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Friday Report: Issue 52

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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.

With effect from 1 October, Public Health England ceases to exist and is replaced by the UK Health Security Agency (UKHSA) headed by Dr Jenny Harries. The statistical analysis provided by PHE over the last 18 months has been exceptional, and a great credit to all involved. We look forward to receiving the same quality of analysis and responsiveness to changing conditions from UKHSE in future.

Vaccines

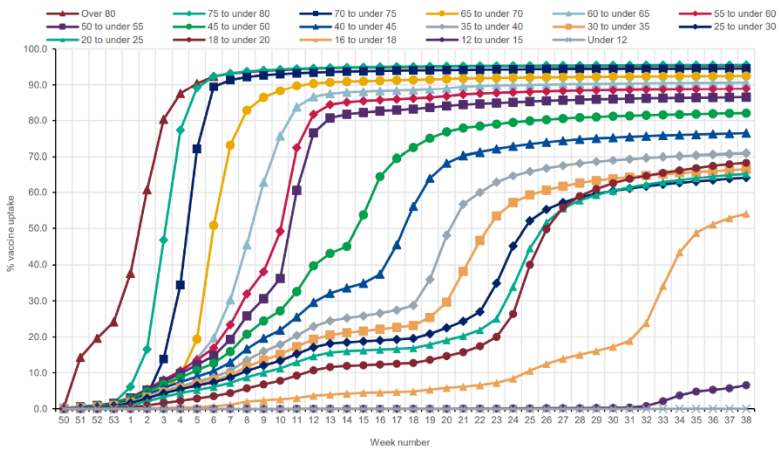
Slow Start to 12 to 15 Year Vaccination

In contrast to other age groups, there's been a very slow start to vaccination of younger teenagers, as evidenced by the final PHE vaccination report (before the PHE's transition to UKHSA noted above).

This age group, unlike others, is being vaccinated by the local school immunisation teams, so there is no opportunity for parents to book their children into one of the large vaccination centres or for them to be vaccinated by their GP practice. Comments seen suggest that these teams, who are also organising the roll-out of this year's flu vaccine, are very stretched, and that it is likely to take a couple of months to get to all schools.

It's a moot point whether the existing model (or at least the option of it for those who want it) would have been a more effective way of delivering doses faster, given the very high numbers of infections we've seen in schools since they reopened.

Figure 61: Cumulative weekly COVID-19 vaccine uptake by age in England for (a) Dose 1 and (b) Dose 2
(a)



