Original Review Article

Journal of Biological Research & Biotechnology

Bio-Research Vol. 22 No.1; pp. 2292-2301 (2024). ISSN (print):1596-7409; eISSN (online):2705-3822

Application of genomic studies in epidemiological surveillance: A mini-overview

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Abstract

The 21st century has already seen the emergence of several pandemics both in developed and developing nations, including the recent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic. The recent upsurge in certain diseases clearly indicates the need for continuous epidemiological surveillance and real-time monitoring of infectious diseases. Interestingly, genomics has found extensive application in monitoring infectious diseases through the sequencing of bacteria, parasites, and virus genomes. The continual scrutiny of pathogens and the examination of their genetic similarities and distinctions constitute genomic surveillance. The potential of genomic sequencing lies in its ability to offer a significantly more detailed depiction of the evolution and transmission of antimicrobial resistance (AMR), thus initiating a transformative impact on how public health surveillance networks address bacterial AMR. The utilization of whole-genome sequencing (WGS) stands as a prevalent technique for identifying and tracking pathogens, establishing transmission routes, and managing outbreaks. However, despite several decades of advancements, the seamless integration of genomics into surveillance pipelines faces substantial barriers that necessitate overcoming. Recent advances in genomics and next-generation sequencing approaches provide new paradigms for monitoring transmission pipelines and reducing overall morbidity and mortality. In this mini-review, we highlight the advances in genomics, how they have been critical in epidemiological surveillance and monitoring outbreaks, and how they can help predict and monitor possible future outbreaks.

Keywords: Genomics, Epidemiological surveillance, Infectious diseases, Sequencing

Received November 23, 2023; **Revised** February 8, 2024; **Accepted** February 12, 2024, **Published** March 18, 2024.

https://dx.doi.org/10.4314/br.v22i1.7
Journal Homepage: http://www.bioresearch.com.ng.
Publisher*: Faculty of Biological Sciences, University of Nigeria, Nsukka, Nigeria.*

INTRODUCTION

In both the business world and the realm of public health, the maxim 'You can't fix what you don't measure' holds true. Epidemiological surveillance plays a vital role in measuring the scope of an epidemic, enabling us to address the

issue effectively. Recent experiences with Ebola and COVID-19 have underscored the importance of continuous epidemiological surveillance, rapid diagnosis, and real-time tracking of emerging infectious diseases (Bavinger *et al*., 2020; Worsley-Tonks *et al*., 2022; Sheikhattari *et al*., 2023). By closely monitoring the spread of disease, epidemiological surveillance allows us to identify patterns of progression and develop timely preventive and control measures (Ryan *et al*., 2022). Regrettably, accurately diagnosing diseases and monitoring infectious diseases still pose challenges, particularly in low- and middle-income countries (LMIC). Despite efforts to enhance epidemiological surveillance, these LMICs, particularly in Africa, struggle to accurately identify, diagnose, and report communicable diseases (Prieto, 2017; Adebowale & Adesokan, 2021; Worsley-Tonks *et al*., 2022).

The COVID-19 pandemic has highlighted the importance of genomics in disease surveillance. Similarly, the Ebola outbreaks in sub-Saharan Africa, characterized by alarming fatality rates of up to 90% (Lisa, 2016), served as eye-opening experiences with significant lessons learned. While progress has been made in vaccine design and discovery, preventive strategies and supportive therapy remain the primary options available for high-risk individuals and infected patients (Rangaka, 2016). Consequently, there is an urgent need for early and prompt detection of diseases.

Real-time investigation and epidemiological surveillance are critical for increasing awareness and timely infection control and prevention. Integrating genomic, especially whole genome sequencing studies into disease detection is very vital for attaining and building a robust digital and pathogen surveillance system (Gardy, 2018). There is also a need for prompt epidemiological surveillance to understand the circulating infection clones and lineages, their genomic features and how best to control and prevent their spread. Therefore, in this mini-review, we briefly discussed the advances in genomics and how they have been critical in epidemiological surveillance and monitoring outbreak. We also highlighted how robust epidemiological surveillance can help to predict and monitor possible future outbreaks.

