Mortality Impact of COVID-19 Vaccination in England

Counterfactual Insights from Gompertz to Machine Learning

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Abstract

The U.K. launched the world's first mass COVID-19 vaccination on 8th December 2020. This paper explores whether the data supports early signs of immunity build up and mortality impact on people 80 years of age and above in England.

By considering percentage weekly change in COVID-19 hospital admission and hospital deaths, this suggests the 80+ age group is seeing a reduction in January 2021. However, the percentage weekly change in COVID-19 associated deaths and registered deaths are less clear.

We measured the relative mortality between the age groups by using the Gompertz function. This approach shows that the rate of age-related increase in mortality (α) has a remarkably consistent weekly pattern in the last 12 weeks of 2020 and throughout various phases of the pandemic before the start of vaccinations. This implies that the mortalities of the younger age groups are great predictors of the mortality of the 80+ age group.

Using this key insight, we constructed the counterfactual scenarios assuming the environment after 8th December 2020 is taken to be the same as before. Then we applied linear regression and machine learning to predict the expected level of mortality in the 80+ age group using the mortality data from the largely unvaccinated younger age groups. The actual versus expected results for ages 80+ show both hospital and registered deaths have statistically significant mortality reductions from middle of January 2021 onwards:

- Registered deaths show an estimated reduction of 32% by 12th February 2021; and
- Hospital deaths show consecutive mortality reductions for many weeks and arrived at an estimated 50% reduction by 20th February 2021.

The timing of the mortality reduction is compatible with the drastic increase in the prevalence of community antibody positivity among the 80+ age group according to data published by the Office of National Statistics.

We then discussed to what extent the mortality reduction is due to other confounding factors such as the January lockdown. However, whilst this may explain some of the effects, there is compelling evidence using the counterfactual scenarios that the key driving force for the mortality reductions in England from middle of January 2021 onwards is likely due to the vaccination roll-out.

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Contents

1   Introduction

The U.K. launched the world's first mass COVID-19 vaccination on 8th December 2020. In England, the percentage of people 80 years of age and above who received the first dose was 18.5% by 27th Dec 2020. By 17th January 2021, this percentage rose to 56.3% [1].

The questions we will attempt to address in this paper include:

1. Are we starting to see early signals of the immunity build up in the 80+ age group and prevention of deaths, compared to the younger age groups?
2. Is it possible to disentangle vaccine impact from other confounding factors?
3. Can actuarial science and data science techniques be employed to provide greater insights?

Initially we will consider hospital admissions, hospital deaths, deaths within 28 days of positive test and registered deaths to compare the weekly percentage change for different age groups to understand if there is a clear difference starting to emerge between the 80+ ages (who are included in the initial vaccination rollout) against the unvaccinated younger age groups.

In the later sections, we consider several counterfactual modelling approaches to understand the change in mortality in the 80+ age group when compared to the younger age groups.

Multiple data sources are considered. In the modelling section, we have used Office of National Statistics (ONS) deaths data by date of registration and hospital deaths data by date of death. Additionally, we have considered in the appendices ONS data by date of occurrence and Public Health England (PHE) data by date of occurrence.

1.1   Hospital admissions

COVID-19 hospital admissions data was sourced from the National Health Service (NHS). The data shows the number of patients admitted with COVID-19 and number of inpatients diagnosed with COVID-19 by reporting date. Figure 1 considers the weekly percentage change in hospital admissions in England, split by three distinct age groups including 55-64, 65-74 and 75+, as well as the broad age group consisting of those less than 75 years old [2].

There are several confounding factors including: a lockdown in November 2020; a stricter lockdown in January 2021 where schools were closed; a higher prevalence of a more transmissible/severe new variant; the death clusters in care homes; and the successful rollout of the vaccination programme that started 8th December 2020. From the 17th January 2021 there appears to be a slight divergence as the weekly percentage change of the 75+ age group falls below that of the under 75 age group, implying a slightly faster rate of decrease in the 75+ age group but isn't conclusive.

Figure 1: Weekly percentage change of COVID-19 hospital admissions by age groups
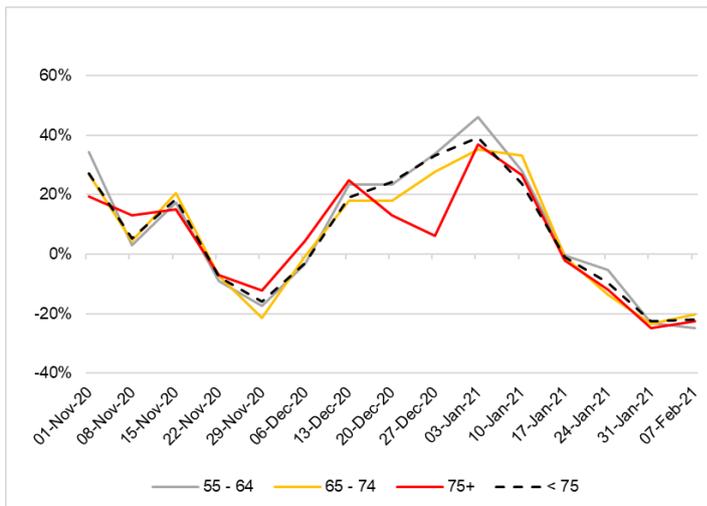
1.2   Hospital deaths

COVID-19 hospital deaths data was sourced from the NHS and recorded against the date of death. Figure 2 considers the weekly percentage change in hospital deaths in England, split by three distinct age groups including 40-59, 60-79 and 80+, as well as the broad age group consisting of those under 80 years of age [3].

As with hospital admission, there are many confounding factors impacting the hospital deaths. The weekly percentage changes in the 80+ age group are slightly more negative than the under 80 age group for most of the time in January 2021. However, from the end of January they do appear to diverge over a 3-week period up to 20th February 2021 which perhaps could be an impact of the vaccine roll out in 80+ age group.

Figure 2: Weekly percentage change of COVID-19 hospital deaths by age groups
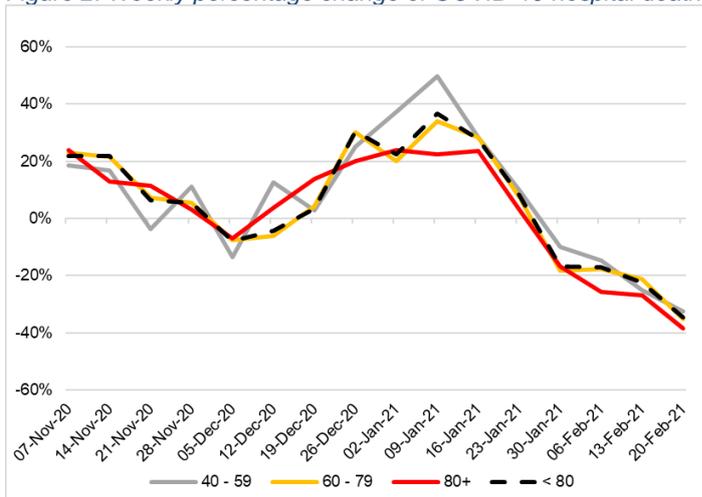
1.3   Deaths within 28 days of positive test

COVID-19 associated deaths data by date of death was sourced from the PHE, where deaths are only included if the deceased had a positive test for COVID-19 and died within 28 days of the positive test [4]. Figure 3 considers the weekly percentage change in PHE's COVID-19 associated deaths in England and Wales, split by four distinct age groups including 50-59, 60-69, 70-79 and 80+, as well as the broad under 80 age group.

The weekly percentage changes in the 80+ age group started to decrease faster and falls below the under 80 age group from week ending 3rd February 2021.

Figure 3: Weekly percentage change of PHE's COVID-19 associated deaths by age groups
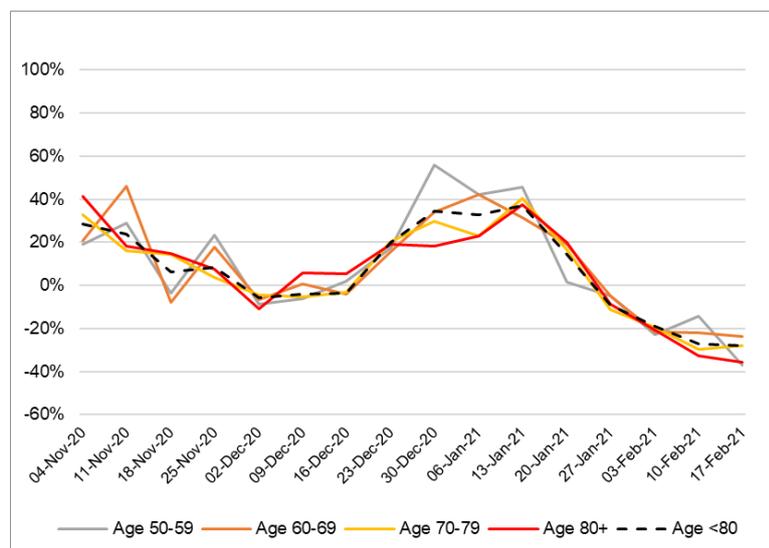
1.4   Registered deaths

COVID-19 registered deaths data was sourced from the Office of National Statistics (ONS). Figure 4 considers the weekly percentage change in registered deaths in England and Wales, split by four distinct age groups including 50-59, 60-69, 70-79 and 80+, as well as the broad under 80 age group [5].

As discussed, there are many confounding factors impacting registered deaths such as clusters of deaths of care homes in January 2021. Based on this information, it is difficult to establish if there is any reduction in mortality up to the end of January 2021 as the 80+ and under 80 age groups are closely aligned from weeks ended 8th to 29th January 2021. However, there is a sign of divergence from week ended 5th February 2021.

Figure 4: Weekly percentage change of ONS' COVID-19 registered deaths by age groups
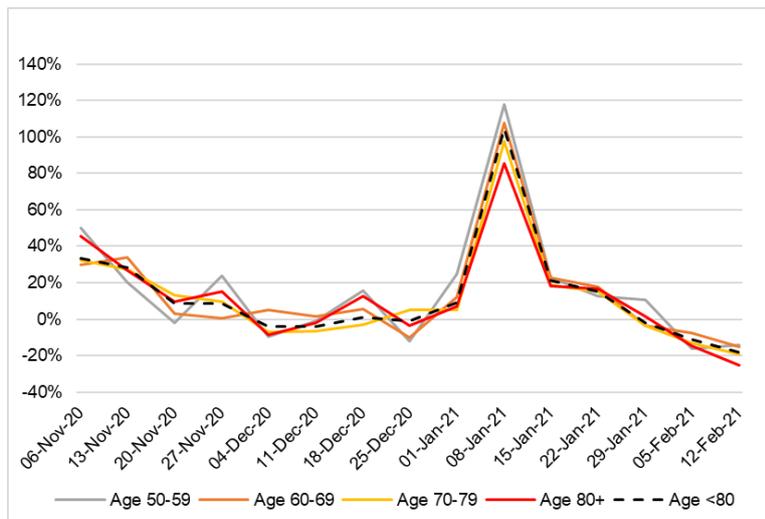
By considering percentage weekly change in COVID-19 hospital admission, hospital deaths, deaths within 28 days of positive test and registered deaths, this suggests there may be an impact in the 80+ age group, but the evidence is not conclusive. We will consider in later sections the impact on mortality using predictive modelling approaches to see if we can glean further insights into differences between the 80+ compared to younger age groups (Section 5).

