Article

All-Cause Mortality According to COVID-19 Vaccination Status: an analysis of the UK Office for National Statistics Public Data

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Abstract: The COVID-19 pandemics has had an unprecedented global impact, and the COVID-19 mass vaccination campaign has been commonly regarded as crucial to overcome the pandemics. Since all-cause mortality is the best way to measure the consequences of a health intervention, the present study was devised to analyze the all-cause mortality data of the United Kingdom (UK), which are made publicly available broken down by vaccination status. Data from January to May 2022 were retrospectively collected and analyzed according to age groups and vaccination status and the relative risk (RR) for all-cause mortality was calculated in comparison to the corresponding unvaccinated groups. All-cause mortality RR was also calculated from January to May 2021 for vaccinated people. Results show that the all-cause mortality RR was higher in people who received one or two doses of COVID-19 vaccines throughout the whole period and in any of the age groups considered. People vaccinated with three doses more than 21 days earlier had RRs lower than unvaccinated people, which however linearly increased over time. RR in vaccinated people of all ages in comparison to unvaccinated people were lower in January-May 2021, however they steadily grew over time. The finding that all-cause mortality RR in vaccinated in comparison to unvaccinated people increases over time requires careful examination to understand the underlying factors. Meanwhile, all the other major countries should undertake a systematic collection of all-causes mortality broken down by vaccination status, and mass vaccination campaigns should be suspended.

Keywords: COVID-19; COVID-19 vaccinations; all-cause mortality; relative risk

1. Introduction

Due to the COVID-19 pandemic crisis and the subsequent COVID-19 mass vaccination campaign, the interest has hugely soared in publicly available data on all-cause mortality. For example, data from England and Wales show in 2022, in comparison to the previous average five-year reference period, an excess mortality with a trend driven by more deaths than expected starting in March 2022 [1]. A similar trend occurs in many other countries in the European Union (EU), as indicated by the graphs and maps provided by the European Mortality Monitoring Project (EuroMoMo), a routine public health mortality monitoring system aimed at detecting and measuring excess deaths related to public health threats across EU countries. According to EuroMoMo, the excess deaths in 2022 were 406,545 in comparison to the reference baseline, and 22,835 in comparison to 2021 (https://www.euromomo.eu/graphs-and-maps/, accessed on 12 February 2023). This is clearly an anomaly, as previous mortality shocks over the past 120 years have almost

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always been followed by immediate rebounds back, in one to two years [2], with normalization of mortality risk.

England and Wales benefit from one of the best public health data collection systems in the world, and are therefore uniquely positioned to monitor and investigate the abovementioned phenomenon [1]. Moreover, the Office for National Statistics (ONS) of the United Kingdom (UK) has published all-cause mortality data [3], stratified according to COVID-19 vaccination status, thus overcoming the intrinsic limitation of just identifying deaths due to COVID-19, as for instance happens so far in Italy and in most if not all EU countries, and allowing a direct assessment of the eventual consequences of COVID-19 vaccination for individual as well as public health in terms of change not only of COVID-19 mortality but also of all-cause mortality. In addition, England and Wales have vaccinated more than 50% of their eligible population in the first months of 2021 [4], thus exceeding the aforementioned threshold earlier than most of the other EU countries. It is therefore possible that the trends observed in England and Wales anticipate what will later occur in EU.

We decided therefore to analyze the ONS public data on all-cause mortality according to vaccination status, starting from the rates already officially provided by the ONS itself on its website [3], calculating the relative risks in the different age groups, and evaluating any potential emerging trends over time.

2. Materials and Methods

In this retrospective study we collected data from the UK ONS web-based platform [3]. This platform gathers total mortality data by vaccination status from January 1, 2021 until May 31, 2022. Data are publicly available under the Open Government license (https://www.nationalarchives.gov.uk/doc/open-government-licence/version/3/, accessed on 12 February 2023), and can therefore be freely analyzed and published provided that the source is properly acknowledged.

Relying on the excel file provided by this platform, we utilized data from the spreadsheet named "Table 2", inasmuch as, differently from other spreadsheets, it provides proper stratification by age and vaccination status and a sufficient number of deaths to perform a reliable estimate of the relative risks (RR). Indeed, this spreadsheet provides 7 age groups (18–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90+ years) and each age group is further subdivided into several classes based on vaccination status:

- Unvaccinated,
- First dose less than 21 days before (1D<21d),
- First dose at least 21 days before (1D≥21d),
- Second dose less than 21 days before (2D<21d),
- Second dose at least 21 days before (2D≥21d),
- Third dose or booster less than 21 days before (3D<21d),
- Third dose or booster at least 21 days before (3D≥21d).

Even if the ONS marks with a "u" (unreliable) any rates arising from a number of death lower than 20, nonetheless we decided to consider groups with a minimum of 10 deaths. Though being aware that the lower the number of deaths, the greater the uncertainty on both the rates and the RRs, this choice allowed us to identify trends of RR over time for each age group. Anyway, we had to apply this lower threshold only in the case of: group 1D≥21d for the age groups 18-39 (3 months out of 5) and 40-49 (1 month only), and group 3D≥21d for the age group 70-79 (1 month only).