Overview of next generation sequencing

In clinical and public health laboratory settings, NGS is very vital (MacCannell, 2016). The sequencing workflow (Figure 1) usually starts with DNA extraction. This is followed by library Preparation. In library preparation, the DNA is fragmented into smaller segments, often by physical or enzymatic methods. Then adapters are added to the DNA fragments. Adapters are short DNA sequences that allow the DNA to be attached to the sequencing platform and provide necessary information for sequencing. The next step is library Amplification – this process uses polymerase chain reaction (PCR) to amplify the DNA fragments with attached adapters. This step increases the amount of DNA available for sequencing. Also, the quality of the library is accessed prior to sequencing. Thereafter, the actual sequencing is performed. There are several sequencing technologies available, including Sanger sequencing, Illumina sequencing (also known as next-generation sequencing), and newer technologies like PacBio and Oxford Nanopore sequencing. During sequencing, the DNA fragments are read, and the order of the nucleotides (A, T, C, G) in each fragment is determined. In the sequencing process, the raw sequencing data is generated in the form of short reads (fragments of DNA sequences). These short reads are then aligned to a reference genome or assembled de novo to reconstruct the original DNA sequence. If analyzing genetic variations is a goal (e.g., identifying mutations), the sequenced DNA is compared to a reference genome to identify single nucleotide polymorphisms (SNPs), insertions, deletions, and other structural variations. Finally, the sequenced data is analyzed to answer specific research questions or achieve specific goals. This could include identifying genes, functional elements, regulatory regions, mutations, or other genetic information.

