Friday Report: Issue 63

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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 bi-weekly Friday update with a summary of key papers, articles and data.

Vaccines

Vaccine safety surveillance in the United States (link)

The results of a CDC-funded study into the safety of mRNA vaccines were published in The Lancet on 7 March. The study compared the number of adverse events reported via the VAERS and v-safe reporting systems with the over 298 million doses administered between December 2020 and June 2021.

VAERS is a long-standing US passive reporting system for adverse events relating to vaccines and is co-administered by the FDA and the CDC. VAERS data alone generally cannot establish causality between vaccination and adverse events, so researchers look for unusual patterns for early warnings.

There were 340,522 VAERS reports of which:

- 92.1% were non-serious
- 6.6% were serious but not fatal
- 1.3% were deaths

The v-safe system was developed specifically for the COVID-19 vaccine roll out. v-safe participants receive regular text messages that link to web-based health check-in surveys following vaccination. A limitation of this system is the need for smartphone access which can bias the participation demographics. Results from this system for the first 7 days after each dose are reported in this study. Reactions were more commonly reported after the second than the first dose.

Event	Dose 1	Dose 2
Participant count	6.78 million	4.07 million
Injection site reaction	68.6%	71.7%
Systemic reaction *(*)*	52.7%	70.8%
Unable to do normal activity	9.7%	26.5%
Sought medical care	0.8%	0.9%
Hospitalisations	0.03%	0.04%

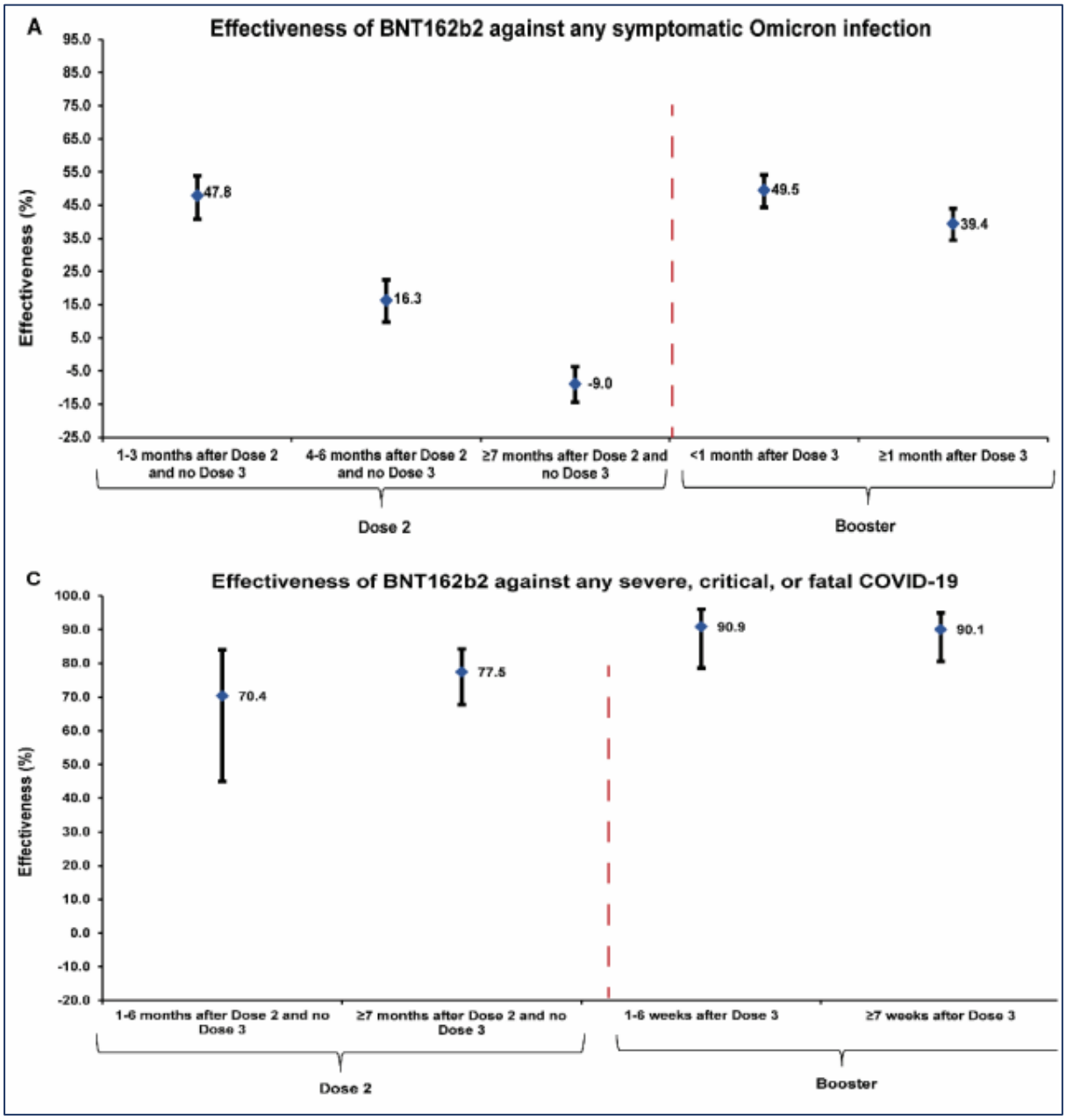
(*) e.g. fatigue, headache

The authors conclude that most reported events were mild and temporary and were consistent with results from pre-authorisation clinical trials.

