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Review

Should SARS-CoV-2 serological testing be used in the decision to deliver a COVID-19 vaccine booster? A pro-con assessment

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ABSTRACT

Anti–SARS-CoV-2 vaccination has saved millions of lives in the past few years. To maintain a high level of protection, particularly in at-risk populations, booster doses are recommended to counter the waning of circulating antibody levels over time and the continuous emergence of immune escape variants of concern (VOCs). As anti-spike serology is now widely available, it may be considered a useful tool to identify individuals needing an additional vaccine dose, i.e., to screen certain populations to identify those whose plasma antibody levels are too low to provide protection. However, no recommendations are currently available on this topic. We reviewed the relevant supporting and opposing arguments, including areas of uncertainty, and concluded that in most populations, spike serology should not be used to decide about the administration of a booster dose. The main counterarguments are as follows: correlates of protection are imperfectly characterised, essentially owing to the emergence of VOCs; spike serology has an intrinsic inability to comprehensively reflect the whole immune memory; and booster vaccines are now VOC-adapted, while the commonly available commercial serological assays explore antibodies against the original virus.

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1. Introduction

The deployment of Covid-19 vaccines began in late 2020. Following multiple vaccine doses and/or episodes of SARS-CoV-2 infection, a large proportion of the global population has now acquired long-term immune memory against SARS-CoV-2. However, viral genome drift (accumulation of mutations in the spike gene sequence) has led to the continuous emergence of new SARS-CoV-2 variants of concern (VOCs) that show immune escape, particularly Omicron and its descendent lineages that began circulating in late 2021 [1].

To cope with viral evolution and waning plasma antibody levels over time [2,3], most countries have issued booster recommendations, especially in high-risk groups. These booster doses enhance the immune response, particularly antibody levels, thus providing additional protection against Covid-19-associated hospitalisations and deaths. In addition, the use of adapted vaccines targeting more recent viral sub-variants (i.e., BA.4/5 in 2022, and XBB.1.5 sub-lineage in 2023) triggers the production of antibodies with higher affinity for the spike protein epitopes exhibited by these sub-variants [4].

As a proxy, the majority of studies on vaccine boosting strategies focus on enhancing these antibody responses. However, it is currently not recommended to perform spike serology to guide the decision to administer vaccine boosters. A test-and-booster strategy is recommended for other vaccines (e.g., hepatitis B) and, for certain population groups, to avoid unnecessary vaccination in individuals with natural immunity (e.g., hepatitis A). From this perspective, it is presently being debated whether this strategy may be pertinent for determining the need for Covid-19 vaccine boosters.

Given these premises, we aimed to review the different arguments for and against the use of quantitative anti-spike serology to identify people who should receive a Covid-19 vaccine booster.

2. Methods

The Vaccine Study Group of the European Society of Clinical Microbiology and Infectious Diseases (EVASG) gathers specialists involved in various aspects of vaccination, from immunologists to public health practitioners, from microbiologists to clinicians and from paediatricians and geriatricians to physicians caring for immunocompromised populations. EVASG members assessed the supporting and opposing arguments regarding the use of quantitative anti-spike serology to identify people who should receive a Covid-19 vaccine booster (regardless of general indications such as comorbidities). Three successive rounds of evaluation were performed: firstly, to identify any arguments; secondly, to determine whether the available research lends weight to each argument; and thirdly, to classify the arguments according to their weight. Pro and con arguments were classified thematically to allow all the stakeholders to appreciate their relevance before reaching a consensus.

The arguments are discussed below in the order of their weight of importance, beginning with those identified as the most relevant.

