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Friday Report: Issue 55

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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.

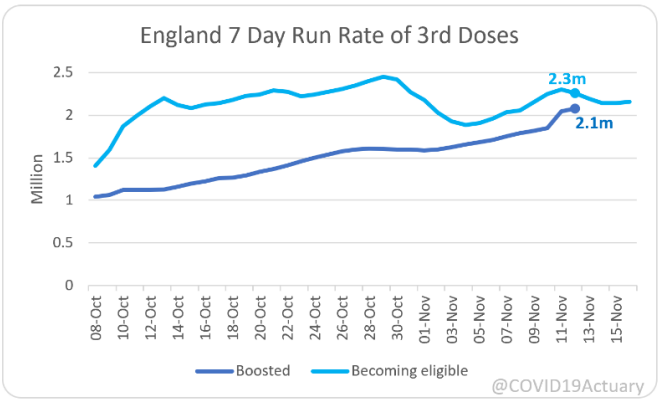
Vaccines

Booster and 12 to 15 Roll-out

As of 12th November, the total number of people given a booster in England has risen to 9.9m, although a further 6m are eligible but yet to be jabbed. Encouragingly, this week has seen a significant increase in the pace (up 23%), as seen in the chart below, (although note that the discontinuity in yesterday's point is a consequence of reporting delays on the previous two days).

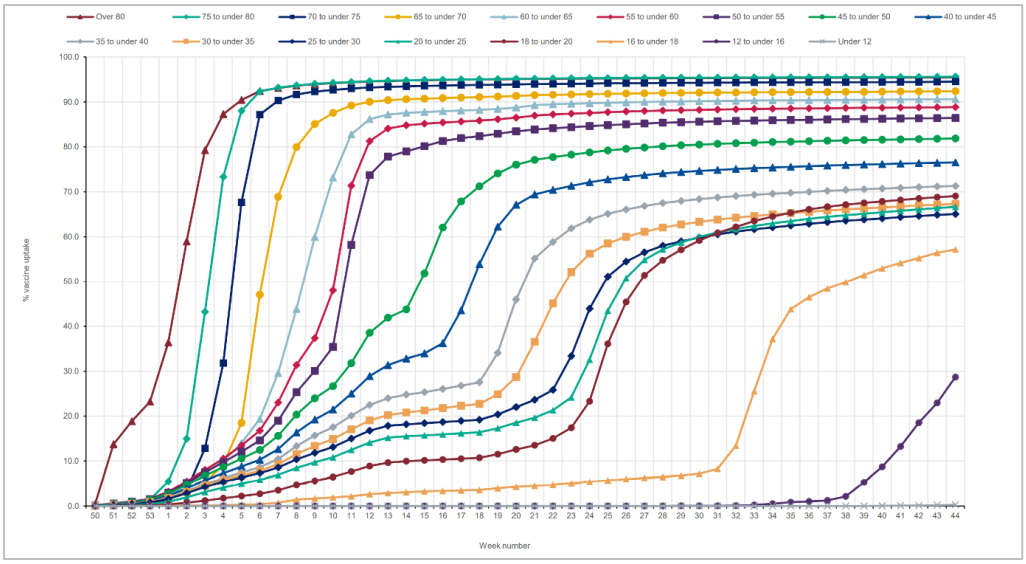
The latest acceleration is likely to be attributable to the change in booking procedure over the weekend which now permits people to pre-book their vaccine well in advance of them becoming eligible.

If the programme can continue at around 2m doses per week then we are likely to have completed Priority Groups 1-9 (the only people for whom a booster has so far been approved) just ahead of the Christmas period, when we would expect much more mixing.



Meanwhile, the vaccination programme for 12 to 15 year olds makes steady, if unspectacular, progress, with around 30% now jabbed. Whilst the opening up of alternative booking arrangements for the half term week didn't appear to result in an acceleration in progress, it may have avoided the slowdown which would likely have resulted from the hiatus of the half term break.

However, no decision has been made regarding second doses for 16 and 17 year olds, nor for any vaccination of the 5 to 11 age band, although many other countries are now pressing ahead with this younger cohort.



More restrictions for those not fully vaccinated

In England an announcement this week stated that NHS front line staff will be required to be double vaccinated by April 2022 (link). This follows on from a prior announcement that Care home staff had to be double vaccinated, which came into force yesterday (link).