Based on this criterion, it was possible to analyze for the first 4 age groups (18–39, 40–49, 50–59, 60–69 years) according to the following vaccination status: 1D≥21d, 2D≥21d, 3D≥21d.

In the remaining age groups (70-79, 80-89, 90+ years), we were able to analyze also the vaccination status: 3D<21d.

The following vaccination statuses: 1D<21d, and 2D<21d, could not be analyzed in any age groups, because of less than 10 deaths in more than 50% of the examined months.

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Furthermore, we estimated the trends of the RRs in the period considered, using a linear regression model and pointing out the coefficients of determination (R^2) and the angular coefficients of the regression lines whenever there was an increase in RRs for each vaccination status. The angular coefficients allowed us to indicate the monthly increase in RRs and to predict the trends in RRs in the months after May 2022.

For children from 10 (vaccination starting age) to 19 years old, the ONS publishes in the spreadsheet named “Table 6” the number of deaths of the entire period 01/01/2021 - 31/05/2022 divided into five-year age groups, vaccination status and cause of death (COVID-19, non-COVID-19 and all causes). The corresponding rates are not shown in “Table 6”, yet given the number of person-years who died they can be easily calculated.

Finally, data used for the calculation of RR comparisons for the first 5 months of 2021 and 2022 were taken from the spreadsheet named “Table 1” [3].

2.1. Statistical analysis

To calculate the relative risk (RR) between the vaccinated and unvaccinated populations, we used the age-standardized rates indicated in the excel files provided by the UK ONS [3]. Their 95% confidence intervals (CI) were calculated according to the following formula [5,6]:

$$CI_{95(RR)} = e^{[\ln(RR) \pm 1{,}96 * SEln(RR)]},$$

where “ln(RR)” is the natural logarithm of the Relative Risk and “$SE_{\ln(RR)}$” is the standard error of the natural logarithm of the RR.

The $SE_{\ln(RR)}$ was calculated for each vaccination status of each of the age groups according to the formula [3]:

$$SE_{\ln(RR)} = \sqrt{\left(\frac{V.Pop. - Stand.D.Exp.}{V.Pop. * Stand.D.Exp.}\right) + \left(\frac{Un.Pop. - Stand.D.Exp.}{Un.Pop. * Stand.D.Exp.}\right)},$$

Where, for each year, “V.Pop.” represents the vaccinated population, “Un.Pop.” represents the unvaccinated population, and “Stand.D.Exp.” represents the expected standardized deaths, that is, the deaths that would occur by applying the standardized rates to the real population, calculated according to the formula:

$$\text{Expected Standardized Deaths} = \frac{Age-standardized\ rate * Population\ of\ each\ vaccine\ status}{100.000}.$$

The choice to use the "Expected Standardized Deaths " is justified by the fact that the calculated RR expresses the ratio between two standardized rates based on the European population [1]. This was not necessary for the five-year age group 15-19 years, for which the observed deaths were used in the formula for calculating the $SE_{\ln(RR)}$, since in this case the rates involved in the calculation of the relative risks are not standardized, but specific rates.

3. Results

All-causes mortality trends according to vaccination status are shown in Figures 1-4 and in Supplementary Tables S1-S9. Hereafter, detailed results are described for each age group.

