

Original Article

Mortality risk factors show similar trends in modern and historic populations exposed to plague

Mauro Rubini¹, Emanuela Gualdi-Russo², Vanessa S. Manzon², Natascia Rinaldo², Raffaella Bianucci³

¹ Anthropological Service, Soprintendenza Archeologia Lazio e Etruria Meridionale, Rome, Italy

² Department of Biomedical and Specialty Surgical Sciences, University of Ferrara, Ferrara, Italy

³ Department of Public Health and Paediatric Sciences, Legal Medicine Section, University of Turin, Turin, Italy

Abstract

Introduction: Plague has been responsible for two major historic pandemics (6th–8th century CE; 14th–19th century CE) and a modern one. The recent Malagasy plague outbreaks raised new concerns on the deadly potential of the plague-causing bacteria *Yersinia pestis*. Between September 2014 and April 2015, outbreaks of bubonic and pneumonic plague hit the Malagasy population. Two hundred and sixty-three cases, including 71 deaths, have been reported in 16 different districts with a case fatality rate of 27%. The scope of our study was to ascertain whether the risk factors for health in modern-day populations exposed to plague and in ancient populations that faced the two historic pandemics varied or remained substantially unaltered.

Methodology: The risk of mortality of the Malagasy population with those obtained from the reconstruction of three samples of European populations exposed to the historic pandemics was contrasted.

Results: The evidence shows that the risks of death are not uniform across age neither in modern nor in historic populations exposed to plague and shows precise concentrations in specific age groups (children between five and nine years of age and young adults).

Conclusions: Although in the post-antibiotic era, the fatality rates have drastically reduced, both modern and historic populations were exposed to the same risk factors that are essentially represented by a low standard of environmental hygiene, poor nutrition, and weak health systems.

Key words: *Yersinia pestis*; risk of death; pre- and post-antibiotic era.

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Introduction

Plague, essentially a rodent disease that can be transmitted accidentally to humans, has been responsible for two major historic pandemics (6th–8th century CE; 14th–19th century CE) and a modern one [1-4]. During the last pandemic that started in China (1894), the disease spread worldwide, entering almost all continents from its main ports [4]. Hence, sylvatic foci have established in various areas of the world, where they expand or regress following complex dynamics [5,6]. Plague has re-emerged in several foci over the past 20 years, and human outbreaks have been registered [4]. The recent Malagasy outbreaks of bubonic and pneumonic plague have raised new concerns about the deadly potential of the plague-causing bacteria *Yersinia pestis* [6]. After its first introduction in Madagascar (1898), the disease became endemic in the animal population of the central highlands, and total eradication has been deemed impossible [4,5]. From 1980 onwards, outbreaks have re-surfaced nearly every year and, over the past three

years, the annual number of cases has steadily increased [6].

Between September 2014 and April 2015, outbreaks of bubonic and pneumonic plague have hit the Malagasy population. Two hundred and sixty-three cases, including 71 deaths, have been reported in 16 different districts with a case fatality rate of 27% [6].

The control of modern plague outbreaks has drastically improved, with a significant reduction of the mortality rates thanks to the early treatment with common antibiotics such as tetracyclines, gentamycin, and streptomycin [6]. Antibiotics are efficient on human plague; their efficacy depends on early detection of the *Yersinia* infection. In the pre-antibiotic era and in modern-day Malagasy remote areas, case fatality due to bubonic plague has been estimated to be around 60%. In the absence of treatment, pneumonic plague and septicemic plague are invariably fatal and kill within 24–48 hours. With prompt antibiotic treatment, case fatality for bubonic plague can be reduced from 60% to less than 15%. Similarly, pneumonic plague, which is

highly contagious, can be cured only if immediate antibiotic treatment takes place [6].

The scope of our study was to ascertain whether the risk factors for health in modern-day populations exposed to plague and in ancient populations that faced the two historic pandemics varied or remained substantially unaltered. Here, we provide evidence that, although in the post-antibiotic era, the fatality rates have declined, both modern and past populations were exposed to the same risk factors that are essentially represented by a low standard of environmental hygiene, poor nutrition, and weak health systems.

