



The history of pertussis: from an ancient scourge to a contemporary health burden

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Summary

The present article offers a historical overview on pertussis (whooping cough) by analysing the ancient epidemic manifestations of the disease and the path towards the discovery of an effective vaccine against it. The original mentions of pertussis are examined with reference to Mediaeval Afghanistan and the

famous AD 1578 Paris epidemic described by the French physician Guillaume de Baillou. The historical data are then matched with information derived from analyses of phylogenetic trees of B. pertussis. Finally, this article also highlights some recent challenges posed to public health by this infectious disease.

Introduction: cough from a physiological reflex to an excessive pathological manifestation

Coughing is one of the most common acts in everyday life. Sometimes it is a matter of little fits, other times of somewhat more bursting accesses, the latter being of interest for clinical medicine and research. Cough involves a highly complex reflex arc, that is an automatic response of the nervous system to a stimulus, namely the stimulation of peripheral sensory fibers that act as cough receptors. This reflex allows for the clearance of the respiratory airways from an obstruction that makes breathing difficult, such as when a food bolus does not enter, as it should, the oesophagus, or in the presence of irritants or excess mucus. This physiologic response, characterised by a coordinated mechanism of vigorous inhalation followed by sudden exhalation with closure of the glottis, *i.e.* the space between the vocal cords and the larynx, and elevation of the soft palate, is mostly an involuntary phenomenon, but it can also be intentional. Moreover, conspicuous differences have been noted between the male and female sexes in the cough reflex [1-3].

With reference to paediatric medicine, the cough reflex is, therefore, a very useful neural pathway for humans in that it is capable of saving children's lives by enabling them to expel foreign bodies that their tender age and unconsciousness have not restrained them from swallowing, almost as a primary cognitive experience and exploration of the world they are beginning to discover, and thus not to suffocate. Like all physiological phenomena of the human organism, however, even a natural response can, if excessive or otherwise very vigorous, prove harassing. This represents the focus

of the pathophysiological studies on the role and mechanisms of coughing in clinical conditions such as infectious diseases, both acute and chronic in their presentation. Indeed, a decidedly exuberant form of cough is that which occurs in pertussis (from the Latin *per-tussis*, per = much, excessive + tussis = cough), also known in English as “whooping cough”, which is an infectious disease that mainly affects children from a few months of age to six years of age (without sparing adolescents and adults), extremely contagious and with a marked epidemic nature, caused by the Gram-negative aerobic coccobacillus *Bordetella pertussis*.

This pathogen produces toxins capable of altering the function of the cilia of the superficial layer of the respiratory tract. These are long, thin organelles that by their movement propel mucus from the lungs to the mouth, also removing bacteria. Once the mechanism is compromised, bacteria are free to reach lung tissue. The disease usually begins as a common cold and with other entirely nonspecific symptoms and low fever, which would by no means suggest a particularly noxious condition, and then alternates with a phase of great catarrh production what in clinical jargon is called the paroxysmal stage, that is, the characteristic phase of the disease, the moment when a series of repetitive coughs are experienced and are followed by an inspiratory whoop. In the most severe cases there can be severe bronchopneumonia, haemorrhage, with obvious neurological damage in the event that the coughing acts lead to a protracted interruption of breathing and poor oxygen supply to the brain (hypoxia). If one is lucky enough to survive the disease, immunity is obtained, but it does not last forever, and the risk of reinfection cannot be ruled out. There appears to be today a trend of trivialisation of the danger posed by a disease such as

whooping cough, superficially arguing that it is a low-risk disease or that we have antibiotics with which to treat it anyway, so vaccinations would be useless (or even risky according to well-noted antivaccination campaigns). Nothing could be falser than such an assumption. First of all, pertussis is an extremely dangerous disease with a high lethality rate with World Health Organization (WHO) statistics clearly indicating that in 2008 there were 195,000 deaths of children worldwide, particularly in developing countries [7]. Secondly, as for all infectious vaccine-preventable diseases, that is, when it is possible to prevent upstream the onset of a disease, it is simply unreasonable to allow it to occur and decide to intervene only when observable symptoms and lesions are present. Indeed, the golden rule of medicine should be prevention [8].

