EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Medicines Agency

Scientific Advice from the Medical Device Expert Panels

Mandate[1] & Advice to the MDCG

[1] According to the section 6.3 of the Rules of procedure of the European Commission expert panels on medical devices and in vitro diagnostic medical devices.

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1. Administrative information

Party requesting the advice

The Medical Device Coordination Group (MDCG)

Legal basis for the request

Article 106 (10) (a) and (b) of Regulation (EU) 2017/745 on medical devices.

Timelines for providing the advice

Start of the advice procedure: 8 July 2024

Advice to be sent to ECDC for comments: by 8 September 2024

Comments from ECDC received on 28 October 2024

Advice delivered to MDCG: by 8 Nov 2024

Relevant medical field and areas of competence required

In vitro diagnostic medical devices, virology, SARS-CoV-2, respiratory viruses, infectious disease epidemiology.

Specific thematic panel or panel sub-group best suited to address the request for advice (if applicable)

In vitro diagnostic medical devices (IVD)

Complexity of the request according to the criteria established in Table 2 of the Commission Implementing Decision (EU) 2019/1396 Annex

☐ Category I — simple matter
☒ Category II — complex matter
☐ Category III — very complex matter

Consultation or collaboration with other scientific bodies for the preparation of the advice (if necessary)

The European Agency for Disease Prevention and control (ECDC) is to be consulted on the draft advice.

2. Scientific context and background information

The disease COVID-19 caused by the SARS CoV-2 virus was declared a pandemic in March 2020 by the World Health Organization. The severity of the clinical forms and the speed of propagation of the virus in the population led the MDCG to consider SARS-CoV-2 as an agent causing life-threatening disease with a high risk of propagation, notably with regards to the definition of 'life threatening' and considerations around 'high risk of propagation' provided in the IVD classification guidance MDCG 2020-16. Therefore, in the context of classification of in vitro diagnostic medical devices (IVDs) according to Annex VIII of Regulation (EU) 2017/746, the MDCG included it as an example of infectious agents under Rule 1 2nd indent in the MDCG 2020-16 guidance, so that IVDs that detect the presence or exposure to SARS-CoV-2 would generally be classified as class D.

Since 2020, many tests with different designs have been placed on the EU market, such as direct detection tests (NAT, antigen) and indirect tests (intended for detection of antibodies, neutralizing or not).

Now, four years after the virus emerged, it continues to circulate in communities and remains a potentially serious risk to human health, albeit less so than previously. An infection with SARS-CoV-2 may also have significant long-term health impacts on a number of patients (long or post COVID). The MDCG wishes to re-evaluate whether the epidemiological criteria mentioned in Rule 1 2nd indent still apply to SARS-CoV-2 in the current context. If this is no longer the case, the MDCG needs further scientific elements to determine which risk class should apply to each type of SARS-CoV-2 IVD depending on the relevant classification rules in Annex VIII of Regulation (EU) 2017/746.

The opinion of the panel of experts is therefore requested on the various scientific questions related to SARS-CoV-2, as well as more generally on respiratory viruses, in the context of the classification rules in Regulation (EU) 2017/746.

Relevant rules from Annex VIII of Regulation (EU) 2017/746:

Rule 1 2nd indent:

Devices intended to be used for the following purposes are classified as class D:

[…]

— detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation; […]

Rule 3 (c) and (e):

Devices are classified as class C if they are intended:

[…]

(c) for detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring;

[…]

(e) for determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; […]

Rule 6:

Devices not covered by the above-mentioned classification rules are classified as class B.

3. Scope of the advice

Addressing the following questions:

1. On which basis could it be concluded that a respiratory infectious agent should be considered as causing a life-threatening disease? According to that basis, should SARS-CoV-2 be considered as causing a life-threatening disease?
2. On which basis could it be concluded that a respiratory infectious agent should be considered of high or suspected high risk of propagation? According to that basis, should SARS-CoV-2 be considered of high or suspected high risk of propagation?
3. Is there a significant risk that an erroneous result of a device intended to detect SARS-CoV-2 would cause death or a severe disability to the individual, foetus or embryo being tested, or to the individual's offspring?
4. Is there a risk that an erroneous result of a device intended to detect neutralising antibodies against SARS-CoV-2 would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring?

