



Friday Report: Issue 56

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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.

New Website

We have recently launched our new website, which we hope you find gives both a fresh new look and is easier to navigate. The new address can be found in the top right corner of the page above.

Variants

New Covid Variant B.1.1.529

The Department of Health of South Africa shared emerging information about variant B.1.1.529 in a [video update](#) on 24 November.

The new variant has a high number of mutations which indicate possible immune evasion and increased transmission. At the time of presenting, it had been found in 77 samples in South Africa and 4 from Botswana and is estimated to account for 90% of cases in the Gauteng province. Like the Alpha variant, it features an S-gene drop out which makes it detectable by PCR assay. Early indications are that the variant has rapidly increased in Gauteng and may already be present in most provinces. Indeed, as we finalise this edition, reports are emerging of cases within Europe and elsewhere too.

It remains unclear what the actual impact of the variant may be – vaccines are highly likely to remain a critical tool against the disease.

This new variant has today been assigned the Greek letter Omicron and designated a Variant of Concern. Locally, UKHSA has today designated it a Variant under Investigation.

Vaccines

WHO interim statement on Covid-19 vaccination for children and adolescents

The WHO has released an [interim statement](#) with the following conclusions:

- As children and adolescents tend to have milder disease compared to adults, unless they are in a group at higher risk of severe COVID-19, it is less urgent to vaccinate them than older people, those with chronic health conditions and health workers.

- Benefits of vaccinating children and adolescents go beyond the direct health benefits including reduction in transmission from children and adolescents to older adults and minimising disruptions to education.
- Given current global inequity in vaccine access, the decision to vaccinate adolescents and children must account for prioritisation to fully protect the highest risk subgroups.
- Countries that have achieved high vaccine coverage in their high-risk populations should prioritise global sharing of COVID-19 vaccines through the COVAX facility before proceeding to vaccination of children and adolescents who are at low risk for severe disease.

European Medicines Agency (EMA) Recommend Vaccination of 5 to 11 Year Olds [\(link\)](#)

Following on from the CDC in the USA, the EMA has recommended vaccination of a reduced dose of the Pfizer vaccine for children aged between 5 and 11. A two dose regime of 10 µg, three weeks apart is recommended, one third of the dose used in older children.

This now goes forward to the European Commission for a final decision.

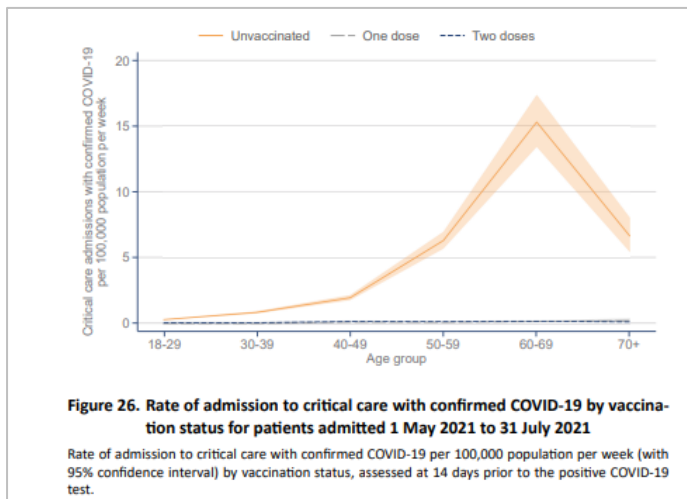
In contrast to the EU and USA, the current situation in the UK regarding any approval process via the MHRA and JCVI is less clear.

Vaccine effectiveness against Critical Care admission [\(link\)](#)

ICNARC reported on rates of admission to critical care by vaccination status for patients admitted between 1 May and 31 July 2021.

The vaccinated population size was determined using the NIMS database and the unvaccinated population was estimated as the mid-2020 ONS population estimate less the number of people vaccinated.

For those vaccinated with 2 doses, the admission rate per 100k per week at the time was approximately 0.1 for under 40s and 0.2 for ages 40+. For the unvaccinated, the critical care admission rates was 3 times this level for the under 30s, rising to 70 times for ages 60 to 69.



