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Review

Drivers of earlier infectious disease outbreak detection: a systematic literature review

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SUMMARY

Background: The early detection of infectious disease outbreaks can reduce the ultimate size of the outbreak, with lower overall morbidity and mortality due to the disease. Numerous approaches to the earlier detection of outbreaks exist, and methods have been developed to measure progress on timeliness. Understanding why these surveillance approaches work and do not work will elucidate key drivers of early detection, and could guide interventions to achieve earlier detection. Without clarity about the conditions necessary for earlier detection and the factors influencing these, attempts to improve surveillance will be ad hoc and unsystematic.
Methods: A systematic review was conducted using the PRISMA framework (Preferred Reporting Items for Systematic Reviews and Meta-analyses) to identify research published between January 1, 1990 and December 31, 2015 in the English language. The MEDLINE (PubMed) database was searched. Influencing factors were organized according to a generic five-step infectious disease detection model.
Results: Five studies were identified and included in the review. These studies evaluated the effect of electronic-based reporting on detection timeliness, impact of laboratory agreements on timeliness, and barriers to notification by general practitioners. Findings were categorized as conditions necessary for earlier detection and factors that influence whether or not these conditions can be in place, and were organized according to the detection model. There is some evidence on reporting, no evidence on assessment, and speculation about local level recognition.
Conclusion: Despite significant investment in early outbreak detection, there is very little evidence with respect to factors that influence earlier detection. More research is needed to guide intervention planning.

1. Introduction

Infectious disease outbreaks can spread rapidly, causing enormous losses to individual health, national economies, and social wellbeing.[1–6] Through the early detection of an infectious disease outbreak, a small outbreak can potentially be contained at the local level, thereby reducing adverse impacts.[7–11] Early detection has been and remains the current narrative of infectious disease surveillance.

A variety of surveillance approaches to the early detection of outbreaks exist, many of these following advances in technology. Traditional indicator-based surveillance (IBS), e.g. mandatory disease-specific notification, laboratory surveillance, and syndromic surveillance, has been complemented by event-based surveillance (EBS), which gathers and analyzes information from drivers, formal or informal.[12,13] This has been done in order to broaden the scope of surveillance to an all-hazard approach, as requested in the International Health Regulations (2005) (IHR), and with the aim of detecting outbreaks earlier and faster using new technologies.

Over the last decade, there has been substantial investment in the development and operation of surveillance systems that use existing health data, both formal and ad hoc—from sources such as emergency department visits and sales of pharmaceuticals—to provide immediate analysis and feedback to those charged with investigating potential outbreaks.[14] New digital data streams for infectious disease surveillance have arisen from developments in

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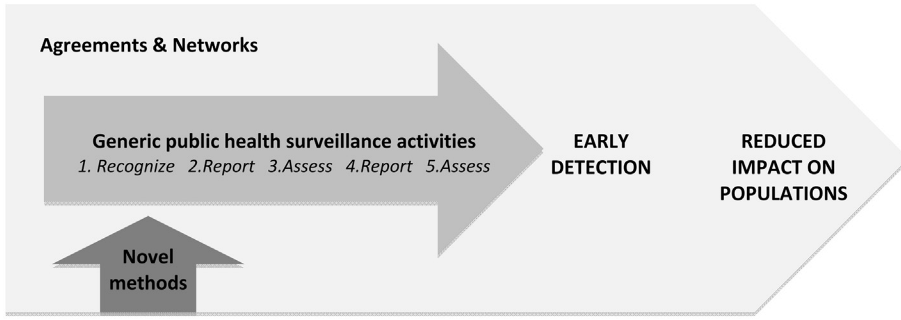

Figure 1. Landscape of approaches for early detection of infectious disease outbreaks.

information communication technology,[15] such as early adopters ProMED-mail and Global Public Health Intelligence Network (GPHIN), and more recently, numerous openly available news aggregators and visualization tools.[16] Diagnostics have progressed as a result of scientific developments, leading to automation and highly multiplexed assays and advances in point-of-care testing, making sample collection and testing possible in remote settings.[17]