Duration of mRNA vaccine protection against Omicron in Qatar (link)

A pre-print study used a matched, test-negative, case-control study to estimate duration of protection of mRNA COVID-19 vaccines, after the second dose and after a third/booster dose, against BA.1 and BA.2 infections in Qatar's population. Vaccinated and unvaccinated participants were matched on sex, age group, nationality and week of PCR test.

The authors found that mRNA vaccines provide only moderate and short-lived protection against symptomatic Omicron infection, with no discernable differences in protection against either the BA.1 or BA.2 subvariants. Vaccine protection against severe COVID-19 outcomes was bewteen 70% and 80% after dose 2 with no sign of waning after 6 months. The protection was more robust (at over 90%) after a booster dose.



COVID-19 vaccination: The road ahead (link)

This interesting article in Science looks at the success of the first generation of SARS-CoV-2 vaccines (noting the issues around inequities in distribution) and considers the remaining challenges and likely development of future vaccines.

The authors note that policy-makers need to be persuaded that vaccine equity is not just altruistic but necessary to limit the emergence of further variants. Looking to the future, they consider that a range of strategies is likely to emerge, ranging from frequent first-generation boosters to pan-coronavirus coverage from further developments in advanced new technologies.

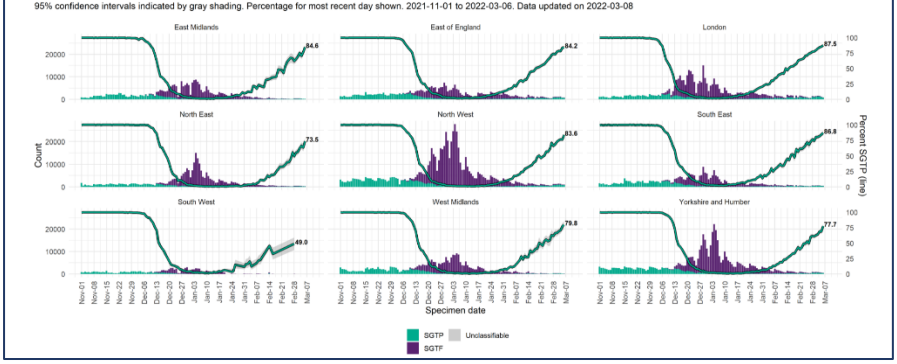
Future protective immunity approach	Pros	Cons
Stop boosting and rely on existing memory	Cheap, simple; all rely on existing primed immunity	Immunity likely to wane; high probability of long-duration COVID-19 waves
Homologous first-generation spike vaccine boosters frequently (as needed)	Simple, safe, established, with supportive evidence of short-term protection against VOC	May be expensive (depending on which platforms); may be increasingly suboptimal against immune-selected variants; suboptimal immune boosting relative to heterologous boosters
Heterologous first-generation spike vaccine boosters frequently (as needed)	Simple, safe, established, with supportive evidence of short-term protection against VOC; strong supportive evidence for enhanced immunity, including the ability to rescue responses in those who may initially have received weaker vaccines	May be expensive (depending on which platforms); may be increasingly suboptimal against oncoming immune-selected variants
As above, but using spike boosters based on wider rollout of **second-generation** production platforms, e.g., DNA vaccines, self-amplifying RNA, recombinant protein with adjuvant	Likely to be effective, globally scalable, cheap, and therefore advantageous for global coverage	Little data thus far in large-scale heterologous boosting protocols
First-generation platforms modified for **specific** VOC spike inserts	Likely to be highly effective against a given VOC; simple, safe, established	VOC waves tend to arise considerably faster than new vaccines can be modified and tested; unpredictability of protective phenotype due to prior imprinting; wave-specific and lacks future-proofing
First-generation platforms modified for **polyvalent** VOC spike inserts	Likely to be highly effective against multiple VOCs; potential for global relevance; simple, safe, established	Unpredictability of protective phenotype due to prior imprinting; lacks future-proofing
Boost with a wider viral immunome: **Polyvalent adjuvanted proteins**	Accessible technologies; Enhanced potential to avoid immune evasion mutants	Lack of strong evidence to date for additional protection through non-spike immunogens; lack of data in heterologous protocols to date
Boost with a wider viral immunome: **Whole inactive virus**	Accessible with much prior data and production line infrastructure and safety; immunogen-agnostic potential to prime with much of the viral immunome; adaptability to modification for oncoming VOCs	In some cases, whole inactivated virus has been less immunogenic; would not give faithful expression of the full proteome as seen in infection
Boost with **live attenuated virus** carrying polyvalent spike for lifelong durability, e.g., YF17 platform	Good prior track record of YF17D platform	Relatively untried; greater safety concerns
Sequential immunization with spike from SARS-CoV clades for pan-coronavirus coverage	Potential for completely future-proofed pan-coronavirus protection	Would need further development; potential for unpredicted effects of immune imprinting
Immunization with **adjuvanted RBD nanoparticles** for pan-coronavirus coverage	Potential for completely future-proofed pan-coronavirus protection	Would need further development; potential for unpredicted effects of immune imprinting

