Looking for vulnerabilities in health security: the need to integrate regional-level and world-scale connectivity networks of disease transmission

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In recent years, we have witnessed severe outbreaks of Emerging Infectious Diseases (EIDs) that drastically impacted our lives from medical, social and economic perspectives. Projecting scenarios for the spread of EIDs well before a possible next "Disease X" pandemic has become a challenge of utmost importance and urgency. The epidemiological, ecological and environmental complexities underlying disease dynamics are just one major element of the puzzle, whereas another is the interplay between the aggregation and local-scale movement of human people in densely inhabited areas and the striking growth of the global mobility network (Brockmann 2017). The World Health Organization has strongly highlighted the major threat specifically posed by zoonotic EIDs - diseases with the potential to jump from animal to human hosts - dedicating three out of the seven main challenges of the innovative One Health framework to understanding, assessing, and reducing risks of pathogen spillover and spread. To enhance global preparedness, the One Health approach is currently declined along four steps – prevention, detection, response and recovery. Most of the post COVID-19 plans have focussed on response and recovery measures, even though investing in prevention and in early-stage containment strategies would be safer and at least two orders of magnitude cheaper than facing the consequences of a pandemic (Dobson *et al.* 2020, Bernstein *et al.* 2022). Significant insights into the dynamics of many EIDs have been gained through either predictive statistics of emergence risk or with local, regional, and global scale transmission modelling. Linking the two approaches through hierarchical network models could provide a significative advancement in our reaction capacity to unforeseen sanitary emergencies.

Our research aims to foster integrated preparedness against a set of known or unknown zoonotic viruses. By employing data-driven demography and information on human mobility, our objective is to bridge the gap between an ecologically sound prediction of disease emergence and a credible spatiotemporal modelling of disease transmission. Pandemics conceptually start as source-to-sink processes. From the viewpoint of modelling, case exportation to other countries has been increasingly investigated in the literature. For instance, airport movement flows have proved to be reliable proxies for forecasting the arrival of infected individuals for the SARS-CoV1 outbreak in 2003, the H1N1 pandemic in 2009, and, more recently, the COVID-19 pandemic (Soriano-Paños et al. 2022). In contrast, understanding how local-scale movement flows interplay with long-range international traffic - thus ultimately shaping spatiotemporal patterns of disease spread - remains to date more than an open challenge (Balcan et al. 2009). After pathogen spillover, local mobility networks typically drive the behavior of epidemic wavefronts (Hufnagel et al. 2004) at the periphery of global transport infrastructures, connecting spillover events to international hubs (i.e. spread centers). Simple metrics such as geographical distances between transmission nodes result inadequate to represent the intricate texture of current transmission networks (Colizza et al. 2006). We therefore need to look for more "effective" distances, to be built on better representative pictures of the spread of diseases. The recent advances in data collection techniques, based on GPS tracks or phone call/internet connections from mobiles, allow researchers to capture the fine-scale daily urban rhythms of humans and to evaluate the role of mobility in characterizing the infection routes and the most exposed areas (Grantz et al 2020). Quantitatively combining and elaborating such high-resolution, device-derived movement data allows us to characterize innovative and detailed insights of local diffusive patterns (following approaches like those of Mari et al, 2017, Ciddio et al. 2017 and Bertuzzo et al. 2020), as well as to elaborate methods for unveiling how the structure of human mobility in high-risk pantropic regions can promote global-scale infections.

Here we consider the country of Indonesia as a first exemplificative case-study to illustrate a methodology for assessing the potential risk of new pandemic. The potential risk is estimated by coupling the probability of pathogens' emergence to the possibility of disease propagation based on human movement at different scales, from sub-regional to international. More specifically, we create simple spillover risk maps by pairing maps of the presence of reservoir animal hosts (the *hazard* factor) with maps of human mobility at the local scale (the *exposure* factor). In so doing, we identify how short-range movements of the people intersect centers of regional- and global-scale diffusion, such as airports of various sizes and importance. As for the exposure, we work on aggregated population and human mobility data of Indonesia provided by Spectus

Social Impact via the Netmob 2024 Challenge. Their data were collected with the informed consent of users, then properly anonymized and aggregated at geohash5 level (ca. 5x5 kms). As for the hazard, we focus on zoonotic diseases circulating in bats, which harbor a vast and dastardly array of viral threats. As reported by Mickleburgh et al (2002), Indonesia is the country with the highest number of bat species (n=175) and it is located in an area at high risk of bat-borne diseases, such as Nipah Virus and other Henipaviruses, identified as priorities by the WHO's blueprint.

We consider the distribution of the number of fruit bats species from the *Pteropodidae* family, the main natural reservoir of Henipaviruses (Weatherman et al. 2018), as a proxy to map the disease hazard, assuming that the number of human-infecting viruses increases proportionately to the total number of viruses maintained by a reservoir group, which is in turn explained by the number of animal species within the groups (Mollentze et al., 2020). Aggregated risk metrics are calculated using actual human mobility data within the source region and propagated to remote areas of interest (sinks) according to the geographical hierarchy of connectivity systems, from potential viral hotspots to destination. The approach proposed here could be enhanced in a number of ways. One avenue for improvement could be to utilize additional proxies for hazard mapping, such as accounting for the potential presence of intermediate hosts, like pigs or horses in the case of henipaviruses. Another, could be to incorporate multimodal patterns of mobility routes inside the source region: for instance, in the case of Indonesia, this could include domestic flights between the islands. Furthermore, the application of our proposed framework to multiple source regions could make it possible to estimate an aggregated risk of importation of emerging pathogens in a specific sink region. Indeed, mobility metrics play a pivotal role in unveiling the vulnerability of human populations to emerging infectious diseases, both in regions of pathogen emergence (sinks) and in other regions of disease transmission (sinks). The integration of mobility data into quantitative modelling could greatly enhance the capacity to inform policy and decision making processes within and beyond the specifically targeted countries.

On the one hand, mobility analysis can produce effective knowledge to support national policies uptake for an improved protection against vulerabilities in the source regions. On the other, a better understanding of how local and global mobility are intrinsically connected may encourage international pandemic preparedness in terms of providing quantitative tools for risk monitoring, efficient prevention and early-intervention measures. Using the framework of the UN SDG Agenda (2015), the strategic objectives of our research are mainly, yet not exclusively, aligned with Goal 3, committed to "ensure healthy lives and promote wellbeing for all at all ages". More specifically, within Goal 3 our project outputs can reduce global infectious disease risk (Target 3.3) and strengthen prevention strategies to identify early warning signals (Target 3.d). Finally, the resulting insights could also have important impacts on land use planning in relation to epidemic risk both in urban and peri-urban (see Target 11.1 aimed to improve conditions in the slums on the outskirts of major cities) and in natural environments (see Target 15.5 dedicated to reducing the degradation of natural habitats).

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