Friday Report: Issue 71

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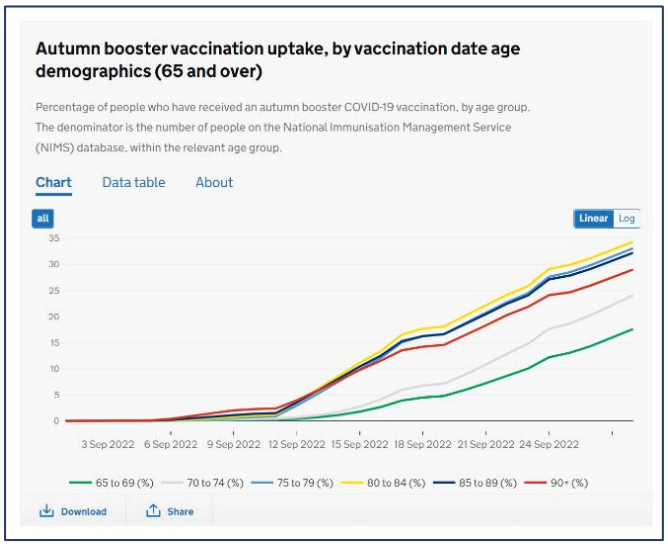
COVID-19 Actuaries Response Group – Learn. Share. Educate. Influence.

COVID-19 is still among the most important health topics for scientific papers and articles. The COVID-19 Actuaries Response Group continues to focus on important Covid-related topics. The group produces an update on the last Friday of every month with a summary of key papers, articles and data.

Vaccines

Autumn Booster Progress (link)

The latest reported figures on the government dashboard show that around a third of over-75s have now received their autumn booster, with lower coverage at the age groups below as would be expected as priority was given to the oldest. In total, around 15% of over-50s (who are all eligible – below this age it is limited to certain priority groups) have now been jabbed.



Of note, for the first time some of the vaccines administered are a bivalent version by Moderna, designed to combat BA.1 as well as the original strain, and also found to generate a good immune response against BA.4 and BA.5

Moderna has since developed an updated version that targets BA.4/BA.5. This is being used in the United States after emergency use approval (link), while the European Medicines Agency has granted conditional marketing authorisation (link).

First Alternatively Administered Vaccines Approved for Use (link)

China has approved the first vaccine which can be administered by inhaler. Made by CanSino, Convidecia Air is said to offer good protection after just one breath. At the moment, this has been approved for use as a booster, for those who have had the primary course through the more traditional method by injection.

Around the same time the Indian company Bharat Biotech announced (link) that a nasally administered vaccine has been approved for restricted use in emergency situations. Unlike the inhaled vaccine by Convidecia it can be used as a primary vaccine.

With inhaled and nasally administered vaccines being much easier to roll out logistically, these developments are a positive step towards improving the penetration of vaccines into regions which so far have struggled to get a good coverage, as well as making booster doses more accessible.

Detection of mRNA Vaccine in Breast Milk (link)

A study in investigated whether mRNA from the COVID-19 vaccine can be detected in the expressed breast milk of 11 lactating mothers who had received the vaccination within 6 months after delivery.

The 11 participants provided 131 samples in total, of which 7 were found to contain trace amounts of the mRNA vaccine (either Moderna or Pfizer). All of the samples containing mRNA were expressed with 45 hours of vaccination, with none detected beyond that.

Table 2. Detection of Vaccine RNA in Whole Expressed Breast Milk and Extracellular Vesicles in 5 Patients at Various Time Points Postvaccination

