Measuring mobility, disease connectivity and individual risk: a review of using mobile phone data and mHealth for travel medicine

Authors: Shengjie Lai, MD, PhD[1,2,3*], Andrea Farnham, MPH, PhD[4,5], Nick W Ruktanonchai, PhD[1,2], and Andrew J Tatem, PhD[1,2]

[1]WorldPop, School of Geography and Environmental Science, University of Southampton, Southampton SO17 1BJ, United Kingdom

[2]Flowminder Foundation, SE-113 55 Stockholm, Sweden

[3]School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, 130 Dongan Road, Shanghai 200032, China

[4]Swiss Tropical and Public Health Institute, Basel, Switzerland

[5]Department of Public Health, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, 8001 Zurich, Switzerland

* To whom correspondence should be addressed. Tel: +44 7849277878; Email: laishengjie@foxmail.com

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Abstract

Rationale for review: The increasing mobility of populations allows pathogens to move rapidly and far, making endemic or epidemic regions more connected to the rest of the world than at any time in history. However, the ability to measure and monitor human mobility, health risk, and their changing patterns across spatial and temporal scales using traditional data sources has been limited. To facilitate a better understanding of the use of emerging mobile phone technology and data in travel medicine, we reviewed relevant work aiming at measuring human mobility, disease connectivity, and health risk in travellers using mobile geopositioning data.

Key findings: Despite some inherent biases of mobile phone data, analysing anonymized positions from mobile users could precisely quantify the dynamical processes associated with contemporary human movements and connectivity of infectious diseases at multiple temporal and spatial scales. Moreover, recent progress in mobile health (mHealth) technology and applications, integrating with mobile positioning data, shows great potential for innovation in travel medicine to monitor and assess real-time health risk for individuals during travel.

Conclusions: Mobile phones and mHealth have become a novel and tremendously powerful source of information on measuring human movements and origin-destination specific risks of infectious and non-infectious health issues. The high penetration rate of mobile phones across the globe provides an unprecedented opportunity to quantify human mobility and accurately estimate the health risks in travellers. Continued efforts are needed to establish the most promising uses of these data and technologies for travel health.

Keywords: Mobile phone, mHealth, population movement, connectivity, epidemiology, risk assessment, travel medicine

Introduction

Human populations are highly mobile in this modern world. The volume of worldwide population travel has expanded at an exceptional rate over the last few decades, with international tourist arrivals increasing from 674 million in 2000 to 1.3 billion in 2017, and expected to reach 1.8 billion by 2030.[1,2] The increasing mobility of populations allows pathogens to move rapidly and far, making endemic or epidemic regions more connected to the rest of the world than at any time in history. The pathogens introduced by travellers may lead to secondary transmission and local outbreaks, as has been observed in severe acute respiratory syndrome (SARS), influenza, Ebola, Zika, yellow fever, and measles, among others, or to the appearance of diseases such as malaria in non-endemic areas following migration for work or travel to visit friends and relatives (VFR).[3-13] The spread of infectious diseases and their potential health risk in travellers has resulted in substantial concerns and challenges to global health systems and economies,[14-17] with a need to place more emphasis on understanding population mobility, infectious disease connectivity and the individual health risk of travellers.

Human movements vary from short, periodically recurring travel to work or school, to rare international migration, but the ability to measure and monitor human mobility and its changing patterns across temporal (hour, day, week, month, or year) and spatial (individual, house, community, city, or nation) scales using traditional data sources has been limited. In resource-poor settings, demographic data collected via traditional censuses and surveys at subnational scales can often be lacking or outdated.[18] However, many recent studies have highlighted how our understanding of human mobility across contexts can be significantly improved through quantitative analyses of positioning data from the huge population of mobile phone users.[19,20] In 2017, there were already over 5 billion unique mobile subscribers globally, with a penetration rate of 66% of the global population, and the total number of mobile cellular subscriptions exceeds the world population at 7.79 billion.[21,22] Moreover, mobile phone penetration is constantly rising and is predicted to nearly reach 6 billion users by 2025 with 5 billion connecting to Internet.[21,23] Even in the most resource-poor regions, such as Sub-Saharan Africa, the penetration rate of mobile cellular subscriptions has reached 75% of the population in 2017 (Figure 1), which is estimated to steadily increase to 85% by 2025.[21,22] As mobile phones are now an integral part of modern life, mobile positioning data has become a novel and tremendously powerful sources of information on measuring human movements and pathogen spread.[12,19,20,24-35]