However, it's not only in the UK that restrictions appear to be increasing. The province of Upper Austria is to place those who are still unvaccinated into home lockdown from next Monday following an upsurge in infections (link). And in France the Pass Sanitaire, used to access hospitality and other venues, will be restricted – the pass will be de-activated for people who are over 65 and who had their second vaccine more than 6 months and 5 weeks ago, until they have a booster. (link)

Waning of SARS-CoV-2 antibodies and risk of breakthrough infections post vaccination (link)

The Virus Watch study is a household community cohort in England & Wales which includes a sub-cohort of adults who participate in antibody testing on a monthly basis. Data from antibody testing of this group between 1 July and 24 October, along with any PCR and lateral flow test results, were studied to understand waning of antibodies post second dose of ChAdOx1 (Oxford AstraZeneca) and BNT162b2 (Pfizer BioNTech) COVID-19 vaccines, and to evaluate the risk of breakthrough infections.

8,858 individuals who remained anti-N negative (i.e. with no antibody evidence of prior infection) were included in the analysis of anti-S (i.e. antibodies targeting the spike protein) waning over time.

Anti-S levels are substantially higher at three weeks after a second dose of BNT162b2 compared to ChAdOx1. Waning in antibody levels was observed for both vaccines following the second dose. Time to reach an anti-S threshold of 500 U/ml was estimated at 96 days for ChAdOx1 and 257 days for BNT162b2.

There was a reduced risk of breakthrough infection post second dose of vaccine for individuals with anti-S levels greater than or equal to 500 U/ml compared to those with levels under 500 U/ml (HR 0.62; 95%CIs:0.44-0.87; p=0.007). There was an increased risk of a breakthrough infection for those who received the ChAdOx1 compared to those who received BNT162b2 (OR: 1.43, 95% CIs:1.18-1.73, p<0.001).

The authors conclude that their data, which is consistent with results from national analyses of vaccine effectiveness, demonstrate the importance of booster doses and suggest that these should be prioritised to those who received ChAdOx1 as their primary course.

Vaccine effectiveness among US Veterans during 2021 (link)

This study was conducted to examine SARS-CoV-2 infection and deaths by vaccination status among 780,225 US Veterans during the period 1 February 2021 to 1 October 2021.

The authors found that, although vaccination remains protective against SARS-CoV-2 infection, protection waned as the Delta variant emerged in the U.S. Vaccine effectiveness against infection declined from 87.9% to 48.1% over the study, and the decline was greatest for the Janssen vaccine.

Despite increasing risk of infection due to the Delta variant, vaccine effectiveness against death remained high. Among those with a positive PCR test on or after 1 July 2021, vaccination was protective against death, although with some differences by age and vaccine type. There was greater effectiveness for those aged below 65 years and for those who received Moderna or Pfizer-BioNTech vaccines rather than the Janssen vaccine.

The table below shows vaccine effectiveness against death among Veterans with a positive PCR test on or after 1 July 2021. Note that this effectiveness will be lower than those reported from most other studies that also include people who test negative.

Vaccine effectiveness against death among US Veterans with a positive PCR test result

	Age <65 years	**Age ≥65 years**
Any vaccine	81.7% (95% CI: 75.7% to 86.2%)	71.6% (95% CI: 68.6% to 74.2%)
Janssen	73.0% (95% CI: 52.0% to 84.8%)	52.2% (95% CI: 37.2% to 63.6%)
Moderna	81.5% (95% CI: 70.7% to 88.4%)	75.5% (95% CI: 71.8% to 78.7%)
Pfizer-BioNTech	84.3% (95% CI: 76.3% to 89.7%)	70.1% (95% CI: 66.1% to 73.6%)

FDA authorises COVID-19 Vaccine in Children 5 to 11 Years of Age (link)

On 29 October the U.S. Food and Drug Administration authorised the emergency use of the Pfizer-BioNTech COVID-19 Vaccine for children aged 5 to 11 years. The authorisation was based on, inter alia, data from an ongoing randomised trial funded by BioNTech and Pfizer.

The Pfizer-BioNTech COVID-19 Vaccine for children aged 5 to 11 years is administered as a two-dose primary series, 3 weeks apart, but is a lower dose (10 micrograms) than that used for individuals 12 years of age and older (30 micrograms).

