Usefulness of vaccine boosters for Covid-19 in Italy and in UK and comparison between in intensive care admissions and deaths of vaccinated and unvaccinated patients.

Surprises and implications [version 2; peer review: 1 not approved]

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Abstract

Background: There is insufficient clarity about the different outcomes between unvaccinated and vaccinated people hospitalized with Covid-19, with reference to the variables “Intensive Care Unit” and “Deaths”. Moreover, it is unclear the real effectiveness of the vaccine boosters on the risks of infection and Covid-19 deaths, beyond the first few months after the booster. To verify the hypotheses that repeated vaccinations might expose to a progressively greater risk of severe Covid-19, and of a growing weakening of the immune response, primarily against infection, as the distance from the booster dose increases.

Methods: Through an analysis of the official Italian data we calculated significant differences, percentage variations and trends in the variables “Intensive Care Units” and “Deaths” in hospitalized patients among four groups with different vaccination status, and between the Unvaccinated and Vaccinated groups.

Through analyses of the UK Security Agency data in the weekly COVID-19 vaccine surveillance reports we explored the vaccine effectiveness against SARS-CoV-2 infections and against COVID-19 deaths in relation to the time elapsed from the booster doses.

Results: Repeated vaccinations seem to expose the recipients to a growing risk of severe Covid-19, and fewer vaccinations might be enough to protect persons at greater risk.

The vaccine effectiveness against infection vanished and reversed in the medium term, and vaccinated persons with three doses become increasingly more infected versus unvaccinated persons.
Conclusions: The starting hypotheses have been supported, together with the need to combine carefully rethought vaccination campaigns with the implementation of other strategies, with the achievement of a healthy living and working environment, healthy lifestyles, and effective, safe and sustainable care.

Keywords
Covid-19 vaccinations, first second dose of Covid-19 vaccination, Covid-19 booster vaccination, Covid-19 vaccination and Intensive Care Unit admission, Covid-19 vaccination and deaths in hospitalized patients, vaccinations and SARS-CoV-2 infections, repeated vaccinations and long-term immune response

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Introduction

Most Italian mainstream media emphasize the success of the Covid-19 vaccination campaign, following the information provided by the Istituto Superiore di Sanità (ISS). However, there is insufficient clarity about the different outcomes between unvaccinated and vaccinated people hospitalized with Covid-19, with reference to the variables “Intensive Care Unit (ICU)” and “Deaths”. Moreover, it is unclear the real effectiveness of the vaccine boosters on the risks of infection and of Covid-19 death in a period of time not limited to the first months after the booster.

The effects of repeated vaccinations on lowering the risk of disease have been shown for other infectious diseases. In the Canadian influenza season 2014–2015 repeated vaccinations increased the risk of medically attended A(H3N2) disease up to 50% versus unvaccinated people. Similar results were also shown in Italy, where most participants had received repeated doses, and in Michigan, where the influenza vaccine effectiveness was lower in subjects vaccinated in both the current and prior season in all age groups. On the contrary, in subjects with no evidence of prior vaccination, the vaccine effectiveness was higher for all age groups. Moreover, the dose-response relationship, calculated with adjusted geometric mean fold rise (MFR) after influenza vaccination, seems to be inversely related to the number of prior vaccinations, with higher protection without prior vaccination and lower protection in subjects up to four prior vaccination.

Some authors provide two hypotheses as potential explanation of these phenomena. The first is the Antigenic Distance hypothesis, meaning that variation in repeated vaccine effectiveness (VE) is due to differences in antigenic distances among vaccine strains and between the vaccine strains and the epidemic strain in each outbreak; if antibody titer is high for more than a year, it has the potential to negatively interfere with a subsequent revaccination if the antigenic similarity between the prior season vaccine strain and the epidemic strain is high. The second hypothesis is the Original Antigenic Sin (OAS), meaning that the immunity response to the previous met viral strain permanently shapes itself in order to boost the antibody production to related strain.

