Journal of Travel Medicine

International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide

Journal of Travel Medicine, 2020, 1–8
doi: 10.1093/jtm/taaa219
Advance Access Publication Date: 13 October 2020
Review

Review

GeoSentinel: past, present and future†

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†This article is dedicated to the memory of Professor Frank von Sonnenburg, Munich, Germany, who provided inspiration, insight, dedication and effort to the growth and success of the GeoSentinel for over 20 years.

Submitted 14 November 2020; Revised 17 November 2020; Editorial Decision 18 November 2020; Accepted 18 November 2020

Abstract

Rationale for review: In response to increased concerns about emerging infectious diseases, GeoSentinel, the Global Surveillance Network of the International Society of Travel Medicine in partnership with the US Centers for Disease Control and Prevention (CDC), was established in 1995 in order to serve as a global provider-based emerging infections sentinel network, conduct surveillance for travel-related infections and communicate and assist global public health responses. This review summarizes the history, past achievements and future directions of the GeoSentinel Network.

Key findings: Funded by the US CDC in 1996, GeoSentinel has grown from a group of eight US-based travel and tropical medicine centers to a global network, which currently consists of 68 sites in 28 countries. GeoSentinel has provided important contributions that have enhanced the ability to use destination-specific differences to guide diagnosis and treatment of returning travelers, migrants and refugees. During the last two decades, GeoSentinel has identified a number of sentinel infectious disease events including previously unrecognized outbreaks and occurrence of diseases in locations thought not to harbor certain infectious agents. GeoSentinel has also provided useful insight into illnesses affecting different traveling populations such as migrants, business travelers and students, while characterizing in greater detail the epidemiology of infectious diseases such as typhoid fever, leishmaniasis and Zika virus disease.

Conclusions: Surveillance of travel- and migration-related infectious diseases has been the main focus of GeoSentinel for the last 25 years. However, GeoSentinel is now evolving into a network that will conduct both research and surveillance. The large number of participating sites and excellent geographic coverage for identification of both common and illnesses in individuals who have traversed international borders uniquely position GeoSentinel to make important contributions of travel-related infectious diseases in the years to come.

Key words: Sentinel event, emerging infectious diseases, surveillance, travel medicine, COVID-19, Zika, antimicrobial resistance

Introduction

Despite improvements in the global burden, morbidity and mortality from infectious diseases over the last two decades, emerging and re-emerging infections continue to present major threats to populations worldwide.[1,2] Global movement of persons whether for tourism, business or migration[3–5]; effects of climate change on the environment; greater host susceptibility for many reasons; and genetic evolution of pathogens all play a role in the emergence (or re-emergence) of pathogens and the appearance and spread of novel diseases.[1,6–8] An estimated 60% or more of emerging infectious diseases are zoonotic.[9] In addition, there has been a substantial rise in antimicrobial resistance (AMR) in resource-limited areas of the world[10,11] and spread of these multi-drug resistant organisms via travelers to their home countries.[12] Returning travelers seen at sentinel sites by collaborative provider networks such as GeoSentinel[13,14] provide insight into the transmission and spread of infectious diseases.

GeoSentinel, the Global Surveillance Network of the International Society of Travel Medicine (ISTM) in partnership with the US Centers for Disease Control and Prevention (CDC), consists of specialized travel and tropical medicine clinics that are ideally situated to detect emerging infections and to track ongoing trends in travel-related illness. Currently, the primary objectives of GeoSentinel are to: (i) operate a global provider-based emerging infections sentinel network; (ii) conduct surveillance for travel-related infections; and (iii) communicate and help guide public health responses.