Variants

BA.2 Growth (link)

The latest Variant Technical Briefing reports that the BA.2 subvariant of Omicron has continued to take over as the dominant strain, increasing from 52% on February 20th to 83% on March 6th. With this data already being 12 days out of date, we can expect the figure to be even higher now.

Figure 4. Number of COVID-19 cases with SGTP/SGTF by day, among those tested in TaqPath labs by region of residence as of 8 March 2022 (95% confidence intervals indicated by grey shading. Percentage for most recent day shown) *
(Find accessible data used in this graph in underlying data.)



Analysis of test and trace data suggests that the secondary attack rate of BA.2 is around 26% higher than BA.1 in both household and non-household settings. A slightly more positive note is that there is still no evidence to suggest that infection with BA.2 results in worse outcomes, although of course higher transmissibility will result in more infections, which will translate into higher hospital admissions and potentially deaths.

Relative risk of severe outcomes for Omicron vs Delta (link)

A large population-based study from England used COVID-19 cases linked to vaccination, hospital and mortality datasets to compare the risk of these severe outcomes for Omicron vs Delta.

In the six weeks between 29 November 2021 and 9 January 2022, 4.1 million COVID-19 cases were detected, of which 1.5 million (37%) had available variant classification data and met the criteria to be included in the study. The relative risk of hospital attendance or admission within 14 days, or death within 28 days after confirmed infection, was estimated using proportional hazards regression. The analyses took into account test date, age, ethnicity, residential region, sex, index of multiple deprivation decile and evidence of a previous infection.

Omicron infection was found to have substantially fewer severe outcomes than for Delta infection.

The hazard ratios for Omicron vs Delta for each of the outcomes were as follows (95% confidence intervals in brackets):

- Hospital attendance: 0.56 (0.54–0.58)
- Hospital admission: 0.41 (0.39–0.43)
- Death: 0.31 (0.26–0.37)

There was significant variation by age with a U-shaped result for hospital attendance and admission. Among children, risk of hospital admission and attendance was similar for both variants and the authors suggest that this more likely reflects cautious hospital admission practice for children with fever and upper respiratory symptoms rather than inherently more severe Omicron disease.

The study shows greater reduction in risk for Omicron vs Delta among unvaccinated individuals. The authors explain that that there is a larger reduction in intrinsic severity which is counterbalanced by a reduction in vaccine effectiveness for Omicron vs Delta.

The study also showed that previous SARS-CoV-2 infection offered some protection in unvaccinated individuals.

Booster vaccination was highly protective against hospitalisation and death in Omicron cases. The hazard ratio for hospital admission 8–11 weeks post-booster vs unvaccinated was 0.22 (0·20–0·24). The protection did not vary by the type of vaccine used for doses 1 and 2.

Clinical and medical news

Evusheld Approval Offers Protection for those with Low Immunity (link)

The medicines regulator in the UK, MHRA has approved a medicine developed by AstraZeneca that will provide protection for those for whom vaccination is unlikely to be beneficial (such as the immunosupressed), or who cannot have the vaccine for clinical reasons.

The medicine is a combination of tixagevimab and cilgavimab, and should be given as two injections into a muscle by a healthcare professional. The patient should be free of infection and at the time of injection should not have had recent known exposure to someone infected. It is expected to be beneficial for at least 6 months before a further dose is required. The announcement cites an efficacy of 77% against symptomatic infection, although it cautions that further study is needed to assess efficacy against Omicron.

Finally the note clarifies that Evusheld is only for those for whom vaccination is not recommended, which appears to be an attempt to pre-empt requests from those who for whatever reason have chosen not to be vaccinated.

More Evidence that Ivermectin Doesn't Improve Outcomes (link)

A study of just under 1,500 patients in a Peruvian hospital between April and August 2020 has suggested that, far from improving mortality, Ivermectin was associated with worse outcomes, with hydroxychloroquine – another oft-touted treatment – offering no improvement.

In contrast, the use of corticosteroids at moderate doses was associated with lower mortality. However, high doses were not associated with a better prognosis and in contrast appeared to result in higher mortality.

