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Heterogeneous immunological landscapes and medieval plague : an invitation to a new dialogue between historians and immunologists.

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RETHINKING THE BLACK DEATH

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HETEROGENEOUS IMMUNOLOGICAL LANDSCAPES AND MEDIEVAL PLAGUE: AN INVITATION TO A NEW DIALOGUE BETWEEN HISTORIANS AND IMMUNOLOGISTS

FABIAN CRESPO and MATTHEW B. LAWRENZ

> I have been asked by some of my friends to write something about the cause of this general pestilence, showing its natural cause, and why it affected so many countries, and why it affected some countries more than others, and why in some countries it affected some cities and towns more than others, and why in one town it affected one street, and even one house, more than another, and why it affected nobles and gentry less than other people.

When the French astrologer and physician Geoffrey de Meaux (fl. 1310–49) wrote these words around 1349, he was trying to assess, from a scientific perspective, the great challenge of applying the universal principles of the science of the stars to the very particular task of explaining why some people survived while others around them died in the wake of the Black Death (Horrox 1994: 165). His close contemporary, the Florentine author Giovanni Boccaccio (1313–75) similarly wrote that "not all those who adopted these diverse opinions died, nor did they all escape" (Boccaccio [1353]/1982: 9): suggesting, as Geoffrey did, that a complex selective process was at work during a plague outbreak.

In his treatise on surgery, Guy de Chauliac (d. *c*. 1368), a leading medical authority and physician to three successive popes, described the causes of mortality as twofold in his discussion of the bubonic plague: one active and universal, one passive and particular. Regarding the latter, Guy wrote: "The particular, passive case was the disposition of each body, such as cachocymia, debility, or obstruction, whence it was that the working men and those living poorly died" (1363/1974: 774). In other words, we can argue that Guy explained that cases of heterogeneous mortality were

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Plate 2. Lancing a Bubo (Chapel of Saint-Sébastien, Lanslevillard)

The image above shows a physician (with a case for medical implements hanging at his belt) lancing a bubo on the neck of a woman afflicted with plague. A young man (probably his assistant) steadies the patient; meanwhile, her husband strips off his tunic to reveal a bubo under his arm, readying himself for the same lancet. A small boy also holds up his arm, perhaps indicating that he, too, feels a bubo developing. A smaller child lies in bed, ill or asleep. Above the scene, a devil brandishes a lancet of his own—one that will inflict plague, rather than treat it—but an angel deflects his aim.

This is one of a series of extraordinary murals that decorate a chapel dedicated to St. Sebastian and located in the remote Alpine village of Lanslevillard, in the Haute-Maurienne region (modern département of Savoie, France), where plague became endemic in the later Middle Ages (see Carmichael 2014, in this issue). The murals were painted between the years 1446 and 1518. St. Sebastian (like St. Roch) was venerated by those seeking to be cured or spared from plague. According to legend, Sebastian had suffered martyrdom at the hands of the Roman emperor Diocletian. Because he had died from the wounds of numerous arrows, his intercession was sought by those who wanted to ward off the sting of deadly pestilence. *Caption: Carol Symes. Photo: Paul Smit.*

due to the previous biological conditions of infected individuals. Moreover, Guy's description of his own infection offers clear evidence that not all exposed individuals died: "I was ill for six weeks, in such a great danger that all my friends believed I would die; but the aposteme ripened, and was treated as I have described, and by God's will I survived." A con-

temporary physician and poet from Almeria (Spain), Abū Ja'far Ahmad Ibn Khātima, also described several cases where the individual "was rid of his pains and fully healed" after different treatments (cited in Aberth 2005: 60). All of these witnesses were well aware that different individuals responded differently to the plague.

During the Black Death, not every person within a family, town, or region was exposed to the plague pathogen. Moreover, if we accept that the major causative organism was *Yersinia pestis*, we must assume that exposure to the bacillus depended upon a complex interplay of factors: the presence of pathogen-bearing fleas (or possibly lice) and rodents, exposure to another human being who had expelled *Y. pestis*-ridden aerosolites from their lungs, or exposure to the lancet of a surgeon who had just lanced the buboes of another patient (a common practice) (see **Plate 2**). These factors suggest that those exposed to the fourteenth-century plague probably did not experience the same symptoms and/or disease progress.

In this essay, we accordingly focus our attention on those individuals who were exposed to the pathogen but had differing fates: survival or death. Paleo-epidemiologist Sharon DeWitte, with other colleagues, has carefully explored Black Death mortality using bone markers that indicate degrees of physiological stress and health, finding that the Black Death was not an indiscriminate killer. This research showed that people varied in risk mortality during the epidemic, and that the medieval plague especially targeted individuals in poor health (DeWitte and Wood 2008; DeWitte 2010; DeWitte and Hughes-Morey 2012; DeWitte 2014, in this issue). Some individuals survived and others not. But why were some people more at risk than others? We could argue, in keeping with common epidemiological assumptions, that babies, elders, or weak adults would normally not survive, once infected. Usually, we suggest that "weak" individuals (or even populations) would have had a higher mortality rate during plague epidemics because of poor nutrition, stress, and prior disease assaults or ongoing co-morbidities. How can we link (biologically speaking) all these factors together with poor health and higher risk of death when infected by plague? Clearly, we must explore with more nuance the specific factors that differentiated historical epidemics from one another, and that differentiated human responses to them.

But is today's science any better at answering such questions than the science of the medieval practitioners? We need to probe more deeply into the human immune system in order to discover how different biological, environmental, and social factors could have affected its function and impacted human health. For part of the answer to the conundrum of differential mortality could depend on which individuals (once infected)

were able to mount an appropriate immune response. This is especially important because it is not a problem isolated in the past. When talking about plague, we are talking about a pathogen and its interaction with several hosts (not only humans), and about a pathogen-host interaction that has a common universal pattern which determines how the pathogen tries to survive and spread,[1] and how the host will contain or stop that process. However, each exposed human host is immersed in a specific environment and social context that could have a significant impact on her/his capacity to counter the plague pathogen. We must therefore attempt to reconstruct medieval environments and demographics with the understanding that they changed constantly in time and space, as did host-pathogen interactions.

In the last century, many historians and scientists have studied the problem of immunological responses to plague by focusing on "immunity" as an acquired and long-lasting response.[2] The historical and scientific evidence is strong enough to show that exposure to plague does not generate a long-lasting immunological memory that will protect the exposed individuals from future plague infections. It is time for a more comprehensive approach to the role of the immune system. In order to explain the differential mortality detected during medieval plague, we must consider the immunological status of individuals when exposed to the plague pathogen.