GeoSentinel—the early years (1995–2013)

During a 1-day meeting in Atlanta in the summer of 1995, Phyllis Kozarsky, David Freedman and Martin Cetron decided to recruit a working group of eight US-based ISTM member travel clinics run by trusted and eminent colleagues to establish a unique surveillance network. GeoSentinel was designed to track emerging infectious diseases at their point of entry into domestic populations, monitor global trends in disease occurrence among travelers, and respond to urgent public health queries. The network was also developed to aid in rapid response by electronically disseminating alerts to surveillance sites, to all ISTM members worldwide and to partner organizations globally. The vision of the then ISTM President Jay Keystone led to the ISTM providing 50 000 USD seed money to develop the network until independent funding could be secured. By May 1996 GeoSentinel was awarded competitive funding through the CDC Division of Quarantine (Table 1), under a US initiative to strengthen surveillance and response to emerging pathogens as strongly suggested by the Institute of Medicine in their 1992 report. By the end of 1997, GeoSentinel went 'live' at participating surveillance sites using a set of data fields that linked destination, date of travel and disease diagnosis in returning travelers. GeoSentinel was expanded internationally and data from all sites were manually aggregated at an Atlanta data center. In 1998, the group began to host annual Site Directors meetings at different locations around the world which brought together the combined expertise and intellect of many of the key leaders in the field of travel medicine and which continue as an epicenter for the development and advancement of research in the field.

In 2020, instantaneous global sharing of information around disease outbreaks is taken for granted. This has been well-demonstrated during the COVID-19, Ebola, Middle East respiratory virus, severe acute respiratory syndrome (SARS) and H1N1 pandemic influenza outbreaks that have occurred in recent years. However, in September 2000, GeoSentinel, which by then had expanded to 26 sites on all continents, provided one of the first demonstrations of the beginning of the exciting adventure in the way global surveillance data can rapidly be turned into information for action. The Borneo Eco-Challenge leptospirosis outbreak[15,16] demonstrated that the growth of partnerships between ISTM, CDC, and other medical societies, governments and private organizations had become one of the surveillance network's greatest assets. This outbreak also demonstrated the value of front-line clinical observations by expert clinicians and the ability of the doctor-patient relationship to rapidly translate into meaningful public health information. The reporting and documentation of patients seen with this unusual illness by network sites in London, Toronto, New York and Melbourne—all in <24 hours—could not have been accomplished otherwise. In 2003, the GeoSentinel site in Toronto saw some of the first SARS cases outside Asia and quickly notified the network that SARS was not just an Asian problem as per the WHO alerts but was now a global problem that demanded a public health response.

A comprehensive analysis of 17 000 ill returned travelers from the developing world, published in 2006, summarized the GeoSentinel experience between 1996 and 2004 and provided a blueprint for all medical providers of what diagnoses to consider in ill travelers, based on from where they returned (Table 1).[17] Physicians were able for the first time to use destination-specific differences to guide diagnosis and treatment of these individuals. This paper has been cited in the medical literature over 1000 times, a record for travel medicine, and still receives at least 10 citations per year (Table 2).

In 2007, the second generation GeoSentinel Data Entry and Reporting web application went live. For the first time, patient records entered at any site worldwide, 24 hours a day, were immediately live on a secure database, accessible for viewing on-screen in real time by project directors. In 2008, 12 European GeoSentinel sites formed a consortium and launched EuroTravNet, a new ISTM initiative in Europe funded by a new partnership with the European Centre for Disease Prevention and Control (ECDC) in Stockholm. The partnership helped aid communications between sites in Europe and those elsewhere.

By 2011, the first generation of 32 GeoSentinel scientific publications had 709 total citations in the medical literature with 177 in 2010 alone. Network-wide original papers published prior to 2009 were cited an average of 104 times/year from 2006 to 2010 and the average GeoSentinel paper had 44 citations. By 2013 the surveillance and communication functions of GeoSentinel were fully mature and a new compilation of surveillance data in 42 000 ill returned travelers seen between 2007 and 2011 at 53 GeoSentinel sites in 24 countries was published.[13] Once again, clinicians were able to use these 5-year GeoSentinel data to help tailor more efficient pretravel preparation strategies and evaluate possible differential diagnoses of ill returned travelers according to destination and reason for travel. With surveillance data

