Friday Report: Issue 57

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COVID-19 Actuaries Response Group – Learn. Share. Educate. Influence.

COVID-19 is still one of the hottest topics for scientific papers and articles. The COVID-19 Actuaries Response Group provides a regular Friday update with a summary of key papers and articles.

Vaccines

Research is shifting to the effectiveness of vaccines against Omicron. In the meantime we report on newly released vaccine effectiveness studies against the 'pre-Omicron' variants.

Risks of heart conditions associated with COVID-19 vaccination or SARS-CoV-2 infection

A study published in Nature investigated hospital admission or death from myocarditis, pericarditis and cardiac arrhythmias in the 28 days following vaccination among over 38 million adults vaccinated in England between 1 December 2020 and 24 August 2021. Hospital admissions and deaths from these conditions were also investigated among over 3 million adults who tested positive for SARS-CoV-2.

The study estimated an additional 2-6 myocarditis events per 1 million people following a first dose of vaccination, varying by vaccine type. The study also estimated an additional 10 myocarditis events per 1 million people following a second dose of Moderna. This compares with an extra 40 myocarditis events per 1 million patients in the 28 days following a SARS-CoV-2 positive test.

The study also observed increased risks of pericarditis and cardiac arrhythmias following a positive SARS-CoV-2 test. Similar associations were not observed with any of the COVID-19 vaccines, apart from an increased risk of arrhythmia following a second dose of Moderna. Increased risk of myocarditis associated with the two mRNA vaccines was present only in those younger than 40.

Safety and immunogenicity of COVID-19 vaccines as a third dose

COV-BOOST is a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19. The 2,878 participants had already received either two doses of AstraZeneca (ChAd) or of Pfizer/BioNTech (BNT) vaccines 10-12 weeks earlier. Either a control or one of the vaccines listed below were administered as a third dose:

- Novavax (full or half dose)
- AstraZeneca
- Pfizer/BioNTech
- Valneva (full or half dose)
- J&J
- Moderna
- CureVac

Neutralising responses were investigated against pseudotype and live virus versions of Wild-type, Delta and Beta.

All study vaccines boosted antibody and neutralising responses after ChAd/ChAd initial course and all except one after BNT/BNT, with no safety concerns. The exception was a half dose of Valneva after BNT/BNT. Participants receiving the Pfizer/BioNTech and Moderna vaccines that are being rolled out in the UK showed 3 to 4x the in vitro neutralising response to Delta compared with participants who were controls.

Protection against SARS-CoV-2 infection conferred by COVID-19 vaccination and previous infection

A pre-print of results from the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study has been released. The study cohort consists of 35,768 UK healthcare workers who undergo fortnightly asymptomatic PCR testing. 27% had a prior SARS-CoV-2 infection and 97% had received two vaccination doses, mostly Pfizer-BioNTech (BNT162b2).

There were 2,747 primary infections and 210 reinfections between 7 December 2020 and 21 September 2021. Adjusted vaccine effectiveness against infection decreased from 81% (95% CI 68%-89%) 14-73 days after dose 2 to 46% (95% CI 22%-63%) more than 6 months after.

Protection from infection-acquired immunity showed evidence of waning in unvaccinated follow-up but remained consistently over 90% in those who received two doses of vaccine, even in those infected over 15-months ago.

The authors conclude that two doses of BNT162b2 vaccination induce high short-term protection to SARS-CoV-2 infection, which wanes significantly after six months. Infection-acquired immunity boosted with vaccination remains high over a year after infection. They state that boosters will be essential to maintain protection in people who are vaccinated in the absence of primary infection.

Vaccine effectiveness against Critical Care admission

In our previous Friday report, we shared ICNARC's analysis of rates of admission to critical care by vaccination status for patients admitted between 1 May 2021 and 31 July 2021. This data has now been updated to include patients admitted up to 15 November 2021.

The vaccinated population size was determined using the NIMS database and the unvaccinated population was estimated as the mid-2020 ONS population estimate less the number of people vaccinated.

