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The future for COVID-19 vaccines: public health assessment and perspectives based on scientific evidence

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SUMMARY

The development and use of messenger RNA-based (mRNA) vaccines against the SARS-CoV-2 spike protein have proven to be highly effective against symptomatic COVID-19, especially for severe forms. Since the declaration of a public health emergency in early 2020, however, the SARS-CoV-2 virus has continuously evolved, giving rise to several variants that have caused and continue to cause concern in the scientific community. Currently, viruses circulating worldwide belong to the Omicron lineage, with several identified sub-variants. In response to virus mutation, mRNA vaccines have been adapted into bivalent vaccines containing two mRNAs: one encoding the original Wuhan SARS-CoV-2 spike protein and one encoding the BA.1 or BA.4-5 spike protein of the Omicron sub-variant. This strategy is based on the hypothesis that the immune system's response improves when variants are included in the vaccine, leading to an increase in the magnitude and diversity of both the humoral and cellular immune response. The evidence gathered to date confirms the use of bivalent vaccines as the optimal strategy.

In the light of current knowledge, and in the awareness of the impossibility of making precise predictions on the evolution of the COVID-19 pandemic, as a group of experts we propose some considerations for the progressive evolution of vaccination against SARS-CoV-2 from pandemic to endemic vaccination.

Keywords: Covid-19, vaccines, public health.

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BACKGROUND

The pandemic caused by SARS-CoV-2 is evolving in a new epidemiological scenario. The emergence of new variants as an attempt by the virus to escape human immunity developed through both vaccines and natural infections, goes along with a trend to acquire a more stable genetic and antigenic form, that, however, SARS-CoV-2 has not yet reached.

Indeed, in many regions of the world, the circulation of the virus is stably high, due to inadequate control measures. Therefore, SARS-CoV-2 evolution remains uncertain, and the genetic and antigenic characteristics of future variants cannot be predicted [1].

Recently, new strains of SARS-CoV-2 have raised concern among scientists, as one or more of the identified Omicron sub-variants could cause new COVID-19 epidemic waves during autumn and winter seasons, and even during warmer seasons, like the wave that was recorded in July 2022 [2].

The most effective tool to finally overcome the health emergency is the vaccine. A joint effort is still needed to modulate the vaccination strategy through vaccination campaigns, active calls targeting fragile categories, and the involvement of all professionals that work close to patients, such as general practitioners, pediatricians, specialist doctors and pharmacists.

Vaccine protection against mild SARS-CoV-2 infections is guaranteed mainly by the presence of neutralizing antibodies (nABs). Differently from severe SARS-CoV-2 infections, immunogenic protection towards mild cases depends on the match between the virus strain contained in the vaccine and the circulating variant [3].

On the other hand, protection against severe infection is essentially generated by the T-lymphocyte response and by the reactivation of the immunological memory, providing cross-protection also against antigenically-distinct variants. This type of protection is therefore only to a minor extent influenced by a mismatch between the vaccine variant and the circulating variant.

Furthermore, the duration of T cell protection is apparently higher than that provided by antibodies, due to both the generation of long living memory cells and the capacity of virus-specific T lymphocytes to exert different functions at the same moment [4, 5].

After the primary vaccination with the ancestral strain, or even a booster of an adapted vaccine, high protection against mild infections caused by the newly circulating variants cannot therefore be expected. However, data showing protection against severe infections, regardless of the variant, is now established.

Despite the need to develop vaccines specifically targeting the Omicron variant, it is important to point out that the original mRNA vaccines partially retained the ability to prevent asymptomatic or pauci-symptomatic infections [6]. Consequently, the original vaccine still had an impact on Omicron's high transmission and infection capacity, even if this variant has several mutations of the spike receptor-binding domain.

It needs to be emphasized that the primary goal of vaccination against COVID-19 is to reduce hospitalizations, severe illness and deaths due to SARS-CoV-2, thus reducing the impact on population health and on the healthcare system.

