# STORY

## pathogenS inTeractiOns: a cRiminal conspiracY

## UNDERSTANDING INTERACTIONS BETWEEN PATHOGENS TO FORECAST THEIR IMPACT ON PUBLIC HEALTH

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### CONTEXT

Studies of infectious disease systems have typically tended to focus solely on the interaction between the host and the causative agent. This approach, inherited from medical methodology, has served epidemiologists well. Indeed, it has allowed understanding how pathogen spread through space (Grenfell, Bjornstad, & Kappey, 2001) and time (Keeling & Grenfell, 1997) in order to inform public health policies (Keeling, Woolhouse, May, Davies, & Grenfell, 2003). Nevertheless, the problem of pathogens interactions has been identified very early in the study of infectious diseases, but generally remains at an intra-species level.

Today, the importance of understanding the transmission, pathogenesis and evolutionary impacts of microbial interactions is increasingly appreciated (Griffiths, Pedersen, Fenton, & Petchey, 2011; Pederson & Fenton, 2006). So far, much different kinds of pathogens interactions have been suggested (summarized in figure 1) that operate at very different scales (temporal and/or spatial, inter and/or intra-species) and levels (individual or populational).

Interestingly, the discovery of such interactions did not stimulate a great interest into the understanding of pathogens communities. However, this idea is not new at all. Mirko Grmek, in 1989, already though that pathogen may form a community, leading to a status of «pathocenosis» (Gonzalez et al., 2010), a translation of biocenosis into the pathogen world. Despite a very low number of pathogens interactions were documented at this time, this idea strongly suggests that pathogen may form a stable community from which every disappearance of pathogens may result in freeing a new niche that another pathogen may fill.

Today, it is documented that pathogens follow similar ecological patterns of community structure than other organisms, such as the increasing diversity along latitudinal gradient showing that specific diversity of pathogens is the highest at latitudes close to the equator (Guernier, Hochberg, & Guegan, 2004), as for many organisms. Such idea starts also to disseminate in medical sciences. Indeed, the possible future success of the poliomyelitis global eradication program raises some concerns about the potential negative consequences of such eradication (Lloyd-smith, 2013).

### MAIN CATEGORIES OF PATHOGEN INTERACTION

When a pathogen attempts to infect a host who is already infected by another pathogen, several mechanisms can be involved:

1. Avoid encounter,
2. Facilitate replication,
3. Constrain replication,
4. Or alter the symptoms expected for one disease or the other one.

All these mechanisms can be expected to act on pathogen spillover capacity.

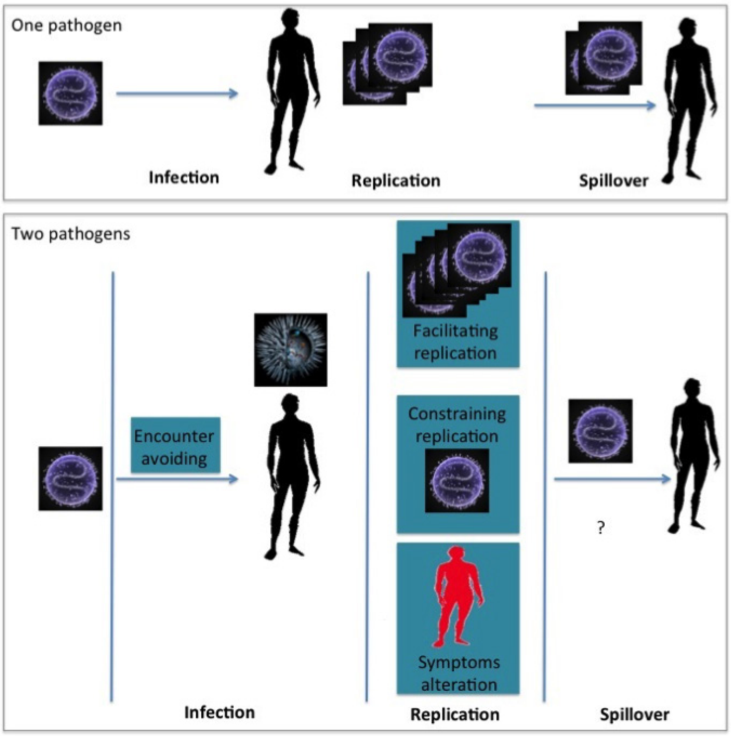

*Figure 1: Main categories of pathogens interactions.*

## OBJECTIVES

STORY aims to quantify interactions between pathogens within human populations in order to characterize the structure of their communities and anticipate potential detrimental consequences of public health strategies targeting a given pathogen. The specific objectives are as follows:

1. Understand how host infection to one pathogen is dependent of presence of other pathogens (detecting pathogens interactions);
2. Quantify the link between these pathogens interactions at individual level and the structure of pathogens community at host population level;
3. Demonstrate the potential of considering pathogens interactions and pathogens communities to open new opportunities for public health strategies.

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## APPROACH

Relying on a dataset describing infection history at 12 different pathogen species across more than 4,500 individuals located within all different Gabonese provinces, we take the advantage of this unique opportunity to reach three main objectives: (i) detecting pathogens interactions at an individual level (ii) characterizing the structure of pathogens community at a population level and figuring out how such structure could emerge from pathogens interactions and (iii) identifying the characteristics of pathogens communities that could improve strategies of infectious diseases control. Such objectives make possible to inform public health authorities about the consequences, for each control strategy envisioned, on the alteration of pathogens community. These objectives will also allow to identify areas that can be considered as a potential hotspot for infectious diseases emergence because their specific structure of pathogens community.

