Interdisciplinary Insights from the Plague of Cyprian

Pathology, Epidemiology, Ecology and History

Mark Orsag · Amanda E. McKinney · DeeAnn M. Reeder

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Dr. Mark Orsag

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of free-ranging African bats to filoviruses in order to test the hypothesis that viral tolerance by these reservoir hosts is mediated through specific adaptations in immune signaling pathways. Dr. Reeder has also contributed significantly to our understanding of the deadly white-nose syndrome (WNS), which has killed millions of bats in North America in the past decade. Dr. Reeder holds a research position at the National Museum of Natural History, Smithsonian Institution in Washington DC. In addition to her bat research, she is recognized internationally for her studies of mammal biodiversity, especially in South Sudan. Her commitment to the conservation of global mammal biodiversity is evident in her editorship and management of the Mammal Species of the World project. Her work has been funded by a number of agencies, including National Institutes of Health, National Science Foundation, National Geographic, US Fish & Wildlife Service, and USAID. In 2021, Dr. Reeder was awarded a $3 million National Institutes of Health grant related to filovirus research in Uganda.

Abbreviations

AHA	American Historical Association
ALIMA	Alliance for International Medical Action
BDBV	Bundibugyo Virus
BOMV	Bombali Virus
BSL-4	Biosafety Level-4
CAFOs	Confined Animal Feeding Operations
CCHF	Crimean-Congo Hemorrhagic Fever
CDC	Centers for Disease Control
CFR	Case Fatality Rate
DNA	Deoxyribonucleic Acid
DRC	Democratic Republic of the Congo
EBOV	Ebola Virus
ECDC	European Center for Disease Prevention and Control
ELISA	Enzyme-Linked Immunoassay
ERB	Egyptian Rousette Bat
EVI	Enhanced Vegetation Index
GARP	Genetic Algorithm for Rule-Set Production
GBIF	Global Biodiversity Information Facility
GP	Glycoprotein
HA	Hectare
HFRS	Hantavirus Hemorrhagic Fever with Renal Syndrome
HPD	Highest Posterior Density (Mathematics)
IHPH	Institute for Human and Planetary Health
IUCN	International Union for Conservation of Nature
LBRF	Louse-Borne Relapsing Fever
LLOV	Lloviu Virus

MARV	Marburg Virus
MERS	Middle East Respiratory Syndrome
MLAV	Mengla Virus
MRCA	Most Recent Common Ancestor
MVD	Marburg Virus Disease
NASA	National Aeronautics and Space Administration
NCDs	Non-Communicable Diseases
NDVI	Normalized Difference Vegetation Index
NERVEs	Non-Retroviral Endogenous RNA Viral Elements
NIH	National Institutes of Health
NS/S/Y	Nucleotide Substitutions/Site/Year
ORA	Oxford University Research Archive
PCR	Polymerase Chain Reaction
POC	Plague of Cyprian
PPE	Personal Protective Equipment
PPV	Posterior Probability Values (Mathematics)
R_0	In epidemiology, the basic reproduction number of a particular pathogen in a given environment
RAVV	Ravn Virus
RCO	Roman Climate Optimum
RESTV	Reston Virus
RNA	Ribonucleic Acid
RVF	Rift Valley fever
SARS	Severe Acute Respiratory Syndrome
SES	Social-Ecological System
SUDV	Sudan Virus
TAFV	Tai Forest Virus
TBRF	Tick-Borne Relapsing Fever
T_g	Epidemiological measure of time between infectiousness in primary and secondary cases of a disease
TMRCA	Time to Most Recent Common Ancestor
TOW/DS	Total Outbreak Window/Dissemination Score
VHF	Viral Hemorrhagic Fever
WGS	Whole Genome Sequencing
WHO	World Health Organization

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CHAPTER 1

Introduction

> It's not the destination, it's the journey.—Ralph Waldo Emerson, *Self-Reliance*, 1841

Our project had several interconnected and complementary wellsprings and later evolved to have four main purposes. More narrowly, it was born from Amanda McKinney's Institute for Human and Planetary Health (IHPH) and its missions of advocacy and education regarding the strongly interdisciplinary, complex, and crucially current mission of understanding the intricate linkages between the health of the planet and human viability. This is a perspective that strongly informed this project. These are interconnections related to diet and food systems, climate, disease, medicine, and strategies for sustainability and resilience in response to a multiplicity of twenty-first-century global challenges. It was the product of DeeAnn M. Reeder's relentless quest to achieve greater understanding of the ecology of globally menacing diseases such as Ebola. It was the indirect result of Dr. Mark Orsag's fascination with interdisciplinary history and search for informative parallels within it. Firstly, this project was also born of the authors' shared belief in the importance of interdisciplinary "systems-synthesis"-based research/analytical methods. We felt these were oft-advocated but far more rarely realized in modern higher educational environments. More disciplinarily defined, established approaches undoubtedly work superbly for many academic research problems. After all, they have become modern conventions for a reason.