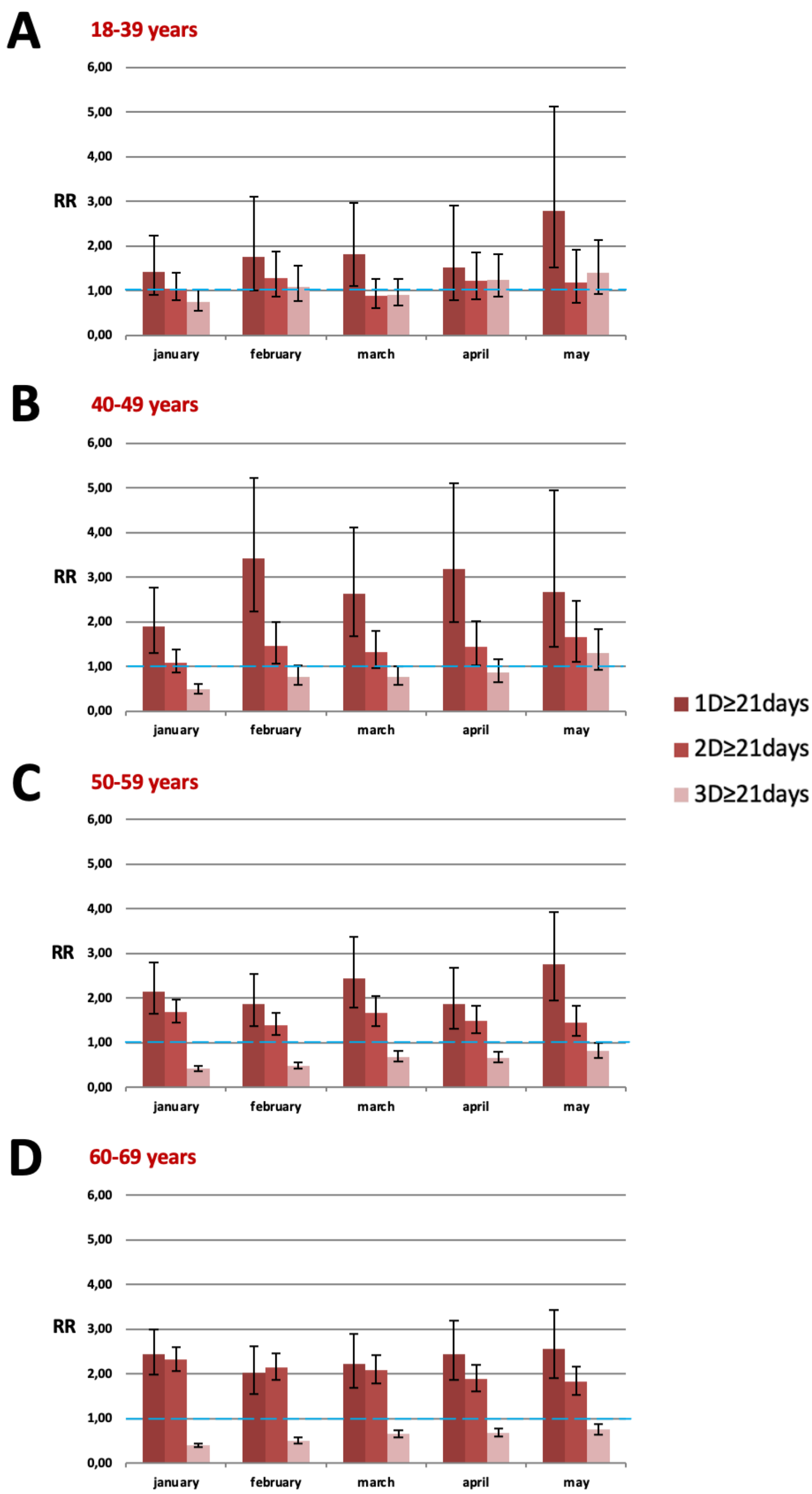

Figure 1. Relative risk (RR) for all-causes mortality according to vaccination status in Jan-May 2022, for the age groups 18-39 years (panel A), 40-49 years (panel B), 50-59 years (panel C) and 60-69 years (panel D), in comparison to unvaccinated groups (blue dashed line). Data are shown as means with 95% CI.

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3.1. Age group 18–39 years

As shown in Figure 1, panel A, a progressive trend in the increase of RR in comparison to the unvaccinated group was observed for the 1D≥21d group, with an average monthly increase in RR of 0.25, even if this variation is only partially in agreement with the linear regression model (R^2 = 0.52). In February, March and May, values significantly above the reference value of the Unvaccinated group were observed, with RR respectively of 1.77 (CI_{95}=1.01–3.10), 1.82 (CI_{95}=1.11–2.98) e 2.78 (CI_{95}=1.51–5.12) (Supplementary Table S1).

There were no statistically significant differences for the other vaccination statuses, although there is an upward trend for the 3D≥21d vaccination status, with values above 1 at the limit of significance for May. For the latter vaccination status, the increase in RR over time is in fair agreement (R^2 = 0.80) with a linear regression model, with an average monthly increase in RR equal to 0.15/month.

3.2. Age group 40–49 years

In comparison to the unvaccinated groups, the 1D≥21d groups show higher RR throughout the whole period (Figure 1, panel B). RR values are 1.90 (CI_{95} = 1.30–2.77) in January, 3.42 (CI_{95} = 2.23–5.23) in February, 2.63 (CI_{95} = 1.68–4.12) in March, 3.19 (CI_{95} = 2.00–5.10) in April, and 2.68 (CI_{95} = 1.44–4.96) in May (Supplementary Table S2). For the 2D≥21d groups, RR values are significantly higher in February, April and May (Figure 1, panel B), being respectively 1.47 (CI_{95} = 1.08–2.00), 1.44 (CI_{95} = 1.04–2.01) and 1.66 (CI_{95} = 1.12–2.47) (Supplementary Table S2). The 3D≥21d groups on the contrary never show significantly different RR, with the exception of January, when the RR is significantly less than 1. In subsequent months, a progressive increase in RR is observed, up to May when the mean value is greater than 1, although not statistically significant. For the 3D≥21d groups, the increase in RR over time is in good agreement (R^2 = 0.85) with a linear regression model, with an average monthly increase in RR equal to 0.17/month.

3.3. Age group 50–59 years

RR values significantly higher than 1 can be observed for both the 1D≥21d and the 2D≥21d groups throughout the whole period (Figure 1, panel C, and Supplementary Table S3). In the 3D≥21d groups, on the contrary, RRs remain significantly below 1, but with a clear upward trend throughout the whole period (Figure 1, panel C). In these groups, the increase in RR over time is in good agreement (R^2 = 0.92) with a linear regression model, with an average monthly increase in RR equal to 0.10/month.

3.4. Age group 60–69 years

RR values significantly higher than 1 were observed for both the 1D≥21d and the 2D≥21d groups over the entire period considered (Figure 1, panel D, and Supplementary Table S4). The 3D≥21d groups on the contrary had RR values significantly lower than 1, but with an upward trend throughout the period considered (Figure 1, panel D). The trend of RR over time is in good agreement (R^2 = 0.95) with a linear regression model, with an average monthly increase of RR equal to 0.09/month.

