Friday Report: Issue 60

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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 and articles.

Vaccines

Vaccine effectiveness against Delta and Omicron

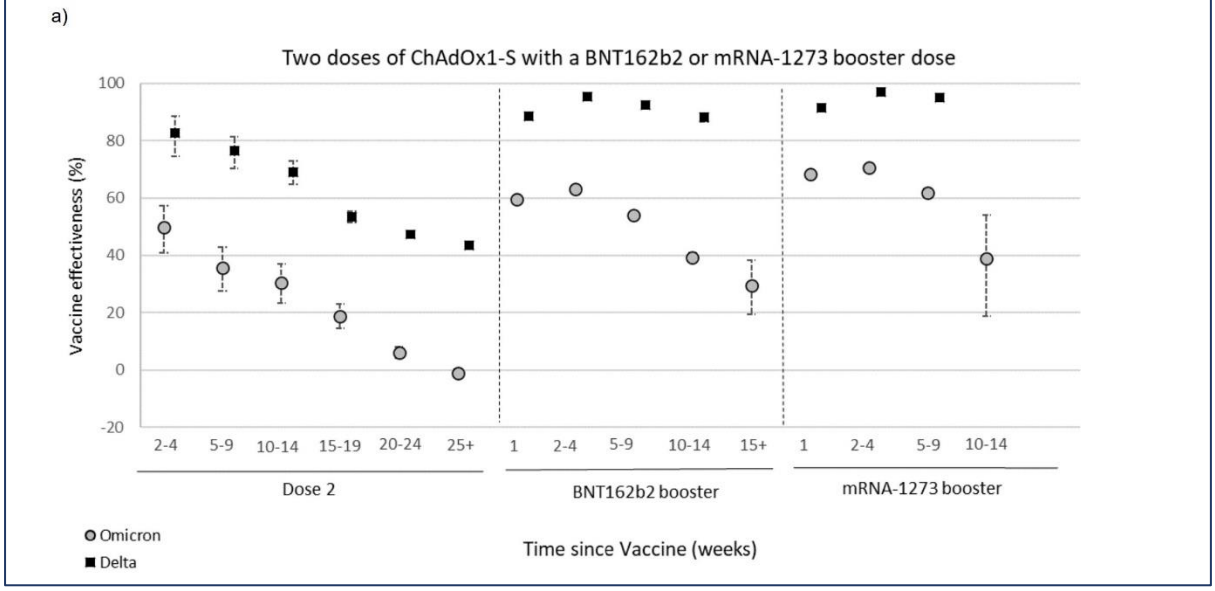
In their 27 January COVID-19 vaccine surveillance report, UKHSA report on vaccine effectiveness against symptomatic disease, hospitalisation and mortality for up to 15 weeks after an mRNA booster.

Symptomatic disease

After two doses of the AstraZeneca vaccine, vaccine effectiveness against the Omicron variant drops to almost no effect from 20 weeks after the second dose. Two to 4 weeks after a booster dose, effectiveness is restored to 60-75% but drops to 25-40% from 15+ weeks after the booster. This illustrates the importance of receiving a booster dose.

Vaccine effectiveness estimates for the booster dose are very similar, irrespective of the primary course received. Effectiveness is generally slightly higher in younger people.

Figure 1. Vaccine effectiveness against symptomatic disease by period after the second and booster doses for Delta (black squares) and Omicron (grey circles) for a) recipients of 2 doses of Astrazeneca (ChAdOx1-S) vaccine as the primary course and Pfizer (BNT162b2) or Moderna (mRNA-1273) as a booster; b) recipients of 2 doses of Pfizer vaccine as the primary course and Pfizer or Moderna as a booster, and c) 2 doses of Moderna as a primary course and Pfizer or Moderna as a booster

