

REVIEW

## Vaccine third dose and cancer patients: necessity or luxury?

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The current state of the SARS-CoV-2 pandemic is an equilibrium between expanding vaccine coverage on the one hand, and emergence of variants of concern which compromise vaccine effectiveness and enhance viral transmission on the other. Inequity in vaccine distribution, primarily an ethical issue, challenges this equilibrium, as industrialized countries prepare to administer a third booster dose to their population.

Solid tumor cancer patients typically respond well to initial full vaccination and someone could argue that they should not be prioritized for an adjuvant third dose, since protection from severe disease has largely been achieved with the two-dose regimen. Nevertheless, their immune status is dynamic and not all of them exhibit an adequate immune response.

A booster third dose is necessary for the inadequate responders, while it will result in better protection of all patients from mild disease as well, which if presented could have ominous consequences due to their overall frailty, and their need to adhere to strict therapeutic schemes. International scientific and public health communities should develop approaches that allow for wide immediate vaccination coverage of the developing world, in parallel with administration of adjuvant doses to solid tumor cancer patients (and other at-risk categories) of the developed nations, in order to avoid prolonging the pandemic, which will be prospectively against cancer patients' best interest.

**Key words:** cancer patients, delta variant, vaccine third dose, vaccine inequity

### INTRODUCTION

The course of the SARS-CoV-2 pandemic in the year 2021 has been shaped by two novel parameters: the wide, but uneven, distribution of effective vaccines, and the emergence of variants of concern (VoCs). These novel viral variants are characterized by remarkable differences, in terms of transmissibility, disease severity, and immune susceptibility. The latest emerging VoC in particular, Delta (PANGO lineage B.1.617.2, one of the variants initially isolated in India), besides being more virulent, is also extremely transmissible. Furthermore, its transmission curve shifts to the left, meaning that a greater percentage of presymptomatic transmission occurs.<sup>1-3</sup> Its gradual dominance worldwide (at least in countries that carry out adequate genotyping) has coincided with evidence of waning vaccine

efficacy in preventing infection, leading to an increased incidence of breakthrough SARS-CoV-2 cases (cases occurring at least 14 days after full vaccination). These breakthrough Delta cases are further characterized by increased, even transiently, viral loads, with obvious consequences in activation or enhancement of further transmission chains. In view of this new reality, certain countries, including the USA and Israel, have programmed or are already offering booster third vaccine doses in their entire eligible population.

### BOOSTER AND ADJUVANT DOSES

It should be noted that a booster third dose for the general population differs from an adjuvant third dose administered in specific populations: these populations include immunocompromised patients, hematological malignancy patients, rheumatologic and solid tumor cancer patients under specific therapy, patients on hemodialysis, individuals with primary or acquired immunodeficiencies, and transplant patients. These individuals often fail to respond adequately to the initial vaccination, and a remarkable minority of them even fail to elicit humoral and cellular immunity. Initial series of administration of a third dose in such patients demonstrated seroconversion in >50% of them: this

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adjuvant dose is, thus, a necessity which may not even be adequate in the long term.<sup>4</sup>

What about a third dose for the general population though? Many questions automatically emerge: how do we define this ‘general population’ when vaccine distribution is vastly unequal? Is this ‘vaccine discrimination’ poised to end soon? And how do we define ‘soon’ when novel virus variants continuously emerge while the morbidity and mortality toll of unvaccinated populations is increasing (since Delta is associated with increased disease severity)?<sup>5</sup>

### ‘VACCINE DISCRIMINATION’

As of 16 October 2021, worldwide vaccine coverage remains shockingly unfair: whereas numerous European countries and the USA have managed to fully vaccinate >60% and 50% of their populations, respectively (Table 1), some countries have barely administered any vaccines at all. With the striking exception of isolated countries, primarily island nations and countries in the north Maghreb region, most African countries have extremely low full vaccination coverage of their population (even South Africa, a country that has been at the epicenter of several large phase II vaccine clinical trials). Twenty-three African countries are currently failing to reach a 2.5% fully vaccinated population limit, with the cumulative number of vaccines administered in these countries being equal to the number of vaccines administered in an industrialized country in a single day. The list of undervaccinated countries is not limited to Africa though, and includes certain central Asian republics, while vaccine coverage in other pandemic hot spots (such as Latin America) is disproportionately low considering their ongoing viral burden.