The palaeopathology of pertussis

Reconstructing the history and evolution of pertussis is by no means simple, since its origins seem to be lost in the mists of time. Highly refined molecular studies that followed the sequencing of the complete genome of its aetiological agent, *B. pertussis*, in 2003 suggested the possibility that the bacterium is truly very ancient, dating back as far as about 2.5 million years ago, thus it may have closely accompanied the journey of the human species from its dawn. Subsequent research aimed at reconstructing the overall phylogenetic tree of the bacterium has shown how its two branches derived their origin from a common ancestor about 2,000 years ago. It is very interesting to note that one of those branches, which collects in itself 98% of all strains of the bacterium, have made its way very rapidly within the human population only in the last five hundred years of our history. This seems to support the available historical evidence [9].

As a matter of fact, although in his *Naturalis Historia* Pliny the Elder (AD 23-79) mentions a pernicious cough (*Perniciosa tussis*) that has led some medical historians, especially Penso, to think of pertussis, there is, however, no firm evidence of the existence of the disease in the ancient world [10].

Equally deficient, especially in terms of the epidemiology and symptoms of the disease described, is the evidence for two more recent epidemics, a late mediaeval one in Paris in 1414 and one in the Early Modern Age in London in 1540, while some possible allusions to pertussis have been identified in the literatures of 14th-century Korea and early 16th-century India [9].

The first ascertained epidemic of pertussis undoubtedly occurred in Europe, in Paris, in the late summer of 1578. Accurately describing it was Guillaume de Baillou (1538-1616, Fig. 1), in his work *Epidemia et Ephemerides*, first published only posthumously in 1635 [11].

The brilliant Parisian physician noted how he was unaware of any such pathological cases in the medical literature available at the time and renamed it quinta

or quintana. This much peculiar name seems to derive alternately either from the characteristic noise emitted during the coughing act (thus it would represent an onomatopoeia, a word that traces a sound or noise) or from the fact that the paroxysms of the cough recurred with maximum intensity at four – or five-hour intervals. De Baillou also made the important epidemiological observation that the disease preferentially affected children between 4 and 10 years of age, but also those of frailer constitution, only a few months old [11, 12]. The picture of the disease given by the French doctor proves as vivid as it is terrifying and leaves no room for imagination:

Huius gravia sunt symptomata. Pulmo ita irritatur, ut omni contentione nitens excutere id quod molestum est, nec admittat spiritum, nec vicissim facile reddat. Intumescere videtur, et quasi strangulabundus aeger mediis faucibus haerentes spiritus habet [12].

Its [*i.e.*, the disease's] symptoms are severe. The lung is so irritated that, at every attempt to expel the cause of his distress, he can neither inhale nor exhale. The sufferer seems to swell up and, as if about to strangle himself, holds his breath (translation by the authors).

Despite these brilliant epidemiological and symptomatological observations, de Baillou was unable

Fig. 1. Guillaume de Baillou. Image in the public domain from: <http://psychiatrie.histoire.free.fr/pers/bio/baillou.htm>.



to understand the mechanism by which the disease manifested itself, nor, more importantly, its cause. He can hardly be blamed for this: just as in the case of another keen observer of pathological phenomena, this time a Mediaeval one, Giovanni Boccaccio (1313-1375), who, short of an accurate clinical description of the plague that ravaged Florence in 1348, was forced to pause helplessly before the mystery of nature, at that time still an absolute ruler over the human condition [13]. The pathophysiological interpretations of the time were, in fact, still strongly influenced by the humoral doctrines of the classical Hippocratic-Galenic school, and the new medical science, based on anatomico-clinical correlations and the Galilean scientific method, had yet to see the light of day. What is more, germ theory, with its leading proponents Koch and Pasteur, would have to wait until the second half of the 19th century, a little over 150 years ago in good measure, to establish itself, supplanting outdated schemes and erroneous reasoning. In light of this backwardness of the medical art, it is hardly surprising that de Baillou thought that the origin of this explosive cough should be sought in the matter of the lung itself and interpreted through the lens of humoral pathology.

For a long time, de Baillou's description was considered the first historical account of a pertussis epidemic. Nonetheless, the recent historical-medical review of Persian medical literature has, however, shown that prior to the Paris epidemic of 1578, more epidemics occurred with all the clinical features of whooping cough. The author of these reports is the Persian physician Mohammad Hussain Nurbakhshi, otherwise

known as Bahā'al-Dawlah Razi (1455-1509, Fig. 2), who summarised them in his work *Summary of Medical Experiences* (finished in 1501) [14].