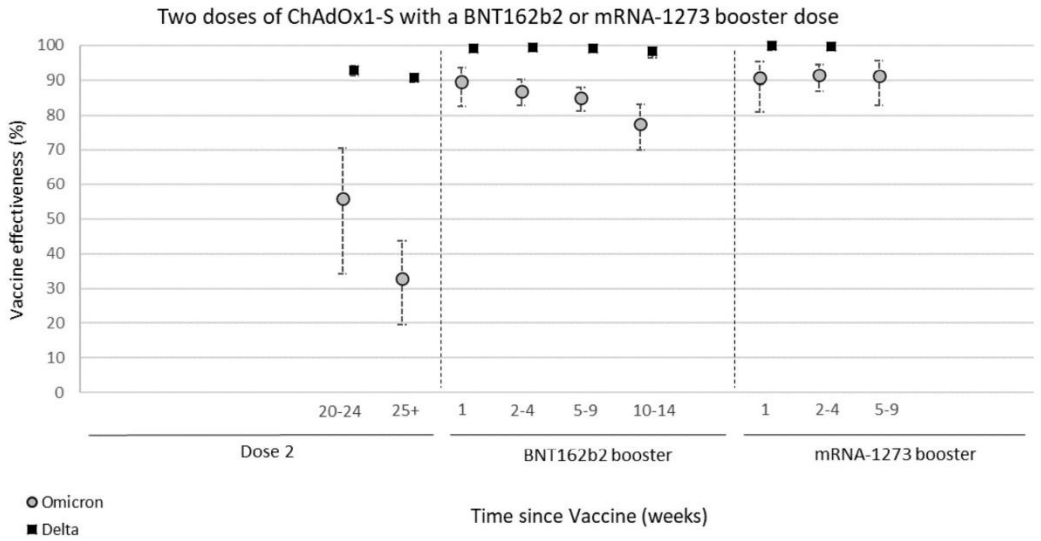


Hospitalisation

After two doses of the AstraZeneca vaccine, vaccine effectiveness against hospitalisation with the Omicron variant drops to 30%, alebit with very wide confidence intervals. Two to 4 weeks after a booster dose, effectiveness is restored to 90% for both mRNA booster vaccines – but by 10 weeks after a Pfizer booster, the effectiveness falls to 80%. While this is still a good level of vaccine effectivenss, the effectiveness gap (i.e. the difference between the measured effectiveness and 100%) has doubled. The follow-up for Moderna boosters is shorter but shows good effectiveness at around 90%.

Figure 2. Vaccine effectiveness against hospitalisation by period after the second and booster doses for Delta (black squares) and Omicron (grey circles) for a) recipients of 2 doses of Astrazeneca (ChAdOx1-S) vaccine as the primary course and Pfizer (BNT162b2) or Moderna (mRNA-1273) as a booster; b) recipients of 2 doses of Pfizer vaccine as the primary course and Pfizer or Moderna as a booster

a)



Vaccine effectiveness against mortality with the Omicron variant has been estimated at 95% (CI 90-98%) two or more weeks following a booster, for those aged 50 years and older.

Durability of Omicron-neutralising effect – mRNA boosters in the elderly

A German pre-print study shows the results of 10 months of follow-up for 37 individuals with a median age of 82, following an initial two-dose BNT162b2 vaccination and up to 4.5 months after a BNT162b2 booster.

Detectable Omicron-neutralising activity was nearly absent after two vaccinations but was elicited in 89% of individuals following the booster immunisation. This compares with neutralising activity among all but one participant for the Wu01 and Delta variants. The study demonstrates the mRNA booster's effectiveness in inducing anti-Omicron activity in an elderly population.

