Syndemics as a positive agenda for disease modeling

Claudia Torres Codeco

Scientific Computing Program, Oswaldo Cruz Foundation, Brazil, codeco@fiocruz.br

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In Brazil, currently circulate six viruses(DENV 1 to 4, Zika and Chik) transmitted by the same mosquito vector. A seventh disease, yellow fever, eradicated in the early XXth's, has its reservoir in the sylvatic regions of the country. Transportation-transmission models suggest that YF reemergence is likely and should have happened already [1]. Why not yet? One possible explanation is dengue infection, very prevalent in the region, reducing the viral load of subsequent yellow fever infections interfering with YF receptivity in urban areas [2, 3]. Is this enough to prevent the emergence of urban yellow fever? It is still an open question. Other examples of direct interference are well documented for HIV and TB, HIV and malaria, rhinovirus and Influenza A.

In the Amazon, *Plasmodium falciparum* and *Plasmodium vivax* are responsible for the high burden of malaria. They differ in the pathology they cause, treatment efficacy, and their lethality. Coinfection is common and is known to interfere with each other's outcome. Dengue is emerging in these areas now. Misdiagnosis can delay the successful treatment of both diseases, their surveillance and their control. It is likely the dynamics of malaria will change with the arrival of dengue.

In Manaus (Amazon), when the river rises above the drainage system, the city floods and many outbreaks occur concomitantly: diarrhea, hepatitis A. Dengue follows next, as mosquitos breed in the new water-filled containers. A few months later, as the water level decreases, pools are formed and the malaria vectors emerge. These diseases form a system, each one interfere with the susceptibility, and transmissibility of the other. Their dynamics is unpredictable if their interaction is not considered.

Diseases interact in indirect ways as well. The attitude towards specific diseases is context specific and depends on how a person values this problem in relation to other problems; decision to vaccinate or to use bednets is influenced by other diseases and events that compete for an individual's attention (and time and resources) [4]. Including competing risks in models introduce complexity but also opens up the possibility of thinking about trade-offs and more dynamic control strategies.

In the 1990's, the concept of syndemics was coined to describe systems formed by sets of interacting infectious diseases and other contagious behaviors such as drug use and violence [5]. This approach broadens up what we can define as 'dependent happening'. The mathematical models we develop for infectious diseases transmission are the paradigm for dependent happening modeling. Still, few have tested their applicability and limits to tackle the syndemics around us. I believe this is a worthwhile effort. The isolation of diseases into independent problems is useful from the pharmacological perspective, considering specific treatments as their targets. However, it becomes more and more evident that a more systemic view is not only mandatory (in contexts with multiple co-occurring epidemics) but also can have very beneficial impacts. By regarding diseases as separate entities,we lose the opportunity to develop a more positive health agenda. For example, it is obvious that sanitation and clean water are important, but only by modeling we can test if investing in basic infrastructure is better than investing in dozens of vaccines. A good example is Eisenberg et al.'s [6] stochastic household model designed to capture the interdependent transmission pathways of enteric pathogens. They identified critical pathways for intervention. Could the same approach be applied to test the benefits of developing greener cities?

Network modeling has been also a source of inspiration for the development of more systemic views of disease ecology (or health). In general, they describe contact networks and the dynamics of pathogen spread through these connections. But there are other networks, social networks, friendship networks, support networks, that can actually promote health, reduce the risk of chronic diseases and infectious diseases [7]. Can we develop models to show how to strength these positive networks?

I believe these are exciting challenges for any modeler willing to refresh the ways we think the complex questions we are faced with everyday.

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