Table 1. Timeline of major GeoSentinel events

Year	Event
1995	GeoSentinel initiated in Atlanta, USA
1996	GeoSentinel awarded competitive funding through the DQ, NCID and CDC
1997	Systematic data collection begins
1999	Cooperative agreement between ISTM and CDC extended for 7 years
2000	Borneo Eco-Challenge 2000 Adventure Race: Cases of leptospirosis
2001	First generation internet-based data entry begins; GeoSentinel Network Member program is inaugurated
2003	GeoSentinel Toronto site identified SARS (among first to determine that SARS was not just a regional Asian situation)
2004	Strategic expansion initiative begins in Asia with sites at three important international gateways (Beijing, Singapore and Yokohama)
2006	Comprehensive analysis of 17 353 ill returned travelers from the developing world summarizing the GeoSentinel experience from 1996 to 2004 is published; Cooperative agreement between ISTM and CDC extended for 5 years
2007	Strategic expansion in Europe begins
2008	Twelve European GeoSentinel sites form a consortium to launch EuroTravNet, a subnetwork
2011	Temporary GeoSentinel site established in Leogane, Haiti to monitor illness in aid and relief workers post-earthquake
2013	Morbidity and mortality weekly report published on surveillance related to travel-related disease: GeoSentinel Surveillance System
2014	Restructuring of GeoSentinel leadership with selection of new principal investigator and formation of four working groups
2019	GeoSentinel database contains >333 000 records of ill travelers

DQ: Division of Quarantine; NICD: National Center for Infectious Diseases.

Table 2. Top five ranked GeoSentinel citations since its inception

Title	Authors	Journal name	Year of publication	Number of citations
1. Spectrum of disease and relation to place of exposure among ill returned travelers[17]	Freedman DO, Weld LH, Kozarsky PE, *et al*.	New England Journal of Medicine	2006	1101
2. GeoSentinel surveillance of illness in returned travelers, 2007–2011[13]	Leder K, Torresi J, Libman M, *et al*.	Annals of Internal Medicine	2013	410
3. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network[33]	Leder K, Tong S, Weld LH, *et al*.	Clinical Infectious Diseases	2006	393
4. Fever in returned travelers: results from the GeoSentinel Surveillance Network[51]	Wilson ME, Boggild A, Keystone JS, *et al*.	Clinical Infectious Diseases	2007	391
5. Malaria in travelers: a review of the GeoSentinel surveillance network[52]	Leder K, Black J, O'Brien D, *et al*.	Clinical Infectious Diseases	2004	238
			Total	2533

flowing smoothly and with global coverage, strategic planning for GeoSentinel v2.0 with more focus on deeper research into symptom causation, clinical outcomes and interventions could begin.

GeoSentinel procedures

The data collection protocol for GeoSentinel has been reviewed by the CDC's National Center for Emerging and Zoonotic Infectious Diseases and has been classified as public health surveillance and therefore ethics committee review is not required. Sites obtain additional ethical clearance as required by their respective institutions. Only individuals who have crossed an international border are eligible for inclusion in the GeoSentinel database. GeoSentinel surveillance data are collected using a standardized case report form and include physician-confirmed patient diagnoses and country of exposure along with more detailed exposure information, chronology of travel, symptom data and antibiotic susceptibility data. Returning travelers and migrants seen at GeoSentinel sites serve as sentinels—they provide a sample of disease agents that may be acquired in 249 countries and territories. Data reported by the sentinel Sites are entered online into a secure central database (Figure 1). Data are reviewed routinely for unusual patterns suggestive of disease outbreaks and novel findings such as the occurrence of a disease in an unexpected location. In addition to daily review of all submitted records, various quality control measures are continuously performed to strengthen the quality of the data.