Quantifying how people move throughout their daily activities within the context of spatial risks enables a better understanding of environmental drivers of infectious disease, as well as chronic disease and other issues that involve long-term differences in exposure and mobility during travel.[36-39] Recent advances in mobile health (mHealth) technology, together with the increasing penetration of smartphones and the internet, have facilitated the monitoring of traveller health behaviour and assessment of environmental risks, e.g. air pollution, and offer more reliable and more frequently updated ‘apps’ that consolidate travel health information from multiple sources in travel medicine research and practice.[36,37,40-45]

To facilitate a better understanding of the use of mobile phone data in travel health, here we review the research work aimed at measuring human movements, disease connectivity, and health risk in travellers using mobile geopositioning data and mHealth technology. We searched PubMed for all related studies, published up until 5 March 2019 and in English, by the queries “(mobile phone OR cell phone OR smartphones OR call detail records OR mHealth OR eHealth) and (travel OR mobility OR movement OR connectivity) AND (disease OR health OR risk OR illness)” in the title and abstract fields. The number of relevant publications resulting from these searches has grown rapidly over the last decade (Figure 2). We also searched the relevant reports and reviews published by the World Health Organization (WHO), and relevant references cited in publications were also reviewed. In this paper, first, we outline traditional and novel data sources for measuring population movements, highlighting the potential of mobile positioning data. Then, we sketch out approaches using human mobility data as a proxy for infectious disease connectivity. Further, the progress of mHealth for individual health risk monitoring and assessment in travel medicine research and public health practice is also summarized. Finally, we discuss the challenges of using mobile phone data and future directions for research in this area.

Measuring Human Mobility using Mobile Phone Data

Traditionally, approaches to measuring human mobility rely on data from population and housing censuses, travel history surveys, or cross-border and traffic surveys (Table 1).[35,46,47] With technological advancements, however, increasing numbers of novel data sources have been used to measure human movements. Data from small scale studies using personal Global Positioning System (GPS) trackers provide information on short-distance, circulatory movement and can directly inform activity spaces, the local areas within which people move or travel during the course of their daily activities.[35,48,49] The trajectories of bank notes were traced to model human mobility over a long time period.[50] Data of global air traffic and itineraries have also been analysed to measure internal and international connectivity and its impact on the spread of pathogens and vectors at city or airport level.[3-8] Infrastructure data have also been used to define the connectivity between regions with the travel time as a proxy of human mobility and health accessibility.[51,52] Moreover, earth observation data, such as satellite imagery of night-time lights can help inform on the changing densities of populations within cities over the course of a year.[35,53] Mobile phone data are particularly promising for analysing travel-related phenomena on a scale previously impossible, providing a “big data” approach to understanding human mobility and its changes.[16-30] Two types of mobile-based positioning data that have so far been increasingly explored in travel-related studies are call detail records (CDRs) and mobile location history.

Call Detail Records

CDRs are routinely collected by mobile phone operators for billing purposes.[20,31] Each CDR contains an entry for each call or text made or received by any user with the subscriber identification module (SIM) card, together with the date and time of each communication and the tower that the communication was routed through within mobile phone networks.[23,24] Every time an individual makes a call or sends a text via a short messaging service (SMS), it normally will be routed through the closest tower in the network. If these data are available in conjunction with geographic coordinates of relevant towers, then the tower-level location of each communication can be identified, and from this, the movement of individual mobile users between different calls can be derived. When mobile penetration rate is high in the population, or mobile users’ movements could be taken to represent the mobility pattern of the general population, spatially and temporarily explicit estimations of human mobility and densities at national scales can be derived from anonymised CDRs. Previous studies for Namibia, Bangladesh, Portugal and France have shown that estimates derived from CDRs can accurately replicate population counts and migration patterns from censuses.[19,30,54-57] In these studies, each individual user was assigned a primary daily location based on either the most frequently used mobile phone tower or the most recently used mobile phone tower if a communication was not placed on the day. However, as the data on very infrequent mobile phone users may introduce noise in defining locations and population mobility, infrequent mobile phone users, e.g. a subscriber with 30 days or less worth of data for each year, could be filtered out to obtain more accurate estimates of population movements.[58]

