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Commentary

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National public health systems often undertake surveillance for infectious diseases in returning travelers. However, such surveillance is usually restricted to certain designated reportable diseases, such as malaria or certain arboviral infections. Country-specific non-governmental networks like Redivi in Spain [1,2] or the Emerging Infection Network in the United States [https://ein.idsociety.org/], and European networks such as TropNet [http://www.tropnet.net/] also concentrate only on selected infectious diseases. By contrast, international surveillance networks such as GeoSentinel and its European sub-network, EuroTravNet, specifically undertake surveillance on travel- and migration-associated infections. Routine surveillance of travel-associated infections, as conducted by GeoSentinel, utilizes the ongoing collection and analysis of standardized core data entered by a large number of surveillance sites with a wide geographical distribution [3] (Table 1). The data are designed to stratify illness by travel destination, demographics and reason for travel, enabling outbreak identification through sentinel cases while also demonstrating changes in the geographic distribution of infectious diseases [4]. International surveillance systems such as GeoSentinel allow for broader sampling of types of travel and geographical sites of exposure, compared to national or regional systems.

Strengths of traveler surveillance systems

Surveillance of travel-associated infections can provide valuable information beyond identifying public health hazards related to individual travelers. In some low-resource regions, access to diagnostic testing is limited, resulting in suboptimal local capacity for documenting endemic and epidemic transmission of infections. Travelers may be exposed in these regions, but then have easier access to more sophisticated diagnostic testing on their return, providing information which may be more complete or more rapid than what is available where the exposure took place. Travelers can therefore become the most efficient available sentinels for local transmission. GeoSentinel sites have been selected for their expertise and diagnostic capacity in travel and tropical medicine, as well as large volumes of ill returned travelers. Another major benefit is that the large databases of surveillance networks can provide a wealth of information on the epidemiology of travel-associated infection and on disease movement across international borders.

Collaboration between national public health surveillance systems and international surveillance networks like GeoSentinel can provide rapid, detailed information on outbreaks. A recent example is the emergence of chikungunya in Thailand [5].

Limitations of traveler surveillance systems

However, these large surveillance systems also have well-known limitations, including sampling and selection biases, and data quality issues. Travel-associated disease surveillance has also been complicated by the difficulty in establishing denominator data, hampering the ability to estimate incidence and risk. Finally, at this time, the complexity of operating these systems has necessarily led to a relatively low level of granularity of the core data, defined as the information which is collected for all cases targeted for routine surveillance.

We describe here our thoughts for addressing some of these problems in the future.

Enhanced surveillance strategies

To improve data granularity without increasing complexity excessively, networks can engage in enhanced surveillance targeting specific questions (Table 1). Relevant data can be collected from pre-defined subgroups of the population being surveyed over a finite period of time, either retrospectively or prospectively. Often only small samples of travelers are needed to address a given question, allowing detailed data collection during a short timeframe, providing a cost-effective, relatively rapid approach to topical issues.

The GeoSentinel network has used this alternative methodology for focused supplemental prospective data collection. As an example, over a fixed period, entry of surveillance records involving post-exposure prophylaxis for rabies triggered a system generated request for participating sites to collect more detailed information designed to answer pre-defined questions about patient management. These questions referred to data which would normally have been collected in the course of routine assessment of these patients, and therefore data collection was classified as “enhanced surveillance” [6]. Similarly, routine entry of surveillance records in GeoSentinel coding for infection involving specified bacteria triggers a system request to also enter pre-defined antibiotic susceptibility data. This project continuously collects data for 9 bacteria that have been targeted by the World Health Organization Global Laboratory Antimicrobial Surveillance System (GLASS), using travelers to provide a world-wide convenience sample for surveillance. Preliminary results demonstrating the power of this approach to characterize the regional susceptibility profile for the enteric fever pathogens, *Salmonella enterica* serovar Typhi and Paratyphi, were recently presented [7].

Challenges and opportunities in performing multi-site surveillance

Large multi-site surveillance networks are ideal for broad based surveillance and enhanced data collection related to specific questions. They function as hypothesis generators for more sophisticated research. In addition, they can provide the infrastructure for conducting prospective translational research in travel medicine [4] by providing an established platform for collaboration and data sharing among travel and tropical medicine experts. Below, we describe the potential for innovative research arising from such collaborations, as well as the challenges inherent in the evolution of these complex multi-site network activities, using GeoSentinel as an illustrative example.

