GLOSSARY

An in-depth analysis of 10 epidemiological terminologies used in the context of COVID-19

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Abstract

Aim: In this paper, we explore the contextual use of 10 epidemiological terminologies, their significance, and interpretation/misinterpretation in explaining various aspects of the 2019 novel coronavirus disease (COVID-19) pandemic. *Methods and Results:* We first establish the different purposes of the terms 'pandemic' and 'Public Health Emergency of International Concern.' We then discuss the confusion caused by using the 'case fatality rate' as opposed to 'infection fatality rate' during the pandemic and the uncertainty surrounding the limited usefulness of identifying someone as 'pre-symptomatic.' We highlight the ambiguity in the 'positivity rate' and the need to be able to generate data on 'excess mortality' during public health emergencies. We discuss the relevance of 'association and causation' in the context of the facemask controversy that existed at the start of the pandemic. We point out how the accepted epidemiological practice of discussing 'herd immunity' in the context of vaccines has been twisted to suit the political motive of a public health approach. Given that a high proportion of COVID-19 cases are asymptomatic, we go on to show how COVID-19 has blurred the lines between 'screening/diagnosis' and 'quarantine/isolation,' while giving birth to the new terminology of 'community quarantine.' *Conclusions:* **Applying the lessons learned from COVID-19 to better understand the above terminologies will help health professionals communicate effectively, strengthen the scientific agenda of epidemiology and public health, and support and manage future outbreaks efficiently.**

Keywords: *COVID-19, glossary, epidemiology*

Introduction

The 2019 novel coronavirus disease (COVID-19) pandemic signifies a critical point in history. While the pandemic continues to wreak havoc on the world, we must continue to track the lessons learned so they are not forgotten in the post-COVID-19 era [1]. In this article, we focus on the field of epidemiology and explore learnings regarding the terminologies being used in an epidemiological context during the COVID-19 pandemic.

Epidemiology, though often a neglected discipline, has no doubt helped save lives by guiding policymakers and programmers to make informed decisions to control past pandemics and the current COVID-19 pandemic [2]. While a plethora of definitions exist for epidemiology, in its simplest form epidemiology is

the study of how often diseases and their consequences occur in a different group of people and why [3]. Similar to a disease's etiopathogenesis and clinical manifestations, disease epidemiology is an essential component of its basic description. While epidemiology as science is over 2500 years old, it came to prominence in 1854 with John Snow's landmark investigation about the cholera outbreak in London.

The use of epidemiological concepts initially focused on acute infectious diseases, particularly those with the potential for an epidemic. In the 1900s, epidemiological science extended its scope to include non-infectious diseases [4]. Since World War II, epidemiology has advanced profoundly to include the distribution and determinants of all health-related states or events in specific populations and

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application of this knowledge to control disease [5]. During its evolution, epidemiology has gained unique techniques in data collection and interpretation supported by well-defined technical terminologies. These terminologies are critical in this field due to its methodological nature for studying populations in complex situations [6]. In this commentary, we explore the contextual use of 10 epidemiological terminologies during the COVID-19 pandemic, and discuss their significance and potential for misinterpretation when used to explain various aspects of the pandemic. These terminologies have been chosen by the authors due to repeated reference of them, both in media reports and in published literature.

Pandemic declaration

In epidemiology, the term pandemic is defined as 'an epidemic occurring over a very wide area, crossing international boundaries, and usually affecting a large number of people' [7]. This definition does not refer to virology, immunity, or severity, as noted by Heath Kelly [8], who argued that the definition of a pandemic cannot be elusive. The definition of a pandemic is often challenged during the actual occurrence of pandemics, as has happened during the current COVID-19 pandemic. For example, the World Health Organization (WHO) was accused of changing the definition of 'pandemic' during the 2009 Influenza A virus H1N1 subtype (H1N1) outbreak in order to label it a pandemic. Records suggest that until May 4, 2009, the WHO's influenza pandemic preparedness page contained the statement: 'New influenza virus appears against which the human population has no immunity, resulting in several simultaneous epidemics worldwide with enormous numbers of deaths and illnesses' [9]. After May 4, 2009, the new statement on the website read as: 'An influenza pandemic may occur when a new influenza virus appears against which the human population has no immunity.' By omitting the reference to an 'enormous number of deaths and illnesses,' the H1N1 outbreak was declared a pandemic [9].