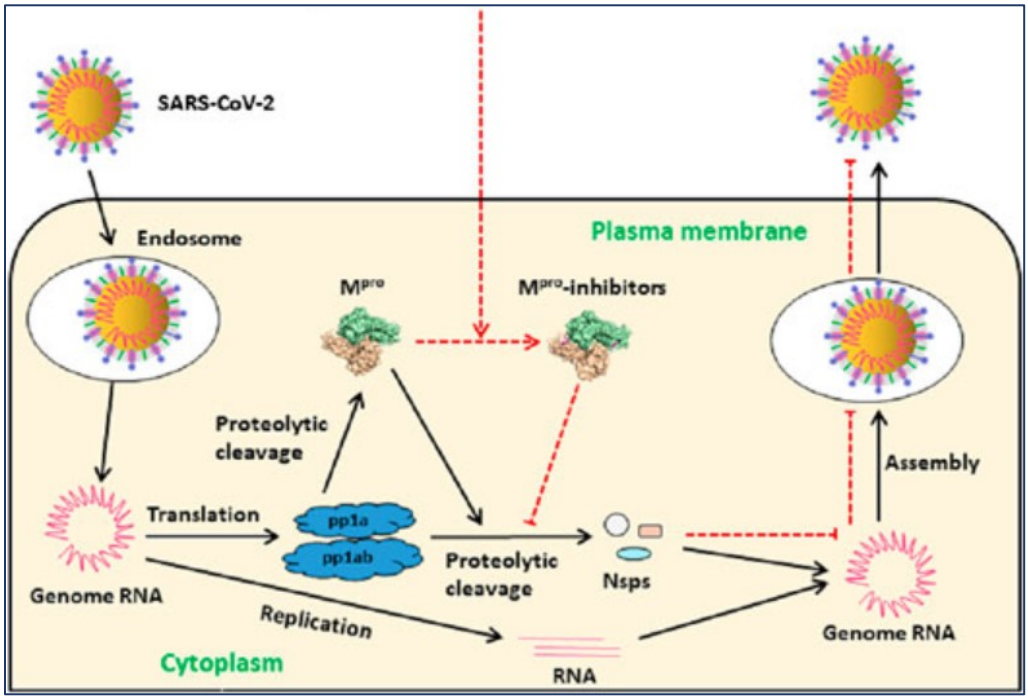
Clinical and medical news

New possibilities for anti-viral treatments

In contrast to the many successful vaccination programmes around the world, progress has been much slower with the development of anti-virals for SARS-CoV-2 that might limit viral transmission or the severity of symptomatic disease by interrupting viral replication. Many will have experienced the benefits of Tamiflu – shortening the period of illness, reducing risk of death by 50% (link) – during the 2009 Swine Flu Pandemic, as well as the chaotic scenes in distribution centres as many tried to get supplies "just in case" rather than as treatment (link). One of the clear benefits of antivirals such as Tamiflu is the cost – currently £23.30 for a course of 10 capsules.

One potential candidate with a long history, if not a catchy name, is **Pfizer's PF-07321332**. Development started during the 2002-2003 SARS-CoV outbreak, but Phase 1 clinical trials started only last year (link). PF-07321332 inhibits the 3CL protease enzyme, which normally splits long protein chains into the components that the virus needs to replicate itself (link).

Last year, PF-07321332 could be given only intravenously, and therefore its use would be restricted to hospitals. However, Pfizer has continued to develop the small molecule's delivery system, and so now it can be taken orally as either a pill or capsule (link). This opens the possibility of using the drug as a preventative measure for anyone who had been exposed to the SARS-CoV-2 virus.



This adds to the list of antiviral treatments that are being explored as prophylactic interventions. The multicentre CORIPREV study (link) registered last March in Canada was a ring-based prevention intervention intended to prevent transmission to household contacts from a confimed SARS-CoV-2 infected individual. The study was evaluating a 14-day combination course of lopanovir and ritonavir.

A new Phase 2/3 study from Pfizer was reported last week (link) investigating 5- or 10-day courses of a combination of **PF-0321332 and ritonavir**. The study is recruiting 2,634 volunteers, started on September 9 and is expected to complete on/by Christmas Day. A positive outcome would be a wonderful present to us all.

In the meantime Merck has announced that **molnupiravir**, an oral antiviral medicine, significanctly reduced risk of subsequent hospitalisation or death in a phase 3 randomised, placebo-controlled, double-blind, multi-site study trial among non-hospitalised patients with mild-to-moderate COVID-19 (link). In the trial 7% of patients who received molnupiravir were either hospitalised or died by Day 29 following randomisation (28/385), compared with 14% of placebo-treated patients (53/377). By Day 29 no deaths were reported in patients who received molnupiravir, compared with 8 deaths in patients who received placebo.

Additionally, based on the participants with available viral sequencing data (approximately 40% of participants), molnupiravir demonstrated consistent efficacy across the Gamma, Delta, and Mu variants.

Due to these positive results, recruitment into the study is being stopped early, and Merck plans to submit an application for Emergency Use Authorisation to the U.S. FDA as soon as possible (as well as marketing applications to other regulatory bodies worldwide).

Incidence and evolution of Long COVID (link)

This retrospective cohort study is based on the electronic health records of 81 million patients mostly in the US, of whom 273,618 were identified as COVID-19 survivors. The study included data with diagnoses on or after 20 January 2020 and patients included were still alive on 16 December 2020.

Long COVID was identified by the presence of one or more of 9 clinical features. Presence of these features among COVID-19 survivors was compared with a matched cohort of patients diagnosed with influenza but not with COVID-19 during the study period.