The present paper reports a short literature review and a set of considerations with regards to the future of SARS-CoV-2 vaccination, by a group of Italian experts in infectious diseases, vaccinology, immunology, public health and communication. The literature review was conducted on Pubmed and was based on high quality secondary publications (systematic reviews and meta-analysis) focusing on the monovalent mRNA vaccine against SARS-CoV-2, and on the high-quality scientific papers evaluating the bivalent mRNA vaccine against SARS-CoV-2 published up to December 2022. The group of experts participated in a structured discussion on the published literature and on the role of the bivalent vaccine against SARS-CoV-2 in the Italian scenario, during an in-person meeting held in Rome in October 2022, and carried on the subsequent discussion and the preparation of the manuscript from remote.

SCIENTIFIC EVIDENCE

In the absence of a correlation to protection, and considering the fast-changing epidemiology of the virus, the best indicator of the benefit achievable with vaccines is the measurement of vaccination effectiveness (VE). VE indicates the efficacy of the vaccine used in a real-life setting and can be measured with different epidemiological study designs by comparing the frequency of cases

and/or of different outcomes in vaccinated individuals to unvaccinated population.
The administration of the original virus (Wuhan) vaccine as a booster dose has been shown to confer high levels of protection against severe disease outcomes for all variants, including Omicron:

- A comprehensive analysis of efficacy and effectiveness data for mRNA vaccines against SARS-CoV-2 indicates that, more than 17 weeks after administration of the first booster dose, VE against severe COVID-19 exceeds 75% [7].
- Similarly, the first available VE data from the second booster dose are encouraging: in a large cohort of nursing home residents, the second booster dose of mRNA vaccine demonstrated a VE towards severe forms of COVID-19 of 74% at 60 days after administration [8].
- Among 1,077 adults with immunocompromising conditions analyzed by the Centers for Disease Controls and Prevention (CDC), a VE of 88% (95% CI=81%-93%) was shown among those who received a third dose to complete a primary series [9].
- In Italy, VE in preventing cases of severe disease during the period of Omicron variant prevalence is 82% in subjects vaccinated with an additional/booster dose. More in detail, the age-standardized hospitalization rate (population ≥12 years) in the period August-September 2022 for the unvaccinated is 43 hospitalizations per 100,000 inhabitants and is 3.5 times higher than for those vaccinated with an add-on/booster dose, in whom it is 13.6 hospitalizations per 100,000 inhabitants [9].

Although effectiveness data confirm the importance of booster dose administration even with the original vaccine, several variants of SARS-CoV-2, the Variants of Concern (VoC), showing increased transmissibility and immune escaping, have emerged since the beginning of the pandemic [11, 12].
Omicron and its sub-variants are the most antigenically divergent from the original variant. These, as possible future variants, or emerging sub-variants, may cause significant morbidity and mortality even in vaccinated and/or previously infected subjects [1].
These observations led to the development of bivalent mRNA vaccines as an optimal approach to induce a more potent, long-lasting, and broad immune response against SARS-CoV-2. The bivalent booster dose strategy is based on the hypothesis that the immune system's response improves when more than one variant is present in the vaccine. This characteristic leads to an increase in the magnitude and diversity of both the humoral and cellular immune response [13].
In addition to the mRNA sequence coding for the Omicron strain spike (BA.1 or BA.4/5), the presently available bivalent mRNA vaccines keep in the formulation the mRNA sequence coding for the Wuhan strain spike protein and add the mRNA sequence coding for the Omicron strain spike (BA.1 or BA.4/5). Recent data demonstrate the advantages of the bivalent mRNA vaccine strategy:

- Cross-neutralization of different VoCs (Beta, Delta and Omicron) consistently observed both with the first candidate, the bivalent vaccine containing Wuhan strain and Beta strain (non-market formulation), and with bivalent vaccines containing Wuhan strain and Omicron sub-variants [13-15].
- Early studies also showed that the antibody response induced by the bivalent vaccines was of superior magnitude and characterized by longer persistence than that induced by the monovalent formulation [13-15].
- Preliminary data suggest that booster with a bivalent vaccine containing strains 'unseen' by the immune system stimulates the germinal center response and engages naïve B cells, which produce B cells towards the variants. With an Omicron-specific monovalent, neither the same enhancement of B-cells nor the same cross-reactivity was evidenced, but simply the production of specific memory cells for the variant included in the formulation [16].