In its 2017 guide for pandemic control to inform and harmonize national and international pandemic preparedness and response, WHO defined the pandemic phase of influenza as the 'period of global spread of human influenza caused by a new subtype based on global surveillance.' The guide further has this quote: 'Declaration of a pandemic: during the period of spread of human influenza caused by a new subtype, based on risk assessment and appropriate to the situation, the WHO Director-General may make a declaration of a pandemic' [10].

Fast forward to 2020, on March 11, 2020, as COVID-19 spread rapidly worldwide, the WHO Director-General said:

> WHO has been assessing this outbreak around the clock and we are deeply concerned both by the alarming levels of spread and severity and by the alarming levels of inaction. We have therefore made the assessment that COVID-19 can be *characterized* as a pandemic. [11] (Page 1)

Thus, WHO chose to characterize COVID-19 as a pandemic, but not to declare it a pandemic. The WHO Director-General further stated that *describing* the situation as a pandemic would not change what WHO was doing and that countries should maintain the status quo in responding to the pandemic. The milestones timeline since provided by WHO to track the COVID-19 response refers to the pandemic *characterization* on March 11 and not a declaration [12]. Interestingly, the WHO's Director-General had already *declared* the novel coronavirus outbreak a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, which is WHO's highest level of alarm [12].

The term 'PHEIC' is defined in the International Health Regulations (2005) as 'an extraordinary event which is determined, as provided in these Regulations to constitute a public health risk to other States through the international spread of disease, and to potentially require a coordinated international response' [13]. The expectation is that a PHEIC declaration will create a sense of seriousness among member states and a sense of urgency for initiating international action. We believe that the epidemiological purity of a pandemic definition – an outbreak, crossing international boundaries, and affecting many people – should not be confused with a PHEIC, a declaration of which calls for coordinated mobilization of resources by the international community. Declaring COVID-19 to be a PHEIC in January 2020 and later characterizing the outbreak as a pandemic in March without declaring it to be a pandemic created confusion and presented challenges to decision- and policymakers in taking decisive action. We hope that there is no debate on whether the next pandemic is indeed a pandemic or not, and that there is a global consensus on actions taken to effectively control the outbreak promptly.

Case fatality and infection fatality

The epidemiological approach to controlling disease involves counting cases or health events (such as deaths); describing them in time, place, and person;

dividing the number of cases by a denominator to calculate rates and ratio, and comparing this over time with different groups of people [14]. Epidemiology places high emphasis on 'cases'; hence, calculating case fatality rate/ratio becomes a logical extension of the emphasis provided for case definition during a pandemic. All initial epidemiological bulletins and reports of COVID-19 (released by global agencies and governments) focused heavily on the case fatality rate/ratio. However, countries used different definitions for 'case fatality rate/ratio' (due to varying case denominators – all symptomatic, only tested, hospitalized, etc.). This meant that no consensus emerged, making meaningful comparisons of case fatality rates/ratios in different countries extremely difficult, often leading to confusion [15]. On a parallel front, however, we see an increasing use of the term 'infection fatality rate' in the emerging literature during the pandemic.