Among COVID-19 survivors, 57% had one or more Long COVID feature recorded during the 6-month period from the index event, whilst 37% had one or more feature between 3 and 6 months after the index event. When this is broken down by specific symptoms, the results are as follows:

- abnormal breathing (19% in the 1- to 180-day period; 8% in the 90- to180-day period)
- fatigue/malaise (13%; 6%)
- chest/throat pain (13%; 6%)
- headache (9%; 5%)
- other pain (12%; 7%)
- abdominal symptoms (16%; 8%),
- myalgia (3%; 1.5%),
- cognitive symptoms (8%; 4%)
- anxiety/depression (23%; 15%)

All 9 features were more frequently reported after COVID-19 than after influenza, co-occurred more commonly, and formed a more interconnected network. Significant differences in incidence and co-occurrence were associated with sex, age and illness severity.

The study did not include patients who had COVID-19 (or flu) but were not diagnosed, nor did it include patients who did not seek medical attention when experiencing symptoms of Long COVID. Therefore the results reflect more severe infections and patients with greater propensity to seek medical attention for initial infection and ongoing symptoms.

Modelling

Risk prediction of COVID-19 related death and hospital admission in adults after COVID-19 vaccination (link)

This paper explains the development of a UK population-based risk algorithm to identify those at highest risk of COVID-19 related death and hospital admission after vaccination. Candidate predictor variables included age, sex, ethnic origin, deprivation, body mass index, a range of comorbidities and SARS-CoV-2 infection rate.

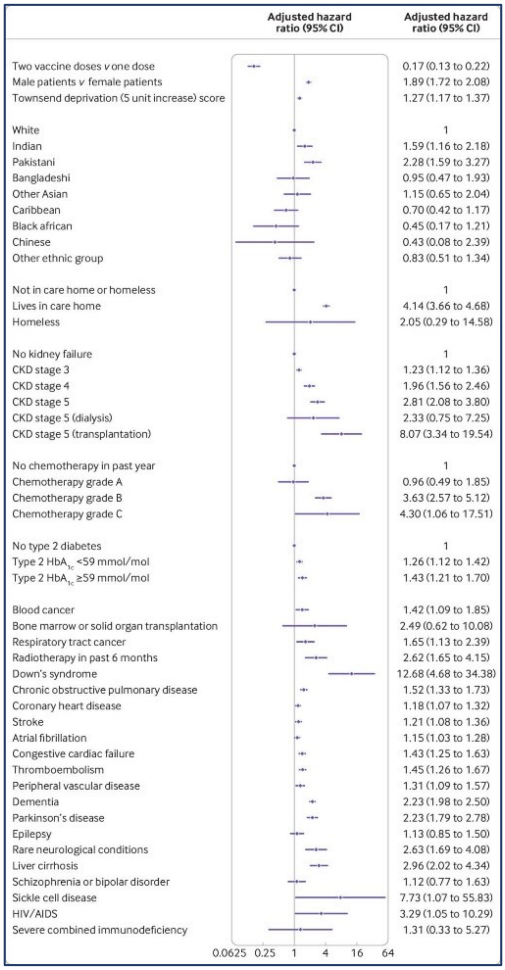
The algorithm was developed using data from adults aged 19-100 with one or two doses of COVID-19 vaccination between 8 December 2020 and 15 June 2021. Almost 7 million people were included in the derivation cohort.

Outcomes were assessed from 14 days after each vaccination dose. Of 2,031 deaths and 1,929 hospital admissions, 81 deaths and 71 admissions occurred 14 days or more after the second vaccine dose.

COVID-19 mortality increased with age, deprivation, male sex and Indian and Pakistani ethnic origin. Hazard ratios were highest for patients with Down's syndrome (12.7-fold increase), kidney transplantation (8.1-fold), sickle cell disease (7.7-fold), care home residency (4.1-fold), chemotherapy grade C (4.3-fold), HIV/AIDS (3.3-fold), liver cirrhosis (3.0-fold), neurological conditions (2.6-fold), recent bone marrow transplantation or a solid organ transplantation ever (2.5-fold), dementia (2.2-fold) and Parkinson's disease (2.2-fold).