Age group	Unvaccinated vs 2-dose vaccinated critical care admission rate multiple
18-29	9
30-39	13
40-49	13
50-59	28
60-69	58
70+	27

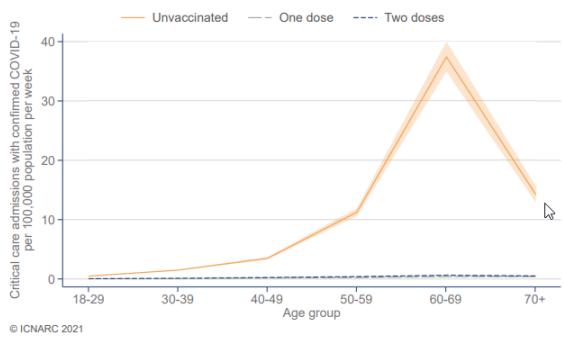


Figure 26. Rate of admission to critical care with confirmed COVID-19 by vaccination status for patients admitted 1 May 2021 to 15 November 2021

Rate of admission to critical care with confirmed COVID-19 per 100,000 population per week (with 95% confidence interval) by vaccination status, assessed at 14 days prior to the positive COVID-19 test.

Booster vaccine effectiveness against mortality

Data from members of Clalit Health Services in Israel was studied to evaluate the impact of BNT162b2 vaccine boosters on mortality among people aged 50 or older. Researchers found a 90% reduction in mortality among those who had received a booster.

All members had received two doses of BNT162b2 at least 5 months earlier. The mortality due to COVID-19 among participants who received the booster during the study period (booster group) was compared with that among participants who did not receive the booster (non-booster group). Adjustment was made for sociodemographic factors and comorbidities.

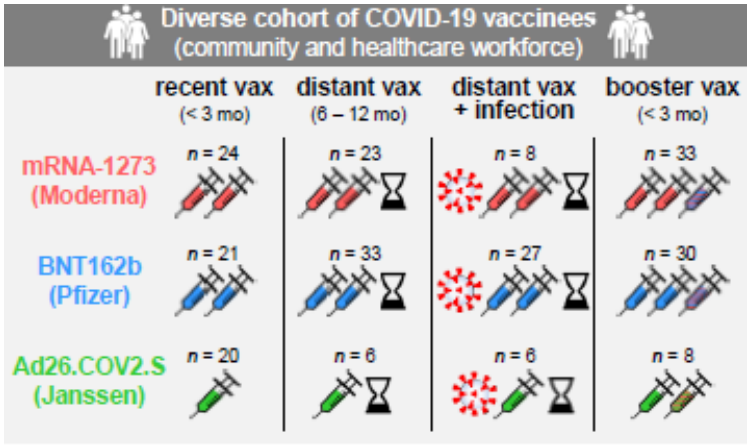
A total of 843,208 participants were included and 90% received a booster during the 54-day study period. 65 participants in the booster group died due to COVID-19, compared with 137 participants in the non-booster group. The adjusted hazard ratio for death due to COVID-19 in the booster group, as compared with the non-booster group, was 0.10 (95% CI 0.07 to 0.14; P<0.001).

COVID-19 vaccine boosters and Omicron

The effect of vaccines and vaccine boosters on the Omicron variant has been investigated with results published in this recent pre-print.

This variant harbors up to 59 mutations throughout its genome, with as many as 36 of these occurring within the spike protein, the mediator of host cell entry and the main target of neutralizing antibodies, including 15 within the receptor binding domain (RBD) region.

This study involved a cohort of 239 COVID-19 vaccinees who were healthcare workers and/or community dwellers from Boston or Chelsea, Massachusetts. The cohort were stratified as displayed in the next figure:



Neutralization analysis was undertaken on blood samples taken from the participants to assess SARS-CoV-2 variant neutralization in wild type, Delta, and Omicron SARS-CoV-2 pseudoviruses.

The following was reported:

- The recently vaccinated with Pfizer or Moderna achieved substantially higher wild type neutralization titers than Janssen
- Individuals vaccinated >6 months prior exhibited substantially lower but mostly detectable wild type neutralization

