

## The Value of Diagnostic Information in Acute Respiratory Infections – Observations from the COVID-19 pandemic

### Case Study

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### Introduction: the surge of a novel, respiratory virus – SARS-CoV-2

#### Key message

Policymakers face the surge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel highly communicable virus that can cause potentially fatal forms of acute respiratory infections (COVID-19) for which no effective immunisation programme was available until almost a year after the start of the outbreak. In particular during the winter season, the co-circulation of SARS-CoV-2 and other respiratory viruses such as influenza, that causes symptoms indistinguishable from COVID-19, adds another level of complexity to this challenge.

*In vitro* diagnostics (IVDs) play a key role as policymakers are looking for a solution to this situation: information derived from IVDs contributes to improved risk management, by slowing down or even breaking the transmission chains of the SARS-CoV-2 virus. Simultaneously, IVD information facilitates sound disease management, ensuring accurate diagnosis, targeted treatment and care for patients suffering from acute respiratory infections.

#### Supporting arguments

- *There is a high burden of COVID-19 in Europe*

COVID-19 is a disease that is caused by SARS-CoV-2, a novel coronavirus which was first recognised in Wuhan, China, in December 2019.<sup>1</sup> By the beginning of February 2021 more than 19 million COVID-19 cases have been reported in the EU/EEA, with 473,139 deaths.<sup>2</sup> When compared to the SARS outbreak (triggered by SARS-CoV in 2003), we can see that between November 2002 and July 2003 a total of 8,098 people worldwide contracted the virus, and of these, 774 people died.<sup>3</sup> The SARS-CoV-2 outbreak has put healthcare systems across Europe under immense pressure, testing their resilience.

- *SARS-CoV-2 and the risk of silent spread:<sup>9</sup> people may carry the virus, without showing symptoms, and still infect others<sup>10</sup>*

- Pre-symptomatic spread is the transmission of the virus by people who have no symptoms yet (e.g. they do not look nor feel sick) but develop symptoms later;
- Asymptomatic spread is the transmission of the virus by people who are infectious but do not have any symptoms and will not develop any – these carriers can still get other people sick.

Since the spread by people showing no symptoms (whether asymptomatic or pre-symptomatic) is a hallmark of SARS-CoV-2,<sup>11</sup> effectively controlling the transmission of the virus constitutes a tremendous challenge.

- *A SARS-CoV-2 infection can cause acute respiratory illness*

Although COVID-19 can present with a spectrum of clinical manifestations including fever and in some cases diarrhoea or vomiting, respiratory symptoms predominate.<sup>12</sup> Most symptomatic people diagnosed with COVID-19 experience mild (40%) to moderate (40%) respiratory illness.<sup>1</sup> However, the virus is most likely to cause severe to critical symptoms, such as dyspnoea (shortness of breath) or respiratory failure, in 15% of the cases, requiring emergency interventions or hospitalisation. These cases especially occur among

vulnerable members of society, such as elderly people and people with underlying medical conditions, including cardiovascular disease, diabetes, chronic respiratory disease or cancer.<sup>13</sup> Both symptomatic and asymptomatic cases may also face (long-term) consequences such as lung fibrosis.<sup>14,15</sup>

- *Other (seasonal) pathogens may also be the cause of respiratory illnesses with clinical manifestations very similar to COVID-19. Thus, diagnosis based on signs and symptoms only may not be sufficient*

Most respiratory symptoms occurring during an infection with SARS-CoV-2 are congruent with those triggered by other (seasonally) co-circulating pathogens (infection agents). Examples of such pathogens are respiratory syncytial virus (RSV) or influenza A and B.<sup>16</sup> In some cases, co-infections of COVID-19 and influenza have been reported.<sup>12,17</sup>

This makes the identification of the causative pathogen(s) to correctly guide the management of patients with respiratory symptoms absolutely critical.

- *COVID-19 vaccine: a unique challenge*

This unprecedented situation has accelerated the development of vaccines with scientists racing to produce safe and effective COVID-19 vaccines.<sup>4</sup> At the time of publication, four vaccines against COVID-19 showed encouraging data of their effectiveness (94.5%<sup>5</sup>, 95%<sup>6</sup>, 67%<sup>85</sup> and 60%<sup>7</sup>) and have started to be administered in Europe,<sup>8</sup> and many others are currently in the pipeline.

Elements around long-term effectiveness and duration of the immunisation are unknown at present. The social response remains uncertain as well. At time of publication, all European countries have started the roll-out of the vaccine.

