

Smallpox's antiquity in doubt

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Abstract: Smallpox, caused by the variola virus (VARV), is prominent in modern histories of the ancient Mediterranean world. The disease, or the diagnosis of it, has shaped estimations of the scale and significance of epidemics and pandemics, notably the 2nd-c. Antonine plague, and the burden of disease in large cities and regions densely populated in antiquity. Here we synthesize recent paleogenetic and evolutionary biological literature that casts significant doubt on the existence of a VARV that caused a disease we would recognize – clinically, ecologically, or epidemiologically – as smallpox in antiquity. On the basis of current data, it is time archaeologists and historians began to eradicate smallpox from their histories of the ancient world.

The place of smallpox in the history of the ancient Mediterranean is rarely contested. Although Enlightenment-era physicians and medical historians debated whether Greco-Roman populations knew the disease,¹ most who commented on smallpox's history before 1850 found little reason to think it was anywhere to be found in the Mediterranean region in antiquity.² Yet, gradually, from the mid-19th c., well-known ancient plagues, like the Athenian and Antonine plagues,³ and less-discussed epidemics, like those encountered

¹ E.g., Hahn 1733; Werlhof 1735.

² E.g., Sennert 1633, 464; Sydenham 1685, 260–61; Porchon 1688, 8–9; le Clerc 1723, 776–77; Freind 1727a, 274; Freind 1727b, 188–89; Mead 1747, 2; Paulet 1768a, 2, 4, 25, 44–45, 51, 57; Woodville 1796, 4–6. Rarely have authoritative studies postdating 1850 also held that smallpox was unknown to Greeks and Romans. Some exceptions: von Becker 1879, 22, 42, 46, 49; Dixon 1962, 187.

³ Willan 1821 found smallpox almost everywhere he looked in Greco-Roman sources. Shortly thereafter Haeser 1845, 17, 78–79, 143, 251, 255, thought ancients knew the disease, though he had doubts about a smallpox identification of the Athenian and Antonine plagues and proposed smallpox is invisible in ancient texts partly because of “wie unbestimmt die Terminologie...ist.” Hirsch 1860, 214–16, initially thought “Andeutungen” of smallpox were discernible in Greco-Roman texts, but that if Galen knew the disease, he did not describe it. Later, in the second edition of his *Handbuch*, Hirsch (1881, 90–91) more confidently identified smallpox in Galen's writings. Smallpox diagnoses of ancient plagues subsequently became more numerous. Baas 1876, 147–48, considered Roman-era Mediterranean plagues possibly smallpox, but 20th-c. and post-20th-c. scholarship has repeatedly identified the Athenian and Antonine plagues as smallpox: e.g., Zinsser 1935, 122–24, 127, 137; Littman and Littman 1969; Littman and Littman 1973; McNeill 1976, 103–5; Littman 1984, 110–11, 115–16; Sallares 1991, 230, 233, 247–49; Hopkins 2002, 19–23; Zelener 2003, 83; Gourevitch 2005, 64–65; Sallares 2007, 37; Little 2007, 4; Cunha and Cunha 2008, 9–13; Littman 2009, 458–59, 464; Andorlini 2012, 16, 24; Bruun 2012, 131; Livi Bacci 2012, 341; Harper 2015, 223; Harper 2017, 67–68, 102–3, 104–7; Green 2018, 8; Harper 2018, 305–6; Harper 2021, 194; McDonald 2021, 387–91. In 2017 and

in Aëtius of Amida's medical compendium and dated to Trajan's reign, and in Eusebius's *Church History* and fixable to 310–11,⁴ were identified as smallpox. The Cypriatic and Justinianic plagues also emerged, on occasion, in scholarship as potential outbreaks of smallpox,⁵ though those diagnoses no longer hold favor.⁶ In this paper, we synthesize recent literature in the fields of paleogenomics and evolutionary biology that casts doubt on smallpox's antiquity and, thereby, on retrospective smallpox diagnoses of ancient plagues. We draw particular attention to the Antonine plague, as a smallpox diagnosis has been assigned some significance in histories of that pandemic.

Retrospectively diagnosing ancient plagues is no straightforward matter.⁷ Without paleogenomic support, which remains hard to obtain for those disease outbreaks for which we have written sources,⁸ no modern diagnosis of a disease reported in an ancient text is unequivocal.⁹ Yet, disease identifications, no matter how disputable, have carried significant weight in histories of ancient disease, shaping our efforts to understand the demographic and economic impact, and determinants, of poor health in antiquity. A prominent example is the smallpox diagnosis of the Antonine plague. Although opinion on the diagnosis of that plague has begun to pivot in recent scholarship, as discussed below, no other ancient disease outbreak is as commonly or confidently identified as smallpox as is the 2nd-c. pandemic.¹⁰

