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Friday Report: Issue 38

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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

Pfizer-BioNTech vaccine efficacy and take-up studies

Clalit Healthcare study (link)

Israel's largest health care organisation, Clalit, conducted a study that matched newly vaccinated individuals to unvaccinated controls. This study design overcomes problems of confounding factors that may affect observational studies and showed the that BNT162b2 mRNA vaccine is effective for a wide range of COVID-19 outcomes.

Each study group included 596,618 people. Study outcomes included documented infection with SARS-CoV-2, symptomatic COVID-19, COVID-19–related hospitalisation, severe illness, and death. Vaccine effectiveness for each outcome was determined as one minus the risk ratio.

The estimated vaccine effectiveness was reported at 14 to 20 days and 21 to 27 days after the first dose, as well as from 7 days after the second dose. There is little difference in infection risk between vaccinated and unvaccinated individuals in the first 14 days as it takes time for immunity to build. The second dose is typically administered 21 days after the first dose.

At days 14 to 20 after the first dose, the vaccine effectiveness (with 95% confidence interval) was:

- 46% (95% CI 41-57) for documented infection, including asymptomatic cases;
- 74% (95% CI 56-86) for hospitalisation;
- 72% (95% CI 19-100) for death.

From 7 days after the second dose, the vaccine effectiveness was:

- 92% (95% CI 88-95) for documented infection;
- 87% (95% CI 55-100) for hospitalisation.

Effectiveness against death 7 days after the second vaccines was not reported because of low numbers of observed deaths across the study population.

The following table shows the key results.

Table 2. Estimated Vaccine Effectiveness against Covid-19 Outcomes during Three Time Periods.*

Period	Documented Infection		Symptomatic Illness		Hospitalization		Severe Disease		Death	
	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference
	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)
14 to 20 days after first dose	46 (40–51)	2.06 (1.70–2.40)	57 (50–63)	1.54 (1.28–1.80)	74 (56–86)	0.21 (0.13–0.29)	62 (39–80)	0.14 (0.07–0.21)	72 (19–100)	0.03 (0.01–0.07)
21 to 27 days after first dose	60 (53–66)	2.31 (1.96–2.69)	66 (57–73)	1.34 (1.09–1.62)	78 (61–91)	0.22 (0.13–0.31)	80 (59–94)	0.18 (0.10–0.27)	84 (44–100)	0.06 (0.02–0.11)
7 days after second dose to end of follow-up	92 (88–95)	8.58 (6.22–11.18)	94 (87–98)	4.61 (3.29–6.53)	87 (55–100)	0.22 (0.08–0.39)	92 (75–100)	0.32 (0.13–0.52)	NA	NA

* Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were calculated only for cells with more than 10 instances of an outcome across the two groups. NA denotes not available, and RR risk ratio.

SIREN study (link)

The SIREN study is a prospective cohort study among staff working in publicly funded hospitals in England. Vaccination status (from 8/12/2020-5/2/2021) and symptoms are recorded at 2 weekly intervals and all SARS-CoV-2 polymerase chain reaction (PCR) and antibody test results are documented.

The pre-print study found that a single dose of BNT162b2 vaccine demonstrated vaccine effectiveness against infection of 72% (95% CI 58-86) 21 days after first dose and 86% (95% CI 76-97) seven days after two doses among staff who tested negative for antibodies at the start of the study cohort.

The study also investigated vaccine take-up and reported at least one dose of vaccine was administered to 20,641 participants (so overall 89% take-up) by 5 February.

Significantly lower take-up, shown by adjusted Odds Ratios (aORs), was associated with:

- Prior infection: aOR 0.59 (95% CI 0.54-0.64)
- Females: aOR 0.72 (95% CI 0.63-0.82)
- Aged under 35 years
- Minority ethnic background (especially Black): aOR 0.26 (95% CI 0.21-0.32)
- Porters/security guards (aOR 0.61, 95% CI 0.42-0.90), midwives (aOR 0.74, 95% CI 0.57-0.97)
- Living in more deprived neighbourhoods: the relative gap from IMD 1 (most deprived) vs. 5 (least deprived) was an aOR of 0.75 (95% CI 0.65-0.87).

