research

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ORIGINAL RESEARCH Longitudinal study of UK electronic health records

Long term impact of prophylactic antibiotic use before incision versus after cord clamping on children born by caesarean section

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Study question What is the impact of the policy to administer prophylactic antibiotics to women before incision for caesarean section on risk of asthma and eczema in their children up to age 5 years?

Methods A controlled interrupted time series study design was used to evaluate the effect of the pre-incision antibiotics policy (fetal exposure to antibiotics) compared with post-cord clamping policy (no exposure), after a UK national recommendation in 2011 to administer antibiotic prophylaxis for caesarean section before incision. Anonymised data on 515 945 children born between 2006 and 2018 with linked maternal records and registered with general practices contributing to two UK-wide primary care databases, and 3 945 351 mother-baby pairs in the secondary care database for England were analysed. The primary outcome measures were incidence rate ratios of asthma and eczema in children born by caesarean section when pre-incision prophylactic antibiotics were recommended compared with those born in the period of post-cord clamping policy, adjusted for temporal changes in the incidence rates in children born by vaginal delivery as controls.

Study answer and limitations This study found no evidence of an association between prophylactic antibiotics administered before incision for caesarean section and risk of asthma (incidence rate ratio 0.91, 95% confidence interval 0.78 to 1.05) and eczema (0.98, 0.94 to 1.03), including hospital admission for asthma and eczema (1.05, 0.99 to 1.11 and 0.96, 0.71 to 1.29, respectively), in children up to age 5 years. Exposure to pre-incision antibiotics at an individual level could not be ascertained.

What this study adds The findings suggest that introduction of pre-incision prophylactic antibiotics policy for caesarean section in the UK was not associated with an increased risk of asthma and eczema in children aged up to 5 years.

Primary outcomes in children and relative risk associated with use of prophylactic antibiotics pre-incision versus post-cord clamping*

Outcomes	Incidence rate ratio (95% CI)	P value
Diagnosis		
Asthma	0.91 (0.78 to 1.05)	0.18
Eczema	0.98 (0.94 to 1.03	0.46
Hospital admission		
Asthma	1.05 (0.99 to 1.11)	0.12
Eczema	0.96 (0.71 to 1.29)	0.77

*For diagnoses recorded in primary care, the model incorporates a probability that each mother received pre-incision antibiotics based on national policy uptake rates in the year of delivery and is adjusted for child's age, year of delivery, and delivery type. For hospital admissions, the model only includes births linked to hospitals for which the year of antibiotic prescribing policy change is known and is adjusted for year of delivery and delivery type.

Funding, competing interests, and data sharing This study was funded by the National Institute for Health and Care Research Health Technology Assessment programme.

See full paper on bmj.com for competing interests.

Data for similar cohorts can be requested from the UK Medicines and Healthcare Products Regulatory Agency, IQVIA World Publications, and NHS Digital subject to protocol approval and license agreements.

Are vaccines a potential treatment for long covid?

ORIGINAL RESEARCH Community based cohort study

Trajectory of long covid symptoms after covid-19 vaccination

Ayoubkhani D, Bermingham C, Pouwels KB, et al
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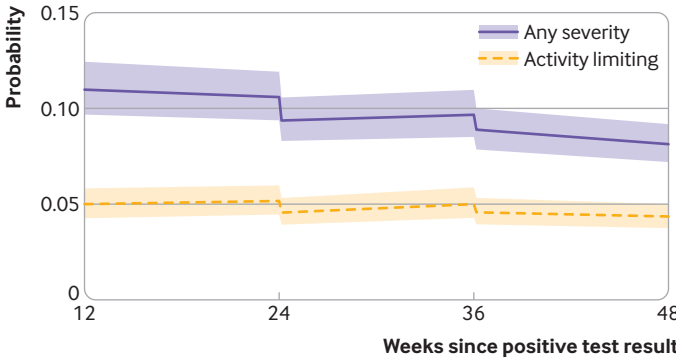
Study question What are the associations between covid-19 vaccination and long covid symptoms in adults infected with SARS-CoV-2 before vaccination?