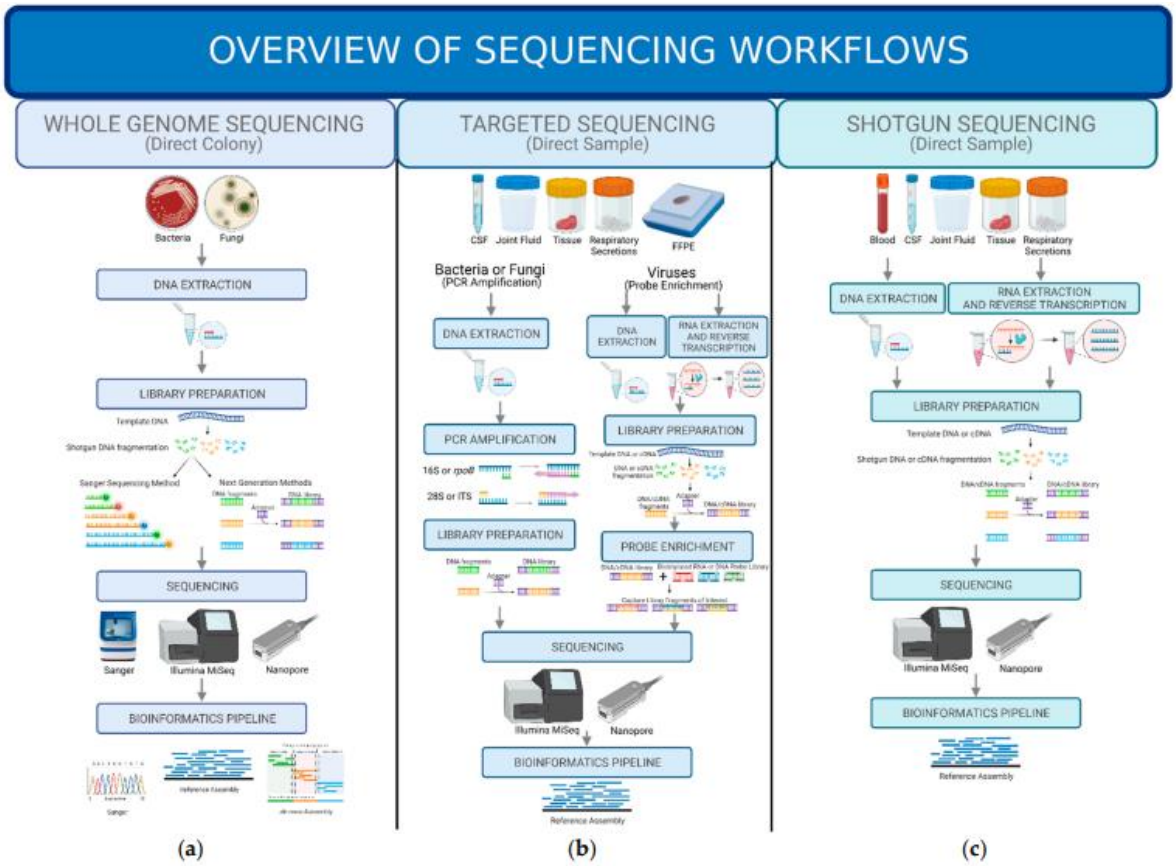

Figure 1. Overview of sequencing workflows. (a) Whole genome sequencing; (b) Targeted sequencing; (c) Shotgun sequencing (Hilt and Ferrieri, 2022).

Epidemiological surveillance in disease tracking and monitoring

Epidemiological surveillance refers to the systematic gathering, analysis, and distribution of health information to facilitate the planning, execution, and evaluation of public health initiatives (McGowan et al., 2022). It involves vigilant monitoring of health events that may arise within a population. Typically integrated into healthcare systems, epidemiological surveillance serves as a fundamental component for monitoring significant health occurrences. Its primary objective is to enhance and fortify disease surveillance and other health-related activities within public health programs (Teutsch, 2015).

The significance of epidemiological surveillance is exemplified by its crucial role in combating infectious diseases. For instance, a study conducted in Wuhan, China, employed a susceptible-exposed-infectious-removed (SEIR) mathematical model to estimate the epidemiological parameters of Covid-19 before the Implementation of preventive measures. The findings revealed that if these measures had been initiated 1, 2, or 3 weeks earlier, the number of cases could have been reduced by 66%, 86%, and 95%, respectively (Yang, 2020). This study underscores the vital role of surveillance not only in controlling Covid-19 but also in managing various other diseases.

According to the WHO, epidemiological surveillance contributes to combating diseases in several ways. It can help define the health problem properly. This is because a health problem must be well-defined before it can be solved. Generating data that aid public health officials in comprehending both established and emerging infectious and non-infectious diseases holds immense significance. Addressing the issue and implementing effective improvements becomes arduous without a comprehensive grasp of the health problem, including its causes, distribution, and infection establishment

mechanisms. Vital data typically gathered includes details about the pathogen, such as its specific clone and lineage, the symptoms it induces, the affected population, as well as morbidity and mortality rates (Nsubuga, 2016). In the absence of robust surveillance, public health officials would be navigating health problems blindly, squandering valuable resources.

Moreover, when data from surveillance programs are compiled and analyzed, a clear picture of the issue can be seen, leading to the development of appropriate health intervention. Also, continued surveillance is vital for monitoring and evaluating an already established program (Heymann, 2016). In addition, the significance of surveillance systems that collect precise data on diseases and geographic regions cannot be overstated in assessing the importance of a particular health event (Klaucke, 2018). Accurate information regarding the distribution and prevalence of diseases is indispensable and typically forms the foundation for decision-making by funders and governmental authorities.