2 Patterns of age dependency of COVID-19 deaths in England

In this section, the weekly COVID-19 registered deaths data of England and Wales, where coronavirus was mentioned on the death certificate, was sourced from the ONS [5].

2.1 Proportion of deaths by age

The COVID-19 deaths data from 2020 is aggregated into four distinct periods of the pandemic in England:

i. Mar - Jun 2020: The first wave and first lockdown.

ii. Jul - Oct 2020: The period between the first wave and second lockdown, coinciding with the summer season.

iii. Nov - early Dec 2020: During the second wave, second lockdown, increasing prevalence of the new coronavirus variant B.1.1.7, but prior to vaccine rollout.

iv. Early Dec 2020 – 1st Jan 2021: Rollout of vaccines begins.

Figure 5: Bar plots of proportion of deaths in different age groups, by time period (a) [Mar - Jun 2020, July - Oct 2020, Nov - early Dec 2020, early Dec 2020 – 1st Jan 2021] and by weeks ended (b) [6th Nov 2020 – 29th Jan 2021]
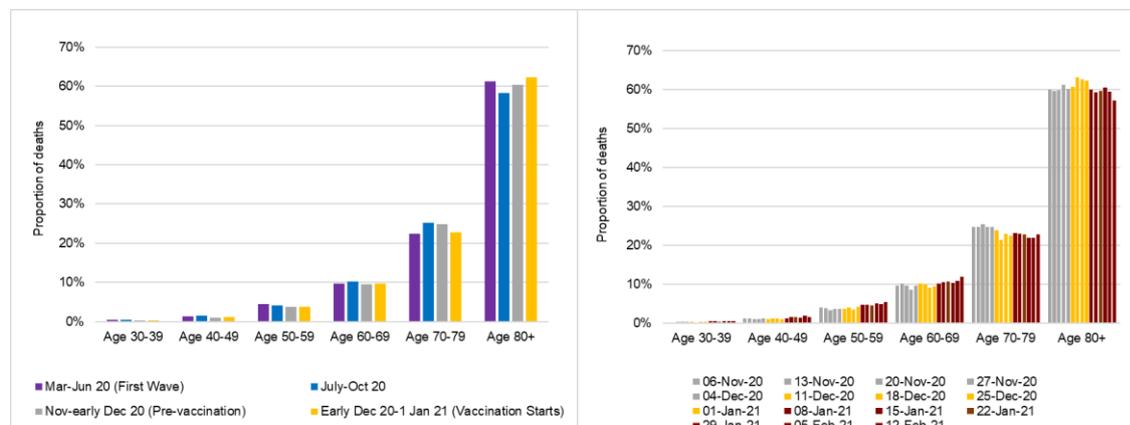
COVID-19 deaths are known to be disproportionately higher in older people. The 80+ age group comprised 60% of total deaths in 2020, whilst the corresponding percentage is 84% for ages 70+ and 98% for ages 50+ (Figure 5).

The proportion of deaths in the older age groups were broadly similar during the four periods and for every week in the last two months of 2020. A reduction in the proportion in the 80+ age group is observed from 8th Jan 2021; however, it is unclear if this is due to lockdown, vaccinations or other confounding factors.

The proportion of deaths by age group is a simple metric that exhibits a crude age-related pattern for the last few months of 2020. It is based on absolute death numbers, but there are other metrics which we will explore further that may provide better insights into the relative mortality relationship between age groups.

2.2   Rate of age-related increase in mortality

An alternative way to consider the impact change in older age groups is to consider the rate of age-related increase in COVID-19 mortality. We have considered the increase in COVID-19 mortality risk by considering mortality ratios (Appendix 10.1 and 10.2) that we then used to calibrate a Gompertz function:

$$m(x) = Ae^{\alpha x}$$

where $m(x)$ is the force of mortality for an adult with age x, where A is the baseline mortality and α is the rate of age-related increase in mortality (also known as the senescent component).

The exponential patterns of COVID-19 mortality rates are observed in many countries and are associated with all-cause mortality. Therefore, α is a useful metric for mortality experience comparisons [6] [7].

The parameter α measures the gradient of the mortality ratios by age, through its derivation from the slope of regression line of log mortality ratios by age. Note α is a generalisation of mortality ratios, because it measures the relative mortalities of the 80+ age group, with respect to the 40-49, 50-59, 60-69, 70-79 age groups simultaneously.

Figure 6: Rate of age-related increase in mortality and by weeks ended 16th Oct 2020 – 12th Feb 2021
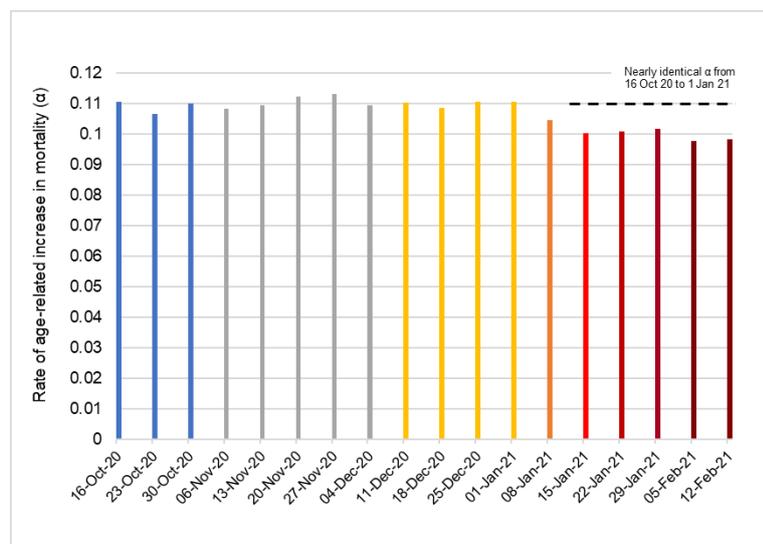
Figure 6 shows that the values of α for each of the final 12 weeks of 2020 are remarkably similar - they are notably consistent even with the introduction of new lockdown measures in November, the continued shielding of vulnerable patients, different levels of acquired immunity, the emergence of a more infectious new variant, as well as increasing levels of infection and death. In other words, the mortality relationship between age groups is preserved under this metric for many weeks under many external influences leading up to the vaccination programme.

In addition to the above, the slope of mortality by age is generally consistent during various periods in 2020 (Appendix 10.2). This implies that the mortality of younger ages is predictive of the mortality of older ages throughout the pandemic prior to the vaccination roll out.

There is a material change from weeks ending 8th January to 12th February 2021 compared to previous weeks. The reduction of age slope coincides with a period when a stricter lockdown was introduced and when a vaccination programme may have begun to take effect.

2.3   The new variant

The SARS-CoV-2 lineage B.1.1.7, also known as VOC 202012/01 (Variant of Concern, year 2020, month 12, variant 01), was first recorded on 20th September 2020 in Kent, UK and sequenced in early October 2020 [8]. Studies showed it had a rate of transmission 71% higher than other variants and had an absolute increase in the R-value of between 0.39 and 0.93 [9].

An Imperial College London study by Volz et al found that there is a larger share of under 20 year olds among reported VOC than non-VOC cases [10]. Neil Ferguson, a NERVTAG member, said that this was expected because of schools remaining open during lockdown, and among those aged under 15 there were slightly more cases of the variant virus in the community than the non-variant, though not significantly so [8].

The fact that the cases of B.1.1.7 are slightly higher for those under 20 years old should not skew the value of α, which is based on mortality of 40+ age groups (section 10.2).

In addition to increased transmissibility, there were concerns that the new variant may be more severe. The London School of Hygiene & Tropical Medicine (LSHTM) reported the relative hazard of death within 28 days of test for VOC-infected individuals was 1.35 compared to non-VOC. Imperial College London reported the mean ratio for COV-infected individuals compared to non-VOC was 1.29-1.36. Both studies demonstrated that the relative increases in case fatality rate (CFR) appeared to be consistent across age groups [11].

If B.1.1.7 can induce a selective mortality effect (including infection and fatality after infection) on any age groups which are more than 40 years old, then it would have manifested in the mortality curves in December 2020, because the proportions of new variant in all cases in England were as high as 20% and 30% in the 25th November 2020 and 2nd December 2020 weeks respectively [12]. However, the trends show remarkably consistent slopes of mortality ratios by age and α to end of 2020 (section 10.1), suggesting it is unlikely that B.1.1.7 has a significant mortality bias on the 40+ age groups.

3   Time lags from vaccine uptake to death registration

3.1   Vaccine build up

The following are some data concerning the time required for the vaccine to build up immunity:

1. The NHS and Public Health England (PHE)'s "COVID-19 vaccination: What to expect" leaflet states that "it may take a week or two for your body to build up some protection from the first dose of vaccine". This advice is given to patients attending vaccination appointments [13].
2. The Commission on Human Medicine says partial immunity occurs after the first dose of Pfizer vaccine and people will be immune seven days after the second dose [14].
3. Based on the timing of cases accrued in the phase 3 study, the PHE's green book said that most of the Pfizer vaccine failures in the period between doses occurred shortly after vaccination, suggesting that short term protection from dose 1 is very high from day 10 after vaccination [15].
4. Preliminary findings of the AstraZeneca vaccine showed that neutralising antibodies were induced at day 14 and 28 after first vaccination and titres increased after a second dose [15].

Compared to the following stages, there is more uncertainty in estimating the duration required for vaccine build up.

3.2   Infection to symptom onset

The median incubation period of COVID-19 was estimated by the Annals of Internal Medicine to be 5.2 days (95% CI 4.5 to 5.8 days). The 25th percentile is 3.8 days and the 75th percentile is 6.7 days [17].

3.3   Symptom onset to death

The ISARIC-CCP-UK study reported that hospital patients in the 80+ age group had a median time of 7 days from symptom onset to death, based on data after 1st August 2020 (before this period the corresponding median time was 14 days). The median duration from hospital admission to death in hospitalised patients aged 80+ is 2 days [18]. This implies the median time from symptom onset to hospital admission is 5 days.

Given a substantial proportion of deaths of age 80+ are from care home patients, who are frailer and may not have immediate access to ICU, the average time from symptomatic infection to death might be shorter than 1 week [5].

3.4   Death registration

For deaths in care homes, notification must be sent to the Care Quality Commission (CQC) without delay, typically within 2-3 days of death [20]. The figures are published as part of the ONS's weekly release. In England & Wales, all deaths must be registered within 5 days [21].