Methods This observational cohort study comprised 28 356 respondents to the Office for National Statistics COVID-19 Infection Survey, which includes a random sample of the UK community dwelling population. Participants were eligible for inclusion in the study if they were aged 18 to 69 years and had received at least a first dose of either an adenovirus vector or an mRNA vaccine after a positive SARS-CoV-2 test result. Using individual level interrupted time series analysis, the presence of long covid symptoms at least 12 weeks after infection was investigated over the follow-up period 3 February to 5 September 2021.

Study answer and limitations Mean age of participants was 46 years, 55.6% (n=15 760) were women, and 88.7% (n=25 141) were of white



Modelled probabilities (and 95% confidence intervals) of long covid for a hypothetical study participant who received a first covid-19 vaccine dose 24 weeks after SARS-CoV-2 infection and a second dose 12 weeks later. Probabilities are shown for participants of mean age (50 years) and in the modal group for other covariates (woman, white ethnicity, resident in London, resident in an area in the least deprived fifth group, not a patient-facing health or social care worker, no pre-existing health conditions, not admitted to hospital during the acute phase of infection, infected on 7 September 2020)

COMMENTARY Benefits are possible, but we need more evidence and a mechanism of action

Covid-19 vaccines reduce the chance of developing long covid by about half among people who are vaccinated before they develop covid-19.[1] However, the effect of vaccines for people who already have long covid is a contentious area for both patients and healthcare professionals. In a linked paper, Ayoubkhani and colleagues report findings from the largest published study on this topic to date.[2]

From a random sample of the UK population, they identified 28 356 adults who were vaccinated after a positive SARS-CoV-2 test result, of whom 6729 (23.7%) reported long covid symptoms (>12 weeks) of any severity at least once during follow-up. Participants were followed for seven months to determine the relation between vaccination, long covid, and symptom profiles after the first and second dose of either an adenovirus vector or mRNA vaccine.[2]

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A clear explanation for how vaccines might reduce the multisystem manifestations of long covid is still lacking

The authors found a 12.8% reduction in the odds of reporting long covid immediately after the first vaccine dose, but this reduction was not sustained over the following 12 weeks. However, an 8.8% reduction in the odds of long covid after a second dose was sustained over the next nine weeks. The authors suggested inadequate immune response as a reason for lack of sustained effect after the first dose.

Other evidence

Although Ayoubkhani and colleagues' study was large, lack of a contemporaneous control arm without vaccination was a limitation. Natural recovery from long covid was accounted for by comparing symptom trajectories before and after vaccination.

Several smaller studies have looked at the effect of vaccination on long covid,[1] including one from France, not yet peer reviewed, exploring the resolution of symptoms post-vaccination in a cohort of 910 adults with long covid.[7] Four hundred and fifty five adults vaccinated in a particular 60 day period were propensity score matched to an equal number of adults who remained unvaccinated during the same period. At 120 days, 16.6% of those vaccinated reported complete resolution of symptoms, compared with 7.5% of those who were unvaccinated.

The difference was significant (hazard ratio for resolution of symptoms was 1.97, 95% confidence interval 1.23 to 3.15). Persistent symptoms were reported by people in both study arms at final follow-up, with only a marginal difference in symptom severity score between the groups.