Moreover, it seems that the hypothesis based entirely on the antibody response to a unique viral antigen is not enough, but it is likely that the adaptive immune response to other virus components might contribute. In fact, a recent study suggests that the presence of pre-existing non-spike cross-reactive memory T cells protects the SARS-CoV-2-naïve contacts from infection.

Although many important questions related to the mechanism of OAS remain unanswered, it seems that the effectiveness of the current vaccine will be higher in people not previously vaccinated, or if the previous vaccine strain cross-reacts minimally with the current vaccine strain, even with no close match to the circulating strain.

Moreover, it has been hypothesized that anti-COVID-19 vaccinations, too frequently or too close repeated, could weaken the immune response or damage the immune system itself.

The aim of this study is to verify significant differences, percentage variations and trends in the ICU and Deaths variables, in the hospitalized population among four groups: an Incomplete Cycle (IC – defined as all reported cases with a confirmed diagnosis of SARS-CoV-2 virus infection, occurring at least 14 days after the first dose – in subjects who have
received a two-dose vaccine course – or, within 14 days days after administration of the second dose\textsuperscript{10}) group, a double
dose since less than 4 months (2D<4) group, a double dose more than 4 months ago (2D>4) group, and a third dose
(3D) group.

Furthermore, we aim to verify significant differences, percentage variations and trends in the same variables between the
Unvaccinated (UV) and Vaccinated (V) groups.

We hypothesize that repeated vaccinations might expose the recipients to a progressively greater risk of Covid-19,
included severe diseases, and that fewer vaccinations might be enough to protect the subjects at greater risk.

Finally, we have verified the hypothesis of a progressive weakening of the immune response as the time elapsed from the
booster dose increased, analyzing the data published weekly by the UK Security Agency in the COVID-19 vaccine
surveillance reports.

**Methods**

The official data relating to Covid-19 Hospitalizations, ICU and Deaths between Unvaccinated and Vaccinated
(and their subgroups: IC, 2D<4, 2D>4, 3D) were collected from the ISS bulletins starting by January 14, 2022 until
February 18, 2022. For the variable Deaths data were collected starting from January 21, 2022 because the division
between <4 and >4 months started from this date.

The reference populations among the bulletins were never aligned with the observation period of all 3 variables taken
into consideration. Therefore, it was necessary to proceed with this alignment considering the “median date” of the
observation period of each variable and using the populations of the previous bulletins whose reference date coincided
with the median date.

The observation period of one month allowed us to carry out analyzes on populations stable enough, despite the changes
of parts of the population among the groups (</> 5 months, </> 4 months, and third doses).

Rates/1,000 were calculated for both total events and for each group on the “Intensive Care Unit (ICU)” and “Deaths”
variables.

The rates of the variable “ICU” were calculated on the hospitalized population, while the rates of the variable Covid-19
“Deaths” were calculated on the hospitalized population added to the ICU population. The reason for this choice is based
on the fact that the number of deaths was higher than the number of accesses to ICU.

The calculation of the variation in the rates rate variations was carried out according to the formula:

\[
\left( \frac{\text{rate latest bulletin}}{\text{rate first bulletin}} - 1 \right) \times 100.
\]

To compare the Unvaccinated group and Vaccinated group, data of IC, 2D<4, 2D>4 and 3D were aggregated and was
calculated the total rate of Vaccinated group. The reason for this choice is that the ISS considers Unvaccinated even
people “… vaccinated with either the first dose or single-dose vaccine within the 14 days prior to diagnosis.” (although, in
our opinion, this can introduce a bias and a systematic error).\textsuperscript{10}

The VIVALDI Study\textsuperscript{11} showed a marginally greater hazard ratio for PCR-positive infection among vaccinated people
after first dose of BNT162b2 vaccine within 7-13 days compared to unvaccinated people. This data, albeit non-
significant, represent a tendency confirmed by data from Qatar in the two weeks following the first dose, mostly for
asymptomatic infections.\textsuperscript{12,13} This phenomenon might be related to a post-vaccination fall in neutrophil and lympho-
cyte.\textsuperscript{14,15}

Examples of some increase in hazard ratio for infections within the 13 days from first injection are are highlighted by
several authors.\textsuperscript{16–19}

The same proceeding above described was used for analysis of the trend of the rates for the all age groups (see
Supplementary material).
Data published weekly by the UK Health Security Agency in the COVID-19 vaccine surveillance reports were analyzed from the time the majority of the population (>30 million people) received the third dose, in order to verify the immune response as the time elapsed from the booster dose increased, calculating the ratio of deaths of unvaccinated versus vaccinated persons with at least 3 doses.