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Yet, these approaches are, by their very nature, often narrow in scope. Our contrasting aim is to build broader, more holistic, and mutually supporting interdisciplinary consilience when tackling the considerable challenge of analyzing a time-obscured complex pandemic which, if looked at from a narrower disciplinary perspective, has many evidentiary pieces missing or open to multiple defensible interpretations. Our overall approach to our topic is, in certain ways, quite novel and will likely engender some controversy. Such approaches do indeed face potential pitfalls of circular or reductionist reasoning. We have striven throughout to remain cognizant of and to avoid, analytically, those problems.

Secondly, we explicitly approached the Plague of Cyprian as a challenging multidisciplinary puzzle to be "solved" to as high a degree of certainty as possible. A convincing retrospective diagnosis in terms of the likely pathogen involved is indeed a key component of it. Though our topic is largely historical, we utilized analytical methods drawn not only from the discipline of history but also from very different ones—such as modeling and other techniques derived and extrapolated from the experimentally based approaches of the natural sciences. We believe that such systems-synthesis-based methodologies could also be important both in gaining greater scholarly understanding of the past but also in helping confront threatening current and interconnected global problems. If our work, in some small way, can help promote wider scholarly use of such explicitly interdisciplinary approaches, that would be a great reward in and of itself. Additionally, for reasons that we will detail, the Plague of Cyprian is also a heinously difficult puzzle unlikely ever to be pieced together or "solved," more narrowly, by history or science alone. An interdisciplinary approach to analyzing this ancient pandemic, producing a "solution" potentially based in interdisciplinary probability as opposed to scientific certainty, seems to us, the best way forward.

As we came to more fully realize as we progressed, the core of our work and methodology fell largely within the confines of the "consilient approach to history" associated with such eminent scholars as Dr. Michael McCormick of Harvard University. As McCormick put it in 2011:

> Consilience refers to the quality of investigations that draw conclusions from forms of evidence that are epistemologically distinct. The term seems particularly apt for conclusions produced by natural-scientific investigations on the one hand and by historical and archaeological studies on the other.

> Consilience points to areas of underlying unity of humanistic and scientific investigation– a unity arising from that of reality itself; it represents a convergence in parallel but independent investigations that results in deductions that are much more robust than any investigation would be able to produce on its own.

Temporally, the origins of our work are situated in the late winter/early spring of 2020 with an interdisciplinary course entitled *Apocalypse: How Societies Survive and Fail to Survive Existential Threats*, co-taught by Amanda and myself. Even as the class began, the early stages of the Covid-19 pandemic were well under way. Our class was structured around, among other topics, the historical and ongoing threat from zoonotic viral pandemics. Soon, the whole world found itself in the middle of one. One of the books that we used, during the period of time that the thirty-four students and two professors were still meeting in person (not yet having been forced onto the virtual world of necessity called *Zoom*), was Dr. Kyle Harper's (Harper had studied under and published with Dr. McCormick at Harvard) *The Fate of Rome*. We were intrigued and impressed by the work's impressive scope, interdisciplinary approaches and bold conclusions. The book also seemed to embody so much about, albeit in an ancient historical context, the critically important (even more so in light of the ongoing pandemic) nexus of ecology, disease and human society that IHPH was dedicated to exploring. We were particularly struck by Harper's impressive marshaling and interpreting of obscure, patchy and open to interpretation evidence and yet coming to what seemed like highly defensible conclusions regarding this "forgotten pandemic"—the mysterious yet vividly described third-century Plague of Cyprian. At first, however, Harper's implication of a filovirus as the pathogenic cause of the pestilence seemed odd to us—a jarring and improbable blending of the ancient and modern, as well as of the biogeographies of the Mediterranean and Sub-Saharan Africa. As we thought more about the relevant issues, we became ever more intrigued and decided to do "a little research" on our own. Our initial aim was to publish a "forty-page" article narrowly agreeing or disagreeing with Harper's conclusions. After all, we had the generally right blend of interdisciplinary skills—a physician and a historian, both with knowledge of and interest in these precise types of issues.