The most up-to-date version of the epidemiology dictionary edited by Michel Porta [7] does not include a definition for the infection fatality rate/ratio. A systematic review of case fatality during the H1N1 pandemic by Wong et al. calls for a consensus in estimating infection fatality as early as possible in a pandemic [16]. Traditional epidemiology still relies on the concept of 'virulence,' defined as disease-evoking power, to estimate the severity of a micro-organism [7]. This has become less relevant during the current COVID-19 pandemic since most infections are asymptomatic or result in mild illness only. Since panic and confusion are rampant during a pandemic, COVID-19 provides a lesson in the importance of being able to compute infection fatality rate/ratio early on to better understand the lethality of the illness and whether it has the potential to lead to death. It is noteworthy that WHO is now recognizing this and has defined the infection fatality ratio in its scientific brief on 'estimating mortality' from COVID-19 [17]. We acknowledge the challenge in interpreting case fatality rates/ratios during a pandemic, and thus call for a more systematic use of infection fatality rates/ratios in future pandemics, and case fatality rate/ratio when appropriate.

The term 'pre-symptomatic' and its usefulness

Commonly used epidemiological terms such as 'clinical cases,' 'sub-clinical cases,' and 'asymptomatic' cases are self-explanatory. However, we did not come across the term 'pre-symptomatic' when we scanned the epidemiological literature published before COVID-19. Given the recent introduction of this term, it is not surprising that there is no consensus on its need and actual usage. We discuss two definitions below to highlight the challenges associated with its usage.

In the COVID-19 situation report 73 [18], WHO stated:

> The incubation period for COVID-19, which is the time between exposure to the virus (becoming infected) and symptom onset, is on average 5–6 days, however, can be up to 14 days. During this period, *also known as the 'pre-symptomatic' period*, some infected persons can be contagious. Therefore, transmission from a pre-symptomatic case can occur before symptom onset.

In its definition, WHO has equated the pre-symptomatic period with the incubation period. We found another definition widely used in the literature where the pre-symptomatic status is related to laboratory confirmation of COVID-19 [19]:

> Asymptomatic individuals are defined as *individuals who test Reverse Transcription–Polymerase Chain Reaction* [RT-PCR] *positive* but exhibit no symptoms that would indicate severe acute respiratory syndrome – Coronavirus-2 [SARS-CoV-2] infection. While some individuals may go the entire course of infection and never experience symptoms, other individuals who initially present as asymptomatic may go on to develop symptoms days or weeks later. The individuals *who will later develop symptoms are defined as being pre-symptomatic.*

If the individual has tested RT-PCR positive for SARS CoV-2 infection, one would expect the person to be isolated and monitored to halt transmission, whether the person is symptomatic, asymptomatic, or pre-symptomatic at that point of time. The key message here though is that people can have no symptoms and still be infected and RT-PCR positive. Epidemiologically speaking, it doesn't matter whether the person will have no symptoms at all (asymptomatic) or develop symptoms later (pre-symptomatic).

Looking at the two definitions above, there is apparent confusion between the terms 'pre-symptomatic' transmission and 'pre-symptomatic' individuals. Our opinions of the definitions are that the latter serves no separate epidemiological purpose and the former just reiterates the transmission that can occur during the incubation period. Therefore, we question the need for these new terminologies of 'pre-symptomatic transmission' and 'pre-symptomatic individuals.'

COVID-19 mortality and excess mortality

Globally, the mortality pattern during this pandemic has raised many questions regarding the deaths, directly and indirectly, attributable to COVID-19. The mortality rates due to COVID-19 and

non-communicable and communicable diseases are available. However, we do not fully know what the measurable mortality is due to the indirect consequences of COVID-19 (overwhelmed health systems, patients postponing emergency care, lack of transport to reach health facilities, etc.). It is also worth noting that the number of deaths due to the social and economic consequences of the pandemic is even more elusive.

As a result of these uncertain mortality data, the indirect mortality attributed to COVID-19 is best measured by 'excess mortality,' a term that is being commonly used in the scientific literature during the current pandemic. This term is predominantly used by epidemiologists who work in settings of natural and human-made disasters. In public health emergencies (which are not always considered humanitarian emergencies) [20], we rarely see estimates of excess mortality. In this context, excess mortality would include deaths due to the indirect effects of the public health emergency, such as health systems being unable to provide sufficient resources for managing other emergency conditions, patients being unwilling to seek emergency care for fear of infection, depression and suicide associated with the loss of job and revenue, etc. This was a lesson learnt during the 2013–2016 Ebola pandemic, but it has not been applied by countries systematically during the COVID-19 pandemic [21].