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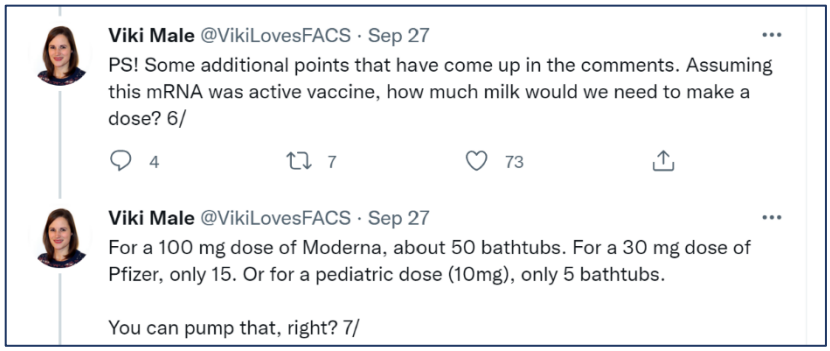
Participant No.	Vaccine type	Time points of vaccine mRNA detection in EBM	Concentration of vaccine mRNA detected in whole milk[a]	Concentration of vaccine mRNA detected in EBM EVs[a]
4	BNT162b2	27-h[b] Sample	Not detected	14.01 pg/mL
6	mRNA-1273	27-h and 42-h[b] Samples	11.7 pg/mL	16.78 pg/mL
7	BNT162b2	37-h[b] Sample	Not detected	4.69 pg/mL
8	BNT162b2	1-h and 3-h[b] Samples	1.3 pg/mL	6.77 pg/mL
10	mRNA-1273	45-h[b] Sample	2.5 pg/mL	2.13 pg/mL

Abbreviation: EBM, expressed breast milk; EVs, extracellular vesicles; mRNA, messenger RNA.

[a] Units for concentration are picogram of mRNA per milliliter of whole milk equivalent.

[b] Sample used for vaccine mRNA concentration detection.

The authors suggest that mothers might wish to be cautious about breast feeding for the first 48 hours after vaccination. However, a lecturer in reproductive immunology at Imperial College, Viki Male, put the (extremely small) amounts found into context using a novel unit of measure, the bathtub. (link)