**Statistical analysis**
A non-parametric statistic was used after performing the Shapiro – Wilk normality test, inasmuch the distribution of the rates of the variables considered (“Intensive Care Unit” and “Deaths”) do not show a normal distribution.

The Kruskal-Wallis test with Dunn’s post-hoc test was used to compare Incomplete Cycle (IC), double dose <4 months (2D<4), double dose >4 months (2D>4) and third doses (3D) groups, while the Mann-Whitney test was used to compare Unvaccinated (UV) and Vaccinated (V) groups.

The level of significance of the rates variation was calculated using the linear regression between rates and date of the bulletins considering the rates as dependent variable.

For the descriptive statistic, data were processed using Excel, while for the inferential statistic was used GraphPad Prism 5 software (GraphPad Software, Inc., USA); the “p” significance level was fixed at <0.05.

**Results**
Comparison between Incomplete Cycle (IC), double dose <4 months (<4), double dose> 4 months (>4) and third doses (3D) groups.

a. **Intensive Care Unit (ICU) variable**

Statistical significant difference (p=0.0001) was observed among groups. Pairwise comparisons using Dunn’s test indicated that IC group was significantly different from the 3D group and 2D>4m. The 2D<4m group was significantly different by the 2D>4m.

The trend of 3D group is growing with an increase of the 253.3% (p=0.0001), while the trend of 2D>4m is degrowing with a decrease of the 39.7% (p=0.0001). The trend of IC group and 2D<4m are overlapping and show a decrease respectively of 45.5% (p=0.001) and 13.9% (p=0.28) (Figure 1 and Table 1).

b. **Deaths variable**

Statistical significant difference (p=0.001) was observed among groups. Pairwise comparisons using Dunn’s test indicated that IC group was significantly different from the 2D>4m. The 2D<4m group was significantly different by the 2D>4m group.

![Figure 1. Significant difference (p<.05) and trend between IC, <4, >4, 3D for the ICU variable.](image-url)
The trend of 3D group and 2D>4m are growing with an increase respectively of 416% (p=0.003) and 3.5%. The trend of IC group and 2D<4m are overlapping and show an increase respectively of 39.9% (p=0.04) and 49.8% (p=0.017) (Figure 2 and Table 2).

Comparison between Unvaccinated (UV) and Vaccinated (V) groups

a. **ICU variable**

Statistical significant difference (p=0.0087) was observed between groups. The trend of UV group and V are both degrowing with an decrease of 51.1% (p=0.0001) and 12.8% (p=0.02) respectively (Figure 3 and Table 3).

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**Table 1. Rate/1,000 ICU variable.**

| Date             | IC  | 2D<4m | 2D>4m | 3D  |
|------------------|-----|-------|-------|-----|
| 1-14/01/2022     | 2.2 | 3.6   | 27.2  | 3   |
| 2-21/01/2022     | 2   | 3.1   | 25.2  | 3.9 |
| 3-28/01/2022     | 1.7 | 2.7   | 22.1  | 5.7 |
| 4-04/02/2022     | 1.6 | 2.8   | 19.6  | 7.1 |
| 5-11/02/2022     | 1.5 | 2.8   | 18.2  | 8.6 |
| 6-18/02/2022     | 1.2 | 3.1   | 16.4  | 10.6|
| **Variations (%)** | **-45.5** | **-13.9** | **-39.7** | **253.3** |
| **P-value**      | **0.001*** | 0.28  | **0.0001*** | **0.0001*** |

*p value is significant.

