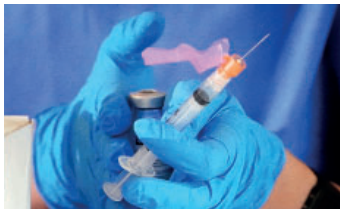
research

Statin treatment and clinical outcomes in covid-19 patients in ICU p 59



Effectiveness of mRNA-1273 vaccine against SARS-CoV-2 variants p 60

Portion of CHEERS 2022 checklist

Section/topic	Item No	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	
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Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	

The CHEERS 2022 statement p 62

ORIGINAL RESEARCH Randomised controlled trial **FAST TRACK**

Atorvastatin versus placebo in patients with covid-19 in intensive care

The INSPIRATION-S Investigators

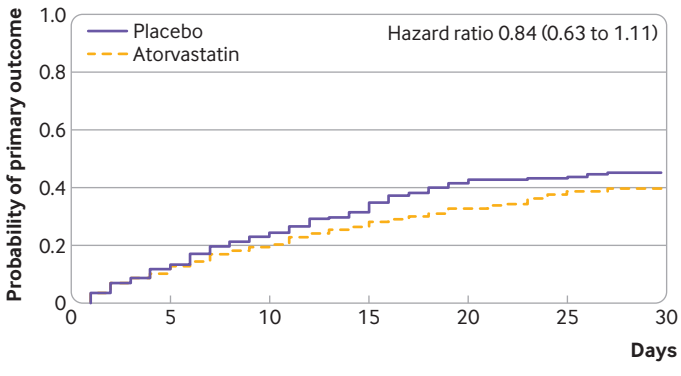
Cite this as: *BMJ* 2022;376:e068407
Find this at doi: 10.1136/bmj-2021-068407

Study question Is statin treatment effective compared with placebo in reducing clinical outcomes in adults with covid-19 admitted to the intensive care unit (ICU)?

Methods The Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label Randomised Controlled Trial (INSPIRATION) and INSPIRATION-statin (INSPIRATION-S) was a multicentre trial with a 2×2 factorial design that randomised patients with covid-19 who were admitted to ICU to intermediate dose versus standard dose prophylactic anticoagulation with heparin based regimens (anticoagulation randomisation) and statin therapy versus placebo (statin randomisation). This study reports the results of the statin randomisation, for which 605 patients were randomised between 29 July 2020 and 4 April 2021. 587 patients were included in the primary analysis: 290 assigned to atorvastatin 20 mg once daily and 297 assigned to placebo. The primary efficacy outcome was a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or all cause mortality within 30 days from randomisation. Prespecified safety outcomes included increases in liver enzyme levels more than three times the upper limit of normal and clinically diagnosed myopathy. A clinical events committee blinded to treatment assignment adjudicated the efficacy and safety outcomes.

Study answer and limitations The primary outcome occurred in 95 (33%) patients assigned to atorvastatin and 108 (36%) assigned to placebo (odds ratio 0.84, 95% confidence interval 0.58 to 1.21). Deaths occurred in 90 (31%) patients in the atorvastatin group and 103 (35%) in the placebo group (odds ratio 0.84, 0.58 to 1.22). Rates for venous thromboembolism were 2% (n=6) in the atorvastatin group and 3% (n=9) in the placebo group (odds ratio 0.71, 0.24 to 2.06). Myopathy was not clinically diagnosed in either group. Liver enzyme levels were increased in five (2%) patients assigned to atorvastatin and six (2%) assigned to placebo (odds ratio 0.85, 0.25 to 2.81). Since the event rates were lower than expected, a smaller treatment effect cannot be excluded.

What this study adds In adults with covid-19 admitted to the ICU, atorvastatin was not associated with a significant reduction in the composite of venous or arterial thrombosis, treatment with ECMO, or all cause mortality compared with placebo. Treatment was found to be safe.



Time to event for primary outcome in prespecified primary cohort of patients who received at least one dose of study drug

Funding, competing interests, and data sharing
Funded by the Rajaie Cardiovascular Medical and Research Centre. No competing interests declared. Data will be available to interested investigators on approval of the trial steering committee.

