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Friday Report: Issue 45

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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 update with a summary of key papers and articles.

We have adopted the WHO's new terminology for variants. ***Alpha*** *refers to B.1.1.7, formerly known as the UK or Kent variant, whilst* ***Delta*** *refers to B.1.617.2, often referred to as the Indian variant. (Beta and Gamma refer to the South African and Brazilian variants respectively.)*

Vaccination

Modified AZ Vaccine for Booster Doses – COV-BOOST and Variant Vaccines

The COV-BOOST multi-site study launched in May, and led by University Hospital Southampton NHS (link), will be the first to investigate the benefits of a third vaccination dose to combat the virus. The study is expected to involve up to 3,000 participants and will investigate a number of different combinations involving seven vaccines (Oxford/AstraZeneca, Pfizer/BioNTech, Moderna, Novavax, Valneva, Janssen and Curevac).

The boosters will be given 10 to 12 weeks after a second vaccination dose, and therefore will be focused on those who were immunised early in the vaccination programme such as healthcare workers and those over 75. Recruitment is ongoing, and members of the public can still join at the NHS COVID-19 Vaccine Research Registry (link).

Whilst COV-BOOST is focused on vaccines that have already undergone clinical trials and been deployed, new variants of the vaccines are under development that are anticipated to be more effective against SARS-CoV-2 variants. A pre-print study (link) from the group led by Professor Sarah Gilbert shared an evaluation of such a vaccine variant (AZD2816) that has been designed specifically to target the B.1.351 (Beta) spike protein. This study based on pre-clinical tests on mice found the following with particular relevance to the booster strategy:

- Comparable levels of antibodies and T-cell responses were seen with AZD2816 against both wild-type and Beta variants in previously unimmunised mice.
- Neutralising antibody levels were higher against Beta, Kappa and Delta variants when different doses involving AZD1222 and AZD2816 were used in a two-dose vaccination strategy.
- Use of a third dose AZD2816 vaccination following a 2 dose AZD1222 vaccination regimen enhanced the antibody response against the Beta variant as well as providing cross-reactivity against other variants.

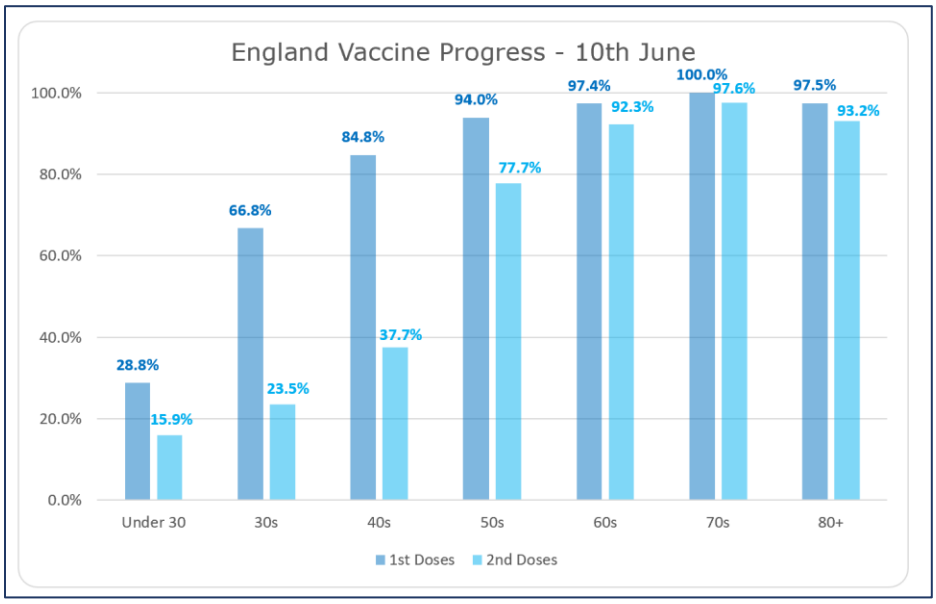
The results from the pre-clinical trials have been warmly welcomed by Professor Gilbert (link), and the group will now move rapidly to clinical trials. Importantly, the research focus will be on developing vaccine variants that are effective against a wide range of virus variants, rather than developing a series of different vaccines that are each optimally effective against a particular virus variant. The latter approach would be impractical to implement.