To answer (or try to answer) the question of who died when exposed to the plague pathogen, we propose that studying the individual immune system's responsiveness, or *immune competence* (IC), can help to explain differential mortality during medieval plague. In this essay, IC represents the capacity of an individual to generate an appropriate immune response involving innate and/or acquired mechanisms (we will explain these differences below). However, IC is not only a biological concept. As noted above, humans are immersed in specific environments and social contexts

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1 That is, all interactions taking place between a pathogen and its host (i.e., human, animal, plant). Host-pathogen interactions can be described at the population, individual, or molecular levels. See Casadevall and Pirofski (2000) for a more comprehensive analysis of this concept.

2 Contributions to the discussion of human immunity and plague include: Hirst 1953; Pollitzer 1954; Ziegler 1969; McNeill 1976; Appleby 1980; Ell 1984; Scott and Duncan 2001; Cohn 2002; Sallares 2007; Benedictow 2010. The acquired immune response involves two different processes: *clonal selection* of B lymphocytes (heightened production of those that have the "right recipe" to combat the pathogen antigens); and the development of *immunological memory* (meaning that specific lymphocytes will retain and remember the "recipe" in case of a future encounter with the same infection).

that can be heterogeneous within the same populations, towns, and even within the same families. During the fourteenth century, some individuals infected with plague survived without modern antibiotics and modern medical treatments: how and why?

We must reconcile historical and scientific information to answer these questions. Some historians study nutrition, stress, and health in medieval daily life; and scientists should take account of these historical findings when attempting to understand who had higher risk of dying during plague epidemics due to a lower IC. Simply put, immunologists should be aware of the heterogeneous environments and social contexts of human populations across time and space, and how these factors can influence the IC of individuals. Historians, for their part, should be aware of the complexity of the immune system, and the fact that it does not only consist of acquired immunity but also changes constantly. Neither populations nor individuals are fixed entities, either biologically or culturally. Demographic variables such as age, sex, socio-economic status, and living conditions can play a significant role in shaping the IC of individuals and populations, and we must also consider environmental and ecological factors. Assuming that all populations had (and have) the same IC before an epidemic is as misleading as assuming that all populations will develop the same type of immunity or immunological memory after exposure to a pathogenic insult. We can't hypothesize a uniform IC for all individuals and human populations.

Therefore, the goals of this essay are: to reformulate the immunological questions regarding differential mortality in those individuals and populations exposed to plague in order to consider the role of immunological competence in determining their fate; and to define a new theoretical framework in which historians and scientists can meet and collaborate on a more comprehensive approach to immunity and plague.

The Later Middle Ages as a "Great Transition"

In the introduction to his recent lectures, "The Great Transition: Climate, Disease and Society in the Thirteenth and Fourteenth Centuries,"[3] Bruce Campbell (a specialist in medieval economic history) observes: "Across the Old World, the late thirteenth and fourteenth centuries witnessed profound and sometimes abrupt changes in the trajectory of established

3 The Ellen McArthur Lectures in Economic and Social History at the University of Cambridge, 2013: <http://www.econsoc.hist.cam.ac.uk/podcast-campbell.html> [accessed September 19, 2014].

historical trends." Specifically, Campbell points out that environmental changes induced "ecological dislocation" across Eurasia. They also affected human biology, probably imposing a significant stress on the individual capacity to develop normal physiological functions. When Campbell calls attention to the "burden of structural poverty," "climatically induced ecological dislocation and political collapse," and the fact that there was "no return to the ecological *status quo ante*," immunologists should be compelled to explore how these catastrophic developments affected the IC of medieval populations, and how changes in IC could have conditioned individual immune responses to plague.

For example, famines could have played a crucial role in the evolution of IC in human populations. As the historian William Chester Jordan (1996: 186) suggests in his book on the Great Famine of the early fourteenth century:

> The horrendous mortality of the Black Death in northern Europe in part should reflect the fact that poor people who were in their thirties and forties during the plague had been young children in the period 1315–1322 and were differentially more susceptible to the disease than those who had been adults during the famine or were born after the famine abated.[4]

Jordan clearly invites scientists to join him in substantiating his hypothesis. Why and how did some individuals present higher susceptibility? Did climate influence IC? What kinds of social and biological differences can we find between populations of high and low susceptibility?

Emerging scientific disciplines such as developmental biology and ecological immunology are helping us to connect the dots and explain how health, nutrition, stress, and climate can affect immunological fitness. These findings should inform our understanding of plague during the Middle Ages, as should consideration of the complex transition that medieval populations faced and its subsequent impact on their IC.

The Human Immune Response and *Yersinia pestis*: Cytokines as Crucial Players and Markers for Immune Competence

As we explained above, IC represents the capacity of an individual to generate an appropriate immune response involving all immunological barriers and mechanisms, innate and/or acquired. While the first line of defense against pathogens are simple physical barriers (skin and mucous membranes), a complex network of immunological responses deflects

4 Jordan arrived at these conclusions based on studies of nutritional biology during famines (e.g., Rivers 1988).

pathogens if the physical barriers fail (Sompayrac 2008). In general, the immune system reacts to infection via two mechanisms: *the cellular response*, which is commonly associated with the *innate immune response* and involves white blood cells (called phagocytes) that recognize, engulf, and destroy pathogens; and *the humoral response*, which is commonly associated with the *acquired immune response*, and involves the secretion of protective molecules (called antibodies). These two responses work in concert and effectively protect us from infection through a complex multilayered network of cooperation that blurs the distinction between innate and acquired responses (Danilova 2008). The power of the immune system lies in the comprehensive capacity of the system to recognize and respond quickly to different pathogens. To achieve this, the immune system depends on fine tuning and a high degree of "immunological plasticity": the capacity to change and adjust responses depending on intra- and extracellular conditions and/or environmental circumstances. Extensive genetic and experimental data (of which we will present only a fraction in this essay) demonstrate that, when facing a pandemic event and its successive manifestations, all individuals who are exposed to the pathogen will not have a similar immune system responsiveness or IC.

Plague is a zoonotic infectious disease, caused by the bacterium *Yersinia pestis*.[5] If we consider the classic ecological model of plague outbreaks, *Y. pestis* is maintained in the wild, mostly in rodent populations, and transmitted by flea vectors; humans are incidental victims of the disease (Perry and Fetherston 1997; Gage and Kosoy 2005). To survive inside the mammalian host, *Y. pestis* utilizes a variety of mechanisms to evade or overcome the immune system (Li and Yang 2008). At the site of infection (e.g., a flea bite), the cells of the innate immune response (neutrophils and macrophages) try to control the infection. Although many invading bacteria are killed by neutrophils, *Y. pestis* is able to survive when ingested by macrophages and can be transported to other tissues, especially the lymph nodes. Eventually, *Y. pestis* escapes from these macrophages and begins to proliferate, ultimately entering into the blood stream to cause a systemic infection and death of the host (Amadei et al. 2011).

