Editorial

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COVID-19: which lessons have we learned?

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Coronavirus disease 2019 (COVID-19), the worst infectious disease that has affected humanity over the past century, is still causing dramatic derangements of healthcare, society and economy, so that nothing will be the same as before. Several months after the World Health Organization (WHO) has declared COVID-19 a pandemic [1], many enquiries remain unanswered [2].

The first and foremost question is, perhaps, if (and when) we will be able to completely eradicate SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), and life could optimistically return to a “new” normal. There is no easy answer to this question. Many expectations have been placed on COVID-19 vaccines at the beginning of this pandemics, when the outbreak was mostly sustained by the virus strain originally appeared in Wuhan, against which vaccine effectiveness has now been proven as high as 90% against infection, and approximating 100% against the risk of developing severe COVID-19 illness, respectively [3]. Nonetheless, after more than one year of worldwide circulation, SARS-CoV-2 is accumulating an impressive number of new mutations, such as K417N, E484K and N501Y, which emerged for selective pressure consequent to prolonged circulation and increasing diffusion of natural (i.e., post-infection) or artificial (i.e., post-vaccine) immunity [4]. This is not really surprising because each infected subject may generate up to 40–50 different SARS-CoV-2 intra-host single-nucleotide variants [5]. For each single SARS-CoV-2 variant “of concern” that can be identified [6], there would be many others still undetected, characterized by different biological and pathogenetic features. Some polymorphisms in the receptor binding domain (RBD) of

the spike protein are associated with higher infectivity and virulence (e.g., N501Y), while others may render the virus less vulnerable to neutralizing antibodies (e.g., E484K) [7]. The most undesirable consequence of such continuous emergence of the so-called variants of concern (e.g., B.1.1.7, B.1.135, B.1.427/9, B.1.526, P.1, among others) [6], is that either natural or post-vaccine immunity may become less efficient, and thereby the infection would not be efficiently prevented and contained by humoral immunity. Recent evidence emerged in South Africa attests that the efficiency of ChAdOx1 nCoV-19 Covid-19 Vaccine may have decreased from 75% to around 10% against the B.1.351 SARS-CoV-2 strain [8].

Therefore, the most likely answer to the question whether SARS-CoV-2 could be completely eradicated is “probably no”, at least for several months (years) to come. We shall not be really surprised by this, since the influenza virus H1N1, which caused the dramatic Spanish flu pandemic nearly 100 years ago [9], is still among us and kills several people during every new outbreak, with a death rate especially high in the older and sick population (i.e., between 0.1 and 1.0%) [10]. Therefore, given for granted that we will need to learn to live with this new (corona)virus for quite a long time, we shall need to think out of the box and envisage strategies aimed to make the healthcare (system) more efficient to withstand the considerable clinical, societal and economic impact of COVID-19. This would actually encompass a complete revolution of the entire system of care, including community-based medicine, hospital medicine, *in vitro* diagnostic testing and rehabilitation medicine, according to a novel, patient-centered system of care, based on the peculiar clinical and organizational aspects characterizing the ongoing SARS-CoV-2 pandemic (Figure 1).

In an opinion paper published in this issue of the journal, Mario Plebani has summarized many lessons garnered by laboratory medicine from the ongoing COVID-19 pandemic outbreak, in keeping with his usual broad knowledge of science and practice [11]. He has proposed to rearrange a famous Italo Calvino’s assertion, to remark some essential aspects in COVID-19 diagnostics. The generation and subsequent release of diagnostic assays for COVID-19 have been extraordinarily rapid and

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straightforward, as has also fortunately occurred for vaccines. The impact of laboratory tests on medicine, as repeatedly outlined by many pathologists, has not been sufficiently taken into consideration by several scientists, clinicians, and even decision makers. The COVID-19 experience could be a spectacular model to demonstrate that clinical laboratories are not only efficient facilities or commodities for hospitals and healthcare services, but instead shall be seen as real and effective clinical specialties, which can guide patient journey and public health processes. The *quickness* needed to face the increasing demand for testing has involved a wide spectrum of activities, such as regulatory processes, ethics committees approvals, industrial and commercial pathways, organizational changes of laboratories and hospitals. The timeliness of these different but tightly interconnected processes is a clear lesson that we have learnt, and that shall be maintained even in the future for allowing better advancement of science and optimal patient engagement, safety, empowerment and care.