Table – Functional ability of antibodies to neutralise virus in vaccinated mice

Prime	Boost	Boost	Time post last vaccine	Original wild-type spike		B.1.351 (Beta)		B.1.617.1 (Kappa)		B.1.617.2 (Delta)	
				ID50	ID80	ID50	ID80	ID50	ID80	ID50	ID80
AZD1222			16 days	186 (70 to 474)	55 (43 to 297)	40	40	40	40	40	40 (40 to 41)
AZD2816			16 days	107 (40 to 297)	40 (40 to 118	81 (51 to 231)	55 (40 to 163)	40 (40 to 42)	40	40	40
AZD1222 & AZD2816			16 days	157 (75 to 248)	65 (40 to 93)	51 (40 to 72)	41 (40 to 51)	40 (40 to 63)	40	40	40
AZD1222	AZD2816		20 days	1285 (541 to 2560)	700 (307 to 1661)	661 (212 to 1719)	235 (167 to 1057)	276 (126 to 964)	177 (85 to 565)	226 (54 to 751)	145 (43 to 467)
AZD1222	AZD1222		48 days	2546 (1789 to 2560)	1158 (627 to 1658)	350 (69 to 630)	111 (51 to 380)	132 (54 to 490)	95 (44 to 185)	40 (40 to 582)	40 (40 to 245)
AZD1222	AZD1222	AZD2816	20 days	2560 (1452 to 2560)	2159 (584 to 2408)	1148 (383 to 2475)	742 (273 to 1628)	724 (397 to 1874)	481 (267 to 947)	637 (87 to 1656)	316 (69 to 1172)

Take-up Rates

With bookings now open in England down to age 25, we are approaching the end of the first phase of the vaccination programme. It appears that limited supplies of the MRNA vaccines being used for younger age groups means slower progress than might be hoped for. Encouragingly, we are still seeing relatively high take-up rates, albeit with some drop off as we progress down the age groups.



Wales is further ahead on first doses, and has vaccinated 63% of 18-29 year olds and 71% of those in their 30s, giving more encouragement that the UK will maintain healthy take-up rates throughout the adult population.

Clinical and medical news

RECOVERY trial finds aspirin does not improve survival (link)

The systemic nature of COVID-19 is driven by the increased risk of blood clots. Since early in the pandemic, the recommended standard of care for patients with moderate to severe COVID-19 patients in hospitals is low-molecular weight heparin (LMWH) with the prophylactic prevention of further thromboembolic events after discharge using direct oral anticoagulants (DOAC) such as Rivaroxaban and Apixaban (link).

Aspirin has a constellation of effects on the cardiovascular system including anticoagulation, antiplatelet aggregation and dampening down the inflammatory response. Given its low cost and wide usage, aspirin was one of the many drugs that has been evaluated for possible efficacy in the treatment of COVID-19 in the RECOVERY trial.

Between November 2020 and March 2021, 15,000 COVID-19 patients have been randomised to either receiving aspirin 150 mg once daily or standard care. Results from the trial released on Wednesday indicate that there was no significant difference in 28-day mortality (17% vs 17%) between the two arms. Whilst patients on aspirin had a marginally shorter hospital stay (8 days vs 9 days), the lack of benefit appears to involve a trade-off between 0.6% more patients experiencing a major bleeding event and 0.6% fewer patients experiencing a thromboembolic event.

Modelling

Given the UK Government's imminent decision on the next roadmap stage, there is great interest in the modelling and projections that will inform the decision. As has been the case on previous occasions modelling papers will likely be released after the decision has been communicated. The most recent modelling outputs from SPI-M in the public domain are dated 26 May (link). Relevant material on the potential impact of Variants of Concern are summarized in our recent Bulletin (link).

Data

PHE Variant Surveillance (link)

Probably the most eagerly anticipated report at the moment is the weekly update from PHE on variants. The latest report notes that over 90% of cases are now Delta, so it is now the dominant strain.