3.5   Estimation of onset time of effect from vaccination

Table 1: Estimation of time lags

	Low estimate of time lags	Middle estimate of time lags	High estimate of time lags
Time from infection to symptomatic onset	4 days	5 days	7 days
Time from symptomatic onset to death	5 days (assuming frailty in care homes)	7 days (for hospital deaths: 5 days from symptomatic onset to hospitalisation, then 2 days to death)	10 days
Delay in registration of death	2 days	4 days	5 days (maximum)
Total	Vaccine build up time + 11 days	Vaccine build up time + 16 days	Vaccine build up time + 22 days

Suppose the vaccine-induced protection occurs after 10-14 days, then the total time lag from vaccine uptake to ONS registered deaths is estimated to have a range of 21-36 days (Table 1).

3.6   Vaccination data

The percentage of vaccine uptake is the number of people vaccinated divided by the size of the population in the cohort. The National Immunisation Management Service (NIMS) data shows the cumulative percentages of vaccine uptake by age groups over different periods of time (Table 2). This data did not have a split by care homes; however, it was reported on 15th January 2021 that the British Prime Minister said 40% of elderly care home residents had been vaccinated at that point [22].

Table 2: Vaccination data for England [1] [23]

	Ages 80+		Age 79 and under	
	First Dose – Cumulative % vaccine uptake	Second Dose – Cumulative % vaccine uptake	First Dose – Cumulative % vaccine uptake	Second Dose – Cumulative % vaccine uptake
8th Dec 2020 – 27th Dec 2020	18.5	0	0.6	0
8th Dec 2020 – 3rd Jan 2021	23.1	0.2	1.0	0.03
8th Dec 2020 – 7th Jan 2021	28.0	5.8	1.6	0.12
8th Dec 2020 – 10th Jan 2021	36.5	9.8	2.3	0.19
8th Dec 2020 – 17th Jan 2021	59.4	10.7	4.4	0.24
8th Dec 2020 – 24th Jan 2021	79.7	11.6	8.3	0.26
8th Dec 2020 – 31st Jan 2021	88.1	11.8	13.1	0.29

Based on vaccination data of England (Table 2), 18.5% of aged 80+ population, nearly a fifth, had received the first dose between 8th December 2020 and 27th December 2020. Based on a weighted average estimation this cohort received the first jab on 21st December 2020 [24].

For this cohort, the onset of impact on the ONS registered deaths is estimated to be between 11th and 26th January 2021, using the time lags estimates of 21-36 days (Section 3.5). Therefore, we may observe some early degree of effect of the vaccination feeding through into mortality in the 2nd half of January 2021.

For hospital deaths in this cohort, the onset time is estimated to be between 9th and 21rd January 2021 using the 19-31 days estimate (as the data is based on date of death and not when registered), and the magnitude of impact, if present, is expected to increase over time.

4   Hospital data in England and Israel

4.1   Consecutive reductions in Hospital Mortality Ratios in England

This section focuses on the deaths data of patients who have died in hospitals in England and have tested positive for COVID-19, sourced from the National Health Service (NHS). Deaths reported in this data are recorded against the date of death rather than the day the deaths were announced [3]

Figure 7: COVID-19 deaths in hospitals in England: Weekly mortality ratios for ages 80+ by weeks ended 31st October 2020 – 20th February 2021, when the reference groups are (a) ages 40-59 (b) ages <80
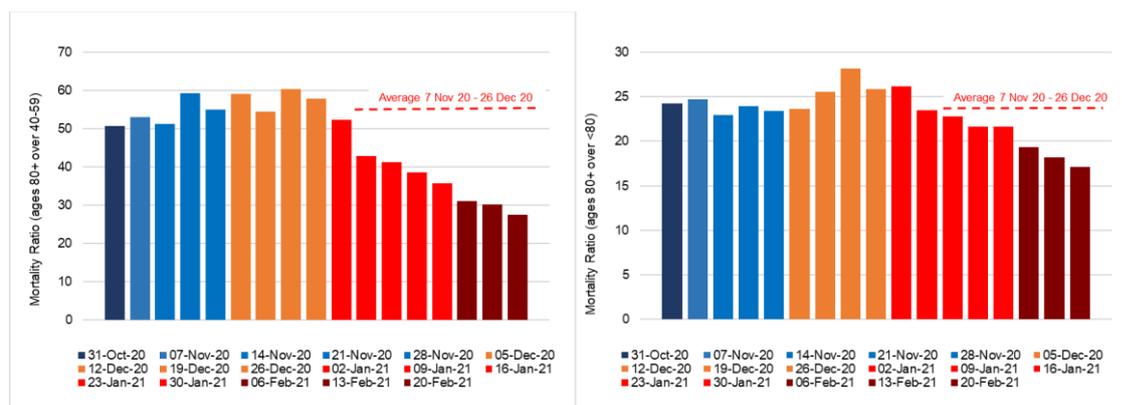
The Hospital Mortality Ratio (HMR) are calculated as the ratio of mortality rate of the 80+ age group with reference to the 40-59 and <80 age group (Figure 7). This illustrates that the HMRs were generally similar in November and December 2020, with slight increases in December 2020, but have reduced consistently from 9th January 2021 for 7 weeks until 20th February 2021.

The selection of a reference group, e.g. 40-59, does highlight a weakness in the mortality ratio approach. The under 80 age group is an aggregated reference with a lower reduction compared to using the 40-59 age group as reference. We proposed in Section 5.5 a methodology where multiple age groups are used as reference groups simultaneously to provide a more credible view of mortality changes.

4.2   60% reduction in hospitalisations for 60+ age group in Israel

It is useful to compare the U.K. experience against the reported impact of the vaccination in Israel, a programme that started on 20th December 2020. However, the data publicly available in the U.K. at time of writing is not available to the same granularity (e.g. from date of first vaccination) so it is more difficult to interpret the U.K. reduction due to timing and speed of the vaccine rollout and other confounding factors such as lockdown.

Israel's initial target group was aimed at people aged 60 or over, nursing home residents, other people at high risk due to serious medical conditions and front-line health workers [25].

Media outlets such as the MailOnline has reported that the KSM Maccabi data from Israel saw 60% drop in hospitalisations for 60+ age group 3 weeks after first doses [26] [16]. It was based on 50,777 members aged over 60 of Maccabi, an Israeli health care provider.

Figure 8: Average additional daily positive PCR and hospitalisation by the number of days from first dose of vaccination, among Maccabi members. Image is sourced from the MailOnline and the KSM Maccabi Research and Innovation Center
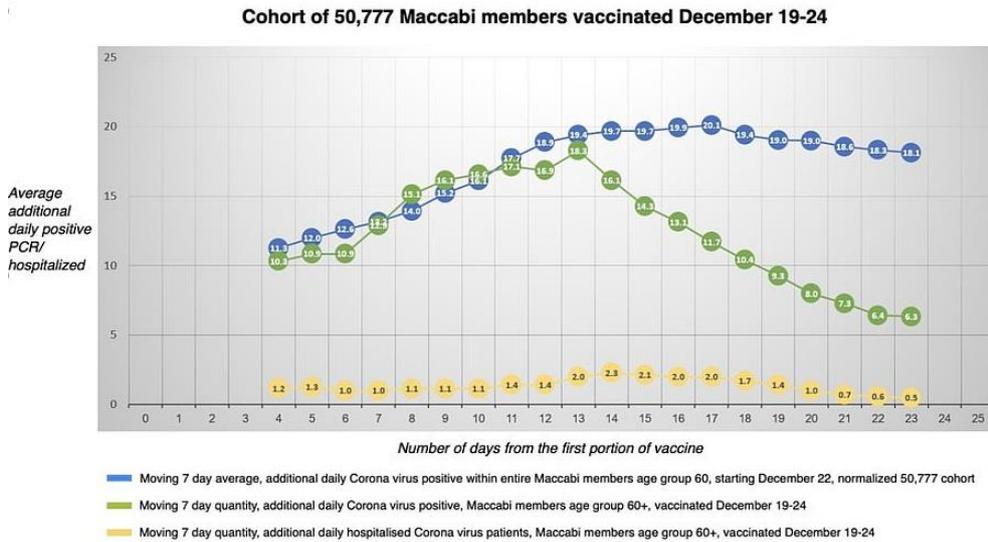
Source: [16]

In Figure 8, the blue line represents the infection rate in the general population, the green line represents the infection rate among those vaccinated in December and the yellow line represents hospitalisation among those vaccinated. The improvement began to show on day 14 after the first dose, where infections in vaccinated group started to fall. Hospitalisation rates of the vaccinated group started to improve on day 18. By 23rd day of vaccination after the first dose, there is a decrease of slightly more than 60 per cent in the number of new hospitalised patients, according to the study [16].

Regarding the emerging positive results from Israel, Prof Ran Balicer, founder director of the Clalit Research Institute, said: "That could have two potential explanations. One is that somehow the over 60s have become much more careful about their daily conduct, and are very careful not to get infected, or that vaccines on the population level begin to show their effects. I would strongly agree that these ecologic data are quite reassuring and are quite promising. I would have been exceedingly worried had we not seen on a population level already such a picture." [27]

5   Counterfactual predictive modelling

The aim of predictive modelling is to estimate the level of deaths in the 80+ age group in the counterfactual scenario, where the modelled environment after 8th December 2020 (start date of vaccination programme in the U.K.) is taken to be the same as that in the period of October to November 2020, including but not limited to no vaccination.

If we hypothetically assume that the vaccination rollout is the cause of the diverging mortality risk observed in hospital deaths and registered deaths, with no other external influences, then this counterfactual scenario becomes a so-called "unvaccinated" scenario.

A variety of predictive models are used to explore the counterfactual scenario for registered deaths:

- a linear regression approach across age groups (Model R1)
- a simple approach based on mortality ratios (Model R2)
- an epidemiological approach based on Gompertz function (Model R3), and
- a hybrid approach of epidemiology and machine learning, known as Gompertz Network (Model R4)

The following predictive models are applied in the counterfactual scenario for hospital deaths:

- a linear regression approach across age groups (Model H1)
- a simple approach based on mortality ratios (Model H2)

The heuristics of the above approaches comes from the observation that the mortality of younger ages is predictive of the mortality of older ages throughout the pandemic and pre-vaccination (Appendix 10.2).

For each model the inputs are mortality rates (derived from COVID-19 registered death counts and population data) of younger age groups, and the model outputs are predicted mortality rates for ages 80+ for a given time period. 70-79 age group was not used due to its vaccination coverage, because the modelling approach assumes the input age groups are unvaccinated. In addition, modelling with or without 70-79 age group as an input gave very similar accuracy, so leaving it out can help with reducing model complexity.

