research

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ORIGINAL RESEARCH Prospective observational study **FAST TRACK**

Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States

Lauring AS, Tenforde MW, Chappell JD, et al; on behalf of the Influenza and Other Viruses in the Acutely Ill (IVY) Network

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Study question Are the covid-19 mRNA vaccines as effective at preventing hospital admissions with covid-19 for the omicron variant as for the alpha and delta variants, and is disease severity different with omicron than with alpha and delta among adults admitted to hospital with covid-19?

Methods This multistate, case-control study in the United States included 11 690 adults (≥18 years) admitted to hospital: 5728 patients with covid-19 (cases) and 5962 concurrent patients without covid-19 (controls). Cases were classified into SARS-CoV-2 variant groups based on viral whole genome sequencing, and, if sequencing did not reveal a lineage, by the predominant circulating variant at the time of hospital admission: alpha (11 March to 3 July 2021), delta (4 July to 25 December 2021), and omicron (26 December 2021 to 14 January 2022). Vaccine effectiveness of two doses and three doses of mRNA vaccines to prevent hospital admissions with covid-19 was calculated using a test negative design for each variant. Disease severity for cases was classified based on the World Health Organization clinical progression scale and compared among variants using proportional odds regression.

Study answer and limitations Vaccine effectiveness of two mRNA vaccine doses was lower for omicron (65%, 95% confidence interval 51% to 75%) than for alpha (85%, 82% to 88%) and delta (85%, 83% to 87%). Three vaccine doses achieved similar effectiveness for omicron (86%, 77% to 91%) as two doses for alpha and delta. Omicron was associated with lower disease severity than delta (adjusted proportional odds ratio 0.61, 95% confidence interval 0.49 to 0.77) but was still associated with substantial critical illness; 84/565 (15%) patients with omicron were treated with invasive mechanical ventilation and 40/565 (7%) died in hospital.

What this study adds mRNA vaccines were found to be effective at preventing severe covid-19 due to the omicron variant. Although disease severity among adults admitted to hospital with covid-19 is lower for the omicron variant compared with alpha and delta variants, covid-19 due to omicron is associated with substantial morbidity and mortality.

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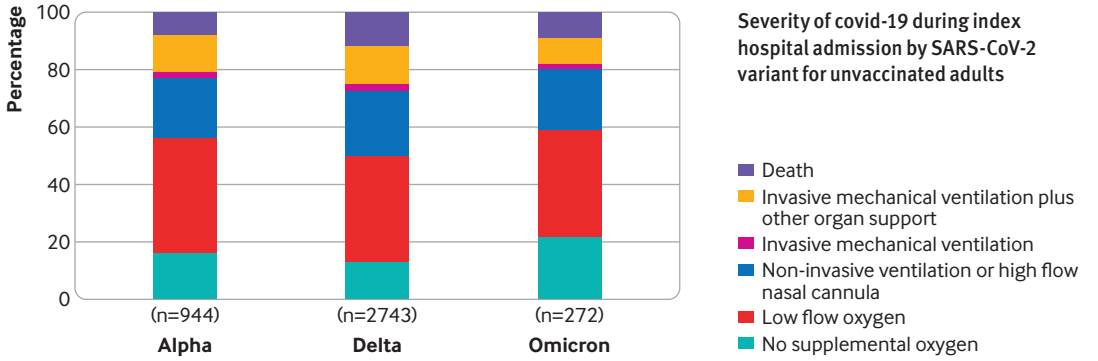
See competing interests in full paper on bmj.com. No additional data available.



Severity of covid-19 during index hospital admission by SARS-CoV-2 variant for unvaccinated adults

Transmission of SARS-CoV-2 from mother to baby is rare

ORIGINAL RESEARCH Living systematic review and meta-analysis

SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission

Allotey J, Chatterjee S, Kew T, et al
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Study question What is the rate of SARS-CoV-2 positivity in babies born to mothers with SARS-CoV-2 infection, the timing of mother-to-child transmission, and factors associated with SARS-CoV-2 positivity in offspring?