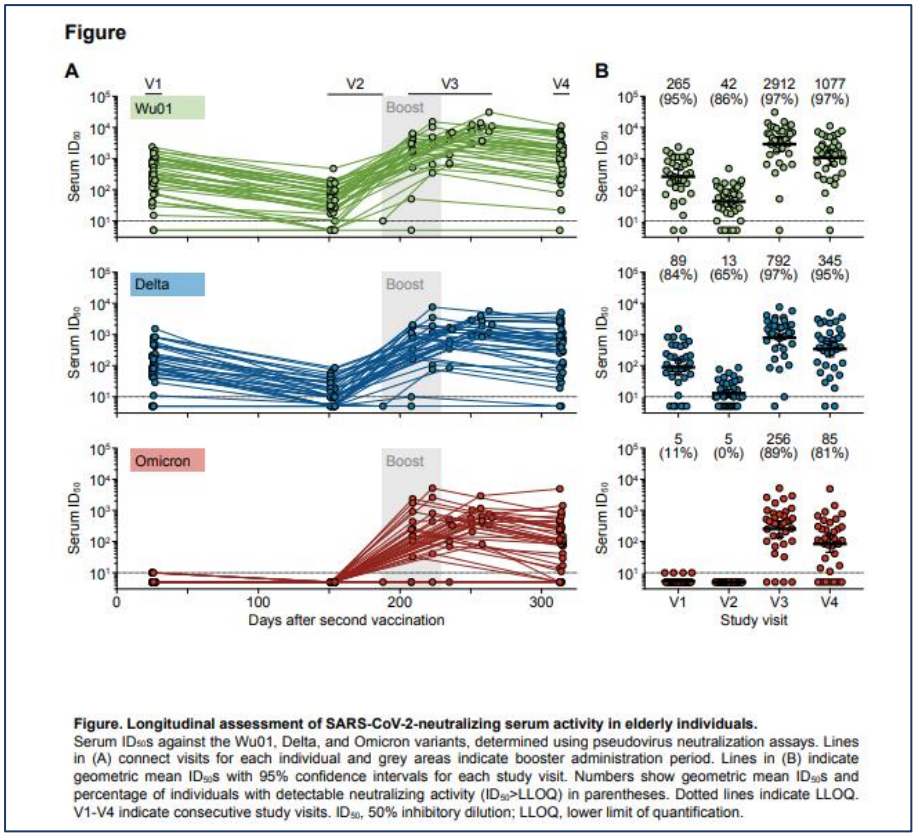


Figure. Longitudinal assessment of SARS-CoV-2-neutralizing serum activity in elderly individuals.
Serum ID_{50}s against the Wu01, Delta, and Omicron variants, determined using pseudovirus neutralization assays. Lines in (A) connect visits for each individual and grey areas indicate booster administration period. Lines in (B) indicate geometric mean ID_{50}s with 95% confidence intervals for each study visit. Numbers show geometric mean ID_{50}s and percentage of individuals with detectable neutralizing activity (ID_{50}>LLOQ) in parentheses. Dotted lines indicate LLOQ. V1-V4 indicate consecutive study visits. ID_{50}, 50% inhibitory dilution; LLOQ, lower limit of quantification.

Novavax approved for use in the UK

The MHRA has approved Novavax, also known as Nuvaxovid, for use in people aged 12 and older (link) The vaccine's US manufacturer also plans to apply for authorisation in the next few weeks.

Novavax is a protein adjuvant vaccine. It delivers copies of the spike protein directly into a person's cells and an extra ingredient helps to boost the immune response trigger by the spike.

Variants

Variant Under Investigation BA.2

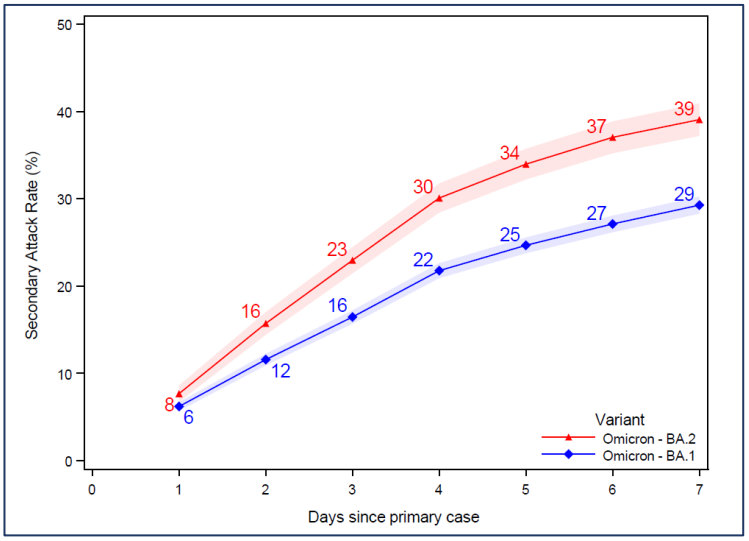
Predictions don't last long in the world of COVID. Just over two months ago, Omicron (B.1.1.529 or BA.1) was identified in South Africa, with an unprecedented number of mutations and a dramatic increase in transmissibility over Delta. Now, Omicron is likely to be overtaken by a further variant in the same stable, BA.2 which has significantly more mutations compared to the original SARS-CoV-2 virus even than BA.1. The figure (included in Technical Briefing 34 from the UK Health Security Agency (link)) illustrates not only the number of mutations but the differences between the two variants – it also highlights that BA.2 lacks the A69/70 deletions that enabled OMICRON to be identified from PCR tests alone.

Figure 9: Proportion of sequences within BA.1 and BA.2 containing mutations in Spike
Supplementary data are not available for this figure.

Last week, the UKHSA designated BA.2 as a Variant Under Investigation (link), and disclosed that 3.4% of variants sequenced as at 16 January were BA.2. In addition, preliminary data confirmed that BA.2 spreads more extensively in households, with a secondary attack rate of 13.4% compared with 10.3% for Omicron .

However, even this data is becoming rapidly out of date. Denmark is a leading indicator of trends, with extensive up-to-date sequencing. The latest data suggests that BA.2 represents 85% of all variants sequenced in Denmark. A further study of viral transmission in Danish households released this week (link) estimated secondary attack rates of 39% for BA.2 as compared to 29% for Omicron (see graph below), and further concluded that

- BA.2 is significantly more transmissible than Omicron
- Full and booster vaccinations are less effective in reducing susceptibility to BA.2 than for Omicron
- Vaccination is still effective in reducing the likelihood of transmission with BA.2



There is no evidence that BA.2 is more virulent that Omicron. However, its ability to evade the immune response, higher transmission rate and greater lags in detection increase the likelihood of a further surge in infections. BA.2 will very likely soon be the dominant variant in the UK and other countries such as South Africa (it may already be so), and will achieve global dominance in coming weeks.

