

Reflections after 2 years of COVID-19 pandemic

Two years into the COVID-19 pandemic, while the world is facing a new surge from another SARS-CoV-2 variant of concern (VOC) and the end of the pandemic is not in clear sight, there is sufficient experience to prevent further communication failures in the current and in future pandemics, and to curb the erosion of trust in science and expertise.^{1,2} We attempt here to draw conclusions on several controversial points.

(1) The futility of containment. Throughout history, respiratory pathogens associated with low morbidity and mortality, whereby the pathogen can spread from human to human before symptoms become apparent, have never been contained at the population level. The problem is that the vast majority of asymptomatic or mildly symptomatic patients are healthy enough to move around, and thus far there is no easy mechanism for identifying infected individuals who are infectious. Stringent “lockdowns” - which should be communicated as strategies to buy time and protect health systems from collapse, not to end the viral epidemic - are incompatible with social life as implemented in westernised societies. Thus far, only societies that accept stringent limits to personal freedoms have been able to reduce spread by lockdowns. Limited lockdowns could be less impactful on economies, and could involve frail subjects: in westernised countries, the average age of death from COVID-19 has been around 80 and, before vaccines were deployed, the elderly population should have been a priority for protection by means of isolation. This did not happen anywhere, perhaps because westernised societies have a high median age, and politicians have not wanted to upset older voters. Among the most nonsensical measures was the halting of direct flights from countries where novel variants were first detected, which often just meant they had the best surveillance systems. Given that at the time of first detection leading to such action, massive spreading had probably already occurred via prior direct and indirect flights or other means of transportation/routes (i.e., train, boat, car, etc.), such measures proved futile with every VOC. In addition to lockdowns, contact tracing (either digital or self-reported) and testing has been often advertised rhetorically as part of the call to action required to “win the war against the virus”. Systematic contact tracing and massive deployment of screening tests only make sense when the incidence of novel cases is low,³ and was successfully implemented in multiple

instances in China⁴⁻⁶), but the majority of westernised countries have instead pretended to continue non-automated contact tracing approaches while having more than 3% of the general population affected at a given time: this is nonsense given that manual tracing has been shown to miss up to two out of 3 contacts.⁷ On the other side, automated tracing with smartphone apps is not affordable in low-to-middle income countries (LMIC) and requires compliance from 56% to 95% of the population⁸: in a perfect oxymoron, this countermeasure is hence mostly available for countries who are too concerned for their privacy to adopt it. Furthermore, massive testing by high-priced molecular or antigenic assays is very costly even for robust economies and, after a certain level of contagion has been reached, produces only marginal benefits for the public. Part of the justification for this effort was the need to understand viral evolution and ecology. Under peak pandemic waves, random sampling of symptomatic cases might be a better approach for real-time monitoring of viral evolution, so that fund allocation could be shifted to more cost-effective programs and strategies (e.g., antiviral research, healthcare staff, or intensive care unit beds). Since a novel VOC could emerge anywhere, those virological surveys are relevant at any location, and WHO should promote random sequencing efforts to LMIC.

(2) The unpredictability of modern pandemics. Mark Twain is often suggested as the originator of the quote “*It's difficult to make predictions, especially about the future*”. Every pathogen is different. Consequently, the trajectory of modern pandemics from low-grade respiratory viruses cannot be predicted based on past examples (including past coronavirus outbreaks). Even for well-known and highly predictable viral threats, like influenza, we have very limited ability to prevent severe seasonal disease (such as the last flu pandemic). While on the one hand, globalisation leading to faster circulation has the potential to accelerate the year-long process of spontaneous viral attenuation/adaptation, on the other hand, chronic replication in an unprecedented number of immunocompromised hosts (a growing slice of the population in Westernised countries) and selective pressure from antibody-based therapeutics (e.g., monoclonal antibodies) and vaccine-elicited antibodies have the potential to alter such trajectory by facilitating the emergence of otherwise rare viral variants that are fit enough to spread.⁹ Predictive models so far have only been validated retrospectively.¹⁰