4. Advice provided by the IVD Expert Panel

4.1 On which basis could it be concluded that a respiratory infectious agent should be considered as causing a life-threatening disease? According to that basis, should SARS-CoV-2 be considered as causing a life-threatening disease?

A respiratory infectious agent can be considered as causing a life-threatening disease based on several key factors (mortality rate, severity of symptoms, complications, transmission rate, and epidemiological data) (CDC COVID Data Tracker; Huang et al., 2022; Zhang et al., 2020; WHO Mortality Database). One can assume that respiratory viruses in general, have the potential to be highly transmissible, and some of these respiratory viruses, like influenza, RSV and SARS-CoV-2 have the ability to generate a life-threatening disease in specific populations. In general, these populations are the elderly (above 60 years of age), and individuals with a specific underlying disease, as well as the very young i.e. in RSV infections.

In that context, SARS-CoV-2 meets the criteria to be considered as causing a life-threatening disease. The past impact of COVID-19 on global health, both in terms of direct mortality and long-term complications, underscores its seriousness as a life-threatening respiratory infection.

In the case of SARS-CoV-2, it has been shown to have a high pandemic impact because the human population had not previously been in contact with this virus all over the globe. The subsequent ability of this virus to infect humans with the ability to transmit between humans, has resulted in the global circulation of the virus. As a result of a virus with a RNA genome, one can also understand that due to the lack of genetic proofreading, genetic changes resulted in replacement of SARS-CoV-2 variants/clades during the subsequent years and did replace the previous clades in time. The dominant virus that emerged can only become a successful and dominant strain, if the replication efficiency is not reduced compared to the previous strains. Also, virulence and fitness of the virus in the population is relevant. Furthermore, antibodies against the virus due to a natural infection or vaccination, may also influence genetic changes of the virus.

Due to these genetic changes, sequentially several variants did arise; Alpha variant B.1.1.7 or British variant, Beta variant (B.1.351 (South African variant), Gamma variant P1 (Brazilian variant), Delta variant B.1.617.2 (Indian variant). All of the above variants are not detected anymore and finally were replaced by the Omicron variant B.1.1.529. This variant did spread globally very fast and replaced the previous ones. Also, it was observed that this Omicron variant has many mutations in the so-called spike protein against which the initial vaccines were directed. As it was assumed that this would impact the efficacy of vaccines, since their introduction, vaccines were continuously updated in line with evolving SARS-CoV-2 variants.

The current strains of SARS-Cov-2 are all genetic descendants of the initial Omicron strain B.1.1.529.

It remains important to put transmissibility and severity into the right perspective, whether for the individual patient or for the Public Health risk. Therefore, epidemiological data are necessary (death rate per age, hospitalization).

From the data collected over the years and focusing on the information available for the last and the present calendar year, the weekly age-adjusted COVID-19 death rate per 100K population, has decreased dramatically to very low levels, (source CDC, August 10, 2024). The number of weekly COVID-19 deaths reported to WHO indicate for the different regions of the world, including Europe, a dramatic decrease of SARS-CoV-2 related mortality after May 2022 (Source: https://data.who.int/dashboards/covid19/deaths?n=o). This is explained by appearance of the Omicron variant characterized by lower pathogenicity combined with population immunity generated by vaccinations and infections. There is a distinct population at risk for serious infections and complications,

like post COVID-19 condition symptoms. However, it is not possible to predict on a scientifically firm basis the potential future evolution of further SARS-CoV-2 variants and their potential interaction with the population immunity raised against past virus variants. In case of emergence of new highly virulent SARS-CoV-2 strains, "regulatory preparedness" regarding SARS-CoV-2 In Vitro Diagnostics would be more advanced compared to the beginning of the pandemic since basic regulatory instruments like Common Specifications have been developed and experience with comparative SARS-CoV-2 IVD evaluation has been gained.