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3.5. Age group 70–79 years

The 1D≥21d and 2D≥21d groups showed significantly higher RR compared to the unvaccinated groups over the entire period considered, while the 3D<21d groups showed significantly higher RR values in all months except for April (Figure 2, panel A, and Supplementary Table S5).

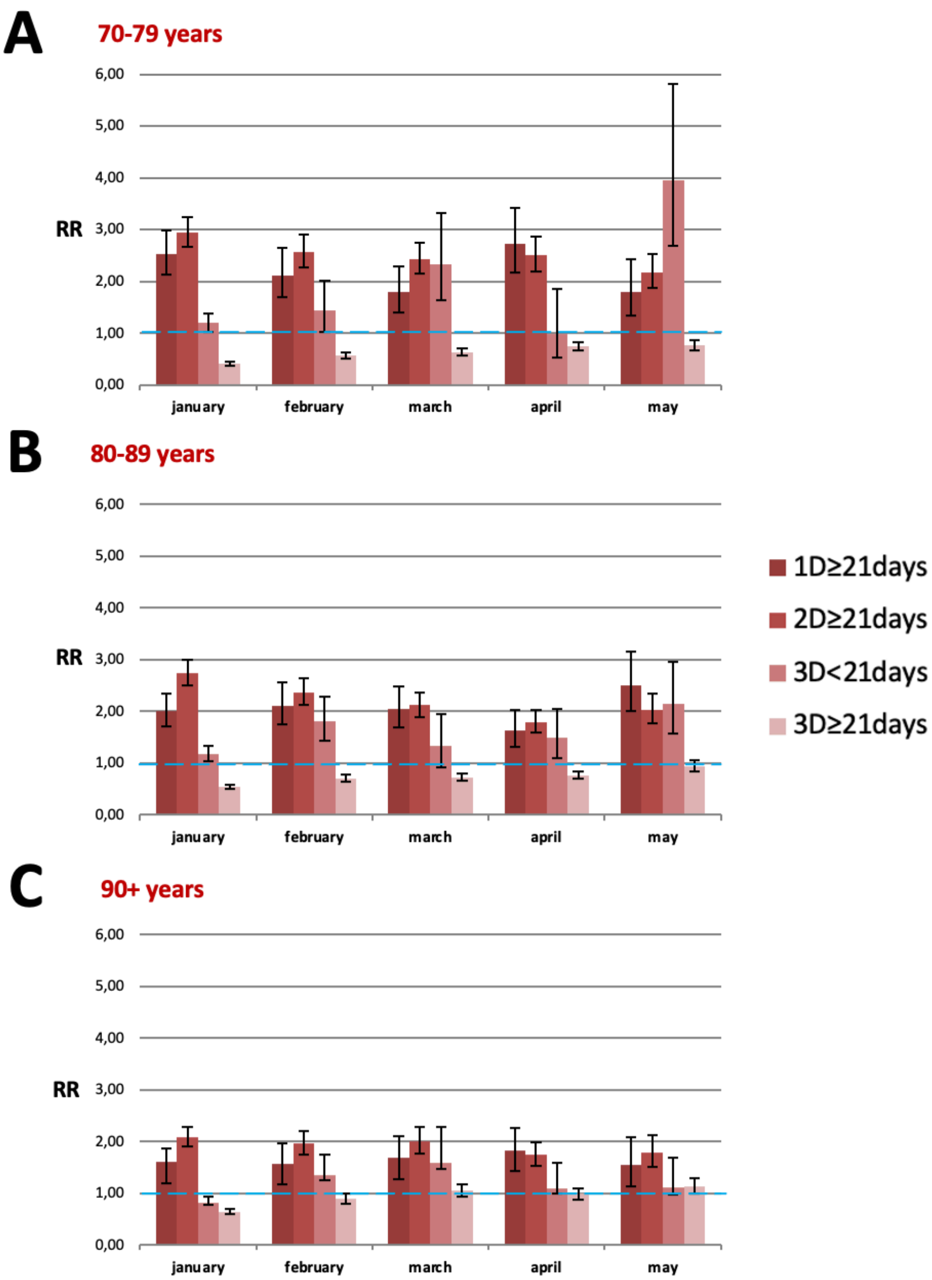

Figure 2. Relative risk (RR) for all-causes mortality according to vaccination status in Jan-May 2022, for the age groups 70-79 years (panel A), 80-89 years (panel B), and 90+ years (panel C), in comparison to unvaccinated groups (blue dashed line). Data are shown as means with 95% CI.

The 3D≥21d groups had RR values significantly lower than 1 throughout the whole period, however – as already observed for all the other age ranges – a progressive increase was observed from January to May. For the 3D≥21d groups, the growth trend of RR over

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time is in good agreement (R^2 = 0.94) with a linear regression model, with an average monthly increase of RR equal to 0.09/month.

3.5. Age group 80–89 years

The 1D≥21d and 2D≥21d groups showed significantly higher RR values in comparison to the unvaccinated groups throughout the whole period, while the 3D<21d groups had higher RR in all months except for March (Figure 2, panel B, and Supplementary Table S6). The 3D≥21d groups' RR values were significantly lower than 1 from January to April, however with an upward trend throughout the whole period. This trend is in good agreement (R^2 = 0.91) with a linear regression model, with an average monthly increase of RR equal to 0.09/month.