2018, Harper initially offered caution against pursuing a smallpox diagnosis, but then pursues one. For alleged artistic evidence of a smallpox diagnosis: Sabbatani and Fiorino 2009, 266. Doubts about the Athenian diagnosis are not uncommon, despite its popularity: e.g., Leven 1991, 142–43; Papagrigrakis et al. 2008; Little 2007, 4. Fewer doubt the Antonine plague's identity. Bruun 2012, 131, 131 n. 44, has commented on the popularity of the Antonine plague's smallpox diagnosis, but earlier observed (2007, 201) that the diagnosis was not definitive. Silver 2012, 214–25, argued for plague, and Flemming 2019, 226, 232–34, offered a rare rebuke of this smallpox diagnosis, drawing in part on paleogenomic data available at the time. Littman and Littman 1973 and Zelener 2003 have been influential. So confident were Littman and Littman in a smallpox diagnosis of the 2nd-c. pandemic that they used it to argue (245 n. 7) that “smallpox seems to have undergone the least change in the course of history.” Similarly, Duncan-Jones 1996, 109, suggested the “disease environment” of the ancient Mediterranean “did not necessarily change significantly in kind between antiquity and much later times” and pointed specifically to smallpox.

⁴ E.g., Hirsch 1881, 90; Brown and McLean 1962, 765; Hopkins 2002, 22, 23; Stathakopoulos 2004, 181; Harper 2015, 247; Harper 2016, 474–75; Harper 2017, 141, 174.

⁵ In whole or in part, e.g., Willan 1821, 12–13, 16; Schnurrer 1823, 126; Zinsser 1935, 147; Hopkins 2002, 23.

⁶ E.g., Scheidel 2001b, 31; Stathakopoulos 2004, 111, 126–67; Wagner et al. 2014; Harper 2015, 245–48; Harper 2016, 474–75; Harper 2017, 141; Keller et al. 2019; Huebner 2021, 170–71; cf. Benedictow 2021, 108–11.

⁷ Arrizabalaga 2002; Cunningham 2002; Leven 2004; Stein 2006.

⁸ Considering both the current limits of paleogenomics (e.g., the commonness of false negatives and the difficulty in identifying viral pathogens, especially those containing RNA) and the problems inherent in attempting to marry what are often very roughly dated molecular results to precisely dated written records of disease outbreaks.

⁹ Marciniak and Poinar 2019, 123–24; Spyrou et al. 2019, 323, 329, 336. As Duncan-Jones 1996, 109, noted: textual limitations “make attempts to identify ancient epidemics relatively hazardous.”

¹⁰ A possible exception is the once infamous smallpox-like pandemic concurrent with outbreaks of first-pandemic plague in the 6th c.: Newfield et al. 2022. Most recently, McCormick 2021, 60, saw smallpox in Gregory of Tours's writings, which have been considered integral to the alleged

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Reference to smallpox in scholarship on the Antonine plague, which appears to have commenced in the reign of Marcus Aurelius,¹¹ is often fleeting.¹² That said, the identification of the Antonine plague as smallpox has been used in a variety of ways in modern histories of the pandemic. Most significantly, the diagnosis has been employed to support the idea that the 2nd-c. outbreak sickened and killed widely, as then contemporary (and particularly non-contemporary¹³) ancient authors claim.¹⁴ The diagnosis has, as such, shored up the thinking that the multiple and varied references we possess to epidemic disease in the 160s–180s, the bulk of which make no reference to symptoms and can therefore be difficult to connect to one another, refer to a singular pandemic-scale disease outbreak, as opposed to multiple discrete epidemics.¹⁵

Some uses of the diagnosis are in opposition. Scholars convinced that there is no evidence for smallpox in the Mediterranean region in the centuries or decades leading up to the Antonine plague have employed the diagnosis to argue that the smallpox of the 2nd-c. pandemic would have been especially devastating, as the population, without previous exposure, would have been immunologically naïve.¹⁶ Conversely, scholars convinced that the Roman world was already acquainted with smallpox have proposed that the outbreak, while demographically significant because it was smallpox, was not as demographically significant as it could have been had the population not been previously exposed.¹⁷ A smallpox diagnosis of the Antonine plague has additionally informed speculation on the pandemic's case fatality rate¹⁸ and on the population cohorts worst affected.¹⁹ It has also

6th-c. smallpox pandemic for centuries: e.g., Pautet 1768a, 79–87; Zinsser 1935, 124–25 n. 8; Dixon 1962, 190; Hopkins 2002, 24–25. This pandemic co-occurred with plague outbreaks in the 560s through 580s. Catalogues of first pandemic plague outbreaks: Biraben and Le Goff 1969; Stathakopoulos 2004, 110–54; Harper 2017, 304–15.

¹¹ Nearly all scholarship on the pandemic has the outbreak starting in 165, but Harper 2017, 99, suggests a vague report of a disease outbreak in Arabia in 156 CE recounted in the *Historia Augusta* may be the earliest mention of the Antonine plague.

¹² E.g., Duncan-Jones 1996, 109, 116 n. 88; Scheidel 2001a, 95, 162; Scheidel 2001b, 31, 74; Greenberg 2003, 413; Bruun 2007, 201 n. 2; Scheidel 2007, 49; Elliott 2016, 5 n. 8; Erdkamp 2021, 435.