Johnson & Johnson vaccine seeks approval by the FDA (link) **and** (link)

A single-dose vaccine that can be stored in an ordinary refrigerator had been developed by Janssen Biotech, the pharmaceutical arm of Johnson & Johnson. The FDA will meet on 26 February to determine whether to authorise the vaccine.

Janssen has submitted safety and efficacy data from an ongoing multi-national Phase 3 randomized, double-blind and placebo-controlled trial of a single dose in approximately 40,000 participants.

Vaccine efficacy (VE) against laboratory-confirmed moderate to severe/critical COVID19 across all geographic areas in which the trial was conducted was 67% (95% CI 59-73%) when considering cases occurring at least 14 days after the single-dose vaccination and 66% (CI 55-75%) when considering cases occurring at least 28 days after vaccination.

The vaccine still appears to be effective, albeit at a lower level, in South Africa and Brazil where virus variants have become dominant.

South Africa began rolling out Johnson & Johnson vaccines to healthcare workers on 17 February as part of an observational study as the vaccination is not yet authorised for use. South Africa paused its rollout of the Oxford-AstraZeneca vaccine after preliminary trial data showed it offered minimal protection against mild to moderate illness caused by the locally dominant variant of the virus. (link)

Table 22. Vaccine Efficacy of First Occurrence of Moderate to Severe/Critical and Severe/Critical COVID-19 Including Non-centrally Confirmed Cases With Onset at Least 14 or at Least 28 Days After Vaccination, by Country of Participation, Per-Protocol Set, Study 3001

	Onset at Least 14 Days			Onset at Least 28 Days		
Country Subgroup	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] 95% CI	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
United States						
Moderate to severe/critical	51 (9119) 1414.0	196 (9086) 1391.3	74.4% (65.0, 81.6)	32 (8958) 1403.4	112 (8835) 1375.6	72.0% (58.2, 81.7)
Severe/critical	4 (9119) 1417.2	18 (9086) 1404.8	78.0% (33.1, 94.6)	1 (8958) 1405.2	7 (8835) 1382.2	85.9% (-9.4, 99.7)
South Africa						
Moderate to severe/critical	43 (2473) 377.6	90 (2496) 379.2	52.0% (30.3, 67.4)	23 (2449) 376.1	64 (2463) 376.9	64.0% (41.2, 78.7)
Severe/critical	8 (2473) 380.2	30 (2496) 382.9	73.1% (40.0, 89.4)	4 (2449) 377.0	22 (2463) 379.0	81.7% (46.2, 95.4)
Brazil						
Moderate to severe/critical	39 (3370) 555.7	114 (3355) 548.8	66.2% (51.0, 77.1)	24 (3354) 554.8	74 (3312) 546.1	68.1% (48.8, 80.7)
Severe/critical	2 (3370) 558.9	11 (3355) 556.8	81.9% (17.0, 98.1)	1 (3354) 556.2	8 (3312) 549.8	87.6% (7.8, 99.7)

Source: Sponsor tables GEFPE09A, GEFPE09C, GEFBO05NC_A, GEFBO05NC_C
N=Total number of participants at risk per category

Scotland Hospitalisations Analysis (link)

Early results published in a paper publicised by Public Health Scotland this week showed that 28 days after a first dose, hospitalisations are reduced by 85% (CI 76%,91%) for recipients of the Pfizer vaccine and 94% (CI 73%,99%) for the Oxford AstraZeneca (OAZ) jab.

However, beyond 7 weeks there are signs that the Pfizer jab starts to become less effective with a single dose. Care must be taken in interpreting this data however, as those contributing to the longer periods will be the most vulnerable, and in particular Scotland adopted a policy of vaccinating care home residents earlier than in other parts of the UK.

Due to the later start of the OAZ roll-out, there's insufficient data yet to ascertain whether it is displaying the same drop off.

