Surveillance strategy for early detection of unusual infectious disease events

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New pathogens continue to emerge, and the increased connectedness of populations across the globe through international travel and trade favors rapid dispersal of any new disease. The ability to respond to such events has increased but the question is what 'preparedness' means at the level of the clinician. Clinicians deal with patients with unexplained illness on a daily basis, and even with syndromes highly indicative of infectious diseases, the cause of illness is often not detected, unless extensive and costly diagnostic work-ups are done. This review discusses innovations in diagnostics and surveillance aimed at early detection of unusual disease. Risk based approaches are promising, but optimal preparedness planning requires multidisciplinary partnerships across domains, and a global translational research agenda to develop tools, systems, and evidence for interventions.

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Introduction

The past decade has been a turning point in our understanding of infectious diseases. The outbreaks of severe acute respiratory syndrome (SARS) and avian influenza have brought the message home that new infectious diseases threaten population health. New pathogens continue to emerge, and the increased connectedness of populations across the globe through international travel and trade creates conditions favoring rapid dispersal of any new disease. Virus discovery projects have found many new viruses that may have zoonotic potential, as illustrated by the recent cases of infection with a novel corona virus, previously only identified in bats [1**,2].

With this comes the notion that preparedness planning is needed to be able to respond to emerging infectious disease cases or outbreaks. However, the pandemic of influenza A/H1N1 2009 is a perfect illustration of challenges in this respect: crucial information on disease severity, ability to transmit, and population immunity were not available at the time when decisions had to be made about vaccine production [3,4•]. When the pandemic turned out to take a fairly mild course, public health authorities, scientists, and politicians were publicly criticized for what was considered a disproportionate response by some groups.

Reviewing emerging infectious disease events since SARS and avian influenza shows one thing: the ability to respond to such events has increased [5–8]. Innovations in laboratory methods now enable characterization of pathogens in clinical specimens in a matter of days, the widespread use of molecular methods in clinical laboratories enable deployment of new methods as soon as a sequence is available and shared [1**,2]. More challenging, however, is the question what 'preparedness' means at the level of the clinician, or public health physician. Clinicians deal with patients with unexplained illness on a daily basis, and even with clinical syndromes highly indicative of infectious diseases, the cause of illness is not detected in a high proportion of patients in many parts of the world, unless extensive and costly diagnostic work-ups are done [9,10,11**,12**]. As symptoms of disease caused by many different pathogens are largely overlapping, clinical triaging is not straightforward. As a consequence of this, diagnosis of new infections may be delayed. This time to diagnosis of an emerging infection is a crucial determinant of successful outbreak control: the longer it takes, the more opportunity for onward transmission is available [13•]. Therefore, surveillance aimed at early detection of unusual disease (outbreaks) is important.

Disease surveillance

Infectious disease surveillance is the monitoring of behavior and other sources of information, for the purpose of influencing, managing, directing or protecting the health of humans or animals or both. This definition already alludes to an important objective, namely that the information can be used for action. What this action is and what data are collected differs, depending on the type of surveillance and the objectives of that particular system. An effective surveillance program is capable of picking up cases of a disease with a certain sensitivity and specificity, in a representative sample of the population at risk, and in time to allow control actions when needed [14,15].