Methodology

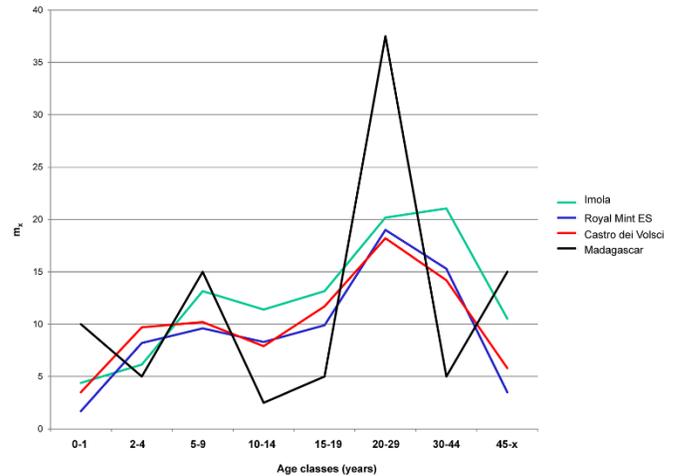
An abridged life table was constructed using TABRIMOR software (developed by one of the authors [MR]) and drew a risk of death curve of the 2014–2015 Malagasy affected population (263 individuals: 62.5% adults and 37.5% sub-adults) [6,7]. An abridged life table is a rectangular matrix showing changes into a standard set of life table functions (columns) across ages (rows). The conventional set of life table functions includes: d_x (number of deaths within the elementary age interval); m_x (death rate [$x \times 100$] for the elementary age interval); l_x (probability of survival from birth to age x); q_x (probability of death within elementary age interval); L_x (number of person-years lived within the elementary age interval); T_x (number of person-years lived after the age x), and e_x (life expectancy at age x).

While some scholars base their studies on the paleodemographic assumption that the sex and age distribution of a skeletal sample reflects the constitution of the original population [8,9], others disagree [10]. Modern clinical studies show that plague is not a selective disease. People who live in unsanitary conditions and poverty are at higher risk of contracting plague due to closer contacts with reservoirs (rats) and vectors (fleas).

Similarly, it has been shown that epidemic mortality in historic populations was apparently not selective with respect to age and sex among adults [8-12]. Conversely, it was shown that mortality associated with the medieval epidemic was selective with respect to frailty [10,11]. Individuals who were in poor health before the epidemics were more likely to die than were their healthy peers [11].

Based on the evidence that plague has never been a selective disease and that sex and age distribution of a skeletal sample reflects the constitution of the original population [8,9], the risk of mortality of the Malagasy population was contrasted with those obtained from the reconstruction of three samples of European

Figure 1. Mortality trends in modern and historic populations exposed to plague. Cyclical peaks correspond to higher concentration of risks of death.



populations exposed to the historic pandemics. These included Castro dei Volsci mass burial, Frosinone, Italy, 6th century CE (179 individuals: 57% adults, 43% sub-adults) (Powel R., personal communication); Royal Mint East Smithfield cemetery, London, UK, 1348–1350 CE (636 individuals: 72.2% adults, 27.8% sub-adults) [3]; and Lazzaretto dell’Osservanza, Imola, Bologna, Italy, 1630–1632 CE (114 individuals: 63% adults, 47% sub-adults) (Bianucci R., personal communication) (Figure 1).

Age and sex were determined by applying the same methodology to all Italian collections. Sex was determined exclusively for the adult population by using standard morphometrical methods [14-16]. The sub-adult age at death was established based on the evaluation of the degree of dental mineralization and eruption [17], the measurement of the diaphyseal length of the long bones [18,10], and the evaluation of the degree of epiphyseal fusion of the long bones and hip bone [20-22]. When the skeletal state of preservation of each sub-adult was complete enough, the three methods were applied simultaneously.

The adult age at death was determined by evaluating the degree of fusion of the spheno-occipital synchondrosis (*sutura sphenooccipitalis*) [23] and by applying Buikstra and Ubelaker’s standard methods [24]. Particular attention was paid to the morphological changes of the pubic symphyseal face [25] and to those of the auricular surface of the *os coxae* [26,27]. The latter methods are routinely used both in the anthropological analysis of ancient populations and in forensic investigations [28]. The method was also applied to the fourth rib, when available [29,30].

The adult age estimation method, based on the closure of cranial suture [27], was cautiously applied to young adult individuals whose pubic symphysis and auricular surface were badly damaged and exclusively after having checked that they did not display evident cranial pathologies. Age and sex of the English collection were assessed in previous studies [10,31] using similar methods.

Furthermore, taking into account that the type and amount of information derived from osteo-archaeological collections are strictly related to the state of preservation of remains, three well-established taphonomic indexes were applied to evaluate the skeletal preservation of the analyzed Italian collections [8]. The consistency of the English collection was assessed in previous studies [10,31].

