR provided some of the first estimates of VE in adults and supported early prioritization of vaccination in frontline workers when initial vaccine supply was limited [28]. Although HR and PROTECT ended enrollment and follow-up in Spring 2023, similar CDC-funded prospective cohorts, including CASCADIA[29], the Virus and Infections in Essential Workers (VIEW) Study, and the COVID-19 VE (CoVE) Study are ongoing and include enrollment and follow-up of adults and children at sites in 4 states.

The *Increasing Community Access to Testing (ICATT)* program leverages data from a federal partnership with national retail pharmacies testing for SARS-CoV-2. At test registration, individuals report their vaccination history, which is combined with test results; this allows estimation of VE using a TND design. ICATT is unique in both its size and the rapid availability of data: at its peak it operated in 49 states and included on average over 400,000 weekly tests between January 1, 2021 and May 11, 2023. This size and speed allowed exploration of questions that required prohibitively large sample sizes for other platforms including waning by month since vaccination and the first national estimates of VE after the emergence of the Omicron variant, VE in children 5 and under, and the first estimates of Omicron sublineage XBB-specific VE [18,30].

The *Respiratory Viruses Transmission Network* (RVTN) is designed to estimate whether vaccines reduce transmission within households. RVTN uses a case-ascertained study design with households enrolled when a person tests positive for influenza or SARS-CoV-2, followed by 10–14 days of monitoring household members for infection (including collection of respiratory specimens). Recent publications have focused on transmission dynamics but will include VE against transmission in the future [31,32].

Finally, the *Emerging Infections Program and PREVENT* networks estimated VE against symptomatic COVID-19 using a case-control study among US healthcare workers in a multisite network across multiple states [33,34]. This network leveraged employer requirements for COVID-19 testing among healthcare workers with COVID-19-like illness symptoms to produce critical early VE estimates among one of the earliest populations in the US to be eligible for COVID-19 vaccination. These estimates provided evidence of the vaccines working consistently across racial and ethnic groups and initial VE estimates among individuals with underlying conditions, including some who had been excluded from clinical trials, e.g., pregnant people and people with immunocompromising conditions. However, the end of employer requirements for COVID-19 testing among healthcare workers presented challenges to enrollment of cases and controls in this network, and the network will be completing COVID-19 VE work in Spring 2024.

4.3. VE against outpatient, medically attended COVID-19

The *US Influenza Vaccine Effectiveness (Flu VE) Network* is a long-standing multi-site platform originally designed to evaluate influenza vaccine effectiveness against mild to moderate outpatient illness; testing for SARS-CoV-2 was added during the COVID-19 pandemic. Strengths of the network include systematic molecular testing of symptomatic patients, whole-genome sequencing of a subset of influenza and SARS-CoV- 2-positive specimens, and the collection of both self-reported and documented vaccination information [35–37]. Within a single season, sample sizes have not allowed evaluation of VE of individual vaccine products or small age groups.

4.4. VE in special populations

Residents of long-term care facilities have experienced some of the highest rates of morbidity and mortality due to COVID-19 and were among the first people in the United States to receive COVID-19 vaccines [38]. However, they were excluded from RCTs studying vaccine efficacy, making VE the only way to determine how well the vaccines work in this important population. One of the earliest COVID-19 VE studies was conducted during an outbreak in two long-term care facilities in Connecticut in December 2020-February 2021 [39]. Since then, VE among residents of long-term care facilities has been estimated in the *National Healthcare Safety Network (NHSN)* [38,40], which includes mandatory reporting for certain healthcare-associated infections in healthcare facilities, including nursing homes certified by the Centers for Medicare and Medicaid Services (CMS). As part of surveillance for SARS-CoV-2, nursing homes reported incident confirmed SARS-CoV-2 infections among residents and staff members, by vaccination status, along with weekly census of residents by vaccination status, allowing estimation of VE through a facility cohort design.

5. Discussion

CDC COVID-19 VE platforms have played a pivotal role in numerous vaccine policy decisions since 2021 and will continue to play a key role in future decisions as the vaccine program moves from an emergency response to a routine schedule. Data from CDC's VE platforms have appeared in over 50 journal and MMWR publications. These platforms

have informed critical COVID-19 vaccine policy decisions with targeted data, including recommendations for: first monovalent booster dose for persons ages ≥ 16 years (Fall 2021) [8]; second monovalent booster dose for adults ≥ 50 years (April 2022) [9]; monovalent boosters in children 5–11 years (May 2022) [10]; primary series for children ages 6 months to 4 years (June 2022) [12]; bivalent vaccine doses (September 2022) [11], updated bivalent vaccine recommendations and simplification of the US COVID-19 vaccination program (April 2023) [13], and recommendations for updated monovalent (2023–2024) formula vaccines [14]. In addition to U.S. policy decisions, VE data have informed risk/benefit analyses after identification of potential vaccine-associated adverse events such as myocarditis and have informed global COVID-19 response through a robust data exchange.