Normally, when invading bacteria are recognized by cells of the innate immune system, these cells produce proteins called cytokines.[6] Cytokines

5 *Yersinia pestis* is a gram-negative facultative intracellular bacterium, mostly living intracellularly (usually within macrophages), but after proliferation can be released into the extracellular environment.

6 The term "cytokine" usually refers to hormone-like messengers which facilitate communication between cells of the immune system (Sompayrac 2008).

signal to other cells that an infection is in progress and recruit additional immune cells to the site of infection to help fight the invading bacteria. However, *Y. pestis* has developed mechanisms to inhibit or alter the production of these cytokines, essentially allowing the bacterium to hide or evade recognition by the innate immune system. For example, proteins produced by the plague pathogen have been shown to inhibit the expression of an important cytokine: tumor necrosis factor-alpha (TNFα),[7] produced by host macrophages where TNFα is a crucial pro-inflammatory cytokine involved in the innate response (Boland and Cornelis 1998). A virulence factor named LcrV also enhances the release of interleukin-10 (IL-10) by host immune cells,[8] where IL-10 is being exploited to down-regulate or decrease the production of pro-inflammatory cytokines such as TNFα and interferon-gamma (IFNγ)[9] (Brubaker 2003). Interestingly, treatment with exogenous IFNγ and TNFα have inhibited the multiplication of *Y. pestis* in a mouse model, showing that both cytokines were crucial for the absolute or longer survival of infected hosts (Lukaszewski et al. 2005; Nakajima and Brubaker 1993).

In recent years, additional research has further suggested that the individual capacity of the host to produce the cytokines TNFα and IFNγ in response to plague infection is an important co-determinant in the ability of the individual to mount an effective immune response (Lin et al. 2011).[10] Most human populations differ in the type and intensity of their immunological responses, which can be observed by differences in the expression of different immune proteins, such as cytokines.[11] Cytokines profoundly

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7 TNFα was originally identified and named after a molecule that caused the necrosis of tumors *in vivo* within specific experimental conditions. Today, TNFα is considered the principal mediator involved in most acute inflammatory responses to gram-negative bacteria such as *Y. pestis* (Abbas and Lichtman 2005).

8 The term "interleukin" refers to the chemical way that different leukocytes communicate with each other. It is now recognized that many interleukins can also communicate with other non-immune cells. Different interleukins have been classified using numbers. IL-10 is one of the main inhibitors (within the immune system) of activated immune cells, controlling most innate immune reactions and cell-mediated immunity (Abbas and Lichtman 2005).

9 IFNγ is a crucial cytokine that mediates cell immunity against intracellular microbes. The term *interferon* derives from the ability of these molecules to *interfere* with the infection.

10 Therefore, we can consider that having an appropriate production of TNFα and IFNγ is a significant immunological component of the host IC when fighting *Y. pestis*.

11 We will expand on this below in the section entitled "Lessons from Immunogenetics Studies."

influence growth, differentiation, and activation functions that determine and regulate the immune response, and ultimately affect the states of health and disease (Borish and Steinke 2003). The types of cytokines that are produced during an immune response determine the effector mechanisms that will predominate. The development of appropriate cytokine networks to combat infections depends on the nature of the pathogen, the genetic background of the individual (Wilson, Seymour, and Henderson 1998), as well as developmental factors during growth and environmental factors (Nelson et al. 2002).

At the end of the last century, the study of cytokine genetic variants or single nucleotide polymorphisms (hereafter SNPs)[12] captured the attention of many researchers trying to explain differences in the success of human tissue transplants (Hutchinson et al. 1998a; Hutchinson et al. 1998b; Sankaran et al. 1999). Preliminary results showed that ethnicity influences cytokine genetic variation at the level of single nucleotide polymorphisms (SNPs) (Hoffman et al. 2002; Meenagh et al. 2002; Delaney et al. 2004; Raj, Govindaraju, and Chakraborty 2007). In some regions, significant cytokine SNP variation was observed in tribes and/or ethnic groups within the same region, suggesting that moderate differentiation among disease-causing factors could occur even among evolutionarily and geographically related ethnic populations (Gadelha et al. 2005; Raj, Govindaraju, and Chakraborty 2007). The cytokine genetic make-up thus has a significant impact on the immune response that is mounted,[13] and this must be understood as a crucial factor for IC. For example, a study conducted by Linda Larcombe and colleagues found that some Canadian aboriginal populations present a high frequency of cytokine SNPs commonly associated with the low expression of cytokines that promote inflammation (Larcombe et al. 2005). The authors postulated that the evolution of that unique cytokine genetic profile may be linked to aboriginal adaptation to an environment in which helminthic, parasitic, and fungal infections predominated. Therefore, depending on the regional interaction of host and pathogens, we find different immunological profiles among human populations. We can assume that, during the Middle Ages, not all populations were exposed to the same pathogenic experience, and the consequence of that is the emergence of different immunological backgrounds in different regions and populations.

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12 Most genetic variants are associated with "point" or single mutations that affect the genetic code ("recipe") for the corresponding cytokine.

13 The cytokine genetic make-up is the observed differential cytokine SNPs distribution in human populations.

Yet we must recognize that because plague has such an inherently complex ecology, it is exceedingly difficult to reconstruct all of the factors that would have gone into determining whether a given individual was even exposed to the disease. Despite all that we know today about the transmission of *Y. pestis* between arthropod vectors and mammalian hosts, we cannot necessarily explain, as Geoffrey de Meaux put it, "why in one town it affected one street, and even one house, more than another." Beyond those basic epidemiological variables of exposure to the pathogen, however, there are also questions arising from the differing immune responses among those who did have the bad luck to be bitten by an infected flea. Not all populations, or even individuals, are able to generate the same immune responses when encountering an infection (Nelson et al. 2002; McDade 2005; French, Moore, and Demas 2009; Martin, Hawley, and Ardia 2011). Therefore, it is possible that, assuming equal risk of infection, different individual capacities to generate an appropriate immune response against pathogens can help us to understand the differential mortality within and between populations during plague outbreaks.