GeoSentinel version 2.0 (2014–2021)

Based on the recommendations of a strategic planning meeting held in November 2013, GeoSentinel underwent a restructuring with the development of GeoSentinel version 2.0. One major result was a new leadership structure, inaugurated in April 2014, which began work in June 2014. This team included the new Principal Investigator, Davidson Hamer (USA), Karin Leder

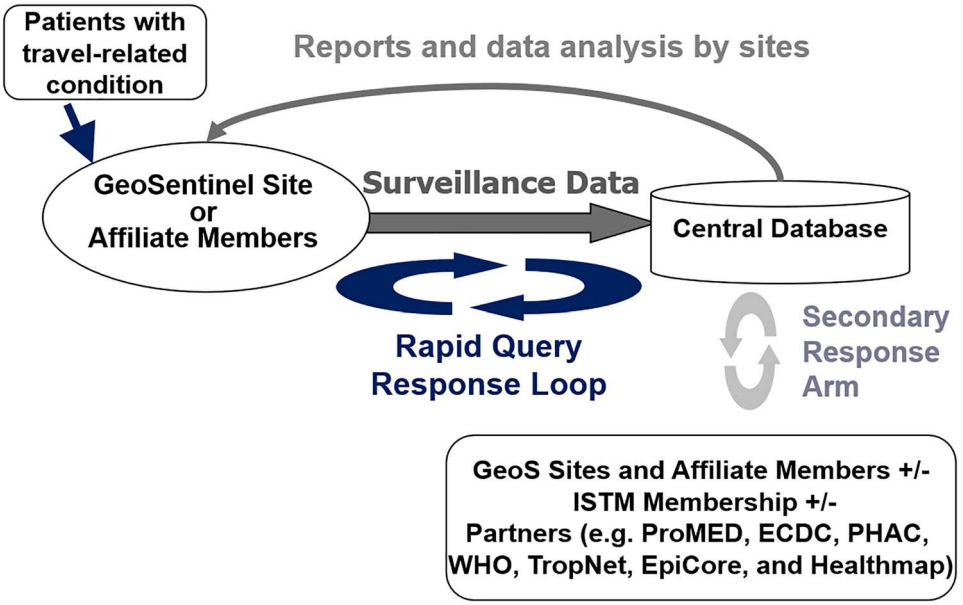

Figure 1. Flow of GeoSentinel surveillance data

(Australia), Chair of the Data Collection Working Group (WG); Elizabeth Barnett (USA), Chair of the Special Populations WG; Marc Mendelson (South Africa), Chair of the Enhanced Clinical Surveillance WG; Patricia Schlagenhauf (Switzerland), Chair of the Tracking and Communications WG; and Phyllis Kozarsky (CDC), Special Advisor to GeoSentinel.

Between 2015 and 2018, the Data Collection WG reviewed and revised all the disease codes (diagnostic criteria for each disease); updated the core surveillance data collection; and developed strategies for data quality control. The Special Populations WG developed several studies with enhanced data collection on defined groups, such as those individuals who received post-exposure prophylaxis for rabies,[18] mass gathering attendees,[19] those who experienced unanticipated and unplanned medical care during travel,[20] and those migrants who were screened for infections on arrival at their destinations.[21] The Enhanced Clinical Surveillance WG spearheaded the initiation of several studies including the SEVere, undiagnosed infections in returning TRAVelers (SEVTRAV) study which has been designed to define etiologies of febrile illness in travelers and migrants and novel pathogen discovery when the cause of illness is not identified. The Chikungunya, Dengue, Zika and Malaria (CHIDEZIMA) project is also ongoing and was designed to assess the medium-term impact of the physical and psychosocial aspects of these four diseases. The Tracking and Communications WG has been responsible for identifying potential sentinel or important travel- or migration-related events and communicating them to ProMED and to public health authorities (e.g. the European CDC, Public Health Agency of Canada, WHO). In 2019, there was a transition in the leadership of three of the working groups with Philippe Gautret (France) now serving as the Chair of the Special Populations WG; Kevin Kain (Canada) as the Chair of the Enhanced Clinical Surveillance WG, and Vanessa Field (United Kingdom) as the Chair of the Tracking and Communications WG.