¹³ Emphasized in Gilliam 1961, 227, 231–34, 248. Cf. Marino 2012, 53, 56.

¹⁴ E.g., Littman and Littman 1973, 254; Lo Cascio 1994, 124–25; Scheidel 2002, 108; Zelener 2003, 90, 95, 109, 110, 111; Rossignol and Durost 2007, 420; Sallares 2007, 37; Zelener 2012, 168–71, 175–76; Harper 2015, 245 (cf. 246 smallpox has “the communicability and fatality rates witnessed” in Cyprianic plague passages); Harper 2017, 67–68, 108–9, 116, 229; Duncan-Jones 2018, 44; Vlach 2020, 29, 32, 36.

¹⁵ The possibility of concurrent epidemics: Zinsser 1935, 136–37; Gilliam 1961, 227; Littman and Littman 1973, 243 n. 3; Newfield 2021.

¹⁶ E.g., McNeill 1976, 103, 105; Zelener 2003, 55, 55 n. 124, 85; Rossignol and Durost 2007, 420; Livi Bacci 2012, 341–44; Zelener 2012, 169, 171; Harper 2017, 68, 115–16; Duncan-Jones 2018, 44; Séguy 2019, 34. Bagnall 2013, 714 comments on the popularity of this view.

¹⁷ Littman and Littman 1973, 254; Zelener 2003, 55, 55 n. 124, 85; Zelener 2012, 169–71; Livi Bacci 2012, 341–44, 345. The former argue that the 2nd-c. pandemic (only) killed 7–10 million people because “it was not attacking a virgin population.” Zelener and Livi Bacci also stress the significance of familiarity with smallpox. Bruun 2012, 132, suggests that a smallpox diagnosis should cause us to pull back on the alleged significance of the pandemic; had it been plague, for example, Bruun suggests we could expect a higher mortality.

¹⁸ E.g., Zelener 2003, 109, 112; Zelener 2012, 169, 171; Harper 2017, 110.

¹⁹ E.g., Littman and Littman 1973, 255; Scheidel 2001a, 165; Bruun 2012, 125; Harper 2017, 109, 111, 229; Duncan-Jones 2018, 44, 50; Vlach 2020, 35.

influenced conjecture on the pandemic's geographical origins²⁰ and association with climate change,²¹ not to mention its seasonality and ecology.²² The diagnosis has even underpinned ideas about the outbreak's duration, periodicity, and relation to the 3rd-c. Cyprianic plague.²³ Considering all of this, it is not surprising that the smallpox diagnosis of the 2nd-c. pandemic has been regarded as "potentially a matter of great significance."²⁴ Indeed, the diagnosis has amassed considerable weight.

That a smallpox identification can support these arguments rests on the knowledge we have of smallpox's more recent history, as well as on the idea that the pathogen that causes smallpox existed in antiquity and then manifested and recognizably behaved as smallpox did in the centuries leading up to its eradication in the 1970s.²⁵ Smallpox is caused by the variola virus (VARV), a highly infectious orthopoxvirus that is host specific (it only infects and causes disease in humans), transmitted primarily via respiratory secretions, and capable of spreading rapidly.²⁶ VARV causes severe disease, though its presentation can vary. A noncontagious incubation period averaging 10–12 days results in fever, body aches, and malaise before a spotted rash forms in the mouth and subsequently spreads to the face, extremities, and appendages before the trunk. A few days later, the spots fill with a cloudy, dense fluid, eventually becoming hard and pustular, "like peas under the skin."²⁷ Five or so days later, the pustules start to crust and scab. For three weeks, from the appearance of the rash to the flaking of the scabs, the sufferer is infectious, though infectivity varies over that period.²⁸

²⁰ Harper 2017, 91–93, 99, argued the pandemic originated in East Africa. This idea is rooted in the aforementioned reference to an epidemic in Arabia in Antoninus Pius's reign and, more primarily, a now dated molecular clock study that speculated VARV emerged in East Africa some 3,000–4,000 years ago: Babkin and Babkina 2015, 1100, 1104, 1107, 1108. This molecular-clock analysis has proved popular among disease historians (Green 2018; Green and Jones 2020, 38–39; Harper 2018, 306; Harper 2021, 195–96; McDonald 2021, 388, 390), but its divergence estimate does not take into consideration all VARV diversity known now and is not calibrated with paleogenomes (none were available). The analysis also rests on a number of assumptions, for instance, that VARV and related orthopoxviruses have the same substitution rate and that orthopoxviruses have shown great consistency regarding host specificity. The East Africa origin hypothesis assumes that the naked sole gerbil was always, as it is now, the only host of taterapox. Cf. Duggan et al. 2016 and Porter et al. 2017 on VARV molecular clocks.

²¹ McDonald 2021, 374, 385, 393. Cf. Rossignol and Durost 2007, 420.

