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Tom Nolan's research reviews—3 March 2022

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The lean green vaccine machine

Green Book, you're a modern masterpiece. You're in-depth, practical, clear, definitive; you're so easy to navigate it's often possible to find the answer to a patient's question about a vaccine in the same time it takes to pause thoughtfully and offer a few words of understanding. How many other medical references are known only by the colour of their cover (and headers and footnotes)? And not just any colour, but the colour of leaves and grass and Spotify. I love your 47 pages on covid vaccination that includes a nice flow chart for what to do for patients who had a reaction to the first vaccine. For anaphylaxis, you say "many individuals do not react when given a dose of the same vaccine." But, oh green and knowledgeable one, how many don't react?

You don't seem to know, but *JAMA Internal Medicine* does: around 5%. A systematic review and meta-analysis on the risk of second allergic reaction to SARS-CoV-2 vaccines found 22 published studies that included 78 people who had a severe immediate allergic reaction after an mRNA covid vaccine. Of those, only four had the same reaction to a second dose.

JAMA Intern Med doi:10.1001/jamaintern-med.2021.8515

Anti-nucleocapsid IgG goes from hero to sero

Remember when we were reassured that things would be better once we had serology tests for covid-19? This was one of the many messages of hope from those early daily covid briefings in 2020 that didn't come true: the serology tests duly came along but were of little clinical value. This left the tests mainly in the hands of epidemiologists to use as a marker for prior covid-19 infection. However, measuring IgG against the SARS-CoV-2 spike protein is of limited value in populations with high vaccination rates—since both vaccination and infection will (usually) give you a positive result. Enter anti-nucleocapsid IgG, which, because it's nothing to do with the spike protein, should in theory be positive only in those who have had a previous infection. Unfortunately, findings from this seroprevalence study suggest it isn't a good marker of prior infection. The study, of covid seroprevalence in the Guateng province of South Africa before the omicron wave, found remarkably high levels of SARS-CoV-2 seropositivity despite a relatively low vaccination uptake. Among those who were unvaccinated, the overall prevalence of anti-spike or anti-nucleocapsid IgG seropositivity was 68.4%, but the prevalence of anti-nucleocapsid IgG seropositivity alone was only 39.7%—showing that it has a low sensitivity as a marker of past covid-19 infection.

N Engl J Med doi:10.1056/NEJMo2119658

More IFR estimates

I remember spending quite a lot of time studying infection fatality rates in the early days of the pandemic: more for existential than clinical reasons, trying to figure out how dire a situation we were in. The *Lancet* has just published the latest stab at estimating infection fatality rates during the pre-vaccine era, by matching seroprevalence studies to covid-19 mortality rates. The study is larger than previous ones, using data from over 3000 surveys across 190 countries and used mortality rates that estimated total covid-19 mortality rather than the generally less reliable death tallies. The paper includes overall infection fatality rates for every age from 1 year to 100 (mine was 0.18%, for a 65 year old it was 1.7%, for centenarians it was 43%), and for each country at three points during the year: globally, infection fatality rates dropped by about a third between 15 April 2020 and 1 January 2021. The authors also found that children under 5 years old may have been at higher risk than older children, although infection fatality rates estimates for all ages under 18 were under 0.01%.

Lancet doi:10.1016/S0140-6736(21)02867-1

Vitamin K and diabetes

A hazard ratio for mortality of 0.78 and a P value of <0.001 makes you sit up and take note. This was one of the results from a retrospective cohort study of patients in Taiwan with atrial fibrillation and diabetes prescribed either a non-vitamin K antagonist oral anticoagulant (NOAC) or warfarin. The authors found similarly lower rates of microvascular and macrovascular complications among those taking NOACs. Unmeasured confounders such as body mass index, INR levels, renal function, and even glucose levels and other methodological limitations mean that the findings can't be taken at face value or applied in practice. But the authors argue that their findings are consistent with a plausible mechanism: studies have found that vitamin K may play a role in insulin sensitivity and glucose tolerance, so antagonising it with warfarin might not be helpful if you have diabetes. Hopefully some randomised controlled trial will one day offer more clinically applicable findings, but will anyone still be taking warfarin by then?

Ann Intern Med doi:10.7326/M21-3498

Antiseizure medication after cardiac arrest

About half of people admitted to critical care after an out-of-hospital cardiac arrest survive to hospital discharge, and only two thirds of these are discharged home. Might treating EEG abnormalities with antiseizure medication improve these outcomes in survivors of cardiac arrests in intensive care? An open-label randomised control trial in 11 intensive

care units in Belgium and the Netherlands recruited 172 patients who were comatose after (mostly out-of-hospital) cardiac arrest. All had abnormal EEGs showing rhythmic and periodic patterns—EEG changes that are seen in up to 35% of patients and are associated with poor neurological outcome. There was no difference in neurological outcome at three months between patients randomised to receive antiseizure medication and those given usual care. Overall mortality was 81%.

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