Highlights of recent GeoSentinel analyses and sentinel events

During the last 25 years, the GeoSentinel Surveillance Network has been highly productive.[22] Recent GeoSentinel articles continue to be frequently cited (Table 3). Some notable analyses of travel-related infections in recent years include descriptions of specific diseases including leishmaniasis,[23] travel-associated pertussis,[24] *Clostridium difficile* in travelers,[25] leptospirosis,[26] hepatitis E,[27] and enteric fever including AMR data for *Salmonella enterica* serovar Typhi and *S.* Paratyphi.[28] There have also been analyses of travel-specific destinations including common febrile illnesses in West African countries confronted with the Ebola outbreak,[29] travelers to the USA[30] and illness among travelers to Brazil.[31] In addition, there have been a number of analyses on special populations such as student travelers,[32] travelers visiting friends and relatives,[33] European travelers,[34] skin diseases among Canadian travelers[35] and animal exposures among travelers[36] as well as migrant health, e.g. US migrants,[37] the spectrum of illness in Syrian migrants[38] and malaria in Eritrean migrants.[39] In addition, there have been several analyses focused on emerging and re-emerging diseases, e.g. the arrival of Zika virus disease in the Americas,[40] Zika outside of the Western Hemisphere[41]; and measles,[42,43] the importance of which has recently been emphasized.

In addition to the global, regional and disease-specific analyses, GeoSentinel has identified many sentinel events during the last two decades (Table 4). In addition to the aforementioned outbreak of leptospirosis at the Eco-Challenge in Borneo,[15] some notable sentinel events have included the identification of dengue in Angola,[44] sarcocystis in Malaysia,[45] schistosomiasis in Corsica,[46] yellow fever in southern Brazil[47] and chikungunya in southern Thailand, Myanmar and the Maldives.[48–50] These events were communicated to relevant public health authorities.

Table 3. Top five ranked GeoSentinel citations from the last 5 years

Title	Authors	Journal name	Year of publication	Citations
1. Travel-associated infection presenting in Europe (2008-12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pretravel consultation[34]	Schlagenhauf P, Weld L, Goorhuis A, *et al.*	Lancet Infectious Diseases	2015	214
2. Profile of illness in Syrian refugees: a GeoSentinel analysis, 2013–2015[38]	Mockenhaupt F, Barbre KA, Jensenius M, *et al.*	Eurosurveillance	2016	74
3. Fatal yellow fever in travelers to Brazil, 2018[53]	Hamer DH, Angelo K, Angelo K, Caumes E, *et al.*	Morbidity and Mortality Weekly Report	2018	70
4. Travel-associated Zika virus disease acquired in the Americas through February 2016: a GeoSentinel analysis[40]	Hamer DH, Barbre KA, Chen LH, *et al.*	Annals of Internal Medicine	2017	61
5. Differential diagnosis of illness in travelers arriving from Sierra Leone, Liberia, or Guinea: a cross-sectional study from the GeoSentinel Surveillance Network[29]	Boggild AK, Esposito DH, Kozarsky PE, *et al.*	Annals of Internal Medicine	2015	48
			Total	467

Future directions

Recent strategic planning discussions, within and outside the network, have focused on making substantive changes in the nature of future projects. The GeoSentinel network remains uniquely valuable as a platform for understanding the emergence and movement of infectious diseases around the globe. It is first and foremost a network of people, bringing together many of the world's recognized experts in travel and tropical health. These experts are backed by the resources of their associated academic institutions, which include the material resources for diagnosing and characterizing both common and esoteric infections, and the scholarly resources for driving new project development and success. The network has access to laboratory expertise in every relevant discipline, renowned researchers in epidemiology and clinical sciences, and globally recognized expert clinicians who provide the interface with ill travelers. Finally, the network has a truly worldwide catchment, with sites across world providing care to large numbers of travelers of every type returning from every region of the globe.