3.7. Age group 90+ years

The 1D≥21d and 2D≥21d groups showed RR values significantly higher than 1 throughout the whole period, while the 3D<21d groups' RRs were lower than 1 in January, higher than 1 in February and March and not different from 1 in April and May (Figure 2, panel C, and Supplementary Table S7). The 3D≥21d groups' RRs were significantly less than 1 from January to April, with a progressive increase throughout the whole period and a growth trend over time in fair agreement (R^2 = 0.82) with a linear regression model. The average increase of RR was equal to 0.11/month.

3.8. Age group 15-19 years

Only the 2D≥6mo groups had RRs significantly higher than the corresponding unvaccinated groups (RR = 2.49; CI_{95} = 1.63 – 3.82), while the RRs for 1D≥21d (RR = 1.20; CI_{95} = 0.93–1.54) and 3D≥21d (RR = 1.38; CI_{95} = 0.95–2.00) were nearly statistically significant (Figure 3 and Supplementary Table S8).

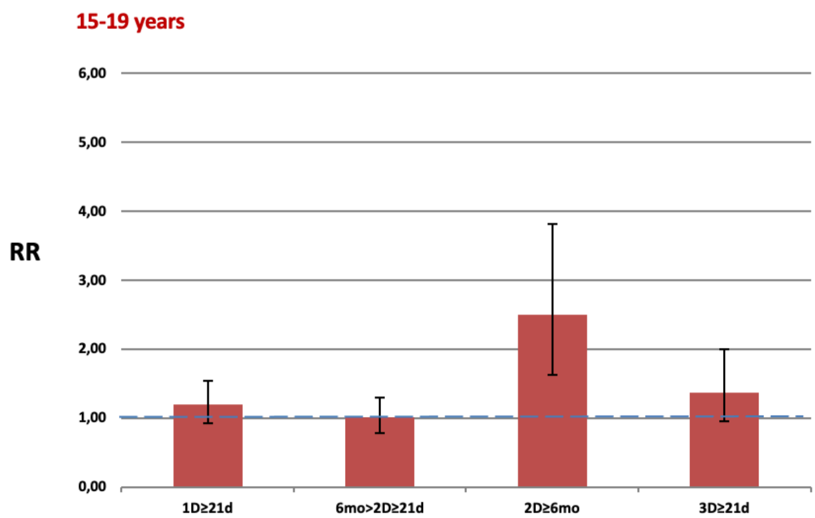

Figure 3. Relative risk (RR) for all-causes mortality according to vaccination status in Jan 2021-May 2022, for the age group 15-19 years, in comparison to unvaccinated groups (blue dashed line). Data are shown as means with 95% CI.

3.9. All-cause mortality comparison between January-May 2021 and January-May 2022

RR values for all-causes mortality in people vaccinated with 2 doses from ≥21 days to <6 months in comparison to unvaccinated people, all ages, in the first 5 months of 2021 and 2022 are shown in Figure 4 and Supplementary Table S9.

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From January to May 2021, RRs were significantly lower than 1, however with a growing trend over time in good agreement (R^2 = 0.94) with a linear regression model, with an average monthly increase of RR equal to 0.11/month.

On the contrary, in January 2022 the RR was significantly higher than 1 and steadily increased throughout the following months, with a linear trend over time (R^2 = 0.90) and an average monthly increase equal to 0.16/month. Remarkably, the monthly increase between 0.11 (in 2021) and 0.16 (in 2022) is in very good agreement with the growth of RR from May 2021, when the mean value was 0.50, to January 2022, when – 7 months later – it was 1.51 (Supplementary Table S9).

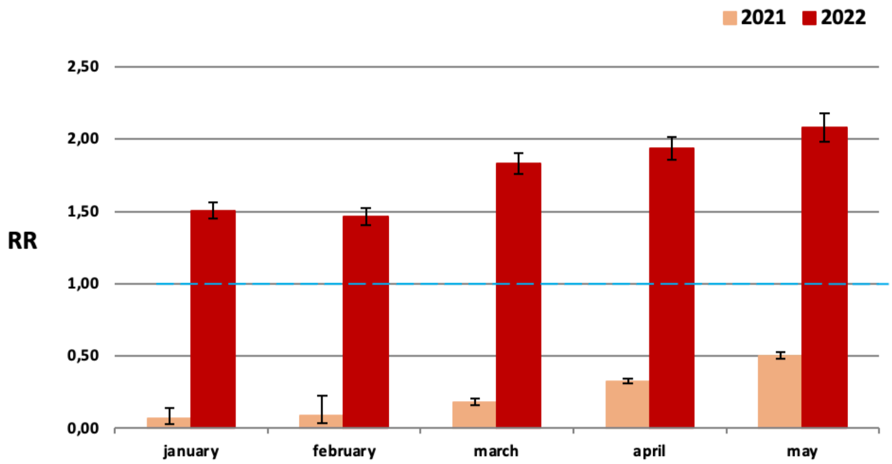

Figure 4. Relative risk (RR) for all-causes mortality in people vaccinated with 2 doses from ≥21 days to <6 months in comparison to unvaccinated people (blue dashed line), all ages, in the first 5 months of 2021 and 2022. Data are shown as means with 95% CI.