Results

A class 4 (70%) anatomical preservation index (API class 4 = 50%–74% preserved bones) and a class 4 (70%) qualitative bone index (QBI class 4 = 50%–74% of sound cortical surface) were recorded. With respect to the bone representation index (BRI), *i.e.*, the ratio between the actual number of bones removed during excavation and the total number of elements of the skeleton that should have been present, 63% of the bones were represented for each skeleton [8]. All analyzed osteo-archaeological collections showed to be qualitatively and quantitatively well represented and well preserved [8].

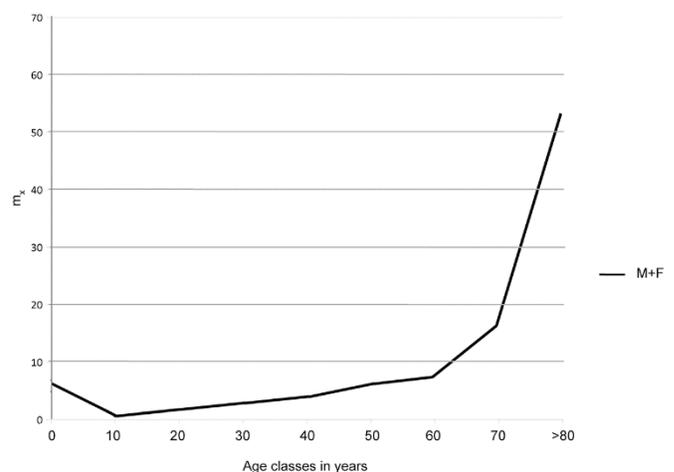
For the sub-adult samples, a five-year age interval was chosen; an exception was made for newborns (0–1 years of age) and small infants (2–4 years of age) whose intrinsic frailty implies higher risks of death both in historic and modern populations. Adults were divided in three main age classes: young adults (20–29 years), adults (30–44 years), and mature/elderly adults (45+ years of age). The distribution was based on the mean age of both sub-adults and adults and the margin of error intrinsic to the method was included in the ranges [32]. According to Masset [33], a demographic sample is reliable when juvenile mortality (d5–15) compared to adult mortality (d20+) ranges between 10% and 30% ($X = [d5-15] / [d20+]$; X index between 0.1 and 0.3). All the analyzed skeletal series showed a reliable X index.

Since the total number of ancient sub-samples (M and F) was too small, an additional gender-based subdivision was avoided, the choice being supported by the knowledge that sex does not strongly affect the risk of death neither in ancient nor in modern plague victims [8,12]. The risks of death (graphically represented by cyclical peaks) are not uniform across age neither in

modern nor in historic populations exposed to plague. Although plague can affect all age classes, during the 2014–2015 outbreak, the highest risks of death were registered mainly in two age groups: 5–9 and 20–29 years of age (Figure 1). This trend fits perfectly with those reported over the past 50 years of Malagasy plague outbreaks [4]. Quite interestingly, the analyzed populations who faced the two major historic pandemics show a similar cyclic trend (Figure 1), with children 5–9 years of age and young adults being the most exposed to the risk of death.

If a comparison is made between the mortality risk trends in diachronic/synchronic populations exposed to plague and a modern population not exposed to plague (*i.e.*, the Italian city of Modena in 2010 [31]), striking differences emerge (Figure 2). The risk factors of death in a plague-free population are homogeneously distributed throughout life and do not produce concentrations (peaks) apart from those usually registered in the perinatal age (*i.e.* delivery, premature birth, stillbirth) and in the elderly adult population (≥ 70 years). This implies that the risk of a person dying of disease (*i.e.* bacterial pneumonia) is distributed equally over all his/her lifetime, and death can occur at any age. The consequence of a homogenous distribution of risk factors for health in plague-free populations is that the corresponding mortality curves are flat and linear with obvious peaks concentrated only in the perinatal age and in older adults (Figure 2). If a population is exposed to a fatal disease such as plague, the mortality patterns appear wavering with peaks. The peaks do not have a random distribution; they have an extremely precise concentration in specific age groups that are the most exposed to the risk of contracting the disease. Depending on the longevity of each population, the

Figure 2. Mortality trends in a modern population not exposed to plague.



adult age group at higher risk for health may vary between 20 and 29 years and 30 and 44 years of age. Due to a different life expectancy in modern and historic populations, the mortality risk curve for plague can moderately shift from young adulthood to adulthood, even though the trend of the curve remains unaltered.