Furthermore, these passive positioning data derived from CDRs can also be used to measure seasonal changes in subnational population numbers and produce density maps of human distribution changes over multiple timescales, providing more precise denominators for health metrics than static measures from censuses.[20] However, CDRs cannot measure spatial movements finer than tower-level spatial resolution, and estimates are limited to domestic movements, as it is more difficult to obtain CDRs from operators in different countries to get estimates of international traveller flows. Nevertheless, mobile phone location history data are promising for measuring cross-border movements, as outlined below.

Mobile Location History

When smartphones are connecting to internet, various applications record user check-in locations with high spatial precision where various services are used.[34,35,59,60] Location history data can be extracted from populations using mobile-based social media, e.g. Tweets, Facebook and WeChat, search engines, e.g. Google and Baidu, and other applications such as mHealth apps.[34,35,56,57] These data are associated with a consolidated user account, allowing for recording of geographic coordinates that are passively recorded across all mobile devices that an individual has owned. Because location is identified using a combination of the phone’s internal GPS and connected

WiFi devices and cell towers, these data are as spatially refined as GPS tracker data and can span years. Moreover, the passively-collected nature of these data avoids many known biases from compliance issues in studies that use GPS trackers, and avoids recall bias found in self-reported travel history data.[35] However, the biases may still exist, as the smartphone penetration is still very low in low income countries. The opt-out nature makes them sensitive and careful controls and ethics clearance need to be in place before accessing to these data.

The high resolution of mobile-based location history data, however, means they are one of few viable sources of information for better understanding and mapping these differences towards mapping activity spaces and travel routes across long periods and countries. For instance, studies using Google location history and Twitter geotag data, being collected in an opt-out, passive fashion for users, demonstrated that mobile location history can be a reliable source to capture rich features of mobility movements within and between cities, and even between countries.[35,59] Further, based on CDRs and social media location history data from different nations, a variety of individual and collective mobility patterns can be accurately predicted by using a universal model at diverse spatial scales.[34] Therefore, mobile phone data provide an unprecedented opportunity to understand global and seasonal dynamics associated with contemporary human mobility.

Mobile-derived Human Movements and Disease Connectivity

Based on the enormously detailed travel itineraries that mobile phone data can produce, patterns of pathogen spread through space and time can be simulated and measured using individual human movement trajectories combined with existing knowledge on pathogens. Though some pathogens are transmitted via vectors or animal hosts, most infectious diseases rely on human movement for wide-scale spread, and even for those spread by vectors, human movement plays a substantial role in transmission dynamics.[61,62] To measure the risk of infectious disease spread via travellers by various modes of transportation, a variety of individual or metapopulation-based statistical and mathematical models have been used to estimate the time, origins, destinations, probability and magnitude of pathogen importation and onward transmission from epidemic or endemic areas (Table S1). To date, mobile-derived human mobility, especially using CDRs, have been used to explore the transmission of malaria,[12,31,55] dengue,[29] cholera,[63] measles,[64] rubella,[28] Ebola,[65,66] and HIV infection.[67]

Taking malaria as an example, we illustrate how spatiotemporally explicit mobility derived from mobile positioning data has been used to define malaria connectivity and inform interventions. Although malaria is a mosquito-borne disease, human travel-mediated transmission on spatial scales that exceed the limits of mosquito dispersal has been undermining the success of malaria control and elimination programs that have been implemented in many countries.[10-12,68] The early detection and treatment of imported parasites due to human travel become high priorities for informing malaria elimination policy. A variety of models, integrating CDR-derived human mobility and malaria epidemiological and entomological data, have investigated the dynamics of human carriers to identify importation routes and locate transmission foci that contribute to malaria epidemiology for endemic countries in sub-Saharan Africa, Mesoamerica, and South-East Asia.[12,26,31,46,55,56,69,70] In these studies, spatial clusters of primary sinks and sources of parasite importation and their seasonal changes were disentangled, with the estimates of net export and import of travellers and infection risks by region. Using near real-time mobile-derived mobility data, this evidence can be rapidly updated and used to identify where active surveillance for both local and imported cases should be increased, which regions would benefit from coordinating efforts, and how spatially progressive elimination plans can be designed.[55] To achieve local or national malaria control or elimination goals, even global malaria eradication, these approaches and findings have significant implications for targeting interventions at source locations to maximally reduce the number of cases exported to other regions, as well as providing health advice and healthcare for the travellers visiting to or returning from source regions.[31,55,56]