Nonetheless, several lines of evidence suggest that quickness may have not been always accompanied (or followed) by high quality. The need of rapidly introducing SARS-CoV-2 diagnostic assays in the market, along with requirements of high throughput and short turnaround time, has enabled commercialization and clinical usage of methods displaying modest or even poor analytical quality (especially low diagnostic sensitivity), thus in many cases partially or totally averting the conventional and universally accepted regulatory procedures and the good laboratory

practice [12]. Laboratory medicine professionals and scientific associations should clearly acknowledge this drawback, and shall also be engaged to define a solid, effective and stable link with manufacturers, aimed to assure the quality of diagnostic kits before these are introduced into routine clinical practice. Consortiums of laboratories and (or) experts shall be established, to enhance preparedness and proactivity. Diagnostic companies have been deeply involved in contrasting this new infectious disease, with rapid and efficient response, though the validation phase of the assays must be equally fast, qualified and independent.

Multiplicity is another good lesson for the future. The methods (e.g., molecular assays) could incorporate and gather a vast array of laboratory medicine subdisciplines. The time has probably come for “turning back to the future”, considering that the separation in many different diagnostic areas that has occurred some decades ago, could be completely reversed by using similar methods and/or common technology (e.g., molecular testing, magnetic resonance imaging, digitalization). Barriers and borders should be abated by modern technologies, although specific knowledge and expertise could be maintained. Laboratory professionals, for example, should be deeply engaged in optimizing and standardizing several preanalytical procedures, which were frequently overlooked during the first period of the COVID-19 pandemic, but were potential causes of bias in testing quality.

Laboratory professional are also experts on *exactitude*. Standardization, or at least harmonization, are essential prerequisites of all diagnostic assays, especially important

Figure 1: Possible adaptations of care system during the coronavirus disease 2019 (COVID-19) pandemic.

for those techniques bearing the highest impact on public health. The very high level of expertise of laboratory professionals in this facet seems to be inadequately addressed in this new COVID-19 era [13, 14]. Despite the recent introduction of the new WHO International Standard 20/136, standardization of anti-SARS-CoV-2 immunoassays is still ongoing and thus largely incomplete [15]. Ambiguous or controversial interpretation of test results, even when these are correct and accurate, may generate detrimental effects on reputation, credibility and *visibility* of laboratory medicine.

Laboratory professionals shall learn that laboratory data not only have a strong medical impact, but may also cause important societal consequences. They shall hence lead the entire evaluation and validation process of new diagnostic assays, defining with *lightness* the characteristics of the methods, which should be ideally simple, inexpensive, accurate and reproducible. The process could not be limited to a conventional analytical assessment, but should encompass also the evaluation of economical, organizational and ethical issues, for example using health technology assessment. Equity of access is a current and future medical challenge, considerably underpinned by the ongoing COVID-19 pandemic outbreak, and which does not only concerns care access, but also entails better accessibility to digital divide and health literacy. Owing to decades of experience in data analytics, health-applied information technology, telematics and mechanization of information (now often emphatically called artificial intelligence, but already part of laboratory instrumentation) [16, 17], laboratory medicine could be forerunner in enhancing *consistency*.

In conclusion, we believe that Mario Plebani shall be thanked (once more) for giving us the privilege to read, in such a lucid and futuristic article, the important lessons that we have (or shall) learn from the ongoing COVID-19 pandemic outbreak, wishing that we could treasure them for such an unpredictable future.

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