²² E.g., if the plague was smallpox, it had no animal reservoirs (Rossignol 2012, 463) and did not afflict other animals, as some sources claim (Marino 2012, 38), and it would have been most prevalent in winter (Duncan-Jones 2018, 44; Vlach 2020, 28; McDonald 2021, 391–93, 400).

²³ E.g., Scheidel 2002, 108; Zelener 2003, 48, 90, 92, 98–109, 110; Livi Bacci 2012, 341; Zelener 2012, 171, 174; Harper 2015, 246; Harper 2017, 110–11; Flemming 2019, 224. On the Cyprianic plague, see Harper 2015; Huebner 2021.

²⁴ Bagnall 2013, 714.

²⁵ Zelener 2003, 84; Harper 2017, 102.

²⁶ Presentation and epidemiology of VARV: Fenner et al. 1988, 1–68, 169–208; www.cdc.gov/smallpox.

²⁷ Wertebaker 1902, 349.

²⁸ Regarding VARV infectivity, there are many variables to consider. The R_0 (number of people an infected individual can be expected to infect) for smallpox (or more specifically a variola virus that causes smallpox) is debated, with values ranging from 1.5 to 20, depending on a myriad of circumstances; values between 3 and 6 are favored for a fully susceptible population. Serial

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In naïve populations, VARV is thought to have caused large-scale outbreaks resulting in significant excess mortality.²⁹ Without prior infection, or widespread variolation or vaccination, the disease could be highly prevalent, with case fatality rates reaching 25–30 percent (or higher).³⁰ That said, considerable variation in VARV prevalence and mortality between regions, settlements, and subpopulations is to be expected in outbreaks, owing to an array of cultural, demographic, and ecological factors, such as population density and distribution, mobility, housing, and preexisting disease burden. In populations where VARV was endemic,³¹ and the adults had some immunity, VARV could still apply near-constant demographic pressure, claiming the lives of many infants and children on an annual basis and, in certain circumstances, irrupting as epidemics.³²

This is, in large part, how smallpox manifested in recent centuries. For generations, historians, both armchair and professional, as well as physicians, have looked for *this* smallpox in antiquity. But can we superimpose *this* smallpox onto the distant past? What of *this* smallpox should we expect to be able to identify in ancient sources? Our ability to overlay our modern knowledge of smallpox onto the ancient world and diagnose ancient plagues as novel emergences of VARV,³³ or surmise that VARV was endemic in large Roman-era cities and regions densely populated in antiquity,³⁴ requires careful consideration of the available evidence, most notably newly emergent data from paleogenomics.

Evidence for smallpox in antiquity is primarily textual. Apart from the quasi-pox-like rashes visible on some New Kingdom Egyptian mummies³⁵ (which though often mentioned in the literature have yet to yield VARV DNA³⁶), reports of osteomyelitis variolosa³⁷ (a nonspecific bony lesion associated with VARV infection which remains very rarely

interval estimates likewise vary. Gani and Leach 2001; Eichner and Dietz 2003; LeGrand et al. 2003, 21, 23–24; MacIntyre 2020.

²⁹ E.g., Rigau-Pérez 1982, 423, 429; Fenner et al. 1988, 1069–1102; Duncan et al. 1993, 406, 407, 409, 410–11, 419; Krebsbach 1996, 30–31; Hopkins 2002, 8; Piper and Sandlos 2007, 764, 765, 786 n. 24; Livi Bacci 2008, 50, 59, 179, 211, 215, 221; White 2018, 139.

³⁰ Littman and Littman 1973, 254; Fenner et al. 1988, 227, 244, 246; Banthia and Dyson 1999, 652–53, 668–69, 677. Some, however, have proposed that smallpox case fatality might surpass 50 percent at first contact.

³¹ VARV is thought to have been able to achieve endemicity in settlements with at least 200,000–300,000 people or in a tightly knit network of smaller settlements with a total population of that sort, e.g., Fenner et al. 1988, 118; Bartlett 1960, 37, 42. Some wager smaller centers of 100,000 would be enough: Newson 2009, 11.

³² For cyclical epidemics in endemic areas and children as the primary smallpox deaths in endemic areas, e.g., Jannetta 1987, 20, 57, 77, 88–89; Duncan et al. 1993, 405, 407, 415–17, 420–21; Banthia and Dyson 1999, 663–67, 677; Scheidel 2001a, 94; Krylova and Earn 2020. Influxes of unexposed persons, possibly in the context of a food shortage or a siege, when previously less-exposed rural populations may have flocked to cities, could, like a build-up of births, result in epidemics.

³³ In the Mediterranean region (or in general), as in Zinsser 1935, 137; Littman and Littman 1973; McNeill 1976, 103–5; Hopkins 2002, 22–23; Harper 2017, 67–68, 91–92, 111.

³⁴ E.g., Scheidel 2001a, 96; Scheidel 2002, 108; Hopkins 2002, 8, 20; Zelener 2003, 62, 63, 109–10; Andorlini 2012, 16, 24; Zelener 2012, 174. Cf. Harper 2017, 116, 127; Vlach 2020, 33. Zelener 2003, 110, notes that urban mortality in the Antonine plague may have prevented smallpox from establishing endemicity in those cities after the plague.