Vaccination status	Person years	Number of events	Age-adjusted Hazard Ratios (95% CI)*	Full-adjusted Hazard Ratios (95% CI)**	Full and inverse propensity adjusted Hazard Ratios (95% CI)***	Vaccine effect (95% CI)
Vaccinated overall						
Unvaccinated	787518	7472	1	1	1	NA
Vaccine dose 1 (7-13 days)	13487	212	0.73 (0.64 to 0.84)	0.74 (0.64 to 0.86)	0.53 (0.47 to 0.61)	47% (39 to 53)
Vaccine dose 1 (14-20 days)	9191	120	0.61 (0.5 to 0.73)	0.63 (0.52 to 0.76)	0.4 (0.34 to 0.48)	60% (52 to 66)
Vaccine dose 1 (21-27 days)	6343	52	0.43 (0.33 to 0.56)	0.44 (0.33 to 0.58)	0.3 (0.23 to 0.38)	70% (62 to 77)
Vaccine dose 1 (28-34 days)	3867	20	0.34 (0.22 to 0.52)	0.31 (0.2 to 0.48)	0.16 (0.1 to 0.26)	84% (74 to 90)
Vaccine dose 1 (35-41 days)	2326	17	0.6 (0.38 to 0.97)	0.46 (0.28 to 0.76)	0.39 (0.26 to 0.58)	61% (42 to 74)
Vaccine dose 1 (42+ days)	3843	21	0.52 (0.34 to 0.81)	0.51 (0.33 to 0.79)	0.42 (0.3 to 0.61)	58% (39 to 70)
BNT162b2 or Pfizer-BioNTech						
Unvaccinated	708129	6690	1	1	1	NA
Vaccine dose 1 (7-13 days)	7766	104	0.71 (0.58 to 0.86)	0.56 (0.46 to 0.68)	0.62 (0.53 to 0.72)	38% (28 to 47)
Vaccine dose 1 (14-20 days)	5758	60	0.61 (0.47 to 0.78)	0.42 (0.32 to 0.55)	0.4 (0.32 to 0.5)	60% (50 to 68)
Vaccine dose 1 (21-27 days)	4688	34	0.43 (0.31 to 0.6)	0.29 (0.21 to 0.41)	0.28 (0.21 to 0.38)	72% (62 to 79)
Vaccine dose 1 (28-34 days)	3346	18	0.33 (0.21 to 0.53)	0.22 (0.14 to 0.35)	0.15 (0.09 to 0.24)	85% (76 to 91)
Vaccine dose 1 (35-41 days)	2275	17	0.46 (0.28 to 0.73)	0.29 (0.18 to 0.48)	0.32 (0.21 to 0.47)	68% (53 to 79)
Vaccine dose 1 (42+ days)	3842	21	0.38 (0.25 to 0.58)	0.32 (0.21 to 0.51)	0.36 (0.25 to 0.51)	64% (49 to 75)

REACT Study on Antibodies (link)

The latest study from the Imperial College REACT study covers antibody prevalence in England, but its most interesting aspect is the analysis it provides on the effect of the vaccination programme.

Overall, the level is put at 14%, with just 10% of those yet to be vaccinated testing positive compared with 38% of those who have had their first dose. (These numbers are considerably lower than comparable ONS data reported in last week's edition, but the paper notes that the use of lateral flow tests is likely to be mean a lower rate is observed than surveys using laboratory testing.)

Looking at the analysis for those who have had the Pfizer vaccination (there is too little data for them to report on OAZ separately), there is a clear and considerable drop off in antibodies at the older ages. Also, as seen in the Scottish analysis above, there is some evidence that antibodies are waning after a relatively short number of weeks, and certainly well before any second dose is due under the current guidelines recommending a three month delay. Again, the wide confidence intervals means that some caution is needed when interpreting the results.

The paper does note that the detection of antibodies is but one factor in assessing the performance of a vaccine, and that a better understanding is needed of the impact on hospitalisation and death. However, there is limited time for research before the delayed second vaccinations of the most vulnerable become due in which to determine whether any adjustment to the regime is desirable.