From an immunological point of view, there are two lines of defense, an immediate one consisting of antibodies, and a more long-lasting one consisting of immunocompetent cells. Seasonal bivalent vaccine might boost humoral immunity and broader the cross-protection against both circulating and new strains that could potentially appear in the future.

RECOMMENDATIONS

- The primary aim of vaccination against COVID-19 is to reduce the disease burden caused by SARS-CoV-2, with reference to severe forms, hospitalizations and deaths.

- In view of the evolution of the SARS-CoV-2 virus and the heterogeneity of the population in relation to vaccination status and/or previous infections, we recommend that the anti-COVID vaccine dose be intended as a seasonal vaccination. Considering that the seasonality of SARS-CoV-2 still needs to be defined, the frequency of the seasonal dose remains to be determined (annual, biennial, or other).
- For seasonal COVID-19 vaccination we recommend the administration of the bivalent formulation mRNA vaccine.
- Seasonal vaccination with a bivalent vaccine should be administered at least 120 days after a previous dose (of any SARS-CoV-2 vaccine) or diagnosed SARS-CoV-2 infection. The optimal extended interval will be further evaluated by balancing advantages and disadvantages.
- We recommend the inclusion of seasonal vaccination against COVID-19 in the vaccination calendar for the population aged 60+ and for all those with fragile conditions (co-morbidities) regardless of age.
- SARS-CoV-2 is highly circulating in the pediatric age bringing to a significant disease burden in this population group. There is an urgent need for a concrete scientific discussion about promoting an active offer of the vaccine in the pediatric age in the most effective way, despite the difficulties that this would entail also in organizational terms.

Conflicts of interest

MA received research grants and personal fees for collaborations, for preparing educational material, and for lectures from Gilead Sciences, Janssen-Cilag Tibotec, Viiv Healthcare, Merck Sharp and Dohme, Abbvie, Angelini, Menarini, Pfizer, Moderna and Astra Zeneca.

PB received grants for epidemiological and HTA research from different vaccine companies (GSK, MSD, Sanofi Pasteur, Pfizer, Seqirus, Astra Zeneca) and fees for taking part to advisory boards or educational events on different vaccines from the same companies and from Janssen and Moderna.

AC received research grants and personal fees for collaborations, for preparing educational material, and for lectures from ViiV Healthcare, Menarini Biomarkers Singapore, Moderna, Beckman Coulter, Thermofisher, Sony Biotech, Miftek and Bio-Rad.

GG received personal fees for advisory board membership and consultancy from Emergent BioSolutions, the GSK group of companies, MSD, Merck, Pfizer, Sanofi Pasteur Italy, Moderna and Seqirus, as well as personal fees for lectures from MSD, Pfizer, and Seqirus.

FG received support for participating in MSD and Moderna meetings.

AG has been a member of advisory boards and was invited speaker at regional, national and international congresses for MSD, Novartis, Moderna.

GI received funding for scientific advisory boards, travel, and speaker honoraria from Pfizer, GSK, MSD, Sanofi Pasteur and Seqirus.

PL has been a member of advisory boards and was invited speaker at regional, national and international congresses for GSK, MSD, Moderna, Pfizer, Sanofi, Seqirus.

FV has been a member of advisory boards; has obtained grants for epidemiological studies and was invited speaker at regional, national and international congresses for GSK, Pfizer, MSD, Sanofi, Seqirus, Moderna, Janssen, AstraZeneca.

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