³⁵ Ruffer and Fergusson 1911; Smith 1912; Ruffer 1914.

³⁶ Hopkins 1980; McCollum et al. 2014.

³⁷ E.g., Eeckels et al. 1964; Darton et al. 2013; Tang et al. 2021.

attested in the archaeological record), or the great age of variolation (and insufflation) purported for several regions of Asia in epidemiologically orientalist writing on smallpox's past,³⁸ what we have are infrequent references to: i) smallpox-like disease, such as Thucydides's small ulcers and pustules,³⁹ Galen's ulcerated and scarring exanthem,⁴⁰ Eusebius's severe carbuncles,⁴¹ Ge Hong's disfiguring epidemic pustules,⁴² and Gregory of Tours's malignant pustules and vesicles;⁴³ and ii) sequelae associated with recovery from smallpox, mainly pox-scarred skin and blindness.⁴⁴ Although more evidence of symptoms and sequelae may yet be recovered,⁴⁵ textual references have been and will continue to be incapable of providing the evidentiary basis needed to definitively confirm or deny the presence of smallpox in antiquity. Other data, however, novel and largely independent of archaeological and textual indications of ancient smallpox,⁴⁶ now strongly suggest that the disease we know as smallpox in fact did *not* exist in antiquity,⁴⁷ but rather has a more recent evolutionary history.

To date, paleogenomics have both solidified some old thinking about ancient disease⁴⁸ and upended some traditional narratives.⁴⁹ As our understanding of the evolutionary history and historical geography of pathogenic disease advances with paleogenomics, historians and archaeologists must remain abreast of developments and, as necessary, reconsider our histories of ancient disease. The ability to detect, capture, and sequence remnants of pathogens continues to improve, but robust results in the subfield of pathogen paleogenomics have been standard now for over a decade.⁵⁰ Although bacterial pathogens causing

³⁸ E.g., d'Entrecolles 1731; Arouet (Voltaire) 1761, 74; Holwell 1767, 7–8; Cibot 1779, 392, 397; Haeser 1845, 255; Hirsch 1860, 215–16; Zinsser 1935, 106–7, 107 n. 1; Dixon 1962, 188.

³⁹ Thuc. 2.48.

⁴⁰ Littman and Littman 1973, 246–47.

⁴¹ Euseb. *Hist. eccl.* 9.8.1–12.

⁴² Lien-Teh 1931, 132.

⁴³ Gregory of Tours *Hist.* 5.34, 6.8, 6.14, 6.15, 8.15, 8.18.

⁴⁴ Naturally, relevant passages must be read in full. That some clinical and epidemiological features appear smallpox-like and others not has long problematized text-based diagnoses.

⁴⁵ Consider Flemming 2019.

⁴⁶ “Largely,” as physical and written indications of smallpox have been problematically used in some molecular clock studies of VARV's evolutionary history (e.g., Li et al. 2007). More recently, such studies have drawn only on irrefutable paleogenetic data (Duggan et al. 2016; Pajer et al. 2017; Ferrari et al. 2020) but contextualize their findings with written evidence. Also “largely” as several of the reconstructed VARV genomes discussed below are dated on the basis of the archaeological context of the individuals whose remains they were recovered from (Mühlemann et al. 2020, SI).

⁴⁷ Flemming 2019, 236, 240, drew on the earliest of the VARV paleogenomes (Duggan et al. 2016) and remarked that “the consensus around [the] smallpox [diagnosis of the Antonine plague] needs to be challenged and questions of identification re-opened” via, in part, further genomic work. We report on that work here.

⁴⁸ E.g., *Plasmodium falciparum*, malaria, and *Mycobacterium tuberculosis*, human tuberculosis, in the ancient Mediterranean region: Marciniak et al. 2016; Lalremruata et al. 2013; *Yersinia pestis*, plague, in Late Antique Europe: Wagner et al. 2014; Feldman et al. 2016; Keller et al. 2019.

⁴⁹ E.g., *Mycobacterium tuberculosis*, human TB, in the Americas “pre-contact”: Bos et al. 2014; human TB preceding bovine TB and not vice versa: Brosch et al. 2002; TB and measles virus younger than expected: Furuse et al. 2010; Düx et al. 2020; Sabin et al. 2020.

⁵⁰ Marciniak and Poinar 2019, 123–24; Spyrou et al. 2019. First pathogen genome: Bos et al. 2011.

acute disease, like *Yersinia pestis* (the cause of plague), have been more often reported⁵¹ than double- or single-stranded DNA viruses,⁵² or viruses containing highly fragile RNA,⁵³ all have now been identified owing to the refinement and ever-increasing sensitivity of paleogenomic methods.