Another small study measured antibody titres and symptoms post-vaccination in 42 adults with long covid: 61% reported no change in symptoms, 21% reported worse symptoms, and 16% reported an improvement during the two weeks after vaccination.[8] Unlike Ayoubkhani and colleagues, these authors measured post-vaccination antibody titre ratios, and they found significantly higher titres in the group reporting worse symptoms after vaccination compared with those with no change or improvement in symptoms. They hypothesised that an excessive immune response induced by the vaccine may be responsible.[8]

The mechanisms underpinning changes in long covid symptoms after vaccination are not fully understood. However, as Ayoubkhani and colleagues

ethnicity. 6729 participants (23.7%) reported long covid symptoms of any severity at least once during follow-up. A first vaccine dose was associated with an initial 12.8% decrease (95% confidence interval −18.6% to −6.6%, P<0.001) in the odds of long covid, with subsequent data compatible with both increases and decreases in the trajectory (0.3% per week, 95% confidence interval −0.6% to 1.2% per week). A second dose was associated with an initial 8.8% decrease (95% confidence interval −14.1% to −3.1%) in the odds of long covid, with a subsequent decrease by 0.8% per week (−1.2% to −0.4% per week). Evidence suggested sustained improvement after the second dose, at least over the median follow-up of 67 days. Causality cannot be inferred from this observational evidence, and more post-vaccination follow-up time (including the effect of booster doses) is needed.

What this study adds The findings suggest that vaccination might contribute to a reduction in the population health burden of long covid.

Funding, competing interests, and data sharing No specific funding. KK chairs the long covid research funded group reporting to the Chief Medical Officer, chairs the Ethnicity Subgroup of the UK Scientific Advisory Group for Emergencies (SAGE), and is a member of SAGE. Deidentified study data are available to accredited researchers (research.support@ons.gov.uk or ons.gov.uk/aboutus/whatwedo/statistics/requestingstatistics/approvedresearcherscheme).

suggest, vaccination can increase antibody titres and potentially eliminate viral reservoirs.[2] Given the small numbers of patients reported to benefit (an 8.8% reduction in odds of long covid after two vaccine doses) and the uncertainty around the true effect of vaccines relative to natural recovery, a clear explanation for how vaccines might reduce the multisystem manifestations of long covid is still lacking, particularly for people already well past the stage of systemic inflammatory responses, and those with end organ damage from covid-19, such as lung fibrosis.

Several plausible mechanisms underlying long covid are currently being investigated, including the persistence of viral antigens and abnormalities in T cells, platelets, vascular endothelium, and clotting factors.[9 10] People with long covid need timely investigation, management, and rehabilitation in specialist clinics, including identification of thrombotic phenomena, cardiac dysrhythmias, and dysautonomia.[11]

Vaccination to reduce risk of reinfection remains important for people with long covid, and evidence so far suggests that benefits are likely to outweigh any harms. Three outcomes are possible after vaccination: no change in symptoms (most likely), improvement (best case), or deterioration (worst case).[1] Unfortunately, many unknowns remain about the long term prognosis of long covid, including the effect of booster vaccines or recurrent covid-19. More research is needed on the link between antibody titres and symptoms over time before we can hope to predict the effects of vaccination on individuals.

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PRIYA SUNDRAM

Visualising harms in publications of randomised controlled trials

Phillips R, Cro S, Wheeler G, et al

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Study question What are researchers' recommendations for visualising harm outcomes in publications of randomised controlled trials?

