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The Role of Clinical Virology Laboratory and the Clinical Virology Laboratorian in Ensuring Effective Surveillance for Influenza and Other Respiratory Viruses: Points to Consider and Pitfalls to Avoid

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Opinion statement

Influenza and respiratory viruses have a global impact on public health. Clinical virology laboratories and laboratorians play an important role in not only the diagnosis but also the surveillance of these pathogens. Surveillance for influenza and other respiratory pathogens is important, as it informs public health decision making in terms of influenza vaccine and antiviral effectiveness, informs clinicians and public health practitioners about the pathogenicity of specific viral strains, guides clinical practice, and supports laboratory panning activities. Key background issues include the following: the fact that the laboratory is only one of several data providers to a surveillance system, the biologic nature of influenza and respiratory viruses and the laboratory needs to keep up to date on the diagnosis of these agents, the need for laboratorians to be involved in case definition development, the impact of push and pull data flow models on laboratory resources, and

the fact that laboratories may be asked to provide more than just test results to surveillance programs. This review also identifies some key issues or questions that arise during the pre-analytic, analytic, and post-analytic phases that could impact on the ability of the laboratory to link to surveillance programs. Finally, issues surrounding virus characterization programs and how they link to surveillance programs are identified and discussed.

Introduction

Respiratory viruses are a significant cause of acute respiratory illness and are considered to have a significant impact on human health globally. The impact is most well described in pediatric patients infected with influenza, with the impact of other viruses less well understood on a global level [1, 2]. Globally, influenza is thought to account for 10 % of respiratory-associated hospitalizations [3]. Large-scale data is less available for the global burden of other respiratory viral pathogens including respiratory syncytial viruses, rhinoviruses, coronaviruses, respiratory adenovirus, parainfluenza viruses, and human metapneumovirus [4, 5]. The lack of this information may be due to a variety of factors, where a pillar of public health is missing. This failure may be due to a lack of diagnostic testing, a lack of access to health care in general, and surveillance systems that do not identify causes of disease or inability to link clinical data to public health infrastructure [6].

This manuscript will focus on a key pillar of public health, surveillance, or, in this case, surveillance of influenza and other respiratory viral pathogens and how clinical virology laboratorians can ensure that this function is effective. Surveillance for influenza and acute respiratory viruses is important because it supports the following functions:

- Informs public health decision making in terms of influenza vaccine effectiveness, vaccine design and content, changes in influenza antiviral resistance profiles, and the populations at risk for infection with influenza and other respiratory pathogens [7, 8].
- Informs clinicians and public health practitioners of changes in the pathogenicity of specific respiratory viral strains [9].
- Allows clinicians to understand disease prevalence and may indirectly guide their practice [10].
- Provides data to administrators and health planners to provide resources to support further spending for the diagnosis, characterization, and control of acute respiratory viral infections [11].

Surveillance requires close cooperation between the clinical virology laboratory and the public health or other groups undertaking surveillance. Laboratories should avoid scenarios where they are simply passive providers of information to surveillance teams. Instead, laboratorians should be involved in the planning of surveillance strategies and offer important expertise that can improve the interpretation of results. The expertise provided may be at several levels and can include the following: an understanding of changes in viral genetics or pathophysiology, changes in test approaches that might impact on the final classification of a case, the origins of data and how it was collected, the critical assessment of surveillance data (e.g., a lack of sensitivity due to a failure to detect the presence of virus in a sample due to poor growth in culture), data patterns which might not be readily apparent, and how data sets are linked with patients.

Objectives

There are several objectives for this manuscript. First, this manuscript will identify the recent and historic issues with structure or virological/biological that can make the laboratory role in surveillance challenging. Second, the manuscript will break down the phases of the laboratory

role in diagnosis of acute respiratory viral infection and how they can be developed to ensure effective laboratory linkages to surveillance systems [12]. Finally, this manuscript will discuss the impact of extensive genetic viral characterization on surveillance processes.

Why is this important?

Problems in capturing clinical and laboratory data can be resolved by effective planning of pre-analytical, analytical, and post-analytical components of the laboratory test process [12]. Apart from their knowledge of the virology and pathophysiology of acute viral pathogens, laboratorians already play a significant role in the planning and design of laboratory systems that not only provide results back to clinicians but also allow for the transfer of information to practitioners involved in surveillance.