There are, presently, a handful of VARV paleogenomes that have been drafted using decades-to-centuries-old human remains from archaeological contexts and medical archives.⁵⁴ These paleogenomes, some of which are only partial (or poorly phylogenetically resolved),⁵⁵ date to the 17th–20th c. and provide unequivocal evidence for VARV before the modern era. They can be studied alongside the ~45 genome-scale sequences obtained from samples taken in the mid-20th c.⁵⁶

Recent phylogenetic analyses using modern 20th-c. genomes coupled with the reconstructed paleogenomes have refined estimates of VARV's evolutionary history. Inferences of these analyses are historically significant. They show, for instance, that the two prominent groups of VARV strains eradicated in the 20th c., variola major (Clade I) and variola minor (Clade II/alastrim), shared a recent common ancestor some 200 or so years ago, potentially the result of a vaccination-induced population bottleneck.⁵⁷ In addition, these analyses have emphasized the recentness of the evolutionary history of variola minor, which caused a less-acute variety of smallpox but granted immunity to more virulent varieties of the disease.⁵⁸ Although a scarcity of VARV paleogenomes continues to hamper our understanding of VARV's evolutionary history, we have also learned, most importantly in relation to ancient pandemics, that VARV associated with smallpox appears to be centuries old not millennia old.

The inactivation of genes (rendering them non-functioning) in orthopoxviruses has been associated with both host specificity and virulence. All inactivated genes found in 17th- and 18th-c. VARV paleogenomes are also found in all sequenced 20th-c. strains. We can be sure, in other words, that the VARV paleogenomes which have been drafted to date caused smallpox.⁵⁹ This contrasts sharply with recently identified “sister lineages” of VARV – the four oldest orthopoxvirus paleogenomes yet recovered.⁶⁰ These early 7th–late 10th-c. genomes⁶¹ are genetically distinct from the VARV we know to cause smallpox, so much so that when they were reported in 2020 they were identified as “aVARV” (“ancient VARV”), as opposed to VARV (or “mVARV” for “modern VARV”).⁶² These

⁵¹ Marciniak and Poinar 2019.

⁵² E.g., Krause-Kyora et al. 2018; Ross et al. 2018; Guzmán-Solís et al. 2021; Kocher et al. 2021.

⁵³ E.g., Düx et al. 2020; Gryseels et al. 2020. Fragility: Duchêne et al. 2020, R1217–18.

⁵⁴ Biagini et al. 2012; Duggan et al. 2016; Pajer et al. 2017; Mühlemann et al. 2020; Ferrari et al. 2020; Meffray et al. 2021.

⁵⁵ Notably, Biagini et al. 2012; Meffray et al. 2021. Mühlemann et al. 2020 likewise present some low-coverage paleogenomes.

⁵⁶ Esposito et al. 2006; Li et al. 2007; Babkin and Babkina 2015.

⁵⁷ For inferences based on VARV's molecular clock: Firth et al. 2010; Duggan et al. 2016.

⁵⁸ Cautious concern about the circulation of Clade II VARV in the 2nd c. (Livi-Bacci 2012, 345) is, therefore, now unnecessary.

⁵⁹ For this reason, those genomes are identified as VARV.

⁶⁰ Mühlemann et al. 2020.

⁶¹ Mühlemann et al. 2020, Table I, SI.

⁶² Emphasized in Newfield et al. 2020.

strains, while ancestral to the reconstructed 17th–20th-c. VARV paleogenomes, contain a different pattern of inactivated genes than the strains associated with clinical smallpox, including some genes known to be associated with virulence.⁶³ Clinically and epidemiologically, therefore, the disease the millennium-old aVARV strains caused is likely to have differed, perhaps considerably, from smallpox as we know it.⁶⁴ Evolutionary analyses of, and genetic relationships between, orthopoxvirus sequences now reconstructed from ancient human remains and medical archives have taught us that it is improbable that a variola virus like the VARV associated with the disease we know as smallpox (“mVARV”) existed in any similar sense in antiquity. As sister lineages, aVARV should not be considered the direct ancestor of mVARV, and it must be underscored that our knowledge of any shared ancestors, intermediary forms, and historical host distributions remains unclear and likely to be clarified only by paleogenomics.

Pathogens evolve, and as they do their host specificity, transmission mechanics, and infectivity, as well as the disease they cause can, among other things, change. DNA viruses, like VARV, may not evolve as fast as RNA ones, but our ongoing experience with the pathogen SARS-CoV-2, the cause of the disease COVID-19, has made clear the ability of viruses to mutate in meaningful ways.⁶⁵ As the evolutionary history of quickly evolving viruses begins to come into focus, our accounts of their past must remain alert to the limits of our knowledge and sensitive to the weight of the terms we use to describe disease caused by pathogens not suffered and studied in the modern era.

As nomenclature may mislead, to be clear, the recently detected VARV “sister lineages” are not the VARV that caused smallpox. The aVARV paleogenomes neither evidence the discovery of smallpox in ancient or Late-Antique human remains nor raise the possibility of the existence or circulation of smallpox in antiquity.⁶⁶ Rather, aVARV is an orthopoxvirus, now presumably extinct, to which humans were susceptible. Whether it was zoonotic, rodent-borne, or dependent on a nonhuman reservoir, as speculated,⁶⁷ remains uncertain,⁶⁸ but that it has been discovered in early medieval northern Europe, where there were no population centers or regions with a population density even close to approaching the size needed to maintain smallpox, indicates how epidemiologically different aVARV could have been. Its degree of virulence and clinical manifestation are likewise unclear.⁶⁹

⁶³ The significance of aVARV strains not having the full suite of pseudogenized genes of virulent smallpox is hard to overstate.