Vaccine effectiveness against Long COVID and other sequelae [\(link\)](#)

A pre-print study used electronic health records, primarily from the USA, to identify and match 9,479 vaccinated patients to unvaccinated controls, where both cases and controls tested positive for SARS-CoV-2 infection as a criterion for inclusion in the study. Outcomes were ICD-10 codes representing documented COVID-19 sequelae in the 6 months after a confirmed SARS-CoV-2 infection recorded between 1 January and 31 August 2021.

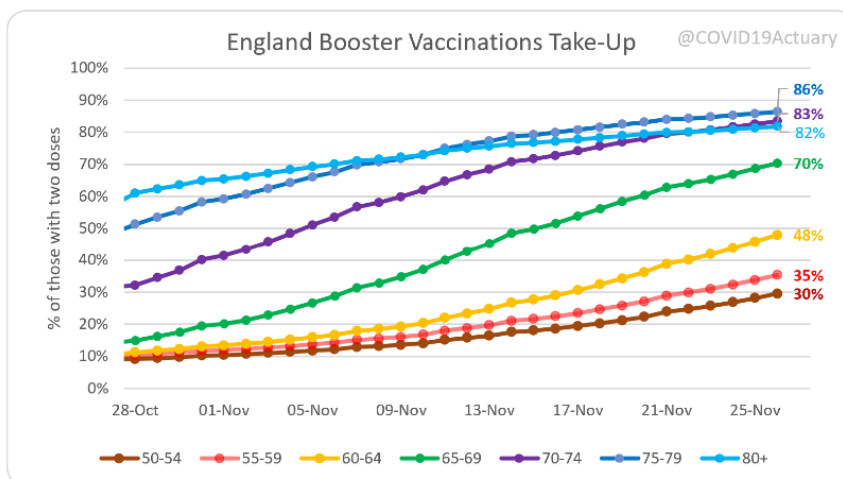
The study confirms that vaccination protects against death and ICU admission following breakthrough SARS-CoV-2 infection. The study also shows that vaccination is associated with lower risk of respiratory failure, hypoxaemia, oxygen requirement, hypercoagulopathy or venous thromboembolism, seizures, psychotic disorder and hair loss.

However, vaccination does not appear to be protective against long-COVID features, arrhythmia, joint pain, type 2 diabetes, liver disease, sleep disorders and mood and anxiety disorders.

Booster Roll-Out

In England the roll-out of boosters has continued to increase pace slowly, and is now at 2.1m doses a week, a considerably better position than a month ago. With the total now at 14m, what does this mean in terms of getting the most vulnerable jabbed before Xmas? Obviously one unknown factor is how many people will actually come forward, although it's looking as though this could reach around 90% at the oldest age groups. With around 7m additional doses administered by the week before Christmas (chosen to allow a minimum of 7 days for some effect to kick in), we could see 90% achieved in all age groups above 50.

This is a better position than some weeks ago, although given increased mixing occurs in the run up to Christmas Day, and around two weeks is needed to be confident that the booster has taken full effect, it is clear that many people in these age groups (as well as those below) will need to continue to be very careful over the festive period given the current high prevalence levels.