Essential for success is that the surveillance is simple, so that clinicians for instance are willing to provide the information that is requested, thus making the surveillance sustainable. Surveillance systems consist of a range of components that combined are designed to achieve the objectives of that particular surveillance program. The degree of surveillance activities is highly variable, reflecting resources and capacity of the healthcare system in different regions of the world. As a consequence, countries may need to choose to focus on a few priority diseases, and priorities may differ in different regions of the world [16]. For instance in Africa, the emphasis is on 19 diseases or syndromes that are major causes of (childhood) mortality such as diarrheal disease, pneumonia, infections with human immunodeficiency virus, malaria and tuberculosis. In addition, a limited number of epidemic prone conditions have been defined, (such as meningitis, cholera, yellow fever and viral hemorrhagic fevers) and for each of these diseases specific criteria have been formulated for training, laboratory confirmation, reporting, and response. In 2007, the countries in the World Health Assembly agreed to share information on any unusual disease event by signing the new International Health Regulations [17]. With that comes an obligation to develop core capacity for surveillance, reporting, sampling, and laboratory testing of the listed priority diseases, as well as sharing of information and samples internationally when such unusual diseases occur. It remains to be seen if this vision for the future is realistic, although for instance the progress of polio eradication shows that much can be achieved despite these limitations [18••,19]. Nevertheless, the polio example also shows that few exceptions may hamper this progress, and societal and scientific challenges remain [20–22].

## Capturing unusual disease events through surveillance

Regular disease surveillance uses data on recognized illness cases for trend monitoring, and therefore does not provide information on rare or emerging infections unless those are known, specific enough to be recognized as unusual, and then diagnosed (Figure 1) [23,24]. An example could be for instance rabies, standing out as a clinical entity due to its typical symptoms once disease progresses [25]. More often than not, however, unusual infections are not recognized, simply because they do not form part of the routine diagnostic work-up of patients, and such patients are the exception (Figure 1a). This is by no means limited to resource poor regions of the world. A patient with Marburg hemorrhagic fever was hospitalized in a ward for more than a week, before being diagnosed when her condition deteriorated. By that time more than 140 persons had been in close enough contact to allow transmission and had to be put under stressful enhanced surveillance [26,27]. Patients with cowpox lesions have been subjected to surgery for removal of so called ulcers, because they had not been recognized as such [28].

Genotype 3 hepatitis E virus infections, widespread in pigs in major pig-producing countries — was not seen as a cause of human illness until studies were done targeting the group of patients with hepatitis for which no cause could be identified [29]. The above examples illustrate another important point: many unusual human infections originate from animal populations. On the basis of a systematic review of emerging infectious disease outbreaks occurring over a period of more than 50 years, Jones *et al.* [30] concluded that 75% of emerging infectious diseases are zoonotic infections. Therefore, it is remarkable that very little is done to enhance surveillance at the human animal interface, except for targeted studies. The ability to detect outbreaks timely increased over the past decade, but this was not paralleled with faster (international) public communication [31]. The need for specifically designed systems, or a review and refocus of existing systems to respond to the emerging disease threats of the 20th century was recognized some 10 years ago, with the outbreaks of SARS, and the emergence of avian influenza A/H5N1 [14]. The major push for enhanced disease detection however followed from the intentional release of anthrax in the US in 2001, and subsequent investments in research into syndromic surveillance and novel detection platforms.

Syndromic surveillance

The challenge of detecting unusual disease events in the pool of 'common illnesses' has received increased attention since the deliberate release of anthrax through direct mailing to persons working in governmental organizations in the US, in 2001. Syndromic surveillance makes use of the fact that most early symptoms of any infection can be grouped in one of six recognized clinical syndromes, defined as unexplained fever, arthritis and rash, neurological illness, respiratory illness, gastrointestinal illness, and hemorrhagic disease [32]. Information on the occurrence of these illnesses may be derived from registries such as emergency department visits (provided physicians record the clinical presentation of their patients), pharmacy sales by category of medication, requests for laboratory diagnostics, or patient records used for billing, for instance. Monitoring counts of patients buying over the counter cough medication provides a trend in respiratory disease in the community, and validation studies have shown that such data quite accurately reflect trends in influenza and other viral respiratory tract infections [32]. Once such trends are known, deviations from this trend can be detected through statistical methods, and then be used for alerting public health authorities (Figure 1b). The use of modern technologies to access and analyze media from all over the world relevance is being used to inform public health specialists and laboratories about possible health threats [24,33,34,35••,36]. As for all syndromic surveillance systems, it is difficult to assess their added value, and particularly the balance between cost and benefit.