To date there have been nearly 400 hospital admissions, and whilst the majority were unvaccinated a not insignificant 10% had been fully vaccinated at least two weeks prior to the specimen date. 42 deaths have been recorded, with 12 of these falling into the fully vaccinated category.

Table 6. Attendance to emergency care and deaths by vaccination status among Delta confirmed cases (sequencing and genotyping) in England, 1 February 2021 to 7 June 2021.

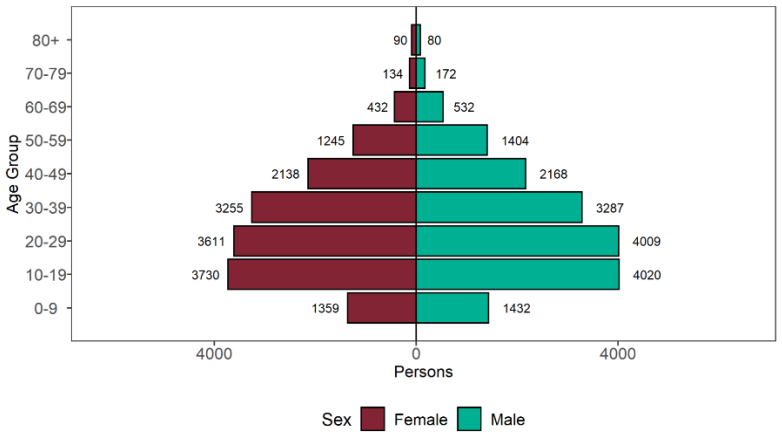
	Total	Cases with specimen date in past 28 days*	Unlinked	Unvaccinated	<21 days post dose 1	≥21 days post dose 1	≥14 days post dose 2
Delta cases since 1 Feb 2021 ¥	33,206	28,738	4,289	19,573	2,166	5,393	1,785
Cases with an A&E visit§ (excluding cases with the same specimen and attendance dates)‡	851	NA	11	567	59	163	51
Cases with an A&E visit§ (including cases with the same specimen and attendance dates)	1,234	NA	16	825	90	220	83
Cases where presentation to A&E resulted in overnight inpatient admission§ (excluding cases with the same specimen and admission dates)‡	223	NA	3	146	9	45	20
Cases where presentation to A&E resulted in overnight inpatient admission§ (including cases with the same specimen and admission dates)	383	NA	4	251	20	66	42
Deaths^	42	NA	0	23	0	7	12

Data sources: Emergency care attendance and admissions from Emergency Care Dataset (ECDS), deaths from PHE daily death data series (deaths within 28 days)

The paper is notable for reducing the estimate of increased transmissibility for the second week running – the best estimate of the transmissibility of Delta is now put at +40% over Alpha. However, household transmission is estimated at +64%. It also confirms the view that Delta gives a likelihood of hospitalisation which is more than double that of Alpha – the confidence intervals remain very wide, reflecting the uncertainty given data volumes.

Finally, a graph shows clearly that the majority of cases are in those groups with low vaccine penetration, particularly those who are not fully vaccinated. The oldest in the infected population may represent those who have declined the vaccine.

Figure 14. Age-sex pyramid of confirmed (sequencing) and probable (genotyping) Delta cases as of 7 June 2021 (Find accessible data used in this graph in underlying data).