Table 5: IgG positivity by days after single dose of Pfizer/BioNTech vaccine, by age, sex and clinical history

	IgG positivity 5 (95% confidence interval)				
Category	**<21 days**	**21-27 days**	**28-34 days**	**35-41 days**	**>=42 days**
All respondents	30 (29.1-31)	68.2 (65.8-70.6)	67.7 (64-71.3)	59.9 (56.2-63.5)	56.7 (50.6-62.6)
18-29	57.1 (53-61.1)	92.5 (86.4-96)	100 (94.4-100)	95.1 (83.9-98.7)	94.4 (74.2-99)
30-39	51 (47.6-54.4)	91.6 (86.1-95)	94.2 (86-97.7)	85.4 (72.8-92.8)	79.3 (61.6-90.2)
40-49	44.5 (41.5-47.6)	84.4 (78.9-88.6)	85.6 (76.8-91.4)	84.8 (76.1-90.7)	78.1 (61.2-89)
50-59	40.3 (37.7-42.9)	83.1 (78.5-86.8)	79.7 (71.5-85.9)	66.4 (57.4-74.3)	62.1 (49.2-73.4)
60-69	28 (25.2-31)	70.6 (63.1-77)	69 (57.5-78.6)	76.3 (64-85.3)	60 (38.7-78.1)
70-79	14 (12.8-15.3)	50.5 (43.7-57.2)	42.1 (30.2-55)	50 (32.6-67.4)	45.5 (21.3-72)
80+	20.8 (18.6-23.2)	30.3 (25.3-35.8)	38 (30.9-45.5)	38 (32.6-43.7)	32.3 (23.6-42.3)
Female	34.6 (33.4-35.9)	73.9 (71.1-76.5)	72.4 (68.1-76.3)	66.2 (61.7-70.4)	64.5 (56.9-71.3)
Male	21.6 (20.2-23.1)	56 (51.4-60.4)	55.4 (47.8-62.7)	47.3 (40.9-53.8)	43.2 (33.7-53.2)
Not clinically vulnerable	31.2 (30.2-32.2)	70.1 (67.6-72.5)	70.6 (66.7-74.3)	61.3 (57.3-65.1)	58.8 (52.3-65.1)
Clinically vulnerable/ advised to shield	20.2 (17.7-22.9)	48.4 (39.8-57.1)	41.9 (30.5-54.3)	50.6 (40.3-60.8)	42.9 (28-59.1)
COVID suspected or confirmed	62.1 (59.4-64.8)	90.1 (85.8-93.2)	93.1 (87-96.5)	86 (77.9-91.5)	91.9 (78.7-97.2)
No COVID	24.8 (23.8-25.8)	63.6 (60.9-66.3)	61.9 (57.5-66)	55.4 (51.3-59.4)	50.9 (44.4-57.4)

Clinical and medical news

Long COVID

A study (link) by the University of Washington indicates that the health consequences of COVID-19 extend far beyond acute infection, even among those who experience mild illness.

This longitudinal prospective cohort study included 177 adults with laboratory-confirmed SARS-CoV-2, along with 21 healthy controls. Between 3 to 9 months after the onset of illness, participants were asked to complete an electronic follow-up questionnaire regarding persistent symptoms, additional medical care, changes in quality of life and impact on activities of daily living.

Overall, 49 of 150 outpatients (33%), 5 of 16 hospitalised patients (31%), and 1 of 21 healthy participants (5%) in the control group reported at least one persistent symptom. No persistent symptoms were reported among 11 asymptomatic individuals.

The most common persistent symptoms were fatigue (24 of 177 patients [14%]) and loss of sense of smell or taste (24 patients [14%]). Overall, 23 patients (13%) reported other symptoms, including brain fog. A total of 51 outpatients and hospitalized patients (31%) reported worse health-related quality of life compared with baseline vs four healthy participants and asymptomatic patients (13%).

The following table shows the main results.