Figure 1
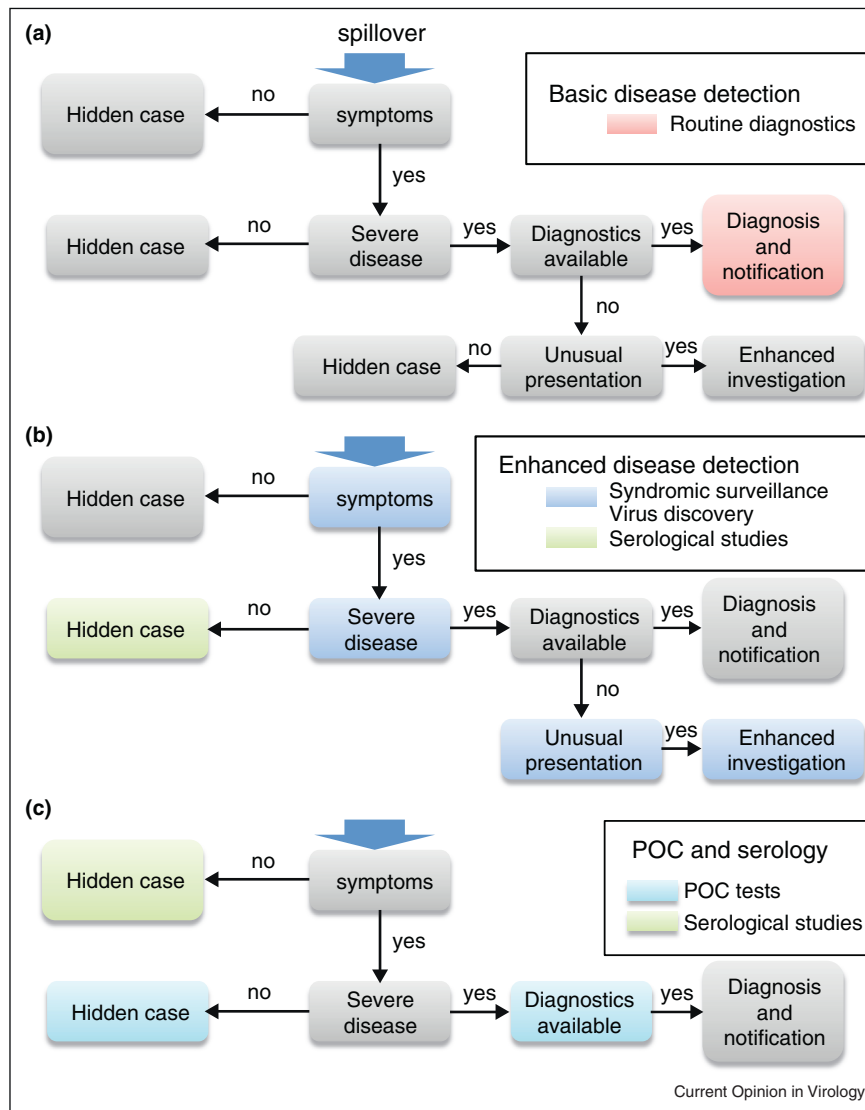
Approaches used to increase ability to detect unusual disease outbreaks, showing cases captured through current healthcare system (a), with syndromic surveillance combined with novel pathogen detection methods and serological diagnostics (b), and wider use of generic point of care tests and sero-surveys (c). POC = point of care.