In the phase 2–3 trial, trial participants were randomly assigned to receive the BNT162b2 vaccine (1,517 children) or placebo (751 children). At data cut-off, the median follow-up was 2.3 months.

No vaccine-related serious adverse events were noted.

Effectiveness was inferred by an “immunobridging” approach, in which neutralising titres elicited by BNT162b2 in 5-to-11-year-olds were compared with titres elicited in 16-to-25-year-olds. The level of these neutralising titres was found to be similar between the age groups one month after the second dose.

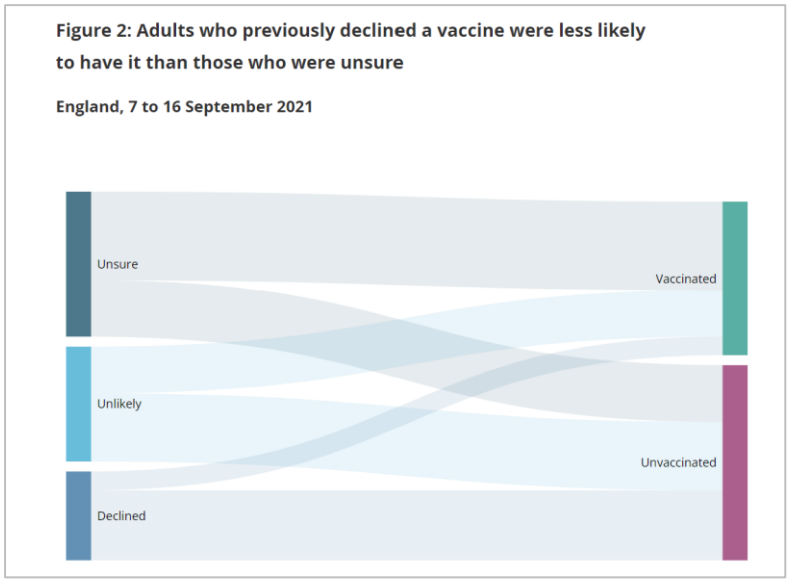
Covid-19 with onset 7 days or more after the second dose was reported in three recipients of the BNT162b2 vaccine and in 16 placebo recipients (vaccine efficacy, 90.7%; 95% CI, 67.7 to 98.3).

Changing Attitudes to Vaccination (link)

The ONS has been studying people’s attitude to vaccination for around a year now, initially in advance of vaccines becoming available, and subsequently through the roll-out process. In an interesting exercise, it has now looked at how attitudes have changed of those who expressed varying degrees of resistance initially to being vaccinated.

The results are fairly logical in that those most resistant at the outset have seen a smaller proportion subsequently change their mind. In the visual below, of those “unsure”, 60% have now been jabbed, falling to 40% of those who said they were unlikely. Of those who initially declined the vaccine, the proportion is still a relatively low 21%.

With compelling evidence that vaccination dramatically reduces serious illness and death, and also reduces pressure on the NHS enabling other services to be maintained, the survey is a reminder that despite high vaccination rates for many age groups, there is still work to be done to persuade those continuing to be hesitant of the personal and wider benefits of vaccination.



Clinical and medical news

Long COVID symptom associations with self-reported and serology-evidenced SARS-CoV-2 infection (link)

A study conducted in France sought to investigate whether belief in having had COVID-19 infection and actually having had the infection as verified by SARS-CoV-2 serology testing was associated with persistent physical symptoms.

This cross-sectional analysis included 26,823 participants. Between May and November 2020, a dried blood spot test was used to detect anti–SARS-CoV-2 antibodies. Between December 2020 and January 2021, the participants reported whether they believed they had experienced COVID-19 infection and had physical symptoms during the previous 4 weeks that had persisted for at least 8 weeks. 17 symptoms plus an "other" category were considered separately.

After performing logistic regression which adjusted for age, sex, income and education level, self-reported infection was positively associated with all considered persistent physical symptoms, except for hearing impairment and sleep problems.

A positive serology test result was positively associated only with persistent anosmia (odds ratio, 2.72; 95% CI, 1.66-4.46).