Innovative governance structures have been established to promote early detection. Disease surveillance networks have formed, such as the World Health Organization (WHO) Global Outbreak Alert and Response Network (GOARN), combining human and technical resources around the world to rapidly identify, confirm, and respond to outbreaks. Cross-border regional disease surveillance networks have been established across the globe, connecting epidemiologists, scientists, ministry officials, health workers, border officers, and community members to engage in activities, such as training, capacity-building, and multidisciplinary research.[18] Agreements have been instituted, setting legal mandates around surveillance activities, such as the IHR (2005), which call for all WHO Member States to build, improve, and strengthen their capacity to prevent, detect, and respond to infectious diseases outbreaks that can have global spread.[19]

The proliferation of zoonotic diseases has demonstrated that the timely identification of future emerging microbial threats requires an integrated international approach to disease surveillance. Programmes working at the human–animal interface employ many of the same techniques as those for human health, such as the Global Avian Influenza Network for Surveillance (GAINS), which trains individuals and organizations to collect samples and disseminates laboratory results through an open-access electronic database.[7]

The list of novel strategies described above is not exhaustive, yet demonstrates the breadth and intricacy of surveillance approaches aimed at detecting outbreaks early. These approaches work in concert with generic infectious disease surveillance activities, which remain essential to public health practice, particularly at the local level.[7] Together, these approaches ultimately aim to decrease the impact of outbreaks on populations (Figure 1).

Generic infectious disease surveillance follows a multi-level public health model, where a case or an event must first be recognized as unusual, and then reported and assessed (as a signal). If the case or event meets criteria for further notification, it is reported to higher level authorities and subsequent assessment/investigation ensues. This detection process can be categorized into the following five generic steps: (1) recognition (of a case or an event), (2) low-level reporting, (3) low-level assessment, (4) higher level reporting, and (5) higher level assessment (when outbreak declaration occurs). While the key players involved at each step will vary by region/country and disease, the basic structure is the same. Inputs into the system include human and animal health events, risks (indicating a potential outbreak), and data.

Novel approaches link up with the generic five-step model at different stages. For example, alarms from syndromic surveillance input into the system as risk (of a potential outbreak), and ProMED-mail and GPHIN provide new data into the system. Both must be followed-up with an epidemiological investigation to determine whether a public health response is needed and what that response should be. Diagnostic tools aid in the assessment steps, and agreements and networks reinforce the entire system by building and strengthening overall capacity for carrying out surveillance activities.

Given the enormous amounts of time and money invested, measuring impact is a priority. A number of studies have aimed to quantitatively measure (in days) the timeliness of infectious disease surveillance systems, seeking to answer the question of how effective these interventions have been.[20–23] Additionally, the IHR (2005), Global Health Security Agenda (GHSA), and US Centers for Disease Control and Prevention (CDC) present useful frameworks for the evaluation of infectious disease surveillance systems, including timeliness of disease detection.[24–26]

Measuring change in timeliness can help us to hypothesize about effective approaches; however, it does not provide information about the causal mechanisms at play. Understanding why these surveillance approaches work and do not work will elucidate key drivers of early detection and enable us to refine and design interventions for earlier detection. The important question becomes: Why do certain approaches/interventions lead to early detection?

Leading organizations have offered guidelines on how early detection can be achieved. For example, the CDC Working Group produced a prominent guide that is useful and consistent with the landscape of approaches currently operating.[27] However, the recommendations are broad and it is unclear whether they are based on evidence.

In this study, a systematic review of the peer-reviewed literature was performed to identify what evidence exists about factors that influence earlier detection of infectious disease outbreaks. Focus was placed on the generic public health surveillance infrastructure, including inputs that novel approaches generate, i.e. risks and data. The goals of this review were (1) to synthesize what is currently known, and (2) to identify gaps and limitations that can be addressed by future research efforts. Understanding the evidence-base of influencing factors could guide approaches to achieve earlier detection.