Soon, however, the project began to grow far past our original conception of it. As the Covid-19 pandemic around us engulfed a terrified and

baffled world, we began to realize that we didn't understand everything that we needed to "solve" the heinously complicated puzzle of this third-century pandemic on our own. Amanda and I reached out for help and found the exact right person, Dr. DeeAnn M. Reeder of Bucknell University. DeeAnn graciously signed on and brought her invaluable wealth of knowledge and experience to the project. From then on, it was impossible to conceive of this work successfully "standing" without each author in our "tripod." Three other contributors, our Doane University friend and colleague Melissa Clouse (Program Director Health Sciences), Lindsay Sears of Omaha's Henry Doorly Zoo and Aquarium, and then Doane University student (and liberal arts computing specialist) Catie Welty, supplemented the work of the three main authors.

While our rather diverse group of scholars (whose academic skill-sets ranged from that of a more generalist historian to that of a truly world class biologist) worked, perhaps surprisingly, very well and cooperatively together, we did encounter numerous instances that demonstrated why interdisciplinary research in the discipline-defined world of modern higher education has a number of inherent difficulties. We frequently used digital sources and methodologies. Due to operating in spaces that effectively fell between, or were relatively untreated within, traditional disciplinary boundaries, we occasionally were forced to rely on government or commercial sources as opposed to more purely academic ones. Such, even limited, reliance created its own set of complications. We also encountered fundamental differences in research and analytical approaches and methods. Certain words had completely different meanings in various disciplinary contexts. Differing citation and reference conventions also became apparent. We also encountered, at times, mutual incomprehension whether in matters of terminology or more fundamentally in terms of knowledge. We patiently worked to educate each other. This usually consisted of teaching, as well as correction, in the fields of science and medicine for the generalist historian. This sort of education, however, also allowed the generalist, at times, to act as a kind of translator between the two more erudite scientists. Hopefully, if such interdisciplinary team-based approaches are applied more consistently, there can be continuing refinement in terms of working toward ever more specifically knowledgeable and effective multidisciplinary team compositions.

In analytically linking details from the disciplines of history, archeology, numismatics, wildlife biology, ecology, virology, medicine, molecular phylogenetics, etc., we also often found ourselves connecting

the ancient Roman and modern worlds in ways that seemed to demonstrate the intense relevance of the former for the latter. We were exploring complex interdisciplinary connections among Mediterraneanization, animals, ecosystems, anthropogenesis, patterns of human movement, climate, social practices and institutions, medicine (including both epidemiology and pathology), and disease in ways that seemed particularly timeless and highly relevant. The world of the Plague of Cyprian and the Roman Third-Century Crisis indeed had, we believed, relevance for the globalized, destabilized, and fossil-fueled third decade of the twenty-first century.

The other main work that Amanda and I used in that foundational 2020 class, back at the Covid pandemic's beginning that now seems a different world entirely, was Ugo Bardi's *The Seneca Effect: Why Growth Is Slow but Collapse Is Rapid* [Springer, 2017]. This is an impressive and thought-provoking work of complex systems theory devoted to examining, in myriad ways, the mechanics of the collapse of complex systems as a phenomenon. Or, as the book's preface more memorably puts it, analyzing collapse as "a feature of the universe." Like the Plague of Cyprian in the Roman third century or, alternatively, the "forcing generated by the depletion of precious metal mines" that Bardi implicates in the Western Roman Empire's fifth-century "Fall," the Covid-19 pandemic seems to have put the problems of the twenty-first century's globalized world "…in high relief." Bardi further notes applicably that "…a complex system may multiply the effect of the [external] perturbation many times, as when you scratch a match against a rough surface." Such amplification can bring destructive collapse and entropy. Alternatively, it can (also conversely through dampening as opposed to amplification) promote adaptation, transformation, and resilience in response to collapse; or result in some complex combination of the two. Kyle Harper seems, quite eloquently, to embody the former interpretation/outcome in the following passage from *The Fate of Rome: Climate Disease & the End of an Empire* [Princeton, 2017]:

> The story of Rome's end is a human one. There were tense moments when human action decided the margin between triumph and defeat. And there were deeper, material dynamics-- of agrarian production and tax collection, demographic struggle and social evolution-- that determined the scope and success of Rome's power…The Romans built a giant Mediterranean empire