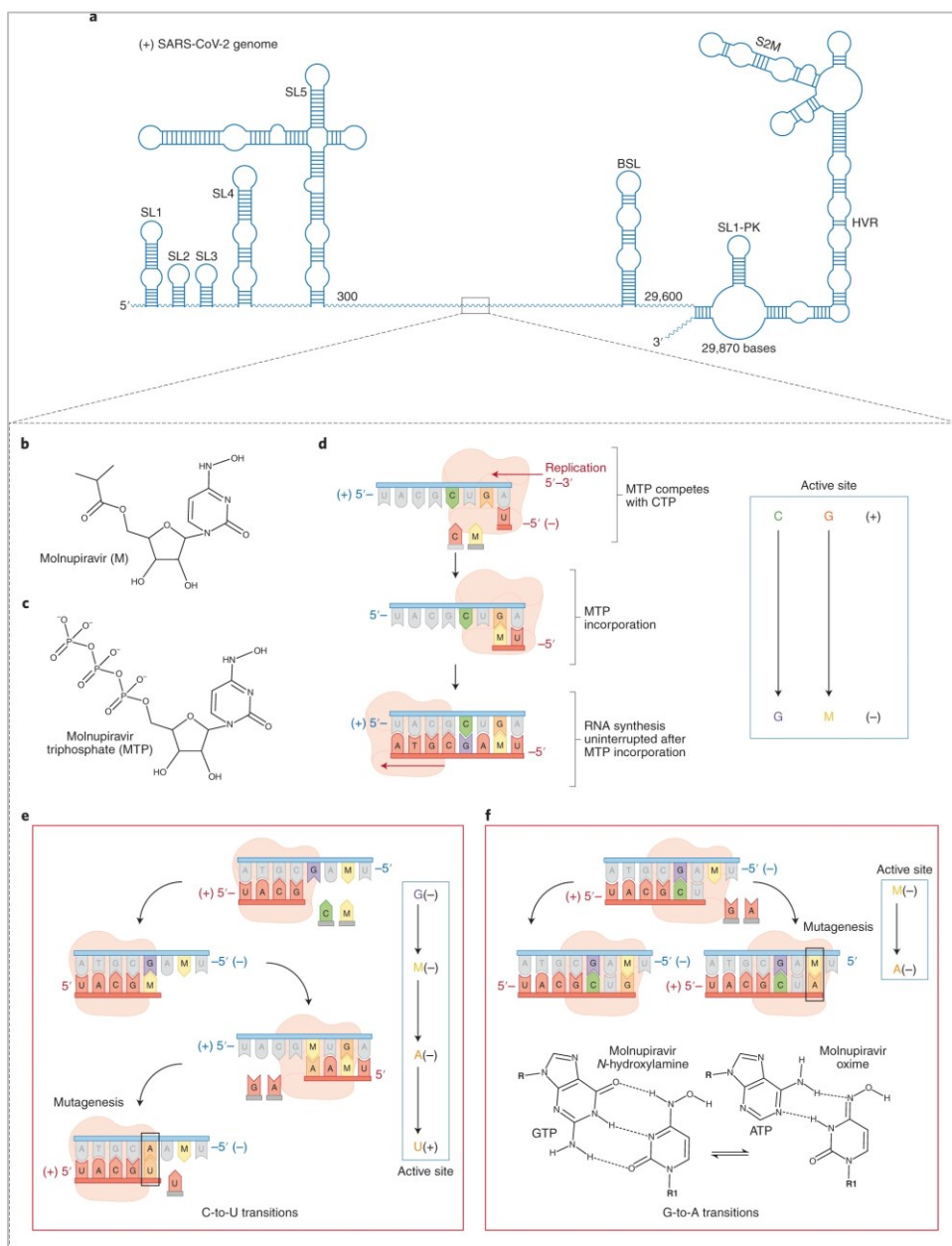


Clinical and medical news

Transparency over risks from anti-viral agents

Returning to B.1.1.529, whilst there are significant concerns that it may be able to successfully evade neutralising antibodies, it is being stressed that the virus should still be vulnerable to anti-viral agents, such as molnupiravir and paxlovid that interfere with different stages of viral replication and production. However, there have been concerns raised over the mechanism of action of molnupiravir.

Molnupiravir acts by interjecting itself into the replication process ([link](#)), and hence increasing the likelihood of base-pair transition mutations, either substituting a G for an A or a C for a U within the RNA genetic code. These changes in the genetic code lead to the selection of different amino acids, and hence affect the folding of the resulting proteins. As we have seen with B.1.1.529 and prior variants, it is these mutations that affect the shape and function of the proteins. If there are too many mutations or “lethal mutagenesis”, the virus may breach an “error threshold” and that viral reproduction line will become extinct.



The treatment regimen for molnupiravir is short, consisting of twice daily pills for 5 days. In its submission for authorisation ([link](#)), Merck recognised the potential of molnupiravir to cause mutation in non-viral cells, but observed that mammalian studies of longer and higher doses of molnupiravir than those proposed for human treatment had not shown evidence of mutagenesis or toxicity to the DNA genome.

This indiscriminate and widespread introduction of base-pair transition mutations by molnupiravir means that its use does not provide a potential path to future more transmissible variants. However, some have voiced concerns that molnupiravir may increase the likelihood of mutations in human DNA. Once again, the overwhelming majority of such mutations in the much larger DNA genome would have no impact, but further research may be indicated to determine whether interruption of signalling and regulatory sequences in the host DNA genome could lead to loss of control over cellular growth and the possibility of an increased risk of cancerous cells ([link](#)).