Other conditions with increased risk (ranging from 1.2-fold to 2.0-fold increases) included chronic kidney disease, blood cancer, epilepsy, chronic obstructive pulmonary disease, coronary heart disease, stroke, atrial fibrillation, heart failure, thromboembolism, peripheral vascular disease and type 2 diabetes.

A similar pattern of associations was seen for COVID-19 related hospital admissions.



There was no evidence to indicate that associations differed after the second dose, although absolute risks were materially reduced as the hazard ratio for two vs one dose was 0.17 (95% CI 0.13 to 0.22).

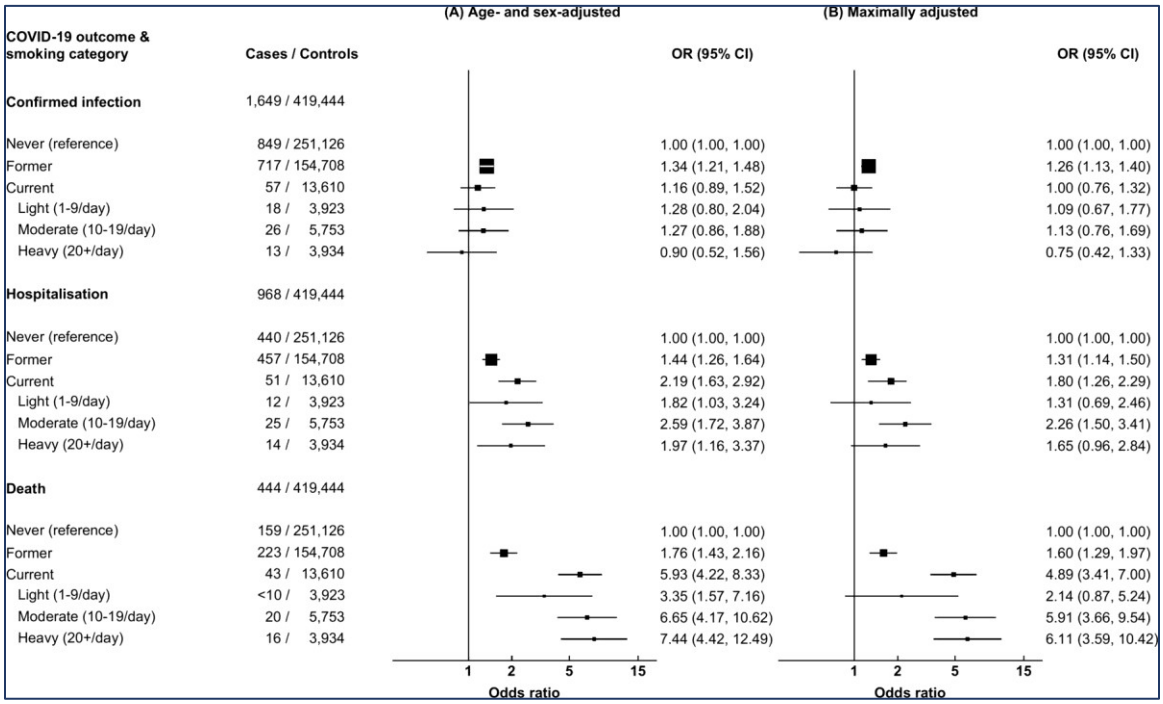
The risk algorithm explained 74% (95% confidence interval 71% to 77%) of the variation in time to COVID-19 death in the validation cohort. In the top 5% of patients with the highest predicted covid-19 mortality risk, the sensitivity for identifying COVID-19 deaths within 70 days was 79%.