- (3) The peculiarities of SARS-CoV-2. Several factors peculiar to coronaviruses make the trajectory of the SARS-CoV-2 pandemic even less predictable. First, SARS-CoV-2 is not a pandemic - it is a panzootic event¹¹ - and numerous other species (including pets) are being infected.¹² Confinement of mammals from human lives is not possible worldwide, increasing the chances for reverse zoonoses. Accordingly, reverse zoonosis from mice currently represents a likely explanation for the emergence of the Omicron VOC,^{13,14} as suggested by mouse adapted mutation sites.¹⁵ Second, the SARS-CoV-2 genome is prone to recombination, with two recombinant sublineages (dubbed XA and XB in PANGO phylogeny) already described, and multiple recombination events (either with seasonal coronaviruses or human transcripts¹⁶) likely also the basis of the Omicron VOC.¹⁷ There are reasons to believe this may happen again in the coming months. During the COVID-19 pandemic, we have seen a progressive growth in the basic reproductive number of subsequent VOCs (from 2.4 to 3.4 for the original Wuhan strain to 4-5 for Alpha to 5-8 for Delta to eight for Omicron). Higher viral loads leading to higher reproductive numbers are generally considered a proxy for viral adaptation to host, although this is not universally true.¹⁸ Paradoxically, with Omicron approaching the asymptote of reproductive number for human respiratory viruses, this VOC could be our best insurance against the dominance of another novel VOC, and the steadiness of pandemic lineages should offer manufacturers much-needed stability to develop novel therapeutics and vaccines.
- (4) The limitations of narrow antigenicity. Spike-based vaccines (especially mRNA and adenoviral vector-based ones) have been incredibly quick to manufacture and have dramatically reduced hospitalisation rates and mortality, but are prone to immune escape, as proven by the sudden and massive emergence of the Omicron VOC. While most manufacturers are just redesigning their Spike-only vaccines with the novel Omicron sequence,¹⁹ traditional whole virus-based (either inactivated or attenuated) vaccines, possibly combined with adjuvants to increase the duration of protection, should continue to be investigated, being less prone to global immune escape. Many such vaccines are almost stuck at the starting line because their proponents slowed development when the undoubted success of mRNA vaccines suggested that they would not be needed. The same generally applies to passive immunotherapies. While lessons have been learnt about the risk of immune escape with single monoclonal antibodies⁹ as opposed to cocktails, the currently approved entities only include strain-specific anti-Spike antibody cocktails. Sotrovimab, the only pansarbecovirus antibody approved to date, has not been combined with a different mAb and is hence prone to immune escape in up to 10% of recipients.²⁰ ACE2 decoys, which by definition are less dependent on Spike mutations, should also be further investigated as therapeutics for the current and for future coronavirus pandemics.²¹⁻²³
- (5) The illusion of herd immunity. The fact that SARS-CoV-2 can replicate in individuals vaccinated with the currently available vaccines means that herd immunity sufficient to stop the pandemic cannot be achieved with the current generation of systemically administered vaccines. Those vaccines prevent severe disease (which represents an extraordinary goal) and partly hasten viral clearance, but lead to viral load peaks similar to those seen in unvaccinated subjects,^{24,25} which is enough to maintain the transmission chain. This is evident in the widespread circulation of the Omicron VOC in regions with vaccine coverages higher than 90%. Sterilising and herd immunity might be eventually achieved more easily by deploying mucosal vaccines, but even in that case animal reservoirs might prevent virus eradication.
- (6) The inadequate pace of progress. Despite the dazzling rapidity with which vaccines, monoclonal antibodies, antivirals, immunomodulators, and rapid diagnostic tests have been developed, it is increasingly apparent that 21st-century science cannot fully keep ahead of a respiratory pandemic such as COVID-19. The recently revised WHO guidelines on drugs to use against COVID-19 make it clear that we do not have drugs that are significant game changers. While there is hope from candidates such as nirmatrelvir or molnupiravir, we still have no certainties on their clinical efficacy or escape, and costs would likely remain prohibitive for LMIC. Nonpharmaceutical interventions and convalescent plasma are potential public health measures that demand further study. To conclude: despite a heart-breaking struggle in the first months of the pandemic, the natural evolution of the coronavirus is a formidable problem that has eluded monoclonal antibody therapies and weakened the power of certain vaccines.
- (7) Lack of solidarity. Whereas respiratory viruses can evolve rapidly, human behaviour is far more constant: the ancient dictum "*Homo homini lupus*," which translates as 'man is wolf to man' remains valid. This can be seen in many instances under the current pandemic.
- First, with vaccine coverage still below 5% in most southern hemisphere countries, westernised economies have largely boycotted the WHO COVAX plan in order to ensure third (and eventually fourth) vaccine doses to their populations, given the predictable manufacturing bottlenecks under pandemic scenarios.²⁶ While it is clear that COVID-19 is mostly a disease of the frail elderly, which is an underrepresented category in LMIC compared to westernised countries, this cannot be used as a justification to deny vaccine access at all, also considering the limited resilience of healthcare systems in LMIC. The same reasoning applies to therapeutics. Both antibodies and small chemical antivirals are not affordable to LMIC and come in short supplies.
 - Secondly, investigator-initiated studies for off-label drug usage typically suffer from poor economic support compared to company-sponsored trials for novel drugs. Additionally, many high-impact factor journals profit on reprint sales to drug manufacturers, which could favour acceptance for publication of company-sponsored trials.²⁷ In the current pandemic, this conflict of interests has translated into better echo for novel