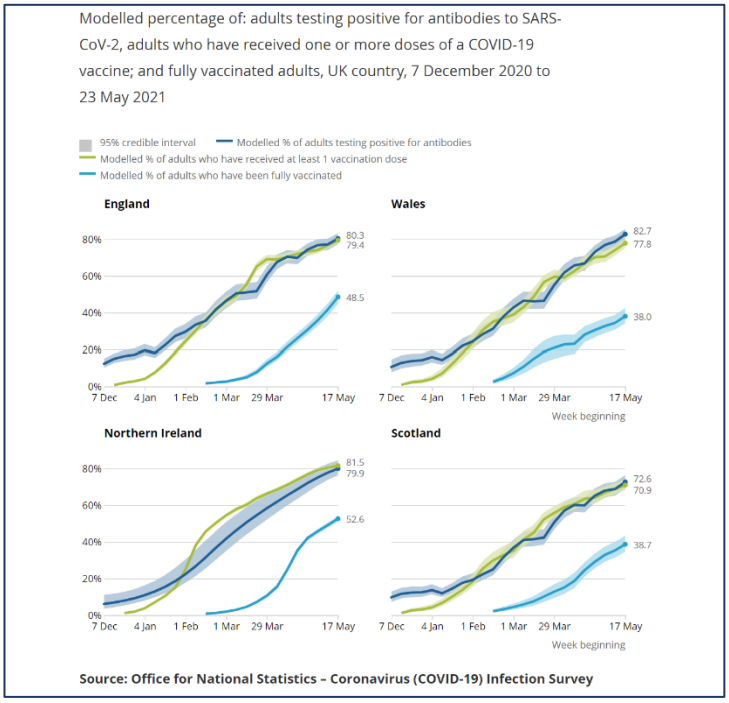


ONS Antibody data (link)

The latest antibody survey shows that levels in England have continued to rise, with levels in England now over 80%, up 4% in the two weeks since the last update. Wales and Northern Ireland are similar, although Scotland is still lagging behind slightly at 71%.

It's noticeable that even in those lower age groups where vaccination penetration is low, antibody levels are already over 50%, reflecting the fact that naturally acquired immunity (through infection) adds considerably to the vaccination effect.

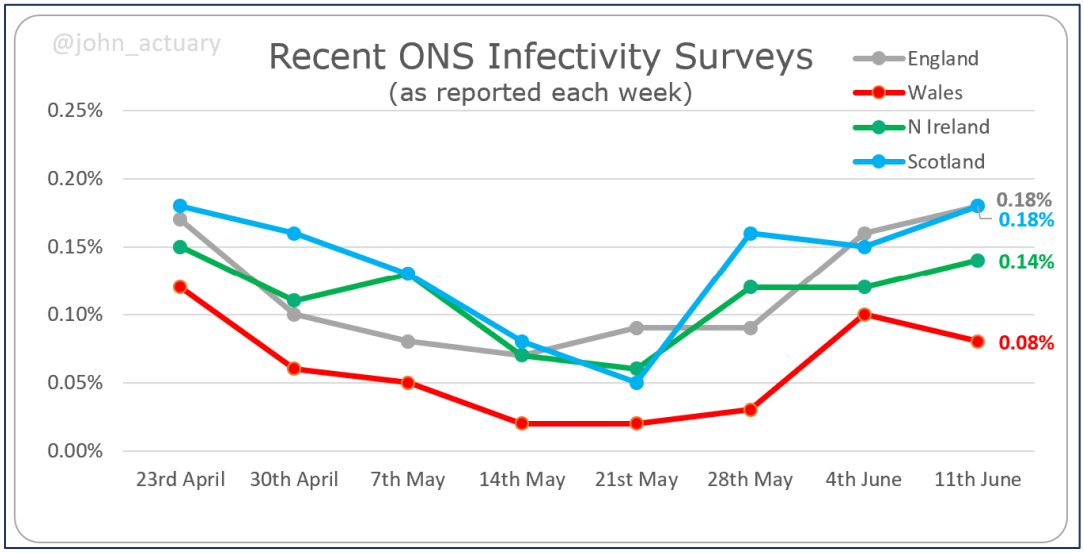
This data is in respect of the week beginning 17 May. With an approximate two-week period after vaccination before antibodies are generated, it reflects vaccination levels in early May. Since then we have vaccinated a further 6m people with their first dose, and 12m with their second dose.



ONS Infection Surveys (link)

In the two weeks since our last update the level of infectivity in England has doubled from 0.09% to 0.18%. We've also seen a big jump in Wales, to 0.08%, although it still remains by some margin the lowest of the four nations. Scotland and Northern Ireland have seen smaller increases, although that may be due to a sharp rise in the previous week.

The regional analysis shows the North West at more than double any other English region, at 0.49%, although some other regions, most notably London, are now starting to show faster increases too.