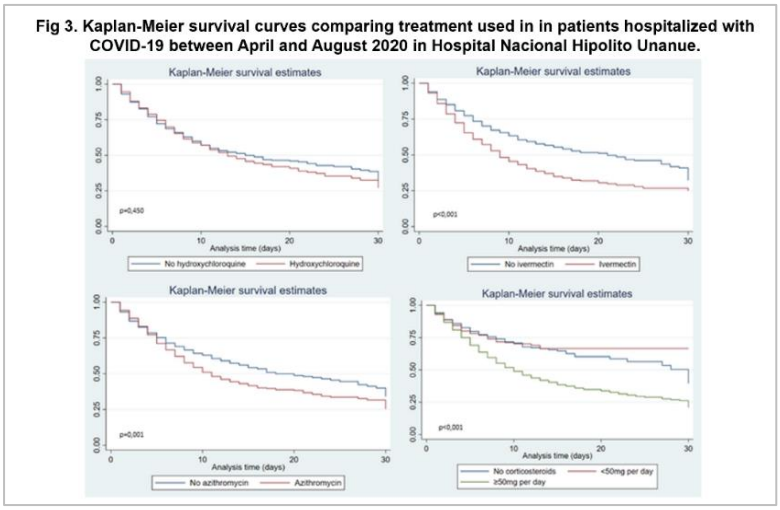


Fig 3. Kaplan-Meier survival curves comparing treatment used in in patients hospitalized with COVID-19 between April and August 2020 in Hospital Nacional Hipolito Unanue.

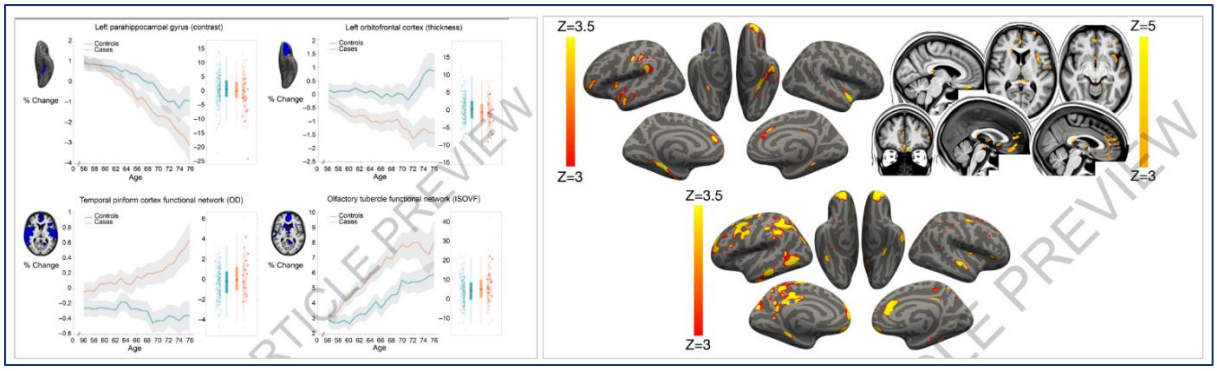
The hazard ratio for Ivermectin is quoted as 1.44 (CI: 1.18 – 1.76), whereas for corticosteroids at moderate doses is put at 0.56 (CI 0.37 – 0.86).

COVID Results in Reduction in Brain Function (link)

A study in Nature (still in pre-print form) and widely reported in the press suggests that COVID has a detrimental effect on the brain. Using the UK Biobank database, two longitudinal images were studied of 785 participants between ages 51 and 81. Of these participants, 401 had tested positive between the two scans. (Note that these were selected from a wider population – it does not mean that of an original population over 50% tested positive between two scans).

Notably, even after exclusion of the 15 patients who were hospitalised from COVID, there was still a noticeable difference in those who had tested positive against those who had not. The effect extended to cognitive function, and was not limited to physical changes to the brain.

The authors note that it is uncertain whether these changes are permanent or are likely to be reversed to some extent over time. Further studies will be carried out in due course to investigate this.



Omicron's Ability to Survive Longer Outside the Body than Expected (link)

A number of recent studies have questioned whether the Omicron spike may be thermodynamically less stable than earlier variant strains, which is surprising because the prior pattern of variant development appeared to be favouring variants with more stable spike proteins.

A new study suggests Omicron may be more stable on various types of surface than the original SARS-CoV-2 virus. The study in Hong Kong investigated smooth surfaces (stainless steel, polypropylene sheets and glass) and porous surfaces (facial tissue paper and printing paper).

The Omicron variant was recovered off smooth surfaces after 7 days of incubation, while the original SARS-CoV-2 spike protein was rarely recovered after 4 days. The Omicron variant was recoverable from porous surfaces after 30 minutes, whereas no original virus was detectable.

These findings show the importance of hand hygiene and frequent disinfection of touch surfaces in public areas.