> at a particular moment… a moment suspended on the edge of tremendous natural climate change. Even more consequentially, the Romans built an interconnected, urbanized empire on the fringes of the tropics, with tendrils creeping across the known world. In an unintended conspiracy with nature, the Romans created a disease ecology that unleashed the latent power of pathogen evolution [and zoonosis]. The Romans were soon engulfed by the overwhelming force of what we would today call emerging infectious diseases. The end of Rome's empire, then, is a story in which humanity and environment cannot be separated. Or, rather, it is one chapter in the still unfolding story of our relationship with the environment. The fate of Rome might serve to remind us that nature is cunning and capricious. The deep power of evolution can change the world in a mere moment. Surprise and paradox lurk in the heart of progress.

Yet other eminent scholars contrastingly see a less clearly defined Roman collapse and more of a complex *longue durée* ambiguous continuation, survival, transformation, and adaptation. The following revelatory quotation is from Dr. Michelle Salzman's (University of California-Riverside) *The Falls of Rome: Crises, Resilience and Resurgence in Late Antiquity* [Cambridge, 2021]*:*

> If we view the world as the Romans at the time did and consider how individuals and groups reacted to these [Salzman had, above, discussed events surrounding the "ruinous" Vandal Sack of Rome in 455 CE] and other events that they themselves regarded as crises, we can see that senators, emperors, bishops and generals also interpreted these events as opportunities to advance their own positions or viewpoints. Roman elites in these centuries demonstrated what social scientists call *resilience,* defined as the marshaling of resources to reorganize and restore social formations in the face of fractures and swerves. Although social scientists have developed this model to analyze environmental shocks on societies or to consider state-level interventions to mitigate the consequences of catastrophic events like plagues or earthquakes, I use the term to consider how Roman elites adapted to the shocks from political and military crises that overtook the city of Rome during the last three centuries of its existence. Thus, I follow scholars who study how the "resilience of a society affects other groups and institutions within the same society" and acknowledge that the burden of recovery and its costs are not shared equally.

Thirdly and fourthly, what indeed are the lessons from the unraveling or alternatively transformation of the ancient Mediterraneanized Roman

world for the twenty-first-century globalized one? There are indeed no simple answers. Could we, however, more fully illuminate, through use of an interdisciplinary "systems-synthesis" approach, the probable cause and mechanics of a single piece of that much vaster puzzle—a significant perturbation of Roman civilization by, in Harper's words, the "elemental forces" of disease and nature and their interaction with imperial society in the third century in terms of the Plague of Cyprian's pathology, epidemiology, ecology, and history? Could we begin to understand how Roman civilization was affected and then adapted and showed resilience (or didn't)? Would that help us gain insight and sustain amidst the challenges (both similar and different) facing us in the twenty-first century? We have also written, in part, in that latter hope.

PART I

"The Theory": The Rediscovery and Reinterpretation of an Ancient Pandemic

"If I have seen further, it is by standing on the shoulders of Giants."—Sir Isaac Newton, 1675.

Check for updates

CHAPTER 2

The Ancient Evidentiary Foundations

In the crisis-ridden mid-third century, an unfamiliar and horrific pandemic disease stalked the Roman Empire. The illness is best known through the detailed, vivid, and remarkable account of its pathology and devastating broader impact by prominent early Christian Church figure St. Cyprian of Carthage; so much so that his name was eventually attached to the disease event. Thascius Caecilius Cyprianus was born around 200 CE and was martyred in 258 CE during a persecution of Christians triggered by the Two Edicts of the Roman Emperor Valerian (r. 253–260). Cyprian was an attorney by training and a skilled rhetorician. As noted by Dr. Barbara Logan of the University of Wyoming, in her paper "Plague, Persecution and Purpose in St. Cyprian's *De Mortalite*" (AHA 2022), Cyprian was famed in the early church for his faith and eloquence. St. Cyprian was described by the fourth–fifth-century Christian poet Prudentius as follows. "...God's grace so expands itself in the exuberance and richness of his discourse that he will never cease to speak, even to the end of the world…". While much remains mysterious about the plague that Cyprian described in detail, the terrifying extreme lethality of the hope-crushing and dread-inducing pathogen involved seems clear, even over a distance of over 1,700 years, from his striking account *De Mortalite*.