4. Discussion

In the present study, we analyzed the UK ONS data on all-cause mortality according to vaccination status, which are publicly available on the ONS institutional website [3]. The main findings of our analysis show that, in the period January-May 2022, the RR for all-cause mortality is higher in people who received one or two doses of COVID-19 vaccines in comparison to unvaccinated people. Such a difference occurs throughout the whole period and in any of the age groups considered, from 18 to 90+ years of age. Remarkably, people vaccinated with three doses more than 21 days earlier had RRs for all-cause mortality lower than the RR of unvaccinated people, which however linearly increased over time from January to May 2022, suggesting that in a few months it will exceed values observed in unvaccinated in any age groups examined.

Unlike the other age groups, in the 15-19 year old only the 2D≥6mo groups have RRs significantly higher than 1. However, in this case the data are means over the entire Jan 2021-May 2022 period and it is impossible to verify the presence of trends as in the other age groups. If there were a similar trend, the RRs in the last months would be significantly higher than the overall mean, which is influenced by the lower RRs in the previous months.

Remarkably, RR values for all-causes mortality in people of all ages vaccinated with 2 doses from ≥21 days to <6 months were lower in comparison to unvaccinated people in the first 5 months of 2021, however they showed a linear trend of growth over time and consequently in the first 5 months of 2022 they significantly exceeded 1, reaching the mean value of 2,08 in May 2022.

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4.1. How to explain excess RR for all-cause mortality in those vaccinated for COVID-19?

These worrying results impose the need to explain the very strong RR increase in all-cause mortality occurring in people who received the COVID-19 vaccines.

In fact, in 2021 a lower mortality among the vaccinated was evident, although this phenomenon, known in epidemiology, can also be explained partly by the healthy adherer effect [7-19]. The healthy-adherer bias, or the healthy-vaccinee bias in the vaccination field, is much more powerful than commonly thought, and independent of the type of treatment to which one adheres voluntarily, being also found in randomized controlled trials in placebo adherers (compared with placebo non-adherers). This bias is more difficult to correct than the opposite effect of confounding by indication (subjects in worse health conditions are vaccinated first) [19]. It is likely that the healthy-vaccinee bias effect will continue to operate to varying degrees in 2022, albeit to a diminishing extent.

Moreover, it is plausible that the increase in the number of the vaccinated has diluted the opposite effect of confounding by indication [19]. Indeed, we are aware that a commonly used argument is the better known confounding by indication effect [19]: it is likely that fragile subjects with multiple diseases have been vaccinated as a priority, followed by the others. However, as the vaccination campaigns proceed, the composition of the vaccinated and unvaccinated populations should result less unbalanced with respect to the pre-existing state of health. The authors of the ONS database declare that “Changes in non-COVID-19 mortality by vaccination status are largely driven by the changing composition of the vaccination status groups. This is because of the priority given to clinically extremely vulnerable people or with underlying health conditions, and differences in timing of vaccination among eligible people" [3]. However, since the most fragile part of the population that completed the vaccination cycle is a smaller portion (especially in the younger ages), the composition of each age group progressively tends to be similar to that of the unvaccinated, in terms of general health conditions. Therefore, a decreasing trend would be expected, both because of the decreasing weight of the fragile fraction compared to the overall group and because of the harvesting effect, caused by excess mortality in the most fragile fraction. It should be added that the all-cause mortality considered is not cumulative mortality, but mortality which occurs month by month.The complementary explanatory hypotheses of this anomalous increase in mortality can only be partly traced back to the well-documented lower lethality of the Omicron variant compared with the previous variants: up to 11 times less lethal according to North American and South African data [20], or even 30 times less lethal according to the Italian data of the Abruzzo Region [21].

Authoritative and influential epidemiologists [22] had put forward some hypotheses, for example to explain the increases in infant mortality highlighted in EuroMoMo. According to EuroMoMo, the excess deaths in the age group 0-14 years in 2022 were 1,261 in comparison to the reference base-line, and 849 in comparison to 2021 (https://www.euromomo.eu/graphs-and-maps/, accessed on 12 February 2023). Association certainly does not mean causation, but interestingly the excess deaths started in the 0-14 age group around week 22 of 2021, approximately when the European Medicines Agency (EMA) granted an extension of the indication for the Pfizer COVID-19 vaccine, to include children aged between 12 and 15. According to those epidemiologists [22], the following hypotheses should be explored:

1) reduction of vaccination coverage, for vaccines such as Measles-Mumps-Rubella (MMR);

2) mental health problems, increase in suicides;

3) neglect, violence/murder or abuse;

4) domestic accidents;

5) maternal or infant mortality during the pandemic.

The hypotheses however are not convincing, first of all as they do not clarify why the effect should be so evident in 2022 as compared with the previous two years, when lock-

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downs and restrictions occurred. Actually, a concrete alternative possibility is that the excess mortality detected by EuroMoMo is due only to some countries, and that it is not a generalized phenomenon.

Recently, an opinion paper published on the BMJ and dealing with the excess deaths in England and Wales [23], put forward various hypotheses, including that:

1) the numbers used by the ONS may not consider the age structure of the population (aging);

2) COVID-19 may increase cardiovascular risks even at a distance of some time;

3) the population may not receive the necessary assistance from a health service under excessive pressure;

4) there might be an effect of heat waves on older people;

5) there might be a possible rebound after the first months of 2022 with lower mortality rates.