- Prior history of infection was associated with high levels of wild type neutralization titers even in distantly vaccinated individuals, particularly with Janssen
- Recently boosted individuals exhibited among the highest neutralization titers against wild type SARS-CoV-2 pseudovirus
- Neutralization of Delta variant pseudovirus was decreased relative to wild type for all subgroups
- Delta neutralization was detectable and only modestly decreased in recently vaccinated, previously infected, and recently boosted vaccinees
- Omicron neutralization was dramatically decreased among all subgroups, including recently vaccinated Moderna and Pfizer recipients, which demonstrated a complete loss of neutralization in >50% of individuals
- Previously infected vaccinees also had a substantial decrease in Omicron neutralization titer, however, recently boosted vaccinees exhibited potent neutralization of Omicron variant pseudovirus that was only moderately decreased relative to wild type neutralization
- Omicron pseudovirus exhibited greater infection of target cells regardless of concentration compared to all other tested variants. Omicron was 4-fold more infectious than wild type and 2-fold more infectious than Delta

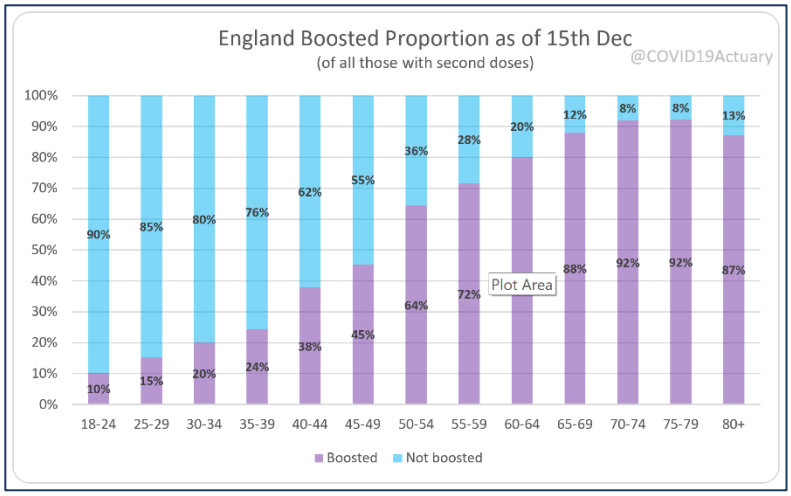
Overall, this study highlights the importance of boosters to broaden neutralizing antibody responses against highly divergent SARS-CoV-2 variants

Boosters Speed-up

Given the threat posed by Omicron, readers will be aware of the announcement on 12 December by the Prime Minister to dramatically accelerate the booster programme, with the intention to offer all eligible adults a booster by the end of the year.

We've been tracking progress in England since the programme started, and this week has seen week on week increases ranging from 50% to 80% each day, with record daily figures each day too. As of Thursday's reported data there are 16m adults who have yet to be boosted but are or will become eligible by the year end. Realistically not all will come forward, but if we get 90% take-up, that would represent around 12.2m remaining to do over 14 days (excluding December 25th/26th). Some of course will also be unable to have their jab because of recent infection.

By age, the latest proportions boosted of all those who have been double jabbed is shown below, with very encouraging take-up rates in the oldest age groups. (Note that above age 80, there is a natural limit of around 94%, due to deaths since the second vaccination.)



Clinical and medical news

Molnupiravir

Molnupiravir is an antiviral drug which was originally developed to treat influenza. Molnupiravir was approved for medical use in the United Kingdom in November 2021 to treat COVID-19. This drug has yet to receive an emergency use authorisation from the US Food and Drug Administration (FDA).

Full trial data submitted to the FDA suggest that molnupiravir is less effective than originally thought (link). This data showed use of molnupiravir decreased the risk of hospitalization from COVID-19 by 30% — down from a 50% reduction observed early in the trial.

The initial study group included 762 people studied between May and early August. A second group included 646 people who received the same treatment (4 pills of either the antiviral or a placebo twice a day, for 5 consecutive days) between August and early October.

In the first group, participants' rate of hospitalization or death dropped by half if they took molnupiravir vs. placebo. In the second group, there was almost no difference in outcome for those on the antiviral compared with those on the placebo. This difference may be as a result of different variants in circulation during the two time periods, or differences between the trial groups' demographics or locations.

Despite this setback, the NHS is pushing ahead with the PANORAMIC study, run by the University of Oxford, that will recruit 10,000 higher risk patients to receive molnupiravir at home after a positive PCR test. The study will be open to those who are over age 50, or younger adults with a prior heart condition, and patients will receive either the oral anti-viral or a placebo in addition to appropriate current standard of care. Given that PANORAMIC stands for "Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community", the study certainly gets the prize for the most convoluted construction of a suitable acronym.