Key background issues and not-so-big stumbling blocks

Laboratories are only one part of a respiratory virus and respiratory illness surveillance system

One existing dilemma is that syndromic surveillance without laboratory confirmation is a common practice and may provide a good indication of influenza activity in the community [13]. Often, influenza-like illness (ILI) data instead of laboratory data is used to determine disease burden and establish thresholds for public health action during the respiratory season. Other data used may include the following: rates or counts of hospitalization and markers of severity including morbidity, ICU admissions, ventilator use, antiviral prescriptions sales, or excess mortality [14, 15]. The laboratorian should engage surveillance partners to identify the benefits of laboratory data. This includes the fact that syndromic data, alone, cannot discriminate influenza from other respiratory viruses [16]. The laboratorian should also work with surveillance partners to identify biases in laboratory and non-laboratory data used in surveillance including variation in antiviral prescribing practices and access to medical care or laboratory or point of care testing [15].

Constantly changing influenza A and B genomes means that surveillance systems are always required

Influenza A seasonal subtypes H3, H1, and two lineages of influenza B cause seasonal illness. The circulation of strains of influenza A in animal populations (e.g., birds, swine) also allows for the possibility of cross species transmission, re-assortment, and emergence in human populations (e.g., H5N1, H5N6, H7N9) [17–20]. The segmented nature of influenza A and B virus genomes promotes the swapping and mixing of large segments of the genome (antigenic shift). In addition, the viral genome of ribonucleic acid (RNA) allows for smaller incremental changes involving single-nucleotide polymorphisms (SNPs) (antigenic drift), which can lead to decreased antiviral susceptibility, reduced vaccine efficacy (due to antigenic mismatch), and/or changes

in virulence of the virus [21, 22]. The laboratorian and the laboratory need to be proactive in the face of these changes and be prepared to identify newly emerging strains of influenza and communicate these changes to surveillance programs. At the extreme, this may include communicating to surveillance partners that a new strain or subtype has emerged. More routinely, during the annual influenza season, laboratorians should ensure that they effectively communicate observed changes in influenza antiviral susceptibility and potential changes in the genotypes or phenotypes of influenza viruses that can impact on vaccine effectiveness or pathogenesis [18•].

The laboratory needs to communicate its capabilities effectively to surveillance partners during the emergence of other non-influenza respiratory viruses

Other non-influenza viruses have emerged within the last two decades, including the severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV), and enterovirus D68 (EV-D68) [23–25]. Key problems identified in the past include the following scenarios. First, clinical and even regional public health laboratories may not have a primary diagnostic test available and are forced to refer specimens to another facility. Second, even when testing is routinely available, laboratories may be overwhelmed with large numbers of test requests due to a variety of factors. Third, laboratories may also become overwhelmed with the large amount of data requests from surveillance partners and may not have sufficient resources to share this information with their partners [26]. From these experiences, it is apparent that laboratorians and laboratories need to engage surveillance partners to ensure that their partners understand laboratory capabilities and how effectively the laboratory can support surveillance functions. This includes discussions on the appropriateness of case definitions, an understanding of the ability of the laboratory to access or implement new tests, and how effectively laboratories can share pre-analytic and analytic data with surveillance partners.

Ensuring the laboratory plays a role in writing case definitions for emerging and routine pathogens

Given the potential of constant change with respiratory viruses, as well as changing technologies in the diagnostics and characterization of these viruses, laboratorians should ensure that they provide practical input during the writing, editing, and review of case definitions for routine seasonal and novel emerging respiratory pathogens [27]. This includes providing background on the characteristics of tests that may be used to define a case and ensuring that the laboratory components identified are realistically attainable and correctly interpreted [28]. The laboratory should also be prepared to ensure that it has the resources to help clinicians meet these new case definitions. During this process, the laboratorian should also assess the direct impact that case definitions will have on routine laboratory operations in terms of test allocation as well as human resource commitments. These not only could include

increased test volumes for case finding purposes but could also include pressure to implement new technologies to meet case definition [29, 30]. There should also be a determination as to whether additional indirect laboratory resources that are not normally a part of the routine testing process (e.g., identifying data, creating line lists, converting specimen data to case data, tracking specimens) are required to support case finding [31, 32].

How does data flow from the laboratory to surveillance partners: push or pull?