What is the significance of this vaccine inequity? We tend to forget that the term pandemic is built up from two Greek words; ‘demic’ which comes from ‘demos’, a term referring to society and state, and ‘pan’ which means ‘the whole’. A pandemic is a universal cause of concern, social and health care disruption, long-term morbidity, and mortality, that may disproportionately affect social and ethnic minorities. Much more than ever before, in an era of massive human movements, either for leisure or due to political and socioeconomic reasons, a minor outbreak in a remote place can rapidly transform into a global concern. Thus, when one discusses ‘herd immunity’ (a term referring to the necessary percentage of the population that must be immune in order for viral circulation to subside) or even better the critical vaccine threshold, one should remember that no country is a ‘sealed herd’.<sup>6</sup> People are moving from one country to another in unpredictable and massive numbers, and a recent model has persuasively demonstrated that when this happens, unequal vaccine administration will result in relapsing viral epidemic flares, even in countries with large vaccination coverage.<sup>7</sup>

The emergence of novel variants is an unavoidable consequence of sustained massive viral circulation in the community: all VoCs were first described in countries with significant epidemic waves—UK, Brazil, South Africa, and

**Table 1. SARS-CoV-2 vaccination coverage in Africa, as of 16 October 2021**

Country	Percentage of population that has received 1st dose	Percentage of fully vaccinated population
Algeria	14.4	9.3
Angola	10.5	4.3
Benin	1.8	1.6
Botswana	24.6	10.9
Burkina Faso	1.3	1.0
Burundi	Not available	Not available
Cameroon	1.6	0.6
Cape Verde	52.9	30.2
Central African Republic	5.2	0.2
Chad	0.9	0.2
Comoros	22.7	18.5
Congo, Democratic Republic of	0.1	<0.1
Congo, Republic of	6.1	2.6
Djibouti	6.1	2.4
Egypt	15.2	8.3
Equatorial Guinea	17.4	13.1
Eritrea	Not Available	Not Available
Eswatini	20.8	20.2
Ethiopia	3.1	1.0
Gabon	5.8	4.2
Gambia	7.9	7.3
Ghana	4.5	2.7
Guinea	9.9	4.8
Guinea-Bissau	6.3	0.5
Ivory Coast	7.5	2.3
Kenya	6.7	2.2
Lesotho	17.0	16.6
Liberia	1.9	0.2
Libya	22.0	4.5
Madagascar	0.7	0.7
Malawi	4.4	2.5
Mali	1.7	1.3
Mauritania	17.5	14.5
Mauritius	69.6	65.7
Morocco	65.0	58.8
Mozambique	6.1	5.7
Namibia	11.6	8.5
Niger	1.8	0.9
Nigeria	2.6	1.2
Rwanda	22.1	13.8
Sao Tome and Principe	35.2	13.0
Senegal	7.8	3.5
Seychelles	80.5	74.1
Sierra Leone	3.7	0.9
Somalia	2.3	1.7
South Africa	23.5	17.9
South Sudan	0.6	0.2
Sudan	1.5	1.3
Tanzania	—	—
Togo	10.0	5.1
Tunisia	45.6	35.2
Uganda	6.0	1.0
Zambia	1.8	?*
Zimbabwe	21.5	16.5

Data derived from Bloomberg Vaccine Tracker, at <https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution>.

\* Data on Zambia second dose indicated as more than first dose, thus omitted.