A potential approach to define a respiratory agent with high transmissibility in the general population as "causing a life-threatening disease" could be based on a significantly increased excess mortality determined for the respective population(s) and caused by the agent. For agents with low transmissibility the infection to fatality rate could be taken into consideration. Actual data on the SARS-CoV-2 strains, infection rate, admissions in ICU with COVID, can be found in databases of WHO and CDC. In addition, current tracking of the virus using almost real-time data on the presence of the SARS-CoV-2 virus in sewage, is available in some countries (Dutch data by RIVM, Public Health Institute, www.rivm.nl/en/coronavirus-covid-19/current/weekly-update).

The conclusion is that SARS-CoV-2 can still give serious illness, but the infection does not any longer cause a life-threatening disease with significant mortality level in the general population. However, risk groups, including individuals with an underlying disease, immunocompromised patients as well as the elderly are nearly exclusively affected with severe disease. Since the immunity in most individuals prevents life-threatening courses of infection, for the present time we would not define SARS-CoV-2 as "causing a life-threatening disease".

4.2 On which basis could it be concluded that a respiratory infectious agent should be considered of high or suspected high risk of propagation? According to that basis, should SARS-CoV-2 be considered of high or suspected high risk of propagation?

Transmissibility is determined by the infectivity of the pathogen, the contagiousness of the infected individual, the susceptibility of the exposed individual, the contact patterns between infected and susceptible individuals, and the effect of environmental factors on the infectivity of the pathogen during transmission (Leung 2021). Furthermore, the mode of transmission, asymptomatic or pre-symptomatic transmission, viral shedding and the infectious period should be considered. Transmissibility is usually assessed by the estimation of the basic reproduction number (R_0) or secondary attack rate (SAR). R_0 is reproduction number at the start of an epidemic and represents the average number of secondary infections caused by a primary infection after its introduction to a completely susceptible population. If $R_0 < 1$, spread in the population is unlikely and the outbreak is contained. If R0 is >1, there is high risk of spread in the population. R0 >1 can be used as a threshold for risk of propagation within the general population as due to the exponential growth even slightly higher R values than 1 can be considered causing a high risk of transmission in the population.

Due to the immunological naivety of the world population early 2020, SARS-CoV-2 had the ability to easily spread within communities of different global geographic regions. This explosive expansion of infections in individuals with no pre-existing immunity resulted in large proportions of symptomatic disease, complications and mortality, which lasted for several waves of variants of the virus in 2020 until 2022. Although in all age group lives were lost; most at risk were the elderly (≥75 years of age) and those with underlying diseases and impaired immunity.

These new variants did have the ability of even higher propagation, but this is not the same as an increased disease severity. However, due to the vaccination campaigns and the increased immunity against the virus and its variants after a natural infection or vaccination, the transmission rates were reduced, and reproductive rate of the virus was significantly less due to at least interim reduction in susceptibility of exposed or vaccinated individuals. This resulted in lower infection rates with subsequent lower complications, hospital admissions and mortality, most notably in those at-risk individuals who were vaccinated.

Despite these developments, there is no doubt that SARS-CoV-2 is characterized by a high level of propagation. Though we are not aware of internationally agreed thresholds differentiating "high" from "medium" or "low", the risk of SARS-CoV-2 propagation is estimated as high, especially with potential future emergence of new variants escaping population immunity.

It also must be noted that there will be a population that will refrain from vaccination. The potential high risk of propagation of SARS-CoV-2 is obvious given the COVID-19 pandemic that spread the world since 2020. Its ability to spread rapidly, even among asymptomatic individuals, combined with its high reproduction rate R0, the role of human behaviour, and the mutational capacity of the virus all contributed to this. However, public health measures, such as vaccination, social distancing, mask-wearing, and ventilation, have been essential in mitigating spread of the virus, but its inherent intrinsic characteristics have not changed and make it a persistent and high-risk agent for widespread transmission. Previous immunisation of individuals by vaccination and/or natural SARS-CoV-2 infection may reduce but not prevent (re-)infections and/or transmissions.