At an unspecified date, but almost certainly between 1484 and 1495, two violent epidemics occurred in Herat, in modern-day Afghanistan, spaced a few months apart. In addition to the typical symptoms of whooping cough, a very interesting fact to consider is that both infants and adults fell ill during the first epidemic [15]. This allows us to understand that at the time of the first epidemic the population could not have developed any immunity, having not come into contact with the pathogen. During the second epidemic, another equally interesting aspect occurred: far fewer people died. Razi attributed the cause of this reduction in the lethality of the disease to the use of ginger as a therapy, however, our modern knowledge firmly allows us to look at this phenomenon in terms of the development of an immune response. It is, therefore, not difficult to understand that it was mainly the infants, who lacked immunity, who suffered in this second epidemic wave [15].

Five hundred years after the Herat epidemics, the principle remains most valid. Giving an infant as soon as possible the opportunity to develop the antibodies necessary to defend against whooping cough is a duty and a responsibility to the overall health of our home communities. While the dates of the Herat epidemics are uncertain, unquestioned is the date of a third major epidemic, that occurred in Rey (in the heart of Iran, not far from Tehran), dating back to 1501. Razi himself provides a further accurate description of the symptomatology of whooping cough and, for the first time in the history of medicine and about a century before de Baillou, understands how the main route of contagion was by air. As lucidly noted by Aslanabadi and colleagues in their study [15], Herat and Rey are roughly 1,000 km apart and were both located along the Silk Road, the route along which trade and cultural exchange between East and West took place. Although definitive evidence is lacking and historical research is still thoroughly investigating these aspects, it is reasonable to think that the descriptions by Razi, chronologically compatible with recent genetic data, testify to the pathogen's transition from a nonepidemic to an epidemic phase. Moreover, the communication routes between East and West allow us to assume that pertussis reached Europe, with its previously mentioned first epidemic manifestation in France, precisely from Asia. One should never make the mistake of thinking that it is only armies, trade goods, fleets and ideas that move from one world to another. Pathogens are, indeed, seasoned travellers.

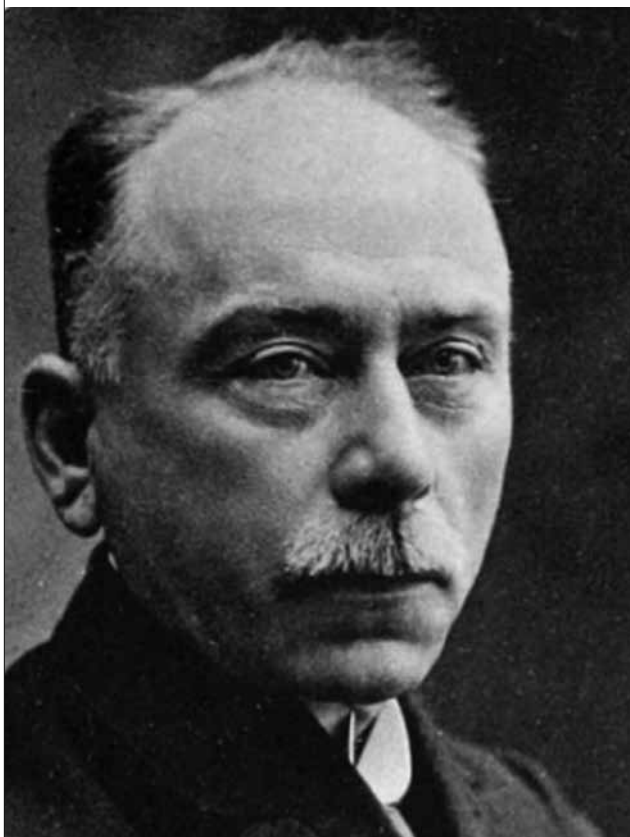
From the past to the future: the return of pertussis

While the origins of pertussis remain, as described above, uncertain, there is absolutely no question that the disease took to reaping victims at an ever-increasing rate.

Fig. 2. Bahā'al-Dawlah Razi, original image from: <https://www.mizajresearch.com/history-of-medicine/baha-al-dawlah-razi/>.



Fig. 3. The Belgian microbiologist Jules Bordet. From Wikimedia Commons, https://en.wikipedia.org/wiki/Jules_Bordet#/media/File:Jules_Bordet_signed.jpg.