A unique strength of the GeoSentinel Surveillance Network is the sheer number and geographic distribution of the participating sites (68 sites in 28 countries), with well over 20,000 records entered annually. A secure, online web platform allows for near real time data collection which complies with diverse international privacy and confidentiality regulations. However, the more people involved, the more vital it becomes to have rapid and effective communication systems. Maintaining efficient communications presents increasing challenges as a network grows in size and sophistication. The solutions being envisaged will harness newer web and mobile application technologies to enhance internal communications and to rapidly disseminate information about projects and findings to outside organizations.

Data collection itself has evolved rapidly. GeoSentinel began with paper data collection forms faxed to a central data entry center. Subsequently, investments were made to enable web-based data entry. The next wave of data collection technology, currently in progress, will bring automated data extraction from electronic medical records, and automated data quality checks. At present, most sites enter data into patient charts, then re-enter some of the same data into the surveillance database. For large volume sites, with data entry personnel, this approach increases administrative support costs. For smaller volume sites where doctors or other clinical staff are responsible for data entry, this extra work limits the number of eligible cases which they are able to enter. Central template design and maintenance can now be envisaged, which will reduce time and effort. Data quality will improve as data abstraction and copying errors are reduced. The current limitations might bias the types of patient records that are entered in systematic or unpredictable ways. By improving data entry capacity, the patient data will be more representative of the total population served by these network sites. Additionally, automated data entry will facilitate the process of rapidly identifying unusual clusters or geographic distributions of cases.

Reliance on diagnostic information from multiple sites in different countries means that there is inevitably non-uniformity in diagnostic methodologies. Sites with access to more sophisticated diagnostic testing (e.g. multiplex PCR) will be able to make more etiologic diagnoses (vs. syndromic ones) than those utilizing less sophisticated testing, whether because of technical or cost limitations. Specific etiologic diagnoses across sites may be made on the basis of varied tests with different sensitivity/specificity profiles. For some diagnoses, combinations of testing including serology, PCR, culture or sophisticated genomic approaches may be used. This results in a spectrum of differing false positive and false negative rates across sites. Moreover, diagnostic capabilities are continuously changing over time, even at a single site, meaning that longitudinal comparisons are difficult. GeoSentinel has dealt with this in two ways. The first method involves more sophisticated collection of the core data using detailed standardized case definitions. This is coupled with an expansion of data collection related to the specific type of diagnostic testing performed. This allows for diagnostic coding in each case to be linked to the specific tests used to establish the etiology. It is now possible to stratify data among cases with the same diagnostic code in terms of certainty of diagnosis. The next step will be a “site mapping” exercise, where the diagnostic methodologies and algorithms at each site will be tracked and updated over time, to improve the detection of trends in the data by mitigating the effect of changing diagnostic methods.

One aim of performing traveler surveillance is to contribute to our understanding of the attribution of illness acquisition according to purpose of travel and specific exposure profiles. In order to accomplish this, surveillance systems must reliably attribute illness to the appropriate risk group or activity. The complexities in travel itineraries and multiple risk characteristics associated with varied types of travelers often make it difficult to link exposure to the proper location or activity. As one example, if travelers have visited multiple countries or regions within a single trip, linking outcomes to a specific exposure country or region can be complex. Travelers may undertake trips with multiple sub-itineraries being undertaken for different purposes. Thus, defining something as ostensibly straightforward as trip purpose, may not be simple. GeoSentinel has approached this problem by once again increasing the sophistication of core data collection, with each diagnosis being tied to a specific geographic exposure and specific reason for travel to that location, rather than the overall trip.

As mentioned above, surveillance data are generally extracted from information routinely entered in the medical record, and the designation of data collection as surveillance rather than research generally reduces or eliminates the need for individual patient consent. However, it is becoming increasingly difficult to navigate regional and global differences in data privacy issues and ethics requirements, as legal frameworks become ever stricter in some jurisdictions. Surveillance networks are inherently designed to highlight interesting and unusual cases as potential alerts to rare sentinel events. However, the publication of rare or unusual events can sometimes lead to cases becoming identifiable when linked to other details of the traveler such as travel history, demographics, and country of origin. In addition, as more patient testing is done and more follow-up and outcome data are collected, projects will eventually cross the ambiguous line from surveillance into human research. Although not unique to traveler-associated research, the variety of sites involved in a surveillance network such as GeoSentinel and the variability in ethical stances across multiple institutions and countries makes securing ethics approval increasingly time-consuming and complex. By contrast, many academic institutions have gradually accepted the concept of "relying on" ethical approval from one site to another, on the premise that ethical standards have become more standardized. GeoSentinel's approach has been to develop a library of approved protocols, agreements, and consent documents as part of a detailed "site mapping" process. This will allow new sites and sites requiring updates to their ethics approval to use templates already approved by other sites from their region, and should thus ease the process.

