Friday Report: Issue 62

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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

Lower efficacy for 5 to 11 year olds (link)

An analysis of 1.2m children between 5 and 17 in the US appears to indicate that efficacy in the under 12 cohort is lower than those aged 12 and over. The younger group has been administered a lower dose, one third of that used for the over 12s.

Whilst efficacy against infection at the outset was comparable between the two groups, rapid waning was evident in the younger cohort. Efficacy against hospital admission appears to hold up better (albeit at a lower level than for the older group), but there are wide confidence intervals given the low rates of admission for young children.

These results have raised questions as to whether Pfizer has achieved the optimal balance between efficacy and tolerance for this younger group.

Figure 1: Vaccine Effectiveness against Infection, by Week and Year of Age

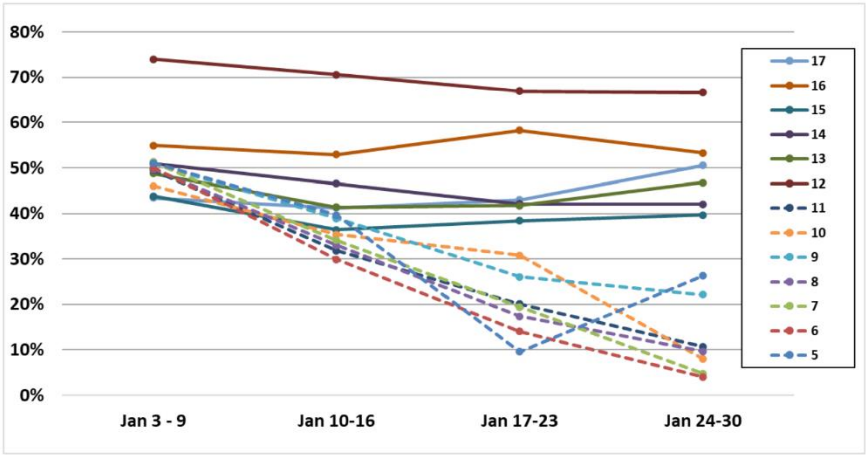


Figure 2: Incidence rate ratios, comparing cases during January 3 - January 30, 2022 for unvaccinated versus children newly fully-vaccinated December 13, 2021-January 2, 2022, by Time Since Full Vaccination

Impact of vaccination on risk of Long COVID

A pre-print study from the UK has shown that COVID-19 vaccination is associated with reduced risk of Long COVID.

The study included participants from the ONS's COVID-19 Infection Survey. Participants were aged 18-69 and tested positive for SARS-CoV-2 between 26 April 2020 and 30 November 2021. Those who were double-vaccinated were matched 1:1 to unvaccinated controls based on socio-demographic characteristics and time from infection to follow-up for Long COVID. There were 3,090 double-vaccinated participants.

The outcome of interest was Long COVID symptoms 12 weeks or more post-infection. Long COVID symptoms were reported by 294 double-vaccinated participants (prevalence 9.5%) compared with 452 unvaccinated participants (14.6%), corresponding to an adjusted Odds Ratio for Long COVID symptoms of 0.59 (95% CI: 0.50 to 0.69). There was no significant difference between adenovirus vector and mRNA vaccines.

Sanofi and GSK seek regulatory authorisation for COVID-19 vaccine (link)

On 23 February, Sanofi and GSK announce their intention to seek regulatory approval for their adjuvenated recombinant protein-based vaccine – importantly from a global supply perspective, the vaccine can be stored at ordinary fridge temperatures. Full study results of their Phase 3 trials will be published later this year but their press release provides some high-level information.

In a video, Sanofi-GSK explain how their technology (already successful in flu vaccines) works. The DNA sequence of the spike protein is used to manufacture copies of the spike protein in the laboratory. These proteins are used in combination with an adjuvant which helps the immune system to mount a response to the spike proteins.