Table: Stability of the ancestral SARS-CoV-2 and Omicron variant on different surfaces

Materials	Time of incubation	Ancestral SARS-CoV-2		Omicron variant	
		Mean $Log_{10}(TCID_{50}/ml)$ ± S.D.	% Reduction in viral titre	Mean $Log_{10}(TCID_{50}/ml)$ ± S.D.	% Reduction in viral titre
Stainless steel	0	5.02 ± 0.39	NA	5.35 ± 0.18	NA
	3 h	4.21 ± 0.36	85.15%	4.82 ± 0.23	69.78%
	6 h	3.73 ± 0.10	95.80%	4.62 ± 0.31	79.86%
	1 day	2.99 ± 0.17	99.21%	4.65 ± 0.17	80.28%
	2 days	2.08 ± 0.11	99.91%	4.51 ± 0.15	85.82%
	4 days	<	>99.93%	3.72 ± 0.12	97.72%
	7 days	<	>99.93%	3.58 ± 0.30	98.19%
Poly-propylene	0	4.85 ± 0.23	NA	5.43 ± 0.16	NA
	3 h	4.12 ± 0.19	81.72%	4.65 ± 0.34	81.27%
	6 h	3.53 ± 0.15	95.43%	4.33 ± 0.14	92.34%
	1 day	3.13 ± 0.34	97.86%	4.45 ± 0.23	89.25%
	2 days	*2.01 ± 0.10	>99.86%	4.34 ± 0.25	91.53%
	4 days	<	>99.88%	3.97 ± 0.19	96.48%
	7 days	<	>99.88%	2.95 ± 0.27	99.65%
Glass	0	5.10 ± 0.24	NA	5.65 ± 0.28	NA
	3 h	4.26 ± 0.05	86.79%	4.90 ± 0.15	83.62%
	6 h	3.69 ± 0.11	96.42%	4.52 ± 0.13	93.20%
	1 day	2.83 ± 0.13	99.49%	4.20 ± 0.01	96.84%
	2 days	2.14 ± 0.13	99.90%	4.43 ± 0.29	93.87%
	4 days	*1.96 ± 0.00	>99.93%	4.06 ± 0.16	97.64%
	7 days	<	>99.93%	3.76 ± 0.10	98.83%
Tissue paper	0	4.70 ± 0.22	NA	5.21 ± 0.14	NA
	5 min	3.85 ± 0.28	84.98%	4.64 ± 0.70	53.94%
	15 min	2.12 ± 0.14	99.75%	3.72 ± 1.22	72.99%
	30 min	<	>99.84%	2.92 ± 0.40	99.34%
	60 min	<	>99.84%	<	>99.95%
Printing paper	0	5.21 ± 0.00	NA	5.34 ± 0.13	NA
	5 min	2.69 ± 0.16	99.68%	3.26 ± 0.42	98.91%
	15 min	<	>99.94%	*2.20 ± 0.33	>99.91%
	30 min	<	>99.94%	*2.16 ± 0.36	>99.92%
	60 min	<	>99.94%	<	>99.96%

< All the triplicates were below detection limit of the $TCID_{50}$ assay.

*One or two out of three replicates were below detection limit of the $TCID_{50}$ assay.

Data

Estimating excess mortality (link)

A new study "Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21" was published in The Lancet. Looking at all-cause mortality for 74 countries and 266 subnational locations, they estimated that a total of 18.2 million people have died due to the pandemic (as measured by excess mortality), to be compared with just under 6 million reported COVID-19 deaths up to the end of 2021. The highest numbers of cumulative excess deaths were estimated in India, USA and Russia.

It is very difficult to produce estimates of excess mortality on a global scale, because not all countries provide data in the same format or to the same schedule. In particular, the figures used in this paper for certain countries (e.g. India) have been challenged.

We have previously reported on other estimates of global excess mortality calculations, in particular this guest blog (link).

Omicron (BA.1) Confirmed to be More Transmissible than Delta (link)

Real-world data studied by UKHSA in the short period from 5th to 11th December (when both Delta and Omicron were circulating in the UK) has confirmed the significantly increased transmissibility of Omicron. Secondary attack rates for Omicron in household settings were raised by around 40%, and by around 120% in non-household settings.

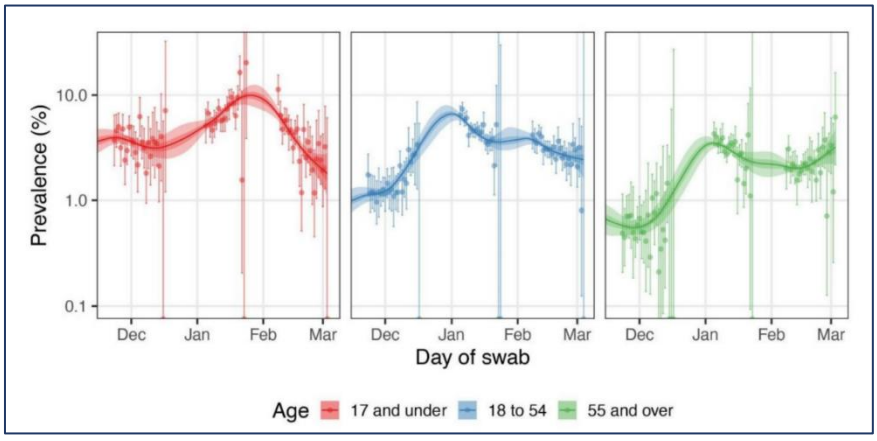
It was also noted that transmission was lower where the infected individual or named contact had received three doses of vaccine, but that this effect was diminished for Omicron in comparison with Delta.