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**Figure 2. Significant difference (p<.05) and trend between IC, <4, >4, 3D for the deaths variable.**

**Table 2. Rate/1,000 deaths variable.**

| Date             | IC  | 2D<4m | 2D>4m | 3D  |
|------------------|-----|-------|-------|-----|
| 1-21/01/2022     | 3.8 | 3.9   | 55.9  | 7.8 |
| 2-28/01/2022     | 3.4 | 3.8   | 50.0  | 12.0|
| 3-04/02/2022     | 4.0 | 4.3   | 51.1  | 19.2|
| 4-11/02/2022     | 4.7 | 4.9   | 53.1  | 28.2|
| 5-18/02/2022     | 5.3 | 5.8   | 57.8  | 40.2|
| **Variations (%)** | **39.9** | **49.8** | **3.5** | **416.0** |
| **P-value**      | **0.04*** | **0.017*** | 0.58  | **0.003** |

*p value is significant.
b. Deaths variable

Statistical significant difference (p=0.0159) was observed between groups. The trend of UV and V groups are both growing with an increase of 9.5% (p=0.178) and 53.2% (p=0.021) respectively (Figure 4 and Table 4).

Figure 3. Significant difference (p<.05) and trend between UV versus V for the ICU variable.

Table 3. Rate/1,000 ICU variable

| Date       | Rate/1,000 UV | Rate/1,000 V |
|------------|--------------|--------------|
| 1-14/01/2022 | 69.6         | 36           |
| 2-21/01/2022 | 61.9         | 34.2         |
| 3-28/01/2022 | 52.7         | 32.1         |
| 4-04/02/2022 | 45.4         | 31.1         |
| 5-11/02/2022 | 38.8         | 31.1         |
| 6-18/02/2022 | 34           | 31.4         |

Variations (%) -51.1 -12.8

P-value 0.0001* 0.02*

*p value is significant.

Figure 4. Significant difference (p<.05) and trend between UV versus V for the deaths variable.
Comparison amongst Incomplete Cycle (IC), double dose <4 months (<4), double dose > 4 months (>4) and third doses (3D) groups, Unvaccinated (UV) and Vaccinated (V) groups for all age groups (see Supplementary material)

The IC group showed rates significant lower for all age groups compared to 2D>4m or 2D<4m doses, both in the ICU variable and Death variable. For the all age groups, the 2D<4m did not show a significant difference compared to IC group both in the ICU variable and Death variable. Only in the 12–39 age group we observed a significant increase of the 2D<4m group compared to IC group in the ICU variable (S1). Furthermore, the trend of IC group shows a significant decrease for the age group 60–79 and 80+ both in the ICU variable and Death variable.

The 2D>4m group showed a significant decrease of the trend in the 60–79 and 80+ age group both in the ICU variable and Death variable while we observed a significant decrease of the trend in the 2D<4m in the 12–39 age group in the ICU variable.

The third doses show a significant increase of the trend in all age groups both in the ICU variable and Death variable. In particular, in the 80+ group we observed a trend reversal between 2D>4m group and 3D group both in the ICU variable and Death variable (S13–S14).

The comparison between UV and V groups shows: 1. no significant difference in the 12–39 age group but a significant decrease in the trend of UV group in the ICU variable. Furthermore we observed a trend reversal near the fifth bulletin in the ICU variable (S3); 2. significant difference in the 40–59 age group both in the ICU variable and Death variable to the disadvantage of the UV group, but a significant decrease in the trend of UV group accompanied by a significant increase on V group in the ICU variable, while in the Death variable we observed a significant increase of the trend of V group; 3. significant difference in the 60–79 age group in the ICU variable to the disadvantage of the UV group but no significant difference in the Death variable. The trend in the ICU variable decrease in both group but to a greater extent in the UV group (S11), while in the Death variable we observed a trend reversal between second and third bulletin (S12); 4. significant difference both in the ICU variable and Death variable to the disadvantage of the V group in the 80+ age group and a decrease trend both UV group and V group only in the ICU variable.