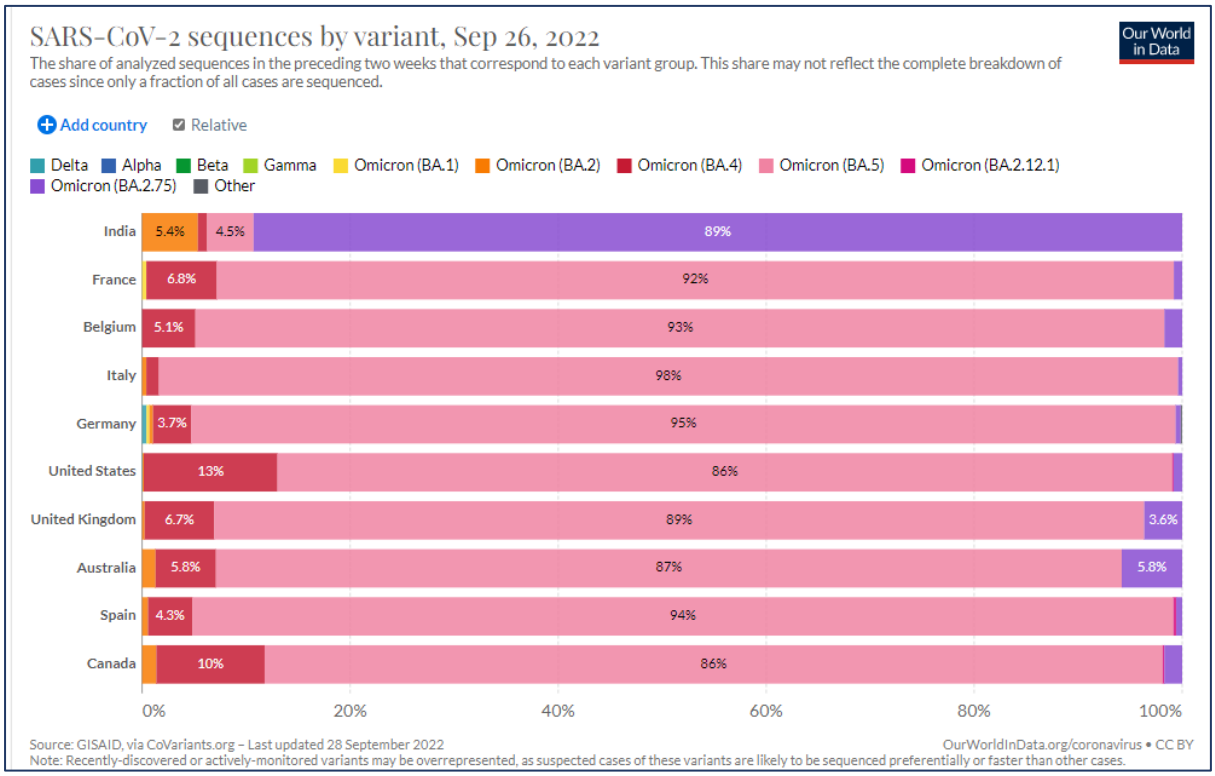


Variants

Frequency of Variants

GISAID data is captured by Our World in Data (link) and shows that BA.5 remains the dominant circulating variant. Compared with data from one month ago, there is a reduction in prevalence of BA.4 and an increase in BA.2.75. (Note though that BA.4 includes BA.4.6, which according to the CDC is currently increasing in prevalence in the USA.) The majority of India's sequences are now BA.2.75, whereas the prevalence in mid-August was 40%.

Note that countries may use targetted sequencing so the contribution of each variant may not necessarily reflect community prevalence.



The UK Health Security Agency issued an update on SARS-CoV-2 variants of public health interest on 9 September and classified the variants as shown in the table below (link).

Variants of concern	Variants	Signals under monitoring and investigation
• BA.1 • BA.2 • BA.4 • BA.5	• BA.2.12.1 • XE recombinant (V-22APR-02/BA.1 x BA.2) • Delta and all sub-lineages • BA.2.75 • BA.4.6	• BA.3 • BA.4.7 • BA.2.75.2 • Delta and Omicron recombinant lineages

BA.2.75 characteristics

A study reported in The Lancet (link) used pseudovirus particles bearing the BA.2.75 spike to investigate the host cell entry and neutralisation characteristics of this variant. The study used antibody sera induced either after vaccination or breakthrough infection during the Delta or early Omicron waves in Germany to investigate BA.2.75 susceptibility to neutralisation.

There was around a 2-fold reduction in neutralisation activity for BA.2.75 and BA.4/BA.5 compared with neutralisation for BA.2. Three of the ten available monoclonal antibodies did not neutralise BBA2.75 and the other 7 all showed reduced neutralisation. Bebtelovimab and cilgavimab (one of the components of Evushield) were the most effective at neutralising BA.2.75.

The authors also found that BA.2.75 may be more adept than BA.2 at infection of the lower airways and inducing cell-cell fusion. The cell–cell fusion capacity of the BA.2.75 spike was similar to that of the BA.4/BA.5 spike, and lower than B.1 and Delta variant spikes. Overall, this suggests that BA.2.75 may be more pathogenic than BA.2.

BA.2.75.2 and BA.4.6 characteristics

A mid-September pre-print study (link) sets out what is known about BA.2.75.2, one the newest emerging variants. BA.2.75.2 is descended from BA.2.75 but has additional mutations.

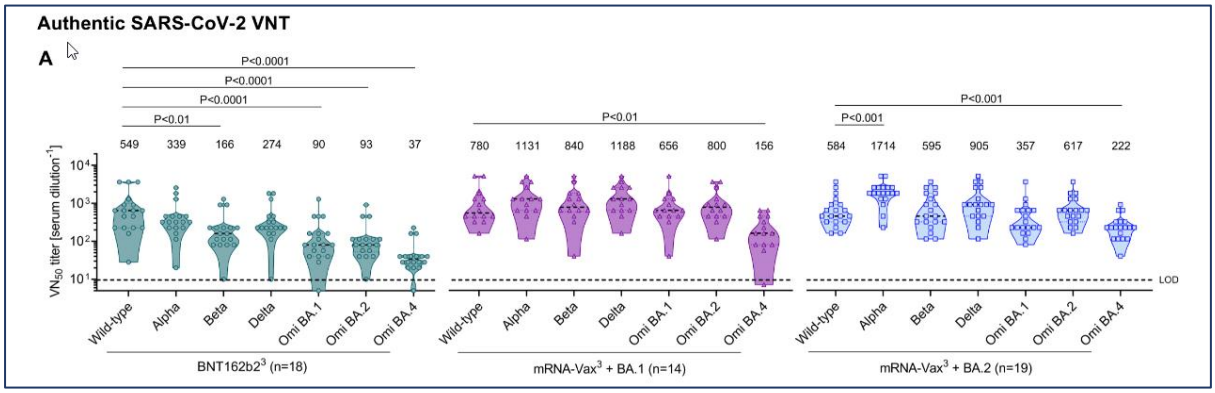
The authors of the study found that BA.2.75.2 showed complete escape from cilgavimab and the Evushield combination (tixagevimab co-packaged with cilgavimab). Their analysis of the neutralising properties of blood serum antibodies showed it to be the most resistant variant yet characterised.