The VAT08 efficacy study evaluated the vaccine's immunogenicity and safety in a seronegative population. Robust levels of neutralising antibodies were observed post-vaccination. Efficacy against symptomatic COVID-19 was 58% (95% CI, 27% - 77%). Early data indicate 77% efficacy against Delta variant-associated symptomatic COVID-19 disease.

Low numbers of severe events were observed in both the vaccinated and placebo groups; the suggestion is that the vaccine is effective with no hospitalisations observed among vaccinated participants. In the placebo group, there were 10 hospitalisations after dose 1 and 4 hospitalisations after dose 2.

In the VAT02 booster trial, the Sanofi-GSK vaccine was able to boost neutralising antibodies 18- to 30-fold when given as a booster to either mRNA or adenovirus primary vaccines.

Sanofi-GSK say that the vaccine was well tolerated with no safety concerns across both trials.

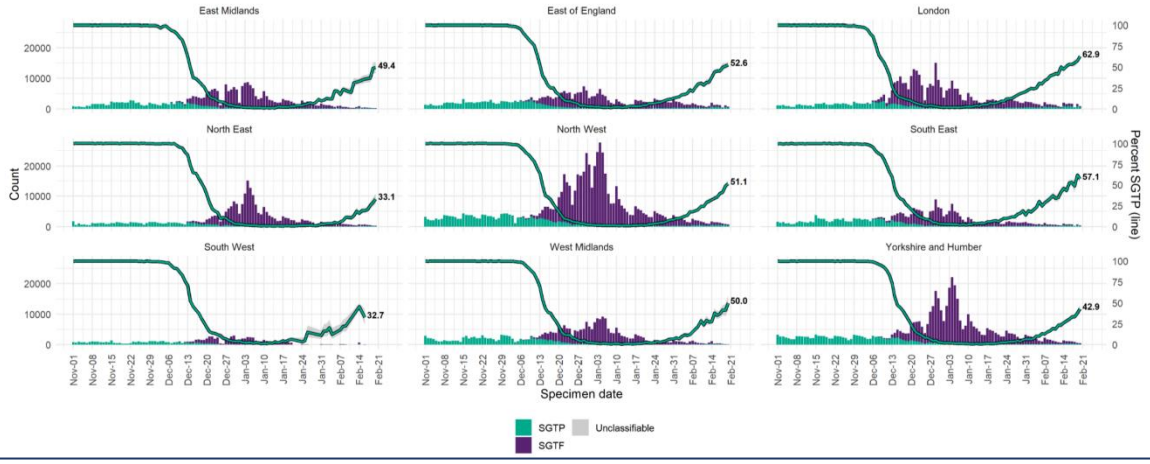
Variants

BA.2 Growth (link)

The latest Variant Technical Briefing continues to show that BA.2 is gradually usurping BA.1 by virtue of a transmission advantage. As of 20 February cases likely to be BA.2 (indicated by being S-gene target positive) were just over 50%, and as much as 63% in London.

The updated risk assessment (link) notes that immune evasion is unlikely to be a contributory factor to BA.2's advantage over BA.1, and that a higher secondary attack rate appears to be the key driver. It also notes that to date there is no evidence that clinical severity is different from BA.1

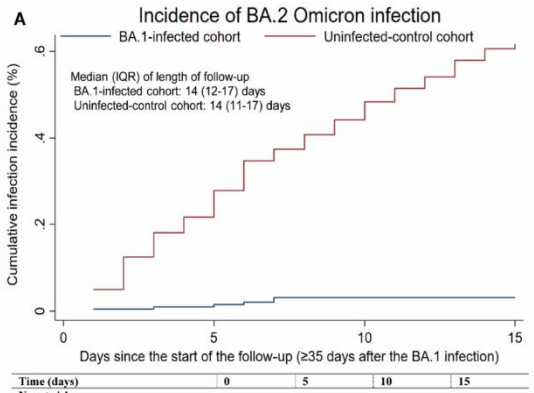
Figure 4. Number of COVID-19 cases with SGTP/SGTF by day, among those tested in TaqPath labs by region of residence as of 22 February 2022 (95% confidence intervals indicated by grey shading. Percentage for most recent day shown)
(Find accessible data used in this graph in underlying data.)