- *Against this background, action is needed in:*

- Risk management, by slowing down or breaking the chains of transmission of SARS-CoV-2;
- Disease management, by ensuring citizens with respiratory symptoms are accurately diagnosed and follow the appropriate treatment and care pathway determined by the responsible infection agent.

- *IVD tests provide information to act:*

For risk management by:

- Detecting a SARS-CoV-2 infection in pre-symptomatic, symptomatic and asymptomatic people;
- Identifying who has been previously infected with SARS-CoV-2, who still has antibodies against the virus and once vaccination has been administered.

For disease management by:

- Differentiating other types of acute respiratory infections with similar presentation from COVID-19, based on pathogen identification;
- Guiding treatment and care of acute respiratory infections following diagnosis.

## Throughout the SARS-COV-2 pandemic, IVD information has brought value at all levels, to healthcare systems and society at large

### A risk management perspective

#### Key message

With the use of IVDs, an ongoing infection with SARS-CoV-2 (even in people with no symptoms) can be detected. Likewise, thanks to IVDs, those who have been previously infected, those who still carry antibodies against the virus or potentially have developed vaccinal immunity can be identified. Based on this information, the level of social distancing on both individual and population level can be adjusted. The transmission of the virus can be further controlled, via targeted screening.

As such, IVD information is key to manage the risk of SARS-CoV-2, delivering value to citizens, healthcare professionals, healthcare providers, healthcare systems and society at large.

#### Supporting arguments

- *National governments had to resort to social distancing to counter the surge of SARS-CoV-2*

Restrictions on social and economic life aim to prevent and/or control the transmission of the virus in the community and 'buy time' to enable healthcare systems to cope with the high numbers of patients and alleviate pressure.<sup>18</sup> This includes closing public spaces, establishing border controls, national or regional lockdowns, as well as curfews.<sup>19</sup>

However, social distancing can have adverse effects on the economy and society at large. For example, the EU-wide unemployment rate rose from 6.6% in 2019 to 8.3% in 2020 and is predicted to increase to 9.4% in 2021.<sup>20</sup> More than 1,500 small and medium-size enterprises (SMEs) in the EU4+1 (France, Germany, Italy, Spain and The United Kingdom) have seen their revenues declining as a result of social distancing.<sup>21</sup> Overall, the EU's GDP has decreased by 11.4% in the second quarter of 2020.<sup>22</sup>

- *The need for social distancing on an individual and population level is informed by IVD tests for the SARS-CoV-2 outbreak*

There are generally two different types of tests used to detect the presence of SARS-CoV-2: (1) molecular-based (RT-PCR) tests which can detect the presence of the virus (viral RNA), but do not detect if one has previously been in contact with the virus; and (2) antigen detection-based tests which can detect the presence of viral antigen (proteins), but do not detect if one has previously been in contact with the virus. In addition, there is one type of test used to detect the immune response to the virus, which are serology tests for COVID-19 (antibody tests). These tests detect the production of antibodies (IgG and IgM), indicating whether the person has previously been in contact with the virus.<sup>23,24</sup>

The information obtained from such tests is determined by their operating principle, while their uptake may depend on the available resources (e.g. laboratory/testing capacity) of each country.<sup>23</sup>

- **Molecular-based SARS-CoV-2 tests** (such as RT-PCR, which is the reference test used at present), via nasopharyngeal or throat swabs or with saliva samples, detect the presence of the nucleic acids of the virus, but do not detect whether one has previously been in contact with the virus. During the COVID-19 outbreak, these tests are being used to identify the presence of the pathogen (SARS-CoV-2), and not as multiple targets detection tests, to identify whether the person is having any other infection. These tests have been effective in providing relevant information for case confirmation, and isolation guidance in symptomatic and asymptomatic people.<sup>24</sup>

These tests generally require a laboratory analysis (35-40 minutes) and need to be mainly performed by healthcare workers or laboratory technicians with appropriate training in sample collection, biosafety and the use of the test. These tests are also available as point-of-care (POC) testing.