The role of genomics in epidemiological surveillance

There are different classifications of genomics which has been studied and exploited for different purposes. For example, structural genomics involves determining the structure of every protein encoded by the genome (Chance et al., 2002; Klimontor *et al*., 2023). It involves characterizing the genome structures in terms of the protein constituent (Vitkup, 2020). Functional genomics also involves describing gene and protein functions using sequencing techniques (Raamsdonk, 2015). Functional genomics seeks to unravel the collaborative functioning of individual elements within a biological system to manifest a specific phenotype. It specifically investigates the dynamic expression of gene products in a given context (Morozova, 2017). Additionally, comparative genomics endeavors to scrutinize genomic attributes across diverse species. Doing so facilitates the examination of evolutionary alterations among organisms, aiding in the identification of genes that are either conserved or shared across species, as well as genes responsible for unique characteristics exhibited by each organism (Hardison, 2015). Essentially, comparative genomics utilizes diverse tools to juxtapose complete genome sequences of distinct species, enabling the discovery of genetic and genomic variations and similarities (Rogic, 2020).

Therefore, when genomic and epidemiological data analyses are integrated, they can provide a real-time picture of an outbreak. Genomic epidemiology can inform the rapid deployment of targeted interventions (Figure 3) to protect the public as an outbreak unfolds. The application of genomic and epidemiological studies to combat infectious is vital and must be implemented at all levels in different regions. This also requires certain comprehensive collaboration to efficiently harness the potential to mitigate and contain outbreaks and the spread of infectious variants.

The utilization of genomic data holds significant practical implications for the field of public health, specifically in infectious disease control. By employing whole genome sequencing (WGS) techniques, it is now possible to analyze pathogens directly from clinical samples, thereby providing valuable information during disease outbreaks, especially when prior knowledge of mutation-related characteristics such as virulence, drug susceptibility, and antigenicity is available (Koks, 2020). This data can further facilitate point-of-care molecular diagnostics and aid in tailoring personalized treatment approaches, similar to the application of human genetic data in precision medicine (Agarwala, 2018).

At a broader population level, the integration of genomics with epidemiological data enables the identification of pathogen mutations as indicators of transmission events. This approach offers a detailed understanding of epidemic transmission patterns at a fine-scale resolution, empowering the development of more precise and targeted large-scale public health interventions compared to traditional methods (Teutsch, 2015). In essence, the genomic sequencing of pathogens aligns with the One Health approach, which encompasses the interconnectedness of human, animal, and environmental health. By employing genomic epidemiology, the surveillance, prevention, and control of diseases can be facilitated within the framework of the One Health approach (Gardy, 2018).

