Variant-adapted COVID-19 Vaccines. Where Are We? (10/10/22)

Multidisciplinary Collaborative Group for the Scientific Monitoring of COVID-19

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1. Status of SARS-CoV-2 Evolution, Current and Future Variants

Omicron BA.4 and BA.5 subvariants remain dominant in most regions worldwide - in Catalonia, BA.5 accounts for around 80% of cases (the remaining 20% is mostly BA.2 and BA.4). However, Omicron subvariants have continued evolving and accumulating mutations, particularly in the receptor binding domain of the Spike protein. The result is the **simultaneous rise of multiple descendants of Omicron BA.2 and BA.4/5**, sharing common mutations that allow the virus to better escape recognition by neutralizing antibodies (a process called convergent evolution). For example, BA.2, BA.4 and BA.5 subvariants with convergent mutations including at position 346 (Arg346) have been identified in several countries (1).

These **new subvariants** (Figure 1A) include:

- BA.2.75.2, showing a high antibody escape profile (2)
- BA4.6, growing in the US (3)
- BA5.2.6 and its derivative BQ.1.1, presenting additional mutations that can make it highly antibody-evading (4); detected in multiple countries around the globe.
- BA.5.2.1.7 (also named BF.7), rising in frequency in the US and other countries such as Denmark, France and Belgium (5),where it already accounts for over 20% of cases.
- XBB, a hybrid of two BA.2 variants, recently reported to be more antibody-evasive than any of the above (4).

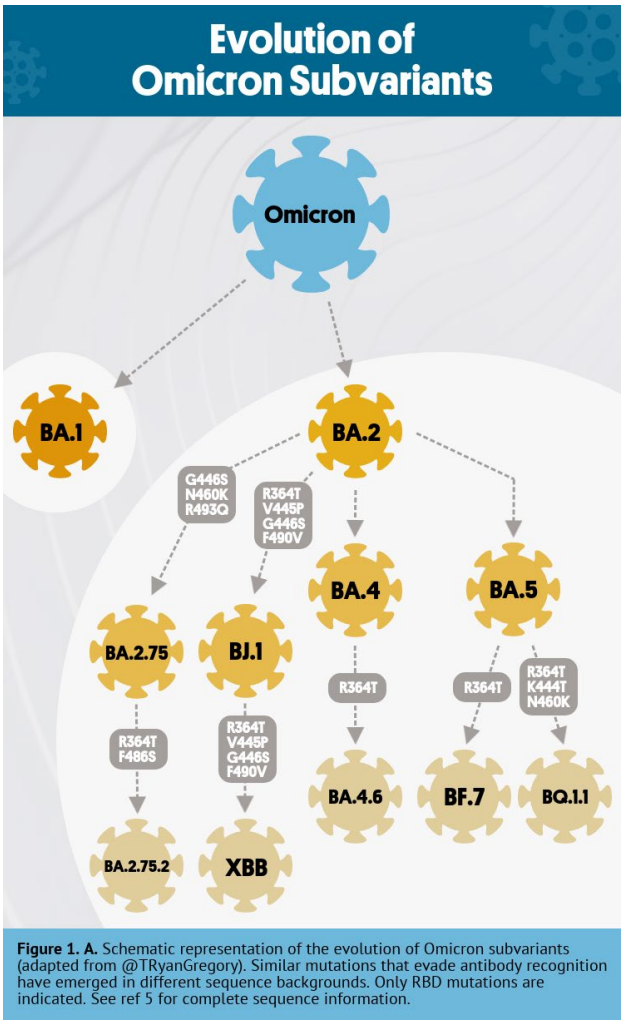

Figure 1. A. Schematic representation of the evolution of Omicron subvariants (adapted from @TRyanGregory). Similar mutations that evade antibody recognition have emerged in different sequence backgrounds. Only RBD mutations are indicated. See ref 5 for complete sequence information.

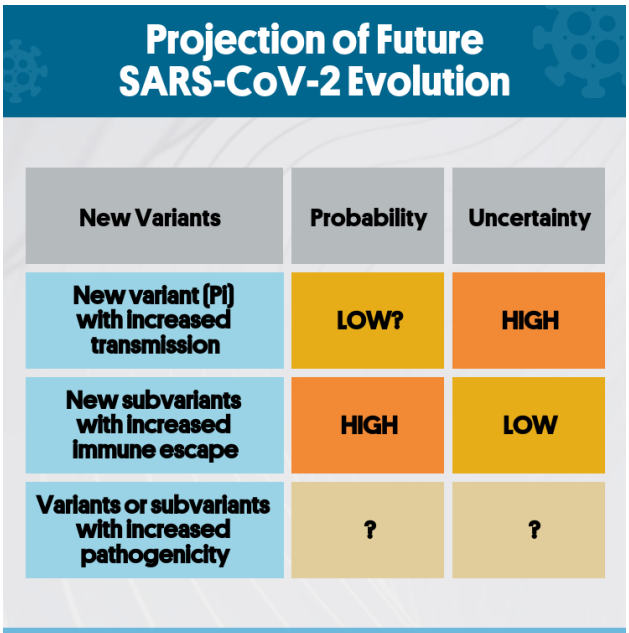

Figure 1. B. Projection of future SARS-CoV-2 evolution. There is high uncertainty regarding the emergence of a new VOC (Pi) and on the pathogenicity of new variants or subvariants.