Smoking and COVID-19 outcomes (link)

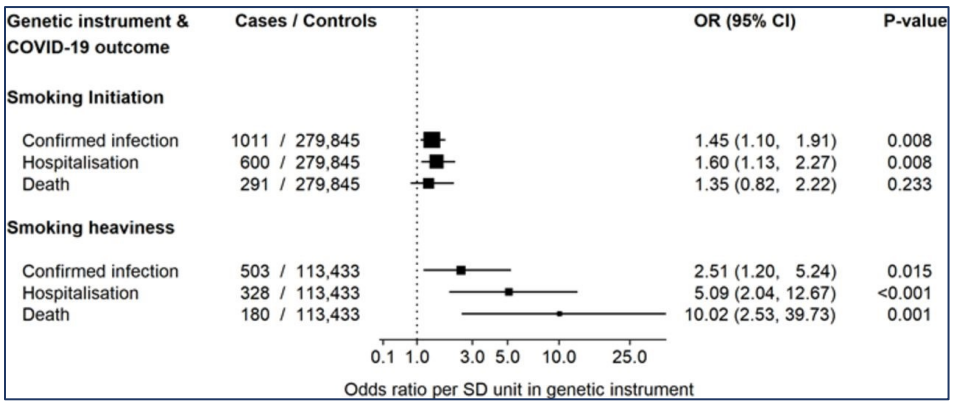
In this study, researchers used UK Biobank data which was linked to testing, hospitalisation and death data up to 18 August 2020. Two analyses were presented:

- An observational study using the latest self-reported smoking status recorded in Biobank questionnaires and primary care data.
- Mendelian Randomisation (MR) which used genetic information as proxies for smoking behaviours as opposed to observed behaviours. This approach can overcome common problems in observational studies such as residual confounding and/or reverse causation because the genetic information provides support for causal associations.

In the observational study current smokers had higher risks of hospitalisation and mortality compared with never smokers but no significant effect was seen for infection.



In the MR analysis, genetically predicted propensity to initiate smoking was associated with significantly higher risks of infection and hospitalisation. Genetically predicted higher number of cigarettes smoked per day was associated with higher risks of infection, hospitalisation and death.



The results of these two analytical approaches support a causal effect of smoking on risk of severe COVID-19 which contrasts with some earlier studies that suggested that smoking may confer a protective effect. The authors of this paper suggest that confounding effects may have influenced the results of the earlier studies.

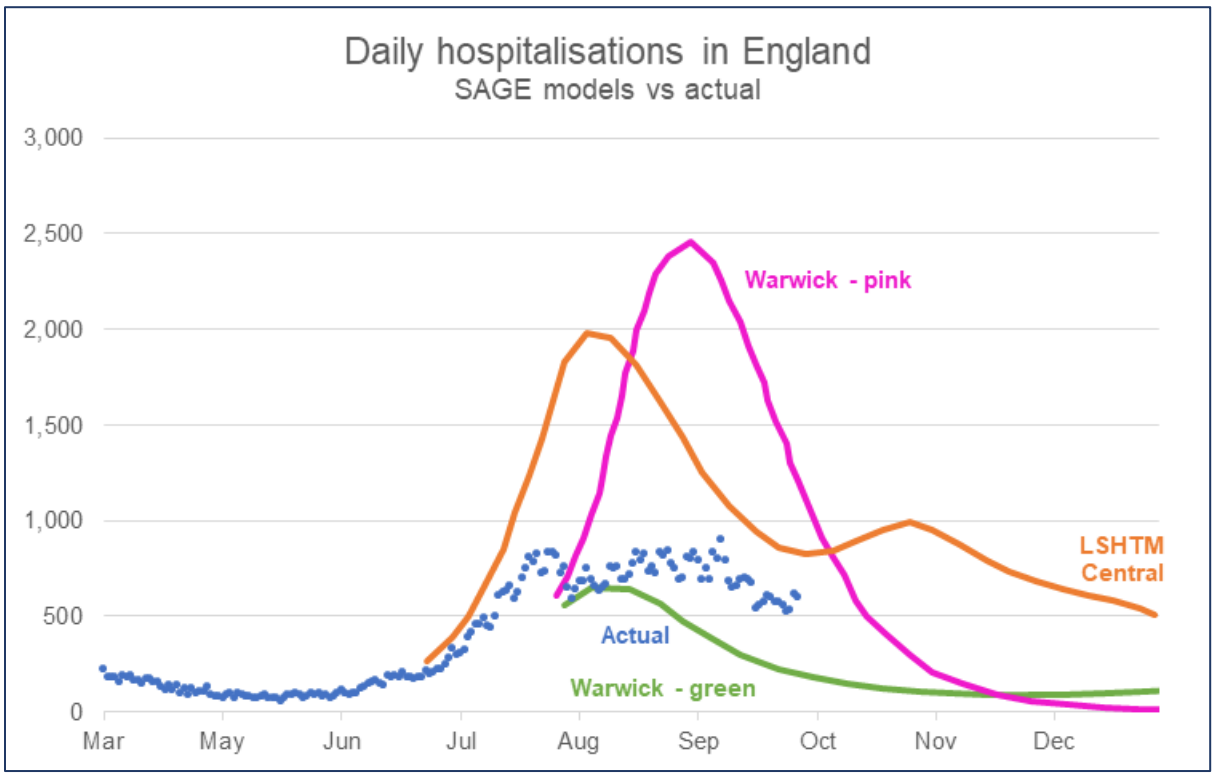
Monitoring actual and modelled hospitalisations