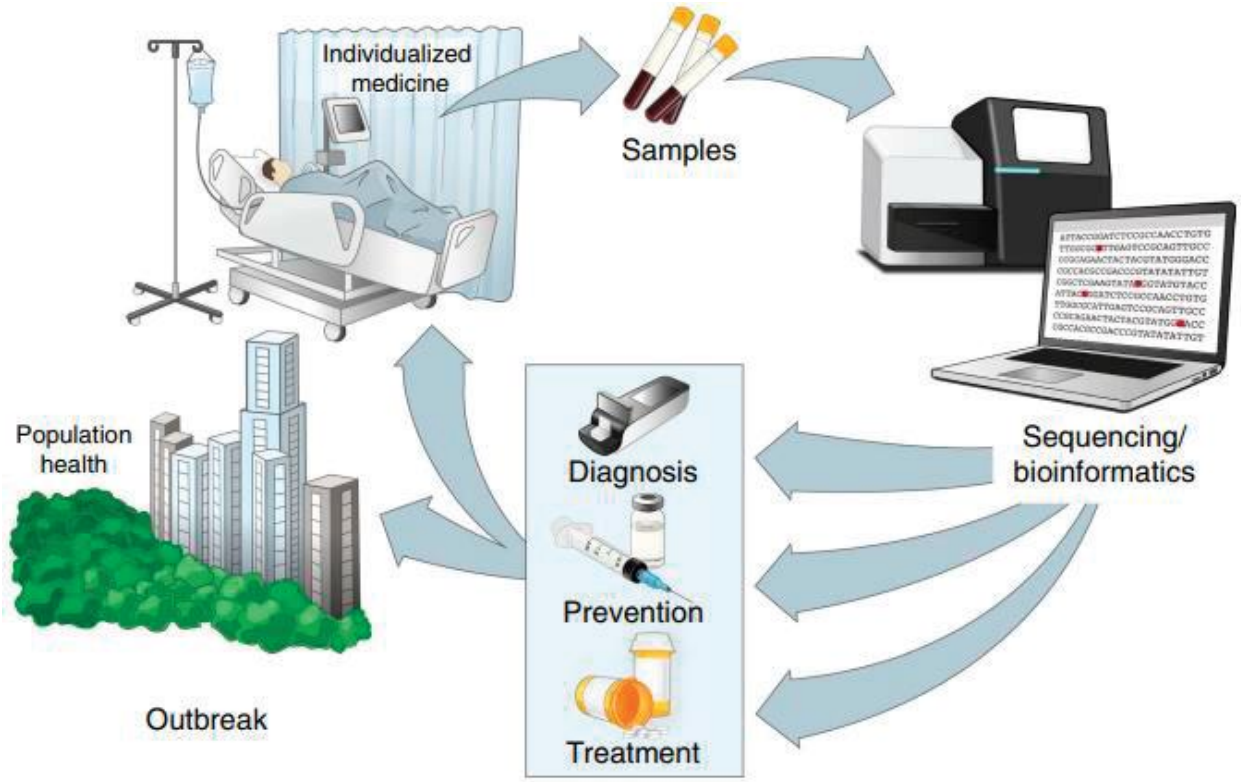

Figure 3: Precise interventions informed by pathogen sequencing during infectious disease outbreaks (Ladner *et al*., 2019)

How genomic epidemiology can inform the rapid deployment of targeted interventions and public health practices

Several longitudinal investigations into antimicrobial resistance (AMR) have underscored the importance of regular genomic monitoring in shaping public health strategies at both national and global scales. This includes guiding treatment suggestions and influencing vaccination plans. The continuous genomic surveillance of Neisseria gonorrhoeae, the agent responsible for the sexually transmitted infection gonorrhoea and classified as a WHO priority 2 pathogen with an urgent need for antimicrobials, has played a crucial role in shaping treatment recommendations. An initial global study identified distinct sub lineages exhibiting varied AMR profiles. Notably, a multidrug-resistant lineage linked to men who have sex with men sequentially developed resistance to the last-line treatment options azithromycin and ceftriaxone (Sánchez-Busó *et al*., 2019). Ongoing genomic surveillance has revealed the rapid evolution of *N. gonorrhoeae* in response to changing treatment guidelines. For instance, an increase in cefixime resistance prompted a shift in EU–European Economic Area treatment recommendations in 2012 to dual therapy with ceftriaxone and azithromycin (Bignell *et al*., 2013). Subsequently, there was a decline in resistance to extended-spectrum cephalosporins but a rise in azithromycin resistance (Cole *et al.,* 2017). Consequently, some countries recommended ceftriaxone monotherapy for treating uncomplicated gonorrhoea.

Furthermore, a substantial body of evidence regarding some bacterial pathogens convincingly demonstrates the enhanced capability of genomic epidemiology in identifying outbreaks across diverse geographical regions and determining their origins (Park *et al.,* 2021; Bottichio *et al*., 2020). Some of these studies explicitly focused on detecting newly emerging lineages with AMR and the spread of mobilizable AMR. These datasets not only contribute to AMR monitoring (Feldgarden *et al.,* 2019) but also validate the use of genomics for surveilling AMR determinants. Multiple studies have indicated reliable genotypic predictions of AMR (Rokney *et al.*, 2020), although this may not hold true for all pathogens.

Detecting threats from antimicrobial resistance (AMR) and providing timely information for interventions is a crucial element in expediting the adoption of genomic surveillance. The UK's experience already indicates that incorporating regular genomic sequencing for Salmonella has revealed a higher number of outbreaks compared to traditional microbiology methods (Paranthaman *et al.,* 2021). Consequently, as genomic surveillance becomes more prevalent, we expect a significant rise in the detection of outbreaks, underscoring the importance of prioritizing interventions based on characteristics of the causative bacterial pathogen.