It is noteworthy that models parametrized by various mobility data sources and spatiotemporal resolutions can generate divergent outcomes.[32] Based on a spatially structured reaction–diffusion metapopulation model where the whole population is divided into sub-populations connected by mobility fluxes, a previous study found that the adequacy of mobile phone data for infectious disease models becomes higher when epidemics spread between highly connected and heavily populated locations, such as large urban areas.[32] Furthermore, seasonal and geographic spread of pathogens depends on connectivity fluctuations through the year, because seasonal travel and directional asymmetries could be across a spectrum from rural nomadic populations to highly urbanized communities, with combined effects of school terms and holidays.[33] These variations in travel impact how fast communities are likely to be reached by an introduced pathogen. In addition to measuring the risk of pathogen spread, mobile-derive population movement data also play an important role in understanding the relationship between geographic isolation and health disparities by measuring the accessibility of health resources,[71] identifying vulnerable and high-risk populations in vaccination campaigns,[28,64] and evaluating interventions, e.g. screen/travel restrictions for epidemic containment.[66]

mHealth Applications and Risk Assessment in Travellers

Because mobile positioning data are opt-out and are passively-collected as a user carries their smartphones, the recent rise of mHealth methodology, e.g. smartphone applications, offers new opportunities to capture the full range of health risks during travel in real time, from travel location, physical activity, health symptoms and sleep to environmental hazards such as extreme weather conditions and air pollution.[42] For instance, mHealth has been used for dynamic assessment of exposure to air pollution during travel.[36,37]

Research on travellers using mHealth applications offers many advantages in improving risk assessment over prior methodologies such as pre- and post-travel risk questionnaires. Using mHealth applications to assess risk in travellers daily during their trips minimises the risk of recall bias that is an inherent problem in administering health questionnaires weeks or months after the event actually occurred during the trip. In addition, novel publicly available data sources (e.g. weather patterns, social media data, traffic patterns) can be integrated with daily self-reported data on symptoms and risk behaviours in order to create a complex picture of how environmental factors, health behaviours, and personal risk factors interact during travel to create health outcomes. The ability to create a real-time map of traveller health events such as traffic accidents or infectious disease transmission has the potential to improve medical advice given prior to travel and enable a faster public health response to major events. Finally, prior research suggests that participants may be more likely to share sensitive or socially unacceptable information on an online form, improving understanding of rates of risky behaviours during travel.[72]

Farnham et al[42-45] used mHealth technology to identify the range of health outcomes during travel using real-time monitoring and daily reporting of health behaviours and outcomes and identify traveller subgroups who may benefit from more targeted advice before and during travel. In this mHealth-based study, non-infectious disease related health issues were commonly found in travellers, despite being largely unaddressed in traditional travel medicine research; in addition, clear patterns of traveller behaviour and health outcomes emerged, suggesting that subgroups of travellers exist for whom specialised medical advice is needed. These results suggest a substantial potential for improving evidence-based travel medicine advice. Rodriguez-Valero et al developed an mHealth application that tracked incidence of disease among travellers in real-time and provide telemedicine care to ill travellers.[73] This study suggests the potential of mHealth for detecting and responding to traveller health issues in real-time, providing a two-way monitoring and response application. These studies also show that the use of a smartphone app to collect health information is technically feasible and acceptable amongst a traveller population, allowing researchers to minimize recall bias, greatly increases the quality and quantity of data collected during travel, and even respond to emergent health issues. Therefore, inferences from data monitored by mHealth apps can yield important insights for health risk assessment that were previously impossible in travel medicine. Moreover, mHealth data from a smartphone application integrated with streaming data sources have supported healthcare delivery, laboratory diagnostic tests and data collection, and allowed for the operation of a national level disease reporting and health surveillance with fine geolocated data at a low cost.[74-79]