The paper also looked at BA.4.6 and BA.2.10.4: BA.4.6 shows complete escape from cilgavimab but BA.2.10.4 retains some sensitivity. BA.4.6 and BA.2.10.4 are moderately more resistant to neutralisation than BA.5.

BA.2 breakthrough infection enhances cross-neutralisation of BA.2.12.1 and BA.4/BA.5

A study by BioNTech (link) used blood from participants recruited from University Hospital, Goethe University Frankfurt to study effectiveness of neutralisation activity against BA.4/BA.5 of prior vaccination, as well as prior vaccination plus a breakthrough infection of either BA.1 or BA.2.

The study found that exposure to Omicron BA.2, in contrast to BA.1, enhances the neutralisation of BA.4/BA.5 sublineages. The authors used the results of this study, along with knowledge of the predominance of BA.2 derived sublineages like BA.4/BA.5 to inform development of their Omicron BA.4/BA.5-adapted vaccine.



Protection against BA.2 reinfection from prior BA.1 or pre-omicron SARS-CoV-2 infection (link)

As BA.2 and its sub-lineages now dominate the circulating variants, it is useful to have studies that show whether prior infection from BA.1 or a non-Omicron confers any protection. A test-negative case-control study was conducted among healthcare workers in Quebec between 27 March and 4 June 2022 (when BA.2 was the dominant circulating variant).

Pre-Omicron primary infection was associated with a 38% (95% CI 19–53) reduction in BA.2 infection risk. There was higher BA.2 protection among those who had also received one (56%, 95% CI 47–63), two (69%, CI 64–73), or three (70%, CI 66–74) mRNA vaccine doses.

Omicron BA.1 primary infection was associated with greater protection against BA.2 infection compared with prior variants. The risk reduction associated with prior BA.1 infection was 72% (CI 65–78), and protection was increased further among those who had received two doses of mRNA vaccine (96%, CI 95–96), but was not improved with a third dose (96%, CI 95–97).

The study shows that there is some protection conferred by prior infection but hybrid immunity involving both vaccine-induced immunity and prior infection is even more protective.

In the UK Covid infection seropositivity among blood donors increased from around 25% at the end of 2021 to over 70% in recent weeks which suggests high prevalence of prior Omicron infection (link).

Medical

Sad news from the multi-treatment RECOVERY programme that has now passed its second anniversary. The anti-inflammatory drug dimethyl fumarate (DMF) which is used to treat multiple sclerosis and psoriasis blocks an inflammatory pathway that was thought to be involved in lung damage caused by COVID-19. However, an early phase trial of DMF with 713 patients did not find any evidence of benefits in disease severity at day 5 for patients admitted to hospital with COVID, nor in time to discharge (link).

As we have mentioned previously, one of the continuing trials within the RECOVERY programme is the PANORAMIC clinical trial that is exploring whether new anti-viral treatments reduce the need for hospital admission. So far 26,348 have been recruited across 65 GP practices, with the requirements that participants have tested positive for COVID, are experiencing COVID-19 symptoms within the last 5 days and are over 50 (or over 18 with specified pre-existing conditions). However, only a limited number of GP practices (link) are recruiting further participants into the Paxlovid arm of the trial. For those interested, the map is here. Are you one of the lucky ones?

Switching from primary care to NHS trusts, NHS England and NHS Improvement publish quarterly data on the number of cancelled elective operations (link). This publication was paused in April 2020 reflecting the need to release capacity across the NHS, but resumed in Quarter 3 2021/22 on the NHS calendar (October – December 2021), with the most recent publication (in August 2022) covering the period from April – June 2022.

This publication is reassuring in that the number of cancelled operations for non-clinical reasons is 1.0% of all elective activity, a similar proportion to that in the same quarter during 2019/2020 (link). However, for those whose operation was cancelled, the proportion who were not treated within 28 days of a cancellation has increased to 23.6% as compared to 8.7% prior to the pandemic. The table below illustrates both these "breaches" and the general reduction in the number of elective operations.

