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Emergence of whooping cough: notes from three early epidemics in Persia

Arash Aslanabadi*, Kamyar Ghabili*, Kaveh Shad, Majid Khalili, Mohammad M Sajadi

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*Contributed equally

Students' Research Committee (A Aslanabadi), Medical Philosophy and History Research Center (K Ghabili MD), Chronic Kidney Disease Research Center (K Shad MD), and Tuberculosis and Lung Disease Research Center (M Khalili PhD), Tabriz University of Medical Sciences, Tabriz, Iran; and Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA (M M Sajadi MD)

Correspondence to: Dr Mohammad M Sajadi, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD 21201, USA
msajadi@ihv.umaryland.edu

Whooping cough is a relatively new infectious disease afflicting human beings, compared with other infectious diseases, and is undergoing a resurgence despite decades of vaccination. The oldest known epidemic is thought to be the Paris outbreak of 1578. In this Historical Review, we describe three epidemics of whooping cough in Persia, which although arising roughly one century before the Paris outbreak, have not been examined in detail. A great amount of epidemiological detail was reported that not only distinguishes the various stages and complications of whooping cough, but also reveals unique immunological aspects of this disease. The first of these epidemics is the oldest recorded whooping cough epidemic. On the basis of epidemiological features, we propose that this whooping cough epidemic was the first to have taken place in Persia and might have been part of the first pandemic. This theory pushes back the date of first documented emergence of whooping cough by almost a century, which matches molecular data about its spread. Here, we discuss features of these early epidemics in relation to their initial emergence, potential origins, and spread to Europe.

Introduction

Throughout their existence, human beings have constantly been exposed to new infectious agents. Although some of these agents (such as severe acute respiratory syndrome coronavirus) have not led to endemicity, others (such as HIV) have joined the pantheon of microbes that continue to afflict us. Whooping cough—induced mainly by *Bordetella pertussis*—is a relatively recent addition to this ever-growing list of diseases. However, before the advent of vaccination, generations of physicians recognised whooping cough as a childhood disease with potentially deadly complications. In the vaccine era, this disease continues to be endemic and has shown a resurgence since the 1980s.^{1–3} Increased understanding of the origins of whooping cough and the factors that led to its rapid spread and persistence in human beings could lead to improved therapeutics or vaccines, or even insight in other diverse disciplines such as ecology, history, or anthropology.

Although contact with *B pertussis* is thought to have happened thousands of years ago, whooping cough has only become endemic in the past 500 years. The earliest known outbreak, considered to have been in Paris in the 16th century, was first described by Ballonius.^{4,5} We present three related epidemics, happening almost a century earlier, which shed light on the initial spread and potential origins of whooping cough.

Whooping cough in historical records

Whooping cough is among a handful of diseases whose classic description enables accurate identification in historical records. The first phase of the infection, the catarrhal phase, is characterised by coryza, lacrimation, and a mild cough with or without a mild temperature elevation;⁶ symptoms that can be caused by various upper respiratory viral infections. This phase has escaped early historical accounts of the disease.

The second phase, the paroxysmal phase, is characterised by so-called whoops. These whoops are short expiratory bursts of dry, non-productive cough followed

by long inspiratory gasps, making the characteristic whooping sound. As many as 50 paroxysms can happen in a day, which can end with an episode of vomiting or be associated with cyanosis.⁷ Attack rates of 50–100% have been noted in susceptible populations,⁸ and complications include pneumonia, haemorrhage, and death. In the prevaccination era (prior to the 1950s), mortality rates of up to 6% were reported in endemic areas with susceptible populations.⁴ Before the advent of the pertussis vaccine, epidemics happened in 3–5 (and up to 7) year cycles coincident with the presence of susceptible people (eg, children) in the population.^{9,10} The third and final phase of whooping cough is the convalescent phase, which consists of a chronic dry cough lasting 2–3 months that slowly abates.^{9,10}

Diseases with the classic symptoms of the paroxysmal phase of whooping cough are absent in reports from Greek and Roman physicians, and from those of the later Persian physicians such as Rhazes and Avicenna.^{4,11,12} Likewise, whooping cough does not seem to have been present in the Americas until after its appearance in Europe. Results from molecular studies have confirmed that although *B pertussis* is more than several million years old, it rapidly expanded within the human population in the past 500 years.¹³

