

Letter to the Editor

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Uncontrolled confounding in COVID-19 epidemiology

<https://doi.org/10.1515/dx-2022-0128>Received November 23, 2022; accepted November 25, 2022;
published online December 7, 2022**Keywords:** COVID-19; epidemiology; SARS-CoV-2.

To the Editor,

Public health policies concerning control and prevention of infectious diseases are deeply driven by epidemiologic data, especially when the pathogens have high propensity to spread as local outbreaks or, even worse, as pandemics, like that more recently caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) [1]. To this end, the necessary foundation for calculating the reproduction numbers (i.e., R_0 or R_t) and for establishing social or individual restrictive measures (i.e., quarantine, isolation, prolonged use of personal protective equipment, mandatory vaccination, etc.) that are effective for mitigating the clinical, social and economic consequences of an infectious disease, is dependent on the fact that the information on the epidemiologic situation is substantially reliable [2].

The gradual evolution of coronavirus disease 2019 (COVID-19) from a serious, life-threatening pathology, to an endemic infection with mortality rates even lower than those of common flu in the general population [3], have contributed to a radical change in its perception by many healthcare agencies, national governments and in the collective imagination, thus paving the ways to a series of factors that may now seriously undermine and deflate the

real epidemiology. Such “unmeasured confounders”, which may hence contribute to generate uncontrolled confounding in COVID-19 epidemiology, are mostly represented by undertesting, underdiagnosis and/or underreporting, the causes of which are summarized in Table 1 and will be briefly discussed in the following paragraphs.

The clinical phenotype of COVID-19 has considerably changed over time due to the combined effect of mutations within the viral genome that have attenuated its pathogenicity, but also for development of widespread vaccination campaigns, combined with widespread community transmission of highly infectious variants (i.e., Omicron), generating host immunologic responses which have contributed to mitigate the harm directly caused by the virus to its human host [4]. As earlier discussed, the different perception of the biological injury that the virus can now generate may lead to a substantial burden of underdiagnosis or underreporting. This is mainly due to confusion of symptoms with those caused by other endemic respiratory diseases (i.e., seasonal flu, common cold, etc.), underestimation of the risk of clinical deterioration, as well as by deliberate aversion of quarantine and/or isolation, thus avoiding social segregation and potential economic losses. The widespread diffusion of SARS-CoV-2 antigen rapid diagnostic tests (Ag:RDTs), also known as lateral flow immunoassays (LFAs), may also contribute to deflate the official statistics [5]. These self-tests can be purchased in pharmacies, markets and in many other facilities, can be easily used by the patient, and their results are not mandatorily recorded within public health tracking systems, surveillance programs and healthcare safety networks, thus contributing to reduce further the number of officially confirmed cases. Diagnostic tests availability is another important determinant of COVID-19 statistics, in that shortage of economic, technical and human resources in many geographies leads the way to a substantial undertesting and consequent underestimation of the real number of SARS-CoV-2 infections [6]. This is especially true considering that nearly 99% of all SARS-CoV-2 infections cannot be classified as confirmed cases in the African region [7].

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Table 1: Uncontrolled confounding in COVID-19 (coronavirus disease 2019) epidemiology.

Leasing unmeasured confounders
– Undertesting
– Underdiagnosis
– Underreporting of positive cases
Causes
– Lack of economic, technical and/or human resources for testing
– Confusion of symptoms with other respiratory infectious diseases
– Motivations for averting mandatory isolation
– Self-testing
– Ample variation of clinical phenotypes and viral loads due to:
– Use of different vaccines
– Widespread immunity in the community
– Emergence of new SARS-CoV-2 variants and sublineages
– Unreliability of serological testing

Widespread vaccination is another aspect that may contribute to bias the official number of SARS-CoV-2 infections. COVID-19 vaccination varies widely all around the world, but even within the same countries and regions, in terms of population coverage, vaccine type (mRNA-based, protein-based, adenoviral, attenuated and so forth), vaccine formulation (i.e., monovalent, bivalent) and number of immunizations (i.e., primary cycle, one or more booster doses) [8]. The clinical efficacy of different COVID-19 vaccines is wide, as is their potential impact on the viral load in respiratory specimens [9], thus impairing diagnostic sensitivity and accuracy of certain SARS-CoV-2 tests, especially Ag:RDTs [10]. Last but not least, different SARS-CoV-2 variants, even those belonging the “Omicron family”, are characterized by wide variability of clinical phenotypes and viral loads [9], which may also concur to bias the accuracy of SARS-CoV-2 testing. The use of serological testing cannot help obtain a more accurate picture of COVID-19 epidemiology, since SARS-Cov-2 seropositivity or seronegativity are biased by a variety of confounding factors that make the currently marked anti-SARS-CoV-2 immunoassays outdated and mostly unfit for this purpose [11].

According to the World Health Organization (WHO), the “official” number of SARS-CoV-2 cases and COVID-19 related deaths at the end of November 2022 has now exceeded 636 and 6.6 million, respectively [12]. Owing to the bias generated by the unmeasured confounders and their most likely causes summarized in Table 1, we proffer that the reliability of these figures may be questionable, as would be all those others generated by public health agencies, institutes of health, safety networks and surveillance programs, as also

implicitly acknowledged by the WHO which states that case definition, testing policies and reporting practices differ largely around the world, thus biasing final numbers with variable under- or overestimation [12]. The “underestimation window” not only varies widely according to the target setting (i.e., between <5% in some hospitals where regular SARS-CoV-2 testing is mandatory, up to 99% in geographical areas where testing is mostly unavailable), but is also increasing exponentially. Before “official cases” will become the tip of the iceberg of all worldwide SARS-CoV-2 infections, we need to certify the technical failure of current epidemiological systems only based on laboratory diagnosis, for the various reasons summarized in Table 1. Neither complementing molecular or antigenic testing with clinical case definitions would help improve the final estimation, due to the coincident circulation of other respiratory pathogens causing similar illness. Thus, the deepest and discouraging truth is that no magic bullet seems to exist so far for improving the accuracy of official COVID-19 epidemiology to the best of our knowledge. Nevertheless, the use of probabilistic bias analysis, aimed at mitigating the effect of uncontrolled confounding, has held premises in other medical fields, such that consideration could be made to test its effectiveness also for COVID-19 epidemiology [13].

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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