In addition, from 16th December molnupiravir will be available through the COVID Medicines Delivery Unit to those at highest risk of severe disease with COVID outside the study, such as those who are immunocompromised or those with Down's syndrome. These restrictions will focus this relatively expensive treatment (approx. $700 per course) on those most in need and improve the likelihood that courses of treatment are completed and adequately monitored.

Omicron disease severity

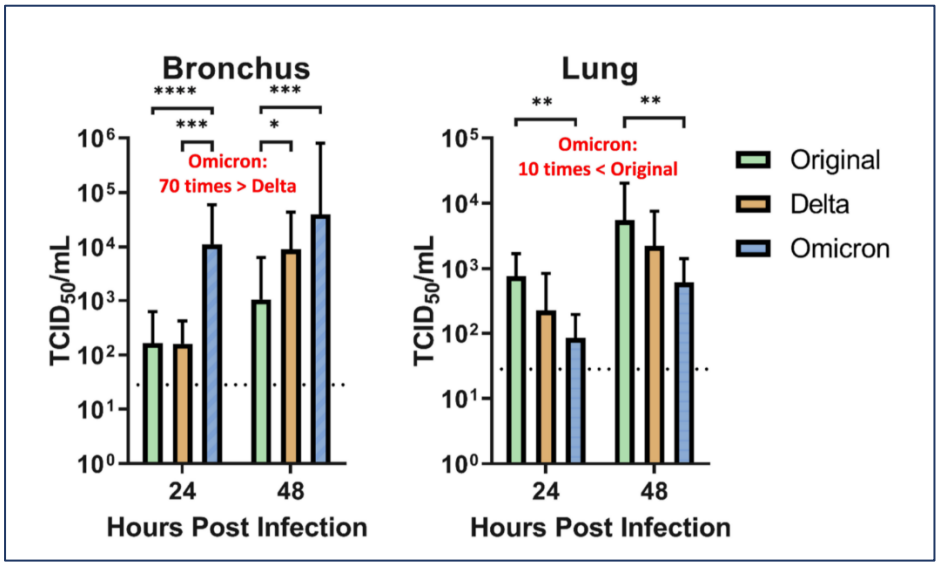
Initial findings from a yet-to-be published study provide some early insights into the potential transmissibility and severity of the new SARS-CoV-2 variant of concern, Omicron.

The study, led by researchers from the LKS Faculty of Medicine at The University of Hong Kong (HKUMed), used a technique pioneered by the faculty to examine emerging viral infections. This technique, known as ex vivo culture, involves analysing lung tissue specimens.

In the press release, Dr Michael Chan Chi-wai, Associate Professor of School of Public Health and Principal Investigator, describes how the team were able to isolate the Omicron SARS-CoV-2 variant and to compare infection with the original SARS-CoV-2 from 2020, and the Delta variant.

In particular, the team looked at the rate of viral replication of Omicron compared to the previous variants in the bronchus, the tubes that leads from the trachea, (windpipe), to the lungs, and the lungs themselves.

In the bronchus, Omicron was found to replicate much faster than Delta and the original SARS-CoV-2 virus, up to 70 times faster. However, this replication rate in the lungs was 10 times lower in the lungs when comparing Omicron to the previous variants. This may suggest lower severity of disease.