The reports of COVID-19 vaccine surveillance, weekly published by the UK Health Security Agency, show a clear trend towards an increase in infections in vaccinated persons versus not vaccinated persons per 100,000, compared in each of eight age classes: under 18, 18 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, 80 or over. Indeed, the Week 36 of 2021 showed an unbalancement in age classes from 40 to 79 years, in which COVID-19 cases in vaccinated exceeded those in not vaccinated persons, although the entire column of vaccinated persons still outnumbered (~13%) the column of not vaccinated.

In the following weeks the COVID-19 cases among the vaccinated persons continued to increase more than proportionally, until in Week 39 the ratio was reversed, with more COVID-19 cases among the vaccinated persons (+7% overall). Thereafter, the relative increases among the vaccinated persons were always higher than those in their counterpart, up to Week 2 of 2022, when the excess reached +117%. From Week 3 of 2022 the tables published in the reports show the comparison only between unvaccinated versus vaccinated persons “with at least 3 doses”, with an attenuated excess of cases temporarily in vaccinated (+34%). However, in the following weeks the excess of cases has continued incessantly to increase, to reach +275% in Week 13, when the UK Health Security Agency announced the decision to stop the publication of these data and of the related table.
Someone might observe that these are raw data, without multivariable adjustment. However, there are three considerations in this regard.

First, we lack too many informations to implement a multivariable correction.

Second, why UK Health Security Agency itself has not implemented these corrections, owning all the needed informations? A possible answer is that the results are not so striking, and that the substance would not change much.

Third, in the face of an impressive trend such as the one highlighted, we think it is more important to bring it to the attention of the scientific community, to open a debate on the subject, also soliciting the necessary investigations/appropriate adjustments. Suppressing the reporting of the phenomenon because the methodological rules have not been previously and meticulously observed risks further delaying awareness of a trend with profound possible public health implications.

In the weeks when more than half of the English people have received the vaccine booster (from Week 3 of 2022 onwards), the Week 3 shows a death rate of unvaccinated 9.4 times than the one of the vaccinated persons, while Week 11 shows a rate unvaccinated/vaccinated persons only about 1.6 (Table 5). We have now the first consistent Italian data, beginning from the age classes that anticipated a turnaround also in England (Table 6).

**Discussion**

The aim of this study was to understand the impact of the Covid-19 vaccine boosters in the ICU and Deaths variables and to compare the weight of the Unvaccinated and Vaccinated groups in the same variables.

The results support our hypothesis.

In fact, the Kruskal-Wallis test used to compare IC, 2D<4, 2D>4, 3D groups have shown that, from the comparison between the rates, a single dose is already associated with reduced access to ICU and Deaths, and that the third doses are associated with increased accesses in ICU and Deaths, unlike the second doses and incomplete cycles (IC).

Moreover, the 2D>4m are associated with significantly greater values than the IC and 2D<4m both in the ICU and Deaths variables. However, on the whole, the 2D>4m show a progressive and continuous decrease over time up to levels almost comparable for the ICU variable to the 3D values (which instead seem to worsen constantly); instead, in Deaths variable the 2D>4m show a slight rise during the considered period.
Table 6. Relative risk of reported COVID-19 cases, hospitalization, ICU admission and death per 100,000 by vaccination status (Epidemia COVID-19 (iss.it)).