Suffice it to consider that still between 1926 and 1930 as many as 33,013 deaths were recorded in the United States of America. The time for a breakthrough was, however, ripe. In 1906 Jules Bordet (1870-1961, Fig. 3) and Octave Gengou (1875-1957, Fig. 4) identified the pathogen, which ended up being named after the former of the two (*Bordetella pertussis*) [16].

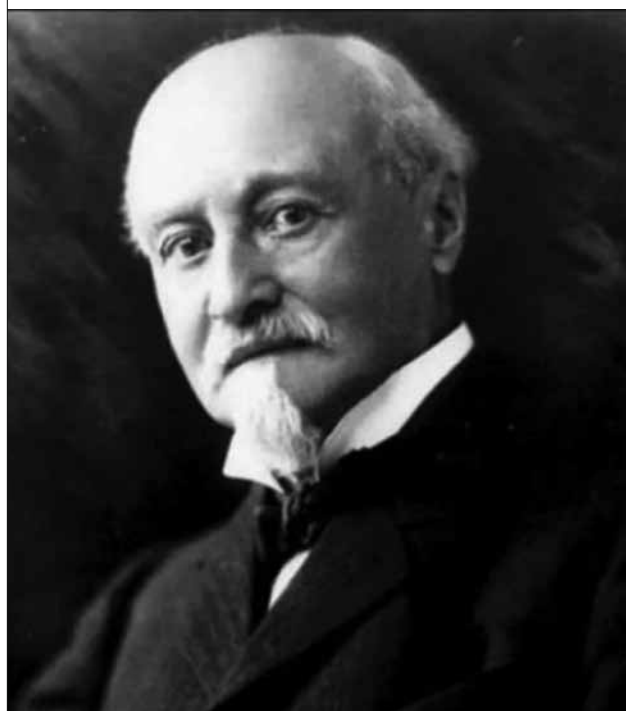
The same researchers are credited with initiating the description of the bacterium's toxins. Then, in the 1930s, whole-cell vaccines were developed in the United States, the large-scale use of which enabled a 157-fold reduction in the incidence of pertussis by 1970 [16]. This was a very hard blow dealt by science to this dangerous enemy of health, especially of children, ready to be "driven back" into the pre-vaccine world from which it had come. In the following years, to solve the problem of adverse reactions observed with the whole-cell vaccine, a new type of vaccine was developed, known as acellular, that is, containing purified components of *B. pertussis*, for example, inactivated toxins of the bacterium. The use of these pertussis vaccinations has resulted in a huge reduction in pertussis mortality, so much so that the WHO estimates that in 2008 the use of vaccinations prevented about 687,000 deaths [17]. Additionally, vaccination in pregnant women also proved effective in preventive pertussis in newborns, especially when performed during the second or early third trimester of pregnancy [18].

Such great achievements, however, should not make science relax. The eradication of the pathogen is a very difficult goal to achieve, not only because of the stubbornness of those who persist in refusing vaccination, but also because of the mutations that occur over time in the genetic makeup of the bacterium. Numerous authors have spoken, causing some alarm, of a "return of pertussis" in recent years. Others, such as J.D. Cherry, however, urge against catastrophic tones [9, 19]. What is certain is that new cases of whooping cough are continually being recorded; in particular, a recent Italian study highlighted the increase in prevalence in Apulia [20]. Finally, recent research highlights how receipt of pertussis vaccine grants short-term protection against pertussis but this status wanes quite rapidly with the acellular pertussis vaccine [21].

Conclusions

To this date the antiquity of pertussis can be confidently estimated to be of around 500 years based on historical sources and phylogenetic trees. Much older strains of the bacterium and potential epidemics cannot be confirmed only based on literary sources and only new biomolecular analyses on ancient human remains could add more light on that. *Bordetella pertussis* remains an insidious pathogen still claiming thousands of victims, while administration of vaccines and long-term efficacy of certain vaccine types remain a key question for public health.

Fig. 4. The Belgian microbiologist Octave Gengou. From <https://alchetron.com/Octave-Gengou>.



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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

FMG: designed the study; FMG conceived the study; FMG drafted the manuscript; EV and MM critically revised the manuscript; FMG, EV and MM performed a search of the literature; furthermore: EV, FMG, MM: methodology; EV and MM: validation and data curation; FMG, EV, MM: formal analysis; EV, MM: final editing; MM: supervision. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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