4.3 Is there a significant risk that an erroneous result of a device intended to detect SARS-CoV-2 would cause death or a severe disability to the individual, foetus or embryo being tested, or to the individual's offspring?

In the general population, an erroneous result usually does not cause death or a severe disability to the individual. There is a risk of post-acute sequelae, but the infection prevention and vaccination are more effective than infection diagnosis. The potential impact of an erroneous result of SARS-CoV-2 infection diagnosis on development of long COVID is considered negligible since the etiology and course of the disease long COVID cannot be influenced by the diagnosis of the SARS-CoV-2 infection, irrespectively of whether the diagnosis is accurate or erroneous. Some key considerations on erroneous results are as follows:

- **Impact of False Negatives**: a false negative result can lead to a delayed diagnosis, delay the initiation of appropriate care or isolation measures, and affect the transmission risk. As such, undetected cases could lead to further community transmission, exposing vulnerable populations to the virus.
- **Impact of False Positives**: false positives may lead to unwarranted isolation in certain clinical settings (e.g., patients with impaired immunity), unnecessary follow-up testing, or unnecessary treatment.

In the current situation, the SARS-CoV-2 virus is still present and there have been numerous variants arising (in the last years, mostly relating to the Omicron variant). Genetic changes of the virus still do occur, and new variants do arise, however, with no indications that the recent variants are more virulent. The virus is now more endemically present. Risk groups for a more serious infection remain the same as before, however tools, such as vaccination, antiviral treatment options and supportive care have reduced their risk of severe course of disease and mortality.

The diagnostic assays generally used to detect an acute infection have a high sensitivity with a low risk of a false negative result. Assays based on nucleic acid amplification are the most sensitive assays available, followed by assays based on antigen detection. In patients with clinical symptoms of a SARS-CoV-2 infection, these assays have a high positive predictive value. We also must realize that molecular diagnostic assays have been adapted where necessary to enable a good detection of the viruses and their variants.

In relation to pregnancy, the risk of complication of an COVID-19 infection is low, but people who are pregnant or were recently pregnant are at an increased risk for illness from COVID-19 compared to those that are or were not pregnant. Furthermore, there is an increased risk of pre-term birth and stillbirth and an increased risk to other pregnancy complications. Therefore, vaccination is recommended. (Adhikari et al, 2020; Deng et al., 2022; Rahmati et al, 2023; Smith et al, 2022). However, it is also known that the risk of complications is lower since the Omicron variant appeared, and the infections were less severe.

In the current epidemiological context, the risk of an erroneous result from COVID-19 testing during pregnancy leading to severe outcomes for the foetus, such as death or disability, is influenced by the health of the mother, the vaccination status and the management of the pregnancy.

Clinical management of COVID-19 in pregnancy is, for the most part, the same as in non-pregnant patients. However, pregnant women are not being offered all therapies as is routine in non-pregnant patients (Vousden et al. 2022), even if pregnancy is not a contraindication for any of the supportive therapies. Antiviral treatment is indicated in pregnant women to prevent severe disease (World Health Organization 2023). A false negative diagnostic result could result in the patient receiving no or delayed treatment. There is little evidence of the possible effect of COVID-19 on early pregnancy (up to 12 weeks of gestation). However, in late pregnancy (more than 24 weeks of pregnancy), SARS-CoV-2, like other viruses, can increase the rate of adverse pregnancy outcomes such as foetal growth restriction, premature birth, and perinatal mortality (Abbasi et al. 2024). These results could indicate not knowing of the infection in the first and second trimesters, which could be due to false negative diagnostic result. (Ko et al. 2021) However, pregnancy did not increase the risk of death compared to non-pregnant females with COVID-19 (Abbasi et al. 2024).

