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Atypical pneumonia—time to breathe new life into a useful term?

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The term atypical pneumonia was originally used to describe an unusual presentation of pneumonia. It is now more widely used in reference to either pneumonia caused by a relatively common group of pathogens, or to a distinct clinical syndrome the existence of which is difficult to demonstrate. As such, the use of atypical pneumonia is often inaccurate, potentially confusing, and of dubious scientific merit. We need to return to the original meaning of atypical pneumonia and restrict its use to describe pneumonia that is truly unusual in clinical presentation, epidemiology, or both.

Introduction

The term atypical pneumonia has become well-established in medical parlance. Originally used to describe an unusual presentation of pneumonia, the term has since evolved to become much broader in meaning. Atypical pneumonia is now more widely used in reference to either pneumonia caused by a relatively common group of pathogens (*Mycoplasma pneumoniae*, *Legionella* spp, and *Chlamydophila pneumoniae*), or to a distinct clinical syndrome the existence of which is difficult to demonstrate. As such, the term atypical pneumonia as most widely used today is often inaccurate, potentially confusing, of dubious scientific merit, and unhelpful.

In this Personal View we review the history and evolution of the term atypical pneumonia. We encourage a return to the original meaning: pneumonia that has truly unusual clinical or epidemiological characteristics, or both, that warrants further investigation or public health response. This restricted definition of atypical pneumonia has both clearer meaning and purpose.

History

The first reference to atypical pneumonia is unknown, although the term was clearly developed at a time when knowledge of the microbial causes of pneumonia extended little beyond the pneumococcus (*Streptococcus pneumoniae*) and the tubercule bacillus (*Mycobacterium tuberculosis*). Medical writings from the late 19th century make no specific mention of this syndrome,[1–4] but there are several references to the term in subsequent decades. Although a 1938 paper by Hobart Reimann,[5] a Philadelphia physician, clearly popularised the concept (figure), many others had made reference to atypical pneumonia in earlier years. Nothnagel's Encylopedia of Practical Medicine[6] from 1903 refers to cases of atypical pneumonia. In 1910, the *British Medical Journal* reported that Sir John Broadbent[7] read a paper on atypical pneumonia to the Medical Society of London, and Thomas Oliver[8] made a passing reference to atypical pneumonias in his lecture to the York Medical Society. In 1911, Jay Perkins[9] devoted a whole article to the topic. He defined atypical pneumonia as those cases of pneumonia for which a specific causative organism was unknown, and noted the variable features and irregular clinical course of this disease. Thomas Hastings and Walter Niles[10] in their 1911 paper on sputum bacteriology, Percy Kidd[11] in his 1912 Lumleian lectures to the Royal College of Physicians of London, and Ernest Glynn[12] in his 1913 description of epidemic pneumonia use the term to refer to a diverse group of pneumonias that differ from the ordinary. In the 1920s and 1930s, atypical pneumonia had become a more accepted term and appeared in a several reports of unusual pneumonia syndromes.[13–18]

Common to these early, often independent, references to atypical pneumonia are descriptions of cases of pneumonia that differed in some manner from typical lobar pneumonia caused by the pneumococcus. These were simply descriptions of unusual presentations of a common disease and there was no attempt to describe a unifying atypical pneumonia syndrome. Indeed, Perkins, in his 1911 paper, made the comment that "in time, I believe, improved methods of diagnosis will remove many of these cases from the category of atypical pneumonia".

In the 1940s, atypical pneumonia became more defined as a distinct clinical entity. Primary atypical pneumonia syndrome was commonly described as "characteristically gradual in onset, with constitutional as well as respiratory symptoms, and pulmonary changes more manifest in roentgenograms than by physical examination. The course of illness varies considerably in duration and severity. Complications are uncommon and although convalescence is frequently protracted the illness almost invariably terminates with complete recovery."[19] Others further refined the description by noting the ineffectiveness of sulphonamide or penicillin therapy and the lack of laboratory evidence for infection with pneumococcus or other known pathogens.