For registered deaths, the training data from weeks ending 16th October 2020 to 4th December 2020 is used to fit the model parameters. The model is then evaluated on an out-of-sample test dataset covering the weeks ending 11th December 2020 to 1st January 2021. The best performing model is used to predict the expected level of deaths in ages 80+, in the counterfactual scenario, for the future weeks.

For hospital deaths, the training period is from weeks ending 3rd October 2020 to 5th December 2020 while the out-of-sample evaluation period is from weeks ending 12th December 2020 to 2nd January 2021.

Model accuracy or performance is measured by mean absolute percentage error (MAPE), which is calculated as the average of the absolute difference in the residual (predicted mortality less actual mortality of 80+ age group) over the actual mortality.

The comparisons of time series results are presented using the "Actual vs Expected" (AvE) metric, calculated as dividing the actual mortality over the expected mortality of ages 80+, where the expected mortality is the mortality prediction under the counterfactual scenario.

Table 3: Overview of predictive models for registered deaths

	Model R1 - Linear regression	Model R2 – Mortality Ratio	Model R3- Simple Gompertz	Model R4 - Gompertz Network
Description	Weighted average of mortality from age groups 30-39, 40-49, 50-59 and 60-69.	Estimate the average mortality ratio of ages 80+ and ages 50-59 from training data. Thereafter use it for model scoring.	Derive α (rate of age-related increase in mortality) from training data. Thereafter use it for model scoring.	Four Gompertz models are derived from four age groups: 30-39, 40-49, 50-59 and 60-69. They are combined using a weighted average approach, using Lasso regularisation.
Train Accuracy (MAPE[1])	4.4%	5.9%	5.7%	5.4%
Test Accuracy (MAPE)	4.5%	4.4%	5.3%	3.5%
Advantage	Good accuracy Easy to understand	Simple calculation and decent accuracy	α considers multiple age groups	Best test accuracy
Disadvantage	Slightly less test accuracy than Gompertz Network	Subject to fluctuations in the reference age group	Subject to fluctuations in the reference age group	Less intuitive to understand

Table 4: Overview of predictive models for hospital deaths

	Model H1 - Linear regression	Model H2 – Mortality Ratio
Train Accuracy (MAPE)	4.2%	6.8%
Test Accuracy (MAPE)	7.1%	6.5%

We also constructed counterfactual modelling for:

- PHE's COVID-19 associated deaths, where deaths are only included if the deceased had a positive test for COVID-19 and died within 28 days of the positive test [4].
- ONS' COVID-19 associated deaths, where deaths are based on date of occurrence [5].

PHE and ONS show similar results but are more volatile. The corresponding linear regression approach has a training error of 7.8% and test error of 12.6% for PHE, and a training error of 6.4% and test error of 7.8% for ONS. Hence the associated models were not used. For completeness, we included the results for these models in Appendices 10.3.

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[1] MAPE is the mean absolute percentage error. Assuming a MAPR of 3%, a death count of 100 is expected (on average) to be accurate to the degree of +/- 3 deaths.

5.1 Model R1 – Linear Regression for registered deaths

Method:

$$M_{80+} = W_{30\_39} * M_{30\_39} + W_{40\_49} * M_{40\_49} + W_{50\_59} * M_{50\_59} + W_{60\_69} * M_{60\_69}$$

M is the force of mortality (central rate of mortality) and the 30-39, 40-49, 50-59, 60-69 and 80+ refer to the age groups. W is the weight that is estimated by minimising the MAPE.

This weighted average approach simultaneously takes all of the age groups (30-39, 40-49, 50-59, 60-69) as reference groups, hence the fluctuations are decreased and the prediction are driven more by common patterns present in all of the age groups, rather than from just a single reference group. The model automatically allocates more weights to the age groups that are more credible, for example some of the lower age groups can suffer from little data and some of the older age groups have more heterogeneity [28].

Figure 9: Results of the Model R1 (Linear Regression) by (a) Actual vs Expected (b) Registered deaths
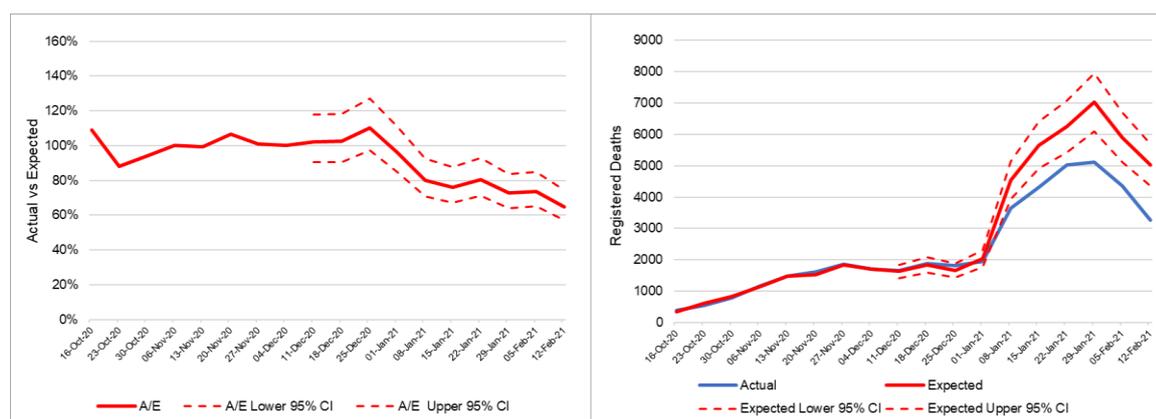
The AvE was stable, i.e. close to the 100% line from 16th October 2020 to 1st January 2021, showing the model is generalisable to many weeks in the last three months of 2020, despite the lockdown in November, the emergence of new variant as well as varying levels of infections and deaths (Figure 9).

It is worth noting that the predictive model seemed capable to capture the upward trends, downward trends and peak of the mortality of 80+ age group, through translating the patterns from the younger age groups.

## 5.2 Model R2 – Mortality Ratio for registered deaths

Method:

$$M_{80+} = R_{50\_59} * M_{50\_59}$$

R_{50-59} is the average mortality ratio calculated by averaging the ratios of 80+ mortality rate over 50-59 mortality rate during the training period. The estimated value of R_{50-59} is 43.4.

The reference group of 50-59 is chosen based on variable importance test on the age groups. This approach is very simple to use and understand, but the accuracy is less than the linear regression

approach because the prediction is subject to fluctuations in the reference age group. The shape of the AvE is similar to the linear regression approach (Figure 10).

Figure 10: Results of the Model R2 (Mortality Ratio) by (a) Actual vs Expected (b) Registered deaths
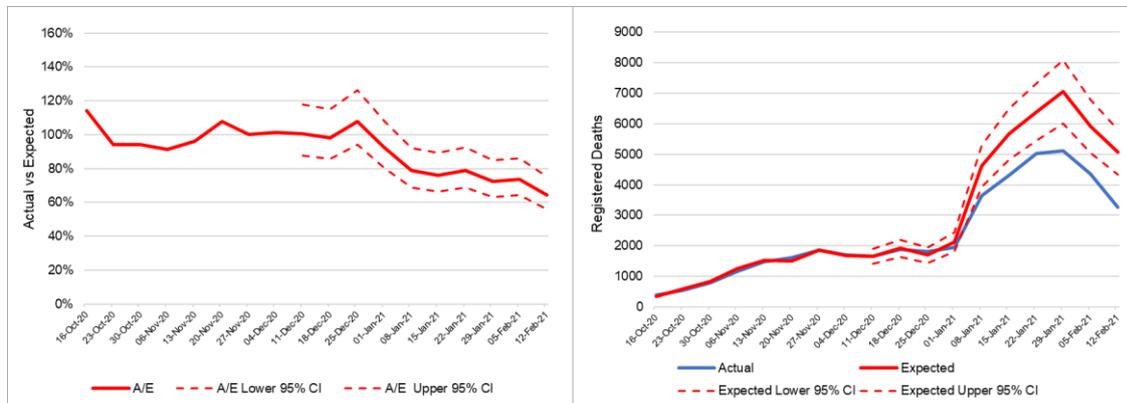
## 5.3   Model R3 – Simple Gompertz for registered deaths

Method:

$$M_{80_+} = M_{40\_59} * e^{\alpha t}$$

α is the rate of age-related increase in mortality (section 2.2) and estimated to be 0.107.

The Simple Gompertz model has a similar structure to the Mortality Ratio model, but the derivation of α involves multiple age groups' mortality rather than just the mortality of ages 50-59. However, this approach still has the weakness of extrapolating from a reference age group. The shape of the AvE is similar to models R1 and R2 (Figure 11).

Figure 11: Results of the Model R3 (Simple Gompertz) by (a) Actual vs Expected (b) Registered deaths
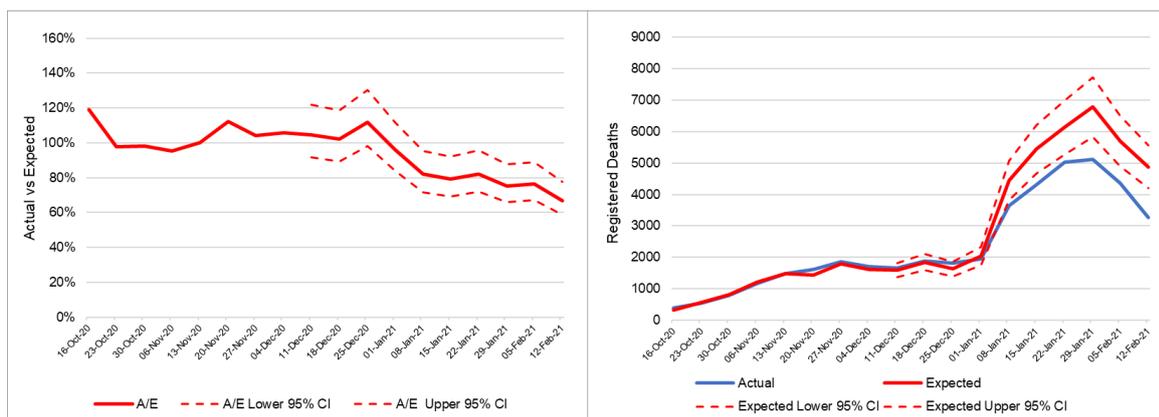
5.4   Model R4 – Gompertz Network for registered deaths

Method:

The "Gompertz Network" mortality model demonstrated the best out-of-sample accuracy. It is made up of a few layers, as seen in Figure 12. The Gompertz function takes advantage of the "invariant"

metric discussed in section 2.2 and section 10.2, i.e. the rate of the age-related increase in mortality. The weighted average approach considers the Gompertz projections from each age group onto ages 80+, reducing variance while allocating more weights to the age groups that are more credible, ultimately improving accuracy. The shape of the AvE is similar to models R1, R2 and R3 (Figure 13).