A recent review (Stolojanu et al. 2024) emphasizes the importance of reliable diagnostic tests, particularly for detecting infections during pregnancy, including COVID-19. The main points of this review are:

- Early diagnosis is crucial: The review highlights that early and accurate diagnosis of infections like COVID-19 during pregnancy is essential for mitigating risks to both the mother and foetus. Early intervention can prevent complications such as preterm birth, foetal growth restriction, or developmental issues.
- Importance of accurate detection: Reliable diagnostic methods are needed to detect maternal infections promptly, ensuring that appropriate management strategies can be implemented to minimize risks.
- Impact on treatment strategies: The choice of treatment depends heavily on the accuracy of diagnostics, especially during pregnancy, when certain medications may pose risks to the foetus. Reliable tests allow healthcare providers to balance maternal and foetal safety effectively.
- Role in long-term monitoring: Diagnostics also play a key role in monitoring maternal and foetal health over time, to understand the potential long-term impacts of maternal infections on children.

Young children and adolescents have an increased risk of severe disease, especially in case of underlying disease or immunosuppression.

In summary, the risk that an erroneous result from a SARS-CoV-2 detection device (such as a nucleic acid-based assay, antigen test, or other diagnostic tools) would directly cause death or severe disability to the individual, foetus, embryo, or offspring is generally considered low. However, this assessment needs to be understood in two different contexts:

(1) Risk for the General Population: For the general population, an erroneous test result (either false positive or false negative) is unlikely to directly lead to death or severe disability. The most common outcome of an erroneous result might be unnecessary isolation (in the case of a false positive) or continued exposure to others (in the case of a false negative). For most healthy individuals, these scenarios, while inconvenient or potentially spreading the virus, do not usually lead to severe outcomes. The potential impact of an erroneous result of SARS-CoV-2 infection diagnosis on development of long COVID is considered negligible since the etiology and course of the long-covid disease cannot be influenced by the diagnosis of the infection by the IVD-kit, irrespectively whether the diagnosis is accurate or erroneous.

(2) Risk in Vulnerable Populations: In contrast, for specific vulnerable groups—such as pregnant individuals, the elderly, or those with underlying health conditions—the consequences of an erroneous result can be more severe. For example, a false negative result in a pregnant individual could lead to untreated COVID-19, which has been linked to complications such as preterm birth and, in rare cases, maternal and foetal mortality. While maternal COVID-19 infection should be taken seriously, the impact of a false negative result of SARS-CoV-2 infection during pregnancy on the fate of a foetus is considered considerably lower compared to the TORCH pathogens, and depends on the maternal health, vaccination status, comorbidities, stage of pregnancy and disease severity. A false positive result might lead to unnecessary stress or medical interventions.

4.4 Is there a risk that an erroneous result of a device intended to detect neutralising antibodies against SARS-CoV-2 would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring?

In the current situation, approximately four years after the start of the pandemic, most individuals have developed antibodies against the virus through a natural infection, or because of vaccination. Antibody detection is not a diagnostic tool to determine whether an individual is currently and actively infected with the virus. Even in those cases where the antibody assays would fail to provide a result in an infected individual, so providing a false negative result, this would clinically have no or limited implication, such as in immunocompromised individuals or in individuals with an underlying health condition with an impaired immune response. Diagnosis of an acute, current infectious episode is also not based on an antibody response against SARS-CoV-2. Assays measuring neutralising antibodies have been developed and used as potential surrogate marker for SARS-CoV-2 vaccine efficacy in respective clinical trials or for characterization of convalescent plasma donations used in clinical trials as potential therapeutic drug. Those assays detecting neutralising antibodies do neither play a role in routine diagnosis of patients nor are they used for predicting putative protection from infection. Furthermore, to our knowledge, there are no commercial serological assays available that measure neutralising antibodies specific for the different SARS-CoV-2 strains.

In conclusion, the ability to detect neutralising antibodies against the virus, has no impact on patient management, even when there is a life-threatening situation. The risks that an erroneous result from a device could lead to a life-threatening situation for a patient or their offspring is generally considered low.

5. Literature

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