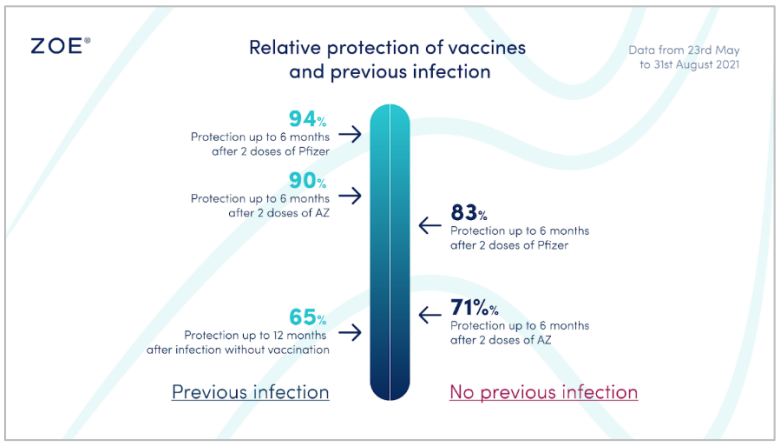
The authors conclude that physical symptoms persisting 10 to 12 months after the COVID-19 pandemic first wave may be associated more with the belief in having experienced COVID-19 infection than with actually being infected with the SARS-CoV-2 virus. They recommend that patients should be offered a medical evaluation to prevent their symptoms being erroneously attributed to COVID-19 infection and to identify cognitive and behavioural mechanisms that may be targeted to relieve the symptoms.

One of the criticisms levelled at the study is that some people with previous SARS-CoV-2 infection do not develop detectable antibodies, so those who believe they have been infected but have a negative serology test could still be correct in their belief.

Does SARS-CoV-2 infection always generate anti-N antibodies? (link)

Between April and August 2021, the ZOE COVID Study invited contributors who had logged a positive COVID test in their smartphone app to do an anti-N antibody test at home. Anti-N tests look for antibodies that are only produced via natural infection.

Out of 8,193 contributors who tested positive, 6,609 (80.67%) had a positive anti-N antibody test result.



People who had a greater number of symptoms while they were ill with COVID were more likely to have gained antibodies against the virus. However, smokers and people with one or more comorbidities were less likely to have antibodies after being infected.

The study data also suggests that two dose vaccination provides greater protection from infection than prior infection only. Vaccination in addition to prior infection conferred even higher protection.

Lack of antibodies following a COVID infection

A study in Nature (link) identified that a subset of healthcare workers in Wuhan were able to resist the SARS-CoV-2 virus without developing antibodies to the virus (seroconvert). These individuals were likely to have been repeatedly exposed to the virus at different levels. The study proposed that this protection was likely to be as a result of the mobilisation of previously activated T-cells against prior coronavirus infections, and targeting of different structures such as the reverse transcription complex that forms temporarily after the virus enters the cell.

The implication of this study is that a subset of UK unvaccinated healthcare workers will be able to resist infection and not infect others. However, this would also be true of a subset of UK vaccinated healthcare workers whose protection against the virus predated their vaccination.

Without evidence of their immunological protection, there is no reason to suppose that any individual healthcare worker who is unvaccinated is definitely in this subset, nor that they pose a lower risk to themselves or those under their care. One final caution – the Delta variant is considerably more transmissible than the virus at the beginning of the pandemic in Wuhan. The subset of naturally protected individuals against Delta is likely to be smaller in consequence.

How long do infection acquired antibodies last? (link)

Further on the topic of seroconversion, we report later on the most recent ONS Antibody surveillance. One challenge has been estimating how many of these have developed antibodies because of prior infection or because of vaccination, or indeed both. The difficulty is that the common antibody assays monitor antibodies against the spike protein, and therefore are unable to differentiate between a prior infection and those vaccines focused on the SARS-CoV-2 spike protein (e.g., Pfizer, Moderna, AstraZeneca). Previous studies had identified that anti-membrane IgG antibodies developed after COVID-19 infection but it was not clear how long this antibody response lasted, which it would be very helpful to understand.

A new study has confirmed that the anti-membrane IgG antibody response lasts at least 1 year, as does anti-receptor binding domain antibody response. Evaluating the relative concentration of these different antibody responses would therefore provide a clear indication as to prior infection.