In recent years, it has become apparent that the network needed to move beyond sentinel surveillance and retrospective review of surveillance data. Over the past 25 years, communication networks for transmitting surveillance information have multiplied in nature and speed, diluting GeoSentinel's unique advantages in this regard. Many of the analyses of the database concentrated on 'who gets what where' questions, both broadly speaking as well as focused on specific illnesses and syndromes. As described above, some of these larger analyses provided for the first time a detailed understanding of the epidemiology of imported infections, replacing information which had previous been gleaned from single center reviews, or small collaborations.[13,17] It has also become evident that the basic epidemiology of many of the illnesses investigated is not changing in the short-term, and that broadening the scope of GeoSentinel's mission would be important for future discoveries.

The first step forward was the development of the enhanced surveillance projects described above. Rather than simply mining the accumulated data, looking for patterns, the orientation shifted toward identifying gaps in knowledge, and designing prospective data collection instruments to be able to answer more relevant questions. This approach led to a number of successful projects.[18–20] Nevertheless, projects were restricted in scope owing to the need to restrict the information collected to surveillance data, linked to routine patient care.

Sentinel surveillance continues to be where GeoSentinel excels. Despite advances in low cost diagnostics, many regions of the world still do not have sufficient human and material infrastructure to optimally survey endemic and emerging diseases. Using individuals who have traversed international borders to 'sample' local transmission remains critical and maintaining a geographically extensive and high patient volume network will continue to be an invaluable resource. Antibiotic susceptibility surveillance will also remain important. In the future, more sophisticated technology will be added to assist in interpreting data, and techniques using machine learning are likely to improve the ability to signal sentinel events—infections emerging in unexpected locations, unusual clusters and unanticipated trends—all signals which can trigger a more focused investigation.

The next step in understanding imported infections will necessarily involve developing a more traditional research-based approach including the use of molecular epidemiology. Even simple modifications of the existing enhanced surveillance model with the addition of questionnaires, more detailed clinical outcomes data, and project driven collection of biologic samples greatly expands the potential for advances in the field. More detailed clinical information, serosurveys and biomarkers are examples of relatively inexpensive data which can enhance our understanding of risks, costs and populations to target for interventions.

The network is also well positioned for comparative evaluations of laboratory diagnostics, markers of illness outcomes and interventions. In this domain, the network strength lies in numbers and breadth of catchment. Rare infections can be captured in sufficient volume for analysis. Common infections, such as malaria or dengue, can now be stratified by geographic

Table 4. Seven important sentinel events identified by the GeoSentinel Surveillance Network

Year	Event	Topic	Citation	Comments
2000	Leptospirosis in 'Eco-Challenge' Athletes, Malaysian Borneo	Leptospirosis	Sejvar J. *et al*. Leptospirosis in 'Eco-Challenge' athletes, Malaysian Borneo, 2000. Emerging Infect Dis (2000).[15]	Rapid communication led to global alert of leptospirosis outbreak among Eco-Challenge athletes and subsequent outbreak investigation
2012	Ongoing outbreak of an acute muscular *Sarcocystis*-like illness among travellers returning from Tioman Island, Malaysia	Sarcocystis	Esposito DH, et al. Ongoing outbreak of an acute muscular Sarcocystis-like illness among travellers returning from Tioman Island, Malaysia, 2011-2012. Euro Surveill. (2012) [54]	Rare disease identified in travelers to a tropical island in Malaysia through GeoSentinel and affiliated networks
2013	Detection on four continents of dengue fever cases related to an ongoing outbreak in Luanda, Angola, March–May 2013	Dengue	Schwartz E, *et al*. Detection on four continents of dengue fever cases related to an ongoing outbreak in Luanda, Angola, March–May 2013. Euro Surveill. (2013)[44]	An early identification of dengue in sub-Saharan Africa through returning travelers seen at GeoSentinel sites
2016	Zika diagnosed in returning travel to Massachusetts, USA after travel to Costa Rica	Zika	Hamer DH, *et al*. Travel-associated Zika virus disease acquired in the Americas through February 2016: a GeoSentinel analysis. Ann Int Med (2016)[40,55]	First case of Zika virus identified in Costa Rica
2017	Zika identified in an Israeli after travel to Vietnam	Zika	Leder K, *et al*. Zika beyond the Americas: Travelers as sentinels of virus transmission. A GeoSentinel analysis, 2012 to 2016. PLoS ONE (2017)[41]	First case of Zika virus identified in Vietnam
2018	Fatal yellow fever in travelers to Brazil	Yellow fever	Hamer DH, *et al*. Fatal yellow fever in travelers to Brazil, 2018. Morb Mortal Wkly Rep (2018).[47]	Yellow fever was identified in 10 travelers, including five seen at GeoSentinel sites. Many had been infected on Ilha Grande off Rio de Janeiro. Public health response by the WHO and PAHO led to remapping of yellow fever risk areas in southern Brazil
2019	Travel-associated chikungunya acquired in Myanmar in 2019	Chikungunya	Díaz-Menéndez M, *et al*. Travel-associated chikungunya acquired in Myanmar in 2019. Euro Surveill. (2020)[49]	Returning travelers provided an early warning signal of a chikungunya outbreak in Myanmar