- **Antigen detection-based SARS-CoV-2 tests**, via nasopharyngeal or throat swabs, identify the presence of proteins of the virus, but do not detect if one has previously been in contact. These tests identify the presence of SARS-CoV-2, but they do not offer any information on whether the person has any other infection ongoing. These tests have been effective in providing relevant information for case

confirmation and isolation guidance in symptomatic and asymptomatic people in areas with many confirmed cases, while there is limited data concerning their efficiency on asymptomatic ones in low prevalence settings.<sup>26</sup>

They can be rapid tests that can be performed outside of laboratories at routine and ad-hoc triage/screening points run, and hence in a very timely manner, by healthcare facilities, by healthcare workers or laboratory technicians, with appropriate training in sample collection, biosafety and the use of the test. These tests can also be developed and validated for self-testing.<sup>27</sup>

While rapid antigen tests are generally less sensitive than molecular-based tests, their sensitivity increases if tested in specimens with high viral load, and in populations up to five days of symptom onset.<sup>25</sup>

- **Serology tests for COVID-19 detection** (also called antibody tests) via blood samples, detect if a person has developed antibodies against SARS-CoV-2 by identifying the presence of antibodies (either with specific test to IgM and IgG, or measuring the addition of all antibodies, including IgA + IgM + IgG)<sup>23</sup> These tests deliver comprehensive information on the virus' epidemiology in the general population. They may also deliver important information for monitoring vaccinal immunity.<sup>23</sup> These tests require a laboratory analysis and can be performed in healthcare facilities by healthcare workers.<sup>27</sup> They can also be performed with mobile hand-held devices in clinics, doctors' offices or even mobile drive-in sites (point-of-care serology tests).<sup>23</sup>
- *Together with effective contact tracing and case isolation, a testing strategy that includes targeted screening can further control the transmission of SARS-CoV-2*
  - At the time of publication, several studies have indicated that contact tracing is an effective measure to control or even prevent the spread of SARS-CoV-2.<sup>28</sup> However, since large shares of individuals are asymptomatic, contact tracing may be in fact difficult to be performed. Hence, it can be most meaningful if it is integrated with other measures such as quarantine and screening ('beyond symptoms testing').<sup>28</sup> Next to targeted screening in local communities with high prevalence, this also includes recurring screening of people living in nursing homes as well as healthcare professionals/social caregivers.<sup>26</sup>
  - Needless to say, it is important for any testing strategy to contextualise each type of test for its intended purpose (please refer to information above) and the respective setting (high or low prevalence).<sup>29</sup> For example, a testing strategy can encompass the use of both molecular-based tests and (rapid) antigen detection-based tests complementing each other.<sup>27</sup> Rapid antigen detection-based tests can help identify a high number of cases quickly – without the involvement of a laboratory analysis and allow for rapid implementation of control measures (e.g. self-isolation).<sup>26</sup> Given the lower sensitivity of (rapid) antigen detection-based, these test results are assumed to be particularly useful in high prevalence settings where a positive test result is likely to indicate a true infection.<sup>26</sup> In areas with less confirmed cases (lower prevalence), (rapid) antigen detection-based tests may need to be confirmed by a molecular-based test.<sup>26</sup> Automated version of these antigen detection assays, while requesting laboratory analysers, show consistent diagnostic performances in symptomatic patients and might allow a faster identification of SARS-CoV-2 contagious patients, which is very critical at time of intense viral spreading.
- *As information retrieved from IVDs helps control the risk of SARS-CoV-2, it delivers value to citizens, healthcare professionals, healthcare providers, healthcare systems and society at large*

#### **Citizens:**

- Conducting molecular-based SARS-CoV-2 tests in asymptomatic or pre-symptomatic people when a substantial risk of transmission has occurred (e.g. household clusters, contact tracing) will ensure citizens benefit from the **value of knowing** whether they contract the virus to avoid infecting others, especially vulnerable parts of society. A similar value is generated when screening (by the use rapid antigen detection-based test) of asymptomatic people in areas with a confirmed high SARS-CoV-2 prevalence.

The information gained from a molecular-based SARS-CoV-2 test result ruling out an infection with SARS-CoV-2 prevents **unnecessary interference with activities of daily life** (e.g. discontinuation of quarantine, return to work, essential cross-border travel).

- By performing recurring screenings (ideally several times per week) with rapid antigen detection-based SARS-CoV-2 tests in people living in nursing homes (alongside the staff), the risk of virus exposure can be controlled and the safety in the facility increased.<sup>26</sup> Once there is a positive antigen detection-based result, case confirmation can be sought via the information gained from a molecular-based SARS-CoV-2 test.<sup>26</sup> Hence, people in nursing homes, who are generally at high risk of developing severe COVID-19, may enjoy an increased **sense of security** in the care facility thanks to the information gained from regular testing.
- Symptomatic people with a confirmed SARS-CoV-2 infection (either by a molecular-based test, a rapid antigen detection-based test in high prevalence settings,<sup>26</sup> or the combination of these two in low prevalence settings with limited availability of molecular-based testing capacity) benefit from the **value of knowing** whether they carry the virus, especially since symptoms can be similar to other respiratory infections such as influenza. The earlier this information is available (ideally within 5-7 days following onset of the symptoms),<sup>25</sup> the faster it allows people to make adjustments to their behaviour (e.g. self-isolation)<sup>30</sup> and to promptly inform people around them to take precautionary measures and to minimise direct contact. Especially, the timely information gained from rapid antigen detection-based tests in high SARS-CoV-2 prevalence settings can facilitate early detection of further cases as part of contact tracing.<sup>26</sup>