Study registration ClinicalTrials.gov NCT04486508.

Covid-19 vaccines, immunity, and boosters

ORIGINAL RESEARCH Test negative case-control study

FAST TRACK

Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2

Bruxvoort KJ, Sy LS, Qian L, et al

Cite this as: *BMJ* 2021;375:e068848
Find this at doi: 10.1136/bmj-2021-068848

Study question What is the effectiveness of the mRNA-1273 vaccine against SARS-CoV-2 variants, and how does effectiveness against the delta variant differ by time since vaccination?

Methods This test negative case-control study included adult Kaiser Permanente Southern California members who had a SARS-CoV-2 positive test result sent for whole genome sequencing or a negative test result from 1 March to 27 July 2021. Outcomes included SARS-CoV-2 infection and admission to hospital with covid-19. For each variant type, test positive cases were matched 1:5 to test negative controls on age, sex, race/ethnicity, and specimen collection date. Interventions were two doses or one dose of mRNA-1273 ≥14 days before specimen collection or no covid-19 vaccination. Conditional logistic regression was used to compare odds of vaccination among cases versus controls, adjusting for confounders. Vaccine effectiveness was calculated as (1−odds ratio)×100%.

Study answer and limitations The study included 8153 cases and their matched controls. Two dose vaccine effectiveness was 86.7% (95% confidence interval 84.3% to 88.7%) against infection with the delta variant, 98.4% (96.9% to 99.1%) against alpha, 90.4% (73.9% to 96.5%) against mu, 96-98% against other identified variants, and 79.9% (76.9% to 82.5%) against unidentified variants (specimens that failed sequencing). Vaccine effectiveness against hospital

COMMENTARY Many people still lack essential (and enduring) protection from primary vaccination

Well conducted real world studies of vaccine effectiveness are an important complement to randomised controlled trials. For example, two recent BMJ studies use test negative designs to analyse rich datasets from large health systems. In November 2021, Israel and colleagues (doi:10.1136/bmj-2021-067873) reported changes over time in the effectiveness of the Pfizer-BioNTech BNT162b2 vaccine against SARS-CoV-2 infection among members of a nationwide healthcare system in Israel during a period dominated by the delta variant.[3] They found an increased risk of infection associated with intervals longer than three months since full vaccination. Adjusted odds ratios were 2.37 at three to four months after vaccination but increased only slightly to 2.82 at six months or more.

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Policies that preferentially stockpile vaccine doses in high income settings remain indefensible

The second study, by Bruxvoort and colleagues (see abstract above), evaluated the effectiveness of Moderna's mRNA vaccine against SARS-CoV-2 variants, including delta, alpha, mu, and others among 8153 cases and matched controls in an integrated healthcare system in California.[4] Vaccine effectiveness against infection with the delta variant was 94.1% at two months or less after vaccination, declining to 80.0% at five to six months. Importantly, vaccine effectiveness against admission to hospital with the delta variant remained at 97.5%.

Valuable insights

Although these studies provide valuable insights, all observational studies are vulnerable to biases related to underlying differences between the studied populations, which can lead to differences between the estimated and true effectiveness. For context, consider the initial randomised trial evaluating the Pfizer-BioNTech vaccine, conducted before the emergence of the delta variant, which reported an estimated efficacy against symptomatic infection by pre-delta variants of 96.2% at two months or less, 90.1% at two to four months, and 83.7% at four to six months after vaccination.[5] These changes over time are consistent with Israel and colleagues' findings, indicating that residual bias in that study is likely small. We can have confidence in their observation that effectiveness remains relatively stable beyond six months, even in the context of delta.