3. "Pros": Anti-spike serology may be used to identify the individuals who should receive a SARS-CoV-2 vaccine booster

3.1. Anti-spike antibodies are a relative correlate of protection against SARS-CoV-2 infection and severe disease

Anti-spike antibodies, particularly those with a neutralising effect (i.e., neutralising antibodies), have been shown to be protective against SARS-CoV-2 infection [5–14]. Known for other coronaviruses before the Covid-19 pandemic, this allowed the rapid development of spike-based vaccine candidates in the first quarter of 2020. In addition, this led to the use of monoclonal anti-spike antibodies, first as therapeutic and then as prophylactic agents, particularly in immunocompromised individuals. This link between anti-spike antibody levels and risk of severe disease has been reported in non-human primates [15] as well as in both immunocompetent [9] and immunocompromised [16] individuals. These observations led to the consideration that specific correlates of protection could be identified regarding anti-spike antibodies [17,18], and may lead to use spike serology, particularly neutralising antibodies, to identify the most suitable candidates for a booster dose.

The protective efficacy of anti-spike antibodies has been observed for both IgG and IgA antibody types. Several studies showed that despite similar levels of anti-spike IgG antibodies, individuals experiencing breakthrough infections had lower plasma/serum and/or mucosal anti-spike IgA antibodies compared with those not acquiring SARS-CoV-2 infection, suggesting that anti-spike IgA may be the more accurate correlate of protection against infection [19,20]. This observation may lead to propose determining anti-spike IgA antibody levels from plasma or mucosal specimens to guide vaccine boosting strategies.

3.2. In some situations, there is a correlation between binding antibodies and neutralising antibodies

Plasma-neutralising antibodies have been shown to be protective against both asymptomatic SARS-CoV-2 infections and severe Covid-19. Therefore, most of the considerations focus on neutralising antibodies as a correlate of protection. However, a strong correlation between spike-binding antibodies and neutralising antibodies has been reported in several studies [9,21–23]. Owing to this correlation, binding antibodies may be used to identify individuals who may benefit from a booster vaccination in a real-life setting, since they are easier and less expensive to detect than neutralising antibodies in clinical laboratory settings.

3.3. Serology allows the identification of immunocompromised individuals whose antibody levels have rapidly decreased

As previously observed for most vaccines, the waning of the anti-spike antibody plasma levels obtained after vaccination occurs more rapidly in immunocompromised individuals [24]. Monitoring antibody levels may therefore help identify those with the greatest decrease, and who should therefore be prioritised to receive a prompt booster. In addition, in some situations (e.g., solid organ transplant recipients [25], particularly those on belatacept [26]), patients may poorly respond to primary vaccination, so their antibody levels should be systematically checked after the first two or three doses. In particular, these subjects may receive prophylactic anti-spike monoclonal antibody in case of low or absent vaccine response (provided such antibody efficient against the circulating (sub)variants is available).

3.4. Other specific identifiable populations (apart from immunocompromised) may develop a low immune response.

Apart from immunocompromised individuals, certain conditions have been reported to be associated with a lower immune response to Covid-19 vaccines such as smoking [27,28], recreational drug use [29], influenza vaccine coadministration [30] or insomnia [31] and, in some studies [32] (but not others [28]), an elevated body mass index. Therefore, spike serology in individuals with these features would better characterise those needing an additional booster dose, even if the clinical correlates (i.e., higher risk of breakthrough infection) for each specific category are not defined.

3.5. A rational vaccine-allocating process is important in case of vaccine shortage

Identifying persons who may benefit from receiving a booster dose by not only considering predisposing conditions (e.g., immunosuppression, heart/lung comorbidities) but also assessing the existing anti-spike serology might help refine the strategies for allocating vaccine doses in compliance with the equity and efficiency of health resources. Different

theoretical models suggest that a serology-based strategy for vaccination may be more efficient from an operational and economic standpoint [33] and may maximise the benefits of Covid-19 vaccines [34].

3.6. Anti-spike serology may be used during pregnancy when considering antibody transfer to newborns

As observed with other antibodies [35], mother-to-foetus transfer of anti-spike IgG has been reported, and maternal-transferred anti-spike IgG has been shown to be protective against SARS-CoV-2 infection in infants [36]. Furthermore, infants have a higher antibody concentration if their mother receives a booster dose [37]. Assessing the antibody levels in pregnant women may therefore represent a means to estimate the need for booster administration and ultimately enhance protection in infants.