Nonetheless, the recent ONS data [3] do not support any of the aforementioned hypotheses, because the increased mortality in 2022 in England affect in a particular and selective way the people vaccinated against COVID-19 and not the whole population to a similar extent. The other hypothesis that the vaccinated and unvaccinated populations are different does not seem convincing either: in fact, although we do not have such information, the consistency of the increased risks in all ages makes this explanation unlikely. Lastly, the hypothesis that among the reasons for not revaccinating there is a serious disease does not seem likely, because there are increased risks not only in those who have received only one, or two doses but also in those who received three doses.

It is therefore necessary at least to consider the hypothesis of a progressive damage due to repeated vaccinations, which should curb the push for universal vaccination, and carry out the necessary investigations in order to verify and hopefully rule out this possibility.

4.2. Mortality data by vaccination status from two recent Italian studies

A large Italian study [24] measured the overall mortality by vaccination status from October to December 2021 in the population ≥19 years of age living in a wide area comprised in the metropolitan City of Milan, including in the provinces of Milan and Lodi (about 3 million people as a whole).

Results resemble to some extent those from the UK ONS data, showing a transient decrease in all-cause death rates after vaccination, followed by progressive increase as the distance from the 2nd dose increased, up to 7+ months, when the death rates in the vaccinated clearly surpassed the death rate in the unvaccinated. The 3rd dose seemed to restore lower death rates, however the subsequent follow-up lasted only a few weeks, so precluding the continuation of a comparison with the trends shown by ONS data. Remarkably, in this study data were adjusted by gender, age, socioeconomic status, nationality, numbers of comorbidities, and date of last dose as time-dependent variable [24].

Another retrospective cohort study [25] has been just published on the entire population of the Italian Province of Pescara, where 259,821 subjects were vaccinated with ≥1 dose and 56,494 remained unvaccinated from January 2021 to July 2022. The authors reported much lower rates of all-cause mortality in the vaccinated group. This study will be commented in detail elsewhere, but here we point out at least one substantial bias: the authors have not considered that before vaccination the vaccinated cohort belonged to the unvaccinated cohort. Accordingly, they have greatly reduced the real denominator of the unvaccinated cohort: correcting even only this error, the excess of all-cause mortality attributed to the unvaccinated group disappears completely.

Another limitation is that the study [25] does not seem to have considered the evolution of risks over time. The risks of the vaccinated, expressed as averages over the entire follow-up period, could underestimate those of the last few months of 2022. In fact, even

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in the English population the relative risks are greatly reduced if the averages are calculated over the entire period, but this would not help to understand the real evolution of the phenomenon.

4.3. Mortality by vaccination status in a study performed in Indiana over 2021 to February 9, 2022

The study [26] matched individuals who received at least 1 dose of COVID-19 vaccines (note: all of which are recorded) with individuals with previous SARS-CoV-2 infection (note: infections serious enough to be formally diagnosed: that is, by introducing a disadvantageous bias towards the unvaccinated) on index date, age, gender, race/ethnicity, and clinical diagnoses, comparing the cumulative incidence of infection, all-cause emergency department (ED) visits, hospitalizations, and mortality. Results claim significantly lower rates of all-cause ED visits, hospitalizations, and mortality in the vaccinated. However, its findings should not inform today's health policy decisions, and the design and conduct of the study are burdened by many problems, which will be just summarized:

a) the follow-up essentially stops at the pre-Omicron eras, when SARS-CoV-2 variants were much more lethal;

b) the follow-up stops 6 months after the index date, when vaccine protection is still high, to decline thereafter (even more in the Omicron era), when a follow-up could show a much different trend;

c) over 2,500,000 vaccinated and 400,000 infected subjects were excluded from the study, i.e. the vast majority, without reporting their COVID-19 incidence, hospitalization and death. Moreover, the loss of patients during follow-up is very high: 260,000 per group at the start were reduced to less than one third in six months. Such a low follow-up percentage of subjects invalidates the study;

d) the authors report the cases of covid-19 infection, but not those of hospitalization and death, why?

e) the match between infected and vaccinated is by number of comorbidities but not by their severity;

f) the participants were considered unvaccinated up until 30 days after receiving their dose: so every infection diagnosed during this window was attributed to unvaccinated (or not counted as an infection in a vaccinated subject);

g) the study design is wrong. In fact, the follow-up of the vaccinated-infected couple is interrupted when the infected person gets vaccinated (correct), or when the vaccinated person becomes infected, but this is wrong. Indeed, if she/he later dies of COVID-19, this death is not counted; instead, if the unvaccinated infected gets reinfected and dies, the death is counted. Since COVID-19 is responsible for at least a part of the difference in mortality, excluding COVID-19 deaths from the vaccinated group is wrong;

h) the study does not takes in due account the "healthy-vaccinee-effect" [27], particularly strong in the voluntary early adherers to a treatment. This effect is confirmed because the calculable mortality in vaccinated people would be less than 0.6%, much lower than a realistic rate: therefore the study has likely selected much healthier vaccinated subjects;

i) anyhow, the inconsistency with the reported ONS data is only apparent, because the follow-up of this study stops on February 9, 2022, and also from the ONS data emerged a clear overall advantage in all-cause mortality in vaccinated people in 2021, persisting – albeit weakening – in January-February 2022.