Clearly, the usefulness of syndromic surveillance depends on how reliably the data used predict known disease trends, in part determined by the coverage of the particular registry, and the discipline of persons entering the data by syndrome. Other factors are the specificity of the syndrome: for instance 'fever of unknown origin' or 'respiratory illness' are much broader syndrome categories than 'hemorrhagic illness', limiting the practical use of such broad syndromes due to low specificity and low positive predictive value [37]. The specificity can be increased by adding symptoms to the syndrome definition, for instance for 'neurological illness' by adding 'paralytic symptoms'. This approach has been used worldwide to detect polio virus cases, and the world

health organization has developed surveillance performance criteria by setting a minimum rate for the number of children with acute flaccid paralysis that was tested for absence of poliovirus as a cause of infection [38]. Similarly, smallpox eradication would not have been possible without door to door clinical case finding, using cards that clearly described the symptoms of smallpox, again one of the few diseases with a clear clinical presentation once the full-blown disease develops [39] When considering the use of syndromic surveillance as early warning for new introduction, however, the problem is its coverage. Spill-over events at the human-animal interface most likely occur more often than is currently recognized, as indicated by serological studies (Figure 1b, c) [40–42]. However, the

same studies are subject to considerable debate, as standardization of serological tests is difficult and differences in interpretation may lead to fundamentally different risk assessments [42,43]. Case based surveillance by default is biased for disease severity, which is relevant for individual patients but only partly related to public health impact. An epidemic of a certain new pathogen with a case fatality rate of 2–3% is quite serious, but means that 'only' one out of 30–50 patients has a severe course of illness thereby potentially misleading the clinician or public. The pandemic of 2009 was a clear illustration of the difficulty of assessing severity during an emerging disease outbreak: initial reports suggested severe impact, because they were based on hospitalized cases that turned out to be only a small selection of the infected cases. Having reliable serological tools would have helped to define the true clinical spectrum, information that was crucial in assessing he need for control activities [4•]. The lack of immunity is specifically stated as a condition to be met before declaring a pandemic.

Although widely deployed, there is considerable debate about the usefulness of syndromic surveillance against the cost of developing and maintaining such systems. Measuring cost-effectiveness is difficult, because it is difficult to define effectiveness: is this the number of cases or outbreaks averted by syndromic surveillance? How realistic is that? A systematic evaluation of the potential uses of syndromic surveillance concluded that — arguably — the most frequently used application was demonstrating the absence of a problem [32]. During the recent pandemic, syndromic surveillance was used to monitor population impact, for instance by looking at trends in mortality by age group [44]. Without the ability to confirm syndrome surveillance trends by laboratory testing, however, its applications remain limited.

Virus discovery and assessing human health risk

The development of generic polymerase chain reaction-based assays and sequence independent genome amplification and sequencing has revolutionized diagnostic medicine [45]. These virus discovery approaches have unraveled presence of previously unknown pathogens in samples from humans and animals with different clinical