*Figure 12: The Gompertz Network mortality model*
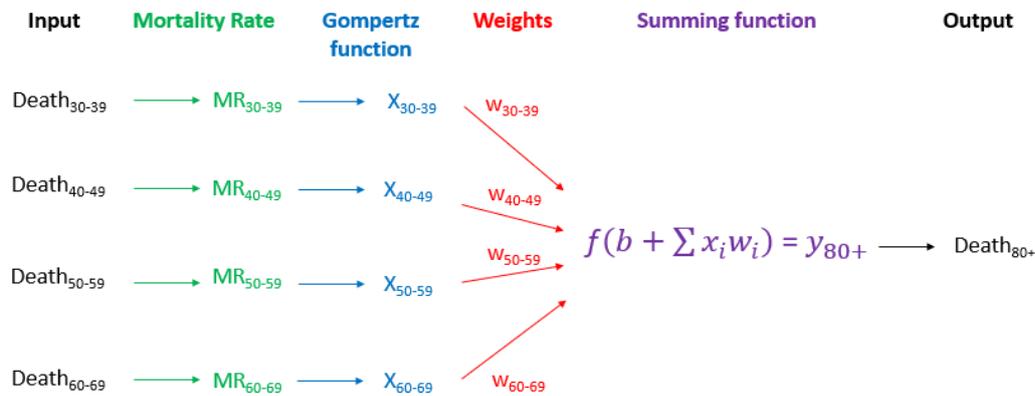
Figure 13: Results of the Model R4 (Gompertz Network) by (a) Actual vs Expected (b) Registered deaths
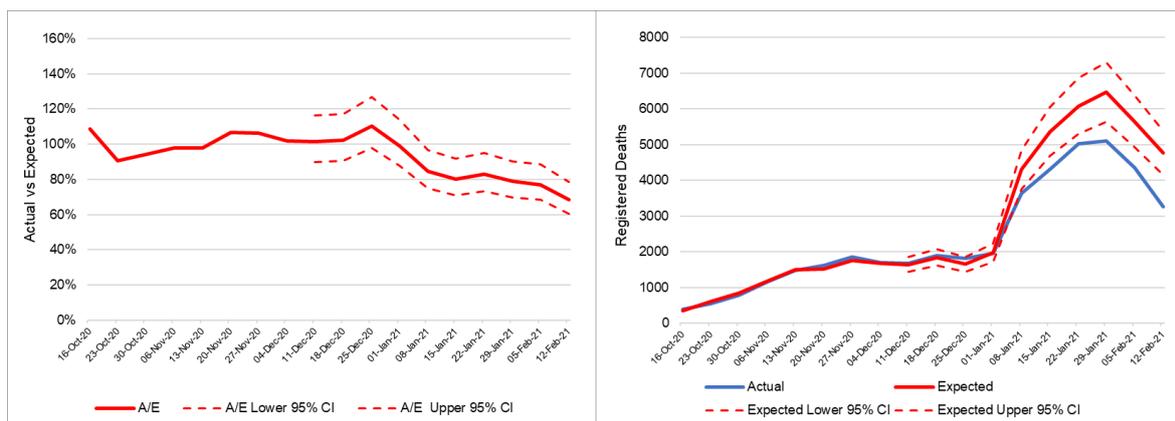
5.5 Model H1 – Linear Regression for hospital deaths

Method:

$$M(80+) = W_{0\_19} * M_{0\_19} + W_{20\_39} * M_{20\_39} + W_{40\_59} * M_{40\_59} + W_{40\_59} * M_{40\_59}$$

M is the force of mortality (central rate of mortality) and the 0-19, 20-39 and 40-59 refer to the age groups. W is the weight that is calculated by minimising the mean absolute percentage error.

Figure 14: Results of the Model H1 (Linear Regression) by (a) Actual vs Expected (b) Hospital Deaths
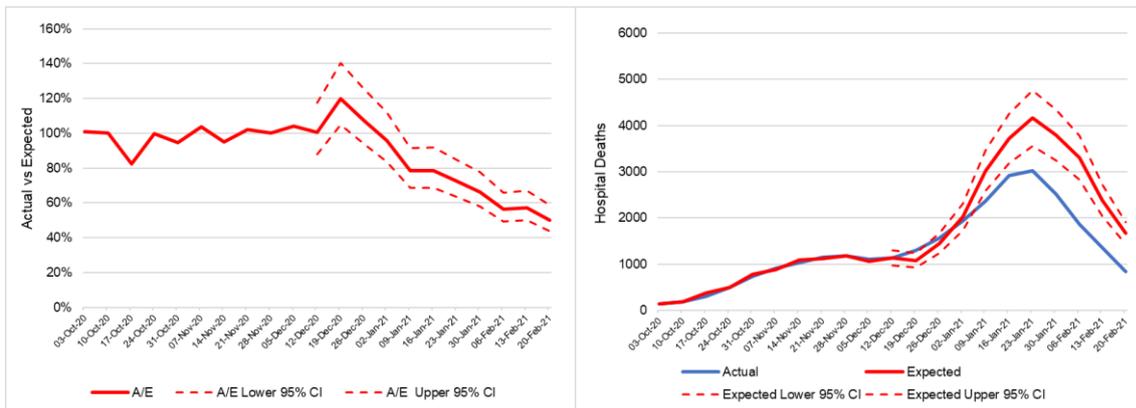
Compared to registered deaths, there are slightly more fluctuation in predictions of hospital death between October and December 2020. Nevertheless, the model accuracy of 4.2% (in October and November 2020) is reasonable showing that the model is generalisable to predict 80+ mortality despite only having 3 inputs. There is a visible increase in actual hospital deaths in ages 80+ in December 2020 which results in a higher error during that period (Figure 14).

5.6 Model H2 – Mortality Ratio for hospital deaths

Method:

$$M_{80_+} = R_{40\_59} * M_{40\_59}$$

$R_{40\text{-}59}$ is the average mortality ratio calculated by averaging the ratios of 80+ mortality rate over 40-59 mortality rate during the training period. The estimated value of $R_{40\text{-}59}$ is 52.7.

The reference group of 40-59 is chosen based on variable importance test on the age groups. As discussed, the predictions given by this approach is subject to noise in the reference age group (Figure 15).

Figure 15: Results of the Model H2 (Mortality Ratio) by (a) Actual vs Expected (b) Hospital Deaths
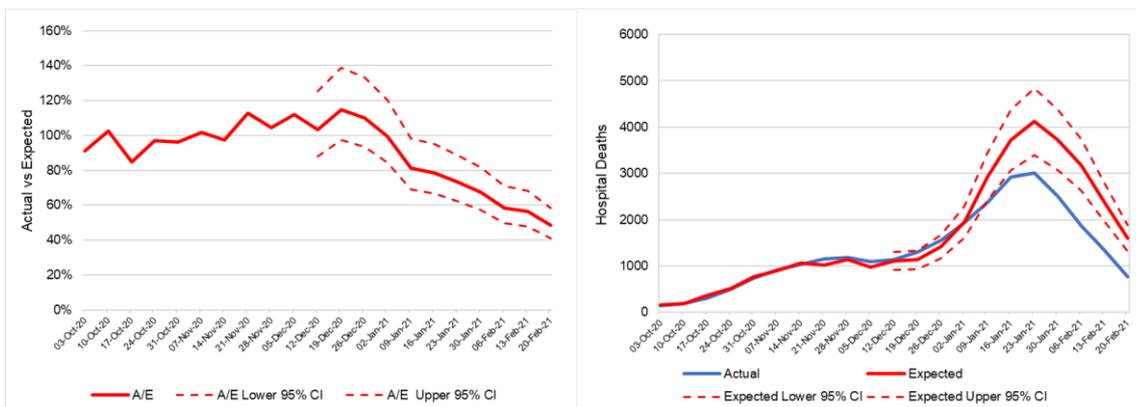
5.7   Summary of results

5.7.1   Registered deaths

Overall, the registered deaths results are similar across the different approaches where Model R4 (Gompertz Network) is showing a slightly lower reduction compared to other models (Figure 16). The Gompertz Network has the best test accuracy and is a more sophisticated approach but less intuitive to understand compared to the simpler models (Models R1, R2 and R3). As with other models, the Gompertz Network model shows a statistically significant reduction in mortality, where the confidence interval no longer overlaps with 100%, from mid-January that is sustained up to 12th February 2021 and the associated reduction is 32%.

Figure 16: Registered deaths: Actual vs Expected comparison of predictive models
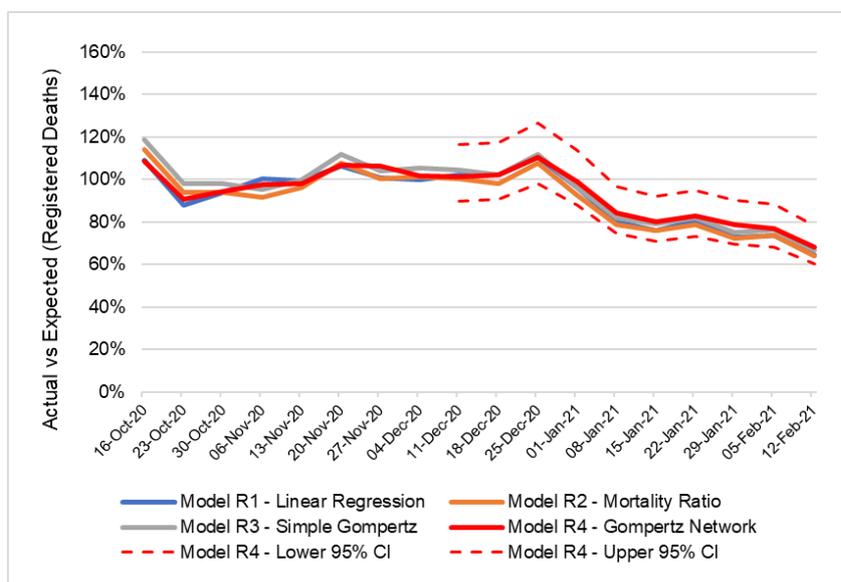
5.7.2   Hospital deaths

Overall, the results are similar across the two models H1 (Linear regression) and H2 (Mortality ratio). The reduction of deaths becomes statistically significant, like the registered deaths, from mid-January onwards (Figure 17). Since then, the hospital mortality reduces consistently for many weeks, and the AvE level was 50% in the week ending 20th February 2021.