"R" Estimate (link)

The latest SAGE estimate of R in England has the range 1.2 to 1.4, a marked jump of 0.2 on the previous week. Notably the regional estimates show the North West at between 1.3 and 1.5, which is broadly consistent with the ONS infection data reported on above.

Even this increase may understate the current position, as estimates based on case numbers over the last few days put R at around 1.5.

These estimates provide essential information for the government's decision making as to whether and when to proceed with the last stage of the roadmap.

Latest by NHS England regions

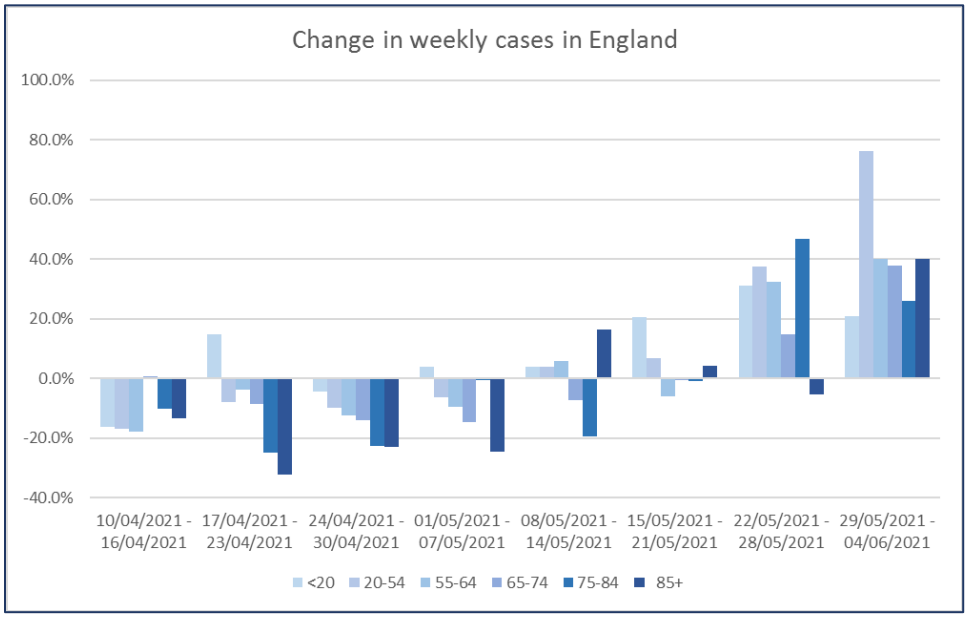
These are the latest R and growth rate estimates by NHS England regions.

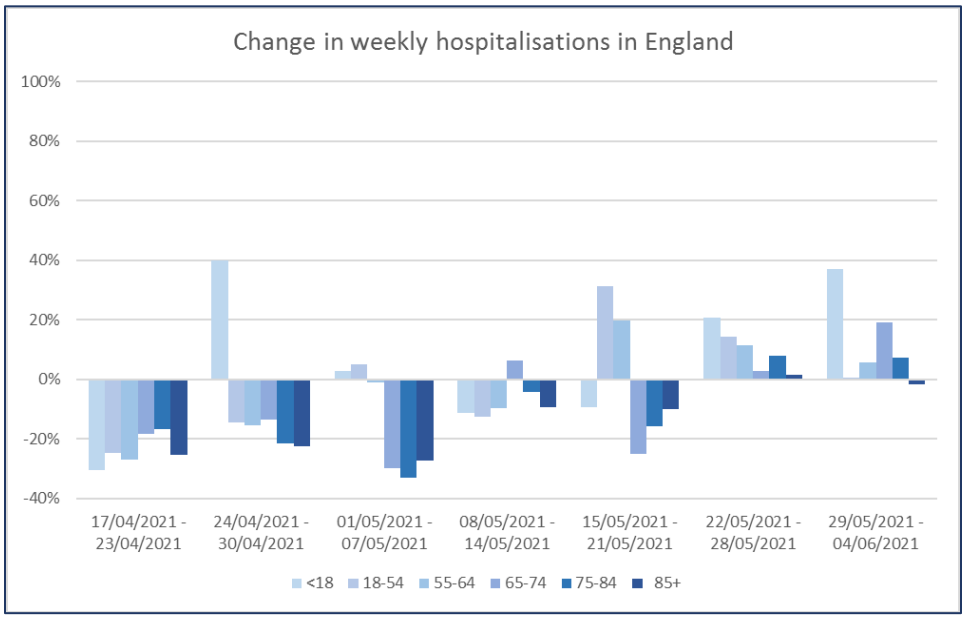
Region	R	Growth rate % per day
England	1.2 to 1.4	3 to 6
East of England	1.1 to 1.4	2 to 6
London	1.1 to 1.4	2 to 6
Midlands	1.1 to 1.3	1 to 5
North East and Yorkshire	1.0 to 1.2	0 to 4
North West	1.3 to 1.5	4 to 8
South East	1.1 to 1.4	1 to 6
South West*	1.0 to 1.3	0 to 6