2. Methods

2.1. Search strategy and selection criteria

A systematic review was conducted using the PRISMA framework (Preferred Reporting Items for Systematic Reviews and Meta-analyses) to identify research articles published between January 1, 1990 and December 31, 2015 in the English language, answering either of the following questions: (1) What are the factors that (a) facilitate earlier disease detection and (b) block earlier disease detection? (2) How can we measure whether these factors contribute to an earlier detection time?

The research question focuses on the drivers of earlier detection and how these facilitating or blocking factors can be measured. This research focus determined the review selection. The following inclusion criteria were set: any study design; study outcomes include timeliness of event-based infectious disease surveillance (time from event to outbreak realization); measurement of outcomes are quantitative or qualitative; study objectives include the identification of factors that influence the timeliness of infectious disease surveillance or the evaluation of interventions targeting specific influencing factors; events of interest include human, animal, data, or risks; and factors must be modifiable, i.e., amenable to intervention considering the research focus on how influencing factors can be measured. Any studies not meeting all of the above inclusion criteria were excluded.

In addition, the following exclusion criteria were used: surveillance of non-communicable diseases; syndromic surveillance; active surveillance; individual case detection. Articles published in the grey literature and perspective pieces were not included in this review.

MEDLINE (PubMed) was searched using the following terms: (Disease notification[mesh] OR Population surveillance[mesh] OR Public health surveillance[mesh] OR surveillance[Title]) AND (Time factors[mesh] OR Timeliness[Title] OR Timelier[Title] OR Time[Title] OR early[Title] OR earlier[Title] OR evaluation[Title] OR evaluating[Title]) AND (Disease outbreaks[Title] OR Infectious disease[Title] OR infectious diseases[Title]).

2.2. Study selection

Two independent reviewers appraised each title and abstract for relevance according to the pre-determined inclusion/exclusion criteria. The inter-reviewer agreement rate was 70%. Disagreements among the reviewers were resolved by discussion. Full articles were obtained for all papers included after this first screen. One researcher screened the full texts applying the inclusion/exclusion criteria to determine eligibility.

Using a standardized form, one researcher extracted data from each eligible study. Data extracted included study characteristics, methodology, intervention or surveillance system details, study aim(s), study outcome(s), and influencing factors. The researcher determined whether or not the influencing factors identified in the study were based on evidence or speculation. If they were based on speculation, they were excluded from the review. Influencing factors were extracted manually and organized according to the five-step disease detection model.

3. Results

3.1. Description of the studies

The search identified five studies.[22,28–31] Table 1 summarizes the studies in terms of general characteristics.

3.2. Study outcomes

Four of the five studies evaluated the effect of electronic-based reporting on detection timeliness.[22,29–31] These studies were conducted in the USA and the Netherlands, and each defined outcome intervals of interest in days. Of the two studies conducted in the USA, one looked at the time interval between the date/time that the automatic electronic laboratory-based system notification was generated at the hospital and the date/time that the laboratory result was reported to the county health department by the conventional paper-based system.[28] The other US study assessed the time from symptom onset to county health department case notification.[31] Of the two studies that examined electronic reporting timeliness in the Netherlands, one looked at the time intervals of symptom to municipal notification, and laboratory diagnosis to municipal notification,[22] and the other at the intervals between symptom onset and national notification, and municipal and national notification.[30]

The fifth study was performed in Australia and examined barriers to notification of infectious diseases by general practitioners and identified strategies for improving the notification process.[29] One of the Dutch studies, in addition to measuring the impact of different methods of reporting, also measured how the existence of physician–laboratory–municipal health service agreements (that authorize direct reporting by one or more local laboratories) influence timeliness.[22]

The present search did not result in more specific publications revealing evidence on drivers of earlier infectious disease outbreak detection.