There have also been considerable global endeavors to standardize AMR surveillance for healthcare-associated infections across networks (WHO, 2024). Various extensive studies have identified dominant lineages at regional levels and situated them within a worldwide context (Karlsson *et al*., 2022). The recognition of globally emerging or prevailing lineages with AMR has aided in directing research and control efforts.

Improving preparedness and response to epidemics through the application of genomic studies in epidemiological surveillance

The emergence of infectious diseases, such as COVID-19 and Ebola, represents a significant peril to public health (Worsley-Tonks *et al*., 2022). Despite the Ebola virus being present in central and West Africa for many years, numerous African nations have not fully embraced the use of genomic studies and epidemiological surveillance in public health. Including genomic data is crucial for achieving sufficient detail in monitoring local transmission and understanding the routes and timing of pathogen importation between countries. Additionally, the genomic surveillance of evolving pathogens in LMIC has the potential to guide the development of tailored and effective molecular assays for treatment and prevention. It can also aid in monitoring factors that contribute to these pathogens' adaptation and virulence capabilities.

Furthermore, data from genomic surveillance is very crucial for vaccine design. For most viral diseases, there are commercially available vaccines (Mba *et al.,* 2023). However, no vaccines are available for other pathogens like bacteria and even fungi. Genomic data is crucial to developing and designing an efficient vaccine to help curtail the infectious disease crisis. This data type is essential in understanding the exact clones and lineages circulating in most regions. Identifying antigenic components (usually surface-exposed materials) that could be leveraged to design vaccines is also important, and this type of data can only be generated with the help of genomics.

Therefore, genomic data is not only utilized in investigating known outbreaks or epidemics; they have other crucial importance. Another important aspect of omics techniques is metagenomics and transcriptomics (von Fricken *et al*., 2023). The utilization of these two advancements holds great potential for diagnosing unknown infections and enhancing our understanding of circulating microbial pathogens. Such knowledge is vital for informed preparedness and control measures against future epidemics. Particularly in regions with limited resources and infrastructure, like LMIC, significant investments in infrastructure for research and capacity development are still required to harness the benefits of genomic studies fully. By offering adequate support to local institutions engaged in genomics research, these institutions can serve as key hubs for investigating future epidemics or pandemics. It is also imperative to advocate for the widespread adoption and integration of genomics in public health across various regions and at all levels. However, strengthening genomic-based epidemiological surveillance systems requires collaborative efforts at different levels, as previously mentioned.

Given the continuous shifts in climate, biodiversity, and human behavior, it is imperative to recognize the immense significance of genomics. In view of the fact that LMICs, particularly Africa bear the greatest burden of endemic infectious diseases, the integration of genomics into public health holds the potential to save countless lives, both within the affected regions and beyond.

Limitations and challenges in integrating genomics studies in epidemiological surveillance

While new initiatives are being established, the effectiveness of these efforts is hampered by various limitations, including inadequate funding, poor coordination, limited capacity for data integration, non-representative data, and a lack of properly trained personnel with the necessary expertise. Furthermore, instability in governance

and poor policy-making at local and national levels has led to fragmented approaches and inconsistent capabilities.

Surveillance does not need to be flawless to be valuable; however, it can have limitations, particularly in terms of underreporting, lack of representativeness, and timeliness, which undermine its usefulness. It is important to integrate effort into devising and implementing measures to overcome these challenges. For most notifiable diseases, surveillance data relies on passive reporting by physicians and other healthcare providers. Underreporting significantly delays effective action and allows preventable cases to occur due to delayed reporting and the delayed Implementation of control measures.

Another critical issue is the lack of representativeness in reported cases. Underreporting is neither consistent nor random. Two significant biases distort the completeness of reporting. Firstly, healthcare providers are more likely to report cases that involve severe illness and hospitalization, neglecting milder cases, despite individuals with mild illness being more likely to transmit the infection to others due to their unrestricted movement. Consequently, this bias leads to an inflated estimate of disease severity, such as the death-to-case ratio. Secondly, healthcare providers are more inclined to report cases when the disease garners media attention. This bias results in an underestimation of the baseline disease incidence once media coverage diminishes.