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In a series of articles and opinion pieces, as well as in his groundbreaking historical monograph *The Fate of Rome: Climate, Disease, and the End of an Empire* (Princeton University Press, 2017), prominent classicist Dr. Kyle Harper hypothesized that this apparently unique and highly destructive pestilence that ravaged the Roman Empire was probably caused by an outbreak of one of the members of the deadly *filoviridae* (a family of diseases that encompasses the modern Ebola and Marburg viruses—two of the deadliest pathogens on Earth). It is notable that the appellation "The Plague of Cyprian" is very modern in origin. The Romans certainly did not refer to the disease in that way, and specific terms such as "The Great Pestilence," which the famed Greco-Roman physician Galen applied to the second-century Antonine Plague, are missing from surviving ancient accounts of this mid-third-century pandemic. It was perhaps, from an ancient Roman perspective, a nameless, unstoppable, unfamiliar, and unfathomable dread.

Harper's filovirus hypothesis disputed the rather limited existing historiographical consensus initially developed by historians such as Dr. William Hardy McNeill of the University of Chicago and Dr. Dionysios Stathakopoulos of the University of Cyprus. They had blamed the Plague of Cyprian on the aerosolized pathogen smallpox; or, in McNeill's case, perhaps, alternatively, on the also airborne and highly infectious disease measles. In his classic 1976 monograph *Plagues and Peoples*, McNeill noted Cyprian's account of the disease (but still did not use the appellation "The Plague of Cyprian") and the "intrinsically persuasive" if "unproven" possibility that the plague outbreak had contributed to the rise of Christianity in late antiquity. McNeill also believed the mid-third-century pandemic to be "fully comparable" in its impact to the earlier Antonine Plague. He notes high levels of mortality from the pestilence in both urban (5,000 deaths a day in Rome at one point) and rural settings; this was, in McNeill's view, a terrible and truly universal pestilence. Harper's groundbreaking work provoked some renewed scholarly interest (including our own) in the topic. In the summer of 2021, the noted classicist Dr. Sabine Huebner of the University of Basel published a lengthy and detailed article, "The 'Plague of Cyprian': A Revised View of the Origin and Spread of a Third Century, CE Pandemic" in the *Journal of Roman Archaeology*. This work offered a significant and highly developed critical and contrasting counterpart/alternative theory of the pestilential event to

Harper's re-conceptualization of the Plague of Cyprian. Yet, despite her questioning of a number of Harper's conclusions regarding the Plague of Cyprian, Huebner noted "Harper's very useful series of articles on this epidemic, which constitute its first comprehensive treatment and filled a real lacuna in our knowledge about ancient epidemics" [21, p. 152; 27, pp. 104–108].

Harper's research and analysis, while grounded in a close and historically expert reading of various ancient sources, was also somewhat interdisciplinary in that the author drew upon twenty-first-century medical, molecular-phylogenetic, and climate science knowledge as well as numismatic and archaeological evidence to reach his conclusions. Huebner's later article also drew upon a wide range of interdisciplinary evidence in examining the Plague of Cyprian. Harper's entire corpus of scholarship regarding the Plague of Cyprian—his later (2017 onward) academic articles, the Plague of Cyprian-focused section of his broader scholarly monograph and other more popularly oriented works—also build upon detailed evidentiary and source analyses contained in a series of articles that he published in 2015–2016 in the *Journal of Roman Archeology* and the *Journal of Economic History*. At the heart of his extensive research (and very important as well as to Dr. Huebner's), are a variety of contemporary early Christian sources, including the eyewitness testimony of Bishop Dionysius of Alexandria (whose work survives today through the writings of fourth-century church chronicler Eusebius Pamphilus) and the thoroughly remarkable aforementioned account of Cyprian, Bishop of Carthage. Dr. Harper, holistically, makes a convincing initial case that a filovirus was potentially responsible for a deadly pandemic that was a contributing factor in the Roman Empire's Third-Century Crisis. Filoviruses, along with a handful of other virus groups (e.g., flaviviruses, arenaviruses, and hantaviruses) make up the broader group of diseases collectively known as viral hemorrhagic fevers (VHFs). The factors behind this consensus-challenging conclusion gleaned from a combination of Harper's reading of the ancient sources and differential analysis of the evidence concerning the pathology and epidemiology of the Plague of Cyprian, are conveniently summarized in *The Fate of Rome's* Table 4.1 [16, p. 144]. Its overall results indeed seem to strongly indicate that the likely pathogen that caused the Plague of Cyprian was a VHF. We have created our own broader list of thirty elements of