New COVID research projects from HDR UK and Turing Institute

Health Data Research UK and The Alan Turing Institute announced 9 new data projects across 16 collaborating universities on 11 November ([link](#)) with total funding of £2 million that will use large-scale linked data to improve understanding of the pandemic and inform policy response. The projects will use the Trusted Research Environments in England, Northern Ireland, Scotland and Wales, using data on genomic sequencing, vaccination and clinical records on the following topics:

- Will changes in the genome of the SARS-CoV-2 virus result in a decrease in vaccine effectiveness in the Scottish population?
- Do children and young people need extra follow-up care after having SARS-CoV-2 infection?
- Using AI as an aid to predict the risk of hospital readmission in patients with COVID-19
- Are those with chronic lung diseases at a higher risk of cardiovascular complications after having COVID-19 than those without lung disease?
- The impact of COVID-19 vaccines in pregnancy, children, young people and vulnerable groups
- The impact of previous exposure to COVID-19 and the safety of COVID-19 vaccination for fertility and pregnancy outcomes
- Impact of COVID-19 pandemic on the health of individuals with long term conditions
- Using medicines data to understand the effect of COVID-19 on clinical care
- Improving methods in health technology to reduce inequalities, particularly ethnicity bias, using COVID-19 as an example

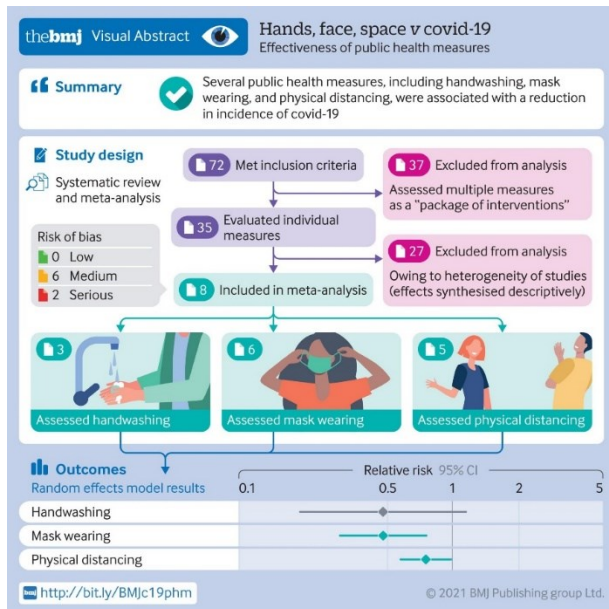
The 9 data projects will start this month and are expected to complete by September 2022.

Effectiveness of public health measures in reducing the incidence of COVID-19, SARS-CoV-2 transmission, and COVID-19 mortality

A variety of containment and mitigation strategies have been adopted to respond adequately to COVID-19 including the introduction of mask wearing by the general public, physical distancing, and increased hand washing. The introduction of effective vaccination programmes confers considerable protection, but no vaccine is 100% effective, and vaccine escape by emerging variants remains a concern. Therefore, continued efforts in the form of the public health measures outlined above are crucial in helping reduce transmission. But exactly how effective are these measures?

In this systematic [review](#), a group of public health experts examine the evidence on the effectiveness of both individual and multiple public health measures in reducing the incidence of Covid-19, SARS-CoV-2 transmission, and COVID-19 mortality. This review focused only on empirical studies.

As you can see in the visual abstract, this review suggests that these measures are associated with reduced incidence of COVID-19.



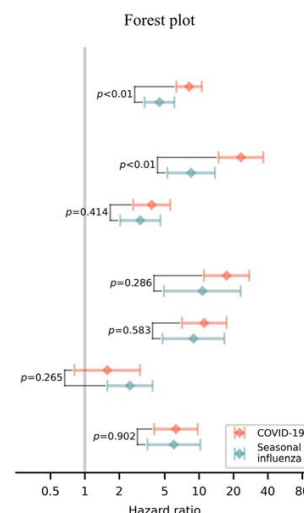
COVID-19 and risk of subsequent life-threatening secondary infections

Secondary bacterial infections develop in patients during or after initial infection with an infective pathogen, often a virus, and are associated with high morbidity and mortality rates. Using UK Biobank data, this [paper](#) reports on analysis of the association between COVID-19 and subsequent risk of life-threatening secondary infections.