Many countries have reduced their viral sequencing efforts over the last months, and the next major variant of concern (Pi) could already be circulating somewhere in the world. However, the current situation suggests that **the upcoming Covid wave(s) will be fuelled by multiple Omicron subvariants** that are rising and circulating simultaneously, and that present mutations that allow them to better escape immunity elicited by vaccines or previous infections. Which subvariants take over in each country or region will likely be dictated by the **local immune context** (i.e. vaccination coverage, number and type of booster doses, percentage of people infected with previous variants). Moreover, the potential pathogenicity of emerging variants or subvariants is hardly predictable (Figure 1B). Although they will likely be controlled by cellular responses induced by vaccines or previous infection, a change in viral tropism cannot be ruled out.

2. Immunogenicity and Efficacy of Variant-adapted COVID-19 Vaccines (Mono and Bivalent)

Until September 2022, all vaccines administered worldwide (primary series and booster doses) were made with the original Wuhan strain. For the next boosting campaigns this coming autumn/winter, many countries will start using **variant-adapted vaccines** developed by different vaccine manufacturers to better match the circulating SARS-CoV-2 variants.

a) Bivalent mRNA vaccines with Wuhan + BA.1 Spike

Both Pfizer and Moderna developed bivalent vaccines, including both the original and Omicron BA.1 Spike mRNA sequences. These vaccines were approved by EMA (6) on September 1, 2022, based on clinical data on their safety and immunogenicity (7). They have been authorized for use as booster in people aged 12 years and above who have received at least a primary vaccination against COVID-19. The original vaccines are **still recommended for primary vaccination**. Although BA.1 is no longer circulating (it was displaced by BA.2 and BA.4/5 subvariants), experimental data indicate that boosting with the BA.1 bivalent vaccine enhances immunogenicity and protection against BA.5 and other related subvariants (8).

b) Bivalent mRNA vaccines with Wuhan + BA.5 Spike

Given that Omicron BA.4/BA.5 rapidly displaced BA.1 worldwide, Pfizer and Moderna developed a bivalent vaccine including the original and Omicron BA.5 mRNa sequences (BA.4 and BA.5 Spike are identical). Pfizer's BA.5 bivalent vaccine was approved by the EMA on September 12, 2022, based on preclinical data plus clinical data on the BA.1-adapted vaccine (9). This BA.5 adapted vaccine is expected to be more effective than the original or bivalent BA.1 vaccine in triggering an immune response against BA.4 and BA.5 subvariants. Again, this bivalent BA.5 vaccine is **to be used as booster and not as primary vaccination**, and should be offered in priority to people who are at most risk of severe disease.

Bivalent vaccines retain the original version of Spike to ensure protection against a broader variety of VOC. No safety concerns have been observed with bivalent vaccines (7), which contain the same total mRNA quantity as the original booster doses (50ug for Moderna, 30ug for Pfizer).

c) Other variant-adapted vaccines

Alpha/Beta bivalent vaccine. The Hipra vaccine is an adjuvanted recombinant protein vaccine that includes the receptor binding domain of the Alpha and Beta variants of SARS-CoV-2. It has shown good safety and tolerability in primovaccination regimen (10), and, when used as a heterologous booster dose, it induced a potent and more sustained

neutralising antibody response against all variants studied,including Omicron BA.1 (11). More recently, the company announced results showing an increase in neutralising antibodies against BA-2, BA.4 and BA.5 subvariants in people boosted with this bivalent (Alpha/Beta) vaccine (12). This vaccine is under evaluation by EMA for authorisation to use as a booster.

Monovalent BA.5 vaccine. In addition to bivalent vaccines, Pfizer and Moderna are also developing a monovalent BA.4/5 vaccine. Although preclinical studies show improved responses to the different Omicron subvariants compared to bivalent vaccines (13), the vaccines are not yet approved by EMA.

Expected impact of variant-adapted vaccines.

There is a large volume of evidence on the **benefits of a booster dose** with ancestral vaccines. However, a direct comparison of ancestral and bivalent boosters shows that the latter further improve the neutralizing responses elicited by ancestral vaccines and may therefore confer higher protection against symptomatic infection.

A recent mathematical model attempted to measure the extent of this benefit (14). This study suggests that the **added protection of variant-adapted vaccines to protection** will be much higher in populations with low levels of neutralizing antibodies (elderly, immunocompromised), while a low impact is expected for the general population.

