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Anaesth Crit Care Pain Med 41 (2022) 101114

Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Editorial

# Update on rapid diagnostic testing for SARS-CoV-2

ARTICLE INFO

*Keywords:*
Covid-19
SARS-CoV-2
Rapid diagnostic tests

According to the World Health Organization (WHO), more than 400 million confirmed reported cases of COVID-19 and close to 6 million reported deaths are to be reported by the end of February 2022 [1]. In November 2021, a new variant of concern of SARS-CoV-2, named B.1.1.529 or Omicron, appeared in the Gauteng province of South Africa [2]. This variant rapidly became the most prevalent one in Europe, replacing the former Delta variant. The Omicron variant is known to have around 30 mutations in his Spike protein [3], which is the reason why an enhanced transmissibility has been observed. The question, which rapidly was raised, was what will happen with our testing strategy at that turning point of the pandemic?

In this context, *The New England Journal of Medicine* (NEJM) published an article on the 7th of January 2022, written by Dr. Paul K. Drain, about rapid diagnostic testing for SARS-CoV-2 [4], reviewing current guidelines on testing. Before analysing this article, it is important to first precise a definition. The rapid diagnostic tests (RDT) as defined by Dr. Drain include either a molecular test (molecular nucleic acid amplification tests that detect viral gene targets) or an antigen-based immunoassay (that detect domains of the surface proteins). However, in current daily medical life and especially in Europe, RDTs is a term that is often used solely for antigen-based immunoassays tests and not for molecular tests. In the rest of this editorial, in order to avoid any confusion, we will use Ag-RDTs to refer to the usual rapid diagnostic tests using antigen-based immunoassays. The other ones, we will specify as molecular-RDTs.

Apart from the testing recommendations, this article highlights several points that should be acknowledged. First of all, as underlined by Dr. Drain, underserved communities generally have limited access to tests. It is important to highlight, that the pandemic reaches communities unevenly, with disadvantaged communities being the most affected ones. As reported by Bambra et al. [5], there are several examples worldwide showing a link between social inequalities and COVID-19 infections. The same was already the case for the 2009 H1N1 influenza pandemic or the 1918 Spanish influenza pandemic. As observed with the current pandemic, the RT-PCR tests put a lot of pressure on laboratories. This is the reason why it is questionable whether the RDTs could help reduce disparities in testing between high and low income countries.

A second point that is addressed by Dr. Drain is the rationale behind the development of Ag-RDTs. As already mentioned, RT-PCR tests represent an intensive work for health care teams and laboratories, which consume a lot of time and resources. Additionally, it also bears a financial challenge. In this context, a reliable, easy-to-use and inexpensive Ag-RDT was quickly called for to relieve the already strained healthcare system. Such an easy-to-use tool can help facilitate the diagnosis and treatment, by allowing faster diagnoses and breaks the chains of transmission. That way it can allow an early treatment onset through effective oral antivirals or monoclonal antibodies when appropriate. According to the article, more than 1000 types of molecular and antigen-based immunoassays tests for SARS-CoV-2 are now available worldwide. These figures might underestimate the reality.

A third point we want to highlight is validity of RDTs in terms of sensitivity and specificity. According to the article of Dr. Drain, molecular-RDTs have a higher sensitivity than Ag-RDTs (sensitivity of 36%–82%; specificity, of 98%–100% for the last). However, as explained by Mina et al. in 2020 [6], while specificity is not an issue, sensitivity should be interpreted in the overall context and physicians should refrain from focusing only on sensitivity values when using tests in practice. For example, the fact that Ag-RDTs have a lower sensitivity can be compensated at population level, to some extent, through their availability and rapidity of result compared to RT-PCR tests.

Regarding current guidelines concerning testing, Dr. Drain presents three indications: an individual experiencing COVID-19 symptoms, an asymptomatic individual who has been in close contact with someone with COVID-19 and an asymptomatic individual who has been in a high risk transmission setting (*e.g.* airplane or indoor event or party). Additionally, the author suggests the possibility to consider a RDT for people who plan to gather in larger groups. The strategy for testing is then divided into three categories according to the pretest's probability of infection (high, moderate and low). Concerning the high pretest probability category, if the RDT is positive then the diagnosis is confirmed. If the RDT is negative, it is recommended to repeat the test 2 days later if there is a high clinical suspicion or if symptoms

https://doi.org/10.1016/j.accpm.2022.101114

worsen. Concerning the low pretest probability category, if the RDT is negative then the diagnosis is reasonably ruled out. If the RDT is positive and if there is a low prevalence in the community setting, it is recommended to repeat the RDT a second time, which then should confirm the positive or negative diagnosis. At last, regarding the moderate pretest probability category, if the RDT is positive the diagnosis is confirmed. If the RDT is negative and if the patient does not show any symptoms, it is recommended to repeat the test 2 days later or if symptoms develop, and to monitor the symptom occurrence during the next 14 days.