3.3. Findings of the studies

The study by Reijn et al. had the following findings: the presence of physician–laboratory–municipal health service agreements showed a significant reduction in notification time to the

Table 1
Summary of the studies

Authors	Year	Location	Data	Diseases
Reijn et al.[22]	2003–2008	Netherlands	Dutch national database	Shigellosis, EHEC/STEC infection, typhoid fever, measles, meningococcal disease, hepatitis A, hepatitis B
Panackal et al.[28]	2000	Allegheny County, Pennsylvania, USA	UPMC electronic and Allegheny County Health Department paper-based systems databases (derived from the National Electronic Telecommunications System of Surveillance)	Campylobacter, Cryptosporidium, *Escherichia coli* O157:H7, Giardia, Listeria, Legionella, *Neisseria meningitidis*, Salmonella, Shigella, Yersinia
Ward et al.[30]	2001–2003	Netherlands	National infectious disease surveillance reports	Legionellosis, bacillary dysentery, hepatitis A, pertussis, malaria
Allen and Ferson[29]	1998	Sydney, Australia	South Eastern Sydney Public Health Unit reports	Hepatitis A, pertussis, and measles
CDC[31]	2002–2006	Florida, USA	Florida Department of Health web-based reportable disease surveillance database (Merlin)	Salmonellosis, shigellosis, meningococcal disease, hepatitis A

EHEC, enterohaemorrhagic *Escherichia coli*; STEC, Shiga toxin-producing *Escherichia coli*; UPMC, University of Pittsburgh Medical Center; CDC, Centers for Disease Control and Prevention.

municipal health service by 5.3 days ($p < 0.01$; 95% confidence interval (CI) 1.7–8.9 days), compared to the municipal health service without agreements for reporting of hepatitis B in 2008. The municipal health service, which received most reports by fax, showed an average improvement in notification time of 3.3 days ($p < 0.05$; 95% CI 0.5–6.1 days) compared to the municipal health service that received reports by post; e-mail was slower than fax, although not significantly, and showed no significant improvement compared to post. Municipal health services receiving 10–20 report cards per week from physicians showed a significant delay of an average of 19.1 days for laboratory diagnosis to municipal health service report, compared to other municipal health services with an average of 7.3 days for laboratory diagnosis to municipal health service report. The authors concluded that an increase in direct and immediate laboratory reporting of diagnoses to the municipal health service would improve timeliness, and that physicians and laboratories were not aware of the importance of rapidly reporting cases.[22]

The study by Panackal et al. found that electronic alerts were reported a median of 4 days (interquartile range 4 days) sooner than through paper-based reporting.[28]

Ward et al. found that the overall median central delay (defined as the time between regional and national reporting) was reduced from 10 days (interquartile range 4 days) in 2001 with a paper-based reporting system to 1 day (interquartile range 1 day) in 2003 with an electronic system. Furthermore, they reported that, except for malaria, the total delay (defined as the time between symptom onset and reporting at the national level) was also significantly reduced with the electronic system.[30] The authors commented that astute clinicians remain important for the timely reporting of certain notifiable diseases.

The study by Allen and Ferson found the following barriers to physician notification of cases: physicians expected that the laboratory would notify cases (and if doctors left notification to the laboratories, there was an increased delay of 7–19 days); physician uncertainty of diagnosis; lack of remuneration for notifying; notifying is time-consuming; and poor specificity of clinical diagnosis or concerns about implications for the patient of notifying a disease later found to be incorrect.[29]

The CDC report found that electronic laboratory reporting would reduce the total time from symptom onset to county health department notification of a case by nearly half for salmonellosis (from 12 days to 7 days) and shigellosis (from 10 days to 6 days), but would produce no change for meningococcal disease (4 days) and a minimal improvement for hepatitis A (from 13 days to 10 days).[31]

3.4. Analysis of the findings

The findings were categorized as conditions necessary for earlier detection or factors that influence whether or not these conditions can be in place. The conditions and influencing factors were then organized according to the five generic steps in the disease detection model. One study also speculated on factors that may contribute to earlier detection, which is included (and indicated) in the presentation below (Table 2).