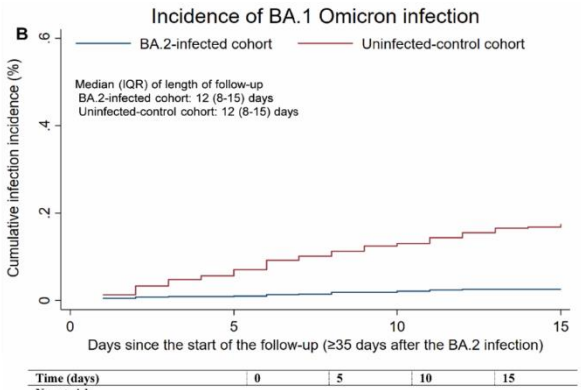
BA.1 and BA.2 infections offer mutual protection (link)

A study in Qatar of over 120,000 people has shown that both the main subvariants of Omicron offer a high degree of mutual protection against each other.

Infection with BA.1 resulted in a 95% reduction in the rate of infection with BA.2, whilst in the other direction, infection with BA.2 offered an 86% level of protection against BA.1.



Time (days)	0	5	10	15
No. at risk				
BA.1-infected cohort	20,197	19,260	16,855	9,081
Uninfected-control cohort	20,197	19,210	16,762	8,995



Time (days)	0	5	10	15
No. at risk				
BA.2-infected cohort	100,925	91,825	70,976	28,912
Uninfected-control cohort	100,925	91,648	70,665	28,735

Mapping antigenic relationships among variants (link)

A pre-print study from the Netherlands has used a technique called “antigenic cartography” to show the relationships of neutralising activity between SARS-CoV-2 variants. Antigenic cartography is a tool to quantitatively analyse antigenic drift and visualise the emergence of new antigenic clusters, which is why it is used biannually to inform influenza virus vaccine strain selection.

Th researchers inoculated Syrian golden hamsters with SARS-CoV-2 variants 614G, Alpha, Beta, Gamma, Delta, Zeta, Mu and Omicron (lineage BA.1). At 26 days post-infection, blood was collected for serological analysis. These hamster sera were assessed for neutralising antibodies against SARS-CoV-2, capturing the number of dilutions that would still achieve 50% plaque reduction. Variants that cross-neutralise each other well are presented close together on the map, while those with poor cross-neutralisation are presented further apart.