Modelling

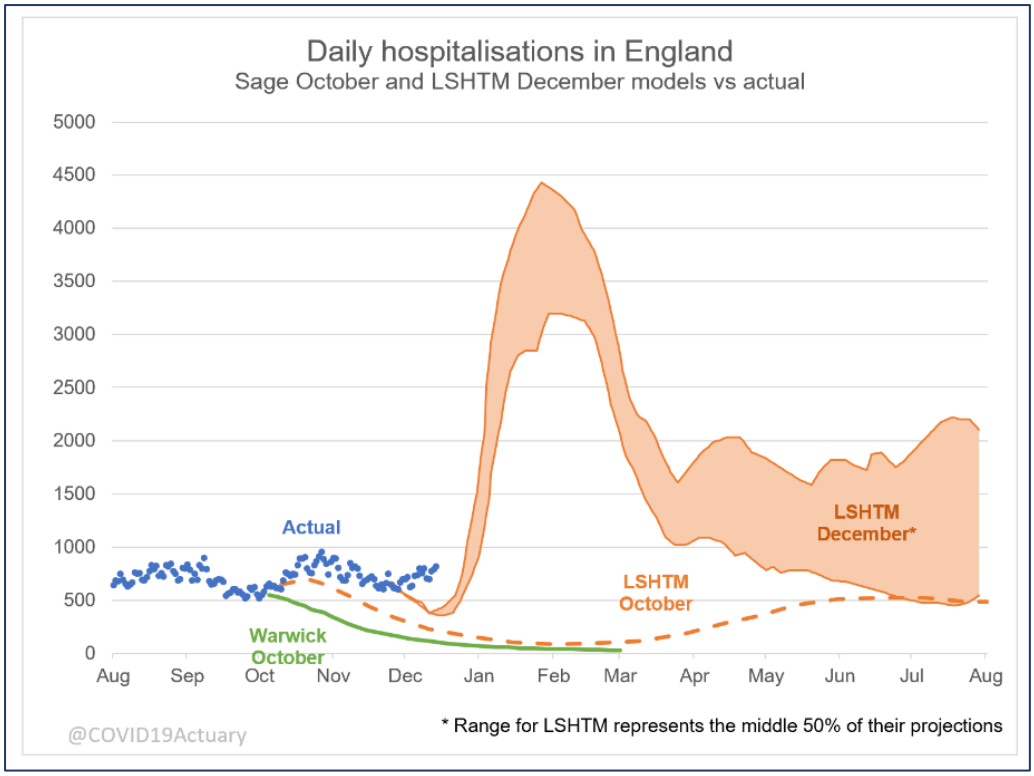
We first monitored actual hospitalisations in England against projections in Friday Report 48 (link). This updated our bulletin (link) summarising papers from London School of Hygiene and Tropical Medicine (LSHTM), Warwick University and Imperial College London which modelled the move to step 4.

We noted in Friday Report 54 that the group of universities had published updated papers, setting out projections from October through the winter, and focussing on the impact of boosters and the mixing behaviour of individuals.

The papers set out a large range of possible outcomes – the trajectories in the chart below show two example projections from these papers.

Following the discovery of the Omicron variant, on 11 December, LSHTM issued an updated report (link), modelling the potential consequences of the variant on transmission and health outcomes in England. It's worth noting that this is currently a preprint, and has not yet been peer reviewed. Again, there are a number of projections produced, depending on the extent of immune escape, various aspects of the booster rollout, and the reintroduction of control measures. In the chart, we have illustrated the numbers of hospitalisations projected, based on their "High immune escape, High booster efficacy" scenario.

In their new paper, LSHTM did not publish a single projection for each scenario, instead they have produced a range based on their simulations. In the chart, we have illustrated the middle 50% of their projections (that is, based on their modelling, there is a 25% chance of an outcome better than the simulation, and 25% worse).



It is clear that, based on the modelling, the Omicron variant has significantly increased the projected number of hospitalisations expected. We will continue to monitor how actual experience lines up with this projection.

Omicron Immune Escape (link)

A paper by Imperial College estimates that Omicron is 5.4 times more likely than Delta to result in a reinfection, suggesting a much higher immune escape than previous variants.