Historical Perspectives on Human Immunity and Medieval Plague: The First Dialogue between Historians and Immunologists

Many historians and scientists of the plague have recognized that the study of the immune system and its corresponding mechanisms could be an important factor in understanding the differential mortality exhibited by medieval plague outbreaks. However, such studies have not focused on IC. As noted above, these early studies were focused on *acquired immunity* due to previous exposure to the plague pathogen (Hirst 1953; Pollitzer 1954; Ziegler 1969; McNeill 1976). Indeed, we must make a clear statement here: most historians use the term "immunity" to mean *acquired immune response* (explained above) without considering the *innate or cellular response* (also explained above) that is a crucial immunological barrier, especially when mounting an effective and fast response to the plague pathogen. To take an example: Andrew Appleby, a historian specializing in agrarian history and demography, suggested a hypothetical scenario in which "those people with little natural resistance died when they caught plague, while those with greater resistance lived, and passed on their natural resistance to their children" (Appleby 1980). But for those populations that were not previously exposed to plague, what does it mean to have a "natural" or "greater" resistance? It is important to highlight again that, from an immunological perspective, the term "resistance" does not solely imply the physiological capacity to recognize

a pathogenic antigen (a non-self molecule) and to mount an appropriate immune response that usually leads to a short- or long-term memory (i.e., acquired immune response). The innate or cellular response is also an important component of the individual IC and must also be taken into consideration when conducting historical research on past plagues.

Until very recently, this type of scholarship was stymied because arguments over human immunity and medieval plague also revolved around a different kind of debate: what disease was plague? This question has since been resolved, yet it is worth revisiting how historians' understanding of "acquired immunity" has impacted that debate to date. In fact, one powerful argument against *Y. pestis* as the pathogen that caused the Black Death has been based on the human lack of a capacity to develop immunological memory once exposed to the plague pathogen (again, "immunity" in this case has been understood solely as *acquired* immunity). Most notably, Samuel Cohn has insisted that medieval plague cannot be compared with modern bubonic plague, citing early bacteriological studies (e.g., Burgess 1930) which pointed out that humans (unlike rats) cannot develop immunity to plague (Cohn 2002: 33). Moreover, he has been skeptical about the possibility of differential immunity when comparing the medieval "Second Pandemic" with the "Third Pandemic" that began in the late nineteenth century:

> Why would human populations that once possessed natural immunity to a bacillus with the ability to adapt to it with remarkable speed in the fourteenth to eighteenth centuries have then lost all traces of that ability by the end of the nineteenth century? (Cohn 2002: 249)

But if our approach to IC is correct, we must expect that not all individuals within and between populations will be able to develop the same type of immunological memory, thus enabling the same disease to flourish even in the same population at a later time.

When the medieval historian and demographer Ole Benedictow tried to answer and critique Cohn's arguments in an extensive monograph, he referred to acquired immunity and pointed out that

> epidemic diseases which do not produce good persistent immunity in survivors will have much larger powers of spread, recurrence and mortality than diseases conferring persistent immunity. Consequently, other factors being equal, they will also tend to produce much higher mortality rates over time, since the whole population will be at risk every time they recur. (Benedictow 2010: 207)

Stephen Ell, a medievalist and specialist on plagues, may have been one of the first historians to employ a more nuanced concept of immunity as a

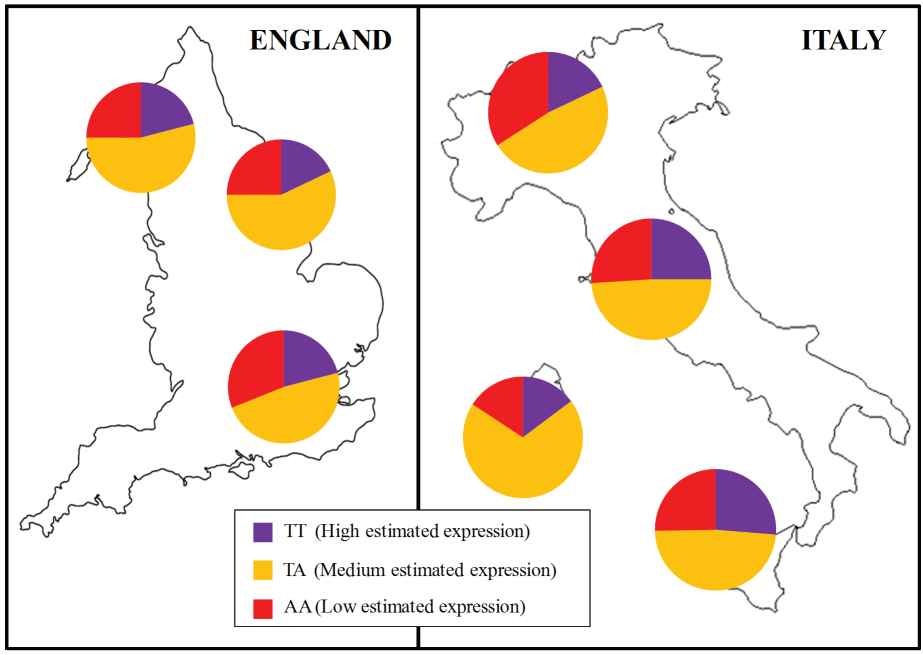
factor in the epidemiology of medieval plague (Ell 1984).[14] He suggested that "Human immunity to plague probably helps to account for much of the age and sex distribution and geographical variation of plague." While Ell focused his attention on the human host's capacity to develop immunological memory (acquired immunity) after exposure to the plague pathogen, he argued against the idea of "uniform immunity or resistance," meaning that not all populations were able to develop the same type of immunity. Scientist Robert Sallares followed this line of thought when he wrote that "the fact that different plague epidemics were caused by essentially the same organism at the DNA level does not necessarily mean that the epidemiology of plague must always be the same" (Sallares 2007: 256). And it is worth remembering that, in the mid-twentieth century, microbiologist G. B. Mackaness clearly pointed out that the process involved in the development of acquired immunity also depends on the "state of immunological reactivity" of the host (Mackaness 1964), or what we now refer to as IC.

As we have now established, instead of focusing on one aspect of the immune response—either as a genetic legacy or as an acquired long-lasting response—historians and scientists can adopt a more comprehensive and collaborative approach, analyzing and estimating the IC of medieval populations and their susceptibility to plague. These findings, in turn, can be used to help us understand and respond to future outbreaks. The challenge that remains is how to study variation in IC within and between historical populations, and to determine how we can apply modern immunological models while carefully considering that populations do not represent fixed entities.

Lessons from Immunogenetic Studies: Can We See the Whole Picture without Looking at Historical Contexts?