3.7. The "test-and-boost" policy is simple to explain

Proposing the use of serology before vaccination, at least in some populations, would be simple to explain, although communication strategies would need to target both physicians and the general population. In the early months of 2021, some health authorities recommended [38] that those with a past positive SARS-CoV-2 PCR or a positive SARS-CoV-2 antibody rapid test should only receive one vaccine dose for primary vaccination; these past recommendations aimed to ease the path to pre-boost serology. This concept has already been implemented for hepatitis B vaccination in solid organ transplant recipients: anti-HBs antibody level is already monitored to identify those needing a boosted vaccine dose. A similar recommendation for SARS-CoV-2 would probably be easily understood and implemented.

3.8. Vaccine administration in individuals with pre-existing high antibody levels may be associated with a lower response to the booster

Pre-existing humoral immunity modulates subsequent immune responses to mRNA boosters; in particular, higher anti-spike antibody levels before the vaccine booster in individuals primed with mRNA-1273 or BNT162b2 vaccines have been associated with a lower fold-increase in antibody levels after boost [39]. Experiments carried out in mice models suggested that this phenomenon may be due to pre-existing antibodies accelerating the clearance of vaccine-encoded antigen, thus limiting the amount of antigen available to de novo prime B cell responses [39]. Likewise, circulating antibodies from primary humoral responses have been shown to shape the recruitment of naive B cells to germinal centres during second antigen exposure [40]. From this perspective, the evaluation of spike serology may help identify individuals who are more likely to benefit from boosters (i.e., those with low anti-spike antibody levels), thus maximising the booster-elicited humoral response.

4. "Cons": spike serology should not be used to guide SARS-CoV-2 booster vaccination

4.1. An antibody level may result in different types of protection according to past immune stimulations (i.e., vaccine characteristics and dose(s), number of past infection(s), variants)

Currently, serological profiles are highly heterogenous, as they may reflect either or both i) repeated infections with different variants and ii) different vaccine doses, types and regimens [41,42]. Therefore, two individuals with the same binding antibody level may have antibodies with a very different affinity and variant specificity. Investigating whether and to what extent a possible immune correlate is affected or not by past immune stimulations (i.e., vaccine type and schedule, SARS-CoV-2 infection stratified by VOC) is necessary before basing any decision on binding antibody levels.

4.2. Correlates of protection are imperfect

Even if the role of anti-spike antibodies as correlates of protection from infection and severe disease has been largely evidenced, an exact cut-off value that would indicate whether a person is protected is unknown. This is mainly related to immune escape as shown by the continual emergence of VOCs. The mutations accumulated by these new strains led to the decreased affinity of pre-existing antibodies for the mutated spike; this "moving target" makes complex the task of determining a threshold for immunological protection. For example, the threshold (<264 binding antibody units (BAU)/mL) chosen in 2021 to identify individuals who should receive anti-spike monoclonal antibodies (first as therapeutic and then as prophylactic agents) was based on a 2021 study mainly with the Alpha VOC [43]. However, at this date, the Alpha VOC had already been replaced by the Delta VOC, meaning that this threshold had lost most of its relevance, which became even more marked when Omicron became the dominant VOC. This "moving target" behaviour was also illustrated by in vitro studies showing that monoclonal antibodies or natural post-vaccination antibodies lose their neutralisation potential every time a new VOC or SARS-CoV-2 variant of interest (VOI) takes over [44,45]. The efforts to establish a cut-off value for each new VOC or VOI have therefore been mostly inconclusive [46]. In a case-control study [47] of SARS-CoV-2 breakthrough infections in healthcare workers, there was no measurable difference between cases and controls in terms of post-vaccination neutralising antibody titres against the original SARS-CoV-2 and Alpha and Delta VOCs. In another study [48], the risk of breakthrough infection was different when considering different antibody levels for the Delta but not the Omicron VOC.