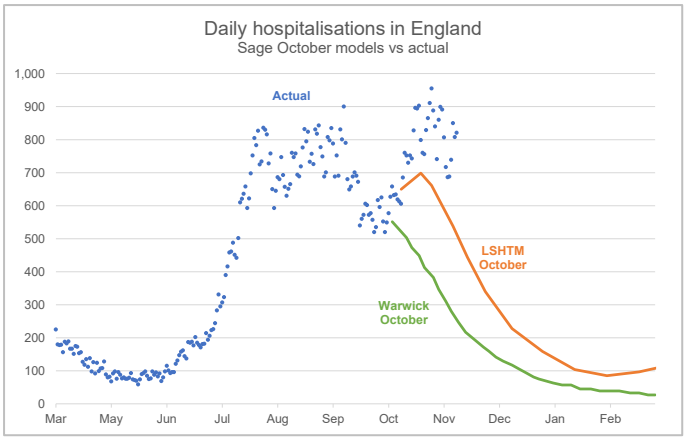
Modelling

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 this group of universities had published updated models, 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 chart below shows an updated actual trajectory of hospitalisations in England against two example projections produced.

Actual hospitalisations are significantly above the groups' expectations currently, but are now starting to fall. We will track these figures on a regular basis.



Data

Increased household transmission of SAS-CoV-2 Delta variant vs Alpha variant (link)

A study conducted in England and published in The Lancet has shown that the odds ratio of household transmission was 1.70 among Delta variant cases (95% CI 1.48-1.95, p <0.001) compared to Alpha cases after adjusting for age, sex, ethnicity, index of multiple deprivation (IMD), number of household contacts and vaccination status of index case.

The findings support existing evidence that the Delta variant has a substantially increased transmissibility advantage over the Alpha variant. This advantage has contributed to the rapid increase in the number of Delta variant cases in the UK and around the world.

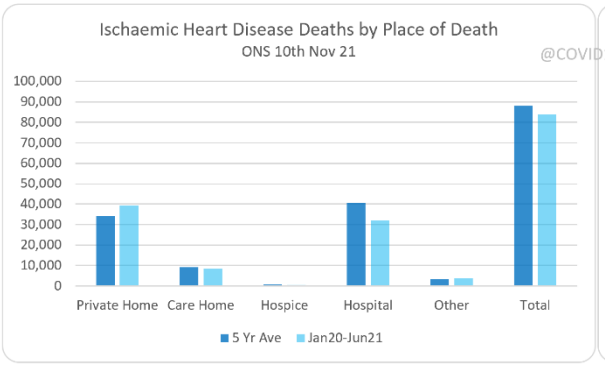
This was a matched case-control study in which 5,976 genomically sequenced index cases in households with 2 or more infections were matched to 11,952 sporadic index cases (single case within a household). The study population consisted of sequenced Delta and Alpha variant SARS-CoV2-positive cases who had a first positive specimen date between 18 March 2021 and 7 June 2021.

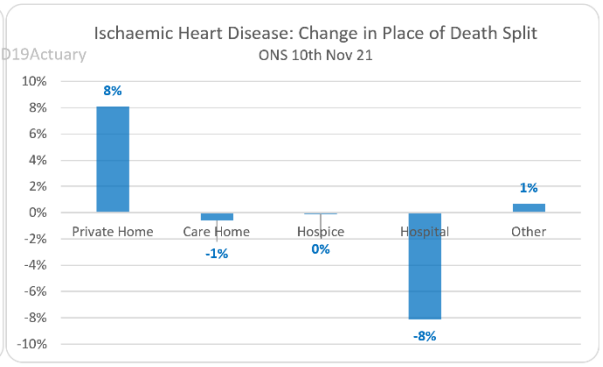
ONS Home Deaths Analysis (link)

The topic of increased home deaths throughout the pandemic has frequently been raised, and some commentators have sought to make a link between this excess and failures in the health system resulting in increased deaths unrelated to COVID.

The latest in an occasional series of updates from the ONS confirms that over the pandemic, deaths at home have risen by around a third. However, an analysis of the data shows that the majority of this increase is attributable to displacement from other places, most notably hospitals, with little sign of an overall increase in deaths from non-COVID related causes.