India. When this epidemic intensity coincides with community over-representation of immunocompromised populations (as in the case of South Africa with its human immunodeficiency virus burden) the emergence of novel

variants may be boosted. We do know that viral mutation potential is lower in countries that have higher vaccination coverage.<sup>8</sup> In addition, we also know that the virus itself in an infected vaccinated individual is less prone to mutations than in an unvaccinated one.<sup>9</sup> Thus, vaccine inequity increases the mutational pressure. Furthermore, we should bear in mind that we do not know yet whether there is a mutational upper limit, beyond which the specific virus will not evolve in terms of transmission or immune escape potential. The emergence of Delta has already underlined that, in terms of transmissibility. Certain models have warned of the risk of the virus following a hyperexponential growth in its transmission potential. Should this happen, humanity will face the need for draconian mitigation and implementation of suppression measures.<sup>10</sup>

Was this health inequity not predictable? Certainly. And we theoretically tried to avoid it. The development of COVAX (Covid-19 Vaccines Global Access), supported by the World Health Organization (WHO), the Vaccine Alliance Gavi, and CEPI (Coalition for Epidemic Preparedness Innovations)<sup>11</sup> aimed to facilitate an equal distribution of produced vaccines worldwide, in order to ensure that every vulnerable individual and frontline health care worker, irrespective of their country of residency, will have priority in vaccination. Unfortunately, this effort failed, as demonstrated in Table 1. COVAX soon became an ethical alibi for most industrialized countries,<sup>12</sup> with promises of financial or direct product support, but only after the individual country vaccine stockpile was maximized. The Joint Statement of the Multilateral Leaders Taskforce on Scaling Covid-19 Tools (including the heads of the International Monetary Fund, the World Bank, the World Trade Organization, and WHO) characteristically mentions that <10% of the 900 million vaccine doses committed as a donation to COVAX had been made available.<sup>13</sup> Certain rich countries took advantage of COVAX in order to rapidly achieve vaccine availability for their whole eligible population, whereas most other developed nations independently negotiated with vaccine manufacturers and prioritized their population, irrespective of individual risks. Even worse, many countries tend to safe-keep vaccine doses despite the risk of having them expire. In fact, numerous countries have already discarded their expired vaccine doses, failing to utilize them in time. Some developing countries have been hesitant or even hostile in accepting such soon-to-expire doses, while bureaucracy further undermined any effort of a successful and timely transfer of such vaccine doses. Finally, ‘vaccine nationalism’ has emerged as a reason of restrictions in vaccine exports, despite legally binding international agreements.<sup>14</sup>

Another organization aiming at vaccine equity for Africa, AVAT (African Vaccine Acquisition Trust) has also failed to antagonize industrialized countries to achieve vaccine delivery priority. Other proposed platforms, such as C-TAP (Covid-19 Technology Access Pool), which call to sharing vaccine expertise and techniques, remain dormant. One should take into account that even if patents and technical details are being shared, much more will be needed for the

developing countries to overcome the barriers of vaccine manufacturing, particularly with novel platforms such as mRNA vaccines or vaccines that use novel immunostimulant adjuvants. Vaccine manufacturing remains a sophisticated process that needs technical expertise, basic materials that are not abundant, and a guarantee that any novel manufacturing unit can meet the quality standards. At times such as these, when delays cost lives, this is an issue that seems to be important only as a lesson for future pandemics. Another potential setback for the developed world, particularly when dealing with mRNA vaccines, is the existence of inappropriate storage properties.

Nevertheless, today, any eligible individual in the developed world can be vaccinated immediately, and it is vaccine hesitancy that troubles western societies at present. In this situation, while developing nations desperately await their share of public health resources, the developed world, once more, demands additional vaccine doses in order to ensure that each eligible adult will have a third dose available. And while they most probably succeed in this task, the real question is: do all individuals actually need an additional dose?