Discussion

In areas of the world where plague once was and currently is endemic, the behaviour of children 5–9 years of age may expose them to a greater risk of contamination. Children, especially those sleeping or playing on the ground, have a much higher level of exposure to the bites of infected fleas [35,36]. Furthermore, since the immune system becomes stronger with age, young children may be less able to defend themselves by developing a semi-immunity against the plague bacterium in endemic areas (*i.e.* the Malagasy central plateau and Medieval and Modern Europe) [35,36].

For young adults, both in historic and modern populations, the highest risks can be linked to agricultural occupations, local manufacture (*i.e.* wheat markets, butcheries), and trades. These activities bring people into greater contact with the rat/flea plague reservoir and may act as a bridgehead between the countryside and cities. Where no agricultural occupation takes place (*i.e.* in cities and towns), severe overcrowding, promiscuity, lack of hygiene, absence of medical care, and poor nutrition represent the major risk factors of death. A similar scenario, once described by historians in Europe's most important commercial hubs during the Medieval and Modern periods [37,38], can be found today in the largest Malagasy detention facilities (Antanimora, Vatomandry, Toamasina, and Toliary), where conditions are harsh and life threatening [39]. Antanimora penitentiary, the main prison in the heart of the capital Antananarivo, for example, was designed for 481 inmates but held, in 2012, nearly 3,000 detainees. Juveniles were not always held separately from the adult prison population, and some preschool-age children shared cells with their incarcerated mothers [40]. A deteriorating prison infrastructure, often lacking sanitation facilities and potable water, may result in disease and infestations of insects and rodents. During an urban outbreak, plague-carrying rats are potentially able to spread infected fleas through food supplies, bedding, and clothing. In turn, infected fleas may infect prisoners, prison guards, and visitors, who can spread the disease when they return to their communities [39].

Early to late Middle-Ages populations that lived in urban centers faced a similar scenario [37,38]. In the early Middle Ages, the fall of the Western Roman Empire brought about a rapid decay of the Roman health system. Cities and towns bordering the main routes through which armies travelled were abandoned, and people migrated. Old abandoned sites (*i.e.* the Roman *villae*) were re-occupied and people were forced to live in overcrowded houses, in promiscuous and unsanitary conditions, often experiencing food shortages. The latter conditions were typical of historic cities throughout the Middle Ages, when the feudal system was instituted, and in the early modern period. Communities of large populations, which resided in crowded cities, suffered from several hazardous conditions such as poor sanitation, high levels of poverty, and poor sources of uncontaminated food and water [41-43]. They were inevitably exposed to fecal-borne infections [44-45]. Intestinal infections, which resulted in chronic anemia and fatal diarrhea (known as the flux), represented the real scourge of European populations throughout the Middle Ages and the modern period [44-45]. As a matter of fact, in urban European archaeological sites, eggs of *Ascaris lumbricoides* and *Trichuris trichiura* can be found in virtually any context, including latrines, yards, and streets. The intestinal parasitism alone or coupled with concurrent infections such as influenza, pneumonia, and tuberculosis was responsible for a great number of deaths. When the European populations were finally hit by medieval plague, the risk factors further increased.

Conclusions

Thanks to the steady progress in prevention, early diagnosis, and antibiotic treatment of suspected and confirmed cases, plague casualties have been remarkably reduced over the decades [4,5]. Nevertheless, plague outbreaks cannot be prevented [4,5]. Even if case fatality was reduced in the post-antibiotic era, our findings show that the risk factors of death, both in historic and modern populations exposed to the disease, are not uniformly distributed and have remained essentially unmodified. These conditions call for constant surveillance in areas of the world where socio-economical inequalities (*i.e.* famine, poverty, unsanitary conditions, promiscuity, wars) expose human populations to higher risks of contracting *Yersinia pestis*.

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Corresponding author

Prof. Emanuela Gualdi-Russo
 Department of Biomedical and Specialty Surgical Sciences
 Corso Ercole I D’Este 32, University of Ferrara
 44121 Ferrara, Italy
 Phone: + 39 053 2293793
 Fax: + 39 053 2293793
 Email: emanuela.gualdi@unife.it
 Dr. Raffaella Bianucci
 Department of Public Health and Paediatric Sciences, Legal
 Medicine Section
 Corso Galileo Galilei, 22, University of Turin
 10126 Turin, Italy
 Phone: +39 011 6705939
 Email: raffaella.bianucci@unito.it

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