Clinical and medical news

Safety and viral kinetics during SARS-CoV-2 human challenge

A pre-print of a study reports on the results of a human challenge trial where 36 volunteers aged 18-29 years without evidence of previous infection or vaccination were inoculated with wild-type SARS-CoV-2 via the nose. Participants were admitted to an in-patient unit with 24-hour monitoring and access to clinical support if needed. Twice-daily nose and throat samples were taken and tested using PCR and lateral flow tests. Focus Forming Assays (FFA) were used to assess viable virus.

A key outcome of the study is that it was found to be safe with no serious adverse events occurring. As a result, further challenge studies are now underway that will allow rapid evaluation of vaccines, antivirals and diagnostics by generating efficacy data early during clinical development and avoiding the uncertainties of studies that require ongoing community transmission.

The study also provided good data on viral kinetics.

Eighteen participants became infected after inoculation, of whom 16 experienced mild-to-moderate symptoms, beginning 2-4 days post-inoculation. 16 participants remained uninfected. (Note two participants were excluded because they became infected prior to inoculation.)

We summarise some of the measurements of interest over time post-inoculation.

qPCR test measurements

- Viral shedding became quantifiable in throat swabs from 40 hours (median, 95% CI [40,52]).
- Measurements peaked in the throat at 112 hours (CI 76-160) (~4.7 days) and in the nose at 148 hours (CI 112-184) (~6.2 days).
- Quantifiable virus was still present at day 14.
- At day 28, 6/18 remained qPCR positive in the nose and 2/18 in the throat.
- By day 90 all participants were qPCR negative.

Lateral flow test measurements

- None of the uninfected participants had a positive lateral flow test at any time.
- All infected individuals had positive lateral flow test results for 2 days or longer.
- Median time to first detection by daily lateral tests was the same in nose and throat at 4 days (range 2-8) post-inoculation, which was on average 24-48 hours after first qPCR positivity.
- The modelling suggests that routine testing as little as every 7 days is able to interrupt more than half the virus still to be shed by an individual, if acted upon.

FFA tests for viable virus

- In 9 of 18 infected individuals, viable virus became detectable by FFA one or more days before the first positive lateral flow test.
- Lateral flow results were strongly associated with viable virus and modelling showed that twice-weekly rapid tests could diagnose infection before 70-80% of viable virus had been generated.
- Lateral flow tets results were highly reliable in predicting the disappearance of viable virus which supports “test to release” strategies to shorten the period of self-isolation.
- On average, viable virus was still detectable 10 days post-inoculation (up to 8 days after symptom onset) which the authors suggest supports the isolation periods of 10 days post-symptom onset advocated in many guidelines to minimise onward transmission.

Rates of Rapid Antigen Test Positivity After 5 Days of Isolation for COVID-19

A pre-print reports on the results of a study of Rapid Antigen Tests (RAT) results conducted among healthcare workers in the US who tested positive, isolated for COVID-19 and then sought to return to work. A negative RAT result was a requirement to return to work, following at least 5 days of isolation after start of symptoms or testing positive if asymptomatic.

Omicron was a dominant variant during the study.

Between 2 and 12 January 2022, 43% (134 of 309) of all RAT results were positive between days 5-10. 58% of tests on day 6 were positive. Healthcare workers returning for a first test on day 8 and 9 were less likely to have a positive test (26%).

These results indicate that a substantial proportion of individuals with COVID-19 are likely still infectious after day 5 of illness, regardless of symptom status.

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.