Figure 17: Hospital deaths: Actual vs Expected comparison of predictive models
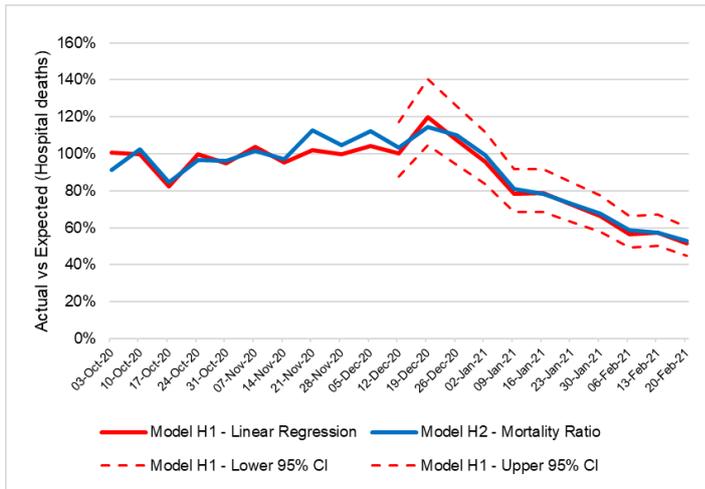
For ease of comparison in Figure 18, the weeks recording the hospital mortality data differs with those of registered deaths by one day, for example the week ending 8th January 2021 for registered deaths was plotted together with the week ending 9th January 2021 for hospital deaths. Note we expect the trend of registered deaths to delay behind the trend of hospital deaths because it is subject to registration delays.

This modelling illustrates a steeper improvement in hospital mortality compared to registered deaths and is again sustained until February 2021.

For registered deaths, there was a slight uptick in the period around 22nd January 2021, which is likely due to outbreaks in care homes. This could mask the potential improvement in mortality if the impact of vaccination is present.

Figure 18: Hospital deaths and registered deaths – Actual vs Expected using model H1 and model R4
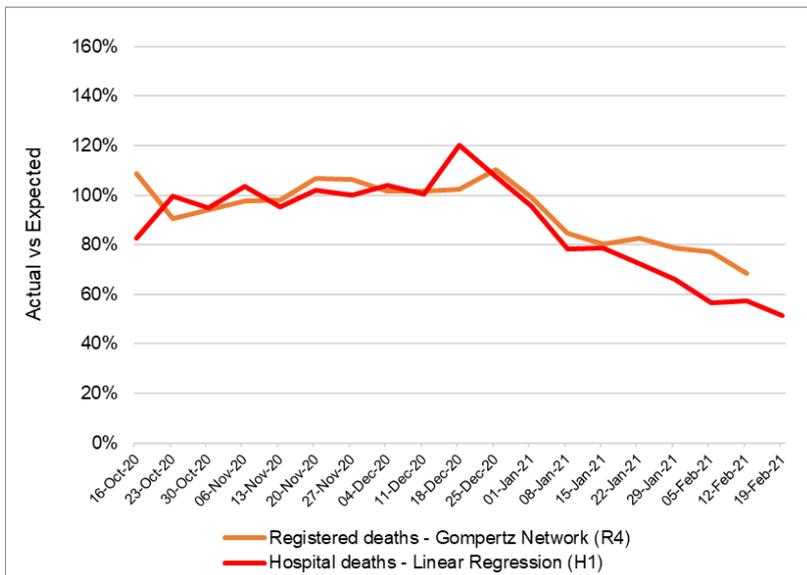
6   Antibody data for the community population in England

The ONS published data on presence of antibody to the coronavirus within the community population, excluding those in care homes or other institutional settings. It is estimated that 90% of people aged 80 years and over live in private households and 10% live in other establishments such as care homes [29] [30].

The ONS analysis is based on blood test results used to test for antibodies, as a result of past infection or vaccination. The analysis shows ages 80+ is the age group with the highest percentage of people testing positive for antibodies for both periods 22nd December 2020 to 18th January 2021 and 5th January 2021 to 1st February 2021 (Figure 19).

Figure 19: Estimated percentage of people testing positive for antibodies to SARS-CoV-2 from a blood sample by age, for the periods 22nd Dec 20 to 18th Jan 21 and 5th Jan 21 to 1st Feb 21
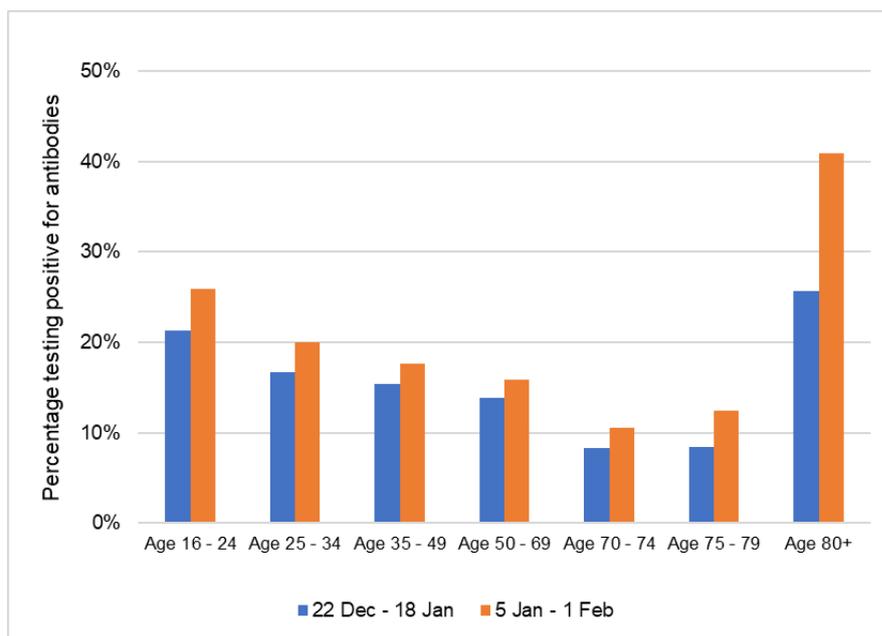
On the other hand, antibody detection remained highest in younger age groups (during the period 5 January to 1 February 2021) in Wales, Scotland and Northern Ireland, which have immunised a smaller proportion of the older population [30].

The Real Time Assessment of Community Transmission (REACT2) study in England between 15th to 28th September 2020, shows that ages 75+ has the lowest prevalence of antibody positivity compared to ages 18-24, ages 25-34, 35-44, 45-54, 55-64 and 65-74 [31].

If the 80+ age group had one of the lowest antibody prevalence leading up to the vaccination programme, then the fact that it became the age group with the highest level in the period 22nd December 2020 to 18th January 2021, and three times the multiple of the percentage of the 75-79 age group, implies that the vaccination is likely starting to give results within this time period.

Figure 20 shows that age 80+ shows the highest increase, i.e. 15.2%, between the two periods, where the percentage testing positive for antibodies increase from 25.7% to 40.9%.

Without access to granular data, we perform a crude estimation on whether the 15.2% increase is associated with an impact on the mortality metrics. Considering the antibody data comes from the community population, hospital death is a more suitable metric than registered death because it is less influenced by deaths of care home residents.

A simplistic approach is adopted by assuming the change comes from the medians of the two periods, i.e. 15.2% from 5th January to 19th January 2021. The duration from infection to hospital deaths is estimated to be 12 days in Section 3, so the corresponding reference period for hospital deaths is 17th January to 31st January 2021. Using results from the predictive models in section 5.5, the estimated reduction in hospital mortality from 17th January to 31st January is 13%, and from 22nd January to 6th February 2021 is 15%. Hence the 15.2% increase in percentage of positive antibody tests to SARS-CoV-2 is associated with 13-15% reduction in hospital mortality for the 80+ age group (Figure 21).

The ONS suggested the high percentage of antibody presence in the 80+ age-group is "mostly likely due to the high vaccination rate in this group" [30], this suggest that the vaccination is likely to play a role in both the increase in antibody prevalence and the reduction in hospital mortality (Figure 22).

Figure 21: Association between the increase in percentage of community population testing positive for antibodies to SARS-CoV-2 and the increase in estimated mortality improvement of hospital deaths
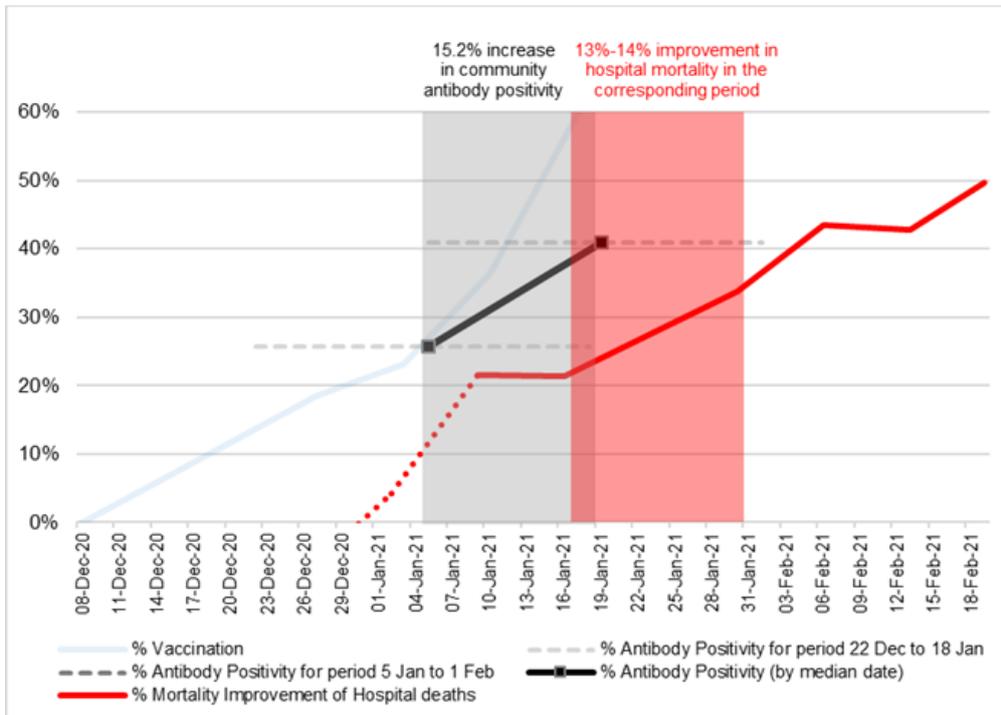