Table. Demographic and Clinical Characteristics of the Study Cohort

Characteristic	No. (%) Total recovered individuals (n = 177)	Inpatients (n = 16)	Outpatients (n = 150)	Asymptomatic individuals (n = 11)	Healthy controls (n = 21)
Age, mean (SD), y	48.0 (15.2)	54 (15.1)	46.3 (14.3)	63.8 (18.8)	50.8 (15.8)
Sex					
Women	101 (57.1)	8 (50.0)	87 (58.0)	6 (54.5)	11 (52.4)
Men	76 (42.9)	8 (50.0)	63 (42.0)	5 (45.5)	10 (47.6)
BMI, mean (SD)	27.1 (5.8)	28.7 (9.1)	26.4 (6.6)	26.3 (5.4)	25.2 (7.1)
Race/ethnicity					
Non-Hispanic/Latino					
White	135 (76.3)	6 (37.5)	121 (80.7)	8 (72.7)	16 (76.2)
Black	3 (1.7)	1 (6.2)	2 (1.3)	0	0
Other[a]	31 (17.5)	8 (50.0)	21 (14.0)	2 (18.2)	5 (23.8)
Hispanic/Latino	7 (4.0)	1 (6.2)	5 (3.3)	1 (9.1)	0
Missing	1 (0.6)	0	1 (0.7)	0	0
Influenza vaccination	130 (73.4)	12 (75.0)	109 (72.7)	9 (81.8)	18 (85.7)
Comorbidities					
Hypertension	23 (13.0)	3 (18.8)	18 (12.0)	2 (18.2)	0
Diabetes	9 (5.1)	4 (25.0)	4 (2.7)	1 (9.1)	1 (4.8)
Active smoking	8 (4.5)	0	7 (4.7)	1 (9.1)	1 (4.8)
Highest level of care accessed during acute illness					
None	107 (60.5)	0	96 (64.0)	11 (100)	21 (100)
Primary care	37 (20.9)	0	37 (24.7)	0	0
Urgent room or emergency department	17 (9.6)	0	17 (11.3)	0	0
Admitted to hospital or ICU	16 (9.0)	16 (100)	0	0	0
Post-COVID-19 follow-up characteristics					
Time after illness onset, median (SD), d[b]	169 (39.5)	179 (44.9)	169 (37.1)	139 (47.1)	87 (31.3)
Persistent symptoms[c]					
0	119 (67.2)	10 (62.5)	98 (65.3)	11 (100.0)	20 (95.2)
1-2	29 (16.4)	2 (12.5)	28 (18.7)	0	0
≥3	24 (13.6)	3 (18.8)	21 (14.0)	0	1 (4.8)
Missing	7 (4.0)	1 (6.3)	3 (2.0)	0	0
Worsened quality of life[d]	53 (29.9)	7 (43.8)	44 (29.3)	2 (18.2)	2 (1.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COVID-19, coronavirus disease 2019; ICU, intensive care unit.

[a] Other race/ethnicity included American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and more than 1 race.

[b] Time since symptom onset in severe/mild cohorts, time since first positive test in asymptomatic individuals, time since enrollment in healthy controls.

[c] Participants with COVID-19 were asked whether they experienced continued symptoms from their COVID-19 illness. Healthy patients in the control group were asked whether they experienced symptoms from an illness at the time of follow up survey completion.

[d] Quality of life was assessed using a sliding scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). Worsened quality of life was defined as a 10-point decrease in health status from before COVID-19 to the time of survey completion.

Modelling

Model-informed COVID-19 vaccine prioritization strategies by age and serostatus (Bubar et al) (link)

This study looks at the optimal distribution strategies for the world's limited supply of vaccine. It models vaccine efficacy and its ability to block disease and transmission, accounting for variation by age in susceptibility and mortality.

The modelling approach found that the optimum strategy to reduce fatalities is almost always to vaccinate the oldest in the population (typically over-60s) as well as those with comorbidities. The only scenarios where they found priority could be given to younger age groups was if a vaccine is either leaky (vaccinated individuals have reduced but non-zero probability of infection after vaccination) or not found to be effective in the older population (as yet, this has not been proven in existing vaccines).