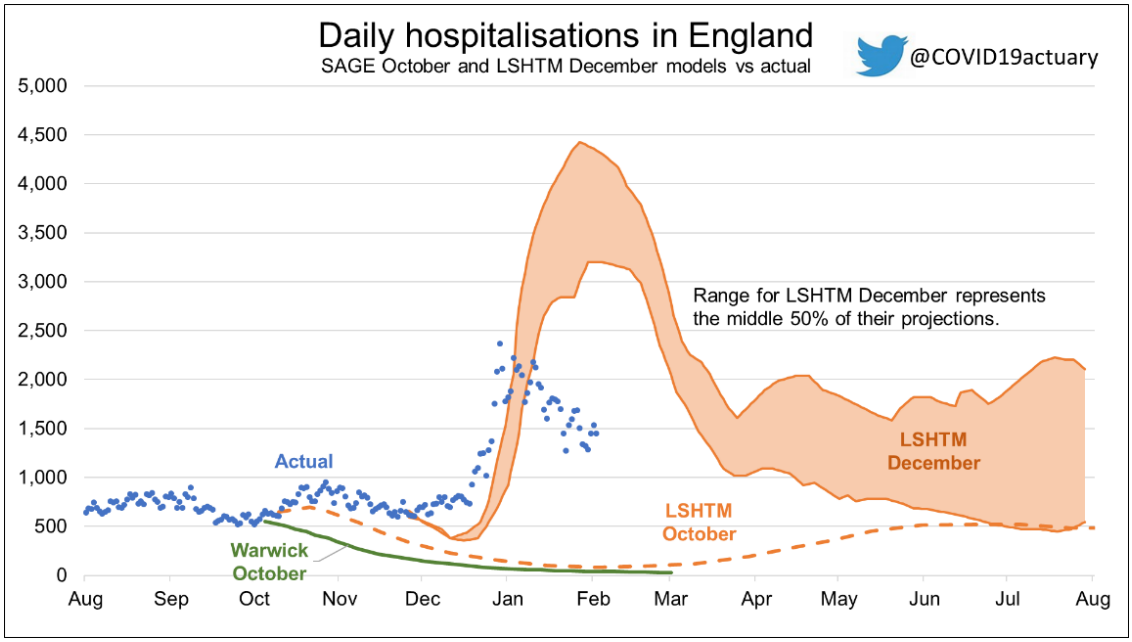
We noted in Friday Report 54 that the group of universities had published updated papers, setting out projections from October through the winter, and focussing on the impact of boosters and the mixing behaviour of individuals.

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.

On 22 December, an update was published with additional scenarios. As with previous papers, there are a large 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 papers, 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 significantly increased the projected number of hospitalisations, and that until recently the numbers were broadly in line with projections.

The most recent data suggests that hospital admissions from the Omicron wave have peaked at a level significantly lower than the modelled scenarios. We will continue to monitor how actual experience lines up with this projection.

Data

Obesity, ethnicity and COVID-19 deaths and hospitalisations

A study of linked data sources in England has shown that BMI was more strongly associated with COVID-19 mortality in ethnic minority groups than among those of white ethnicity. The figure on the left compared mortality risk with that of a person of white ethnicity with BMI of 22.5 kg/m^2. The figure on the right compares the mortality risk for corresponding levels of BMI by ethnicity. The figure on the right shows that for all ethnic minority groups, mortality rates are higher and the gap relative to mortality for those of white ethnicity widens with increasing BMI.

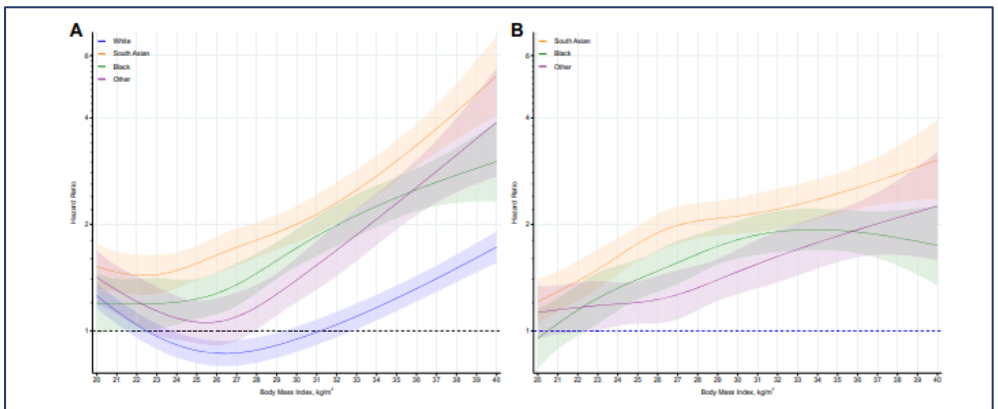


Fig. 1 Association of BMI and ethnicity with COVID-19 mortality. A (left): Association of body mass index with COVID-19 mortality stratified by ethnic group, with the reference (HR = 1) placed at body mass index of 22.5 kg/m^2 for white ethnicities. **B** (right): Hazard of COVID-19 mortality in South Asian, Black and other ethnic minority groups, relative to white ethnicities (HR = 1), across body mass index as a continuous variable. Shaded area as 95% CI. Data adjusted for region, population density, urban/rural classification, deprivation (area and household), social grade, qualification, household size and tenure, household composition (multigenerational, with children), key worker status and type, occupational exposure to disease, occupational exposure to others. The c-index for the model was 0.902, indicating a strong fit.

