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The neurological safety of covid-19 vaccines

Real world evidence is broadly reassuring

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Leveraging data on 8.3 million people from two large electronic health record databases in the UK and Spain, Li and colleagues (doi:10.1136/bmj-2021-068373) studied the association between covid-19 vaccines, either vector based or mRNA, and immune mediated neurological outcomes.[1] Neither the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) nor the BNT162b2 (Pfizer-BioNTech) vaccine was associated with an increased risk of neurological adverse events. Conversely, increased risks of all studied neurological outcomes were seen after SARS-CoV-2 infection. However, the power to detect small or even moderate increases in rare neurological outcomes—such as Bell's palsy, encephalomyelitis, Guillain-Barré syndrome, and transverse myelitis—after vaccination was limited, despite the relatively large study population. Another key limitation acknowledged by the authors was lack of adjustment for patient characteristics other than age in the majority of the analyses. This might have led to overestimation of risks associated with SARS-CoV-2 infection, as patients with the infection had more comorbidity than the background population.

Concern about neurological events has been driven by small differences in event rates between trial arms in phase 3 vaccine trials,[2 3] and reports of spontaneous adverse events.[4 5] To explore such concerns properly, large scale epidemiological studies are needed, and only two such studies are available: the new study by Li and colleagues and a previous study by Patone and colleagues.[6] The latter found a slightly increased risk of Guillain-Barré syndrome and Bell's palsy associated with ChAdOx1 nCoV-19, and of haemorrhagic stroke with BNT162b2. In line with Li and colleagues' findings, the risks of all neurological outcomes in the 28 days after a positive SARS-CoV-2 test result were substantially higher.

Similarities between these studies include the self-controlled case series design and populations studied. The UK Clinical Practice Research Datalink (CPRD) cohort analysed by Li and colleagues is a subset of the larger UK dataset analysed by Patone and colleagues. It is not clear why the two analyses arrived at different conclusions about the risks of the ChAdOx1 nCoV-19 vaccine; however, Li and colleagues' smaller sample size and the resulting statistical uncertainty could be one explanation. Another might be found in the measurement of outcomes, which was mainly based on primary care diagnoses in the UK CPRD analysis, but on hospital admissions for neurological conditions in Patone and colleagues' study.

Identifying causes of discrepancies between epidemiological studies can be difficult, and we commend Li and colleagues for providing very detailed and interactive supplementary data, and for making their source code public through Github. Such measures to ensure transparency in the conduct of real world studies is important to the trustworthiness of biomedical science and should be a priority for all researchers performing these studies. An additional measure to facilitate transparency in observational research is the registration of study protocols at publicly available registries such as the European Union Register of Post-Authorisation Studies[7] or the Real World Evidence registry.[8]

From the two large scale studies currently available,[1 6] we can conclude: firstly, that mRNA based vaccines do not appear to be associated with an increased risk of neurological adverse events; secondly, that risks of Guillain-Barré syndrome and Bell's palsy are slightly increased after immunisation with ChAdOx1 nCoV; and, thirdly, that SARS-CoV-2 infection is associated with the highest risks across all neurological outcomes.

Importantly, all risks—even those observed after SARS-CoV-2 infection—are small in absolute terms for the single individual. Even small absolute risks can, however, lead to a substantial burden on the healthcare system in the context of mass vaccination and widespread infection. One remaining question is the slightly increased risk of stroke among female recipients of the mRNA vaccines reported by Patone and colleagues,[6] which, although smaller than the risks associated with SARS-CoV-2 infection, warrants further scrutiny.

Overall, the findings of both studies[1 6] are reassuring about the safety of the vaccines, particularly compared with the observed risks associated with SARS-CoV-2 infection. Neither study should therefore lead to any changes in communications to the public about the positive benefit-risk balance of vaccines. However, a specific and important communication challenge remains for individuals who develop a neurological complication shortly after vaccination, their families, and others hearing about their history. Reassuring them that the two events are likely unrelated will be difficult, even with the knowledge generated by these two large real world studies. Researchers and clinicians have a responsibility to discuss these findings with affected patients and their families, while at the same time acknowledging the inherent uncertainties in making patient level inferences from population level studies.

One approach would be to explain that although neurological conditions do occasionally occur shortly after covid-19 vaccination, good evidence from very large studies shows that these conditions are no more common among vaccinated people than among unvaccinated people. We may never be able to tell

exactly what caused an individual to develop a neurological condition, but covid-19 vaccination is a highly unlikely reason for most.

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