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.

The chart below shows an updated actual trajectory of hospitalisations in England against four of the projections produced by the groups:

- LSHTM central model (assuming waning immunity of 15% over the next 12 months)
- Warwick "**green**" and "**pink**" models which represent the two extremes of their assumptions on precautionary behaviour
    - "**Green**" assumes a gradual move towards pre-pandemic behaviour over the period to March 2022
    - "**Pink**" assumes an immediate step-change to a state close to pre-pandemic behaviour, with a full return to pre-COVID mixing reached by September 2021

In order to see the actual figures more clearly, we have removed the central Imperial projection which indicated much higher levels of hospitalisation than the other models.



This update shows that actual hospitalisations (**blue**) have fallen in recent weeks, having reached a peak around mid-September. They are tracking below the LSHTM estimate and above the Warwick "**green**" estimate, which is towards the lower end of the trajectories produced in the intial modelling papers. We will continue to track the figures regularly.

Data

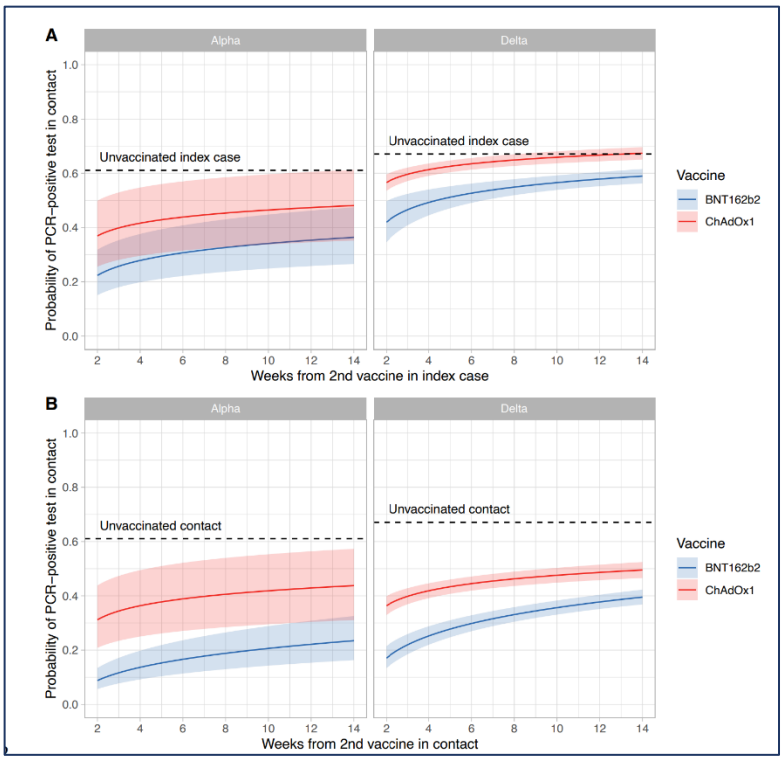
Efficacy of Vaccines in Reducing Transmission (link)

A major new study using test and trace data over the first seven months of 2021 has looked at the effect of vaccines in reducing transmission, both from the perspective of the person who is already positive (the "index case") and contacts of that person, who are at risk of being infected.