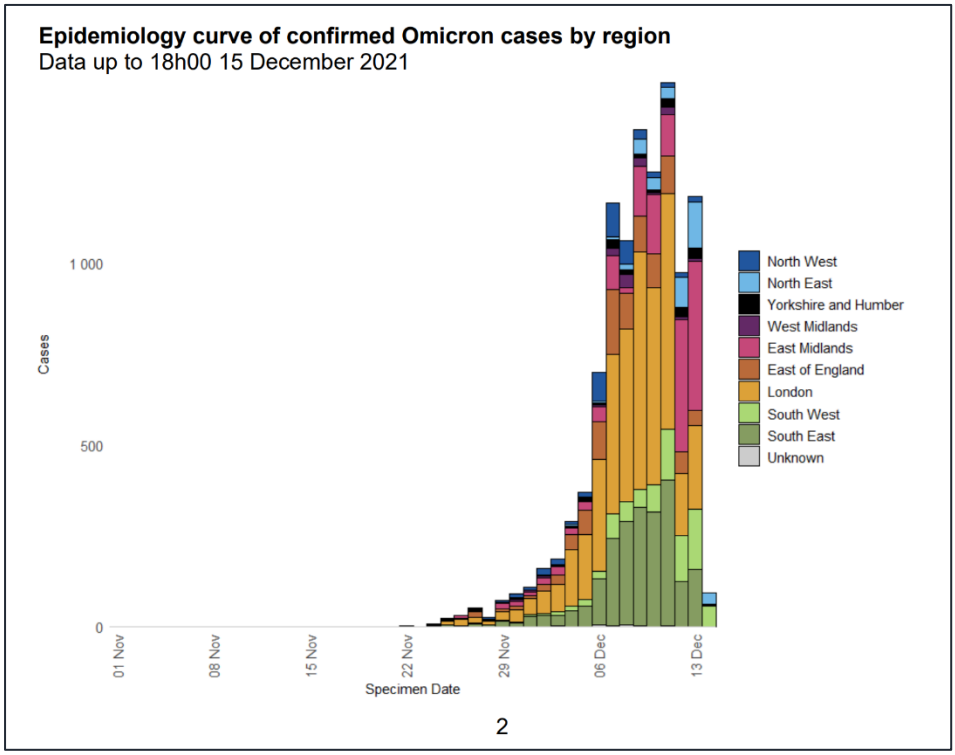
It also estimates the likely impact of immune escape on vaccine efficacy, looking at the situation after two and three doses. The results are consistent with other messaging that prior to Omicron, a third dose is highly effective in increasing immunity. A similar pattern is seen for Omicron although the absolute levels of efficacy are reduced after both 2 and 3 doses, again consistent with other reports.

Vaccination category	S+	S-	Mean delay since last dose (days)	Hazard ratio	Delta VE (%)	Omicron VE (%)	p-value
None	49716	1547	-	1			-
AZ:D1:<21	3	0	4	-			0.936
AZ:D1:21+	832	34	233	1.16 (0.89-1.51)			0.266
AZ:D2:<14	65	7	6	2.62 (1.5-4.61)	46 (44.8-47.2)	-42 (-154-21)	<1e-3
AZ:D2:14+	32887	1676	178	1.86 (1.74-1.98)	25 (24.3-25.7)	-39 (-50--30)	<1e-6
AZ:D3:<14	4926	250	5	1.86 (1.67-2.08)	53.9 (52.5-55.2)	14 (1-25)	<1e-6
AZ:D3:14+	1192	230	36	4.32 (3.84-4.85)	89.7 (88.9-90.4)	55 (46-63)	<1e-6
PF:D1:<21	1250	44	9	1.02 (0.81-1.28)			0.866
PF:D1:21+	6706	362	90	1.46 (1.34-1.6)	33.1 (32.7-33.6)	2 (-7-11)	<1e-6
PF:D2:<14	391	28	5	1.36 (1.04-1.78)	66.7 (66.2-67.3)	55 (40-66)	0.026
PF:D2:14+	17544	2888	141	2.68 (2.54-2.83)	55.9 (55.5-56.3)	-18 (-26--11)	<1e-6
PF:D3:<14	890	60	6	2.49 (2.06-3.01)	65.4 (64.5-66.4)	14 (-7-31)	<1e-6
PF:D3:14+	1801	288	48	4.07 (3.66-4.51)	88.6 (88.1-89.1)	54 (46-60)	<1e-6