The study also finds that where supply is limited, priority could be given to seronegative individuals – although this would require individuals to be tested before vaccination.

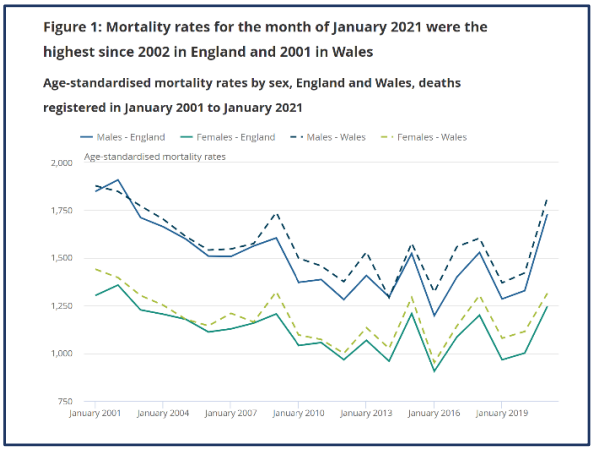
Data

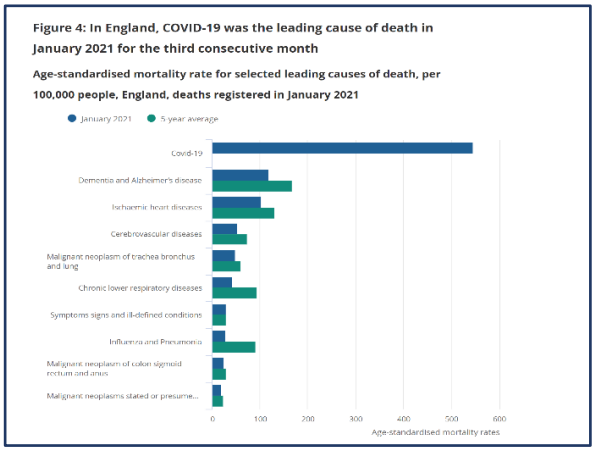
ONS January Mortality Analysis (link)

Each month the ONS produces a more detailed analysis of mortality, with particular reference to the impact of COVID on the overall figures. The latest update covers the peak of the second wave, and helps put the experience in context of both the first wave and overall historic mortality.

Amongst the points of interest are that age-standardised mortality was the highest in England since 2002, despite the heavy non-pharmaceutical interventions in place prior to and during the month to suppress transmission. However, neither on a "COVID deaths" or "excess deaths" basis was the first wave peak surpassed, despite that being the case for the various hospital metrics published regularly.

Another startling statistic is that COVID mortality in the month was equivalent to the total of the average of the five leading causes of mortality in the five years prior to the pandemic.





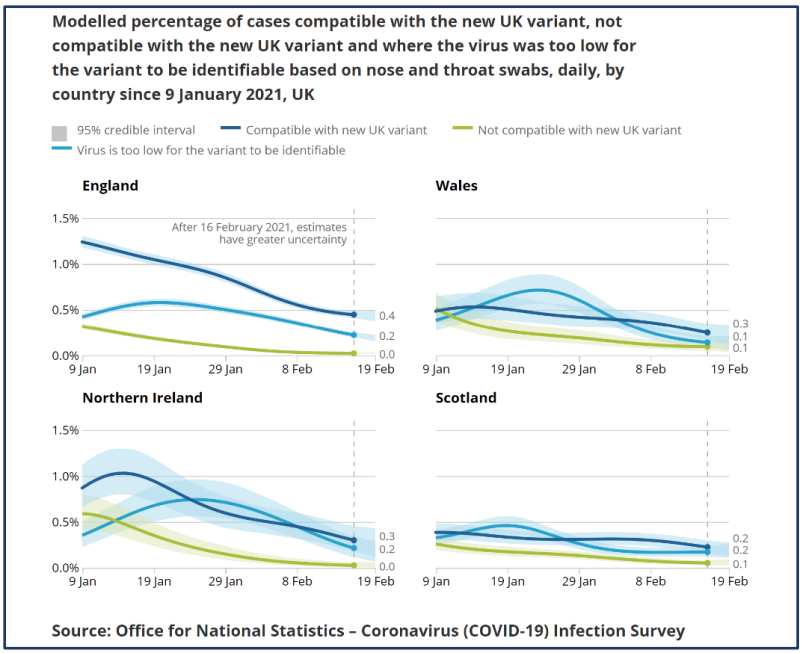
ONS Infection Survey (link)