We have already established that the most common immunological reasoning employed by historians and scientists to explain the differences in mortality during plague epidemics is a diverse history of exposure to plague (resulting or not in acquired immunity) between populations in different regions. In response, we have argued that differences in IC could help to explain differential plague mortality. This means that we must search for evidence that human populations present different immunological profiles, and the first evidence will come from genetic analyses of genes that code for cytokines and other immune proteins. As we explained

14 Stephen Ell received a Master's degree and PhD in medieval history from the University of Chicago, and later he received a medical degree from Loyola University.



Map 5. Distribution of Genetic Variants for IFN γ (+874). Based on Contemporaneous Populations (www.allelefrequencies.net).

above, heritable cytokine SNPs are common in human populations, and some SNPs can alter how much of that cytokine will be produced (either at a basal level or in response to infection). Since the levels of cytokines, such as IFNγ, are targeted and reduced by *Y. pestis* during infection (Brubaker 2003), differences in the basal level of cytokine production by individuals could be an important contributing factor in mounting an effective innate immune response against the plague pathogen (again, without necessarily implying acquired immune responses).[15] To demonstrate cytokine genetic variation in human populations we used a worldwide database of modern populations to calculate the genetic variants in IFNγ distribution for England and Italy.[16] The goal here is not to attempt an historical

15 While these studies were conducted on animal models (mouse and rat) we could potentially extrapolate these findings to generate novel hypotheses on humans.

16 *Allelefrequencies.net* is an internet database maintained by a consortium composed of the Royal Liverpool and Broadgreen University Hospitals and the University of Liverpool in the United Kingdom. Most samples come from regional hospital and clinical studies all around the globe. While these samples do not represent past demographic scenarios and can show high admixture levels, they can be used to show regional trends for immunological profiles. One of these variants has a specific

reconstruction using modern populations but to highlight the heterogeneity of any population (**Map 5**).

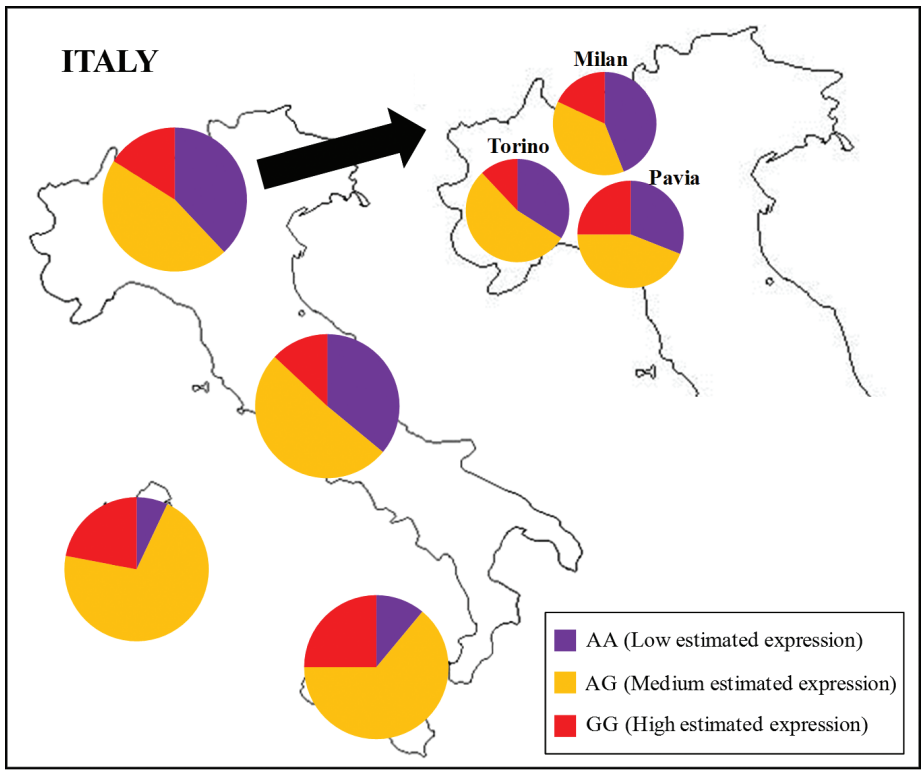
For example, combined modern populations in northern Italy show a higher frequency of individuals with low IFNγ systemic expression (possibly associated with a weaker innate inflammatory response). Meanwhile, modern populations in England show regional differences in IFNγ, indicating that we should not underestimate regional immunological variation. Another cytokine, such as IL-10, presents genetic variability that can impact the amount of cytokine an individual can express (Turner et al. 1997).[17] IL-10 is also exploited by the plague pathogen to inhibit the immune response (Brubaker 2003). Interestingly, the genetic variation for IL-10 also shows high variability within the same region and among the neighboring cities of Milan, Torino, and Pavia (**Map 6**).

This analysis demonstrates that not all modern populations have the same baseline production of IFNγ, and IL-10, two cytokines crucial to generating an appropriate immune response to *Y. pestis*. Since this data highlights regional differences, we must consider historical and demographic contexts to make sense of this regional diversity. Moreover, we cannot extrapolate from this data to make assumptions about past populations in the same regions. Therefore, this is a perfect example of one of our key points: historians must step in and help scientists put all these biological differences into context.

But let us now pose a new question: how do we translate these immunogenetic maps into epidemiological scenarios for a historical plague epidemic? The most simplistic approach is to consider that a population combining a high frequency of individuals who are high producers of IL-10 (an anti-inflammatory cytokine that usually tries to counterbalance an excessive inflammatory response) with a high frequency of individuals who are low producers of IFNγ and/or TNFα (both pro-inflammatory cytokines) could face a weak innate (cellular) response at the site of the infection (e.g., the site of a flea bite), thus facilitating the replication and spread of the pathogen in their bodies and the community at large.

"address" in the IFNγ gene: +874. In that specific position (+874), human populations can differ in one chemical component: nitrogen base T (thymine) or nitrogen base A (adenine). Because each human has two copies for each nitrogen base (what in biology is called "diploidy") an individual can be coded AA, TT, or TA. If a human possesses AA, the baseline production of IFNγ is low; if a human has TT, then baseline production of IFNγ is high; finally, TA represents an intermediate production of IFNγ (Pravica et al. 2000).

17 In this case, the specific genetic "address" for the SNP in this cytokine is -1082.



Map 6. Distribution of Genetic Variants for IL-10 (-1082) Based on Contemporaneous Populations (www.allelefrequencies.net).