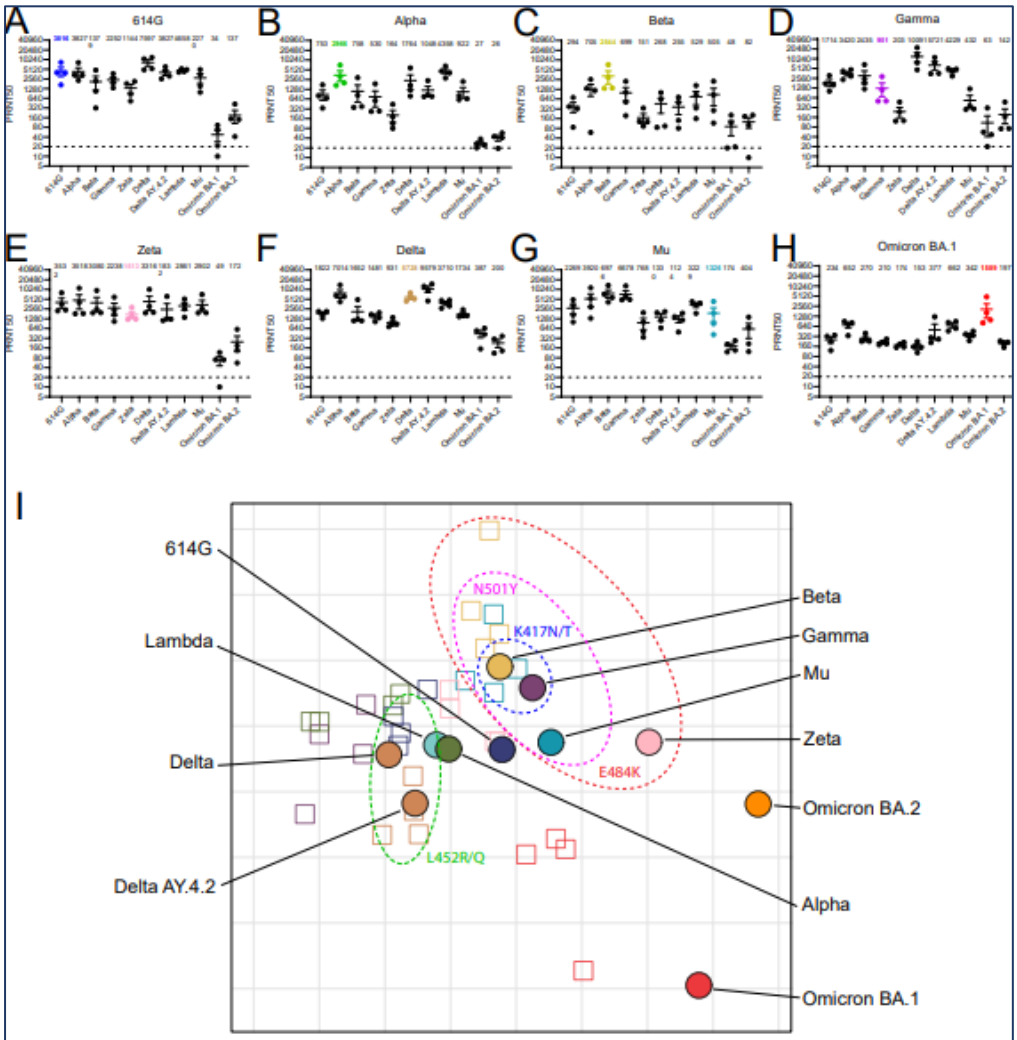


Fig. 4. Antigenic cartography using authentic SARS-CoV-2. a-h, Neutralizing titers of hamsters infected with either (**a**) 614G, (**b**) Alpha, (**c**) Beta, (**d**) Gamma, (**e**) Zeta, (**f**) Delta, (**g**) Mu or (**h**) Omicron BA.1 viruses. **i,** Multidimensional scaling was used to create an antigenic map utilizing PRNT50 titers generated from authentic SARS-CoV-2 on Calu-3 cells. See legend to Fig. 3 for details. Subdivided by dotted ellipses ar variants possessing overlapping substitutions as indicated. Geometric mean is displayed above each graph. PRNT50: plaque reduction neutralization titers resulting in 50% plaque reduction. Dotted lines indicate limits of detection. Error bars indicate SEM.

Viruses containing E484K (Beta, Gamma, Zeta and Mu) cluster together, while Alpha, Delta and Lambda are considered antigenically similar. There is generally poor neutralisation of Omicron by other variants’ sera. The Omicron variants BA.1 and BA.2 are positioned as distinct antigenic variants, reflecting limited cross-neutralisation to each other and the original cluster.

The antigenic cartography of SARS-CoV-2 shows how BA.1 and BA.2 can both escape antibody responses without being antigenically similar. The authors explain that emergence of both Omicron variants indicates that population immunity is selecting for SARS-CoV-2 variants that efficiently escape from neutralising antibody responses, leading to the first signs of antigenic drift. The authors propose that their study lays the foundation for the continuous monitoring of the antigenic evolution of SARS-CoV-2, which may inform the selection of vaccine strains in the future.