Table 1: A Summary of the above results compared to previous quarters

Year	Quarter	Elective Spells	Breaches of Standard	Cancelled Operations	Breach Rate (%)	Cancelled Operations (%)
2022/23	Q1	1,809,200	4,145	17,579	23.6	1.0
2021/22	Q4	1,767,671	4,015	17,477	23.0	1.0
2021/22	Q3	1,764,595	4,603	19,338	23.8	1.1
2019/20	Q3	2,054,503	2,138	23,503	9.1	1.1
2019/20	Q2	2,056,552	1,548	20,961	7.4	1.0
2019/20	Q1	1,999,615	1,730	19,969	8.7	1.0
2018/19	Q4	2,009,119	2,157	21,931	9.8	1.1

Long Covid

Long Term Neurological Outcomes after COVID-19 Infection (link)

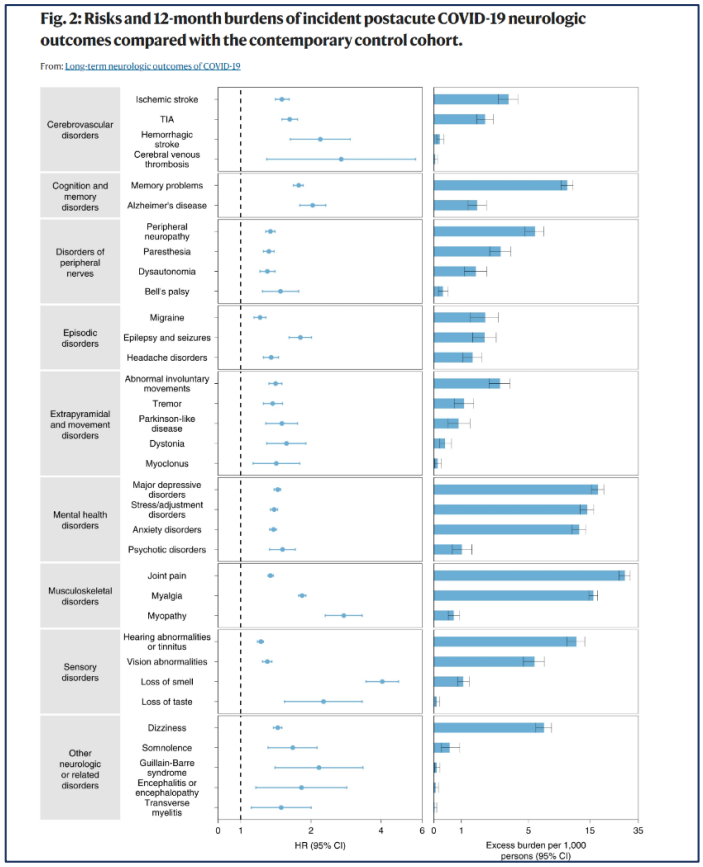
A study published in Nature investigated neurological conditions post COVID in over 150,000 US veterans, with a control group of over 5m.

It found that across all conditions, there was a near 50% excess at 12 months.

Conditions studied were varied, and ranged from a stroke at the most severe to loss of smell and dizziness.

The hazard ratio for an ischaemic stroke was put at 1.50 (CI 1.41-1.61), and for Alzheimer's, 2.03 (CI 1.79-2.31).

For mental health disorders, hazard ratios were typically in the 1.3 to 1.5 range.



Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases (link)

A study using English and Welsh electronic health records of 48 million adults in 2020 has found high relative incidence of vascular events after COVID-19 diagnosis.

The adjusted hazard ratio for arterial thrombosis was 21.7 (95% CI 21.0–22.4) in the first week after COVID-19 diagnosis and then declined to 1.34 (CI 1.21–1.48) during weeks 27 to 49.

