Review of: "First long-term safety analysis of the ChAdOx1-nCoV-19 corona virus vaccine: results from a prospective observational study in priority vaccinated groups in North India"

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Potential competing interests: No potential competing interests to declare.

While much has been published from post-authorisation observational studies on the acute adverse events after Covid-19 vaccines there is a paucity of data on longer term safety outcomes obtained from the prospective follow up of cohorts vaccinated as part of a national vaccination programme. This study reports adverse events in a cohort of around 1500 recipients of the ChAdOx1-nCov-19 coronavirus vaccine manufactured by the Serum Institute of India (COVISHIELD). The study cohort was actively followed up by regular telephone calls over a one year post-vaccination period to identify new and persisting AESIs; participants were also asked to spontaneously report events to the study team.

The method for creation of the cohort and the interim results of the adverse events in the first 7 days post vaccination in 730 participants – all health care workers – were previously reported (ref 5 in the paper). In the current analysis, participants, who now include some elderly vaccine recipients, were followed out to 12 months for the occurrence of adverse events of special interest, including those that persist for at least a month and the results used to investigate risk factors for the occurrence of an AESI. The analysis of risk factors for reporting an AESI was done by binary logistic regression using covariates such as demographics, pre-existing comorbidities and history of Covid-19 before and after vaccination. The AESI were classified by System Organ Class (SOC) using MedDRA classifications.

The authors also recorded the occurrence of Covid-19 both before and after vaccination in the study cohort which was followed up during the second and third pandemic waves in India. While participants were asked to obtain a Covid-19 test in the event of symptoms suggesting SARS-CoV-2 infection, this was not enforced and left to the discretion of the participants to pursue.

The risk factor analysis identified the following that were significantly associated with the reporting of an AESI persisting for at least 4 weeks; being female, having a history of hypothyroidism and being vaccinated after having had Covid-19; adjusted odds ratios for reporting a persistent AESI were also raised for those with pre-existing cardiac disease or arthropathy though p values were 0.07 and 0.09 respectively.

The main limitation of this study is that it is reporting associations and given the study design it is difficult to infer causality. Those with pre-existing comorbidities may just have a lower threshold for reporting adverse events than those without such a history. Also the outcome in the binary logistic regression was any reported AESI which comprises a disparate

group of conditions with varying aetiologies and clinical significance. No information on the timing of events was provided in this analysis and will have included those occurring shortly after vaccination which may have a causal aetiology and those occurring with a longer latency whose causal association is difficult to assess without a matched control group. Similarly those that sought out a Covid-19 test for symptoms before the study began may also comprise individuals who are more likely to report an adverse event after vaccination. That there is likely to be selection bias in who elects to get tested is supported by the finding that those who reported that they had Covid-19 during the second wave were also more likely to report it during the third wave which is a biologically implausible finding, given other studies showing some protection from prior infection on acquiring a later infection with another variant. The authors mention a number of limitations in their study including lack of a control group and potential for recall bias as there was an interval of six months between the last two follow up telephone calls. With respect to recall bias the authors say that medical records were obtained for the majority of the diagnosed or serious AEs but based on the information given about study design this would only have been done for those who volunteered information about an adverse event.

While it is important that active follow up of vaccine recipients is done to obtain real world safety data, caution should be exercised when interpreting any associations that emerge because of the likelihood of reporting bias.