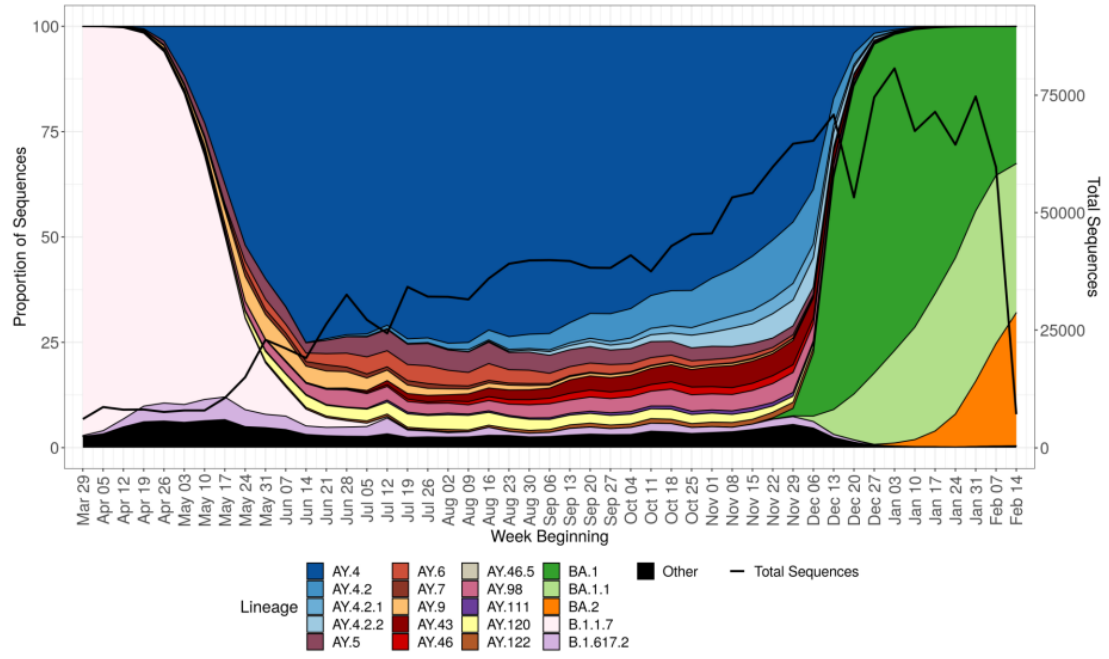
Omicron sublineages and antibody evasion

The speed with which Omicron achieved worldwide dominance was unprecedented, and it has captured our collective attention in recent months. However, this has led to the importance of further variants or sublineages being downplayed in terms of their uniqueness, particularly with descriptors such as “stealth Omicron”.

The prevalence of the original Omicron (BA.1) has been decreasing since January 2022. The less altered BA.1 + R346K sublineage is responsible for 40% of Omicron sequences worldwide, and may be achieving dominance in UK and USA. The more altered BA.2 is dominant in Denmark, India and South Africa. All three sublineages have 21 shared mutations on the spike protein, but BA.1 and BA.2 have a further 13 and 8 unique mutations respectively (compared with eg Delta’s 13 mutations on the spike protein).

So BA.2 could be as genetically distinct from Omicron as Delta was to the original SARS-CoV-2 virus. The prevalence of the all variants sequenced is set out below from Technical briefing 37 published by UKHSA on 25 February (link).

Figure 5. Prevalence of Pangolin lineages in UK with sequence data from 1 April 2021 to 22 February 2022
The total number of valid sequence results per week is shown by the black line. Only lineages with more than 5,000 sequences are shown. Smaller lineages are either merged with parent lineages (for example, AY.3.1 is included in AY.3) or are included in ‘Other’.
(Find accessible data used in this graph in underlying data)



However, not all mutations are of equivalent importance or impact, and a recent study by Ikutani et al (link) examined the ability of the different sublineages to evade various different monoclonal antibodies, and casts light on the likely ability to evade prior vaccine or naturally induced immunity.