Methods This living systematic review included pregnant and recently pregnant women with a diagnosis of SARS-CoV-2 infection. Rates of SARS-CoV-2 positivity in offspring diagnosed using reverse transcriptase polymerase chain reaction (RT-PCR) or serological tests, or both, are reported. The World Health Organization classification system was used to determine the timing of mother-to-child transmission. The odds of SARS-CoV-2 positivity in offspring were compared for various maternal and perinatal risk factors. Dichotomous data are summarised using random effects meta-analysis and reported as odds ratios with 95% CIs.

Study answer and limitations 472 studies (206 cohort studies, 266 case series and case reports; 28 952 mothers, 18 237 babies) were included. Overall, 1.8% (95% confidence interval 1.2% to 2.5%; 140 studies, 14 271 babies) of babies born to mothers with SARS-CoV-2 infection tested positive by RT-PCR. Of the 592 SARS-CoV-2 positive babies with relevant data, 14 had confirmed mother-to-child transmission: seven in utero (448 assessed), two intrapartum (18 assessed), and five during the early postnatal period (70 assessed).

Maternal factors such as severe covid-19 (odds ratio 2.4, 95% confidence interval 1.3 to 4.4), death (14.1, 4.1 to 48.0), admission to the intensive care unit (3.5, 1.7 to 6.9), and postnatal infection (5.0, 1.2 to 20.1) were associated with SARS-CoV-2 positivity in offspring.

The types and timing of tests used to diagnose SARS-CoV-2 infection in babies varied between studies. Clinical outcomes of babies born to mothers with SARS-CoV-2 infection were inconsistently reported.

COMMENTARY Latest evidence looks reassuring, but data collection must continue

Despite hundreds of millions of confirmed SARS-CoV-2 infections and more than five million related deaths worldwide,[1] major gaps remain in our knowledge about the risks to babies when their mothers are infected with SARS-CoV-2. Allotey and colleagues, in their work for the PregCOV-19 Living Systematic Review Consortium, help address this gap with a review of nearly 500 studies.[2]

Overall, findings from this review seem reassuring. Although the results indicate that mother-to-child transmission is possible in utero during the antenatal period, during labour or delivery (intrapartum), and after delivery (postpartum), rates of positivity among infants born to mothers with SARS-CoV-2 are low (<2%). They are even lower when analyses are limited to cases of likely antenatal and intrapartum exposure to the virus, such as babies testing positive in the first 24 hours after delivery (0.9%). Furthermore, in affluent world regions such as North America, SARS-CoV-2 positivity among exposed infants appears to be extremely rare (0.1%). Combined, the results suggest that when proper preventive measures are taken during intrapartum and early postpartum periods, such as consistent and appropriate use of personal protective equipment, infection of newborn babies is unlikely.

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Source of exposure

However, the grouping by the authors of in utero, intrapartum, and postpartum infections to determine positivity among exposed babies might seem confusing when interpreting risk, as the sources of exposure vary across all three periods. In utero exposure typically occurs when a pathogen—in this case SARS-CoV-2—crosses the maternal-placental interface to infect the developing fetus. This transmission route is more characteristic of blood-borne pathogens than respiratory ones.[3] Case studies confirming in utero infection for seven infants, along with biomarker evidence, indicate that in utero transmission is possible but exceedingly rare. Intrapartum transmission, typically from exposure to virus in maternal blood, vaginal secretions, or faeces during the birth process, is also rare for respiratory infections,[3] and it was only confirmed by two (0.06%) cases in this review. Thus, vertical transmission (in utero and intrapartum) from mother to baby is unlikely—a finding that is critical to convey to new families should the mother become infected during pregnancy.