| Persons 40-59 years | DIAGNOSIS Not vacc. vs vacc. complete cycle ≤ 120 days | DIAGNOSIS Not vaccinated vs vacc. complete cycle + booster | HOSPITALIZATION Not vaccinated vs vacc. complete cycle ≤ 120 days | HOSPITALIZATION Not vaccinated vs vacc. complete cycle + booster | Intensive Care Unit Not vaccinated vs vacc. complete cycle ≤ 120 days | Intensive Care Unit Not vacc. vs vacc. complete cycle + booster | DECEASED Not vacc. vs vacc. complete cycle ≤ 120 days | DECEASED Not vacc. vs vacc. complete cycle + booster |
|---------------------|---------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| 19/01/2022          | 2.1                                                     | 2.6                                                        | 13.8                                                          | 9.4                                                           | 27.6                                                          | 32.2                                                          | 27.0                                                          | 7.7                                                           |
| 26/01/2022          | 2.0                                                     | 2.8                                                        | 9.1                                                           | 7.7                                                           | 21.3                                                          | 21.3                                                          | 16.2                                                          | 9.3                                                           |
| 02/02/2022          | 1.9                                                     | 3.1                                                        | 6.8                                                           | 7.4                                                           | 21.3                                                          | 17.8                                                          | 18.0                                                          | 18.0                                                          |
| 09/02/2022          | 1.9                                                     | 3.4                                                        | 5.1                                                           | 6.9                                                           | 15.1                                                          | 16.3                                                          | 15.1                                                          | 17.7                                                          |
| 16/02/2022          | 1.9                                                     | 3.5                                                        | 3.8                                                           | 5.8                                                           | 8.8                                                           | 12.2                                                          | 11.9                                                          | 13.6                                                          |
| 23/02/2022          | 1.8                                                     | 3.5                                                        | 3.0                                                           | 5.4                                                           | 5.4                                                           | 10.3                                                          | 8.0                                                           | 11.0                                                          |
| 02/03/2022          | 1.7                                                     | 3.2                                                        | 2.6                                                           | 5.3                                                           | 3.6                                                           | 10.7                                                          | 5.0                                                           | 7.8                                                           |
| 09/03/2022          | 1.7                                                     | 2.8                                                        | 2.3                                                           | 4.9                                                           | 2.5                                                           | 8.9                                                           | 3.1                                                           | 7.6                                                           |
| 16/03/2022          | 1.6                                                     | 2.2                                                        | 2.2                                                           | 4.6                                                           | 2.0                                                           | 6.8                                                           | 2.4                                                           | 8.2                                                           |
| 23/03/2022          | 1.4                                                     | 1.7                                                        | 2.0                                                           | 4.0                                                           | 2.0                                                           | 5.3                                                           | 2.0                                                           | 6.0                                                           |
| 30/03/2022          | 1.2                                                     | 1.4                                                        | 1.8                                                           | 3.3                                                           | 2.0                                                           | 4.4                                                           | 1.8                                                           | 8.0                                                           |
| 06/04/2022          | 1.2                                                     | 1.3                                                        | 1.6                                                           | 2.5                                                           | 1.7                                                           | 3.2                                                           | 2.6                                                           | 6.0                                                           |
| 13/04/2022          | 1.1                                                     | 1.2                                                        | 1.6                                                           | 2.3                                                           | 1.8                                                           | 3.7                                                           | 4.2                                                           | 7.0                                                           |
| 20/04/2022          | 1.0                                                     | 1.1                                                        | 1.4                                                           | 2.0                                                           | 2.4                                                           | 3.4                                                           | 5.2                                                           | 7.0                                                           |
| 27/04/2022          | 1.0                                                     | 1.1                                                        | 1.4                                                           | 2.0                                                           | 3.7                                                           | 3.1                                                           | 4.2                                                           | 5.2                                                           |
| 04/05/2022          | 0.9                                                     | 0.9                                                        | 1.2                                                           | 1.8                                                           | 3.1                                                           | 3.1                                                           | 5.2                                                           | 5.2                                                           |
| 11/05/2022          | 0.9                                                     | 0.9                                                        | 1.2                                                           | 1.7                                                           | 3.3                                                           | 2.9                                                           | 3.3                                                           | 5.0                                                           |
| 18/05/2022          | 0.9                                                     | 0.9                                                        | 1.2                                                           | 1.5                                                           | 2.4                                                           | 2.0                                                           | 2.6                                                           | 4.5                                                           |
| 25/05/2022          | 0.9                                                     | 0.9                                                        | 1.2                                                           | 1.5                                                           | 2.4                                                           | 2.0                                                           | 2.6                                                           | 4.5                                                           |
| 31/05/2022          | 0.8                                                     | 0.8                                                        | 1.1                                                           | 1.3                                                           | 2.2                                                           | 2.2                                                           | 1.4                                                           | 2.8                                                           |
| 08/06/2022          | 0.8                                                     | 0.9                                                        | 1.0                                                           | 1.4                                                           | 1.5                                                           | 2.2                                                           | 1.3                                                           | 3.0                                                           |
| 15/06/2022          | 0.8                                                     | 0.9                                                        | 0.9                                                           | 1.5                                                           | 2.0                                                           | 2.5                                                           | 2.7                                                           | 2.7                                                           |
| 22/06/2022          | 0.9                                                     | 0.8                                                        | 0.9                                                           | 1.6                                                           | 2.0                                                           | 3.3                                                           | 1.0                                                           | 2.5                                                           |
| 28/06/2022          | 1.0                                                     | 0.8                                                        | 0.8                                                           | 1.6                                                           | 0.7                                                           | 2.0                                                           | 2.3                                                           | 3.5                                                           |
| 06/07/2022          | 1.0                                                     | 0.8                                                        | 0.9                                                           | 1.6                                                           | 0.7                                                           | 1.7                                                           | inf                                                           | 6.0                                                           |
Overall, the 2D <4m do not seem to improve ICU accesses and deaths, if compared to the single doses (IC) and, moreover, they show a trend over time similar to the IC group.