Data flow to surveillance programs can occur as either a push model or a pull model. A push model is the outward flow of laboratory user controlled by the producer that best suits routine surveillance systems where information can be sent either as a constant flow or a timed release [33, 34]. In contrast, a pull model provides information to the use on the demand of the data user. A pull model might be implemented when novel pathogens emerge and a pre-established data flow mechanisms do not exist. In this case, decision makers may ask for data not routinely provided in push models and laboratorians should consider what resources would be required to more effectively operationalize these requests. The problems arising include the possibility that the laboratory is more routinely focused on a push model and that a pull model is less routinely used or the data requested is novel. The laboratory should ensure that it has standard operating procedures to allow for both dataflow processes and the flexibility to transfer novel data during emerging events [35]. Changes in push and pull models should still ensure timely transfers of information while still ensuring data confidentiality and also that any changes in data interpretation are quickly communicated [36].

The laboratory may be asked to help identify specific patient populations

Depending on the quality of data within the health system, the laboratory may be asked to assist in identifying patient populations or provide special testing on specimens from specific patient populations. The laboratorian must determine whether these requests for specific population information on patients are feasible or whether that information could be obtained from another source. In many cases, patient settings or risk factors may not be easily identifiable or they may change following collection of a respiratory specimen by the clinician. In other cases, the laboratory may not have the resources to easily extract this data from the laboratory information system. Specific patient information that the laboratory may be asked to provide could include one or more of the following:

- Patient setting (e.g., community or hospital) [37]
- Travel history as a risk for infection with a novel strain of an emerging viral pathogen (e.g., avian influenza, MERS-CoV).
- Animal exposure history as a risk for exposure to an emerging virus (e.g., avian influenza, MERS-CoV) [38]
- Risks for an adverse outcome (e.g., immunocompromised status, pregnancy, admission to ICU) [37].

- Whether the specimens were collected from an outbreak or not [37].
- Patient demographics to allow for data stratification (e.g., age, sex, location/region) [39].
- Other data not routinely captured (e.g., chemistry, immunology, bacteriology results) [40].

Improving laboratory linkages to surveillance at during pre-analytic, analytic, and post-analytic phases of the testing process

Pre-analytic

As described earlier, generating good data for surveillance may require thinking about pre-analytical issues that may not be, at first, apparent to laboratorians. The classic approach generally focuses on capturing information which allows the laboratory to determine which testing needs to be carried out on a specimen [41]. However, in the event of a change in strain type, changes in associated pathophysiology, or a new viral pathogen, laboratories may be asked to also provide other information not routinely collected [42]. This additional information may include an indication of signs and symptoms, a description of patient location or setting, whether antibiotic or antiviral treatment was undertaken, and other underlying factor or outcomes that were captured on tests requisitions [43].

The following are specific pre-analytic issues that the laboratorian should consider:

- During the development of a test ordering system (e.g., manual or automated), has the laboratorian engaged surveillance groups to determine whether specific information should be requested or be made mandatory on test requisitions [44].
- How well do your laboratory test requisitions or online ordering systems capture basic and more advanced clinical information? [45•]
- How effectively can this information be entered into your laboratory information system or other linked databases? [46]
- Are you even able to extract this information from your laboratory information system and is so how easily? [47]
- Do you have the resources to support what may be considered "non-essential" work by laboratory management? [48]

Analytic

Laboratories face increasing pressure to implement and utilize the most accurate and clinically useful test with the best turnaround times [49]. This means that laboratories are constantly striving to improve their test menus and introduce newer cutting edge tests [50•]. During the test implementation process, laboratorians should remember to engage stakeholders involved in both utilization of data for clinical purposes and surveillance. Changes in technology can change the information collected in the pre-analytic steps but may also change the outputs that

impact on disease prevalence and incidence. This is increasingly apparent, as non-molecular tests such as point of care tests, direct fluorescent detection of viral antigen, and culture viral are replaced with more sensitive molecular techniques [51, 52].

The laboratorian should consider the following analytic issues when engaging surveillance partners:

- Communicate that even when molecular techniques are used, different platforms will vary in sensitivity and specificity [53].
- Communicate that new sequence-based molecular techniques may not be able to identify new strains that emerge with mutations or changes in the genetic sequence [54].
- With the cost of molecular panels, determine if there are any impacts to the laboratory that are driven by a surveillance system that are over and above the routine cost of testing [55–57].