### DO WE REALLY NEED BOOSTER SHOTS?

The discussion about the necessity of a booster dose (not the adjuvant dose that should be administered to immunocompromised individuals previously analyzed) emerged when an increase in breakthrough cases was observed during early summer of 2021. Studies from Israel exhibited a relationship between time of vaccine administration and breakthrough infection incidence, with persons vaccinated in January having at least a double risk of suffering a breakthrough infection, compared with individuals vaccinated in March.<sup>15</sup> A similar pattern of waning immunity against infection was observed in large population studies from the USA.<sup>16</sup> It should be noted though, that this waning immunity has minimal effect on the risk of severe disease and death, based on the currently available data.<sup>17</sup> There has also been ample evidence that both vaccination and natural disease result in the development of humoral and cellular immunological memory that may be efficient against novel variants. Thus, waning immunity at present seems to exert a small to moderate effect on health care system burden and mortality. One may argue that breakthrough infections may lead to long COVID (the coalition of symptoms that continue after the initial infection or emerge shortly thereafter and may disrupt an individual’s life due to their severity and limited therapeutic options available), and this is indeed a valid point that warrants intensive scientific interest in the weeks to come. Another argument is that breakthrough infections participate in further viral community circulation, although the infected vaccinated person is largely less significant as an infectious unit, compared with the non-vaccinated one.

These factors should be counterbalanced by the fact that the additional vaccine dose in the western world will jeopardize vaccine distribution in developing countries, and

will result in a significant increase in mortality and morbidity of the more vulnerable or 'continuously exposed' populations that have not received any vaccine dose. It will also facilitate the emergence of novel variants.

### WHERE DOES THE ONCOLOGY PATIENT STAND ON THIS DILEMMA?

Do oncology patients need a third dose? Undoubtedly, patients with hematologic malignancies do need it, in order to have increased chances of seroconversion. Most studies, though, on solid tumor cancer patients have demonstrated a different pattern, with seroconversion achieved for the majority of them after the standard two doses of vaccine. Furthermore, in many studies the minority of patients not seroconverting often had underlying hematologic disorders, as shown in a Danish series<sup>18</sup> and a French lung cancer series.<sup>19</sup> Admittedly, some of these studies have also demonstrated that seroconversion after the first dose is observed less often, and the overall antibody levels are lower in solid tumor cancer patients compared with the general population. A large Greek prospective cohort study, ReCOVER,<sup>20</sup> demonstrated seroconversion in 90.5% of solid tumor patients studied. Antibody levels were lower when compared with healthy controls, but still significant, and were positively correlated with female gender, younger age, non-smoking history, and breast or ovarian malignancy. These results were similar to those observed in an Israeli cohort,<sup>21</sup> with 90% seroconversion but at lower levels compared with controls. A slightly lower percentage of seroconversion was reported in another Israeli study,<sup>22</sup> with active chemotherapy correlating with non-seroconversion. A similar French study also demonstrated seroconversion in 95.2% of solid tumor cancer patients, but also observed a tendency for lower antibody levels and a delay in seroconversion (less than half converted at 3-4 weeks after the first dose).<sup>23</sup> These findings were further reproduced in another, larger, French study,<sup>24</sup> where metastatic disease and ongoing chemotherapy were prevalent characteristics of the 6% of non-seroconverters. Yet, seroconversion was observed (a joint US-Swiss study showed positive response to vaccination in 98% of solid tumor cancer patients,<sup>25</sup> a percentage reproduced in another US study as well<sup>26</sup>) and we now know that seroconversion is a reliable indicator of protection from infection overall. Additionally, an adequate and sustained cellular immune response has been documented in solid tumor cancer patients.<sup>27,28</sup> Recently, the Dutch VOICE study (Vaccination against COVID in Cancer)<sup>29</sup> evaluated the immunogenicity of mRNA 1273 vaccination in solid tumor cancer patients, mainly stage IV, but with life expectancy >12 months, demonstrating encouragingly adequate response rates in most participants after the second dose (93.1% for patients on immunotherapy, 88.8% for patients on chemo-immunotherapy, and 83.8% for patients on chemotherapy, compared with 99.8% for controls). Response after the first dose was inferior to that of controls, as with other studies. Importantly, the study also demonstrated that certain of the inadequate responders managed