Discussion

It has long been appreciated that population movements drive the transmission patterns and intensity of many infectious diseases. Understanding the changing patterns of human travel over time is critical for tailoring and updating evidence-driven surveillance and strategies to address travel-related health issues.[80] In this study, although a systematic literature review approach was not performed by using a comprehensive search strategy to collate all relevant empirical evidence, we still found the highly detailed mobile positioning data undoubtedly provide one of the most powerful, scalable, and real-time data sets on human mobility available, yielding insight into individual's movement trajectories across various time and space scales. The advantages of using this innovative data source for travel-related aspects are linked to its potential to overcome many limitations of traditional data sources and other approaches. Moreover, the recent advance of mHealth technology, together with mobile positioning data, shows great potential for innovation in travel medicine to monitor and assess real-time health risks for individuals during travel.[32,42] However, there are a number of challenges that must be met to ensure the success of using mobile-derived human movement data.

First, there are always confidentiality and ethical issues in using mobile positioning data automatically generated by individuals. This makes the location data held by individual, private or state actors logistically difficult to be accessed, as it is limited by telecom, internet, and data protection regulations in many countries.[23,81] To facilitate data sharing and avoid privacy and commercial concerns, appropriate safeguards should be in place to ensure data security, with data anonymization and aggregation taking place on separate servers hosted by operators behind operators' firewall before sharing.[82] As the public health usefulness of these data continues to be demonstrated, mobile phone operators and technology companies are becoming more receptive to providing these anonymous data for research and public health purposes. Currently, however, access to these data has primarily been through negotiated agreements between operators and research groups. To make outputs from CDRs more accessible, the initiatives like the Open Algorithms (OPAL) project and the FlowKit, a CDR analytics toolset developed by the Flowminder Foundation and the WorldPop research group at the University of Southampton, aim to unlock the potential of private data for public good in a privacy-conscientious, scalable, socially and economically sustainable manner.[83,84] Moreover, it is necessary to create adequate legislative and regulatory frameworks to safeguard confidentiality of the information and ensure the ethical use of data for development projects.[81]

Second, as mobile phone or social media users only represent a proportion of the whole population, the interpretation of mobility estimates must account for biases introduced by heterogeneous use of mobile phones, social media platforms and internet.[81] It is often assumed that mobile phones are sufficiently widespread that users represent a true random sample of a population. However, mobile users are not necessarily representative of the population at large, as the differences in the use of mobile devices, social media platforms and internet are still significant by level of socioeconomic development, sex, age and urban/rural areas. In many low-resource settings, for instance, the users are commonly disproportionately male, educated and from larger households, compared with the general population.[20,85,86] Moreover, the behaviours of using mobile phones and social media as well as the possibility that individuals own multiple SIM cards or mobiles affect the ability to produce accurate and representative estimates of population mobility.[20,23,25] Though these potential biases are decreasing as mobile phone ownership rises,[20] a prerequisite for these studies is still to understand the demographic features of mobile phone owners or users of social media and mHealth apps. For instance, household surveys such as the Demographic and Health Surveys (DHS) program, can provide information on mobile phone usage and ownership patterns and allow assessment of spatial differences that could bias results.[20]

Third, given the increasing volume of these huge, complex and "noisy" mobile data as well as the spatiotemporal heterogeneity of disease transmission,[81] another major challenge is the methodological difficulties of measuring transmission risk of infectious diseases at appropriate spatial and temporal spatial scales. Regarding the diverse biological aspects of pathogens, population immunity, and entomology and ecology of vectors, the complexity can be very different in the inference of the arrivals and spread risk of different pathogens. For instance, for pathogens with sufficiently high transmissibility, higher transmissibility could result in more rapid spatial spread. However, for pathogens with weak transmission, both seasonal patterns and the impact of distance might be obscured, and many locations might not be affected.[28,29,33] Moreover, modelling results are also sensitive to the choices in the parametrization of population movements, considering the variety of individual travel activities and data sources.[23,32] Understanding how modelling results are affected by limitations inherent to the mobile phone data will help to increase the predictive capacity of models based on such novel data sources, and facilitate the interpretation in uncertainties of travel-mediate epidemic modelling and the sensible use of big data for decision-making.[23,81,87,88]