This study concluded that BA.2 showed resistance to 17 of the 19 neutralising monoclonal antibodies, including sotrovimab which was able to neutralise the other Omicron sublineages. Only the recently released bebtelovimab could treat all three sublineages.

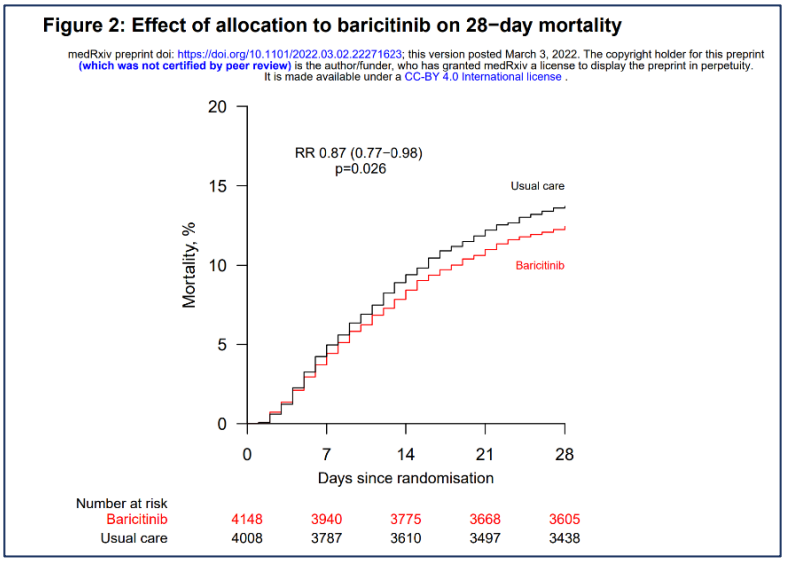
This is also worrying as BA.2 shows a greater propensity to cause lower respiratory damage through forming 'syncytia' (amalgams of cells fused together) that damage the structure of the lungs and prolong infections. It is reassuring that the loss of neutralising activity was less for those who had recently received a booster vaccine.

Clinical and medical news

Another success for RECOVERY trial with baricitinib (link)

Baricitinib, an anti-inflammatory drug usually used to treat arthritis, has been shown to reduce 28-day mortality in hospitalised COVID-19 patients by 13%, i.e. a risk ratio of 0.87 (CI 0.77 - 0.98).

At over 8,000 patients, this is the largest of nine trials of baricitinib. Looking across the trials in total, covering over 12,000 patients, the mortality reduction is put at 20% - risk ratio 0.80 (0.71, 0.89).



Of particular note is that the patients receiving baricitinib were typically receiving other drugs already shown to improve outcomes, (such as tocilizumab, remdesivir, and in nearly all cases dexamethasone), and the improvement seen was regardless of what other treatments were used. This suggests that baricitinib offers a further incremental improvement, as opposed to being an alternative to other treatments.

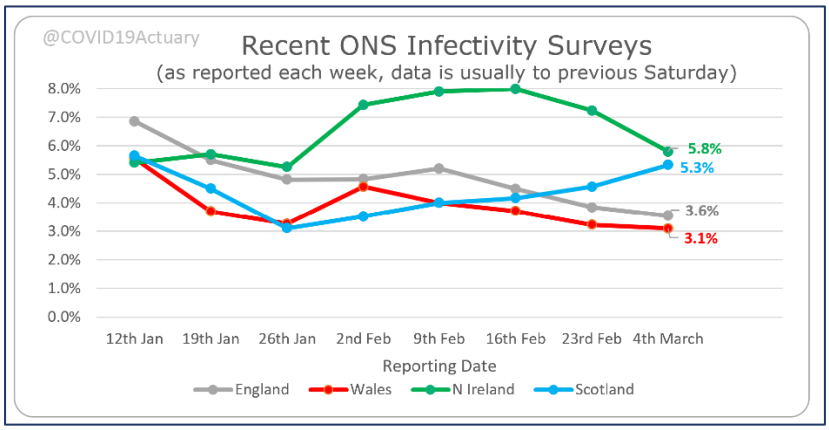
Data

ONS Infection Study Blog (link)