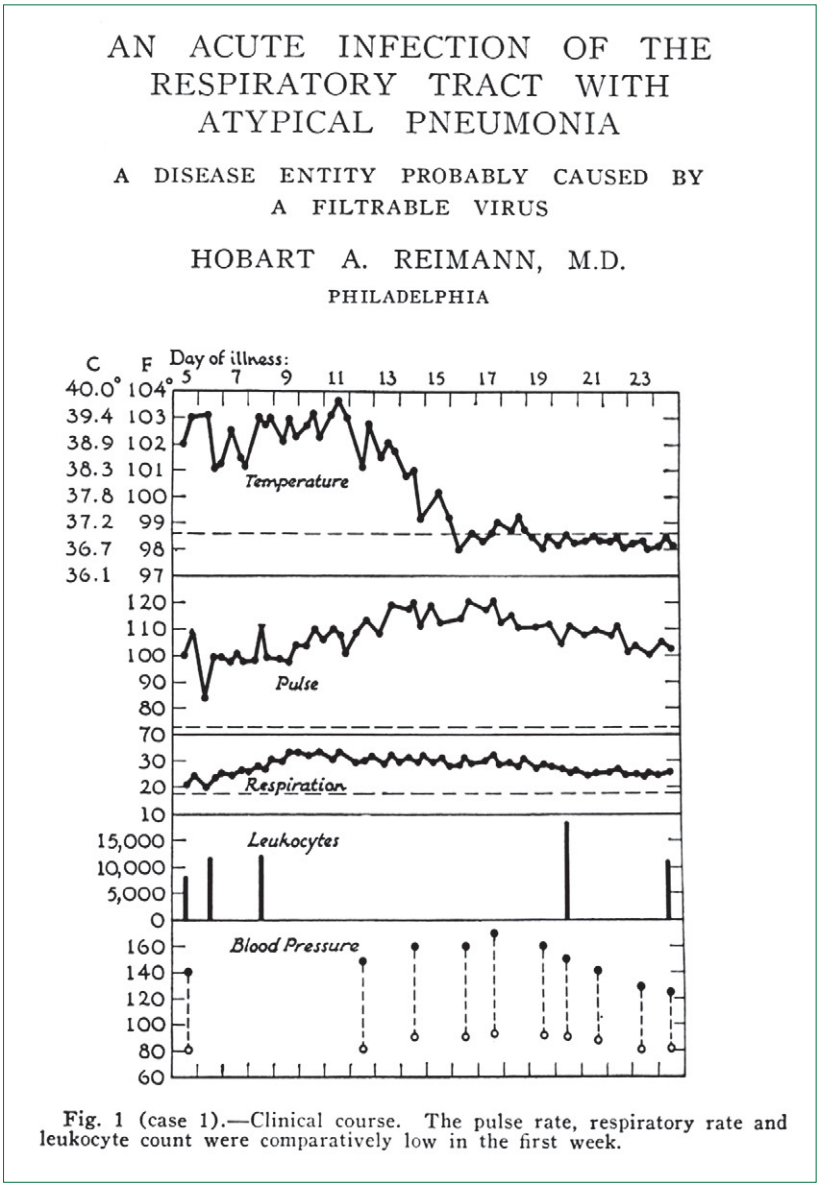
Atypical pneumonia was the subject of intense study during World War 2, especially by the US military. During periods of the 1940s, atypical pneumonia was reported as being almost continuously present in the large army post at Fort Bragg, NC, USA.[20] There was a high incidence among new recruits, with the first 4 weeks of army life being particularly noted for increased susceptibility to respiratory diseases. Outbreaks of atypical pneumonia were also described among military personnel from other regions of the world.[21–24] Clinicians recognised that atypical

pneumonia had diverse causes rather than a single cause. However, there were many descriptions of clusters of atypical pneumonia syndrome among military recruits. Each cluster probably represented an outbreak caused by a single pathogen, and many were likely to have been due to *M pneumoniae*. Indeed, this was confirmed by retrospective testing of stored sera from some patients with primary atypical pneumonia from Fort Bragg.[25] Descriptions of these outbreaks gave credence to the concept of a distinct atypical pneumonia syndrome and the vigorous adoption of the term by some authorities.[20,26,27]