#### Healthcare professionals:

- Recurring screening via rapid antigen detection-based SARS-CoV-2 tests (along with molecular-based SARS-CoV-2 test case confirmation in case of a first positive test result)<sup>26</sup> amongst healthcare professionals informs them about their **safety at work**.<sup>31</sup> This was especially relevant at the beginning of the COVID-19 pandemic, when personal protective equipment (PPE) was scarce.<sup>32</sup> One study found a 43% infection rate among healthcare workers in regular/non-surgical/non-COVID-19 wards, 40% of whom were asymptomatic.<sup>33</sup> Especially, healthcare workers at the frontline do not only get exposed to the physical risk of contracting the virus,<sup>34</sup> but are also likely to suffer from mental stress, including reported anxiety, depression, sleep problems and distress.<sup>35</sup>
- The information gained from recurring screening (as described above) helps healthcare professionals ensure the **safety of the citizen** during care provision. When healthcare professionals are aware of their SARS-CoV-2 infection, they can go into isolation to avoid (further) spreading the virus amongst vulnerable citizens.<sup>26</sup>

#### Healthcare providers:

- Information retrieved from IVD testing in hospitals on both healthcare professionals and citizens, helps healthcare providers control the transmission of SARS-CoV-2, ensuring that facilities remain operational. It is estimated that weekly screenings (using PCR point-of-care SARS-CoV-2 tests irrespective of symptoms) amongst healthcare professionals and other at-risk groups can reduce the transmission by 25-33%.<sup>36</sup> Likewise, testing citizens (via molecular-based and antigen detection-based SARS-CoV-2) at the time of hospital admission (irrespective of whether they show symptoms of COVID-19) allows to take immediate isolation measures (if needed) and to mitigate the overall impact of COVID-19 in the healthcare facility. This way, healthcare providers can **ensure uninterrupted care** for both COVID-19 and non-COVID-19 patients. For instance, in the UK, a lot of cancer screenings and routine diagnostic work have been postponed since the start of the lockdown in March 2020, and only urgent cases have been prioritised. This resulted in late diagnoses (on average a 12-month delay), decrease in survival rates (3.5% for lung cancer) and, consequently, it is expected it will result in an increase of mortality rates in the coming years.<sup>37</sup> All these measures, including keeping healthcare facilities operational and providing uninterrupted care, can be avoided with the use of diagnostics information. Additionally, some specific invasive procedures (e.g. endoscopies) can be executed when testing is available.<sup>38</sup> This has a potential impact on detection and treatment of other diseases (e.g. cancer).

## Healthcare systems:

- Based on the information gained from IVD testing for SARS-CoV-2 healthcare systems can conduct **recourse planning** in order to cope with the high numbers of incoming COVID-19 patients (e.g. avoiding hospital overcapacity).<sup>39,40</sup>
- The information derived from molecular-based tests and antigen detection-based tests can generate **public health benefits**: detecting (as early as possible) who is infected (even without showing symptoms) allows to take measures that can contain the spread of SARS-CoV-2 (e.g. self-isolation or quarantine, contact tracing, and/or social distancing). This, in turn, particularly protects vulnerable parts of society (such as the elderly), who may suffer from chronic conditions already and are prone to develop severe COVID-19. Avoiding that these people get infected with SARS-CoV-2 can **reduce pressure on healthcare systems' budget**.