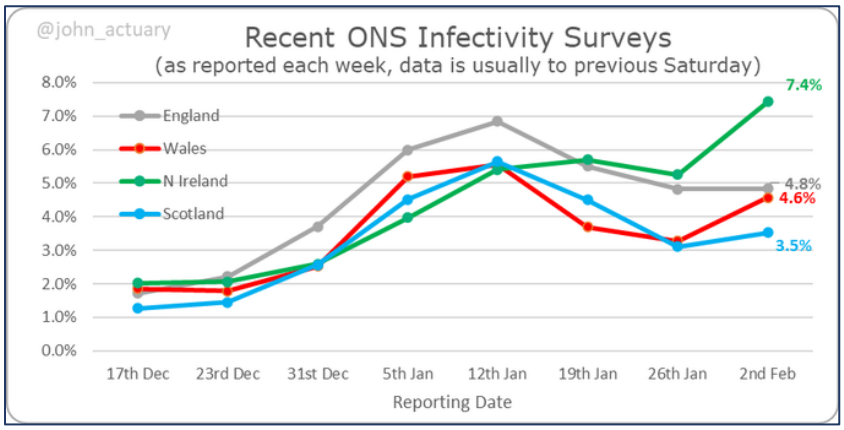
The study also found similar associations when looking at risk of hospitalisation.

The authors report that reasons underpinning the observed interactions between ethnicity and obesity are unclear. A possible explanation is that ethnic minority groups may have a stronger innate inflammatory response to viral infection and the presence of greater levels of adiposity interacts with and accelerates this inflammatory response. The authors suggest that further research, including the potential of genetic and epigenetic factors, is warranted.

The study made use of linked 2011 Census data, electronic health records and mortality datasets. 12.6 million adults aged 40 and older at 31 December 2019 whose health records included a BMI measure were included in the study. 33,951 COVID-19 deaths and 100,003 hospitalisations were recorded among these individuals. The study adjusted for socio-demographic data and comorbidities.

ONS Infection Study (link)

The latest ONS survey results (2 February) shows a mixed picture across the UK. Infection levels are flat in England, have risen moderately in Scotland and have increased markedly in Northern Ireland and Wales.



By region, infection levels have converged in the 4.4% to 5.3% range

Infection levels are highest for children up to school Year 6. They increased from 11.8% in the previous week's report to 13.1% in this report. Infection levels for school years 7 to 11 rose from 6.5% to 7.6% between the two reports, whilst at older ages infection levels have remained broadly stable.

Note that the ONS study is a randomly sampled exercise, and recent changes in the PCR testing regime for community testing will not affect it.

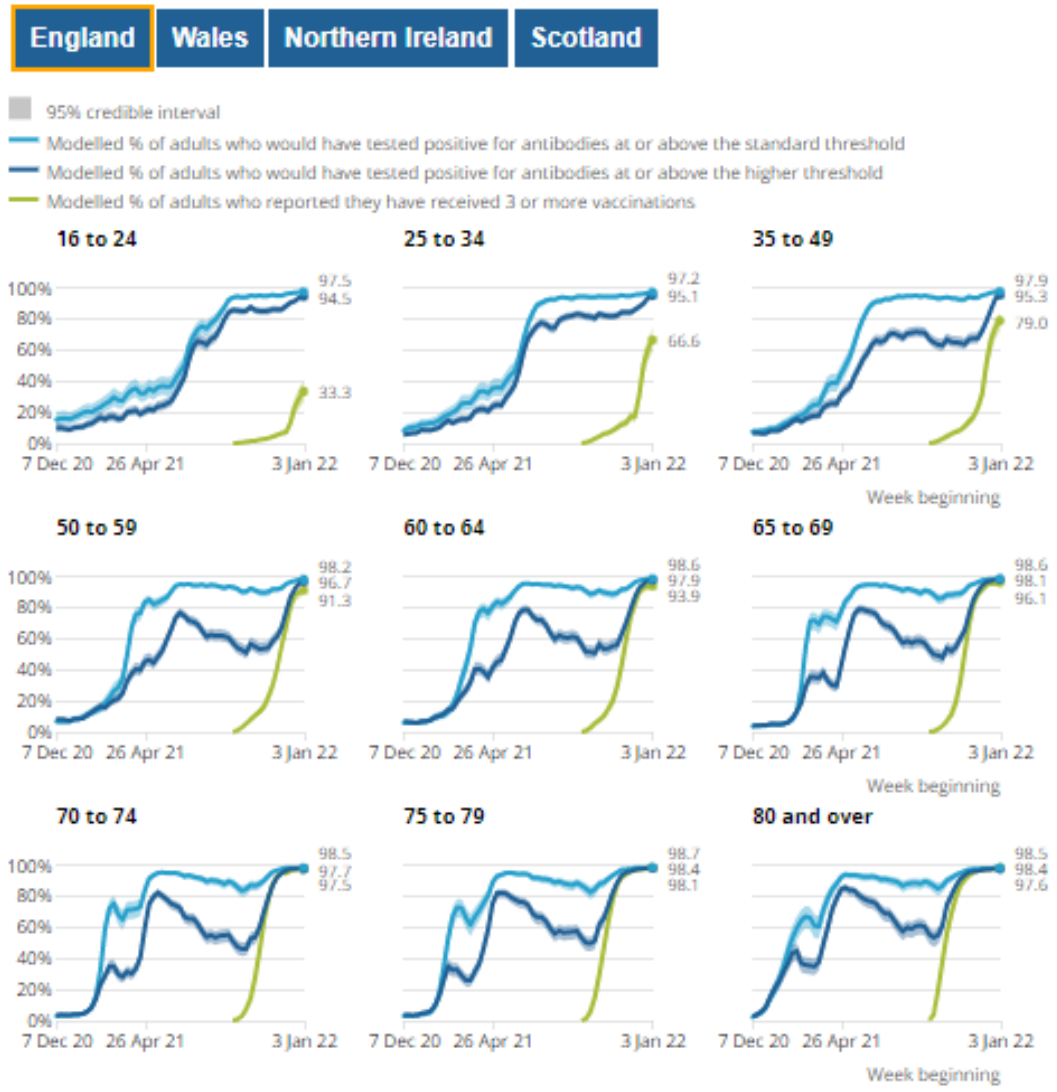
ONS Antibody Report (link)