Several points need to be underlined here. First of all, some concerns may arise in implementing these guidelines as this strategy does not differentiate Ag-RDTs and molecular-RDTs. Other guidelines, for example those from the US Centers for Disease Control and Prevention (US-CDC), include a two-step-algorithm, differentiating the Ag-RDTs and the molecular-RDTs. This seems more adequate since sensitivity differs between both and it is more relevant to the European context. A second point of concern should be to differentiate the Ag-RDT done by health professionals (*e.g.* with point-of-care tests) and self-tests that are done by patients themselves. Point-of-care testing (POCT) is very useful in the emergency department in order to have a rapid result, especially for patients who may require hospitalisation or rapid surgery. An interesting meta-analysis, conducted by Dinnes et al. in 2020, was investigating point-of-care antigen and molecular-based tests [7]. This meta-analysis found that the sensitivity of antigen-POCT was much lower (average 56.2%, 95% CI: 29.5%–79.8%), but still showed high specificity (average 99.5%, 95% CI: 98.1%–99.9%), compared to the molecular-POCT, which showed a better sensitivity (average 95.2%, 95% CI: 86.7%, 98.3%) and a high specificity at 98.9% (95% CI: 97.3, 99.5%). According to Dinnes et al., RDTs could be used in two settings: to replace RT-PCR if accurate enough and as a triage to RT-PCR, "allowing earlier detection and rapid management". We support this statement. For example, a RDT could be used by patients themselves to allow a rapid diagnosis when still at home (enabling self-isolation as quickly as possible to avoid contaminating other people). It can also be used by health professionals in emergency settings in order to quickly refer their patients to the right wards, increasing patients' and health care professionals' safety and at the same time contributing to a better surveillance of nosocomial infections. These recommendations underline a graded strategy that is already in use: Ag-RDTs are used in communities as a strategy to quickly identify sick people (with a detailed algorithm to discuss when a RT-PCR test should be done as the second line diagnosis) and Ag-RDTs or molecular-RDTs are used as a triage strategy in the emergency settings in order to refer the patient while awaiting the result of the RT-PCR. If this strategy is generalised, these two-step algorithms could help to reduce the burden of RT-PCR tests for laboratories. However, RT-PCR tests should be kept as the gold standard for reference test.

Apart from diagnosing people with COVID-19, an important role of these RDTs should also be to allow people without COVID-19 to continue their daily activities. As presented by Peeling et al. [8], an Ag-RDT that has at least an 80% sensitivity and a 97% specificity (WHO requirements) "will result in negative predictive values of 99%–100% which means that most people testing negative are likely to be true negatives". This is the last domain where Ag-RDTs are of paramount importance in order to allow people without the disease to live as normally as possible. Peeling et al. estimated that a strategy with a combination of Ag-RDT and molecular testing should be implemented instead of weighting one against the other.

The last point from the article written by Dr. Drain we want to highlight is, that the Infectious Diseases Society of America (IDSA) does not recommend the use of antigen-based RDT but rather recommends the use of NAAT or RT-PCR tests [9], compared to the official recommendations of the WHO or US-CDC. According to their own guidelines, IDSA only recommends the use of molecular-RDT because of their higher sensitivity rates compared to Ag-RDT.

In order to illustrate the guidelines proposed by Dr. Drain, here is an overview on the local guidelines edited by the University Hospitals of Geneva [10]. According to our guidelines, Ag-RDTs are restricted to outpatients only, with specific criteria (*e.g.* asymptomatic individual that had a contact with a COVID-19 patient, with no risk factors). In regards to COVID-19 symptomatic patients admitted to the emergency room (who need to be hospitalised or need to undergo a surgery) our guidelines recommend to perform a molecular-RDT on a POCT. If the molecular-RDT is positive, the patient will be hospitalised in a COVID-19 ward and a RT-PCR will be sent in for diagnosis confirmation and variant sequencing. If the molecular-RDT is negative, no other test will be performed and the patient will be hospitalised in a non COVID-19 ward. If the patient is asymptomatic and has one or more of the specific screening criteria (*e.g.* immunosuppression, operating theatre forecasted in $< 12$ h, hospitalisation in an oncology ward), a molecular-RDT will be performed on the POCT. If the result is positive, the patient will be hospitalised in the intended ward (*e.g.* surgery ward), with some specific protection measures, while awaiting result of the RT-PCR. If the result is negative, the patient will be hospitalised in a non-COVID-19 ward as planned. Finally, if the patient is asymptomatic and is going to be hospitalised in a normal unit (a unit that is not at high risk like oncology), only a RT-PCR will be done and the patient will be hospitalised in the non-COVID-19 ward with specific measures awaiting the results of the RT-PCR. These kind of multi-steps guidelines, combining both Ag-RDT and molecular-RDT, are an example of a possible application of the testing strategy depending on the pretest probability of the patient, the availability of different kind of tests and the orientation of the patient in the healthcare system.

To conclude, the author of the NEJM article, Dr. Drain, proposes a review on the current guidelines about rapid diagnostic testing for SARS-CoV-2, highlighting important points in the global strategy of testing. We suggest to add more details to the current guidelines, by differentiating between Ag-RDTs and molecular-RDTs, which could be the last interesting step to completing these guidelines.

Note: This editorial was written in February 2022 and is therefore based on the recommendations of the University Hospitals of Geneva at that time.

### Disclosure of interest

The authors declare that they have no competing interest.

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Available online 16 June 2022