Despite inherent biases in mobile phone data, the progress of analytic tools for adjusting estimates and increasing penetration rate of mobile devices and internet-based platforms in populations may diminish the impact of these biases on measures of human movements.[71,85,86] More research is needed to establish the most promising uses of these data for travel health, and the combination of information extracted from traditional and innovative data sources are beginning to be produced and yield a proof of concept and road map for future studies on individual's risk assessment in travel medicine.[43-45] For instance, phylogeographic analyses can relate travel and epidemiological dynamics by integrating mobile data with expanding genetic data.

However, given the mobile location data being collected every second across the world, as well as the upcoming 5G networks and advances of artificial intelligence (AI) technology, these digital records provide an unprecedented opportunity to quantify human mobility and accurately estimate the health risks through the sheer numbers of individuals reflected in the data streams.[23,81]

Author Contributions

1. Shengjie Lai, PhD: Conception and study design, literature search, and writing
2. Andrea Farnham, PhD: Literature search, technical editing and critical revision, and writing
3. Nick W Ruktanonchai, PhD: Technical editing, critical revision, and writing
4. Andrew J Tatem, PhD: Conception and study design, technical editing and critical revision, and writing

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Conflict of interest

None declared.

Tables

Table 1. Traditional and innovative data sources for measuring human movements.

Data Type	Description	Strengths	Challenges
Traditional data source			
Population and housing census	Assembly of population and housing census data on place of residence 1-5 years ago.	• Primary source for migration statistics; • Global extent, consistent measure for complete population; • Shows strong correlations to shorter scale domestic and international movements; • Of value for global, continental, regional connectivity assessments.	• Long-term movements and permanent migrations only; • Coarse spatial scale, bias to longer spatial scales; • Lack of census data in countries affected by conflicts; • Normally collected once every decade.
Travel history surveys	Travel log collected at health facilities, or through active surveillance/surveys.	• Valuable data on relevant population pathogen movements; • High value for measuring temporal trends in domestic and international travel;	• Not collected in many settings; • Sample a small proportion of population; • Selection and recall biases;

Data Type	Description	Strengths	Challenges
		• Important data for refining and validating models.	• Difficult to access, inconsistent coverage/quality.
Cross-border and traffic surveys	Counting the number of cars and people that are crossing a border.	• Cross-border movements • Measuring seasonal patterns by multiple cross-sectional surveys	• Difficult to obtain the origins and destination locations of travel; • Difficult to capture the whole picture of movements in where there are porous borders.
Novel data source – Mobile phone			
Call Detail Records (CDRs)	Individual-level records routinely collected by mobile phone operators for billing purposes, located to cell towers.	• Cover large population of mobile users, potential to track hard-to-reach populations; • Rich spatiotemporal data on individual, fine-scale movements; • Capture long time series and seasonality with timely information;	• Difficult to access and share; • Ownership biases; • Privacy issues and loss of information due to anonymization; • Difficult to capture international movements.

Data Type	Description	Strengths	Challenges
		• Of value for national-scale analyses, assessing population distributions, disease connectivity, and the parameterisation of mobility models.	
Smartphone-based Internet/social media location histories	Geo-located data on use of internet/social-media connected devices, integrating online media content.	• Timely, spatially precise positioning data on users' locations; • Long time series to capture seasonal domestic and international travel of users; • Rapidly increasing penetration, potential to track hard-to-reach populations; • Richness of information to understanding social connections and behaviours.	• Ownership and selection biases, changing sample over time; • Data availability and loss of information due to anonymization; • Privacy and ethical issues; • Additional logistical, technical issues for analysis.
mHealth apps data	Individual travel history and health risk monitoring data collected by the mobile applications for mHealth.	• Timely information on users' location; • High value in real-time individual travel patterns, environmental exposure	• Reliability of self-reported information;