At this early stage of the Omicron wave it was, of course, BA.1 in circulation. We noted earlier that BA.2 has a further transmission advantage in comparison to BA.1 (estimated by REACT in the study discussed next to increasing R by approximately 0.4). This further advantage will not be reflected in this study, but reinforces the extent to which the current variant circulating is much more contagious than Delta was just four months ago.

REACT Infection Study (link)

The latest update from Imperial College's REACT Study covers the period Feb 8th to March 3rd.

It shows a significant fall in prevalence from the previous round (4.4% to 2.9%).

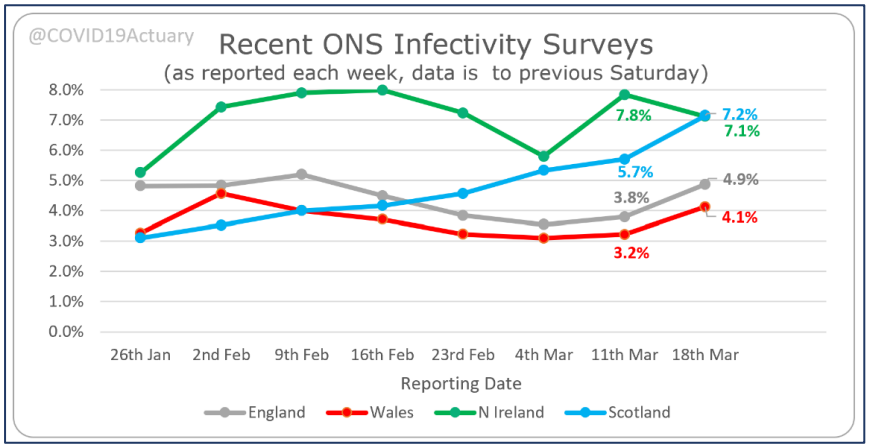


However, it notes that within the period there is evidence of infections levelling and starting to pick up again, most particularly in the older age groups (55+).

With confirmation that funding for REACT has been withdrawn from April, it's to be hoped that there will be at least one more report, which would be the study's 19th round. Unfortunately, with other indicators suggesting rising infection levels again, it is possible that the study will be going out on a high, but not in a positive way.

ONS Infection Study (link)

The latest estimates of prevalence show that there is now a clear upward trend again in England, Wales and (most notably) Scotland. The latest week shows increases in excess of 25% in each of these countries, and whilst Northern Ireland is down this week, the trend is upwards over the last two weeks (and note that it has much wider confidence intervals due to the smallest sample size, so any individual point needs to be taken with a degree of caution).



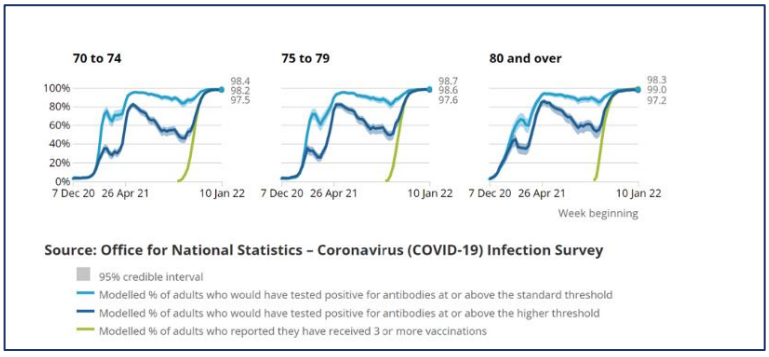
Of most concern is the increase seen in the oldest age group. The 70+ cohort has doubled in around a month from 2% to 4%, at a time when the effect of the booster is likely to be waning, it being around 5 months since this group was boosted.

It is likely that the rise of BA.2, along with the removal of all remaining restrictions in England and the majority elsewhere, is the driver for the increases that we are now seeing.

ONS Antibody Study (link)