4.4. How do data from the UK ONS compare with data from the Italian National Institute of Health?

Mortality data provided by the The Istituto Superiore di Sanità (ISS) (Italian National Institute of Health, literally 'Higher Health Institute') (https://www.epicentro.iss.it/coronavirus/, accessed on 12 February 2023) are affected by many critical issues (also present in other institutional communications). Hereafter we would like to list the major ones:

- it is important to note that data from ISS are not total mortality, as many intend, but generally only mortality from COVID-19. The latter in Italy is only a modest fraction of total mortality, currently less than 5%;
- it would, instead, be very important to always report total mortality, both because it is less subject to possible attribution distortions, and because it also incorporates the possible of vaccine-associated adverse effects (known and unknown, in the short and longer term). For serious adverse events and Serious Adverse Events of Special Concern (AESI) [28], it would also be appropriate to report all known cases and not only those attributed to the COVID-19 vaccines. High-validity comparisons, such as those in the pivotal randomized controlled trials of mRNA vaccines in adults, showed a divergent pattern in the set of serious adverse events compared to those associated with COVID-19.

In fact, it was found that in the experimental groups that received mRNA vaccines, the excess of total AESI exceeded by more than 2 times (with the Moderna vaccines) and by more than 4 times (with the Pfizer vaccines) the hospitalizations saved, compared to the groups that received the placebo [28].

The divergent trend between COVID-19 mortality and total mortality is also noted from the ONS data: see the case of adolescents 15-19 years, where mortality rates for COVID-19 in the period of January 2021-May 2022 are higher among the unvaccinated (1.20) than among those vaccinated with 1, 2 or 3 doses (respectively 0.34, 0.44, 1.02), while the opposite happens more than proportionally for non-COVID-19 mortality, where total mortality rates are lower in the unvaccinated (14.5) than in any single vaccination status (16.2, 15.1, 17.9) and in the vaccinated overall (15.9) (Figure 3 and Supplementary Table S8).

- The ISS also considers "unvaccinated" any person who received the 1st dose less than 14 days before (a distinction that does not seem justified in the assessment of safety or consequences). If such a person dies in this 14-day time interval, his/her death would not be included in the Vaccinated group, and would weigh on that of the Unvaccinated.
- The above definition by the ISS, already very questionable when it comes to assessing the *safety* of a health technology, does not necessarily coincide with what various hospital Operating Units (OUs) intend. Think of the repeated public statements, even in popular television broadcasts, about the fact that: "a vaccinated person is one who had the booster dose". It is thus not certain how many OUs followed the ISS definition in communicating the number of the Unvaccinated among their hospitalized, intensive care or deceased patients.
- Last but not least, while vaccinations and boosters have been proven to reduce cases of severe COVID-19, the duration of this benefit needs to be clarified. If the benefit is reduced to the point of losing significance over several months [29,30], and in order to restore it one has to undergo other doses of the vaccine, with non-negligible adverse effects that add up with subsequent doses (as shown by the CDC v-safe survey for each of the mRNA vaccines) [31], the overall balance may not be favorable.

To this could be added a deterioration over time in the immune response capacity, as may be suggested by the fairly rapid loss of vaccine efficacy (VE) against COVID-19 diagnoses (especially with regard to infections) [32], which reaches a significant negativization of VE in studies of high methodological quality [33-35], expressly when the asymptomatically infected [36] are also included in the analysis.

5. Conclusions

The new data showing total mortality increases in England, which in the first 5 months of 2022 seem to affect the vaccinated in comparison to the unvaccinated, irrespective of the vaccination status, in our opinion call for an urgent scientific debate to explore the hypothesis of damage from accumulation of vaccine doses, which so far has not been considered by the majority of the scientific community. Evidence also requires the continued and careful monitoring and analysis of the UK ONS data, as well as the activation also in other countries of a systematic collection of all-causes mortality data according to vaccination status, corrected as best as possible for major confounders such as gender, health status, and social conditions.

A confirmation of the hypothesis put forward would open up alarming scenarios, which could possibly require a moratorium, based on the precautionary principle, including:

- vaccination of children aged 0-11 years, who currently run minimal risks from COVID-19, especially with the variants dominant nowadays, and who – in case of vaccination – would not provide any benefit in terms of protection of others [37-40];
- vaccination/revaccination of children and young adults not yet vaccinated, and in general, pushing for more doses in those who do not have specific medical indications (fragile patients, etc.).

As for healthcare workers in contact with high-risk populations, the guarantees offered by antigenic swabs repeated every working week [41,42] should be carefully reevaluated as a safer alternative in comparison repeated vaccination cycles.

Finally, but of course not least, besides vaccination many more containment and management strategies exist to fight the COVID-19 pandemic, including primary environmental prevention [43,44], healthy lifestyles [45] such as physical exercise (for example [46-50]), healthy diet (for example [50-52]), safe and sustainable therapeutic approaches of documented effectiveness (for example [53-59]), as well as abandonment of unproven and potentially dangerous treatments [59,60].

Supplementary Materials: Supplementary Tables S1-S8.

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