The Mann-Whitney test was used to compare Unvaccinated (UV) and Vaccinated (V) groups shows that, overall, the UV group has significantly higher ICU accesses, but it shows a sharp declining trend over the whole period considered (-51%), while the V group shows only a 13% decrease.

There is an overlap of values between UV and V groups in the last bulletin of the period considered for the ICU variable; instead, the Deaths variable shows a progressive divergence of values throughout the considered period.

In contrast to the ICU variable, the deaths in the UV group are significantly lower than those in V group, with an increase of 9.5% over the considered period, while the increase in the V group is 53.2%.

The analysis by age groups shows an increase in rates both in the ICU variable and in the Death variable in all age groups in the 3D group. Furthermore, the weaker age groups seem to show greater sensitivity to this phenomenon inasmuch a trend reversal is observed between the 2D group>4m and the 3D group. This observation seems to be congruent with what has already been observed in Canada, Italy and Michigan, where it has been shown that repeated vaccinations increase the risk of disease.

The hypothesis of a progressive weakening of the immune response with the increase of the time from the booster dose is supported by the data in the weekly publications of the UK Health Security Agency - COVID-19 vaccine surveillance reports.

In fact, such a clear trend not only argues for the waning of the 3rd dose effectiveness in preventing SARS-CoV-2 infection, but also for a possible, progressive worsening of the immune response.

Note that the Authors of the UK Health Security Agency Report always repeat that: “Comparing case rates among vaccinated and unvaccinated populations should not be used to estimate vaccine effectiveness against COVID-19 infection. Vaccine effectiveness (VE) has been formally estimated from a number of different sources and is summarised on pages 4 to 15 in this report.” However, the four cohort studies mentioned in the Report in the paragraph “Effectiveness against infection” have a short follow-up, ranging on average from 45 to 80 days, during the so-called honeymoon between the vaccine and the vaccinated persons. In this period the protection is at its maximum, also against the infection, and it is before the beginning of its rapid decline. Moreover, these inconsistent arguments of the Report authors do not stand up to comparison with the very strong and linear trend of increasing infections in vaccinated individuals shown by the weekly data, albeit unadjusted.

It is not enough. Looking at the weeks when more than half of the English people have received the vaccine booster (from Week 3 of 2022 onwards, it is detectable a clear trend to an attenuation of the VE even towards deaths, because in Week 3 the death rate of unvaccinated was 9.4 times the vaccinated rate, while in the Week 10 the rate unvaccinated/vaccinated was only about 1.4 (Table 5). [Note that this trend seems in place in Italy as well, starting from the age group 40-59 (Table 6)]. The rate in England week 11, nearly 1.6, might be an interruption of this trend, or an effect of chance, or an interference with the (temporary?) effects of the fourth dose, reported only from 9 March 2022.