In summary, all booster vaccines generate a higher level of neutralzing antibodies against the newest circulating variants, even against those that do not fully match the vaccine sequence. This is due to the beneficial impact of any booster dose (ancestral or variant-adapted) on the diversity of the antibody repertoire (15).

d) "Pancoronavirus" vaccines

This pandemic has greatly underscored the urgent need to develop universal coronavirus vaccines that confer broad protection not only against all SARS-CoV-2 variants but against other coronaviruses (16). While a universal vaccine against all coronaviruses may not be realistic, a vaccine targeting SARS-like betacoronaviruses is a more achievable objective. However, **further research is needed** to identify the best viral antigens, vaccine platforms and administration routes to achieve robust, durable, and broadly protective immunity against the diverse and highly adaptive family of betacoronaviruses. The CEPI coalition has awarded almost 200 million USD to 11 institutions or companies that are exploring different ways of developing broadly protective vaccines that could prevent a future coronavirus pandemic (17). Some candidates, including one developed by Caltech, have given promising preclinical results (18).

3. Current Boosting Strategy in Catalonia

Starting September 26, Spanish health authorities (19) are offering an **additional booster using the bivalent mRNA vaccines** (with BA.1 or with BA.5) to:

- Severely **immunocompromised patients** (the only group to have already received four doses)
- People aged **over 80**
- People living in l**ong-term care facilities and nursing homes**
- **Healthcare workers**, people working in long-term care facilities, in nursing homes, and caregivers of disabled people
- People aged **over 60**
- People **under 60 with underlying risk factors** such as diabetes mellitus, morbid obesity, chronic kidney disease, chronic cardiovascular disease, chronic pulmonary disease, chronic liver disease, chronic inflammatory diseases, asplenia, severe neurological and neurodevelopmental disorders (Down syndrome, dementia,…), cerebrospinal fluid fistula, haematological diseases, celiac disease, cancer, and cochlear implant
- **Pregnant women** at any stage of pregnancy, and women up to 6 months postpartum
- People **living with immunosuppressed patients**

Coadministration of the seasonal influenza vaccine and the COVID-19 booster is recommended and may increase programme efficiency. No interference in the immune response or safety issues have been described with the simultaneous administration of both vaccines (20).

The **prevalence of natural infection** is high among the population, particularly after the Omicron waves. This is relevant since the timing between infection and vaccination determines the reponse to booster doses. In fact, vaccination early after infection (<180 days) results in suboptimal immunogencity (21). Therefore, **at least five months should have passed after the last booster or infection**. However, considering the low immune responses of severely compromised individuals, **for the first two groups and for people living in nursing homes, the minimal period between previous infection and vaccination is reduced to 3 month**s.

Importantly, depending on the evolution of circulating viral variants and of the epidemiological situation, a second booster could be justified for the rest of the population, especially for those who do not have hybrid immunity (vaccination plus infection with Omicron or previous variants).

4. Conclusions

- A **new wave is expected this coming fall/winter**, fuelled in part by increased social mixing and in part by the spread of multiple emerging Omicron subvariants that are more immune evasive than BA.2 or BA.4/5.

- Which **subvariant(s)** take over in each country or region will likely **depend on the vaccination coverage and infection history** of the local population.

- The decrease in vaccine effectiveness over time and the higher immune evasion properties of emerging Omicron subvariants justify the **need to administer a second booster in people at high risk of severe disease**.

- Although boosters containing BA.5 are expected to be the most effective against currently circulating subvariants, **any type of booster vaccine** (original, bivalent BA.1 or other variant-adapted vaccines not yet approved) **will provide additional protection.**

- For the upcoming booster campaign, **we recommend**:

    - For the **general population**: **increase coverage of the third dose** (first booster) with the original vaccine or, if available, with variant-adapted vaccines. In Catalonia, current coverage is high (90%) in people >70 years old, but it drops to 66% in those aged 45-59 years (22).
    - For **those with greater risk of severe disease** (aged over 60 or with risk factors): **offer an additional booster (fourth dose)**, preferably with the new bivalent vaccines including BA.1 or BA.5.
    - **Wait for at least five months between last infection or boost** before getting a new booster dose (3 months for immunosuppressed people, people aged over 80 and people living in nursing homes).
    - **Bivalent vaccines are as safe as monovalent vaccines** and the booster can be given together with the flu vaccine.

- Until a high booster coverage is achieved, **the general use of facemasks in healthcare centers, nursing homes and public transportation should be maintained**, and people displaying respiratory symptoms should stay at home if possible, or use a facemask in public places.

- **Primary vaccination with original vaccines is strongly recommended** for all eligible ages (from age 4 onwards, according to current guidelines).

- Supporting and maintaining **viral surveillance efforts** in each country or region is key for the prompt identification of viral variants/subvariants with potential impact on diagnosis, vaccine strategies or treatment.

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Multidisciplinary Collaborative Group for the Scientific Monitoring of COVID-19 (GCMSC)

The GCMSC is a group of experts from different disciplines and research backgrounds, whose specialities are relevant to the COVID-19 context. It was formed by the Barcelona Institute for Global Health (ISGlobal) and the Barcelona Medical Council (COMB) in collaboration with the Catalan Association of Research Centres (ACER)—three complementary institutions dedicated to health research and the translation of research findings to society as a whole.

The group, which came together for the first time in September 2020, aims to follow the scientific evidence regarding the pandemic in order to guide technical and political decisions in the COVID-19 response through reports that can be consulted by authorities, private entities and the society as a whole.

More information: https://www.isglobal.org/en/gcmsc