⁶⁴ Although the Antonine plague has long been associated with smallpox, that tentative diagnosis is not evidence that aVARV caused a recognizable “ancient form” of smallpox or that the Antonine plague was aVARV. That aVARV behaved and manifested something like smallpox, as has already been multiple times speculated (Harper 2021, 195–96; McCormick 2021, 60; McDonald 2021, 387–91), is not known.

⁶⁵ González-Candelas et al. 2021; Karim and de Oliveira 2021.

⁶⁶ Cf. Harper 2021, 195, where these aVARV genomes are mischaracterized as both “ancient” and “smallpox,” and said to have a “close resemblance” to VARV. McCormick 2021, 60, assumes the novel aVARV genomes evidence smallpox.

⁶⁷ Alcamí 2020.

⁶⁸ The available evidence of aVARV is scattered over multiple centuries and a large region of northern Europe. Whether aVARV spread quickly or slowly over northern Europe is not known.

⁶⁹ That it was detected at all indicates that aVARV could, perhaps in concert with comorbidities, kill, but its virulence is unknown. Alcamí 2020 proposed the disease aVARV caused was mild

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What we know for certain is that the sequences of VARV so far obtained from 17th-c. and later samples are remarkably similar to the VARV we understand causes smallpox, so much so that they have been collectively referred to as mVARV. On the other hand, aVARV sequences are more distantly related but, barring intervention and subdivision from the International Committee for Taxonomy of Viruses, must be considered of a single species and taxonomic unit with mVARV. Nevertheless, the genomic content of aVARV DNA, and the inferences for its virulence, and the uncertainty of its host specificity and/or reservoirs, suggest that its expression and behavior are very likely not that of smallpox but rather something for which we do not have a name. These semantics are important. Indiscriminate use of “smallpox” confuses matters. Recent scholarship notably continues to use “smallpox” in its discussion of the Antonine plague and aVARV. This loose usage has a long tradition: over 175 years ago, Haeser suggested smallpox symptoms may have differed in antiquity.⁷⁰ Yet, if the symptoms and epidemiology differed, the diagnosis loses its value, interpretive and heuristic, and becomes a hazard, as diagnoses, certainly ones of smallpox, carry considerable cultural, demographic and epidemiological weight.

Importantly, the aVARV sequences help us to pinpoint a minimum date range for the window during which VARV emerged as the virulent and highly infectious pathogen later described as the etiological agent of smallpox. These “time to the most recent common ancestor” (tMRCA) analyses are Bayesian analyses that attempt to estimate a date that reflects the point in time when aVARV and mVARV shared a common ancestor. Current analyses date this theoretical ancestor – with large confidence intervals – to the 4th c. CE.⁷¹ Crucially, we do not know whether this theoretical ancestor resembled mVARV or was capable of causing a disease we would recognize as smallpox. A smallpox-causing VARV, therefore, could have emerged in the 4th c. or *after* the 4th c., not *by* the 4th c.⁷² Molecular-clock analyses can only estimate the evolutionary history of sampled pathogen diversity, however, and on the basis of all available reconstructed mVARV and aVARV sequences, we must presently conclude that a VARV capable of causing smallpox could have emerged any time between the 4th c. and 16th c. CE. The time frame suggested by all available sequence data (paleogenomes and genomes), suggests a tMRCA closer to the early modern period than the Late-Antique one.⁷³ As such, smallpox's antiquity is very much in doubt and its Late Antiquity is in doubt too.⁷⁴

on the basis of activations of genes associated with virulence and immunomodulation detected by Mühlemann et al. 2020.

⁷⁰ Haeser 1845, 255.

⁷¹ Mühlemann et al. 2020.

⁷² “By” the fourth century: McCormick 2021, 60.

⁷³ This contrasts with speculation that a smallpox-causing VARV emerged in Late Antiquity: Harper 2021, 195–96, and McCormick 2021, 60. That smallpox's emergence dates closer to 1500 than 500 was long ago suggested on the basis of historical evidence, Carmichael and Silverstein, 1987. The place of Rhazes's detailed account of *judari*, long read as smallpox (Paulet 1768b, 1–102; Willan 1821, 1–2; Dixon 1962, 187–88; Hopkins 2002, 27; Green 2018, 8; McCormick 2021, 60; cf. Flemming 2019, 236–40), in the history of smallpox remains to be sorted out, so too other alleged early evidence of smallpox from other world regions.