CDC's portfolio of VE platforms will continue monitoring VE for COVID-19, as well as other respiratory viruses, including influenza and respiratory syncytial virus (RSV), and could be leveraged in the event of new emerging viruses in the future. Methodological considerations discussed above will likely continue to play a role in how VE is assessed with varying levels of impact on ability to rapidly measure VE. As with all observational data, VE data can be susceptible to limitations and appropriate interpretation is needed, in this case including context around prior SARS-CoV-2 infection, SARS-CoV-2 testing, and access to care. CDC VE platforms also afford many benefits, including large sample sizes, extensive, in-depth data collection, verification of vaccination history, and a focus on high-risk populations, aimed at fulfilling the goals outlined in the VE Framework. Platforms include a diversity of racial and ethnic groups, urban and rural populations, and high-risk groups, allowing for stratification by these factors. Taken as a whole, the CDC VE program is well-positioned to continue providing valuable data for policy decisions.

In addition to supporting policy decisions, VE data can play a significant role in educating providers and the public about the benefits of vaccination and support transparency and public confidence in the U.S. vaccine program. CDC VE platforms have shown longer-lasting protection against more severe COVID-19 outcomes, even in the presence of rapid waning of VE against symptomatic infection [30,41]. During Omicron variant predominance, data have consistently shown durable protection of COVID-19 vaccination against the most critical COVID-19 illness, including admission to intensive care, invasive mechanical ventilation, and death [21,23]. These insights have informed public communication and will continue playing an important role as the U.S and global communities adapt vaccine policy recommendations to a future of endemic COVID-19.

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Data availability

No data was used for the research described in the article.

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Table 1

Characteristics of CDC COVID-29 vaccine effectiveness platforms.

VE Platform	Population (ages included)	Study Design	Outcome(s) Studied	Major strengths	Selected publications
CASCADIA, Virus and Infections in Essential Workers (VIEW), and COVID-19 VE (CoVE)	Participating adults and children (CASCADIA and CoVE); participating adults (≥18 years, VIEW)	Cohort	Infection	Robust testing, including serologic testing and routine respiratory swabs; in-depth demographic and behavioral information	[29]
HEROES-RECOVER & PROTECT	HEROES-RECOVER: Participating adults (≥18 years)PROTECT: Participating children (4 months–17 years)	Cohort	Infection	Robust testing, including serologic testing and routine respiratory swabs; in-depth demographic and behavioral information	[28,42,43]
National Healthcare Safety Network (NHSN)	Nursing home residents (any nursing home resident)	Other*	Infection	Focused on nursing home population	[38,40,44]
Increasing Community Access to Testing (ICATT)	Persons seeking SARS-CoV-2 testing at participating commercial pharmacies (≥3 years)	Test negative design	Symptomatic infection	Largest VE platform, including testing from national pharmacy chains; near real-time data	[18,30,45–49]
Emerging Infections Program, PREVENT	Healthcare workers (≥18 years)	Test negative design	Symptomatic infection	Focused on healthcare workers, in-depth interview and chart reviews	[33,34,50]
Respiratory Virus Transmission Network (RVTN)	Households	Case-ascertained	Household transmission	In-depth data collection allowing modeling of transmission dynamics	[51] Analyses underway; COVID-19 VE publications forthcoming
Flu VE Network	Adults and children (all ages ≥ 6 months)	Test-negative design	Outpatient medically attended, laboratory-confirmed SARS-CoV-	In-depth enrollment interview with focus on outpatient illness	[35–37,52]
New Vaccine Surveillance Network (NVSN)	Children (0–17 years)	Test negative design	Emergency department encounters, hospitalization	Population-based surveillance allowing calculation of rates of disease in addition to VE	[53]Analyses underway; COVID-19 VE publications forthcoming
VISION	Adults and children visiting/admitted to emergency department/urgent care or hospital (all ages)	Test negative design, cohort	Emergency department/ urgent care encounters, hospitalization, critical outcomes	Largest hospitalization network, allowing rapid VE estimates by age and other strata	[20,21,41,54–58]
IVY	Hospitalized adults (≥18 years)	Case-control	Hospitalization, critical outcomes	In-depth interview and chart reviews, along with centralized testing and sequencing	[59–65]
Overcoming COVID-19	Hospitalized children (0–18 years)	Case-control	Hospitalization, multisystem inflammatory syndrome, critical outcomes, infant outcomes after maternal vaccination	In-depth interview and chart reviews; only platform designed to assess VE against MIS-C	[25,26,66–69]