Guillaume de Baillou (also known as Ballonius; 1538–1616) provided what is considered to be the earliest European description of the paroxysmal phase of whooping cough. He described the earliest account of epidemic spread of the illness in Paris in 1578.¹⁴ He described an autumn and then a summer epidemic. The description of the summer epidemic is especially detailed and described a new disease that was termed “quinta”. This disease is clearly recognisable as whooping cough to modern clinicians. Children aged 4–10 years were mainly affected, with a violent dry cough that ended in vomiting (or cyanosis) with a high mortality. Ballonius states: “The lung is so irritated that in the effort it makes to get rid of that which affects it, it can inhale and exhale only with

difficulty...The patient swells up and nearly suffocated, feels as though his breath was stopped in the middle of his throat...Some believe that this name [quinta] was made-up because of the sound of the patient in coughing. The torment of the cough is sometimes suspended for 4–5 hours after which the paroxysm returns, which is often so violent that it causes blood to issue from the nose and mouth and very frequently...causes vomiting”.¹¹

Several earlier epidemics, some of which shared features of whooping cough, had also been reported, but were not thought to be this same disease. These include the 1540 epidemic in England, and a 1414 epidemic in Paris that caused coryza, hoarseness, and death (especially in elderly people). The 1414 Paris epidemic has been rejected as whooping cough by several scholars because of a missing mention of cough, absence of infant mortality, and the short-lived span of the epidemic (a maximum of 2 months) that seems more akin to influenza.^{11,12,15} A cough similar to whooping cough was also mentioned in a Korean medical and pharmaceutical textbook from 1433.¹⁶ However, we are not aware of description of any other associated symptoms or an epidemic disposition of this disease that would be consistent with whooping cough rather than croup. Although Bahā’ al-Dawlah Rāzī is credited with having described whooping cough in 16th century Persia,¹⁷ his writing on the subject has not been examined in detail. Here, we describe three epidemics in 15th and 16th century

Persia, the first of which is probably the first epidemic of whooping cough in Persia, and the earliest recorded whooping cough epidemic in the world, which at the time was probably becoming pandemic.

Bahā’ al-Dawlah Rāzī

15th century Persia was under control of the Timurid dynasty (1370–1501), which spanned from modern-day Iran into parts of central Asia and India. Medicine at that time was largely dominated by the traditions of Hippocrates and Galen, as well as indigenous Persian physicians represented by individuals such as Razi (Rhazes) and Ibn Sina (Avicenna).

Mohammad Hussain Nurbakhshi, a physician also known as Bahā’ al-Dawlah Rāzī (1455–1509), was born in Tarasht of Rey (near present-day Tehran, Iran) and studied medicine in Rey and Herat under various Persian and Indian physicians. He spent most of his life in Rey; however, according to his own manuscripts, he had travelled to (and practised medicine in) Herat, Kashan, Natanz, Isfahan, and Saveh. Figure 1 shows the map of Persia around the end of Bahā’ al-Dawlah’s life.^{18,19}

Bahā’ al-Dawlah’s book, the *Khulāsāt al-tajārib* (The Summary of Experiences), which was completed in 1501 CE, is considered as one of the most coherent problem-based medical textbooks of its time.²⁰ This book consists of 28 chapters and contains clinical records of



Figure 1: Map of Persia of around 1512 (reign of Shah Ismail I, founder of the Safavid dynasty)

patients treated by Bahā' al-Dawlah, diagnostic impressions, and management strategies, which combine Indian and Galenic (or Persian) medicine. In the book, Bahā' al-Dawlah mentions the teachings of Hippocrates, Galen, Rhazes, Avicenna, and Jorjani. Furthermore, he refers to the teachings of his father, Shāh Qāsim Nurbakhsh, and his brother, Shāh Shams al-Din, who were also physicians.^{18,21}

The Herat epidemics

Bahā' al-Dawlah Rāzī described three distinct epidemics of whooping cough in the *Khulāsāt al-tajārib*. The following is an English translation of a section in the *Khulāsāt al-tajārib* related to two whooping cough epidemics in Herat:

“In Herat, there were two occurrences of a mild infection of the air, causing an epidemic cough without catarrh and the intensity of cough was to such an extent that it did not cease until vomiting occurred and weakness developed. And children became unconscious, and many people, old and young, died in the first epidemic because of this fainting and the intensity of cough. At last, an Indian physician ordered people to eat a mithkal [1 mithkal is about 4.6 g] or more of raw ginger dissolved in warm water. Most were cured with this treatment, and fewer died in the second epidemic and it was in the springtime...I and my household caught this cough, and it was reduced with the above treatment within two months, and was not cured until there was a change in the air...”²²

The two Herat epidemics are noteworthy for several reasons. In their descriptions, we note many of the classic signs and symptoms of whooping cough. First, the disease affected many people (children and adults), signifying that it was an epidemic that was not present before. There was spread through households, implying a high attack rate characteristic of whooping cough. The disease caused widespread death, as whooping cough is known to do, especially when affecting regions where the population had no previous immunity. In terms of symptoms, the disease caused the classic chronic non-productive cough. This cough was reported to end with vomiting or fainting, which are well known complications of the paroxysmal phase. Finally, the cough was noted to

last for up to 2 months, essentially describing the convalescent phase of the disease.