Postnatal infection of the infant can relate to a variety of exposures. These include maternal respiratory secretions, contact with infected caregivers or healthcare providers, contaminated surfaces, or, possibly, but as of yet unconfirmed, breastmilk.[3] In Allotey and colleagues' review, infection during the early postpartum period was defined vaguely as "infection near the time of birth" and was categorised in the results as mother-to-child transmission. It is, however, worth noting that mothers are not the only possible source of transmission to newborn babies. Hospital deliveries often put new mothers and babies in contact with dozens of people, such as family and friends; doctors, nurses, and medical assistants; receptionists and administrative assistants; custodians; and those preparing and delivering food. Precautions applied in healthcare settings have varied tremendously over the course of the pandemic, and by location. Thus, pinpointing the source of infection in newborn babies is challenging.

Maternal and perinatal factors associated with SARS-CoV-2 positivity in offspring						
Risk factors	**No of studies**	**No of mother-baby dyads**	**No of test positive babies*/ No with risk factors**	**No of test positive babies*/ No without factors**	**Odds ratio (95% CI)**	**I^2 (%)**
Maternal factors						
Severe covid-19	22	2842	18/331	125/2511	2.36 (1.28 to 4.36)	10
Maternal death	7	725	6/15	28/710	14.09 (4.14 to 47.97)	0
Admission to ICU	19	2851	7/92	123/2759	3.46 (1.74 to 6.91)	0
Timing of maternal infection						
Postnatal *v* antenatal	12	750	19/122	54/628	4.99 (1.24 to 20.13)	65
3rd *v* 1st or 2nd trimester	13	1422	104/1403	2/19	0.29 (0.08 to 1.10)	0
Intrapartum factors						
Preterm *v* term	40	4126	55/618	203/3508	1.47 (0.99 to 2.17)	2
Mode of delivery	49	4814	159/2429	99/2385	1.38 (0.97 to 1.95)	18
Postnatal care						
Not separated *v* separated at birth	11	1617	42/658	48/959	1.37 (0.47 to 3.98)	64
Breastfed *v* not breastfed	13	1545	43/783	39/762	0.74 (0.34 to 1.62)	29

ICU=intensive care unit; CI=confidence interval.
*Reverse transcriptase polymerase chain reaction.

What this study adds SARS-CoV-2 positivity rates are low in babies born to mothers with SARS-CoV-2 infection. Evidence suggests confirmed vertical transmission of SARS-CoV-2, although this is likely to be rare. Severity of maternal covid-19 appears to be associated with SARS-CoV-2 positivity in offspring.

Funding, competing interests, and data sharing
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No competing interests declared.
No additional data available.
Systematic review registration PROSPERO CRD42020178076.

In utero transmission is possible but exceedingly rare

Findings from Allotey and colleagues' review also show no association between breastfeeding and infection in newborn babies, despite the detection of SARS-CoV-2 from a few breastmilk samples (seven positive results from 422 samples using RT-PCR). Similarly, no association was observed when infections in newborn babies were compared between mothers who were separated from their babies versus those who were not. Thus, there is currently still no evidence that changes need to be made in postnatal care best practices.

Although some important conclusions can be drawn from this review, the paucity of high quality data on risks to infants from covid-19 is also highlighted. Despite hundreds of millions of infections and a review of nearly 500 studies from across the globe, sufficient data were only available for 14 518 exposed babies worldwide to determine positivity rates, with large variability in the numbers of studies, events, and total exposed cases by world region. Furthermore, data to determine outcomes, such as death, were available from only 800 babies positive for SARS-CoV-2. Sufficient data to ascertain the timing of exposure and likelihood of infection among exposed babies were only available for 592 babies. Given that vaccines are not available for babies and young children, it is critical that better data become available to inform appropriate shared decision making on perinatal care between parents and healthcare providers.