Supporting this, in a post hoc analysis during a period dominated by delta, differences in infection rates between trial participants originally randomised to the vaccine and those who received the vaccine after unblinding six months later suggest a minimal and more gradual decline in efficacy from 83.7% at four to six months to 78% at 10-12 months.[6]

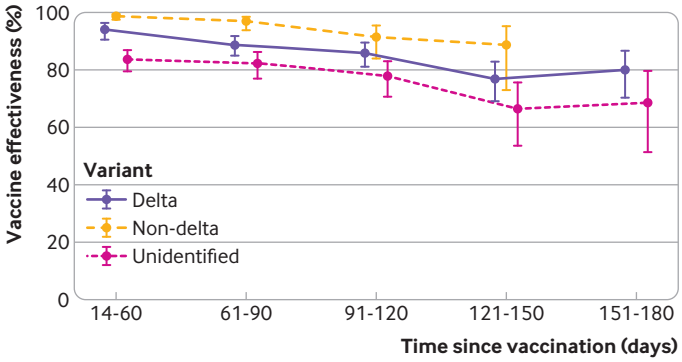
Together, both observational and randomised data suggest that after an initial decline, protection may become more stable, even in the context of delta.

We previously argued[1] that studies showing modest waning of immunity do not support indiscriminate use of

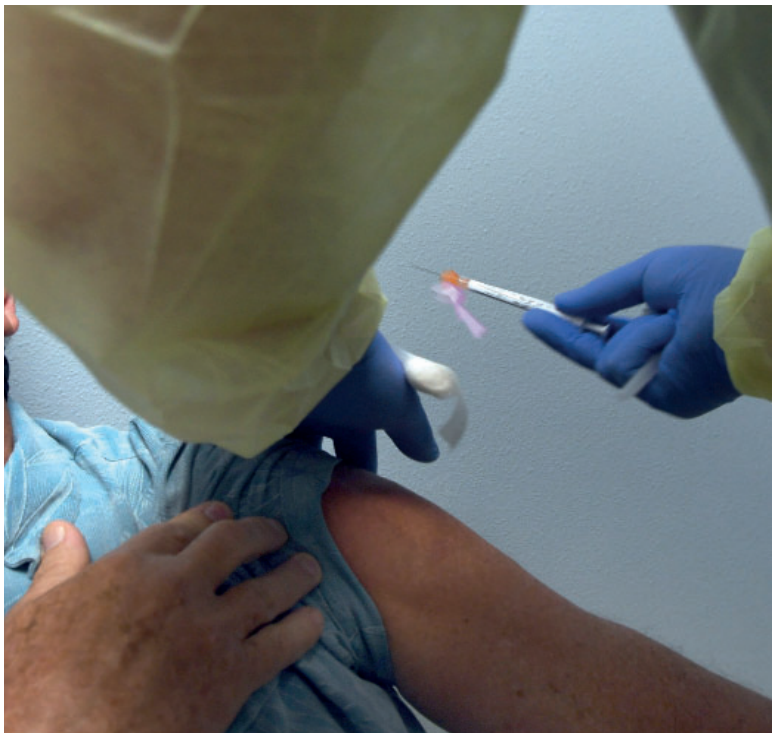
admission with the delta variant was 97.5% (92.7% to 99.2%). Vaccine effectiveness against infection with the delta variant declined from 94.1% (90.5% to 96.3%) 14-60 days after vaccination to 80.0% (70.2% to 86.6%) 151-180 days after vaccination. Waning was less pronounced for non-delta variants. Limitations include potential for residual confounding due to unmeasured factors associated with both testing and vaccination.

What this study adds Two doses of mRNA-1273 were highly effective against infection and hospital admission with all SARS-CoV-2 variants. Vaccine effectiveness against infection with the delta variant moderately declined with increasing time since vaccination.

Funding, competing interests, and data sharing
The study was supported by Moderna.
See bmj.com for competing interests.
Individual level data reported in this study are not publicly shared.