## Society:

- Information gained from IVD tests indicates the infection incidences in the population.<sup>41</sup> Information on who tested positive provides crucial data points feeding into the mortality rate,<sup>42</sup> hospital admissions, or the reproduction number R (an indicator for SARS-CoV-2's ability to spread). This information can help policymakers take **informed decisions** on whether to tighten, lift, or ease restrictions on social and economic activity, ultimately minimising adverse effects on society.<sup>43</sup>
- Targeted screening in a high prevalence community through the usage of rapid antigen detection-based tests for SARS-CoV-2, and, if needed, a confirmatory molecular-based test in case the rapid antigen-test result is negative, provides timely information to the infected persons who do not experience any symptoms.<sup>18,26</sup> In conjunction with effective contract tracing and case isolation, the information gained from such screening practice helps control transmission and identify clusters or outbreaks in specific settings. This, in turn, can help **avoid the introduction of more stringent, and ultimately costly, social distancing measures** in the broader population (e.g. city or even country-wide).<sup>18</sup> Additionally, essential cross-border traffic is only possible to certain countries if an IVD test is negative<sup>44</sup>. This brings value by **preventing outbreaks and avoiding the spreading of dangerous mutations**.
- Large-scale serologic testing to detect antibodies against SARS-CoV-2 delivers useful information for **epidemiological surveillance** of the virus. This includes an enhanced understanding of transmission patterns and the detection of mutant strains (such as the ones found in the United Kingdom, South Africa, California and Brazil). Given the presumably significant rate of asymptomatic infections (reported rates ranging between 20% and 75%),<sup>45</sup> the information gained from these tests can establish a more accurate regional or national denominator for the number of infected individuals, allowing to determine a true case fatality rate.<sup>46</sup> Hence, complementing the information gained from molecular-based and (rapid) antigen detection-based tests, serologic testing can equally inform policy decisions to control the spread of SARS-CoV-2.
- By determining a baseline of neutralizing antibodies presence and monitoring how this is affected by the different vaccination campaigns, antibody testing will, on the long haul, **define vaccine efficacy** in combating SARS-CoV-2.

## A disease management perspective

### Key message

IVD tests provide vital information supporting the disease management of respiratory infections, not only stemming from SARS-CoV-2 but also from other viruses and bacteria. Information obtained from IVD tests allows to differentiate other types of respiratory infections with similar presentation to COVID-19 and guide treatment and care. This is particularly important given the co-circulation of SARS-CoV-2 and other respiratory pathogens, such as influenza and RSV, during the winter season.

### Supporting arguments

- *Before the COVID-19 pandemic, acute respiratory infections had already been a significant burden in Europe, even when vaccination is available and regularly administered*
  - Acute respiratory infections, affecting the upper or lower respiratory tract, are among the most common and important conditions in clinical medicine<sup>47</sup> and cause substantial morbidity and mortality worldwide. In 2015, the total number of deaths attributable to lower respiratory infections was ‘only’ 31,582 in Germany, 25,009 in France and 15,172 in Italy.<sup>48</sup>
  - Next to lung cancer and chronic obstructive pulmonary disease (COPD), lower respiratory tract infections (being far more serious than infections of the upper respiratory tract) are among the leading cause of respiratory death in Europe.<sup>49</sup> From an epidemiological point of view, the definition of acute lower respiratory tract infections usually includes acute bronchitis, bronchiolitis, influenza and pneumonia.<sup>50</sup>
  - In Europe approximately 16,500,000 cases of acute bronchitis are diagnosed each year. Moreover, about 3,370,000 cases of pneumonia are registered every year in the EU, along with approximately 1 million hospital admissions<sup>51</sup> because of community-acquired pneumonia.<sup>52</sup>
  - Seasonal influenza causes between 4 to 50 million symptomatic cases in the EU/EEA each year, and 15,000 – 70,000 deaths every year of causes associated with influenza.<sup>53</sup> The burden of influenza is significant not only because of its mortality, but also for its greater economic impact (e.g. reduced productivity, loss of working days), and its pressure on healthcare systems.
- *COVID-19 can present with symptoms typical of multiple respiratory infections, creating a particular challenge for citizens, healthcare professionals and healthcare systems*
  - In general, respiratory tract infections can be caused by a wide array of bacterial and viral pathogens. The most common causative viral and bacterial agents for both upper and lower respiratory tract infections include influenza A and B, coronaviruses (including SARS-CoV-2), RSV and the bacterium streptococcus pyogenes.
  - Viruses account for the majority of upper respiratory tract infections but are also a common cause of lower respiratory tract infections, including bronchiolitis and bronchitis. In contrast, bacterial pathogens rarely cause upper respiratory tract infections, such as a common cold (which is usually a viral infection), but are known to infect the lower respiratory tract (e.g. pneumonia).
  - The surge of many of these respiratory pathogens is seasonal. For instance, influenza mostly affects Europe in winter, intensifying the burden of respiratory infections during this time of the year. The clinical presentation for citizens infected with these pathogens is typically indistinguishable, while treatment and care may greatly differ depending on the aetiology (cause) of the infection.<sup>54</sup> For example, RSV is sometimes mistaken for bacterial infections causing similar symptoms. Antibiotics are mistakenly used as treatment before confirmation of RSV diagnosis, exposing society to other threats, such as antimicrobial resistance (AMR).<sup>55</sup>
  - The convergence of SARS-CoV-2 with other (seasonal) respiratory pathogens such as influenza viruses, creates a challenge for citizens, healthcare professionals and healthcare systems, which is further increased by the possibility of a co-infection (e.g. of SARS-CoV-2 and influenza virus).<sup>56</sup>