Figure 22: Timeline of percentage of vaccination uptake, percentage of community population testing positive for antibodies to SARS-CoV-2, as well as estimated mortality improvement of hospital deaths and registered deaths of ages 80+ in England
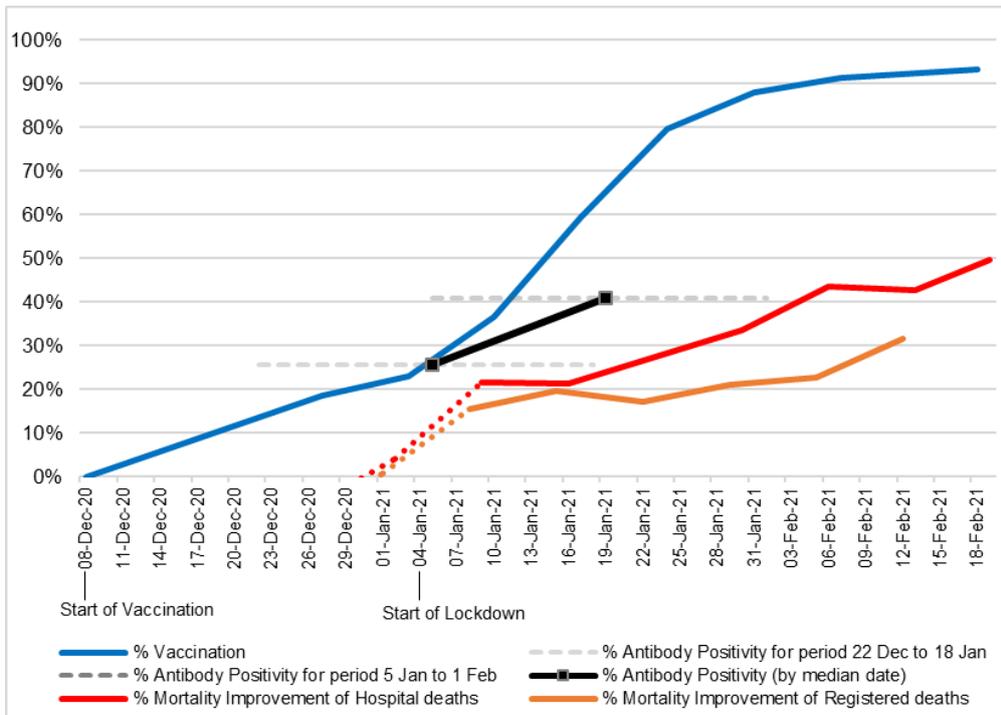
7   Discussion of the causes of mortality reduction in the 80+ age group

In order to better understand the impact of the vaccination rollout on mortality of the 80+ age group, we have used various actuarial and data science techniques to model the relative mortality in the 80+ age group compared to younger ages groups, where the latter is relatively unaffected by vaccinations.

Are we starting to see early signals of the immunity build up in the 80+ age group and preventing deaths, compared to younger age groups?

Considering the time lags from infection to death due to COVID-19, for the cohort of lives vaccinated between the 8th and 27th December 2020 (nearly a fifth of the 80+ age group), we expect to start seeing an effect between the dates 9th to 21st January 2021 for hospital deaths and 11st to 26th January 2021 for registered deaths. Therefore, we expect the vaccine roll out to start reducing mortality even more in the second half of January 2021 and onwards.

We do see a fall in hospital and registered mortality of 80+ age group in the first half of January but it is still within 95% confidence intervals. There might be a mild vaccination effect, but we suspect the reductions are mostly due to noise and other confounding factors. However, we are seeing statistically significant reductions in deaths against the counterfactual scenario from mid-January 2021 (section 5) that is consistent with what we expect from the time lag for vaccination to translate into mortality impacts in the 80+ age group.

A pre-requisite for the plausibility of vaccination-induced mortality reduction depends on the existence of antibody build up from vaccination. Evidence from the ONS and REACT study (section 6) suggests drastic increases in prevalence of antibody positivity in the 80+ age group in England, which achieved 25.7% for the period 22nd Dec 2020 – 18th January 2021 and 40.9% for the period 5th January 2021 – 1st February 2021, especially considering their lower levels than younger age groups historically and in Wales, Scotland and Northern Ireland. These timings suggest a degree of immunity build up could have happened by the end of December 2020 or early January 2021. There is more certainty in seeing how the 15.2% increase in prevalence between the two periods is associated with a similar magnitude of hospital mortality reduction (section 6).

If one believes the deviation of mortality experience is solely due to vaccination, then the above counterfactual scenario becomes a so-called "unvaccinated" scenario. However, we have seen a much tighter lockdown going into January (compared to November) where schools were closed, people's behaviour may have changed given the government messaging and the intensive pressure in hospitals around the end of December 2020. This could lead to people in the 80+ age group changing behaviour and becoming more cautious compared to other age groups. We believe this could be possible, but unlikely to have caused the observed significant change in mortality based on evidence from previous lockdowns.

Is it possible to disentangle vaccine impact from other cofounding factors?

The predictive modelling work in section 5 was carried out using four different approaches for registered deaths and two different approaches for hospital deaths. Each of them gave a similar shape indicating of mortality reduction for the 80+ age group when compared to the counterfactual scenario.

The lockdown in November 2020 had little effect (looking at data from mid Nov – mid Dec) on the rate of age-related increase in mortality (α). Similarly, "Actual" is still very close to "Expected" across a range of different predictive models for both November and December 2020. On the contrary, there are signs of actual mortality slightly higher than expected in December 2020. The November 2020 lockdown is less strict than the January 2021 lockdown which involved school closures. However, if lockdown is a significant factor affecting the model (in the form of mortality reduction in 80+ age

group) then we would expect to see at least "some reduction effect" from mid-November to mid-December, which is not the case.

The stricter national lockdown started on 4th January 2021. If the lockdown has a steep mortality impact, we expect to see a step change in the second half of January 2021 and this reduction is expected to plateau afterwards as there is a limit to behavioural change and the lockdown has not become stricter. However, there is no sign of slowing down because the hospital mortality reduction continued consistently, going from 28% reduction by 23rd January 2021 to 50% reduction by 20th February 2021.

The rising and descending levels of infection and death are accounted for because the predictive models are capable of credibly picking up upwards trends, downwards trends and peaks, as evidenced by the actual vs predicted number of deaths charts in section 5.

We also considered the new variant where the evidence suggested that there isn't a significant age bias for ages 40+ (section 2.3).

The shape of the counterfactual modelling scenarios tells us that if there is one main source driving the change in the mortality of ages 80+, then this single force was:

1. non-existent between October and December 2020
2. started to exert impact in January 2021
3. increases in intensity since January 2021

Compared to other factors listed in this paper, the immunity build-up from vaccination is most likely to exhibit the above characteristics.

On the other hand, one of the advantages of the counterfactual modelling approach is that upon seeing an effect, one can perform scenario testing on whether 100% or 80% or even none of the observed effect is due to vaccination. To better account for the confounding factors, the predictive models would benefit from more granular data of those factors.

We attempted to mitigate model risk by using several different approaches. There exist some differences but overall, they all suggest a slightly fall early January followed by a statistically significant reduction in the 80+ age group compared to younger age group from mid-January 2021.

Overall, we are seeing good evidence of the impact of vaccination roll-out was starting to reduce mortality in the 80+ age group in the second half of January 2021. The results also suggest that the impact of the vaccination is increasing over time as the reduction continues to reduce as the 80+ age group builds up immunity.

8 Limitations

It is important to highlight the following limitations and caveats on the calculations performed and results presented within this paper:

- Hospital deaths made up 76% of registered deaths in the last three months of 2020. It reflects a majority of deaths in the population, but it missed out a sizeable proportion too, particularly those from care homes. However, this death metric is less skewed by care home outbreak when compared to total deaths.
- Deaths registered in the week ending 8th January 2021 should be interpreted with caution due to possible registration delays over the Christmas period. It is assumed that any delay affected all age groups similarly, so that the effect is nullified in mortality ratio calculations.
- Our calculations focused on mortality impact and does not estimate infection risk explicitly. However, infection risk is implicitly accounted for, since mortality risk is the combination of infection risk and fatality after infection. Note that α remained consistent throughout the final 12 weeks of 2020 despite being subject to different levels of infection.
- The vaccination roll-out consists of first doses, second doses and two types of vaccines, which could be difficult to unpick. Generally, the early effect of vaccination, if present, is likely due to the first dose of the Pfizer-BioNTech vaccine. The Oxford-AstraZeneca vaccine was only rolled out after 4 January 2021.
- More accurate estimates of population mortality impact due to vaccination require controlled trial or matched demographics with granular data of timing for first and second doses as well as tracking of infections, hospitalisations and deaths.
- Could the relative time lag underestimate deaths in the 80+ age group? This is unlikely because the younger age groups (40 to 69 years old) have similar median of days from symptom onset to death as the 80+ age group, according to ISARIC-CCP-UK study [18]. The average timing of death registration for 80+ age group is likely to be slightly faster than younger age groups due to care home registrations, potentially contributing to a little overestimation of relative mortality rather than underestimation.
- There was divergence of coverage and regional variation in vaccinated patients aged 80 or over and not living in a care home. OpenSAFELY reported lower rates among ethnic minority and deprived groups. Patients with pre-existing medical conditions were equally likely, or more likely, to have received a vaccine, except those with severe mental illness or a learning disability [32]. These differences have not been allowed for.
- There could be other confounding factors that have been allowed for such as a step change improvement in administered treatments used in 80+ age group but not younger age groups, however, we consider this unlikely.
- Insights derived from α and the predictive models assume that the younger age groups are not vaccinated. As the vaccination is rolled out to younger age groups, the trends of these metrics are expected to revert at some point.

9   Conclusion

There is good evidence that the vaccination roll-out is starting to impact the mortality in the 80+ age group from mid-January onwards, and more evidence of such impact in February 2021. The results also suggest that the impact of the vaccination is increasing over time as the reduction persists as the 80+ age group builds up immunity.

We discussed to what extent the mortality reduction observed could have been due to other confounding factors such as the January lockdown, however, whilst this may explain some of the effect, there is compelling evidence using counterfactual scenarios that a key driving force for the mortality reductions in 80+ age group from mid-January 2021 onwards is due to the vaccination roll-out.

As a summary, actual versus expected results for ages 80+ under the counterfactual scenarios show both hospital and registered deaths have statistically significant mortality reductions from middle of January 2021 onwards:

- Registered deaths show an estimated reduction of 32% up to 12th February 2021; and
- Hospital deaths show consecutive mortality reductions for weeks and arrived at an estimated 50% reduction by 20th February 2021.

The timing of the mortality reduction is compatible with the drastic increase in the prevalence of community antibody positivity among the 80+ age group according to data published by the Office of National Statistics.

We considered a range of modelling approaches which have provided greater insights, in addition to looking at weekly changes in hospital admissions, hospital deaths or registered deaths. The key concept is that younger age groups are great predictors of the mortality of the 80+ age group. This enabled us to extract patterns and changes in mortality to give insights into the possible impact of vaccination in the older age groups in England. It is imperative to continue monitoring the data to see whether these results persist over the coming weeks.

10   Appendices

10.1   Mortality ratios by age

When standardising death counts by population size, more meaningful comparisons can be made between different age groups. The population data for England and Wales is extracted from the Office of National Statistics [33].