Before covering this week's data, the ONS has released a very interesting podcast "Statistically Speaking" which gives some interesting background as to how the survey came about, and how it operates. With the very welcome news that the survey will continue, albeit in reduced form, the podcast is a timely insight as to what goes on behind the scenes (including some interesting anecdotes about some of the researchers' doorstep experiences!).

A second blog and video has also been published covering the School Infection Survey and how it has been used to assess the impact of the pandemic on children. (link)

Turning now to the latest figures, Northern Ireland has reduced from recent very high levels, and there have been smaller falls in England and Wales too. However, Scotland is showing a different trend, with a fifth consecutive increase recorded, driven by a much faster growth of BA.2.



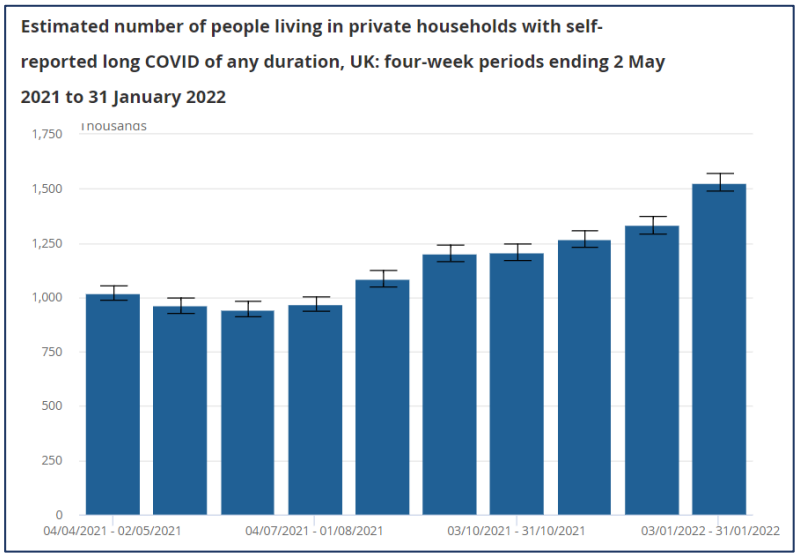
In England there's less positive news in the South West, which is seeing growing prevalence, and similarly there has been recent growth in the over 70 age group too. These two features are likely to be behind recent admissions growth, most apparent in the South West and older age groups.

The other regular randomly sampled prevalence study, Imperial College's REACT study, appears likely to have its government funding terminated at the end of the month. Hopefully we will see and report on one more report before the study winds up. Whilst REACT has provided an extremely valuable insight into the spread of the virus over the last two years, and has been complementary to the ONS surveillance, there is logic in focusing resources on just one study.

ONS Long COVID study (link)

ONS have updated their estimates of the prevalence of Long COVID in the UK, based on data at 31 January 2022.

Their latest estimate is that 1.5 million people (2.4% of the population) were experiencing self-reported Long COVID (definited as COVID symptoms persisting for more than four weeks after the first suspected COVID infection, with no alternative explanation)



This is a significant increase from previous estimates, the last of which (based on data at 2 January 2022), suggested that Long COVID was affecting 1.3 million individuals (2.1%).

ONS note that Long COVID symptoms adversely affected day to day activities for almost 1 million people (65% of those with self-reported long COVID), with 18% reporting day to day activities having been limited "a lot". Their figures also suggest that 45% of those reporting Long COVID first had (or suspected they had) COVID at least one year previously.

