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COMMENTARY

Seroepidemiological studies: a cornerstone of public health strategies

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Abstract
Well-designed population-based seroepidemiological studies can be useful to refine estimates of infectious agent transmission and disease severity, thus representing an important component of epidemiological surveillance. However, the interpretation of results may be hampered by heterogeneous data quality and the lack of standardized methodology in some cases.
The development and use of highly sensitive and accurate tools, refined over the past decades, have facilitated the study of current and past exposure to infectious agents in target populations. In particular, seroepidemiological studies provide a detailed overview of past and current infection burdens (i.e., respiratory infectious diseases), helping to identify high-risk groups and biomarkers of disease severity. They also help to understand the evolutionary dynamics of the disease over time, providing crucial information on its spread and community impact. Investing time and resources in seroepidemiological studies is essential, not only for monitoring the population's immunological status, but also for implementing strategies that promote public health and predict future infectious diseases scenarios.

Key words
- seroepidemiology
- infectious diseases

Emerging and re-emerging infectious diseases pose a global threat to public health (https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death). Every year, frail individuals, elderly, and people with comorbidities are the main victims and carriers of serious complications [1]. Epidemiologic investigations, combined with the use of laboratory techniques, are essential to study the transmission of pathogens causing infections in humans, the emergence of new viral variants, host-virus interactions, and the influence of the environment on the spread of pathogens, for example, viruses. They are also important to identify the main risk factors in the population and for implementing targeted intervention strategies [2, 3]. The systematic collection and analysis of blood samples from a target population sample may permit the study of the distribution and determinants of infection or the impact of vaccination. Seroepidemiological data can reveal the prevalence and/or the incidence of infections in a population, in order to monitor the emergence of new pathogens and/or the re-emergence of old pathogens and their transmission rate, and to evaluate immunization programs and the level of community immunity [4].

One of the main advantages of seroepidemiological techniques is their ability to utilize biological samples, such as serum samples, routinely collected for clinical or diagnostic purposes. This approach permits the minimization of both costs and logistical complexity because, by creating databases with clinical and demographic data on a large number of individuals, it is possible, for example, to retrospectively identify and select the desired target population without the need to prospectively recruit participants exclusively for the study.

The opportunity to collect and analyse serum samples has also facilitated the conduct of more in-depth studies, since the analysis of the level of IgG and IgM antibodies in response to exposure to specific pathogens may enable to distinguish between an acute or recent infection and a response to a previous infection [5]. In general, the immune response to pathogens is initially expressed with an increase in IgM antibody titer and subsequently with an increase in IgG antibody titer. The strength of using antibody-based techniques is represented by the high sensitivity and specificity of the methods, as antibodies rapidly detect the presence of antigens, even at

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low concentrations, and their molecular structure allows them to precisely recognize and bind to specific parts of a pathogen's antigen with high affinity.

Subjects are classified as seropositive or seronegative based on antibody levels above or below a specified threshold, or as seroconverted following increases in antibody levels above a predefined threshold between two time points. A bias in the interpretation of serological status data relative to a defined threshold could be due to sensitivity and specificity in defining seroconversion, declining antibody levels over time, or cross-reactivity within or between pathogens of the same species [6].

Furthermore, high IgG titers allow the detection of a past infection regardless of the development of symptoms, and the presence of different types of antibodies, some directed against a vaccine target and others against the target of natural infection, permits the differentiation between post-infection and post-vaccination. The ability to test for different antibodies on the same sample facilitates the simultaneous examination of antibody response [7].

The tests employed in the seroepidemiological studies can present limitations, including low specificity that can lead to false-positive results, or even low sensitivity that can lead to false-negatives, and cross-reactivity. The analytical limitations related to test performance have been partially overcome by technological advances.

To obtain good results from a seroepidemiological study, a solid study design and a proper selection of the target population are necessary. Defining the study's objectives is another prerequisite, as it is crucial to decide whether to choose a longitudinal or a cross-sectional study design. The former, i.e., seroincidence study, involves the follow-up of a given cohort of individuals for months or years, allowing to determine the rate at which they develop antibodies over time. These studies are useful for estimating infection rates and identifying some of the factors that may contribute to an increase in the risk of infection. This latter design is also called a "seroprevalence study", and is used to determine the percentage of people with antibodies against a specific pathogen at a given time [8]. Obviously, longitudinal studies are more expensive and have the disadvantage of potentially losing a percentage of participants over time. However, cross-sectional studies can be useful for obtaining a snapshot of population immunity at a specific time, although they do not provide information on cause-effect relationships or changes in individuals' immune status over time.

Another possible limitation of seroepidemiological studies may be due to bias in the selection of the population sample [9]. It is important to emphasize that the sample must be representative of the target population, possess certain demographic and clinical characteristics, and be randomly selected. Furthermore, determining the appropriate sample size is also of fundamental importance in the design of any seroepidemiological study, as it can influence both the level of precision and the statistical power of the study results. An inadequately sized sample can lead to inaccurate estimates and a reduced ability to detect real associations; conversely, an excessively large sample size can lead to an unnecessary increase in overall cost and complexity of the research [10]. A well-designed seroepidemiological study can offer significant advantages.

For example, a seroprevalence study conducted in five municipalities of the autonomous province of Trento, Northeastern Italy, during the COVID-19 pandemic, provided a better understanding of the extent of viral circulation and contributed to the estimate of the proportion of asymptomatic infections. Its purpose was to estimate the number of people exposed to SARS-CoV-2 virus and assess the spread of the infection. This study revealed a higher number of seropositive individuals compared with reported cases, likely due to a high proportion of people with mild or asymptomatic disease or who had not been tested. It also demonstrated that the youngest age groups had higher seroprevalence, and that symptoms such as anosmia and ageusia were strongly associated with the presence of antibodies [11].

In another study, data on IgG antibodies against SARS-CoV-2 spike protein suggested that children were significantly less likely to be infected than adults, useful data for providing infection control policy planning [12].

Seroprevalence studies can be used to study various pathogens and can support the formulation of public health strategies. In the context of vaccine-preventable pathogens, an example can be found in a study conducted on an unexpected increase in meningococcus serogroup C, Sequence Type (ST)11 and clonal complex (cc)11, in the Tuscany region of Italy few years ago [13]. In this case, the study was conducted to further investigate and obtain evidence that could explain the dynamics that led to the sudden increase in meningococcal serogroup C disease and to identify population groups at highest risk of infection. The results suggested a significantly higher incidence of cases compared to previous years with the C:P1.5–1,10–8:F3–6:ST-11(cc11) meningococcal strain as predominant and a particular incidence in the 20-29 age group. Information on vaccination status suggested that the protection provided by a single dose may be inconsistent in some cases.

In the United Kingdom (UK), a 2014 national serological survey of population immunity identified the rapid decline in immunity after infant and toddler immunization as well as the low proportion of teenagers protected against meningococci of serogroup C (MenC) invasive disease around the time the adolescent vaccination programme was introduced [14].

As described, seroprevalence studies provide a precise picture of past and recent infections, allowing estimates of the extent of spread of human pathogens such as viruses or bacteria. If properly designed and conducted, these studies can provide important support for public health strategies. To maximize their benefits, it is essential to follow standardized epidemiological and serological protocols that may facilitate comparisons between studies (over time and space), allow for accurate data analysis, and support the response to emerging and re-emerging infectious threats.

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

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