The latest weekly report shows significant falls across all four nations, with Northern Ireland recording the largest fall, of 46%, to an infection rate of 0.52%. Wales comes next with a fall of 41% to 0.48%, whilst England and Scotland both record falls of around 20% to 0.69% and 0.45% respectively.

Regionally, all areas continue to fall, except in Yorkshire and the Humber, where the direction is less clear. Similarly, by age group, most are falling, although the Year 7 to Age 24 groups appear more level.

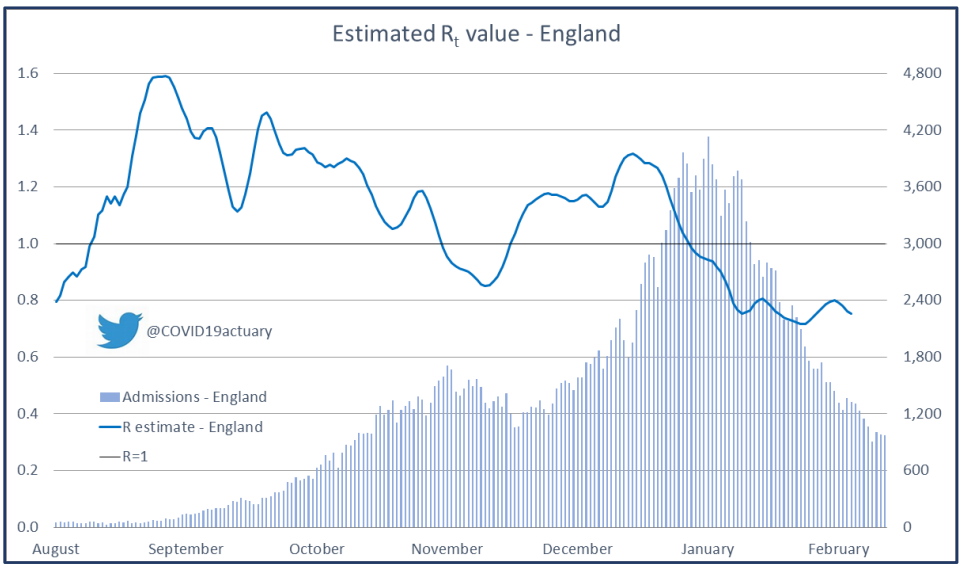
One of the recent additions to the analysis has been a breakdown of the variant of virus. We can see now that the original variant (identified as "not compatible with the new variant") has almost completely disappeared, with the "Kent" variant having taken over.

The report notes that any South African cases will be included in this "not the new variant" category, so it's encouraging to see that there is no obvious pick-up.



'R' Estimate

SAGE's estimate of R remains unchanged this week at 0.6 to 0.9 for the UK and 0.7 to 0.9 for England. Similarly, our own estimate continues to move within a relatively narrow range between 0.7 and 0.8. We continue to look for signs that this measure becomes unrepresentative of the population as, due to vaccination, we expect hospitalisations in the upper age groups to decrease faster than would be consistent with a given population rate of transmission.



And finally …

Air traffic at Heathrow is almost 90% lower than normal January levels but the Perseverance Rover is enjoying an exotic, extremely socially distanced getaway after touching down on the surface of Mars on 22 February.

Watch the landing at https://mars.nasa.gov/mars2020/multimedia/videos/?v=461