The period investigated saw the predominant variant switch from Alpha to Delta, so an additional benefit has been to identify any differences between vaccine effectiveness for these two.

As can be seen from the graphs below, Pfizer is considerably better than AZ, both in respect of the index case being vaccinated, and also the contact. However, the effect is significantly reduced for Delta for index cases.

A notable finding is that with Delta, the effect for index cases wanes more quickly, until by ten weeks there is negligible benefit. However, it should be noted that as having an AZ vaccine reduces the chance of being infected in the first place (evidenced by the bottom right-hand graph), it is still effective in reducing transmission as one can only transmit if infected.

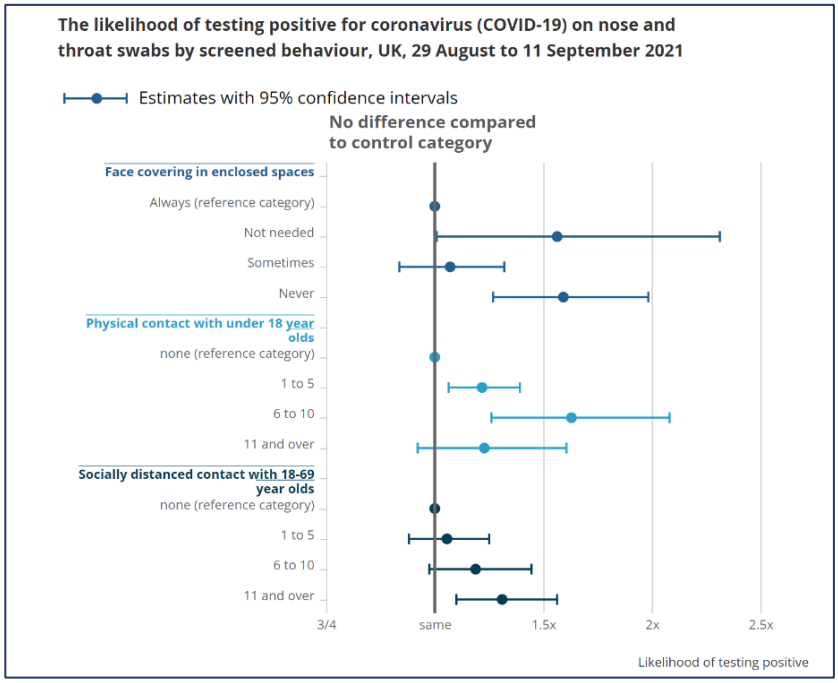


Another interesting finding is in respect of the likelihood of transmitting as viral load decreases. For Alpha this dropped off quite quickly, whereas Delta appears to still transmit at much lower viral loads. This may well be a key contributor behind Delta having a higher R_0 than Alpha.

Mask Wearing and COVID Positivity (link)

A study by the ONS has shown that those people who didn't wear face coverings on a regular basis were around 50% more likely to become infected than those that did, based on data from the first two weeks of September. Of note, the study carefully steps through the analysis done to identify and remove potential confounding effects (in particular age and vaccination status).

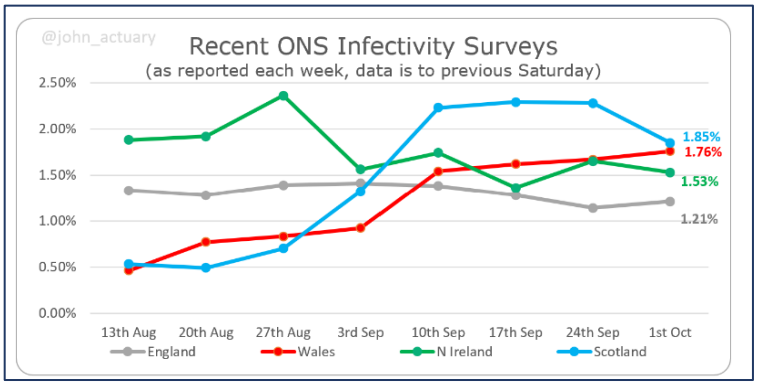
Given the polarised views on mask wearing, it's possible that this has been done to try and reduce the likelihood of inaccurate criticism of the study. However, it is highly likely that those using face coverings on a regular basis are generally more cautious than those who have chosen not to now that it is voluntary. Therefore we cannot say for sure that the whole of the difference identified is attributable to the wearing of masks.