The usual explanation is to acknowledge a progressive attenuation of the VE against the infection (although for now, despite mounting evidence, most main stream researchers are far from admitting a VE negativization in the medium period, in comparison to the unvaccinated persons). But, together, the typical narrative states definitely that the VE remains very good against a severe or critical COVID-19. Unfortunately, the data in Tables 5 and 6 show a clear trend towards an attenuation of the VE even for deaths, and the data should call into question the strategy of repeated, continuous vaccine boosters. Other strategies as well should be debated and studied in depth and implemented, from allowing natural infections (as Icelandic Public Healthcare is proposing, in the setting of a mild dominant variant such as Omicron), to implementation of safer environments, healthy lifestyles and reasonably effective, safe and sustainable early care.

Conclusion
The results do not provide support to vaccination campaigns with multiple and repeated doses (and related obligations), both because of the doubtful net advantage of subsequent doses, and because of the suspicion that the repeated stimulation of the immune system with this type of vaccine may expose the vaccinated people to an increased risk of serious disease.
The negative effect of this uninterrupted vaccination campaign seems to affect particularly the age groups that the campaign aims to protect; moreover, the net benefits declared for the younger are not evident.

In addition to continuing researching for better vaccines, it would be time to implement different strategies as well, to tackle this and other pandemics: from the achievement of a healthy living and working environment, to healthy lifestyles, to accessible early, safe and sustainable care.

Data availability

As the data are not owned by the authors, it is not possible to upload the data to a repository. Data analysed will be available in an accessible form by contacting the corresponding author.

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Major comments and concerns

The authors have not stratified their data at all, simply looking at whole populations just based on how many vaccines participants have had is not enough. The analysis would need to be redone with multivariate analysis corrections for age, sex, time after vaccination and ethnicity at the very least.

The quality of the figures is not up to standard and a Y-axis should be provided in the longitudinal subfigures. We should be able to understand the data by looking at the figures and legends alone.

"The VIVALDI Study showed a marginally greater hazard ratio for PCR-positive infection among vaccinated people after first dose of BNT162b2 vaccine within 7-13 days compared to unvaccinated people."

- In this study, this was not significantly different - authors should either remove this reference or state that the difference seen was not statistically significant in the VIVALDI study.

"The trend of 3D group is growing with an increase of the 253.3%, while the trend of 2D>4m is degrowing with a decrease of the 39.7%. The trend of IC group and 2D<4m are overlapping and show a decrease respectively of 45.5% and 13.9%"

- Is this statistically significant on the longitudinal graph? Again, this should be checked for every figure.

"The reason for this choice is that the ISS considers Unvaccinated even people "... vaccinated with either the first dose or single-dose vaccine within the 14 days prior to diagnosis." (although, in our opinion, this can introduce a bias and a systematic error)."

- I do not understand this sentence. It takes at least 14 days for the immune response to mature, therefore only counting those after 14 days of vaccination will provide the true response to vaccination. Days 1-14 the immune response is not yet complete.

"Indeed, the Week 36 of 2021 showed an unbalancement in age classes from 40 to 79 years, in which COVID-19 cases in vaccinated exceeded those in not vaccinated persons, although the entire column of
vaccinated persons still outnumbered (-17.2%) the column of not vaccinated."

The authors would need to adjust the analysis to account for the larger number of vaccinated donors in this cohort.

The fundamental conclusions drawn from the analysis would need to be revisited after the multivariant analysis corrections have been implemented.

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

No

**Are sufficient details of methods and analysis provided to allow replication by others?**

No

**If applicable, is the statistical analysis and its interpretation appropriate?**

No

**Are all the source data underlying the results available to ensure full reproducibility?**

No

**Are the conclusions drawn adequately supported by the results?**

No

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** COVID-19 immunology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.
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