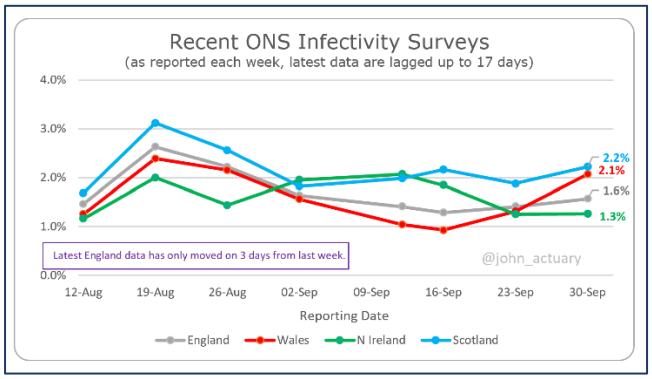
The adjusted hazard ratio for venous thromboembolic event (VTE) was 33.2 (CI 31.3–35.2) in the first week after COVID-19 diagnosis and declines to 1.80 (CI 1.50–2.17) during weeks 27 to 49.

For both arterial thrombosis and VTE, incidence remains elevated up to 49 weeks after COVID-19 diagnosis which supports policies to prevent severe COVID-19 and the use of secondary preventive agents in high-risk patients.

Data

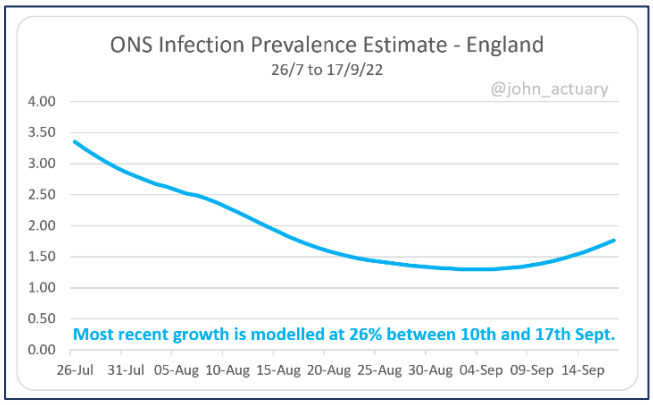
ONS Infection Study (link)

Latest data from this continuing study shows that rates are generally increasing, although there is some volatility in the devolved administrations' figures that limit the reliance that can be taken on weekly variations. Northern Ireland appears the outlier, having fallen over the last month.



Whilst the figure for England has only risen by 11% this week, to 1.6%, this doesn't reflect the true picture, as the data was only rolled forward 3 days, so 11% reflects 3 days of growth.

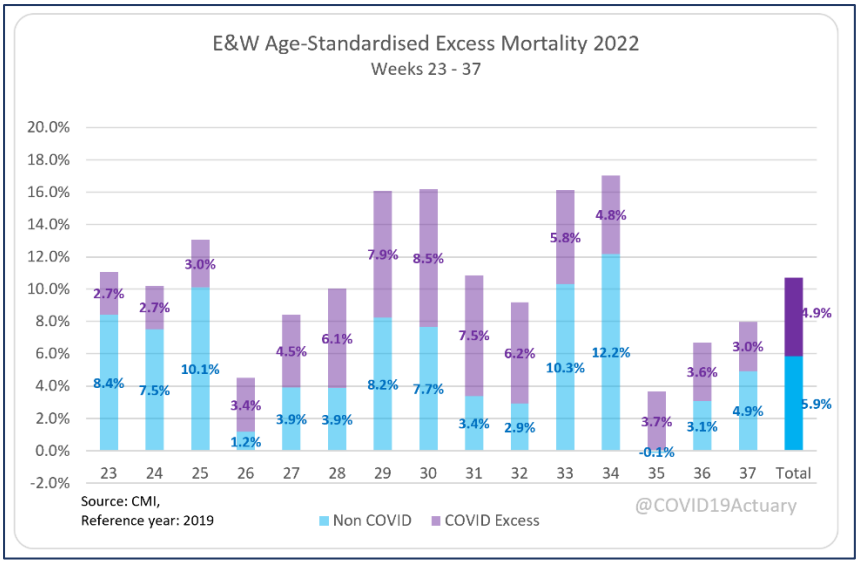
Looking at the daily estimates up to 17 Sep (the latest date) shows a weekly increase of 26%, which intuitively feels more reasonable given the increase in admissions we are seeing (discussed below).



High Excess Mortality (link)

Over the summer we've continued to see high excess mortality, despite COVID deaths being relatively low (in the context of previous periods during the pandemic).