As we've made clear, these maps represent modern genetic data, and we cannot argue that a similar genetic distribution pertained during the Middle Ages. The challenge that remains is to study the cytokine SNPs in medieval populations in conjunction with the distribution and impact of plague in those populations. But the challenge could be met if techniques of ancient DNA (aDNA) analysis are applied. Similar molecules, such as CCR5,[18] have been analyzed in this way, using data from medieval populations. CCR5 belongs to a group of immune proteins similar to cytokines. Called "chemokines," most act to induce "chemotaxis" or chemical-induced cell movement. (Basically, immune cells that release chemokines will call for "help" to other immune cells, which will migrate to the site of infection). The research conducted on CCR5Δ32 and plague resistance over the past ten years is both interesting and controversial, but it does establish the technological foundation for studying and expanding the genetic analysis of other immune genes, such as those producing cytokines.

18 CC stands for "Chemo-Kine," and R stands for "Receptor."

CCR5 has a SNP named Δ32 that is commonly associated with human immunodeficiency virus (HIV) resistance. Initially, some researchers suggested that the high frequency of CCR5Δ32 detected in modern European populations can't be explained by HIV's recent arrival and selective process. It was further suggested that past epidemics of plague (especially the Black Death) generated the selective process that can explain the high frequency of CCR5Δ32 (Stephens et al. 1998). But this argument was contested, due to ambiguous results and the uncertainty as to whether CCR5Δ32 really offers some type of resistance to plague (Mecsas et al. 2004; Elvin et al. 2004). It did not take too long for researchers to apply aDNA technologies to the problem and to estimate the frequency of CCR5Δ32 in the past (Hummel et al. 2005; Kremeyer, Hummel, and Herrmann 2005). Preliminary results have (so far) rejected the idea that the increased frequency of CCR5Δ32 in European populations was due to plague, but ongoing studies have revived the debate (Biloglav et al. 2009). As historian Samuel Cohn and scientist L. T. Weaver have put it: "The exciting correlations discovered by geneticists and epidemiologists between present-day genotypes in human populations, and varying levels of resistance to diseases, now demand a new cooperation between scientists and historians" (Cohn and Weaver 2006).

Recently, a more complex immunogenetic reconstruction was published using modern populations but inferring a selective process generated by medieval plague (Laayouni et al. 2014). In this study, the authors exploited what they called "a special historic demographic situation in Europe" represented by two populations with different genetic ancestry: European Romanians and the Rroma people (commonly known as "Gypsies"). The authors argue that these two populations, who have ostensibly shared the same geographic region for the past thousand years, have therefore experienced similar environmental conditions, including infectious diseases. The Rroma people migrated into Europe before the last millennium from northern India, but they intermarried little with European Romanians. Even after one thousand years, there is still a clearly detectable genetic similarity between the Rroma people and people from northern India. However, not all genes of these two groups showed that correspondence. Toll-like receptor (TLR) genes are among those genes which differed significantly between the Rroma and present-day north Indians.[19] These immune genes play a crucial role in recognizing and launching an

19 TLRs are proteins localized on the cell membrane of immune cells which recognize (directly or indirectly) molecules that are characteristic of broad classes of invaders (Sompayrac 2008).

immune response, especially in fighting back a broad spectrum of pathogens, such as *Y. pestis*. Conversely, and surprisingly, the authors found strong genetic similarity in TLRs between the Rroma people and European Romanians, despite their distinctiveness. Laayouni and colleagues identified plague as the selective factor that shaped the genetic similarities between the Rroma and the European Romanians, on the grounds that both populations were exposed to the Second Plague Pandemic.[20]

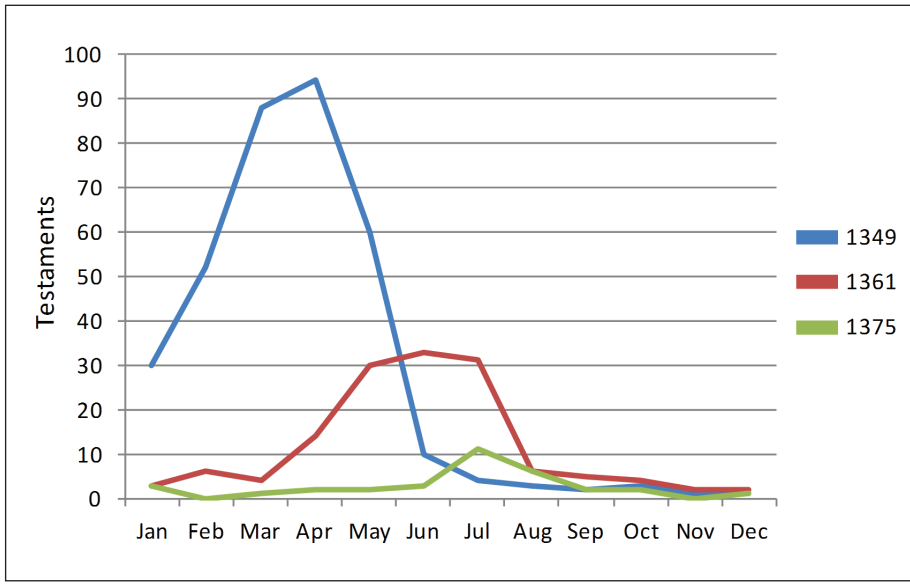
Crucial to this analysis is the assumption that the Second Plague Pandemic did not impact northern India. That assumption may now be open to question (see Green 2014, in this issue). But even though some of this study's findings are controversial, we must welcome this kind of research, in which there is cross-fertilization of biological data and historical evidence. This kind of study can help us to identify specific selective agents (such as plague) when understanding the reshaping of immunological profiles in human populations. Precisely because today's demographic and environmental data does not reflect past population structures and/or dynamics, or past environments, all immunogenetic reconstructions will only make sense within the environmental and historical contexts reconstructed by historians, paleodemographers, and bioarcheologists. Accordingly, to test the hypothesis proposed in this essay, we must understand the complex dynamics of medieval populations and how environmental and social factors affected the IC in those populations. While we can argue that different factors at different times can have different impacts on the regional variation of IC, we must consider that climatic fluctuations and famines could have played a significant role in constantly reshaping the IC in human populations.[21]

Differential Immune Competence: The Potential Role of Climate and Famines

The role of seasonality has been the most frequently cited factor when correlating climate with the incidence of plague (Hirst 1953; Pollitzer 1954; Ziegler 1969; McNeill 1976; Slack 1990; Scott and Duncan 2001; Cohn 2002 and 2008; Benedictow 2004; Campbell 2013). However, it is not

20 The authors of this study acknowledge that other infectious diseases (such as tuberculosis and leprosy) were common in the region at that time; but they argue that these infections were as common in India as in Europe.