to elicit a spike-specific T-cell response after vaccination. CAPTURE is a UK study on vaccination response of cancer patients,<sup>30</sup> with the majority of patients vaccinated with the AZD1222 (ChAdOx1) viral vector vaccine, in a period extending to the Delta variant dominance. Solid tumor patients retained neutralizing activity against the Delta variant after their second dose (albeit in diminished levels), roughly similar to a healthy cohort, and contrary to the profound immune response suppression observed in hematological malignancy patients. T-cell responses remained unaffected in all subgroups and to all variants though. A subgroup of patients in this study with SARS-CoV-2 infection before vaccination demonstrated a superior response, indirectly indicating that a third vaccine dose may act in a similar immunostimulant fashion. Thus, the initial target of a two-dose vaccine schedule (there are no data available for patients vaccinated with the single dose Ad26 vaccine) is adequately achieved, and long-term protection from severe disease and death can be expected.

There is, at the moment, limited experience with the use of a third dose in cancer patients. In an Arizona phase I trial,<sup>31</sup> administration of a third BNT162b2 mRNA vaccine dose in solid tumor cancer patients demonstrated a significant increase in median neutralizing antibody titer 1 week after the third dose (although in lower levels than those seen in healthy controls after the second dose). The researchers further observed that T-cell response was not augmented by the additional dose, and that, contrary to healthy individuals, SARS-CoV-2 specific memory B-cell frequencies did not correlate with the robustness of response to a third dose, indicating an underlying non-coordinated immune response in cancer patients.

So, could we offer this solid tumor cancer patients' third dose to the population of the developing world, which will be their very first dose?

Not exactly. First of all, the small but significant percentage of non-seroconverted cancer patients must be taken into account: this percentage of patients, reaching 16% in some of the aforementioned studies, are essentially as vulnerable as non-vaccinated individuals, and are furthermore high-risk patients for COVID-19 and death. Thus, these patients should be viewed as a priority for vaccination, even if this is their third dose. Can we differentiate which patients will be non-responders to the first two doses and offer a third dose just to them? Most studies have been inconclusive about risk factors for non-seroconversion in solid tumor cancer patients, and furthermore there is no unanimously accepted definition of adequate response, nor a specific time-frame for expected seroconversion (a delay in its appearance has been noted in some studies<sup>31</sup>). It is thus logistically and technically impossible to differentiate between patients, and moreover, the immune status of a solid tumor cancer patient may evolve according to new treatments necessary for him/her. But even if we focus on initial responders, whereas for the majority of breakthrough infections one may expect a benign disease course, for the solid tumor cancer patient, particularly one under active treatment, a breakthrough



infection is a major disruption for two reasons. Firstly, it will probably delay any therapeutic schedule, with potential consequences for the course of the patient's disease course. Secondly, it will impose further morbidity on a usually frail patient, potentially deranging other underlying pathology. Oncology patients are already surviving on a delicate balance and it is in everybody's best interest not to disrupt this equilibrium with a breakthrough infection.

In the long run, it is in the best interest of us all to end this pandemic, as soon as possible. There are many available models that predict the long-term impact of the pandemic in overall cancer mortality in the years to follow, after cancellations in routine screening, delays in early cancer treatment, and disruptions in therapeutic schedules.<sup>32</sup> Ending the pandemic though is not going to happen unless we address this issue globally: the oncology community should be at the forefront of vaccine equity, pursuing rapid vaccine access for cancer patients of developing countries, while promoting coordinated actions that will act against the emergence of novel viral variants and against further viral resurgences. This is the universal approach to end a pandemic, one that will allow oncology patients to deal with no further interruptions with their other ongoing pandemic.

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## DISCLOSURE

The authors have declared no conflicts of interest.

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