Future directions for surveillance networks

There are challenges in translating surveillance findings into diagnostic, therapeutic or public health interventions. In some cases, this would require projects which clearly cross into the domain of research, rather than simple surveillance.

While surveillance networks such as GeoSentinel have been very successful in terms of their surveillance function and enhancing our understanding of the epidemiology of travel-related infections, it is now time to leverage these established platforms in order to move beyond descriptive epidemiology and begin to address the next level of clinically relevant and mechanistic questions. These investigations represent a natural evolution for these well established networks which already link clinical centres around the world, with their associated academic and laboratory resources. GeoSentinel has already begun moving in this direction. Currently, studies are starting which will track clinical sequelae of arboviral infections and malaria. Other studies will involve, for the first time, collection of biological specimens for evaluation of biomarkers predictive of disease severity at centralized laboratories. The existing surveillance infrastructure provides the ability to enroll types and quantities of patients impossible for a single or small number of sites to gather. This in turn will provide unprecedented opportunities: elucidating the molecular epidemiology of emerging pathogens; using artificial intelligence and other novel approaches to detect and predict outbreaks of vector- and water-borne disease; tracking the emergence and spread of antimicrobial resistance; employing new diagnostics and interventions to improve the recognition and outcome of important travel and migration-related diseases; understanding the role of the human microbiome in susceptibility and resistance to travel–related disease; obtaining an enhanced understanding of the pathobiology of travel-related infections, especially predictors of and mechanisms behind variations in severity of infections, complications, and long-term sequelae. The ultimate goals would include learning how we can risk stratify these patients, and more appropriately intervene to improve outcomes.

These important and exciting new questions, which move these surveillance networks into the realm of translational research, will raise new logistical challenges, including more complex institutional review board approval, and developing mechanisms to acquire, store and share clinical samples linked with the associated clinical data. Last but certainly not least, high quality translational research will require increased funding from both existing and new sources, including traditional research funding agencies. Collectively and collaboratively addressing these barriers will allow these networks to transform, greatly enhance their potential for generating important new knowledge, and become not only viable and sustainable into the future, but key platforms for improving our understanding of many issues in travel and tropical medicine.

Conclusions

GeoSentinel has a successful history of identifying sentinel events and outbreaks, notably from areas of the world where surveillance and/or laboratory capacity may be lacking. It is able to rapidly collect, corroborate, collate, and disseminate information internally to its network members and affiliates, and also externally to partners with whom it collaborates closely, such as TropNet, EpiCore, and the International Society of Travel Medicine (ISTM). Widespread public notification of events has occurred through rapid publication of reports on ProMed, in Eurosurveillance, CDC's Morbidity and Mortality Weekly (MMWR) and various international journals, including the Journal of Travel Medicine, Travel Medicine and Infectious Diseases, and the Annals of Internal Medicine. Significant contributions to public health agency outbreak situation reports and risk assessments have also been made, such as those written by the European CDC, US CDC, and Public Health Agency of Canada. The redesign of GeoSentinel's website, and planned use of social media, will open up new channels for dissemination of this information in the future. Surveillance has evolved from routine core surveillance to targeted, "enhanced" surveillance, in order to move beyond the more basic questions which have largely been successfully addressed over the past 25 years. The most important anticipated development will be the adaptation of the surveillance infrastructure, which already links scientific capacity, clinical expertise, and elaborate medical and diagnostic resources, in order to serve as a platform for research and knowledge translation in the relatively neglected areas of travel and tropical medicine.

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Table. GeoSentinel strategies for routine and enhance surveillance

	Routine surveillance	Enhanced surveillance
Data	Core data form: general demographics, travel destination and travel date, reason for travel, main symptoms, final diagnosis, methods of diagnosis	Additional data form: specific detailed data depending on study objective
Participating sites	All GeoSentinel sites	Selection of sites
Study population	All travelers presenting to GeoSentinel network sites	Pre-defined subgroups of travelers or migrants
Study design	Retrospective	Retrospective or prospective
Timing	Permanent	Finite period of time
Objectives	1) To document outbreaks of infections through sentinel travelers 2) To provide detailed information on the epidemiology of travel-associated infection in general, and on disease movement across international borders.	To answer specific questions