Post-analytic

After testing, the laboratory will still be engaged by those undertaking surveillance. As described earlier, laboratory results may be directly reported to surveillance teams as part of a routine reporting system or data may need to be actively extracted from the laboratory information system using push or pull models. Discussions should occur to ensure that the data extracted is of appropriate quality for analysis [58]. The laboratory should continue to be engaged to ensure that laboratory data is analyzed and interpreted correctly [39, 59].

The laboratory should consider the following post-analytic issues:

- How will data be extracted from the laboratory information system (actual mechanism as well as push-pull model)? [60]
- What laboratory resources will be required to extract this data and what are the expectations on the laboratory? [61]
- How will quality of data be assured during the extraction process? [62]
- Does the laboratory need to ensure appropriate data interpretation following extraction? [59]

Characterization of influenza and other respiratory viruses

Multiple approaches can be used for the characterization of influenza and other respiratory viruses [63]. Traditional methods have relied on culture followed by phenotypic characterization of strain type as well as influenza antiviral susceptibility profiles [64]. Over the last 10–15 years, many of these phenotypic approaches have been replaced completely or party by genetic analysis, often done using Sanger sequencing approaches or polymerase chain reactions based on detecting specific SNPs [65]. More recently, full-genome sequence analysis has been used to characterize viral strains [66•]. As expected, genotypic data may not align with phenotypic data especially for strain-type analysis and influenza antiviral susceptibility profiles. Some of this work, such genetic analysis of antiviral susceptibility profiles in influenza A (H1N1) strains, may be well established and standardized in

clinical virology laboratories. In other cases, genetic strain analysis of viruses may not be completely standardized and may be viewed as research or academic in nature. Due to the heavy resource requirements of whole-genome sequencing, in some settings, whole-genome sequencing and analysis may be done completely in clinical virology laboratories, while in other settings, the clinical laboratorian and laboratory may play a more peripheral role. However, the early release of sequence data inferring changes in pathogenicity, mutations leading to changes in influenza vaccine effectiveness, or changes in influenza antiviral resistance can have a direct positive impact on public health and clinical decision making [67, 68].

Laboratorians should consider the following issues related to linking viral characterization data to surveillance teams:

- Are you characterizing your viral respiratory targets, and are you sharing this information with your surveillance partners?
- Are there any legal or laboratory accreditation issues around sharing this information? [69]
- Is any of this information stored in a standard laboratory information system?
- If so, do they see all types of characterization data or just a subset? What data do you share? Phenotypic, partial genetic, full-genome data?
- How do you chose the specimens to characterize, and do you involve your surveillance partners or others to ensure that you avoid selection biases?
- Is the data shared real time or with a lag, and is this timing useful for decision making in your location?
- What messaging do you provide regarding the potential mismatches between genotypic and phenotypic characterization?
- As this may be work generated outside of a traditional clinical laboratory setting, how are you ensuring the quality of your primary data?
- Can you afford to do this work on a more routine basis?

Conclusions

Surveillance supports a variety of important clinical and public health decisions related to acute respiratory viral pathogens. The laboratory and the laboratorian are key members of the surveillance team and should be engaged in planning, decision making, and surveillance data interpretation. Most importantly, the laboratorian is a key resource in ensuring that non-laboratory teams get the data right. The members of the laboratory should understand where their laboratory is positioned in relation to their surveillance partners and should make sure that they build strong links with these groups. This will ensure that both groups understand the resources that it takes to implement and maintain these systems. As pre-analytical, analytical, and post analytical technologies change and become more complex, laboratorians must consider how their interactions with their surveillance partners will also change.

These interactions may change in the face of new technologies, but the clinical laboratorian will still continue to play an important role in ensuring data quality and providing clinical interpretations of data. With this changing landscape, clinical virology laboratorians who traditionally only considered their interactions with attending physicians or members of a direct health care team may find that they play a stronger role in clinical and public health decision making when they interact more with their surveillance partners.

Compliance with Ethical Standards

Conflict of Interest
Dr. Steven Drews declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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This paper describes the operationalization of a whole genome sequencing approach to support a surveillance program. These new approaches will at some point replace older phenotypic technologies.

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