Thus, this project, deeply rooted within ecological thinking, will allow a better fundamental comprehension of ecological mechanisms involved in pathogens communities assemblage as well as may help to prevent, or even mitigate, devastating effects of pathogen epidemics.

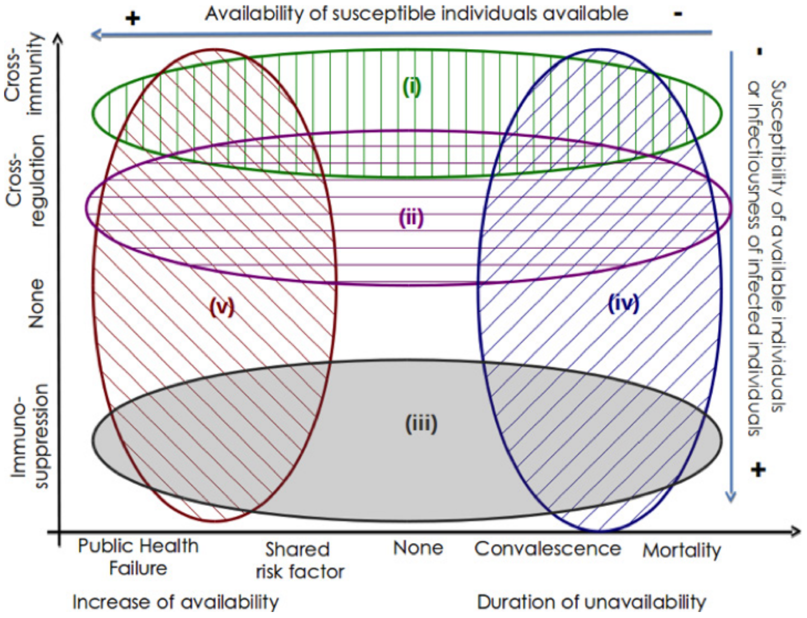

*Figure 2: Summary of pathogen interactions.*

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## SPECIFIC CHALLENGES

The main specific challenges are to develop:

1. Statistical analyses able to disentangle direct versus indirect pathogen interactions,
2. Mathematical models considering large pathogen assemblages.

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## RESULTS

The first step has been to develop a statistical framework able to identify interactions between pathogens. This has been applied on the Gabonese cohort, and has allowed to identify several intriguing interactions (the network of interactions is depicted in figure 2).

The key results are as follows:

1. We have been able to show that parasites Plasmodium falciparum and Plasmodium malariae interact synergistically, resulting in co-infections more important than expected;
2. We have also observed that different arboviruses, which are vector-borne transmitted, have a scheme of reciprocal constraints between them
3. Finally, we have shown that helminths single and double infection have complex outcomes on malaria severity (figure 3).

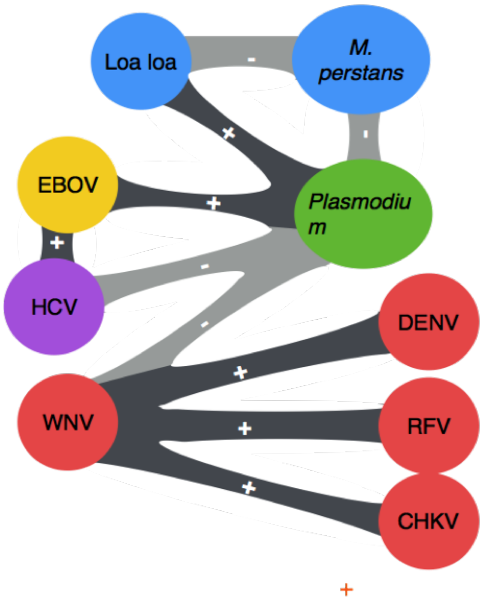

*Figure 3: Network of pathogens interactions within the Gabonese cohort.*

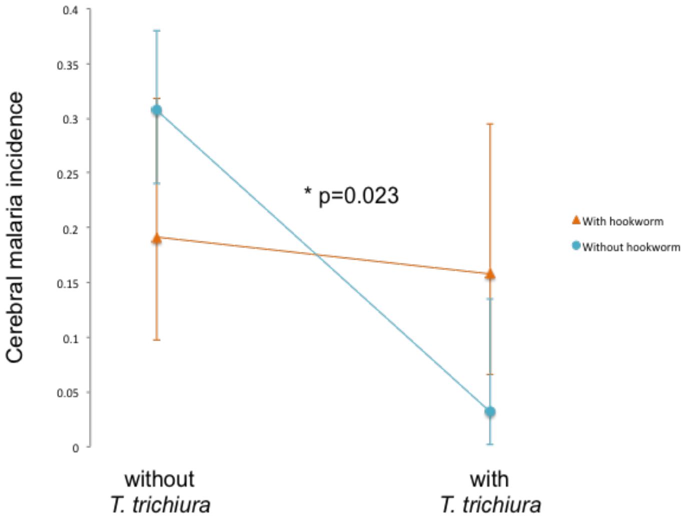

*Figure 4: Example of an interaction between Plasmodium falciparum and two helminths species. Infection by T. trichiura decrease the incidence of cerebral malaria, but this benegits is avoided by infection with hookworm.*