Using data published weekly by the Continuous Mortality Investigation (CMI), we can separate COVID related deaths (defined as a mention on the death certificate as a contributory factor) from non-COVID deaths. In the last 15 weeks, over half of the total excess of 10.8% have not been COVID related.

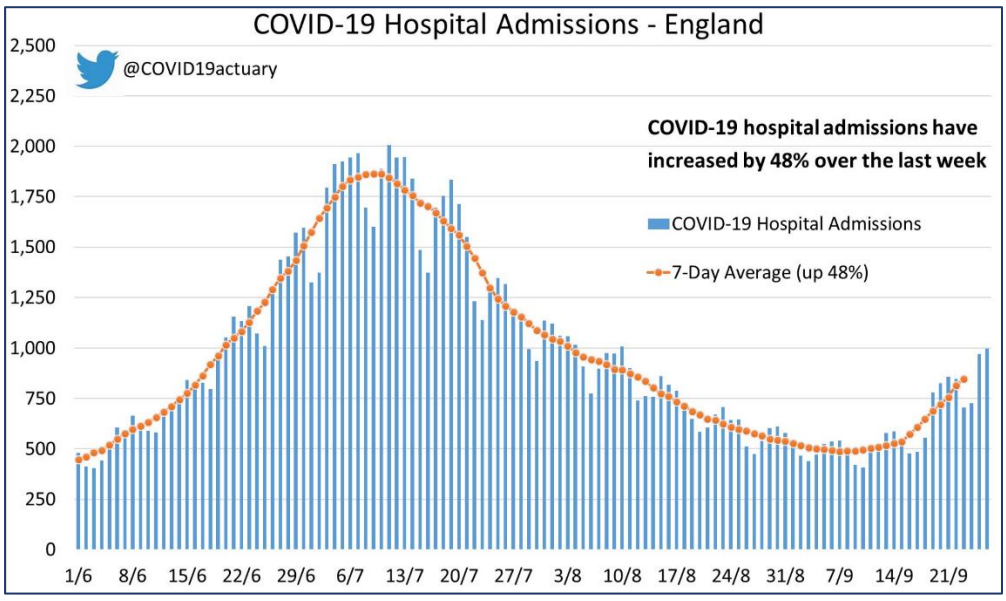


An excess of 6% over the summer period, when mortality is normally relatively stable, is quite exceptional, and there has been a lot of speculation over the causes (including on Newsnight, where our co-chair Stuart McDonald explained why the CMI's age-standardised analysis is preferred to simple death counts).

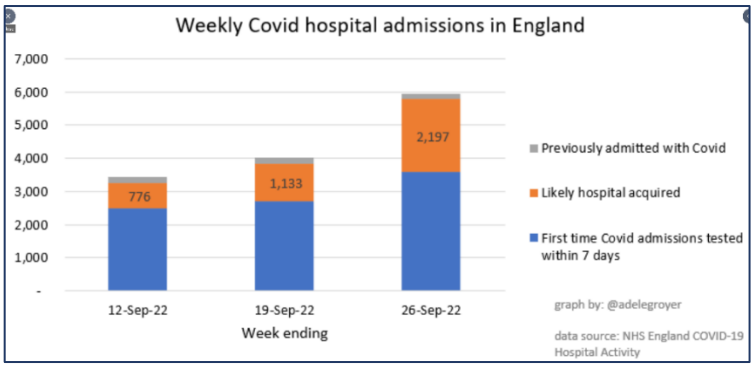
The reasons are undoubtedly varied and difficult to quantify with any degree of certainty, but may include stresses in the health system and latent health issues following COVID infection, particularly cardiovascular. We published a blog on the topic recently (link).

Hospital Statistics

After reaching a relative low at the end of August, all of the usual COVID hospital metrics in England are now increasing, with the latest data showing very rapid growth. For admissions, growth was 48% over the week, and beds occupied where COVID is the primary diagnosis grew by 46%.