exposure, variants of clinical presentation and mechanisms of treatment and follow-up.

Recently, the network has completed an internal survey of the research capacity and technical resources at each site. Some studies, such as controlled trials, may be feasible at single sites or through collaborations, but GeoSentinel has the advantage of being able to create customized 'subnetworks' which are well adapted for these types of projects, based on local expertise, lab capacity and detailed knowledge of the local patient population.

Insight into these new avenues for network development has led the CDC to modify their funding opportunity to include research, as well as surveillance activities. Simultaneously, the network has worked on expanding its sources of funding to be able to support the unavoidably higher costs of research projects. Investigators within the network have applied for peer-reviewed funding for several projects. GeoSentinel has set up collaborations with other funded researchers to bring the broad data gathering capacity of the network together with established expertise at other institutions. Fundraising through philanthropic donations to the GeoSentinel Foundation, a new charitable foundation dedicated to the support of GeoSentinel projects and led by Dr Bradley Connor, a long-time GeoSentinel site director, has already been highly successful as the general public becomes increasing aware of the need to better detect and understand transmission and importation of infections, emerging and established.

COVID-19 has had a major impact on GeoSentinel, by virtue of the massive decline in travel and migration which has severely limited the network's ability to 'sample' imported infections. Although we expect effects of the pandemic to be temporary and for travel to resume, the time this will require is unpredictable, and will likely depend on the widespread distribution of an effective vaccine. However, the pandemic has also been an opportunity for the network to examine COVID-19 itself as a travel-related illness, which will surely remain a problem into the future. GeoSentinel has already been successful at obtaining supplemental funding from the CDC for a multi-part project which includes sentinel surveillance for COVID-19 and other

respiratory infections, pre- and post-travel screening for infection in order to accurately define risk of transmission, and the collection of biomarkers which may be associated with severe disease. Through funds raised by the GeoSentinel Foundation and in collaboration with other agencies, the network was also able to demonstrate the capacity to fund and organize a multi-center adaptive controlled trial of prophylactic regimens for health care workers.

Twenty-five years after a small group of practitioners created GeoSentinel around the idea that travel medicine was not only needed to improve the care of travelers but could also be the key to understanding the emergence and movement of illness itself, the network continues to evolve and expand. Travel medicine has turned out to be a unique tool providing insight into the epidemiology and pathogenicity of endemic illness. This venture has become a success not simply by using modern diagnostic and communications resources, but mostly though the dedication, initiative and collaborations among a network of colleagues around the world with a vision that transcended their own borders.

Authors' contributions

DHH, AR, DOF and ML each drafted sections of the initial draft. All authors reviewed and provided input on the final versions of the manuscript.

Acknowledgments

GeoSentinel, the Global Surveillance Network of the International Society of Travel Medicine (ISTM), is supported by Cooperative Agreement 5 NU50CK000478-02-00 from the Centers for Disease Control and Prevention (CDC), as well as the ISTM and Public Health Agency of Canada (PHAC).

Conflict of interest

Drs Hamer and Libman, and Ms Rizwan receive salary support from GeoSentinel through subcontracts from ISTM.

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