* Particular care should be taken when interpreting these estimates as they are based on low numbers of cases, hospitalisations or deaths, and/or dominated by clustered outbreaks. They should not be treated as robust enough to inform policy decisions alone.

Case and hospitalisation data

Case data from the Government Coronavirus Dashboard (link) and hospitalisation data from NHS reports on COVID-19 hospital activity (link) show that increases in both began in mid-May for under-65s but in more recent weeks there are signs that the increase has moved up the age range in England.





PHE surveillance report

The weekly Flu and COVID-19 surveillance report confirms that cases increased in week 22 (ending 4 June 2021) vs week 21 across all ages, ethnicities and regions (link).

The report also shows that educational settings were the most common setting for outbreaks in week 22, although this is likely to reflect infections acquired in the prior week as week 22 was half term for most schools.

There's positive news that care home outbreaks remain low although they are not zero, despite a highly vaccinated resident population (note that care home outbreaks may include staff incidents).

Worldwide excess mortality

On 9 June, Karlinsky and Kobak released an update to their World Mortality Dataset consisting of all cause and COVID-attributed mortality (link). The authors also provided us with a guest blog this week.

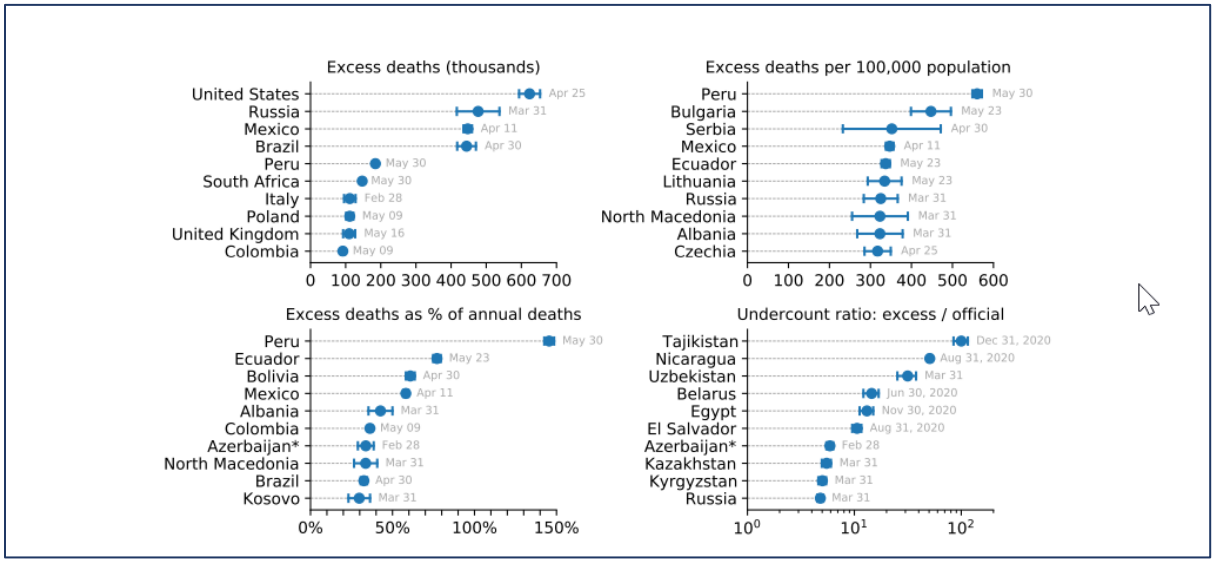
The data set includes all-cause mortality from 94 countries. For each country 'baseline' mortality was predicted based on 2015–2019 data (allowing for linear trend and seasonal variation). Excess mortality was calculated as the difference between actual all-cause mortality and the predicted baseline.