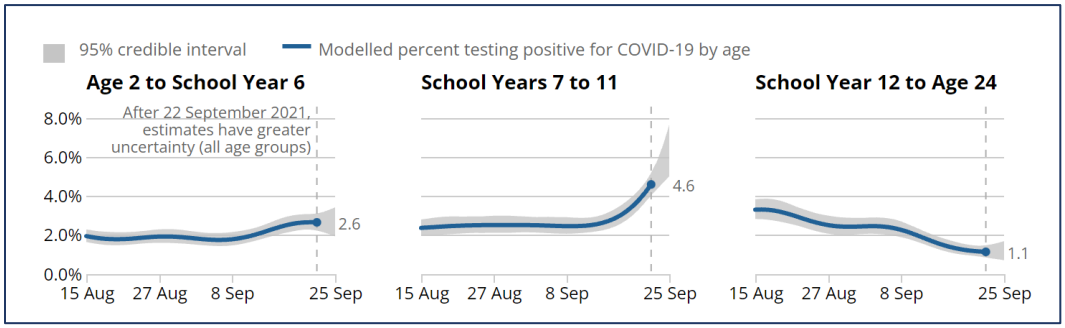
Nevertheless it is clear that those adopting more cautious behaviours, including continuing to cover their face, are less likely to become infected, and thus are helping to keep transmission rates down.

ONS Infection Survey (link)

The weekly report continues to show broadly static prevalence of infections in England and Northern Ireland, whilst Wales has drifted slightly higher for the third successive week and posted its 7th consecutive increase. In contrast, Scotland has shown a significant fall this week from its previous high level.



Probably the most noteworthy point about this week's report is the dramatic increase in prevalence in the school year 7 to 11 age group (broadly ages 11 to 16), which has doubled in just a fortnight. However, this increase has not been repeated in the younger school years, and on the other side, Yrs 12 (generally age 16-17) to age 24 has fallen.



R Estimate (link)

The latest estimate of R in England from UKHSA is wider this week, at between 0.8 and 1.1, and with the upper and lower bounds either side of 1.0, there is some uncertainty as to whether new infections are rising or falling.

As usual, we show the regional estimate below, which are almost identifical in terms of R, although there are some more differences when translated into a % growth per day.

Region	R	Growth rate % per day
England	0.8 to 1.1	-3 to +1
East of England	0.8 to 1.1	-3 to +2
London	0.8 to 1.0	-3 to +1
Midlands	0.8 to 1.1	-3 to +2
North East and Yorkshire	0.8 to 1.1	-2 to +2
North West	0.8 to 1.1	-2 to +1
South East	0.8 to 1.1	-4 to +1
South West	0.8 to 1.1	-3 to +1

And Finally …

Trusted data has been more important than ever during the pandemic, and one source in Australia has been COVIDBaseAU (link). Until now the identity of the people behind this site has not been known. Maybe university students? Statisticians? Or some other individuals with relevant specialist skills?

All was revealed this week when the team of three decided to publicise the fact that they have just received their first jabs, as Australia rolls out the programme to the 12 to 15 age group.

That's right: Jack, Wesley and Darcy turn out to be just 14-15 years old!

@COVID19Actuary would like to extend its congratulations to the three for the work they've done over the last year to keep people informed. Maybe there's a future actuary in the team? Regardless, we're sure they will do well in their chosen profession judging by their work over the last year or so.

1 October 2021