4. Discussion

The evidence-base of necessary conditions and influencing factors for earlier detection identified in this review is sparse. There is some evidence related to reporting (at the low and higher levels), no evidence about influencers of assessment (at the low or higher levels), and only speculation about recognition at the local level. This limited evidence is surprising given the large and growing size of the field focusing on early detection.

4.1. Recognition

Evidence is missing in the area that could perhaps lead to the greatest improvements in detection timeliness. Local recognition is a critical first intervention area that can enable the detection of an epidemic in its early stage. Epidemics generally begin in small, local areas, and then subsequently spread more widely. While

Table 2
Analysis of studies

	Reijn et al.[22]	Panackal et al.[28]	Ward et al.[30]	Allen et al.[29]	CDC[31]
1. Recognition influencer			*Influencing factors:* Astute clinicians (speculation)		
2. Low-level reporting influencer	*Conditions:* Information technology Governance *Facilitating factors:* Presence of physician–laboratory–MHS reporting agreements Fax reports to MHS (vs. via post) *Blocking factors:* Physicians and laboratories lack of awareness of the importance of rapidly reporting cases	*Conditions:* Information technology		*Conditions:* Attitudes/beliefs *Facilitating factors:* Public health personnel encourage physicians to seek laboratory confirmation of infections and uncertainty of diagnosis *Blocking factors:* Physician expectations that laboratories send notifications Lack of remuneration for notifying Time-consuming to notify Poor specificity of clinical diagnosis or concerns about implications for the patient of notifying a disease later found to be incorrect	
3. Low level assessment influencer					
4. Higher level reporting influencer			*Conditions:* Information technology		*Conditions:* Information technology
5. Higher level assessment influencer					

CDC, Centers for Disease Control and Prevention; MHS, municipal health service.

recognition is the earliest possible point for intervention, there is no evidence as to what factors influence earlier detection at this step.

4.2. Low-level reporting

Low-level reporting has the most evidence. A main finding is that electronic reporting is faster than paper-based reporting. This is the low-hanging fruit of early detection. It is intuitive that electronic-based systems will be timelier than paper-based systems. This does not discount the importance of having this evidence; however, it would be helpful to further explore this to understand the factors that influence whether or not these technical capacities can be in place. For example, available financing would certainly influence whether or not information technology structures can be in place. Perhaps a policy or national-level agreement would also be an influence. These types of factors are amenable to intervention, and could facilitate the implementation of electronic-based reporting.

The findings of Reijn et al. suggest that establishing reporting agreements, implementing a fax-based reporting system, and raising awareness of the importance of rapidly reporting cases are worthwhile areas for intervention for earlier detection in the Netherlands.[22] The findings of Allen et al. show that barriers to reporting relate to physician beliefs and attitudes, so training and educational seminars might seem like effective interventions.[29] However, by understanding why physicians have the beliefs and attitudes that they do could enable us to intervene further upstream and better target the root causes.

4.3. Low-level and higher level assessment

Low-level and higher level assessment are complex steps that can involve many players, often across multiple sectors (especially if the pathogen is zoonotic, which the majority of emerging pathogens are[32]). Assessment at the low level might involve physicians, veterinarians, or community health workers, depending on the region and disease scenario. If the input into the system is data or risk (for example, if information is picked up via a rumour book or online media story), this might involve local public health services, animal health services, and/or laboratories. Higher level assessment might involve district, regional, or national public and animal health services, and laboratories. Vertical and horizontal communication and coordination are required to perform assessment activities, including down to the community level. These stages are very complex, and perhaps require the most in-depth thinking. There is currently no evidence on key drivers of earlier detection during assessment.

4.4. Higher level reporting

Evidence suggests that information technology needs to be in place for higher level reporting to contribute to earlier detection. Higher level reporting can involve any notification following the initial assessment of an event, data, or risk. For example, the study by Ward et al. assessed regional to national level reporting, and the CDC article focused on laboratory to county level reporting.[30] Both of these reports occur after the initial reports are sent by physicians to the laboratory and, perhaps also, to some district public health authority. The exact flow of notification relies on the disease and context. Both of these studies found that information technology is a necessary condition for earlier detection. Similar to low-level reporting, research should build on this to understand the factors that influence whether or not these technical capacities can be in place.