The ONS antibody study for the week beginning 3 January 2022 shows that adult antibodies at the standard level are around 98% – their highest level yet. This is primarily a consequence of the booster programme restoring levels in the older population.

The survey includes additional analysis that shows the percentage of adults testing positive for antibodies at or above a concentration of 179 ng/ml – the percentages are barely distinguishable from those showing any level of antibodies.

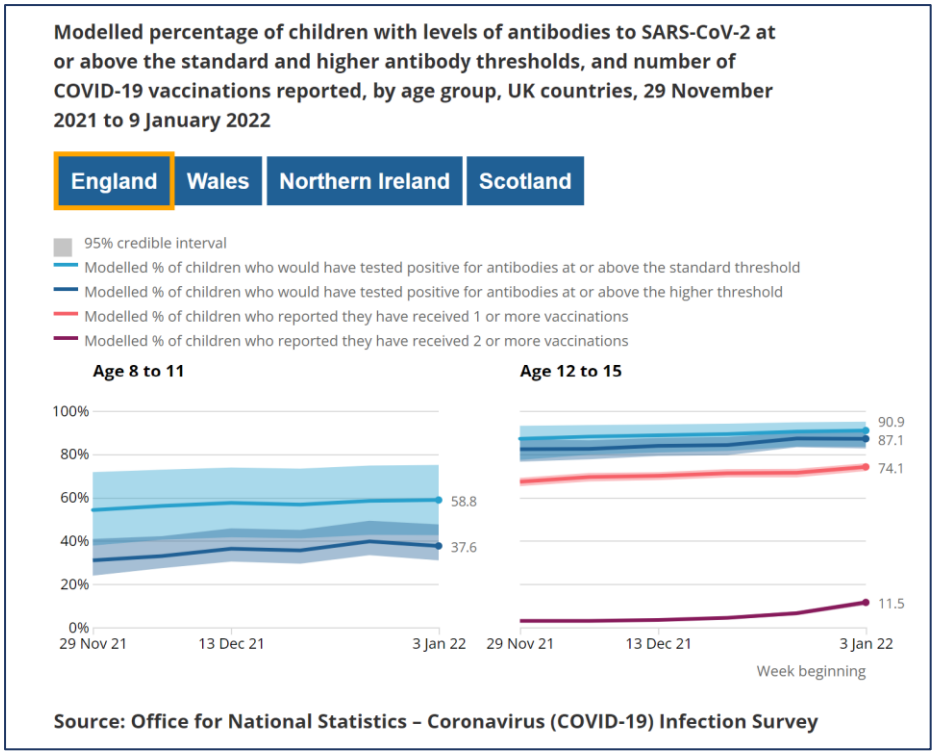
The percentage of adults with antibodies at or above the higher threshold remained high for all age groups across the UK

Modelled percentage of adults with levels of antibodies to SARS-CoV-2 at or above the standard and higher thresholds, and who reported they have received three or more COVID-19 vaccinations, by age group, UK countries, 7 December 2020 to 9 January 2022