Life-threatening secondary infections were defined as diagnoses of severe secondary infections with high mortality rates (i.e., sepsis, endocarditis, and central nervous system infections). Additionally, by using seasonal influenza as a control of the "exposure" condition, the researchers also explored to what extent the observed associations were exclusive to COVID-19.

The figure shows comparison of the hazards of life-threatening secondary infections in COVID-19 and seasonal influenza patients.

	Matched cohort for COVID-19			Matched cohort for seasonal influenza		
	No of cases/1000 person weeks (incidence rate)		Hazard ratio (95% confidence interval)*	No of cases/1000 person weeks (incidence rate)		Hazard ratio (95% confidence interval)*
	Exposed	Unexposed		Exposed	Unexposed	
All life-threatening secondary infections[†]	123/55.15 (2.23)	151/600.55 (0.25)	8.19 (6.33-10.59)	71/77.74 (0.91)	137/783.45 (0.17)	4.50 (3.34-6.08)
By different follow-up period						
0 to 3 weeks	79/14.71 (5.37)	35/153.85 (0.23)	23.26 (14.82-36.52)	36/18.39 (1.96)	40/184.56 (0.22)	8.53 (5.28-13.77)
3 weeks to 3 months	44/40.44 (1.09)	116/446.69 (0.26)	3.86 (2.65-5.60)	35/59.36 (0.59)	97/598.89 (0.16)	3.06 (2.04-4.60)
By severity of virus disease						
Hospitalization and operations/procedures	60/6.36 (9.43)	41/89.47 (0.46)	17.42 (11.04-27.49)	20/1.99 (10.06)	16/23.44 (0.68)	10.68 (4.93-23.15)
Only hospitalization	50/7.26 (6.88)	45/90.71 (0.50)	11.10 (7.08-17.40)	25/5.23 (4.78)	28/54.81 (0.51)	8.95 (4.79-16.70)
Without hospitalization	13/41.53 (0.31)	65/420.36 (0.15)	1.57 (0.81-3.05)	26/70.52 (0.37)	93/705.20 (0.13)	2.48 (1.57-3.92)
Life-threatening secondary infections following hospital discharge[‡]	38/11.02 (3.45)	72/148.69 (0.48)	6.28 (4.05-9.75)	28/6.47 (4.33)	38/69.24 (0.55)	6.01 (3.53-10.26)



COVID-19 was associated with an overall increased risk of subsequent life-threatening secondary infections, after considering multiple important confounders. This was most pronounced among hospitalized COVID-19 patients who received invasive treatment during hospital care.

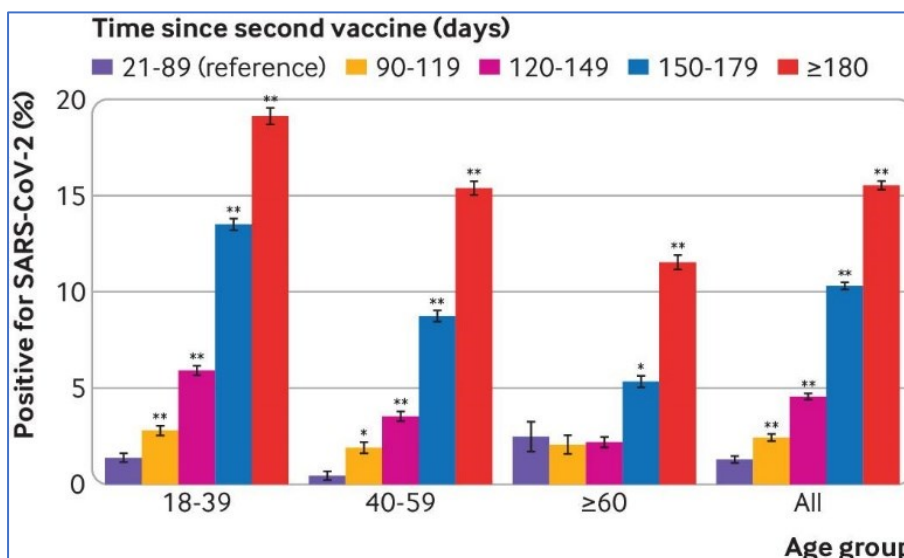
However, patients who had been discharged (both due to COVID-19 and seasonal influenza) were also at an approximately 6-fold increased hazard of life-threatening secondary infections.

Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection ([link](#))

Ariel Israel and colleagues here describe the results of a large-scale study measuring the association between time elapsed since administration of the second dose of the Pfizer-BioNTech BNT162b2 vaccine and the risk of COVID-19 disease.

The primary outcome was SARS-CoV-2 infection detected by the RT-PCR test.

The figure below shows that the rate of positive results increased with time elapsed since the second dose. The increase was statistically significant in all age groups after ≥180 days.



Compared with the initial 90 days after the vaccine, an increased risk of infection with time elapsed since vaccination was observed: adjusted odds ratio 2.37 (95% confidence interval 1.67 to 3.36) after 90-119 days; 2.66 (1.94 to 3.66) after 120-149 days; 2.82 (2.07 to 3.84) after 150-179 days; and 2.82 (2.07 to 3.85) after ≥ 180 days ($P < 0.001$ for all).

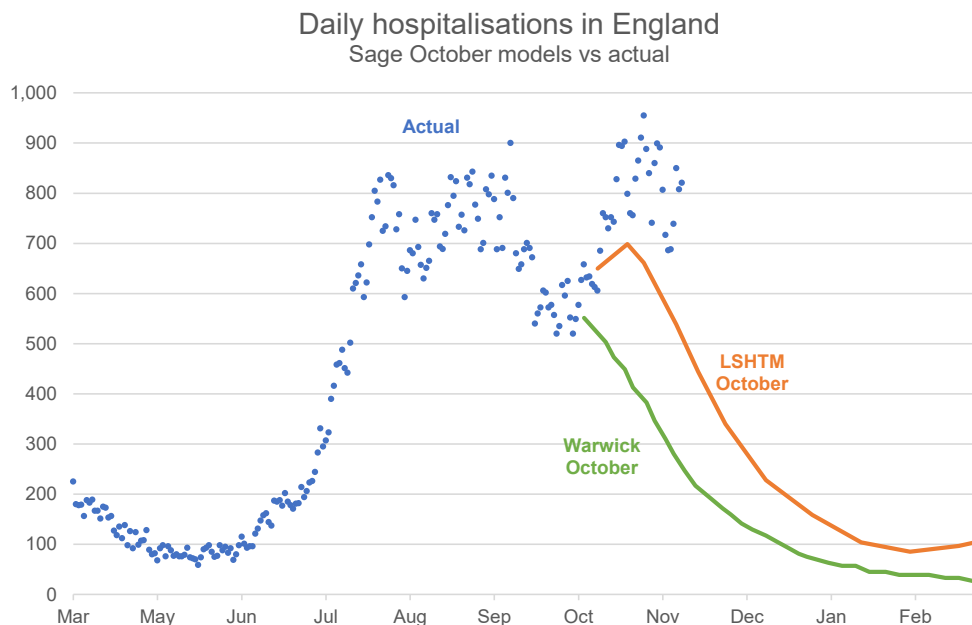
The study also showed that two injections, 21 days apart, provided more protection than one, and that the immune response to the vaccines was influenced by changes in the immune system related to age.

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 chart below shows an updated actual trajectory of hospitalisations in England against two example projections produced:



Actual hospitalisations remain above the groups' expectations currently but they are reducing, which is in line with the projected trajectories. We will track these figures on a regular basis.