Comparing total excess mortality from the beginning of the pandemic (defined as March 2020) across these countries showed that total excess mortality was:

- positive (significantly) in 68 countries;
- not significantly different from zero in 19 countries;
- negative (significantly) in 6 countries.

For each country the authors computed the ratio of the excess mortality to the officially reported COVID-19 death count by consistent date. This ratio differed strongly between countries and within countries over time.

Charts below show the countries with the highest excess death counts, excess deaths per 100,000 population, excess deaths as a % of annual deaths and the ratio of excess deaths to reported COVID-19 deaths. Error bars are 95% confidence intervals. Figures are reported to the latest available extract date which differs by country.



The UK appears in the top 10 for absolute excess deaths counts but after adjusting for expected deaths falls down the rankings.

Peru has the unfortunate distinction of having the top-ranking position for excess deaths per 100k population and as a percentage of expected annual deaths. Some of the reasons Peru has been badly hit are said to be an overstretched public health system, lack of oxygen tanks, absence of fridges in people's homes - forcing many households to make frequent trips to markets to shop for food rather than stocking up - and overcrowding in homes and public places (link).

Other

Events Research Programme (link)

The Events Research Programme aims to examine the risk of transmission of COVID-19 from attendance at events and explore ways to enable people to attend a range of events safely.

The programme aims to explore how a combination of testing and non-pharmaceutical interventions can inform decisions on safely lifting restrictions at events. The first phase of 10-15 pilots were run in April and May. By 20 May, 15 people out of 58,000 attendees at a variety of indoor and outdoor events had tested positive for COVID-19 (25 per 100k). This figure will be influenced by community case rates which have started increasing again in recent weeks.

This weekend a further pilot is taking place at Edgbaston (Birmingham) for the England and New Zealand cricket game. The ground will operate at 70% of spectator capacity. All spectators MUST take a Lateral Flow Test within 24 hours prior to attending. A negative result must then be shown on entry and recorded. Additionally, to aid research, spectators are asked to perform a Polymerase Chain Reaction (PCR) test at home: (i) on the day of the Event; and (ii) 5 days after the Event (link).

For the England vs Croatia football match taking place at Wembley this Sunday, means of gaining entry includes proof of full vaccination or a negative lateral flow test taken within 48 hours of the match. Vaccination status will be demonstrated via the NHS App, and the second dose must have been administered 14 days before the match. It is anticipated only a small number of attendees will be able to gain entry this way. Wembley is due to be at 25 per cent capacity - 22,500 - for England's group games, with the football authorities hoping to increase that significantly for the semi-finals and final, with 45,000 considered a realistic target. A great deal will depend on whether the Government decides to ease restrictions on June 21 (link).

It is positive to see science used to establish how large events can be held in a way that balances risks and investigates the extent of advantage that outdoor events have over indoor events. But against a backdrop of increasing cases and hospitalisations and a possible delay to the Stage 4 date, wider impacts of messaging are an important consideration too.

And Finally …

Many of us have contributed to the fight against COVID-19 by logging our symptoms, or lack thereof, in the COVID Symptom Study app (link) developed by health-science company ZOE. Data on the spread of the virus is analysed by King's College London and shared with Government and the NHS.

We were amused this week to discover another of ZOE's research projects, the #bluepoopchallenge. This examines gut health by means of establishing gut transit time – you bake and eat some blue muffins and then, well you can figure out the rest. The young children of one of our team seemed to enjoy every stage of the project (though one of them did resemble a smurf by the time the muffins were baked). (link)

12 June 2021