Data

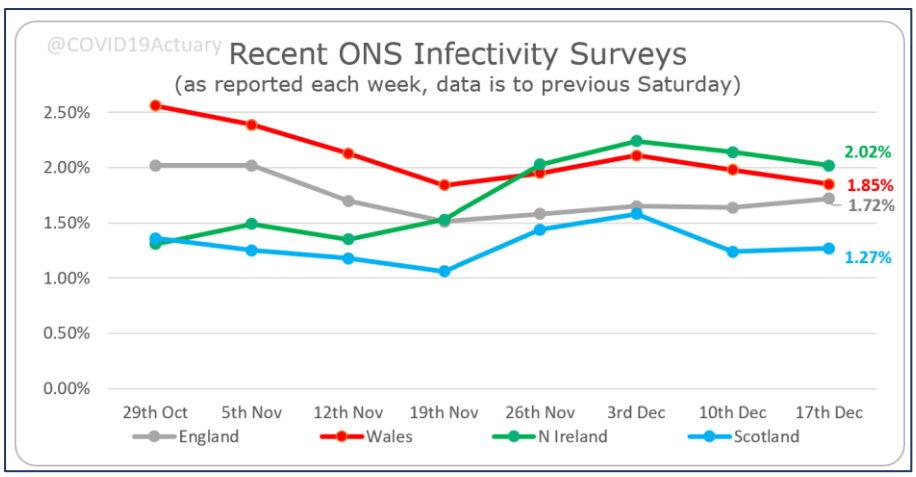
Omicron Daily Statistical Update (link)

The UKHSA has started publishing a short daily update on probable and confirmed Omicron cases. As of 15th Dec there were a cumulative 37,430 probable cases (identified as S-gene target failure cases), up 50% on the previous day, showing the rapid rate of growth we are currently experiencing.



ONS Infection Study (link)

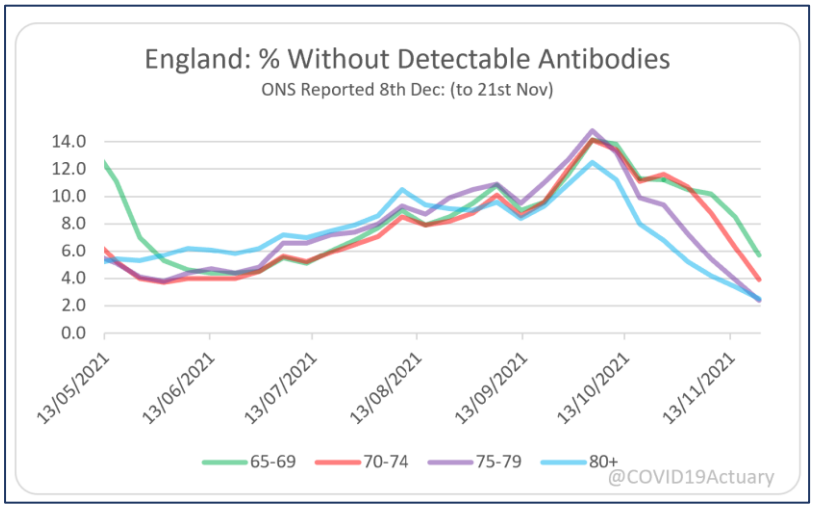
The latest infection study from the ONS is yet to show any clear sign of the recent increase in infections that have been reported via the daily "cases" data. This isn't surprising as there is a considerable lag inherent in the data, firstly because the latest data points relate to an average over the week of 5 to 11 December, and secondly because the survey measures prevalence, not new infections – prevalence will be a result of infections acquired over the previous two weeks.



ONS Antibody Study (link)

The latest fortnightly antibody study from the ONS shows overall levels still in the mid 90% range, and generally increasing by around 1.5% since the previous study. Of particular interest is the trend at older ages, where the proportion of those without detectable antibodies has moved exactly as one would expect following the booster programme, with increases after immunity waned since the second dose reversed. Encouragingly, proportions are reaching even lower levels than immediately after the second dose, suggesting (at least in a pre-Omicron world) that the booster programme is enhancing, rather than simply restoring, levels of immunity.

As usual the study reminds us that the levels of immunity are determined by several factors, and that this is just one measure that is useful in understanding overall population immunity.