Data

ONS and Simpson's Paradox

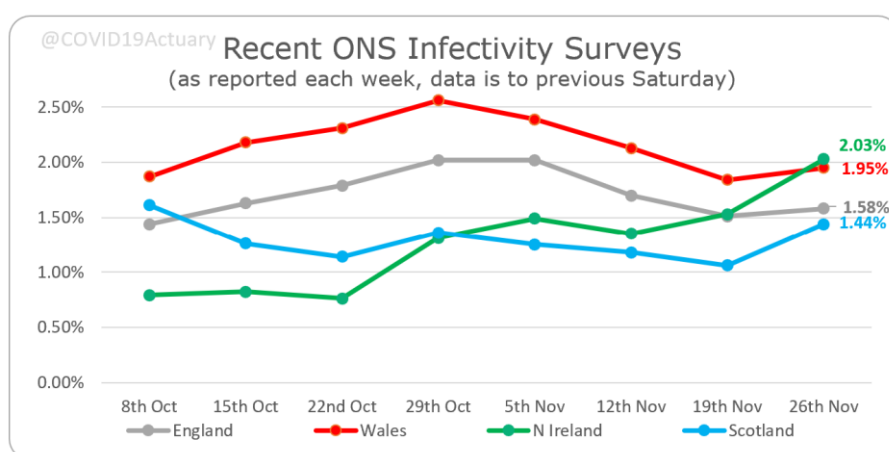
A recent study ([link](#)) by ONS looked at deaths by vaccination status, and concluded that, in total, vaccination has a beneficial impact on mortality, as would be expected. However, the accompanying dataset split the data down into age-bands, including one band for 10-59, which appeared to show the opposite – that the vaccinated were dying in significantly greater numbers. This information was widely reproduced in graphical format, as evidence that vaccination is, at best, unnecessary at younger age groups, and at worst, may be harmful. This “evidence” has typically been shared by those who have consistently been critical of the vaccination programme's aims.

The reality is however somewhat different, and the explanation is a good example of Simpson's Paradox, (disappointingly not named after Homer, Bart, et al, but the statistician who set it out). We know that vaccination rates are very dependent on age, being very high at the upper end of the 10-59 age band, and very low at the bottom of it (where some are not even yet eligible). So the pattern seen simply reflects that mortality (both COVID and normal) is much higher at those age groups where vaccination rates are high, and the converse at the youngest ages.

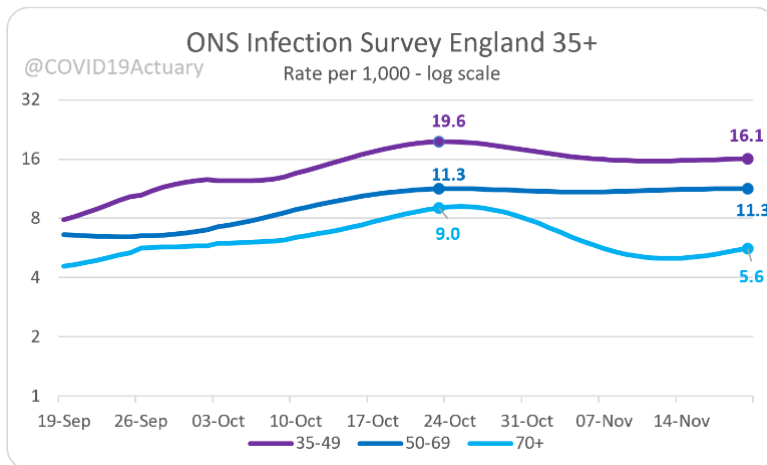
We covered this in a blog ([link](#)), and later in the week the Office for Statistics Regulation wrote to the ONS to express its concerns at risks of releasing these data without sufficient explanation of the likely causes of the patterns seen ([link](#)).

ONS infection Survey ([link](#))

The latest ONS infection survey is now showing increases in all four nations, after steady falls in three of the four in recent weeks (Northern Ireland being the outlier). However, the increase is to be expected following increase in case rates in recent weeks, which tends to be a leading indicator of the ONS study, which measures prevalence, and is also a little more lagged.



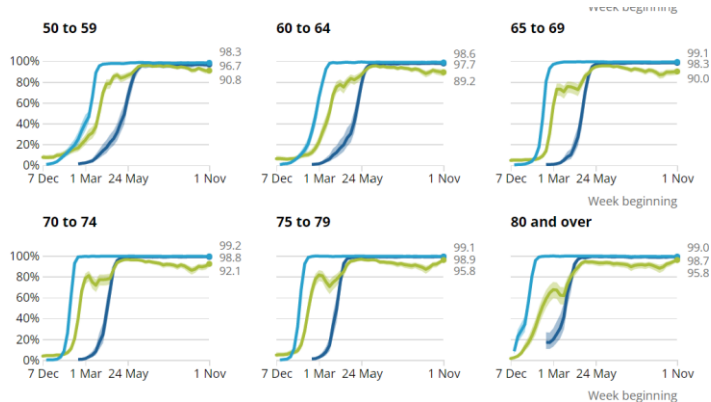
More disappointing is the trend in the oldest age group, 70+. We've seen a big drop over the last month as the impact of the booster jabs starts to take effect, with rates halving. However, that appears to have, at best, levelled off (the latest few days is always regarded as more uncertain by ONS, so it is premature to read too much into the increase seen).