The Centers for Disease Control and Prevention, Atlanta (CDC) has recently included a definition of 'excess deaths' in the context of COVID-19 as the difference between the observed number of deaths in a specific time period and the expected number of deaths in the same time period [22]. Pandemic preparedness should require countries to estimate the mortality rate during the preparedness phase to be able to calculate the indirect mortality rate of the pandemic eventually. We believe that 'excess mortality' is a key epidemiological terminology that should be applied in both humanitarian and public health emergency contexts.

Association, causation, and the body of evidence

One of the primary objectives of epidemiology is to identify factors that contribute to disease causation and control. Most epidemiological research is observational, and, so, determining the cause–effect relationships presents a challenge. Though randomized control and prospective trials are often the Holy Grail in helping to provide the best possible evidence of causation (including establishing the effectiveness of interventions), it may not be possible to carry out such studies in unique situations such as during a

pandemic. Feasibility and ethics need to be considered and there needs to be openness to settle for low-quality evidence in such situations. The recommendation on facemask use exposes this fallacy. While some countries (including the USA) found correlation studies sufficient to recommend facemask use among the general population, WHO waited for more definitive 'causative' evidence before recommending facemask use by the general public [23]. When it became apparent that such robust evidence would be difficult to generate during an ongoing pandemic, the agency relented to the use of available evidence of association and laboratory studies to recommend facemask use.

In many iterations of the WHO guidelines, the agency continued to cite the lack of 'direct evidence' for facemask use by the general public and recommended discretionary facemask use by countries as deemed appropriate [24]. We question the need for direct epidemiological and causative evidence during a pandemic when early decisions on promising 'do no harm' interventions can be lifesaving. We call for more flexibility in the interpretation of association studies during a pandemic caused by a novel agent. While there is no direct evidence for regular handwashing and physical distancing (with the lingering debate regarding 1 m vs 1.5 m vs 2 m) during COVID-19, these measures were recommended immediately after the onset of the pandemic. However, this was not the case for the recommendation of facemask use by the general public. Commonalities in respiratory, feco–oral, vector-borne, sexually transmitted diseases should be recognized to identify a basic package of preventive interventions that can be rolled out at the start of any outbreak/pandemic.

Almost five decades ago, Sir Austin Bradford Hill wrote the below in the context of exploring the phenomenon of association and causation [25]:

> I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. . .
>
> . . . However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances. [25] (Page 2)

Sir Hill identified nine aspects of association that need to be considered before deciding on causation. Of the nine, temporality, strength of association, consistency of results, dose-response, and biological plausibility are the most critical [26]. The need to reinforce these aspects while defining association and causation in epidemiology cannot be over-emphasized.

Herd immunity and its relevance

'Herd immunity' is the immunity of a group or a community. Immunity, in this context, is the resistance to infection among a high proportion of individuals within the group [27]. Herd immunity to many viral diseases can be acquired by prior infection and, more importantly, by vaccination. This term, which originated in veterinary science, has evolved and remains a matter of confusion and debate [28]. When referenced recently in epidemiology, herd immunity has become synonymous with immunity generated through vaccination [29], and any disease for which herd immunity is discussed has an effective vaccine [30]. Herd immunity, when discussed in such contexts as public health, acknowledges that 100% coverage for all services to the whole population is near impossible [31]. Historically, it is said that voluntary exposure to varicella in the form of chickenpox parties was practiced in order to build herd immunity before the advent of the vaccine [32]. We do not see the purpose of taking such a huge risk during a pandemic, given so much uncertainty around any novel disease. Sweden's approach of not mandating lockdowns – and consequently resulting in community transmission – is seen as responsible for the country recording 4.5 to 10 times more deaths per million when compared to its neighbors during the second wave in December 2020 [33]. Serosurveillance studies conducted during the first wave of the COVID-19 pandemic showed that only a small proportion of the population has circulating antibodies post infection, even in countries with large outbreaks [34,35]. We also see mathematical models claiming that herd immunity can be reached with a lesser proportion of the population being naturally infected by the SARS-CoV-2 virus [36]. We believe that the misreading and/or misinterpretation of these findings could set dangerous precedents for future pandemics, with populations paying a heavy price for challenging the standard field-oriented epidemiological practice of discussing herd immunity only in the context of vaccine-preventable diseases.