- *Hence, identifying the infectious agent (pathogen) causing the respiratory infection, and the right aetiology from other possible causes is key*

IVD tests deliver information that can allow for such differential diagnosing:

- Several diagnostic tests already exist and are being produced to detect a single target of respiratory infectious agents, such as SARS-CoV-2 (see description above) and influenza.<sup>57</sup> Similar to test for SARS-CoV-2, tests for influenza virus A and B (either RT-PCR – molecular-based testing, or antigen detection based testing, including rapid influenza diagnostic tests and immunofluorescence assays)<sup>58</sup> are administered by swabbing the nose and nasal cavity, and allow to detect virus antigens or genome in specimens from the respiratory tract.<sup>53</sup>
- Combined multiplex IVD tests also allow for the detection of SARS-CoV-2 and other pathogens in a single test. Several IVD tests are already available to detect SARS-CoV-2 in combination with other (seasonal) infections.<sup>57</sup> SARS-CoV-2 (Flu SC2) Multiplex Assays are a real-time RT-PCR test that detect and differentiate RNA from SARS-CoV-2, influenza A virus, and influenza B virus in upper or lower respiratory specimens.<sup>59</sup>
- Serological testing for influenza is also available, but not recommended for clinical decision-making.<sup>58</sup>
- *Information obtained from IVD tests can then guide clinical decision-making along the pathway and ensure optimal management of respiratory infections*<sup>60,61</sup>
  - Treatment choice: treatment approaches vary depending on aetiology, making accurate diagnosis a prerequisite for a targeted treatment approach.
  - Monitoring: adjustments to the care pathway may be required at any time and can be informed through the means of IVD testing, e.g. updating the status quo of the infection or identifying a secondary infection, which may occur during or after treatment for the initial infection.<sup>62</sup>

*For simplified presentation, this part of the case study looks at the value of diagnostic information with the help of an exemplary pathway of a patient present at the emergency department (ED) with severe symptoms of an acute respiratory tract-like infection during the influenza season and at times of the SARS-CoV-2 pandemic, assuming that the final diagnosis is influenza and not COVID-19. The statements below have a pure illustrative purpose and do not claim to be an exhaustive description of the potential testing procedure to be applied in the situation as described above.*

- *As outlined above, diagnostic information delivers value to citizens, healthcare professionals, healthcare providers, healthcare systems and society at large as it guides clinical decision-making along the pathway and ensures optimal disease management*

#### **Citizens:**

- With the information provided by an influenza SARS-CoV-2 multiplex/syndromic/molecular-based influenza test<sup>63</sup> patients benefit from the **value of knowing**, as they learn about the cause of their symptoms.<sup>58</sup>
- Based on the information generated by the use of an influenza SARS-CoV-2 multiplex/syndromic/molecular-based (RT-PCR) influenza test in combination with molecular-based SARS-CoV-2 tests, patients may profit from the **value of ruling out**. Getting correctly diagnosed (knowing that their symptoms derive from the influenza virus and not SARS-CoV-2) may also relieve some stress and reduce the risk of mental disorders, such as anxiety and depression,<sup>64</sup> due to uncertainty about the origin of their condition or the fear of suffering from COVID-19 and its long-term consequences.<sup>65,66</sup> During the COVID-19 pandemic, experiencing severe respiratory symptoms might be extremely worrying for patients, especially for those with co-morbidities, such as cardiovascular diseases, who are unsure about the impact of the infection on their underlying condition. In addition, patients may fear the social stigma which the SARS-CoV-2 outbreak has provoked against people who are perceived to have been in contact with the virus.
- Providing information on the infection agent, an influenza SARS-CoV-2 multiplex/syndromic/molecular-based influenza test creates **clinical benefits** and **increased safety** for the patient:



- The information provided by influenza SARS-CoV-2 multiplex/syndromic/molecular-based influenza point-of-care (POC) testing, can particularly ensure a timely and correct diagnosis, saving valuable time to initiate the right treatment and minimise side effects due to inappropriate treatment (e.g. antibiotics) based on empirics.<sup>67</sup> Only when patients are diagnosed early with influenza (ideally within 48h after symptom onset), they benefit from antiviral treatments, reducing the severity of the infection, shortening the duration of symptoms, and preventing death.<sup>68</sup> The administration of the anti-viral treatment within 48 hours, in turn, allows patients to reduce hospital stay (if necessary) (5.9 days vs. 7.2 day),<sup>69</sup> consequently minimising the risk of healthcare-associated infections, including clostridium difficile infections.<sup>70,71</sup>
- During treatment and monitoring, an influenza SARS-CoV-2 multiplex/syndromic test, allowing to detect the existence of both respiratory bacterial and viral pathogens, presents valuable information to the patient on progression and potential improvement of the condition, as well as on the risk of events such a secondary (bacterial) infection as for instance post-influenza pneumonia.<sup>72</sup>
- During treatment or at discharge from the hospital, serology tests for COVID-19 detection/influenza detection can provide useful information on the level of immunisation against influenza and the presence of antibodies binding and neutralising SARS-CoV-2. This information as such, may indicate the need for vaccination (or re-vaccination) to limit or avoid another acute respiratory tract infection in the future (e.g. SARS-CoV-2).<sup>73</sup> Patients may thereby benefit from the **value of knowing and deciding** on the preventive measures to take.

#### Healthcare professionals:

- Based on the information retrieved from influenza SARS-CoV-2 IVD testing at point-of-care, healthcare professionals can determine the viral pathogen to confirm the diagnosis. This way, they can conduct **rapid, appropriate clinical management** by bringing the patient onto the correct treatment path as fast as possible. Rapid detection of respiratory viral pathogens therefore also has the potential to reduce the duration of empirically started antibiotics and initiation of appropriate antiviral treatment, as an antiviral treatment for influenza should be started within 48 hours after onset of disease to be effective.<sup>74</sup>
- At the point of diagnosis, thanks to the information gained from influenza SARS-CoV-2 multiplex/syndromic/molecular-based influenza testing, allowing to detect the existence of both respiratory bacterial and viral pathogens, healthcare professionals can tackle the clinical uncertainty about the cause of disease (viral versus bacterial). Knowing that the aetiology of the patient's condition is a virus (and not a bacterium) helps them verify their treatment choice (antiviral vs. antibiotics). With this information at hand, healthcare professionals can **avoid further (unnecessary) testing** as well as **prevent the side effects** for patients arising from non-targeted administration of antibiotics based on empiricism.<sup>75</sup>
- On the grounds of the information gained from influenza SARS-CoV-2 multiplex tests/syndromic/molecular-based influenza tests, healthcare professionals can assess the patient's condition and decide whether the patient presenting to the ED needs to be admitted to hospital to avoid degradation and requires isolated care. Communicating this information helps healthcare professionals **manage patients' expectations regarding prognosis and treatment course**.
- During treatment, the information derived from a multiplex/syndromic test, allowing to detect the existence of both respiratory bacterial and viral pathogens, supports healthcare professionals in **monitoring patients' condition and adjusting the treatment pathway**, especially in case of a secondary (bacterial) infection such as post-influenza pneumonia, which requires the prescription of antibiotics.

#### Healthcare providers (hospitals):

- Thanks to the information gained from an influenza SARS-CoV-2 multiplex/syndromic/molecular-based influenza POC test, healthcare providers can optimise their **operational costs and turnaround time**, due to reduced time-to-diagnosis, unnecessary isolation, hospital stay and, thereby, in-hospital costs. For example, molecular-based influenza POC testing can lower mean costs per patient between € 4,904 and € 4,206. At the hospital level, this can result in a total cost reduction of € 95,937 to € 293,471<sup>74</sup> in a single influenza season, which may especially free up needed resources to treat patients during the COVID-19 pandemic.

- As the use of information retrieved from an influenza SARS-CoV-2 multiplex/syndromic/molecular-based influenza POC test or a multiplex test, allowing to detect the existence of both respiratory bacterial and viral pathogens, allows for rapid, appropriate clinical management of care, it curbs inappropriate (e.g. untargeted administration of antibiotics) or delayed treatment (later than 48 hours). When, for example, a molecular-based influenza POC test is used, the time to initial receipt of antivirals for patients with influenza virus is quicker (0.6 days) than in the case of a laboratory test procedure (1.06 days), contributing to proportionally less post 72 hours influenza virus cases in the facility.<sup>76</sup> This contributes to the **improvement of quality of care** in the hospital.