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Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events

Li X, Raventós B, Roel E, et al

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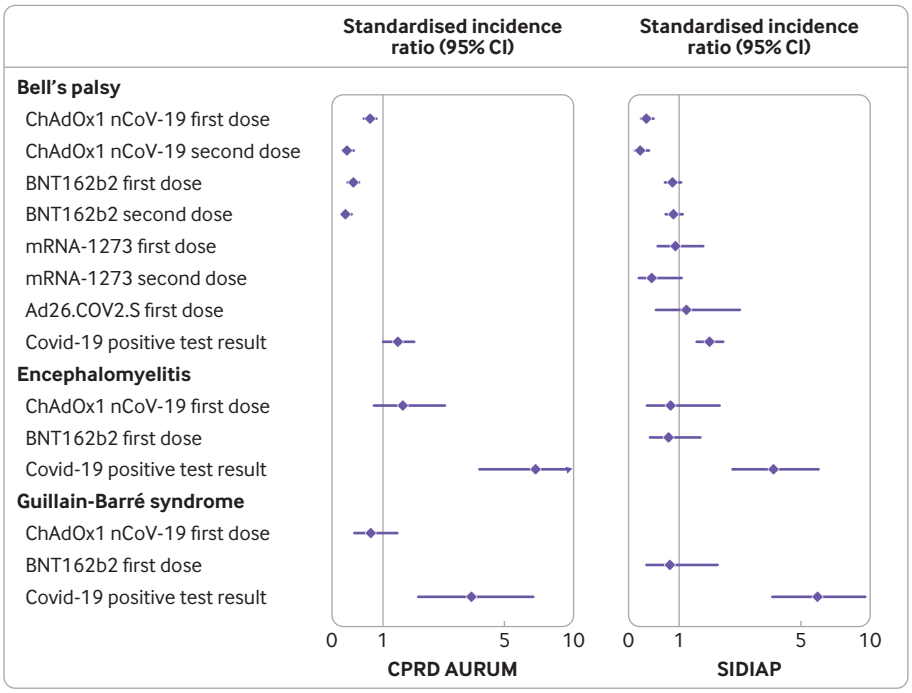
Study question What are the associations between covid-19 vaccines, SARS-CoV-2 infection, and short term risk of immune mediated neurological events?

Methods Data on 8 330 497 people vaccinated against covid-19 (ChAdOx1, BNT162b2, mRNA-1273, or Ad.26.COV2.S vaccines) and 735 870 people with a SARS-CoV-2 positive test result were extracted from primary care records in the UK (Clinical Practice Research Datalink AURUM) and primary care records linked to hospital data in Spain (Information System for Research in Primary Care). The study outcomes were Bell's palsy, encephalomyelitis, Guillain-Barré syndrome, and transverse myelitis. Background incidence of the studied events using data from 2017-19 was compared with the incidence of the same events during the 21 days after vaccination or the 90 days after a SARS-CoV-2 positive test result. In addition, a self-controlled case series analysis compared the rates of events after vaccination or SARS-CoV-2 infection with the rates before vaccination or a SARS-CoV-2 infection.

Study answer and limitations The study included 4 376 535 people who received ChAdOx1 nCoV-19, 3 588 318 who received BNT162b2, 244 913 who received mRNA-1273, and 120 731 who received Ad26.CoV.2; 735 870 people with SARS-CoV-2 infection; and 14 330 080 people from the general population. Overall, post-vaccine rates were consistent with expected (background) rates for Bell's palsy, encephalomyelitis, and Guillain-Barré syndrome but were higher than expected after SARS-CoV-2 infection. For example, in the UK data, the standardised incidence ratio for Bell's palsy was 1.33 (1.02 to 1.74), for encephalomyelitis was 6.89 (3.82 to 12.44), and for Guillain-Barré syndrome was 3.53 (1.83 to 6.77). Self-controlled case series was conducted only for Bell's palsy, given limited statistical power, but with no safety signal seen for those vaccinated. Transverse myelitis was rare (<5 events in all vaccinated cohorts) and could not be analysed.

What this study adds The findings suggest that SARS-CoV-2 infection, and not covid-19 vaccines, is associated with an increased risk of Bell's palsy, encephalomyelitis, and Guillain-Barré syndrome.



Standardised incidence ratios of immune mediated neurological disorders of special interest. CPRD AURUM=Clinical Practice Research Datalink AURUM (UK); SIDIAP=Information System for Research in Primary Care (Spain)

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