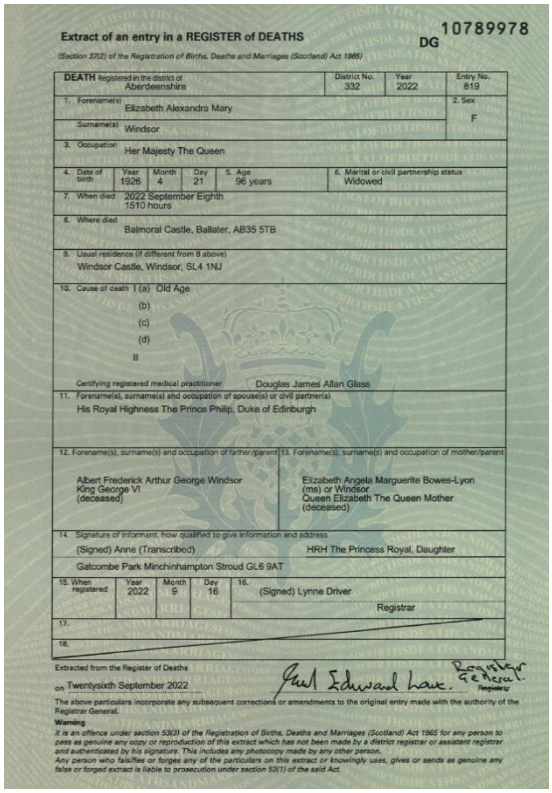
Of even more concern is the jump in admissions where the virus is believed to have been caught whilst already in hospital: this nearly doubled in a week.



And Finally …

September will of course be remembered for the death of Her Majesty Queen Elizabeth II, at the age of 96, and after reigning for an astonishing 70 years. It would be remiss of us not to acknowledge her great service over that period, and the exemplary manner in which she carried out her role.

Her Majesty's death certificate was published yesterday (link), and gives the cause of death as simply "Old Age", although some may view the certificate of interest more for the grand occupations of the deceased and her father, along with similarly grand places of death and usual residence.



Extract of an entry in a REGISTER of DEATHS — 10789978 DG

(Section 37(2) of the Registration of Births, Deaths and Marriages (Scotland) Act 1965)

DEATH registered in the district of Aberdeenshire | District No. 332 | Year 2022 | Entry No. 819

1. Forename(s): Elizabeth Alexandra Mary — 2. Sex: F
Surname(s): Windsor
3. Occupation: Her Majesty The Queen
4. Date of birth: Year 1926 | Month 4 | Day 21 — 5. Age: 96 years — 6. Marital or civil partnership status: Widowed
7. When died: 2022 September Eighth 1510 hours
8. Where died: Balmoral Castle, Ballater, AB35 5TB
9. Usual residence (if different from 8 above): Windsor Castle, Windsor, SL4 1NJ
10. Cause of death: I (a) Old Age; (b); (c); (d); II
Certifying registered medical practitioner: Douglas James Allan Glass
11. Forename(s), surname(s) and occupation of spouse(a) or civil partner(s): His Royal Highness The Prince Philip, Duke of Edinburgh
12. Forename(s), surname(s) and occupation of father/parent: Albert Frederick Arthur George Windsor, King George VI (deceased)
13. Forename(s), surname(s) and occupation of mother/parent: Elizabeth Angela Marguerite Bowes-Lyon (nee) or Windsor, Queen Elizabeth The Queen Mother (deceased)
14. Signature of informant, how qualified to give information and address: (Signed) Anne (Transcribed) — HRH The Princess Royal, Daughter
Gatcombe Park Minchinhampton Stroud GL6 9AT
15. When registered: Year 2022 | Month 9 | Day 16 — 16. (Signed) Lynne Driver — Registrar
17.
18.
Extracted from the Register of Deaths on Twentysixth September 2022 — Registrar General
The above particulars incorporate any subsequent corrections or amendments to the original entry made with the authority of the Registrar General.
Warning
It is an offence under section 53(3) of the Registration of Births, Deaths and Marriages (Scotland) Act 1965 for any person to pass as genuine any copy or reproduction of this extract which has not been made by a district registrar or assistant registrar and authenticated by his signature. This includes any photocopy made by any other person.
Any person who falsifies or forges any of the particulars on this extract or knowingly uses, gives or sends as genuine any false or forged extract is liable to prosecution under section 53(1) of the said Act.

As King Charles III takes to the throne at the age of 73, it is worth noting that with improvements in longevity, it becomes more likely that future monarchs will accede to the throne at a relatively late stage in their own life, and that the reign of Queen Elizabeth II will be unmatched for a very long time.

30 September 2022