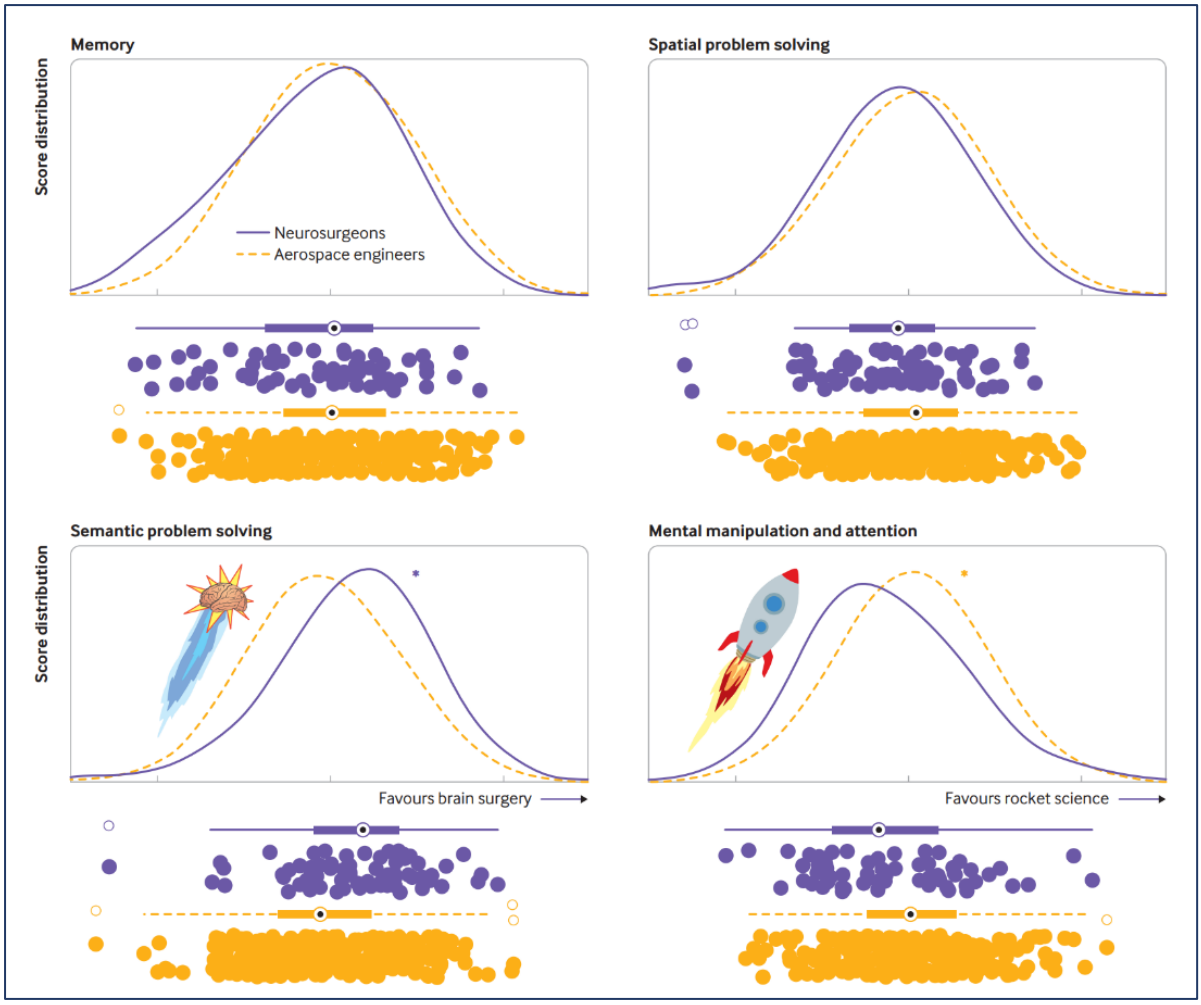
And Finally …

It's Not Rocket Science!

Since the start of the pandemic we've got to used to reading and reviewing papers from publications such as the BMJ, and often grappling with medical and epidemiological concepts that will have previously been unfamiliar to some of us.

So a recent paper (link) which considered the relative cognitive abilities of two professions, focusing on aeronautical engineers and neurosurgeons, attracted our attention. These two professions were chosen as they are often used when describing something that isn't actually that complex ("It's not brain surgery" being the other phrase.)

The conclusion, when the two professions were compared against the wider population is that maybe they are unduly placed on a pedestal with these phrases, and suggests other "profession neutral" alternatives such a "It's a Walk in the Park". It also hints that other professions might be equally worthy candidates and that further work might widen the scope of the study. Maybe that's a challenge that actuaries should step up to, although what an appropriate phrase might be, we'll leave to your imagination.



And Even More Finally …

It's our last Friday Report before the Christmas and New Year break, and we'll return on January 7th. The editorial team would like to wish all readers a happy and safe holiday period, and let's all hope that 2022 sees a return to a more normal situation before too long.

17 December 2021