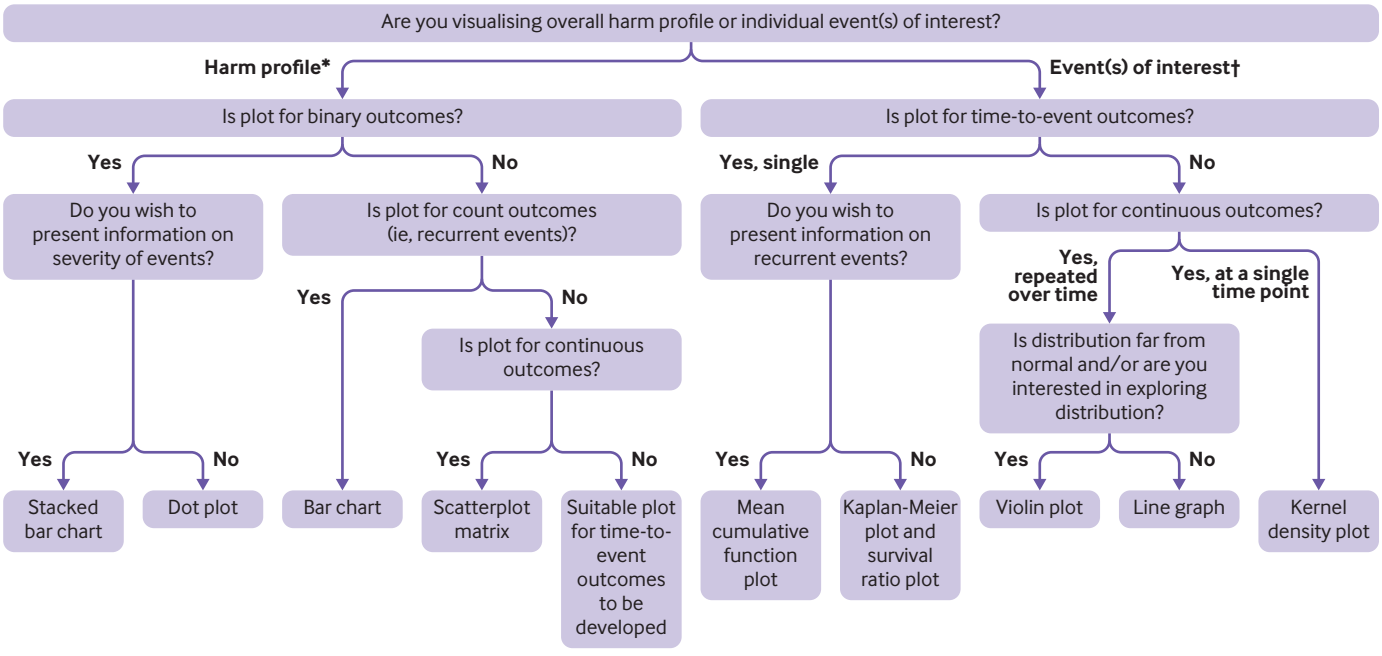
Methods A series of consensus meetings was held with 20 statisticians from 15 UK Clinical Research Collaboration registered clinical trials units, an academic health economist, an industry statistician, and a data graphics designer from *The BMJ*. Visualisations were primarily identified through a methodological review of statistical methods developed specifically to analyse harm outcomes. Consensus on visual recommendations was achieved (at least 60% of the available votes) over a series of three meetings with participants. Participants reviewed and critically appraised candidate visualisations against an agreed framework and voted on whether to endorse each visualisation. Scores marginally below this threshold (50-60%) were revisited until a consensus could be reached. Feedback from two clinicians was incorporated into the explanatory information provided in the recommendations to aid understanding and interpretation.

Study answer and limitations 28 visualisations were considered, of which 10 are recommended to researchers to consider in publications of main research findings. The choice of visualisations to present will depend on outcome type (eg, binary, count, time-to-event, or continuous) and the scenario (eg, summarising multiple emerging events or one event of interest). A decision tree to help trialists decide which visualisations to use is presented; however, the statistician and clinical trial team must ultimately decide the most appropriate visualisations for their data and objectives. Examples of each endorsed visualisation, along with example interpretation, potential limitations, and signposting to code for implementation across a range of standard statistical software are provided.

What this study adds Recommendations and tools to help researchers decide which visualisations to use are provided. Increasing the use of visualisations for harm outcomes in clinical trial manuscripts will provide clearer presentation of harm information and thus enable more informative interpretation, which is especially valuable for assessing the profile of harm.

Funding, competing interests, and data sharing See full paper on bmj.com for funding. No competing interests declared.

The datasets used in this analysis are available from GlaxoSmithKline via ClinicalStudyDataRequest.com, and the synthetic dataset example is available for download via associated Stata packages.



Decision tree for trialists. *Summary of harm outcomes collected. Individual events include individual emerging events (eg, adverse events indicative of harm) and prespecified events of interest. †Can include a single adverse event, single category of events that have been grouped together, or aggregated summary