Source: Office for National Statistics – Coronavirus (COVID-19) Infection Survey

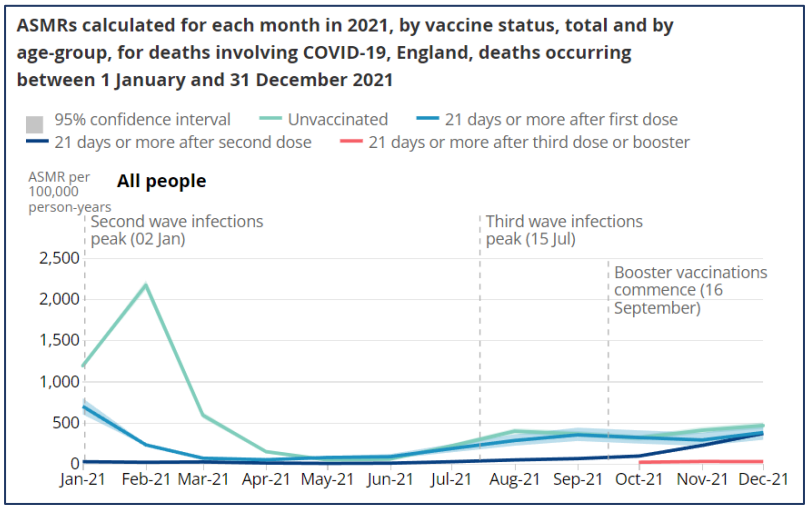
This is the first report to include data on children, seen in the following graphic. For ages 8 to 11, 58.8% are estimated to test positive at the standard threshold, compared to 90.9% for ages 12 to 15 years. For the higher antibody concentration threshold, 37.6% of 8 to 11 year olds are estimated to test positive, comapred with 87.1% of 12 to 15 years olds. 74% of children aged 12 to 15 have received at lease one vaccination, while under 12s remain largely unvaccinated.



Deaths involving COVID-19 by vaccination status

ONS have published their latest analyis of COVID-19 deaths by vaccination status, covering the period July 2021 to December 2021 (link). This shows that the risk of death involving COVID-19 (age-adjusted) was 93% lower for those who are 21 days after their third dose or booster, compared with unvaccinated people.

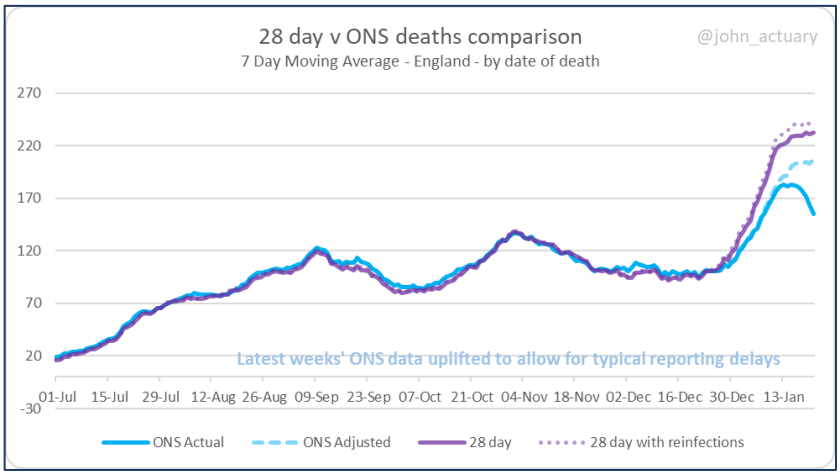
The analysis also provides a possible indication of the waning of the vaccine effectiveness against death (also mentioned above) with the age-adjusted risk over the period being 81% lower compared with unvaccinated people for those who are 21 days after their second dose – this has fallen from 99.5% for the period January to June 2021. ONS note, however, that there may be differences in the underlying health of the two groups that could affect the mortality rates of each, so the figures do not provide a direct equivalent to vaccine effectiveness calculations.



Comparison of COVID deaths under different definitions

In England, for most of 2021, the number of COVID deaths within 28 days of a positive test has been remarkably close to the numbers of deaths where COVID was mentioned as an underlying or contributory cause on the death certificate.

However, there has been increasing divergence in recent weeks: the ONS death certification figure is now around 20% lower than the 28-day figure. This is likely due to the high prevalence of Omicron, meaning that there are now more incidental deaths of those testing positive, that were not directly caused by COVID.



And Finally …

We are proud of producing our "Diamond Jubilee" 60th Friday Bulletin. Perhaps we have had the odd typo in some of tehm?

But spare a thought for a manufacturer that shipped 10,800 teacups, mugs and plates from China to Southampton "to commemorate the Platinum Jubbly", only for the stock to be rejected by their orthographically demanding fulfilment partner!

The job lot is now listed for £32,400 plus VAT on a clearance stock website.

The Friday Report authors have declined to snap up this bargain and instead look forward to celebrating with glasses of "bubilee" on the special bank holiday on Friday, 3 June.

We also look forward to providing commentary on how the Thursday and Friday Bank Holidays will distort vital statistics registrations at the time.

4 February 2022