The closely spaced Herat epidemics were associated with different mortality rates. Bahā' al-Dawlah attributed the decreased spring mortality and less severe epidemic to the treatment with ginger that became popular during spring. However, on the basis of the known attack rates for whooping cough and principles of immunology, in the spring epidemic in Herat, fewer people would have been susceptible because many persons would have developed immunity.

The exact dates of the Herat epidemics are not known. However, on the basis of the date that Bahā' al-Dawlah was in Greater Khorasan on the way to Herat (March 30, 1484), the dates and directions of his later travels (1495–98), the date of the later Rey epidemic (February to March, 1501), and the date of the completion of *Khulāsāt al-tajārib* in Rey (1501),²² we conclude that the first Herat epidemic was between 1484 and 1495 (figure 2).

The Rey epidemic

By contrast with the Herat epidemics, the date of the Rey epidemic was recorded. On the basis of the timeline shown in figure 2, the Rey epidemic happened after the Herat epidemic. The following is Bahā' al-Dawlah's description of the Rey epidemic: “In late winter of 906 HG [1501 CE] in Rey, the air caused cough in infants and children, and it was so intense that the coughs did not diminish until vomiting appeared and weakness developed, and such a pain was in their chests that the small children placed their hands over their chests and moaned...and some neared death...and some became better with this treatment...and some were cured of this chronic illness. And some, by the weakness caused by the cough, developed a fever...and the heat of the fever caused an improvement, and it would remit causing a crisis with sweating, leading to a cessation of the cough and fever”.²²

The Rey epidemic shares many of the features of the Herat epidemic. First, a disease is mentioned causing a chronic cough. Additionally, the cough is so violent that it does not diminish until vomiting or weakness develops. That the Persian words the author uses in this

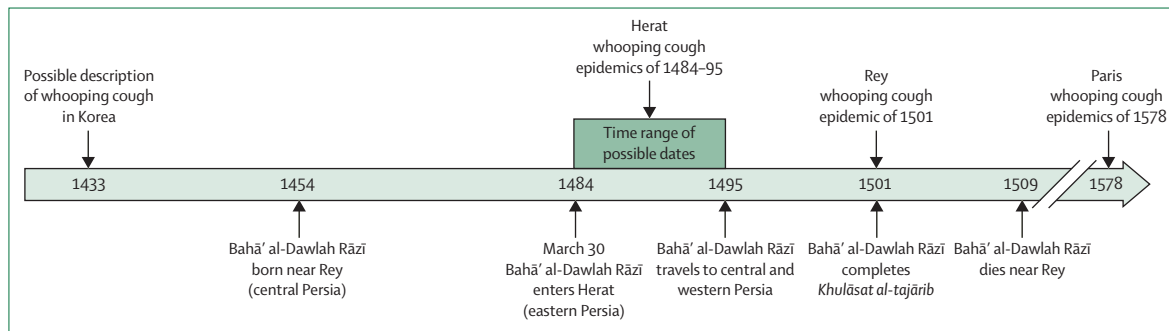


Figure 2: Timeline of whooping cough in the 15th and 16th centuries

sentence for both the Rey and Herat epidemics are almost identical is noteworthy. However, we will examine some notable differences in reference to both mortality and age cohort of those people affected. The little emphasis on death in the Rey epidemic could call into question whether the epidemic truly represents whooping cough. But this should be considered in the context of an established endemic infection and a background of low life expectancy.

An important feature of the Herat epidemics is that both adults and children were affected. This point suggests that previous immunity was not present in adults, and that the disease was not yet endemic. Findings made in the prevaccination era, show that in regions where pertussis is endemic, it causes typical disease in people who are not immune, usually children (adults have prolonged immunity from initial infection and then immune boosting from constant exposure).^{6,23,24} Adults who became infected in the vaccination and prevaccination era represent cases of re-infection after natural infection or vaccination and not first episodes of infection.⁶ However, at one time, a population of susceptible (naïve) adults must have become infected. We believe that the Herat epidemic probably represents the first such epidemic in Persia and probably denotes a time when this disease was becoming pandemic. The Paris epidemic might have likewise been the first in its region, because in the spring epidemic, a disease affecting mostly infants is not mentioned (implying that both adults and infants were infected). However, in the summer epidemic, infants were most affected by the disease. Most of the infants from Paris affected in the summer were probably those born in the spring, whose immunity by maternal transfer of antibody was waning.