Many of the leading causes are those where end of life care is often extended, and the switch to providing that care at home, and thus the displacement seen in the figures is intuitive. What is more interesting is that one of the other major causes, ischaemic heart disease, sees a similar pattern, despite this often being associated with the need for sudden acute treatment and admission to save the patient from death (and thus be more likely to be impacted by a reluctance or inability to get immediate treatment).

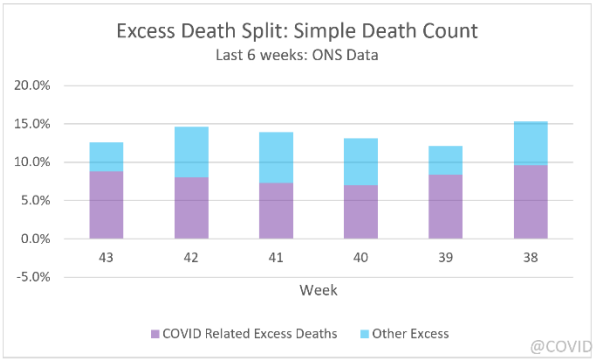


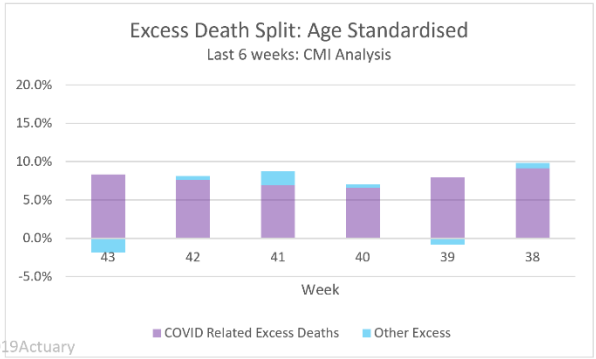


Excess Deaths from Non-COVID causes

We've seen in recent weeks that using the simple ONS death count data (link), excess deaths have typically been considerably greater than the number of deaths identified as COVID related. However, in contrast, the age-standardised analysis produced weekly by the CMI (link) shows a different pattern, with COVID deaths being responsible for the vast majority of the excess.

The reason for this is related to our ageing population which means we expect more deaths each year, even if underlying mortality is unchanged. Thus on a simple death count basis we would expect more deaths in 2021 than in the comparison period 2015 to 2019, and so these deaths should be excluded in any assessment of the excess. An age-standardised approach makes this adjustment, and hence produces a much lower "non-COVID excess".





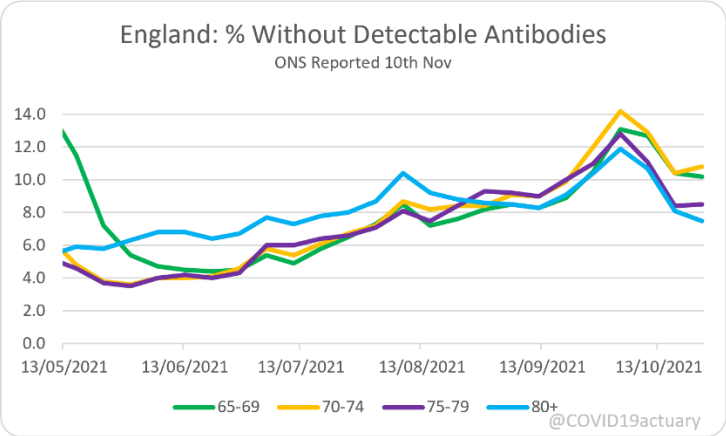
The actual picture is of course more complex, an example being that we expect there to have been some forward displacement of mortality (and thus fewer non-COVID deaths than we are actually seeing). Nevertheless, this analysis shows why the simple approach of using death counts is likely to significantly overstate the level of non-COVID excess mortality.

ONS Antibody Study (link)

The latest antibody study from ONS shows that levels across the UK have nudged up slightly (with the exception of Northern Ireland) and remain in excess of 90%. Of more interest is in the pattern at older ages where previous reports have shown a steady decline. From the graphs below we can clearly see that this trend has now reversed at all ages above 60, which will be a result of the booster programme now taking effect.