Timeliness is yet another issue. Delays in collecting, analyzing, and disseminating data on notifiable diseases can occur at various stages. The causes of these delays vary, including disease-specific factors. For instance, certain diseases require confirmatory laboratory tests before physicians can make a diagnosis. Complicated or inefficient reporting procedures can also contribute to delays. Furthermore, delays in analysis commonly occur when surveillance is not regarded as a program that provides actionable information. Ultimately, delays at any stage can lead to delays in disseminating information, leaving the medical and public health communities without the timely data they need to take swift action.

There are problems of inadequate financial resources in Africa to fund genomic studies of the entire region. Funding is an important aspect of genomic studies, which could be obtained through the government or private sources of funds. Also, most surveillance programs are complex. Traditional and outdated methods of genomic surveillance are still in place, and this should be displaced as soon as possible. Modern surveillance methods should be adopted to yield more authentic results, which will lead to more effective real-time preparedness and response to emerging epidemics.

Recommendations and conclusion

There is a need for improved awareness of practitioners. It is crucial for all individuals engaged in epidemiological surveillance to acknowledge their responsibility. The health department must actively disseminate information about the list of reportable diseases and the mechanisms employed for genomic surveillance. Practitioners should always develop their skills by constantly studying in order to combat the future emergence of diseases. There is also a need for simplified reporting. Genomic surveillance data should be as simple as possible.

Moreover, feedback plays a crucial role that cannot be emphasized enough. It can take various forms, such as written communication like a monthly newsletter or oral updates provided during regular medical staff meetings. To be effective, the feedback should be timely, informative, engaging, and tailored to each healthcare practitioner. Additionally, it should encompass valuable insights into disease patterns and control activities, thus promoting awareness and reinforcing the importance of active involvement in meaningful public health initiatives.

In the past, surveillance of notifiable diseases heavily relied on reports from physicians. However, nowadays, almost all states mandate that commercial and hospital laboratories report positive cultures or diagnostic tests for notifiable illnesses. In some instances, the number of laboratory reports surpasses those from physicians, hospitals, clinics, and other sources. Expanding the scope of surveillance involves utilizing additional healthcare personnel, such as infection control personnel and school nurses, as sources of surveillance data. Another effective approach is to develop alternative methods for conducting surveillance, such as leveraging secondary sources of data. This approach has

proven successful in monitoring influenza outbreaks. Moreover, adequate financial resources, especially in LMIC, cannot be overemphasized. Therefore, there should be an adequate source of finance through the government or other financial establishments. Also, the implementation of mathematical modeling is vital. Therefore, mathematical fields such as modeling should be leveraged as it could help to understand past and current diseases, which gives insights and makes it easier to forecast the nature of emerging diseases.

In general, the close interactions among humans, animals, and the environment pose a risk for the emergence of infectious diseases, and this risk is increasing. Consequently, it is crucial to focus on understanding the intricate dynamics between humans, animals, and the environment, as well as the various farming systems and their bio-security levels. Preventing the introduction of diseases through vaccination and swiftly controlling outbreaks through containment measures are essential aspects of preparing for future epidemics and pandemics. The COVID-19 pandemic has highlighted the critical significance of collaboration that goes beyond conventional infrastructures, networks, and disciplines. This collaboration also extends to leveraging genomics and open data infrastructures. The ongoing investments in global genomic surveillance hold tremendous potential as long as we avoid repeating the mistake of developing them exclusively for the immediate situation but rather for future possible health events.

Conflict of interest

The authors report no conflict of interest

Funding

The authors received no funding for this study

Author contribution

ACC was involved in conceptualization and along with OTC and NCG were also involved in methodology, resources, writing the original draft, review and editing. All authors contributed equally

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