Positivity rate

The 'positivity rate' for any disease is the number of people who are positive in laboratory tests among those who have been tested. A positivity rate provided on its own is meaningless unless the numerators and denominators are defined and the time duration for the tests specified. Two medical conditions for which positivity rates are commonly recorded in public health surveillance are malaria and tuberculosis. For malaria, a slide positivity rate, and for tuberculosis, a sputum smear positivity rate, are used to track trends in transmission and incidence [37,38]. In both conditions, active and passive surveillance is carried out and the criteria determining who should be screened for the disease are simple and established (anyone with fever in a malaria endemic zone for malaria, and anyone with a cough over two weeks in areas where tuberculosis is prevalent). There are major problems using a similar strategy for COVID-19 during the current pandemic, and there possibly will be again in similar future situations. The fundamental problem is that there is no common understanding globally of who is being tested – for each country, testing criteria are different; are these patients, for example, who are passively tested through RT-PCR when they come with symptoms to a health facility? Or are these asymptomatic persons in the community? Or others? This is one of the reasons seen for the wide variation of swab positivity (less than 1% in parts of the USA and Uruguay vs more than 50% in Mexico and Bolivia) in various countries [39]. The lack of a clear definition of the denominator being used by countries worldwide hinders our understanding of these figures [40]. Firstly, we call for a standard terminology to define 'positivity rate' for SARS CoV-2 as a swab positive rate for COVID-19 (with the naming of the test used to put this in the context of the predictive value of these tests). Secondly, the definition of the denominator (the total number of swabs tested for COVID-19 in suspected patients) should accompany the computation of these rates. Positivity rates and their significance are disease-specific and must be defined to appreciate public health significance.

Screening and diagnosis

'Screening,' by definition, is the identification of unrecognized disease in apparently healthy individuals using tests that can provide results rapidly [41]. There are well set criteria for screening tests: the investigated disease must have a gold standard test for diagnosis; disease treatment must be available; and the natural history of the disease must be fully understood [42]. Anonymous screening is also done for surveillance purposes and, as a precautionary measure, during the blood transfusion process. 'Diagnosis,' on the other hand, is about confirming the existence of the disease with high certainty in those who screen positive. In the case of COVID-19, there is no separate gold standard test to confirm the diagnosis. RT-PCR, the most widely used test, is the only test being used for both asymptomatic and symptomatic individuals. As a rule of thumb in epidemiology, screening tests have high sensitivity

whereas diagnostic tests have high sensitivity and specificity (accuracy) [43]. We know that there are different categories of people who are being tested for COVID-19: a) symptomatic individuals, b) their contacts, and c) asymptomatic individuals. During COVID-19, asymptomatic individuals are not being screened for early diagnosis and *treatment* as is the usual goal of screening, but are instead being screened for early diagnosis and *isolation*. In pandemic situations such as COVID-19, there will likely be a lack of clear distinction between the two terminologies – screening and diagnosis – and this limitation should be acknowledged.