Vaccine effectiveness of two doses of mRNA-1273 against infection with SARS-CoV-2 variants by time since vaccination. Non-delta variants included alpha, epsilon, gamma, iota, mu, and other (beta, eta, kappa, and other variants). Unidentified variants were those for which whole genome sequencing failed



booster doses outside of older and medically vulnerable populations.[7] A randomised controlled trial (not yet peer reviewed at the time of writing) has since found that a third dose of BNT162b2, about 11 months after the primary course, gave 95.3% relative efficacy against symptomatic infection during 2.5 months of follow-up, compared with two doses alone.[8] This is consistent with observational data of booster effectiveness,[9-11] including a rigorously conducted matched cohort study showing that these benefits extend to severe outcomes, primarily among older people.[12] Booster doses may also have a role in helping to reduce transmission in well vaccinated populations during periods of substantial community transmission.[13]

Research still in preprint suggests that the new omicron variant is associated with reduced neutralising antibody responses following two doses of vaccine, which is reversed by a booster dose or hybrid immunity from a combination of vaccination and infection.[14 15] A reduction in vaccine effectiveness and improved protection afforded by booster doses is also supported by preliminary clinical data from the UK.[16] That broader and increased antibody titres generated by a third or booster dose may be able to overcome the reduced neutralisation associated with the omicron variant is therefore plausible. Further research evaluating the effectiveness of primary and additional vaccine doses against omicron is clearly a priority.

Although a third or booster dose clearly provides additional protection on top of simply reversing previous waning, the greatest protection from the worst clinical outcomes remains heavily concentrated in the first two doses.[17] The long term durability of protection against hospital admission afforded by two dose vaccine regimens is clear, particularly with an extended interval between the two doses (and even in the face of new variants).[18] Given the importance of reducing disease burden globally, vaccinations in low income settings, where the vast majority of people are yet to receive even a first dose, should be prioritised over additional doses in high income settings. Policies that preferentially stockpile vaccine doses in high income settings remain indefensible. Although we do not know the precise circumstances that led to the emergence of omicron, that the extreme disparities in access to vaccines between high income and low income settings create the ideal conditions for the ongoing evolution of SARS-CoV-2 is clear.

Cite this as: *BMJ* 2021;375:n3105
Find the full version with references at http://dx.doi.org/10.1136/bmj.n3105

Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement

Husereau D, Drummond M, Augustovski F; on behalf of CHEERS 2022 ISPOR Good Research Practices Task Force

Cite this as: *BMJ* 2022;376:e067975
Find this at doi: 10.1136/bmj-2021-067975

Health economic evaluations are comparative analyses of alternative courses of action in terms of their costs and consequences. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement, published in 2013, was created to ensure that health economic evaluations are identifiable, interpretable, and useful for decision making. The statement was intended as guidance to help authors report accurately which health interventions were being compared and in what context, how the evaluation was undertaken, what the findings were, and other details that might aid readers and reviewers in the interpretation and use of the study.

The new CHEERS 2022 statement replaces previous CHEERS reporting guidance. It reflects the need for guidance that can be more easily applied to all types of health economic evaluation, new methods and developments, as well as the increased role of stakeholder involvement including patients and the public. It also broadly applies to any form of intervention intended to improve the health of individuals or the population, whether simple or complex, and without regard to context (eg, healthcare, public health, education, and social care).

This summary article presents the new CHEERS 2022 checklist of 28 items (21 shown in the accompanying box), and recommendations for each item. The CHEERS 2022 statement is primarily intended for researchers reporting economic evaluations for peer reviewed journals as well as the peer reviewers and editors assessing them for publication. However, we anticipate familiarity with reporting requirements will be useful for analysts when planning studies. It might also be useful for health technology assessment bodies seeking guidance on reporting, owing to the increasing emphasis on transparency in decision making.

Portion of CHEERS 2022 checklist

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Setting and location	6	Provide relevant contextual information that may influence findings.	_____
Comparators	7	Describe the interventions or strategies being compared and why chosen.	_____
Perspective	8	State the perspective(s) adopted by the study and why chosen.	_____
Time horizon	9	State the time horizon for the study and why appropriate.	_____
Discount rate	10	Report the discount rate(s) and reason chosen.	_____
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	_____
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	_____
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	_____
Measurement and valuation of resources and costs	14	Describe how costs were valued.	_____
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	_____
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	_____
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	_____
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	_____
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	_____
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	_____
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	_____