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

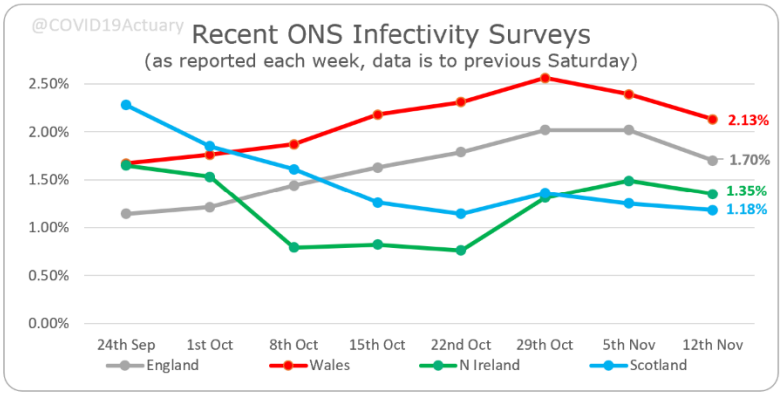
As usual, we prefer to track the proportion of those for whom antibodies have **not** been detected, and here the change is much more apparent. Note too that the data are only to Oct 24th, and it takes at least a week for the boost in antibodies to become apparent, so the reduction seen is likely to only represent those boosted by mid-October.

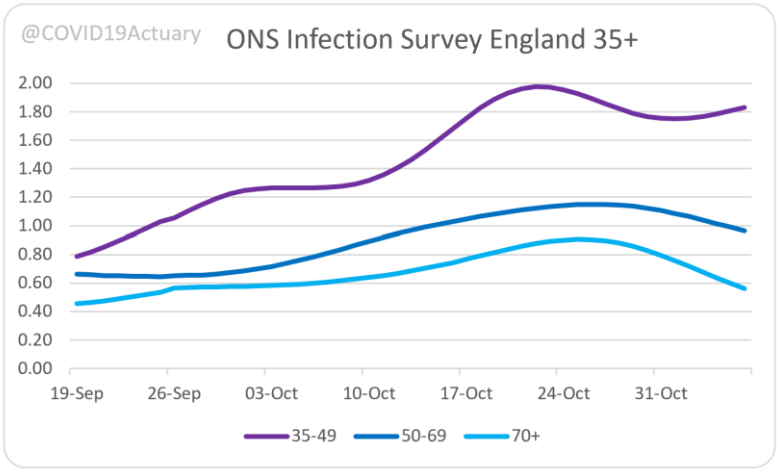


ONS Infection Survey (link)

The latest infection survey from ONS shows that infection levels are now falling across all four nations, driven by a fall in levels in older school children from the exceptionally high rates we were seeing a couple of weeks ago. In England rates peaked at 2.0% and have now fallen to 1.7%.

Whilst the stand out feature in the data is the fall in the Year 7 to 11 rates, which in England have halved in just a fortnight, looking at the underlying data again shows a clear signal that the booster programme is starting to have an impact in rates in the Over 70s, with a faster fall than observed in the age group below.





'R' Estimate (link)

A fortnight ago we reported that the UKHSA estimate of R had increased from 1.1 to 1.3. Since then, the estimate has fallen, and now stands at 0.8 to 1.0, consistent with the trend seen in daily case data as reported on the government dashboard, and with the ONS infection data reported above.

Regional estimates are shown below.

Region	R	Growth rate % per day
England	0.8 to 1.0	-3 to +1
East of England	0.8 to 1.0	-5 to 0
London	0.8 to 1.0	-4 to +1
Midlands	0.8 to 1.0	-4 to +1
North East and Yorkshire	0.8 to 1.0	-5 to 0
North West	0.8 to 1.0	-4 to +1
South East	0.8 to 1.0	-5 to +1
South West	0.7 to 1.0	-5 to +1

And Finally

ChAdOx1, BNT162b2, or H_20 (link)

In a bizarre story being reported from Greece, it appears that many of those reluctant to get a vaccine nevertheless wanted the proof of vaccination to enable them to continue to participate in activities from which they would have otherwise been excluded.

The story goes on to say that many have been bribing vaccinators at centres to inject them with water instead, with a fee of €400 the "going rate". However, having taken the money it would appear that in many instances the vaccinators have gone on to administer the vaccine instead.

Whilst the ethical considerations of injecting a vaccine without consent of the patient is clearly a concern, local media report that complaints are considered unlikely given the admission it would require of an attempt to bribe those involved in the vaccination process.

12 November 2021