Data Type	Description	Strengths	Challenges
		monitoring and health risk assessment during travel; • Improving healthcare access for travel medicine and public health interventions; • Of value for the individual-level quantitative research on travel-related risk exposure and health outcome.	• Selection bias and small sample size; • Indicators for measuring the risk and exposure; • Privacy and ethical issues.
Novel data source – Other			
Air travel data	Route aggregated statistics of flight passengers, and air transportation network data.	• Includes the origins, stops, and destinations at airport or city level; • Captures seasonality in long time series; • High value in route-scale analyses, assessing international connectivity and modelling the risk of pathogen spread.	• Incomplete picture of population movements; • Difficult to access travel itinerary data, and lacks demographic data;

Data Type	Description	Strengths	Challenges
			• Coarse spatial scale and difficult to capture the origins and destinations beyond airports.
Infrastructure	Georeferenced data on transport links that form the basis of regional mobility.	• Global coverage, consistent data; • Useful proxy indicative of mobility, connectivity and healthcare accessibility.	• Based on an assumption that those travel times influence how population's move; no measure of actual movements; • Few time series; • Validation.
Earth observation data	Data collected via remote-sensing technologies to monitor and assess the status of and changes in environments, e.g. satellite nightlight imagery	• Proxy measures of population movements; • Global coverage and high spatial resolution; • High comparability and timely information.	• No actual movements with unknown origins and destinations; • Methodological and technical issues; • Continuity and validation.

Figures

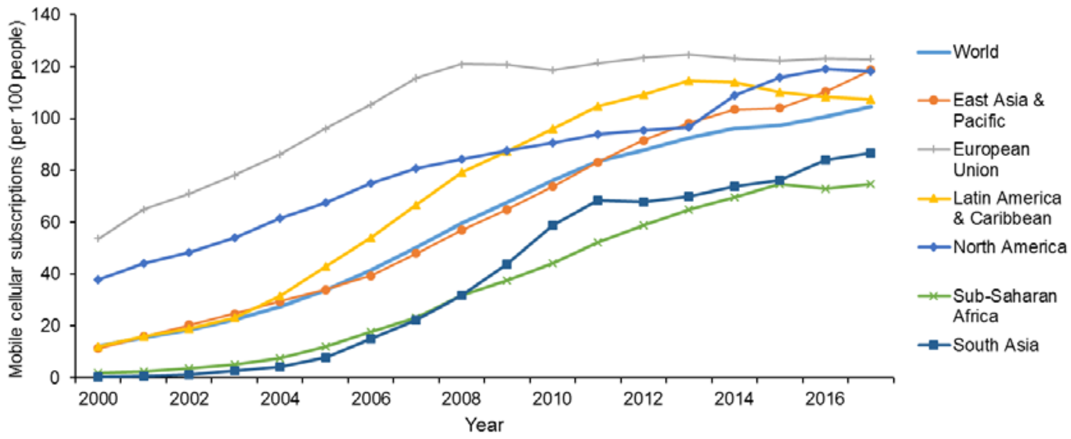

Figure 1. The penetration rate of mobile cellular subscriptions by region, 2000-2017 (Data source: The World Bank [22]).

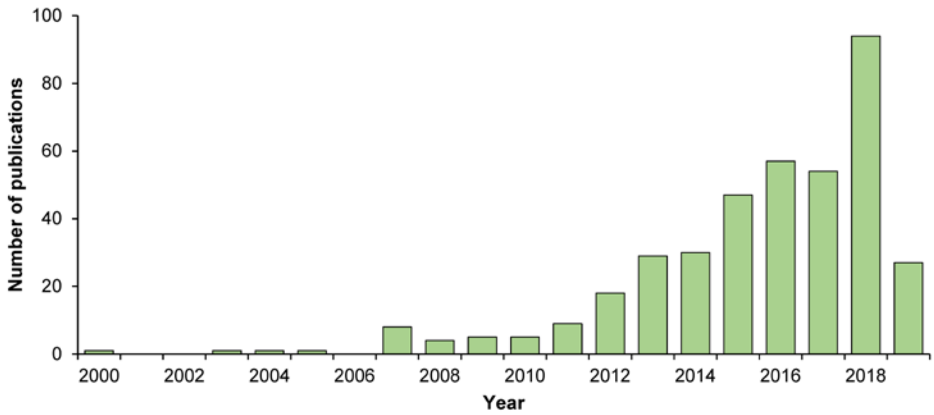

Figure 2. The number of relevant publications searched in the PubMed as of 5 March 2019.

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