21 We must understand that climatic fluctuations (for example, environmental temperature) could represent seasonal variation within the same year, as well as long-lasting climatic shifts with longer and probably more significant stress on the IC.



Graph 5. The Plague in London (1349–1361–1375): Data Based on Wills and Testaments. *Modified from Cohn 2002: 184–85.*

fully clear that all plague outbreaks followed a seasonal pattern. Basing his assessments on the study of medieval testaments, Cohn asserted that plague in Mediterranean Europe was a "summer event" peaking either in June or July (Cohn 2002: 28). But when we inspected the data used by Cohn, we found a different seasonal pattern throughout the northern hemisphere, exemplified by data from three successive waves of plague in London (**Graph 5**).

Seasonal variation in infection and disease prevalence may represent fluctuations in either the host, the pathogen, or the vector. But in the last decade, growing evidence based on animal models suggests that seasonal variation is most often due to changes primarily in the host, not the pathogen (Nelson et al. 2002). This is very significant for the historical study of IC. For example, the circulating immune cells helper T-lymphocytes and B-lymphocytes (important for antibody-mediated immunity) are usually elevated in winter, but cell-mediated immunity (which involves key players in immune response to plague, such as phagocytes) is higher in the summer (Nelson et al. 2002). A recent study conducted in Poland, using healthy male subjects, found that a significant seasonal variation was detected in neutrophils (phagocytes that play a key role in killing plague pathogen at the site of infection), with the highest bactericidal activity of these immune cells observable in summer (Klink

et al. 2012).[22] Such discrepancies of immune cell function among modern human populations reflect differences in environmental and physiological factors, such as energy balance (Nelson et al. 2002). In this context, "energy" implies the energy that an organism is able to expend for conducting all physiological activities at a specific time, including mounting all necessary immune responses.

Nutrition deficiency is among the most important factors that affect the energetic balance of an organism. Famines or catastrophic subsistence have clearly impacted the energy balance of individuals and populations throughout history, and have consequently impacted the energetic supply of the immune system. Most medieval chroniclers and other witnesses, as well as modern historians, have suggested that human fragility due to famines preceding or coincident with plague outbreaks have accounted for the peak in mortality (Herlihy 1997: 32). However, in some populations, plague followed good harvests, likely because the increase in grain production boosted the rat populations (Cohn 2002: 31). While we cannot rule out the link between famines and plague outbreaks in some European regions, we also need to consider the long-term impact of famines and malnutrition on the immune system, and their contribution to mortality rates.

The age at which individuals experience famines may also contribute to IC: this is demonstrable even before birth. The fetus is not a passive organism, and environmental factors during pregnancy will have a strong influence on the biological profile of the individual. Threatening scenarios encountered by the growing fetus generate immediate adaptive responses that may promote survival but may also leave the individual with a potentially disadvantageous phenotype that s/he must "cope with" for life. Simply put, the fetus will receive environmental signals (through the mother) that can "reprogram" different biological components (such as the immune system) during development (Gluckman, Beedle, and Hanson 2009).[23] As noted above, historian William Chester Jordan cited scientific evidence (Rivers 1988) when he pointed out that "there are long-

22 This study included 155 healthy male subjects who had been donors of neutrophils. It has been conducted by the Institute of Medical Biology at the Polish Academy of Science (Lodowa, Poland) since the year 2000.

23 The discipline of developmental biology is also calling for our attention when we attempt to understand how (and when) environmental factors can impact our biological development. As an example, a fetus whose mother faces famine (as well as other biological stressors, such as infections) will receive different environmental signals compared to a fetus that receives an appropriate food supply and/or is not exposed to infections during pregnancy. (Interestingly, if a fetus will receive more food than necessary, that can also affect the future of the individual.)

term effects in children who survive famines, long term effects that are considerably more severe than those on adults who survive starvation rations" (Jordan 1996: 186). The short-term impact of malnutrition during development of the immune system can have long-term effects on how the immune system will respond to maintain the body's homeostasis and especially how it will fight infections (Suskind, Lachney, and Udall 1994; Chandra 1996; Roseboom et al. 2001).

Jordan's insights have been further supported by more recent work. Paleo-epidemiologist Sharon DeWitte and historian Philip Slavin published an interdisciplinary study on patterns of health in the pre-Black Death population of London by examining the effects of the Great Famine (1315–17) and the Great Bovine Pestilence (1319–20) (DeWitte and Slavin 2013). They focused on health or heterogeneity in health among those who ultimately died during the Black Death, and they included individuals born around the year 1319 because their growth *in utero* might have been negatively impacted by the famine.[24] Preliminary analysis revealed no significant differences in skeletal markers among the pre-famine, famine, and post-famine generations of Black Death victims, 491 of whom were buried in a cemetery at East Smithfield. While DeWitte and Slavin argued that the lack of significant results could be an artifact of the small sample size, they also concluded that

> the Great Famine could have reduced the proportion of the frailest individuals between 1315 and 1317. The Great Bovine Pestilence, which followed soon after and resulted in a catastrophic and long-term dearth of dairy products and fertilizer for crops, did not produce high human mortality, whether selective or indiscriminate, but it could have created a generation of relatively weak people who were less resilient than those who survived the famine. (DeWitte and Slavin 2013: 57)

Here is an important argument that speaks to the central hypothesis of our essay: "weak people who were less resilient" can have a compromised IC, while a weak or compromised immune response could result from infection or disease later in life.

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24 In this study, adult ages were calculated using a skeletal age-estimation procedure called "transition analysis." This analysis was applied (for adults) on different skeletal-age markers such as the pubic symphysis, iliac auricular surface, and cranial suture closure. For individuals younger than twenty years, the age was estimated using epiphyseal fusion, dental development, and eruption.

Plague Was Not the Only Infectious Disease: Co-Infections and Immune Competence

Most (if not all) mammals are usually co-infected with more than one pathogen, and such a "co-infective state" will condition the IC and immune responses to individual pathogens. We cannot assume that pathogenic loads within and between human populations are always similar over time and space. As Ann Carmichael, a specialist in historical epidemiology, has put it, "All pre-industrial epidemics, including plagues, had multiple infectious diseases exacerbating morbidity and mortality" (Carmichael 2008: 51). Furthermore, a number of ecological factors likely play an important role in determining pathogen distribution and the immunological responses of human populations. A study on human pathogens has suggested that macroscale distribution patterns of human diseases and human populations exposed to a higher diversity of pathogens display higher genetic diversity for some immune proteins (Guegan, Prugnolle, and Thomas 2008). This is the case for the major histocompatibility complex (MHC) or human leukocyte antigen (HLA),[25] where higher genetic diversity is detected in areas with higher pathogen abundance and diversity (Guegan, Prugnolle, and Thomas 2008; Parham 2005).

