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 1; peer review: awaiting peer review]

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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

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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. 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 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.

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).10

The VIVALDI Study11 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 evidence seems supported by data from Qatar in the two weeks following the first dose, mostly for asymptomatic infections.12,13 This phenomenon might be related to a post-vaccination fall in neutrophil and lymphocyte.14,15

Data published weekly by the UK 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.

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%, 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% (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.

The trend of 3D group and 2D>4m are growing with an increase respectively of the 416 % and 3.5%. The trend of IC group and 2D<4m are overlapping and show an increase respectively of 39.9% and 49.8% (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% and 12.8% respectively (Figure 3 and Table 3).

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% and 53.2% respectively (Figure 4 and Table 4).

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

<table>
<thead>
<tr>
<th>Date</th>
<th>CI</th>
<th>Rate/1,000 2D&lt;4m</th>
<th>Rate/1,000 2D&gt;4m</th>
<th>Rate/1,000 3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/01/2022</td>
<td>2,2</td>
<td>3,6</td>
<td>27,2</td>
<td>3</td>
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<tr>
<td>21/01/2022</td>
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<td>3,1</td>
<td>25,2</td>
<td>3,9</td>
</tr>
<tr>
<td>28/01/2022</td>
<td>1,7</td>
<td>2,7</td>
<td>22,1</td>
<td>5,7</td>
</tr>
<tr>
<td>04/02/2022</td>
<td>1,6</td>
<td>2,8</td>
<td>19,6</td>
<td>7,1</td>
</tr>
<tr>
<td>11/02/2022</td>
<td>1,5</td>
<td>2,8</td>
<td>18,2</td>
<td>8,6</td>
</tr>
<tr>
<td>18/02/2022</td>
<td>1,2</td>
<td>3,1</td>
<td>16,4</td>
<td>10,6</td>
</tr>
<tr>
<td>Variations (%)</td>
<td>-45,5</td>
<td>-13,9</td>
<td>-39,7</td>
<td>253,3</td>
</tr>
</tbody>
</table>

**Figure 1. Significant difference (p<.05) and trend between IC, <4, >4, 3D for the ICU variable.**
Figure 2. Significant difference (p<.05) and trend between IC, <4, >4, 3D for the deaths variable.

Table 2. Rate/1,000 deaths variable.

<table>
<thead>
<tr>
<th>Date</th>
<th>IC</th>
<th>2D&lt;4m</th>
<th>2D&gt;4m</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/01/2022</td>
<td>3.8</td>
<td>3.9</td>
<td>55.9</td>
<td>7.8</td>
</tr>
<tr>
<td>28/01/2022</td>
<td>3.4</td>
<td>3.8</td>
<td>50.0</td>
<td>12.0</td>
</tr>
<tr>
<td>04/02/2022</td>
<td>4.0</td>
<td>4.3</td>
<td>51.1</td>
<td>19.2</td>
</tr>
<tr>
<td>11/02/2022</td>
<td>4.7</td>
<td>4.9</td>
<td>53.1</td>
<td>28.2</td>
</tr>
<tr>
<td>18/02/2022</td>
<td>5.3</td>
<td>5.8</td>
<td>57.8</td>
<td>40.2</td>
</tr>
<tr>
<td>Variations (%)</td>
<td>39.9</td>
<td>49.8</td>
<td>3.5</td>
<td>416.0</td>
</tr>
</tbody>
</table>

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

Table 3. Rate/1,000 ICU variable.

<table>
<thead>
<tr>
<th>Date</th>
<th>UV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/01/2022</td>
<td>69.6</td>
<td>36</td>
</tr>
<tr>
<td>21/01/2022</td>
<td>61.9</td>
<td>34.2</td>
</tr>
<tr>
<td>28/01/2022</td>
<td>52.7</td>
<td>32.1</td>
</tr>
<tr>
<td>04/02/2022</td>
<td>45.4</td>
<td>31.1</td>
</tr>
<tr>
<td>11/02/2022</td>
<td>38.8</td>
<td>31.1</td>
</tr>
<tr>
<td>18/02/2022</td>
<td>34</td>
<td>31.4</td>
</tr>
<tr>
<td>Variations (%)</td>
<td>-51.1</td>
<td>-12.8</td>
</tr>
</tbody>
</table>
The reports of COVID-19 vaccine surveillance, weekly published by the UK 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, although the entire column of vaccinated persons still outnumbered (-17.2%) 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 43 the ratio was reversed, with more COVID-19 cases among the vaccinated persons (+2.5% 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 +91%. 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 (+24%). However, in the following weeks the excess of cases has continued incessantly: +32%, +35%, +48%, +70%, +100%, +133%, +162%, to reach +186% in Week 11.

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).

**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, with an overall increase of 253% and 416% respectively, unlike the second doses and incomplete cycles (IC), which recorded decreases up to 45 % for ICU and increases up to 49.8% for Deaths.

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.

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 (-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 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 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 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

**Table 5. Covid Vaccine Surveillance Report – UK Security Agency – Unadjusted rates of COVID-19 deaths (per 100,000) in vaccinated (≥3 doses) and unvaccinated persons by week 3 to 11 of 2022.**

<table>
<thead>
<tr>
<th>Week/2022</th>
<th>Death within 28 days of positive Covid-19 test</th>
<th>Death within 60 days of positive Covid-19 test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted rates among persons vaccinated ≥3 doses (per 100,000)</td>
<td>Unadjusted rates among persons not vaccinated ≥3 doses (per 100,000)</td>
</tr>
<tr>
<td>3</td>
<td>42.0</td>
<td>438.4</td>
</tr>
<tr>
<td>4</td>
<td>62.2</td>
<td>453.1</td>
</tr>
<tr>
<td>5</td>
<td>86.9</td>
<td>459.6</td>
</tr>
<tr>
<td>6</td>
<td>107.8</td>
<td>431.3</td>
</tr>
<tr>
<td>7</td>
<td>111.6</td>
<td>353.8</td>
</tr>
<tr>
<td>8</td>
<td>105.5</td>
<td>276.2</td>
</tr>
<tr>
<td>9</td>
<td>91.5</td>
<td>197.6</td>
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<tr>
<td>10</td>
<td>71.0</td>
<td>142.4</td>
</tr>
<tr>
<td>11</td>
<td>59.4</td>
<td>118.8</td>
</tr>
</tbody>
</table>
this report.” However, the four cohort studies mentioned in the Report in the paragraph “Effectiveness against infection”\textsuperscript{11,16–18} have a short follow-up, ranging on average from 45 to 80 days, during the so-called \textit{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),\textsuperscript{19} 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). The rate in 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.\textsuperscript{19}

The usual explanation is to acknowledge a progressive \textit{attenuation} of the VE against the infection (although for now, despite mounting evidence,\textsuperscript{12,13,20–22} most main stream researchers are far from admitting a VE \textit{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 Table 5 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 dept and implemented, from allowing natural infections (as Icelandic Public Healthcare is proposing,\textsuperscript{23} in the setting of a mild dominant variant such as Omicron), to implementation of safer environments,\textsuperscript{24–26} healthy lifestyles,\textsuperscript{27–32} and reasonably effective, safe and sustainable early care.\textsuperscript{33–37}

\section*{Conclusion}

The results do not provide support to vaccination campaigns with multiple and repeated doses (and related obligations), both because of the doubtful 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.

\section*{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.

\section*{ISS bulletins}


References


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