The mortality rate for each age segment, X, is calculated as follows:

$$Mortality\ rate\ for\ X = \frac{Total\ number\ of\ deaths\ in\ X}{Total\ population\ of\ X}$$

One way to measure the relative mortality relationship between two age groups is to calculate the ratio of their mortality rates. Using age group 50-59 as the reference group, the mortality ratio for another age segment, Y, is calculated as follows:

$$Mortality\ ratio\ for\ Y = \frac{Mortality\ rate\ for\ Y}{Mortality\ rate\ for\ ages\ 50-59}$$

Age group 50-59 was chosen as the reference group due to a few reasons. The younger age groups have much smaller number of deaths (section 2.1) resulting in low credibility. Ideally, the chosen reference group needs to be unaffected by vaccination to help with data comparison, and the vaccination priority of ages 50-59 is behind ages 60-69, 70-79 and 80+. A final but very important consideration comes from a University of Cambridge study which concluded that the age distribution of deaths under 65 years old is highly consistent across different settings and likely to be a reliable indicator of the number of infections in the population [34]. This study involved COVID-19 deaths data from 45 countries and 22 seroprevalence studies [28]. The conclusion of this study is consistent with the variable importance test which was run during the steps in section 5, which finds that the mortality in ages 50-59 is the most important factor in predicting mortality in ages 80+, compared to ages 30-39, 40-49, 60-69 and 70-79. Perhaps it is because ages 50-59 has more credibility than the younger age groups and less heterogenous than the older age groups.

10.2   Rate of age-related increase in mortality ratio

Mortality ratios, when plotted for each age group in on a logarithmic scale, are remarkably linear, implying that the mortality risk of COVID-19 increases exponentially with age (Figure 23). Furthermore, it is interesting to see consistent slopes of the line for the four time periods considered in 2020, despite experiencing varying level of infections.

Figure 23: Mortality ratio by age groups on a logarithmic scale for four time periods (Mar - Jun 2020, Jul - Oct 2020, Nov - early Dec 2020, early Dec 2020 – 1st Jan 2021)
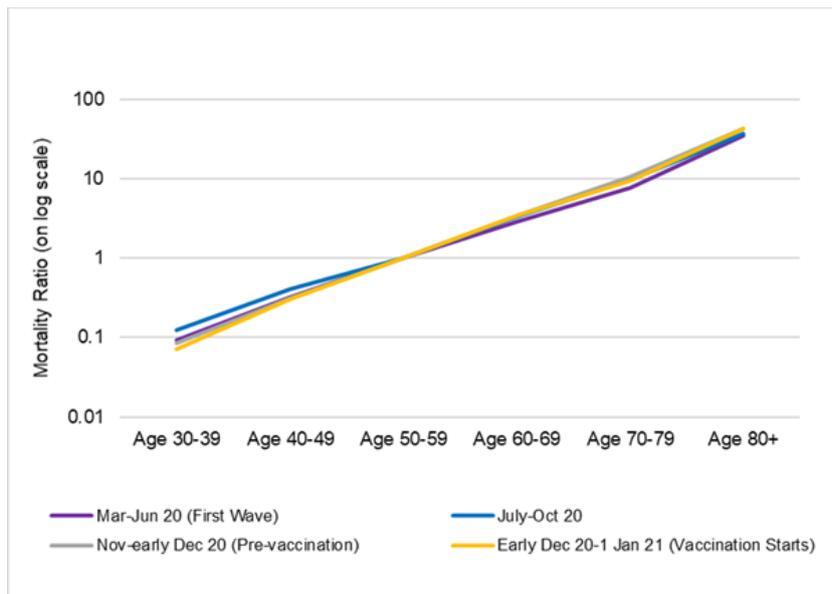
This linearity is also clearly visible in the slopes on a weekly basis for the last two months, however, the weeks ending 8th January to 12th February 2021 appear to have a different pattern to the preceding nine weeks (Figure 24). They are no longer strictly linear on the logarithmic scale and feature a visible kink for the older population.

Changing the scale from logarithmic to a linear scale shows the kink at the 80+ age group more prominently the mortality ratio for the 80+ age group in the weeks ending 8th January to 12th February 2021 are significantly lower than the other levels (Figure 25).

Figure 24: Weekly mortality ratio by age groups on a logarithmic scale, 6th Nov 2020 – 12th Feb 2021
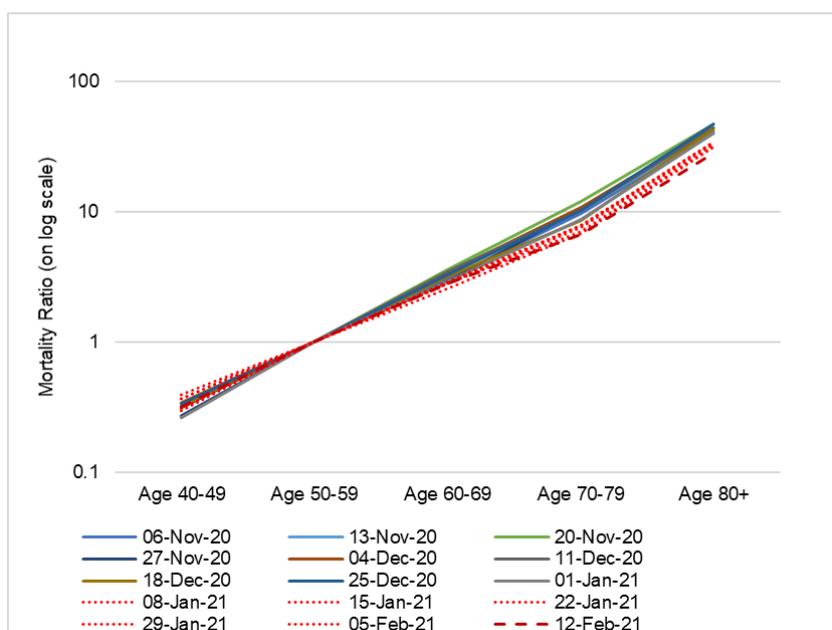
Figure 25: Weekly mortality ratio by age groups, on a linear scale, 6th Nov 2020 – 12th Feb 2021
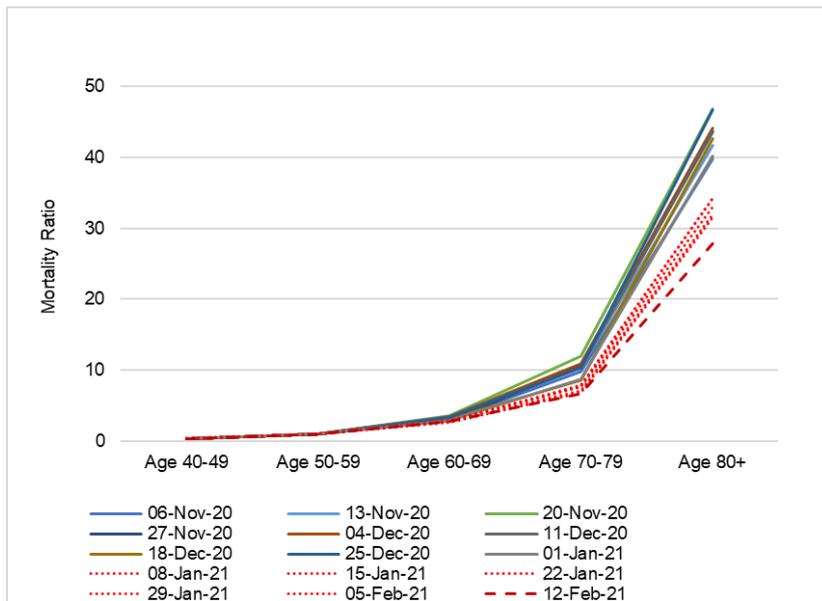

10.3   Additional counterfactual models

We have included the results for two counterfactual models from PHE data (based on deaths within 28 days of positive test) and ONS data (based on occurred date of death). These are referred to in section 5.

10.3.1   Model P1 – Linear Regression for PHE deaths based on date of occurrence

Figure 26: Results of the Model P1 (Linear Regression) by (a) Actual vs Expected (b) Occurred deaths
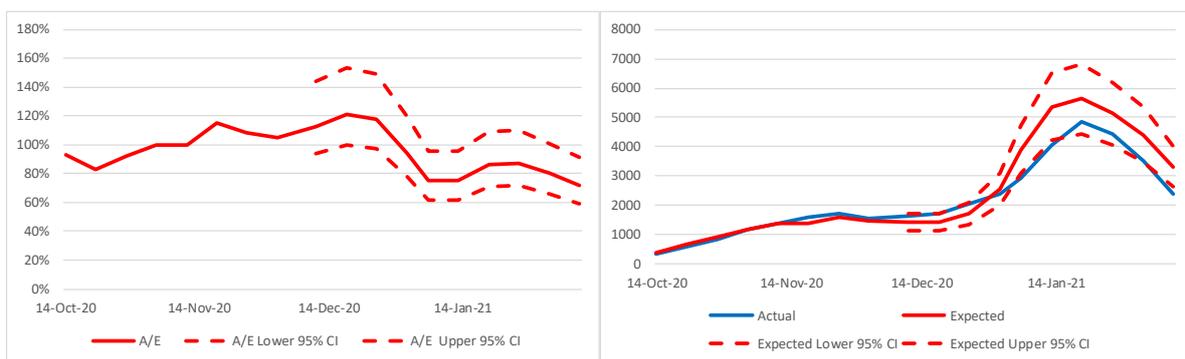
10.3.2   Model O1 – Linear Regression for ONS deaths based on date of occurrence

Figure 27: Results of the Model O1 (Linear Regression) by (a) Actual vs Expected (b) Occurred deaths
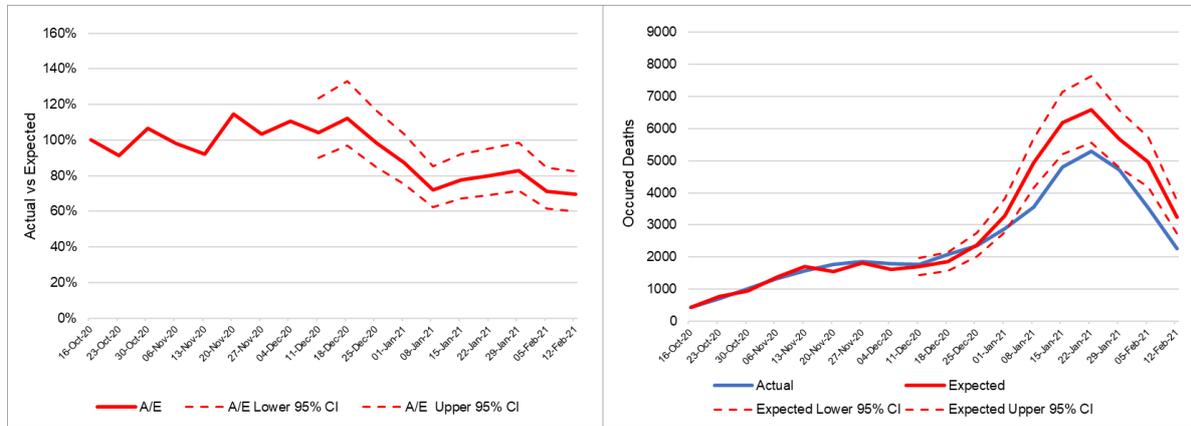
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