4.5. Recommendations

To guide effective interventions and investments for early detection, more research is needed to build evidence on what factors influence earlier detection. EBS was introduced to complement IBS, but for both surveillance systems, it is unclear what leads to earlier detection. Research should consider all steps in the disease detection process, from recognition of a case, an event, or risks and data (indicating a potential outbreak), to outbreak declaration. Understanding if and how the various surveillance activities can contribute to earlier detection could enable proper prioritization to achieve maximum impact. Event recognition is the earliest possible point for intervention, and there is currently no evidence as to what factors influence earlier detection at this step. Low-level and higher level assessment also lack evidence and are potentially the most complex steps, and can involve participation across sectors and national boundaries. These activities should not be ignored.

The studies included cover a range of geographic regions and pathogens. Needs and challenges will differ across regions and diseases. To ensure the utility of findings, studies should focus on regions that are homogeneous with respect to factors that could influence earlier detection, such as infrastructure, governance, environmental vulnerability to infectious disease, surveillance systems, and resources. Additionally, the existing evidence comes from the northern hemisphere. Many low-income countries—where most of the global population resides—lack the resources or infrastructure to support such activities, and are most at risk of epidemic events.[32] Research should specifically address necessary conditions and influencing factors in these vulnerable regions.

The studies by Reijn et al. and Allen et al. measured the contributions of influencing factors to earlier detection, albeit partially.[22,29] (Allen et al. only measured one of the five influencing factors identified.[29]) The other studies only identified necessary conditions, so were unable to measure contributions of upstream factors. Being able to quantify the impact of factors on earlier detection could enable the balancing of costs and benefits, aid in intervention prioritization, and maximize the social return on investments. This will be an important component of future research in this area.

Transparent, replicable, and flexible methodologies can promote the development of earlier detection frameworks for different regions. Using similar systematic methodologies for developing evidence could also enable comparisons and potential synergies across and between regions. Pathogens do not respect borders, so frameworks that build on one another could protect against future regional or global outbreaks. It is suggested that the generic five-step surveillance structure is used as the model, as it can be applied to any context for any infectious disease scenario.

Outbreak management extends beyond the role of public health and often requires communication and coordination across multiple sectors and countries. For example, the detection of zoonotic infectious diseases requires horizontal interaction between the agencies, departments, and ministries responsible for public health, medical professions, veterinary services, and the environment.[33] Vertical interaction is also crucial for outbreak detection. As outbreaks start in communities, involving community members in this early phase could yield important information.

4.6. Limitations

This review was restricted to the MEDLINE database. This database is one of the largest and most well-regarded biomedical databases available, indexing thousands of high-impact journals. Like any database, though, its coverage is not complete and varies according to the field. Because MEDLINE is the most widely used database in the medical sciences, it was decided that restricting the search to MEDLINE was a satisfactory strategy given existing time constraints.

The grey literature and perspective pieces were not included in this review. Given the size of the field, there is likely much written in the grey literature on how to detect early. However, of the guides and frameworks that were found, it was unclear what evidence, if any, these were based on. It was decided to limit the review to the peer-reviewed scientific literature in order to capture only evidence, and not speculation.

The rationale of the review was determined by the research focus to reveal factors that influence earlier detection and ways to measure their impacts. Different surveillance systems and data collection methods were not compared with each other. Thus, the review base was very small. This could indicate that the selection rationale was too strict, or that there is a gap in the evidence that could guide improvements in surveillance methods leading to ad hoc decisions on what and how to improve and speed up detection.

5. Conclusions

Despite significant investment in early outbreak detection, there is very little evidence on factors that influence earlier detection and the measurement of these factors. An evidence-base of the influencing factors could enable more targeted intervention planning. More effective interventions could lead to the earlier detection of infectious disease outbreaks and ultimately decrease the impact of epidemics on populations. More research is needed on evidence-based factors that influence earlier detection.

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