Another noteworthy feature of the Herat epidemics is that they happened consecutively. The author does not specify what time of year the first epidemic took place, but his writing implies that both epidemics were temporally associated, and that the second epidemic was in the spring. This association is reminiscent of what Ballonius would later describe in Paris (ie, a spring and then a summer epidemic). The descriptions of the Parisian and Persian epidemics, in that they spanned many different seasons, are compatible with our knowledge about whooping cough in the prevaccination era (ie, that the disease could be present in any season).⁶ Based on the assumption that the two epidemics that Ballonius described were both due to whooping cough, the short interval of weeks or months before the second epidemic happened might be a feature of an emerging whooping cough infection that infects a susceptible population.

The chance that the Herat epidemics in Persia were happening in isolation is highly unlikely. Rey and Herat were both important and large cities on the Silk Road, a trade route that spanned thousands of kilometres. Although the international component of the Silk Road

was in decline by the 14th century during the Timurid dynasty, both Rey and Herat were major cities in Persia and would have had substantial and ongoing contacts between them. The distance between Rey and Herat is about 1000 km. Therefore, that the initial epidemics took place contemporaneously or within a year or two of each other is not inconceivable. Furthermore, as shown in studies from the prevaccination era in the USA, the rural penetration of whooping cough was extremely high, much more so than that of other diseases such as mumps, measles, rubella, scarlet fever, meningitis, and diphtheria.⁹

By the time of the 1501 Rey epidemic, whooping cough had become endemic in Persia, as corroborated by accounts of the disease similar to the Herat epidemic being described in children and not adults. Furthermore, unlike the Herat epidemic, mortality was not emphasised. We attribute this to a lower overall mortality or a mortality on par with other endemic diseases of the time. In the time between the Herat and Rey epidemics, up to four other whooping cough epidemics could have happened in Persia (depending on the exact year that the Herat epidemic took place and assuming a 3–7 year cycle for an epidemic), with most surviving adults being immune. Another 77 years would pass before whooping cough would be first described in Paris.

A previous study proposed that *B pertussis* was associated with hominids as early as 2.5 million years ago (and thus potentially associated with human beings) since the beginning of that species, but was only more recently introduced into Europe.^{25,26} Genetic data show that the common ancestor of one of two lineages of *B pertussis* dates back about 500 years.¹³ Although *B pertussis* might have infected isolated human populations over time, the unique features of the Herat and Rey epidemics, together with the temporal and geographical association of the 16th century epidemics in Persia and Paris, suggest that whooping cough emerged as a pandemic (and later as an endemic) disease 500–600 years ago.

Our investigation suggests that whooping cough was probably introduced into Europe from western Asia. However, the question of how the disease came to Persia is unresolved. On the basis of trade routes at the time, the most probable candidate routes are through southern Africa and Arabia, or eastern and southeastern Asia. We believe that the Asian routes are more likely. A report that mentions whooping cough (among a list of other diseases) was described in an Indian textbook written in Persian that was completed in 1512.²⁷ When we examined this book, we could find neither a reference to an epidemic nor a cough that was consistent with whooping cough.²⁸ However, in Asia, whooping cough possibly existed in Korea in the 15th century,¹⁶ and whooping cough was known to the Chinese (pertussis is known as the 100 day cough), although the exact dates are not clear.

Search strategy and selection criteria

We selected and translated sections from *Khulāsāt al-tajārib* describing epidemics of whooping cough after reviewing all sections related to coughing in the book. One of the oldest surviving manuscripts (1580 CE edition) of *Khulāsāt al-tajārib*, housed at the University of Tehran Library, was used for this purpose. We have included the relevant parts of the work in the appendix. To investigate the history of whooping cough, we searched PubMed and Google Books from about 1800 to Feb 27, 2015, with the search terms “pertussis” and “history”, and “whooping cough” and “history”.

See Online for appendix

Conclusion

Our findings and description of the earliest recorded whooping cough epidemics, which based on epidemiological features were part of the first epidemic in Persia, strengthen the notion that whooping cough is a fairly new endemic disease. This finding pushes back the date of the initial spread of the disease by almost a century, matching the most recent molecular evidence. Research into the exact dates of the appearance of whooping cough in eastern Asia could shed more light on its origins.

Contributors

AA contributed to study design, scientific literature search, material collection and interpretation, and writing. KG and MMS contributed to study design, scientific literature search, material collection and interpretation, writing, and critical revision. KS and MK contributed to scientific literature search, material collection and interpretation, and writing.

Declaration of interests

We declare no competing interests.

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