### Healthcare systems:

- COVID-19 circulating during the influenza season places additional (financial) pressure on already strained healthcare systems, potentially leading to a draining effect on the pandemic response overall.<sup>77</sup> The information provided by diagnostic information can create **economic efficiencies** to the healthcare systems: a rapid virus detection based on the information from influenza testing contributes to less time-to-diagnosis. That way, information provided by a molecular-based influenza POC test improves **triage decisions** (identification of need for isolation) and allows more efficient investigation, treatment (targeted anti-viral prescribing), and disposition of patients.<sup>78</sup>
- The information based on a molecular-based influenza POC test to detect the causative viral respiratory pathogen is associated with a trend toward decreased antibiotic use, suggesting that it could potentially modify treatment decisions and improve proper utilisation of antimicrobial therapies in up to 19.3% of cases.<sup>67</sup> This generates clear **public health benefits** in terms of improved antimicrobial stewardship.<sup>78</sup> Furthermore, influenza SARS-CoV-2 multiplex tests give public health officials information they need in their efforts to control the spread of COVID-19 and influenza and allow for ongoing influenza surveillance while also testing for SARS-CoV-2.<sup>59,79,80</sup>

## Key lessons learned, and policy asks

During the COVID-19 pandemic, policymakers have been increasingly appreciating the wide spectrum of information offered by diagnostics. The use of IVD information helps control the spread of a novel virus, such as SARS-CoV-2, in the population. Likewise, it can improve the management of patients with acute respiratory tract infections (not only stemming from SARS-CoV-2 but also from other, co-circulating infection agents e.g. influenza viruses) from timely diagnosis to treatment and care.

These exceptional circumstances have shown how information provided by IVDs informs decision-making at the individual, clinical and policy level. Just as outlined in the Value of Diagnostic Information Concept<sup>61</sup> it has thus generated value for citizens, patients, healthcare professionals, healthcare providers, healthcare systems, and society as a whole.

While the SARS-CoV-2 outbreak shed light on the role, and ultimately the value, of diagnostic information in developing a response to an acute public health threat, the potential of IVD-generated information does not stop here. The healthcare challenges now and in the future are immense: respiratory tract infections other than COVID-19, such as influenza, constitute a significant disease burden in many European countries every season (despite available immunisation), while cardiovascular diseases remain the number one cause of death in Europe. Better leveraging diagnostic information can be part of the solution to address these challenges arising from both infectious and chronic diseases.<sup>81</sup>

Against this backdrop, there is a need for collective engagement in encouraging the appropriate use of IVDs. Policy action at EU and Member State level for IVDs can ensure more disease prevention, high-quality and efficient healthcare and improved health outcomes, while strengthening future innovation in IVDs. Our recommendations are the following ones:

### A. Enhance integration of IVD information in healthcare systems

- The COVID-19 pandemic has shed light on the role of data, and eventually information, captured by IVDs. Policymakers, citizens, patients, healthcare professionals and providers alike can make reliable decisions based on the information received from IVDs. Healthcare systems should maximise their true value by significantly improving testing strategies for both non-communicable and communicable diseases.

- Streamlining data from IVD testing with other sources of health data, such as electronic healthcare records, registries or hospital claims, can even further increase the value of diagnostic information. At EU level, initiatives such as the European Health Data Space,<sup>82</sup> which recognises the importance of better exchange and access to different types of health data (including diagnostic information), offers the right support to unlock this very potential.

## **B. Raise awareness of IVDs through multi-stakeholder engagement at EU and national level**

- The health community has an important role to play in promoting the appropriate use of IVDs. Primary care doctors and pharmacists are also key in advising and informing patients and citizens of the value of diagnostic information. Policymakers and stakeholders' attention needs to be directed to raising awareness of the value of IVD information amongst relevant stakeholders at national and EU level, as well as amongst the general public, and this has to be embedded in a comprehensive policy framework.

## **C. Build an enabling ecosystem that recognises and rewards the value of diagnostic information and hence incentivises future IVD innovation**

- IVDs contribute to 70% of clinical decisions and account for 0.8% of total healthcare expenditure.<sup>83</sup> This data reflects the fact that the power of IVD information and data remains undervalued. Investing in IVDs can generate significant returns in terms of more disease prevention, high-quality and efficient healthcare and improved health outcomes, ultimately benefiting society as a whole.
- Investing in IVDs also means appropriately rewarding the multi-dimensional value of diagnostic information (as laid forth in the Value of Diagnostic Information Concept).<sup>61</sup> At present, when IVDs are reimbursed, the decision is typically based on the cost of the test kit itself, the equipment that analyses the sample, and the cost of staff performing the analysis, rather than on the actual value they bring.

With this goal in mind, an innovation ecosystem with appropriate incentives for future research and technological innovation has to be put in place. Public Private Partnerships through e.g. EU's research and innovation programmes (e.g. Horizon Europe)<sup>84</sup> can enhance such an environment.

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