antivirals and immunosuppressive drugs, which have been advertised as magic bullets for every patient, while real-world evidences have instead shown modest benefits in more selected populations. Noninferior benefits are achievable with far cheaper, old-fashioned approaches, which have often been dismissed by opinion leaders. For example, it has taken 2 years before well-designed trials have convinced the US Food and Drug Administration²⁸ and the Infectious Disease Society of America²⁹ to introduce high-titre convalescent plasma within the therapeutic armamentarium for COVID-19 outpatients.

- c. Third, despite an unprecedented success from vaccines, westernised societies have experienced significant growth of anti-vax movements whose anti-scientific quests have gained attention by both media and political parties. In other words, vaccines, long perceived as a success story for science and a benefit for humanity, have instead become, via subjective interpretations, a polarizing topic generating social tensions.

By nature, humans often get bored with chronic situations, and even the most scaring novelties tend to become under-evaluated in time. We authors are concerned about how the ending of the pandemic will be managed. At the time of writing, many governments are proposing solutions that do not match biological realities, such as “green passes” with unlimited validity, or suddenly removing face mask mandates for indoor activities while the virus is circulating at unprecedented rates, just because the peak of the current wave seems to have passed. Such transition from black to white, without any shade of grey, seems supported more by mental tiredness than by factual science, and the complete and sudden removal of nonpharmaceutical interventions comes with the risk of flares that would diminish the achievements made so far. While some modelling studies suggest that high viral transmission amongst populations with high vaccination coverages paradoxically accelerates the endemic transition of COVID-19 with reduced numbers of severe cases,³⁰ caution is needed to avoid leaving frail patients behind. In two years we should have learnt that the old adage about “the possible becoming probable and the probable becoming inevitable” has become consistent.¹⁷ Time has come to look behind us and learn lessons.

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CONFLICTS OF INTEREST

We declare we have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Guido Antonelli conceived the manuscript and revised the manuscript; Daniele Focosi wrote the first draft; Fabrizio Maggi and Arturo Casadevall revised the manuscript. All authors approved the final version.

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