Quarantine and isolation

'Quarantine' is the restriction to activities of well persons who have been exposed to a 'case' of communicable disease during its period of communicability [41]. 'Isolation,' on the other hand, is about separating infected persons from others to prevent or limit transmission [41]. The CDC places emphasis on sickness and denotes isolation as separating sick people with any contagious disease from people who are not sick. According to the CDC, the goal of quarantine and isolation are to protect people by preventing exposure to those exposed and/or infected [44]. WHO sees quarantine as being used to monitor symptoms and ensure early detection of cases, distinguishing it from isolation, which it defines as separating the ill or infected persons from others to prevent spread or contamination [45]. Knowing that the vast majority of COVID-19 cases with no symptoms or only mild symptoms recover fully, using sickness criteria to distinguish quarantine and isolation may not be useful. Similarly, given that many cases could be asymptomatic, and the objective of quarantine is monitoring, this should not be restricted to symptoms but would make better sense if it is combined with testing (at the end of the incubation period) as the definition for isolation is to include all infected and not just those who are ill/sick (with symptoms). Hence, an expanded definition of quarantine is needed to look beyond sickness and symptoms during the quarantine phase.

Community quarantine

Community quarantine is not a standard epidemiological term but has been doing the rounds during past pandemics [46] and has found firm ground during the COVID-19 pandemic. The term community quarantine has been applied to whole communities in which active disease transmission is ongoing [47]. School closures, closure of public places, and stopping public transport are all means to support community quarantine, but are packaged within an all-encompassing term of 'non-pharmaceutical interventions' (NPIs) by the WHO, a term that also includes personal protective measures such as handwashing and the use of facemasks [48]. The CDC, on the other hand, sub-classifies NPIs as personal NPIs, community NPIs, and environmental NPIs [49]. We believe that NPIs are just a group of individual public health interventions that do not offer epidemiological significance as a sum of parts. The term community quarantine provides the holism that NPIs are lacking. Community quarantine was used in Canada in 2002 during the severe acute respiratory syndrome (SARS) epidemic [50] and in Guinea, Liberia, and Sierra Leone during the Ebola outbreak from 2014 to 2016 [51]. During COVID-19, we have seen quarantine advice not only for communities defined by geographies but also for high-risk groups such as older people and those with multiple co-morbidities [52]. As quarantine, in general, is applied to individuals, this phenomenon of community quarantine warrants a place in the epidemiological lexicon.

Discussion

In this compilation of select terminologies, we have discussed their use and misinterpretation during the COVID-19 pandemic. We have presented existing definitions of these terminologies from published textbooks of epidemiology, papers published during the previous pandemics, and the updates by agencies that set standards such as the WHO and the CDC. We acknowledge that COVID-19-related terminologies have been published by agencies such as the Pan American Health Organization [53], Kaiser Family Foundation [54], and academic institutions such as the University of Virginia [55]. Though no one source compiled all terminologies in the context of the pandemic, the compilation provided by the Pan American Health Organization is the most exhaustive in our opinion. These terminologies, in addition to restating existing definitions of epidemiological terms used in epidemic situations, also provide lay-language definitions of popular terminologies used during the COVID-19 pandemic for the understanding of different stakeholders, ranging from journalists to the general public, and the policymakers. We acknowledge the limitation of restricting our analysis to only the 10 most relevant and commonly used epidemiological terminologies in this manuscript. Our evidence-guided and utility-based compilation of these terminologies further helps clarify/expand epidemiological definitions where there is ambiguity, and strengthen those definitions that are related to

emerging public health concepts. This terminology discussion will enable us to help better understand future epidemics and pandemics. We believe that our initial analysis will stimulate further thinking in definitions of other related terminologies too.

Conclusion

COVID-19 is teaching the world lessons on several fronts across many science fields, and epidemiology is no exception. In this commentary, we explore 10 epidemiological terminologies, and their relevance to the understanding of epidemiology, utility for future public health practice, and implications for population health. It is imperative that we develop, continue to redefine, and use these or other related terms so that there is an international consensus and no ambiguity in their interpretation. This will allow for open communication among health professionals in order to advance the science agenda of epidemiology and public health, and at the same help effectively manage future outbreaks/crises.

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