Figure 2
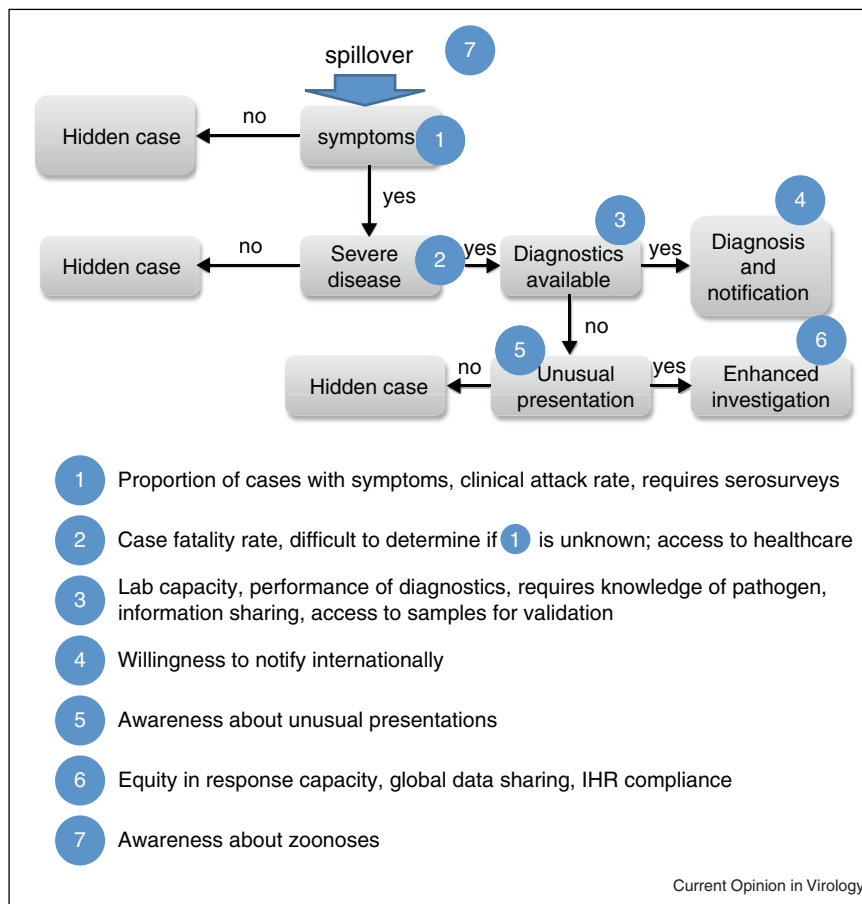
Factors influencing ability and timeliness of detecting zoonotic spill-over events through regular surveillance activities. IHR = International Health Regulations.

syndromes, for instance the arena virus identified in transplant recipients with febrile illness, a novel tick-borne bunya virus causing fever and thrombocytopenia in humans in China, and a novel bunya virus causing diarrhea and congenital malformations in ungulates in Northern Europe [46**,47,48**]. In addition, viruses have been identified in animal reservoirs, particularly bats, raising the question of pathogenic potential for these [49,50**,51–53]. This creates a new problem; there currently is an imbalance between the capacity for virus discovery and the capacity for validation of such findings. The absence of recognized human cases does not mean that zoonotic infection can be excluded, given the large under-diagnosis and high proportion of clinical syndromes that go without diagnosis. A nice illustration of this blind spot is seen for swine influenzas: the possibility of human infection with swine influenza viruses has been demonstrated long time ago, and sero-surveys have indicated that this is not a rare event, given the high seroprevalence of antibodies in humans exposed to pigs [54,55]. Despite this, however, virologically confirmed human cases were rarely identified. A commonly heard misconception is that this signifies the lack of pathogenicity of these viruses for humans. Even for a well-known pathogen like influenza, that majority of cases are not recognized, because the illness ranges from asymptomatic to severe. The likelihood of diagnosis increases with the severity of disease, mirroring diagnostic practice: laboratory testing in persons with mild illness is not necessary for treatment (Figure 2).

Targeting surveillance efforts to increase likelihood of detection of emerging infections

In view of the above, early detection of unusual diseases remains challenging, as summarized in Figure 2. Nevertheless, there is a move toward 'smart' surveillance, in which knowledge about disease ecology is used to target surveillance efforts. Examples of this are the geospatial analysis of farming regions to identify hotspots for disease transmission [56,57], including knowledge on people's behavior [58], GIS-based mapping of risk areas for disease emergence in vector-borne diseases [59,60], and the use of low threshold and syndromic methods for serology or virus detection [61–65]. What is lacking is a global strategy on how to link these components into a sensitive and cost effective approach, which includes deciding where to focus surveillance activities (with the necessary investments), how to share relevant information despite cultural, political, and legal barriers. The International Health Regulations provide the legal basis, but the focus on emerging infections is one that competes with high priority diseases of today. Risk based strengthening of the public health infrastructure, including laboratory capacity, would be a major step forward. Aligning this with a translational research agenda to develop tools, systems, and evidence for interventions would even be

better [66]. This requires multidisciplinary partnerships across domains (veterinary, medical, agricultural, societal), an interesting challenge.

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