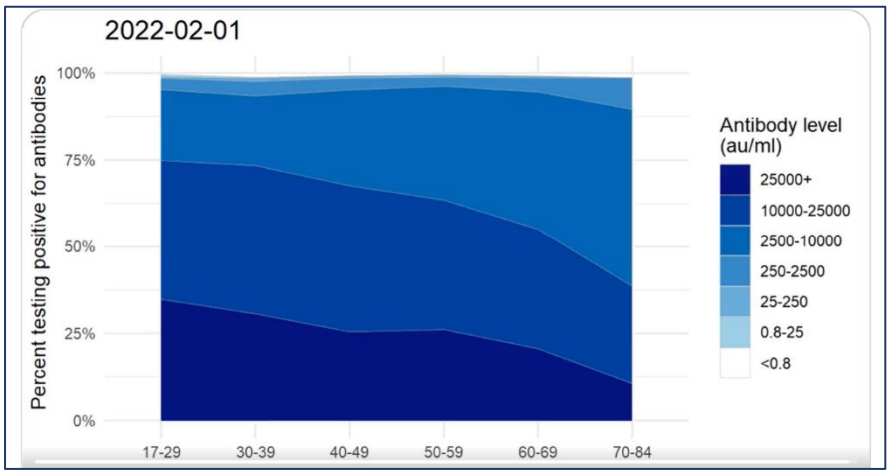
The regular fortnightly update continues to show very high levels of antibodies in all age groups, with a total 98% of adults having antibodies either from natural or vaccine acquired immunity. With other data (notably from UKHSA) noting that efficacy after the booster dose shows a material degree of waning by three months, this would appear to be contradictory evidence.

The threshold used to define antibody levels was recently increased from 42 ng/ml to 179ng/ml, as Delta requiring higher levels for adequate protection. ONS also noted that a further revision upwards may now be appropriate given Omicron has completely usurped Delta.



Looking back to the period when ONS reported both the original and higher thresholds (below), we can see how waning of the higher threshold was much greater last summer, although this would not have been apparent at the time. It might be that we are now in a similar situation, thus explaining the apparent contradiction.

There is a useful visualisation of the movements in antibody levels over time, which show how they are now falling again, here. (link)



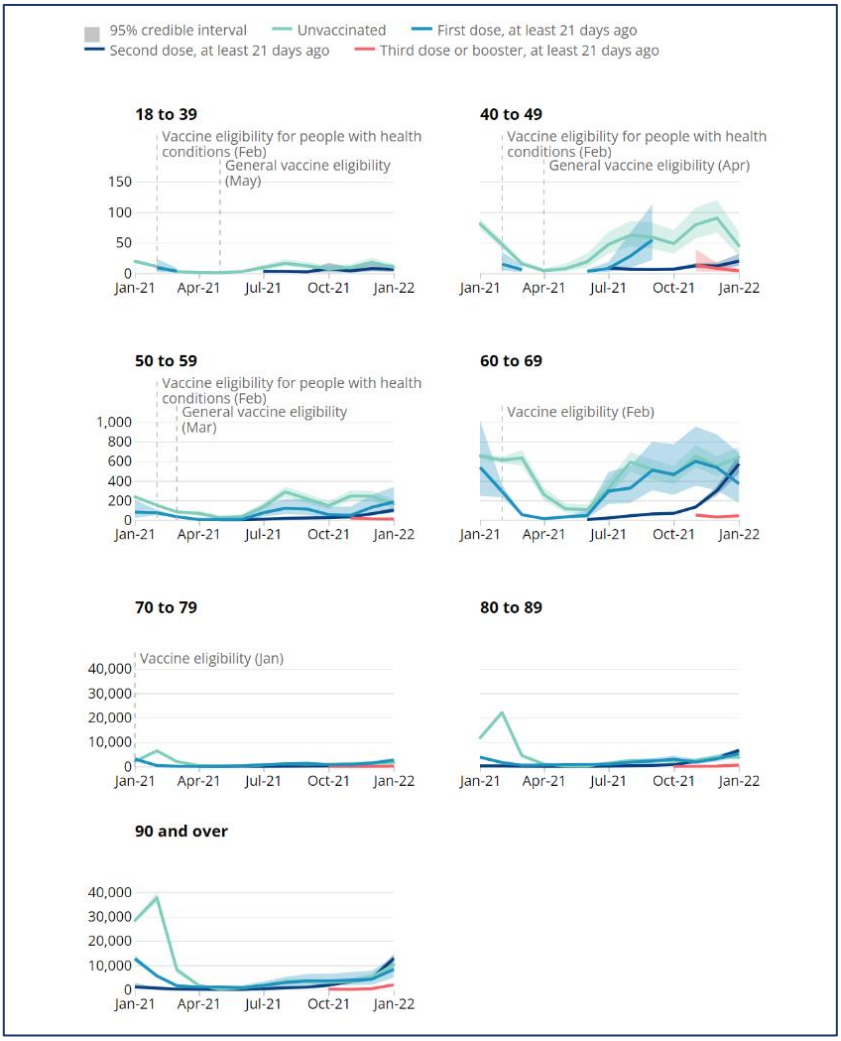
ONS COVID Mortality by Vaccination Status (link)

We have also had an updated analysis of COVID mortality by vaccination status, to include the period up to the end of January. We thus can see the effect of the booster campaign in reducing mortality during the peak of the Omicron (BA.1) surge.

Noting that the y-axis scales change significantly as we move through the age bands reflecting the increased mortality risk, we see a similar pattern in that those who have had all three doses were at considerably lower risk than those with two or fewer jabs.