⁷⁴ That possible marine reservoir effects have not been accounted for in the radiocarbon dating of the human remains from which aVARV paleogenomes have been reconstructed (Mühlemann et al. 2020, SI, 5, 8) is an important issue, as emphasized in McCormick 2021, 60 n. 114, one which could very well pull those remains and the genomes recovered from them closer to the

That smallpox, as known to modern biomedical science, first appeared as recently as 500 years or so ago is not set in stone. We remain in the midst of a paleogenomic revolution, and many more VARV and related orthopoxvirus sequences will yet be drafted from old soft tissues, teeth and bones, guaranteeing that our understanding of VARV's evolutionary history will continue to evolve. However, it must currently be regarded as unlikely that the emergence of a VARV that we understand to have caused smallpox will be pushed back to antiquity or Late Antiquity.

Without smallpox – pandemic, epidemic, or endemic – ancient Mediterranean populations should seem healthier to us.⁷⁵ So should societies in other world regions the disease is likewise thought to have long afflicted.⁷⁶ We are only beginning to grasp the pathogenic load suffered in antiquity anywhere, but the implications of a smallpox-less ancient world are many. For instance, several areas long stigmatized as ancient “cradles” of the disease based on exceptionally weak or nonexistent evidence,⁷⁷ and speculatively othered as sources of ancient Mediterranean smallpox epidemics,⁷⁸ can no longer carry that burden. In the absence of smallpox diagnoses, ancient disease outbreaks will also seem less familiar and understandable. Not being able to employ smallpox, what we know of its symptomatology or epidemiology, in our arguments regarding the demographic import, chronology, origins, or periodicity of ancient epidemics and pandemics will be a challenge to overcome. This is especially true for the Antonine plague, on account of the many roles a smallpox diagnosis has been assigned in our histories of that pandemic.

One option to confront this challenge, albeit one not recommended, would be to assume that plagues previously diagnosed as smallpox were in fact aVARV, or another VARV ancestor, which happened to manifest and behave a lot like VARV.⁷⁹ Although one might propose that the written evidence we have for ancient smallpox-like plagues (Galen, Eusebius, Ge Hong, etc.) corroborates this thinking, the idea is problematic. We know so very little about VARV ancestors – their ecology, epidemiology, or symptomatology – that such a diagnosis is not only unsubstantiated and unhelpful, but also misleading, as the continuity this proposal suggests between a VARV ancestor and VARV is wholly

present. The implication is that, if marine reservoir effects have offset the radiocarbon dating, aVARV, and by extension mVARV, would have even less to do with antiquity than already emphasized here and less to do with Late Antiquity too.

⁷⁵ The reverse was also true. Zelener 2003, 111, observed that to identify smallpox in the Roman world “significantly alters perceptions of Roman demography.” At the same time, the written, skeletal and paleogenetic evidence available for disease in antiquity does not suggest a light disease burden, smallpox or not.

⁷⁶ Schnurrer 1823, 4, 16, 54, 156; Haeser 1845, 255; Zinsser 1935, 105–6; Dixon 1962, 188; Fenner et al. 1988, 118 (cf. 210); Hopkins 2002, 16–18. Cf. App 2010, 297–362; Newfield et al. 2022.

⁷⁷ Notably, East and South Asia, see, e.g., d’Entrecolles 1731; Holwell 1767, 7–8; Cibot 1779, 392, 397; and works cited in n. 76.

⁷⁸ Epidemics reported in Chinese sources have been repeatedly connected to the Antonine plague, and East Asia has sometimes, but not always, been identified as the place of the Antonine plague’s origins: e.g., McNeill 1976, 102–3; Duncan-Jones 1996, 115, 117; Gourevitch 2005, 59; Rossignol and Durost 2007, 420; Andorlini 2012, 24; Duncan-Jones 2018, 44–45; McDonald 2021, 387.

⁷⁹ It has been proposed, before and after the identification of aVARV, that the Antonine plague was instead a smallpox ancestor, possibly (in the 2021 publications) aVARV itself: Gourevitch 2005, 65; Harper 2021, 195–96; McDonald 2021, 387–91.

conjectural and not supported by available evidence. Another option would be to reject diagnosis, to adopt agnosticism and interpret the primary evidence on its own, without the superimposition of modern science.

Whether or not one pursues this second option, they should remain alert to the aspects of our histories of ancient plagues that have been built or buttressed with a smallpox diagnosis. Concerning the Antonine plague, we cannot simply abandon the diagnosis from our histories and move on. We will have to reckon with how the loss of the diagnosis will cause our accounts of that pandemic to change – our confidence regarding its origins, periodicity, and breadth will weaken, and a few ideas present in our histories will have to be given up, like questions concerning the 2nd-c. plague's demographic profile and density dependence.

The Mediterranean antiquity of smallpox gained favor in academic writing from the mid-19th c., when the disease was, in many world regions, in steep decline. On the verge of VARV's eradication, smallpox identifications of ancient plagues gained currency. Commentators on smallpox's past who lived when and where the disease was prevalent, to the contrary, found no place for it in the Greco-Roman past. Paleogenomic data and evolutionary biological analyses now lend support to that thinking and indicate it is time to eradicate smallpox from our histories of the ancient world and ancient plagues from our histories of smallpox.

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