While not all infectious diseases occur at once in any region, or affect the same populations, we can speculate that co-infections happened frequently during the Middle Ages (as they do today). From an immunemodulatory perspective,[26] perhaps the most significant chronic infection is due to helminths. Helminths are parasitic worms that cause a wide variety of infectious diseases and may be classified into nematodes or roundworms, trematodes or flatworms, and cestodes or tapeworms. Helminth infections cause an overall down-regulation or hypo-responsiveness of the immune system, consequently affecting the immune reaction to concomitant infections that occur with high frequencies in helminth-endemic areas, such as malaria and tuberculosis (Van Riet, Hartgers, and Yazdanbakhsh 2007). Such chronic co-infective scenarios can be very complex and cannot be analyzed apart from their corresponding environmental

25 The MHC proteins (or HLA when specifically applied to humans) are the ones that "present" the non-self antigen (pathogen proteins) to other immune cells, consequently triggering the immune reaction or response. Simply put, more diversity of pathogens implies more antigen diversity that must be recognized by more diverse MHC proteins.

26 That is, considering factors that can "modulate" or alter the systemic immune response, creating a quasi-permanent shift in the immunological response and affecting the IC with respect to other pathogens.

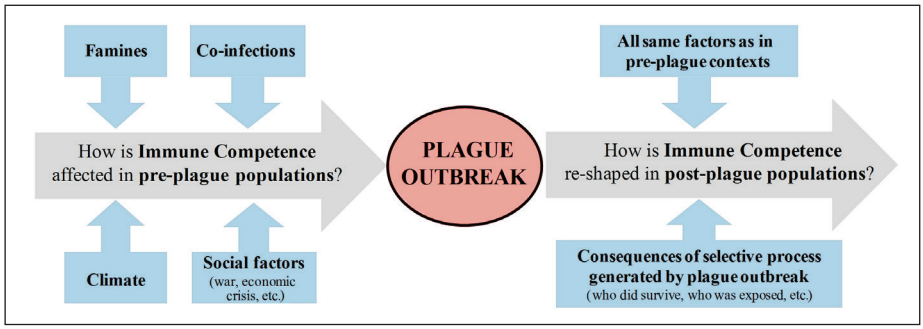
and social contexts. For example, nutritionists have recognized that parasitic infections can have an impact on the nutritional status of the host, but it was also recognized that malnutrition could be a predisposing factor for parasitic infections (Kolski and Scott 2001).

When paleo-parasitologists Evilena Anastasiou and Piers Mitchell analyzed the twelfth-century latrine of a crusader castle on Cyprus, they found eggs of two species of parasitic intestinal helminths. They concluded that "The discovery of these parasites highlights how mediaeval crusaders may have been at risk of malnutrition at times of siege and famine as these worms competed with them for nutrients" (Anastasiou and Mitchell 2013: 218). Shifting the immune response, chronic helminth infections may also affect the IC against *Y. pestis*, exacerbating the production of anti-inflammatory cytokines such as IL-10. This anti-inflammatory scenario could have played a role in the differential mortality detected during medieval plague. It remains to be determined whether populations that had a higher burden of helminthic infection were the ones with higher mortality during plague epidemics. However, not only parasitic (macroparasite) infections should be considered when studying the IC of medieval populations and its potential impact on differential mortality. It has also been suggested that leprosy could, in many instances, generate a "hyper-immune state" (overreactive immune system with increased levels of pro-inflammatory proteins) (Ell 1987) and thus impact the individual IC and the corresponding response to the plague pathogen.

A Historical-Ecological-Immunological Model for Studying Plague

The immune system is characterized by a high degree of plasticity and marked fluctuations can occur as a reaction to environmental factors (French, Moore, and Demas 2009). An emerging discipline such as ecological immunology can therefore help us to understand how ecological and social factors affect and reshape our immune system. While most preliminary studies produced by this young discipline deal with non-human animals, the last decade has seen a growing number dealing with the translation of such findings to human ecology and immunology (McDade 2003, 2005; McDade et al. 2010; Trotter et al. 2013).

However, immunological studies in laboratory settings do not account for social and ecological factors that operate within and between populations. This is problematic, because populations are not static entities fixed in space and time, either biologically and culturally. If malnutrition, climatic fluctuations, and co-infections can have a significant impact on the IC of an individual, how can we apply these findings to past societies?



Graph 6. Proposed Multifactorial Model for Understanding the Impact of Biological, Ecological, and Social Factors on Human Immune Competence (IC) before, during, and after Plague Outbreaks

And can we extrapolate from individual data to a population at large, or to an entire region? We have also stressed that the human immunological response is not uniquely conditioned by the acquisition of (or failure to acquire) long-lasting resistance after exposure to a particular pathogen. As we have explained, the innate immune response is crucial to fighting *Y. pestis* at the site of the infection, and the individual's health and IC will play a significant role in determining which individuals will be able to mount a quick and effective primary/innate response, seconds after the infection (for example, by flea bite).

Every plague outbreak occurs within a unique environmental, biological, and social context. Each outbreak then reshapes the environmental, biological, and cultural profile of the affected population and region. A more comprehensive and accurate reconstruction of medieval demography and ecology will be the only way to reconstruct the IC of individuals and populations in this era (**Graph 6**). If this can be achieved, it will enable us to build better models for understanding how and why plague outbreaks occur now, and in the future. The proposed model offers an invitation to medievalists: the opportunity to make a significant contribution to human health by helping us to study the factors that impacted human immunology in the past, thus helping to combine modern immunological knowledge with the disciplines of history, anthropology, bioarcheology, paleoepidemiology, and paleoimmunology.

We are witnesses to an increasing interest in the study of past disease and the search for lessons that we can apply to the future. As this special issue of *The Medieval Globe* insists, scholars and scientists have a unique opportunity to generate a truly interdisciplinary agenda for future research.

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Abstract Efforts to understand the differential mortality caused by plague must account for many factors, including human immune responses. In this essay we are particularly interested in those people who were exposed to the *Yersinia pestis* pathogen during the Black Death, but who had differing fates—survival or death—that could depend on which individuals (once infected) were able to mount an appropriate immune response as a result of biological, environmental, and social factors. The proposed model suggests that historians of the medieval world could make a significant contribution to the study of human health, and especially the role of human immunology in past environments and societies, by helping to reconstruct these conditions.

Keywords Plague, immunology, differential mortality, medieval Europe, Black Death.

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