ONS Antibody Survey (link)

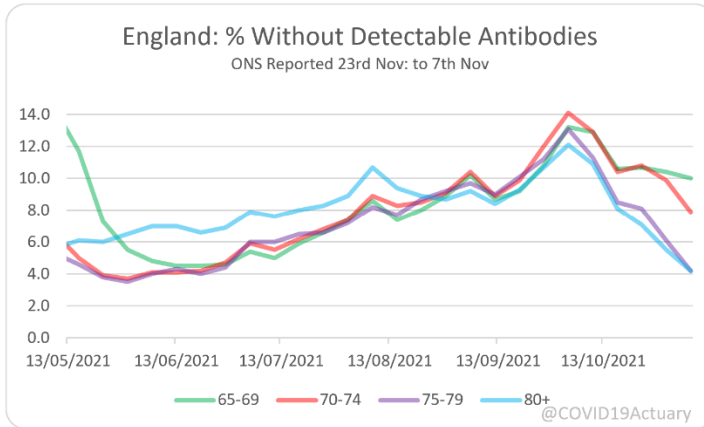
The fortnightly survey continues to show overall levels relatively stable in the low 90% region. In recent weeks, the main interest has been in seeing how levels in the oldest groups have started to wane and then pick up again as booster jabs are administered.

We continue to see that effect in the latest update, which is to 7th November (and thus will reflect the effect of boosters administered to around 7 to 14 days earlier). In the graphs issued with the report (below) it is difficult to discern the extent of the improvement, and so again we prefer to look at the balancing figure, i.e. those without detectable antibodies.



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

To the extent that this is a proxy for those now more at risk, this figure is also useful in assessing the likely increase in serious illness and thus pressure on health services etc. We can see the fall much more clearly now – indeed in the Over 80 age group, the level has now fallen below that seen shortly after completion of second doses, suggesting (consistent with other data) that the booster dose takes levels of protection beyond that seen after the initial primary course of two doses.



'R' Estimate

The latest UKHSA estimate of 'R' for England is put at 1.0 to 1.1, compared with 0.8 to 1.0 for the last two weeks, thus tipping the middle view firmly from a decline to a growth period.

The regional estimates are shown below.

Region	R	Growth rate % per day
England	1.0 to 1.1	-1 to +2
East of England	0.9 to 1.1	-2 to +1
London	0.9 to 1.2	-1 to +2
Midlands	0.9 to 1.1	-2 to +1
North East and Yorkshire	0.9 to 1.1	-2 to +1
North West	0.8 to 1.1	-3 to 0
South East	0.9 to 1.2	-1 to +2
South West	0.9 to 1.1	-2 to +2

Other

WHO launches Scientific Advisory Group for the Origins of Novel Pathogens (SAGO) ([link](#))

SAGO held its first meeting on 23 November 2021. The Group's terms of reference include advising WHO on a framework to guide studies into the origins of emerging and re-emerging pathogens of epidemic and pandemic potential. They will also provide the WHO Secretariat with an independent evaluation of all available scientific and technical findings from global studies on the origins of SARS-CoV-2 and will also give advice on additional WHO studies into the origins of SARS-CoV-2.

And Finally...

In a week that ends with concerning news regarding a new variant, we think it best to steer off COVID altogether for our tailpiece this week. And talking of tails, what better than a tabby tail to lighten up the news reports, with an impromptu appearance during a Georgian news show of a black and white tabby cat.

Maybe Huw Edwards or Tom Bradby should consider a dual anchor to make the late news more enjoyable – your contributors have several potential candidates between them awaiting their chance for an audition.

[Video - Cat causes paws on Georgian TV news show | Offbeat News | Sky News](#)



26 November 2021