Aside from the difficulties in determining a threshold for immunological protection, some studies reported that post-vaccination spike-binding and neutralising antibodies did not decrease among individuals with breakthrough infections compared with controls, indicating that infection can still occur even in the presence of high antibody levels [47,48]. This observation suggests that anti-spike serology may not be a universal correlate of protection to support booster policies.

4.3. As serology methods differ, it may be complex to compare what is obtained with different methods

The use of different methods for IgG antibody detection may create challenges when comparing results and defining a cut-off value for protection [49]. Even if standardisation efforts have been made through the expression of antibody levels in binding antibody units per millilitre (BAU/mL) [50], the test performance of different assays and their correlation with neutralising antibody responses varies widely [51]. As a result, basing boosting strategies on a universally defined antibody threshold is still challenging owing to such heterogeneity. Moreover, IgG serology only reflects an incomplete part of the complex anti-SARS-CoV-2 humoral immune response; however, on this regard, the potential utility of anti-spike IgA antibodies as a correlate of protection to guide boosting strategies is hindered by the lack of standardisation of methodologies that quantify IgA antibodies, particularly from mucosal samples [52].

4.4. Spike serology does not account for cellular immunity

As expected, SARS-CoV-2-specific cellular immunity has been shown to be triggered by both infection and vaccination [53]. In addition, its role in protecting against Covid-19 has been evidenced, not only in the general population [54] but also in immunosuppressed people like kidney transplant patients [55]. Furthermore, as evidenced in haematopoietic stem cell recipients, strong spike-specific T-cell responses to vaccination may develop despite low seroconversion rates, thus contributing to the protection against severe Covid-19 [56]. A measure of anti-spike antibody levels may therefore take into account only a

limited part of immune protection.

4.5. Antibody thresholds required to protect against infection or disease are different

The protection associated with anti-spike antibodies differs when considering asymptomatic infection, symptomatic infection (Covid-19) or severe Covid-19, with the prevention of the first requiring a higher antibody level than the latter [9,43]. Therefore, deciding about the administration of a booster dose based on an antibody threshold requires determining which outcome is being considered for prevention: the infection itself or a severe disease course in the event of infection.

4.6. Current vaccines are VOC-adapted

In the autumn of 2022, mRNA vaccines tailored to the Omicron BA.1/2 and BA.4/5 VOCs were made available, with a further adaptation being made for mRNA and protein vaccines in 2023 with the spike sequence of the XBB.1.5 sub-lineage. When these updated vaccines are used as boosters, higher levels of neutralising antibodies against the corresponding SARS-CoV-2 VOC are achieved [57,58]. Vaccine effectiveness has been evidenced [59,60], even if there are ongoing concerns about immunological imprinting [61]. Since the current variant-adapted vaccines are designed to improve cross-reactivity or induce de novo variant-specific immune responses, spike serology performed with the commonly used commercial assays may not be suitable for a test-and-boost strategy, as they detect the original-type reactive antibodies and may thus not accurately reflect the actual levels of antibodies specific to the current circulating viral variants.

4.7. Decreasing antibody levels do not reflect a decrease in memory cells

Despite the waning of circulating binding and neutralising antibodies, memory B- and T-cells remain relatively stable for months after SARS-CoV-2 infection [62] and/or vaccination [63–65] and are resilient to VOC escape from humoral immunity [66]. Consequently, anti-spike serology may not entirely capture the complex scenario of long-term immune memory against SARS-CoV-2.