Consistent with previous reports, prevalence was higher in those aged 35-49, females, people living in more deprived areas, teachers and those working in education, social care and health care, and those with another activity-limiting condition or disability.

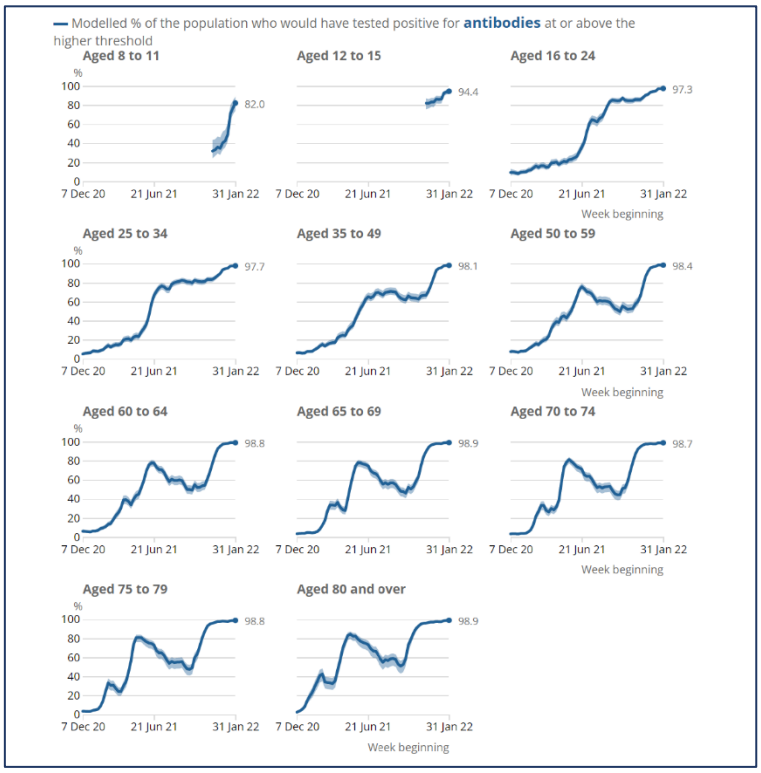
ONS Antibody Study (link)

The latest antibody study continues to show very high level of antibodies, now only measured at the higher threshold (179ng/ml) which the ONS introduced recently. Until then a much lower threshold of 42ng/ml was used, but the higher level was considered more appropriate in relation to preventing infection by Delta. There is a note, however, that a further upward revision may be necessary to give an equivalent level of protection against Omicron.

Across the UK as a whole, the proportion with antibodies is estimated as 98%. Of particular encouragement is that these levels continue to be maintained at the older ages, despite the period since the booster jab now extending beyond three months. In the charts below we can see how boosters restored and even enhanced levels beyond those observed after the second dose, and how they are being sustained, in contrast to the decline seen shortly after the second dose.

One point worthy of note is the rapid growth in antibodies in the under 11s, remembering that this group has yet to be vaccinated, except in specific circumstances.

In just weeks we see an increase from around 30% to over 80%, suggesting that half the cohort has been infected with Omicron – a figure which is broadly consistent with the infection levels seen in this age group in the parallel ONS study.



And Finally …

Whilst much of Europe is emerging from the pandemic, the Russian invasion of Ukraine has thrown the continent into another type of turmoil, with harrowing suffering for the people of Ukraine.

However, the pandemic is far from over. Infection control is, understandably, the last thing in mind for all those fleeing from violence and crossing borders, but we may see further strain on already COVID-weary countries and their health systems.

Our thoughts and sympathies go to all those caught up in the conflict, whether directly affected, caring for the injured, or involved in the humanitarian efforts to assist refugees fleeing their country in such terrible circumstances.

4 March 2022