The report notes that on its own the underlying data should not be used to derive vaccine effectiveness as other factors can influence the results (such as a close correlation between those who have not been vaccinated and who would be at more risk due to other demographic factors).

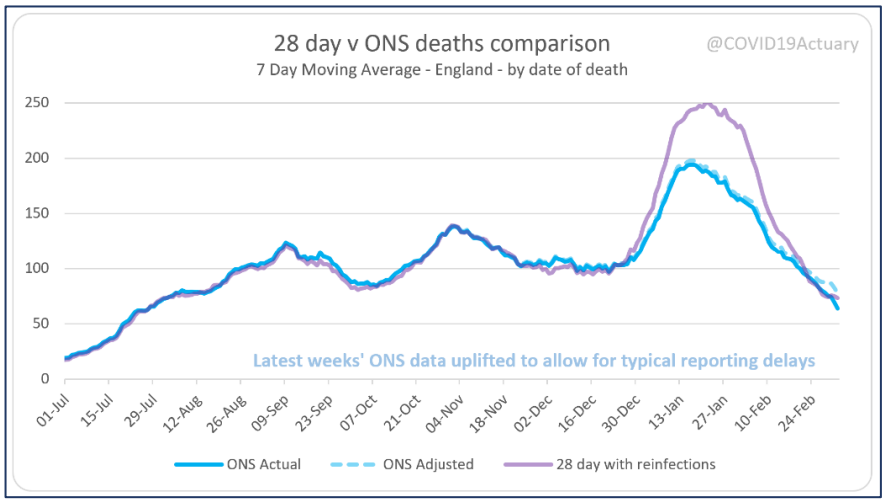
Nevertheless, the results clearly indicate the benefit of the booster campaign in reducing mortality over the winter period.



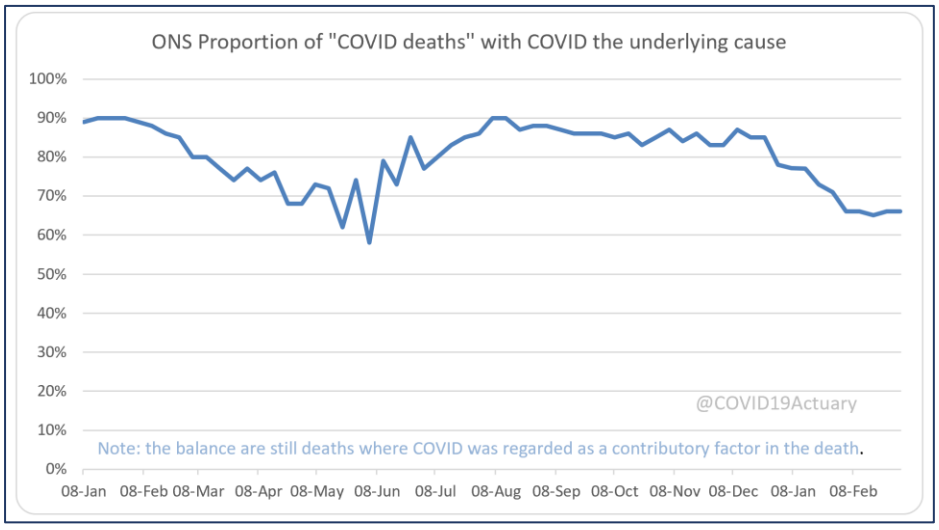
Comparison of 28 Day Measure with ONS Deaths

We reported in Edition 60 (link) that the previous close match between the "Deaths within 28 days of a positive COVID test" and ONS data based on COVID being mentioned on the death certificate had diverged, with the latter being around 20-25% lower following the emergence of Omicron.

However, in recent weeks that divergence has closed again, with the most recent weeks suggesting that if anything ONS reported deaths are emerging (once late registrations are allowed for – there is a reasonably predictable pattern of these) at a slightly higher level than the 28 day measure.



Omicron also saw a change in the proportion of ONS reported deaths where COVID was regarded as the underlying cause (as opposed to simply being a contributory factor). This fell from a relatively stable 85% throughout the autum to around 65%, and it appears to have stablised at this level, having been constant for the last five weeks.



And Finally…

Breathlyse Your Way to a COVID Test (link)

The NewYorker reports that a retired inventor in the USA has tried to address the problem that COVID test kits never seem to be available when you need them (a phenomena that extends beyond the US in our experience), by devising a breathlyser style device that you blow into to give an instant result. He explains that unlike existing tests, which rely on chemistry ("very old technology") to detect traces of the virus, this one works on physics, picking up the presence of lipids which encase all respiratory viruses.

The story notes that he hasn't yet cracked how to determine which respiratory virus the machine might have detected, so there's possibly a little way to go before he is able to patent his invention and make his fortune.

Meanwhile, in the (hopefully unlikely) event of further restrictions on hospitality venues in the UK, we now have images of pub-goers in the UK being breathalysed for COVID on entry, and again on exit for the more conventional purpose of ensuring that they are safe to drive home.

18 March 2022