4.8. Pre-vaccination serology is limited by cost-effectiveness and infrastructural challenges

The cost-effectiveness of a test-and-boost strategy has not yet been specifically evaluated regarding the Covid-19 vaccination. Such studies have been conducted concerning vaccination against other pathogens such as hepatitis A and B viruses [67], highlighting that vaccinating without a screening protocol is more cost-effective, as the "screen-and-defer" vaccination strategy would reduce costs in some populations but at the expense of low effectiveness. Noteworthily, the cases for hepatitis A and B vaccination and Covid-19 vaccine boost are quite different, as only non-immune individuals are targeted for viral hepatitis. In some populations, particularly healthcare workers, serology may be performed before initiating occupational vaccinations. However, again, regarding measles, varicella or hepatitis B, only seronegative subjects receive a vaccination; meanwhile, SARS-CoV-2 serology would be used not to identify subjects without antibodies, but those with low plasma level. In addition, cost-effectiveness studies have been performed for the use of anti-spike neutralising monoclonal antibodies as pre-exposure prophylaxis for SARS-CoV-2 infection [68,69], although the case is very different and thus not directly applicable to this specific topic.

4.9. People receiving immunoglobulin products will have a positive spike serology

Anti-SARS-CoV-2 antibodies are detected in commercial preparations of polyclonal immunoglobulins used for supplementation or immunomodulation [70]. Therefore, in subjects receiving such treatment, spike serology is not a good correlate of individual immunity, as its positivity reflects the passive transfer of antibodies rather than immune memory.

5. Concluding remarks

Anti-spike binding and neutralising antibodies have been associated with protection from SARS-CoV-2 infection and particularly severe Covid-19, suggesting that anti-spike serology may be used to guide booster policies. A test-and-boost approach could hypothetically bring some advantages from an operational and economic standpoint and may help allocate vaccine doses in compliance with the equity and efficiency of health resources; through its simplicity, and its rather wide availability, binding serology could be considered a pragmatic tool. However, even if pre-vaccine serology is appropriate for some other viruses, based on the current state of knowledge, it does not seem appropriate to use serological assessments to determine who should receive a booster SARS-CoV-2 vaccine dose. The main factors hindering the application of a test-and-boost approach are as follows:

i) There is no reliable cut-off value for anti-spike antibodies as a correlate of protection due to both the technical heterogeneity of the different serological assays and the continuous viral antigen evolution leading to immune escape.
ii) The antibodies detected by serological assays may reflect very different past immune stimulations, with the resulting specificity being very heterogeneous between individuals; a certain value of anti-spike antibodies does not thoroughly reflect the whole SARS-CoV-2–specific immune memory, as it does not account for neutralisation capacity, T-cell immunity or immune recognition of viral variants.
iii) Only VOC-adapted vaccines are currently used as boosters with the subsequent enhancement of variant-specific antibodies, which may be inaccurately detected by the commonly used commercial serological assays that target the original virus.

However, spike serology may still be useful to identify those who respond poorly to vaccines or whose immune response wanes more rapidly than in the general population. This would help with proposing a booster dose closer to the last vaccine dose or using prophylactic monoclonal antibodies (when available).

Further clinical studies are needed to investigate whether certain populations may benefit from a serological-based approach to allocate booster vaccinations in times of shortage. Such studies should explore 1) the correlation between serological (binding) cut-offs and in vitro neutralisation and of 2) the correlation between antibody levels against a relevant form of spike (reflecting the appropriate, circulating SARS-CoV-2 (sub)variants) and the risk of different breakthrough infections (asymptomatic, symptomatic non severe, or severe) by this/these same (sub)variant(s). However, as already stated, the continuous roll-on of new VoC may limit the impact of such studies. Future research should also explore the cost-effectiveness of booster vaccination policies based on spike serology versus the general recommendations.

All authors attest that they meet the ICMJE criteria for authorship.

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Declaration of competing interest

Anna L. Goodman reports grants from Novavax to run vaccine trials and non-commercial funding from the INSIGHT network (NIH-TICO trial) to her institution outside of the submitted work; moreover, ALG is named on a patent AstraZeneca vaccine issued to the University of Oxford and has received personal financial contributions for this.

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All other authors have not conflict of interest to declare.

Data availability

No data was used for the research described in the article.

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