Other studies of atypical pneumonia in more diverse populations with sporadic disease reported a more varied clinical picture, presumably reflecting the presence of various causative agents. One such study[19] at the Hospital of The Rockefeller Institute, NY, USA, during 1942–44 described 106 patients diagnosed with primary atypical pneumonia. Pneumococci were isolated from half of these patients, mostly by inoculation of sputum into mice. However, a few patients had pneumococci detected in their sputum by direct examination with the quellung technique, and no patient had a positive blood culture. Of the pneumococcal isolates, none belonged to serotypes 1 or 2 that were most commonly associated at the time with lobar pneumonia and severe disease. Many patients might have had pneumococcal pneumonia, perhaps due to pneumococcal strains less strongly associated with severe disease.

Through the second half of the 20th century, several newly described microorganisms were identified as causes of the atypical pneumonia syndrome. In 1944, Eaton and colleagues[28] described a filterable agent from patients with pneumonia that could be transmitted to rodents. First thought to be a virus, the Eaton agent was eventually recognised as a mycoplasma and named *M pneumoniae*.[29] This organism is now regarded as the archetypal agent of atypical pneumonia. Although psittacosis (now known to be caused by *Chlamydophila psittaci*) was first described in 1880[30] and was well-recognised by the 1930s,[31–33] pneumonia caused by *Chlamydophila pneumoniae* was first recognised much later. Originally referred to as the TWAR strain, *C pneumoniae* became recognised as a cause of pneumonia in the 1980s[34–37] and was designated as a new species in 1989.[38] An outbreak of pneumonia among delegates to an American Legion convention in Philadelphia, PA, USA, in 1976 first brought legionnaires' disease to the world's attention.[39,40] Subsequently, *Legionella* spp were recognised as important causes of both sporadic and epidemic pneumonia around the world.

As time has gone on, emphasis has shifted away from the syndromic definition of atypical pneumonia to that of pneumonia caused by specific microorganisms (the atypical pneumonia pathogens or, simply, the atypicals). To further complicate matters, no clear definition exists of exactly which microorganisms are the so-called atypical


AN ACUTE INFECTION OF THE RESPIRATORY TRACT WITH ATYPICAL PNEUMONIA

A DISEASE ENTITY PROBABLY CAUSED BY A FILTRABLE VIRUS

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Fig. 1 (case 1).—Clinical course. The pulse rate, respiratory rate and leukocyte count were comparatively low in the first week.

Figure: **Title and figure from Reimann's 1938 paper on atypical pneumonia**
The graph shows the clinical course of a patient with atypical pneumonia. Reproduced from with permission from the American Medical Association.[9]

pneumonia pathogens. Some lists are extensive, and include most non-pneumococcal pathogens associated with pneumonia, including respiratory viruses and agents of bioterrorism.[41–43] However, for many clinicians today, the atypical pneumonia pathogens comprise only *M pneumoniae*, *Legionella* spp, *C pneumoniae*, and, occasionally, *C psittaci*. More than any other pathogens, these organisms have become firmly linked to the concept of atypical pneumonia. A review of publications on PubMed from the past 10 years (January, 1999, to January, 2009) that have "atypical pneumonia" in their titles, abstracts, or both, showed that 90 (30%) of 302 focused specifically on severe acute respiratory syndrome

	Year	Sample size	Prevalence (%)		
			M pneumoniae	*C pneumoniae*	*Legionella* spp
Asia					
Japan[53]	1998–2000	200	9·5	7·5	1
Thailand[54]	1998–2001	98	6·8	16·3	5·4
South Korea[55]	1999–2000	81	8·6	12·3	0
Thailand[56]	2001–02	292	14	3·4	2·1
China, Hong Kong, South Korea, Taiwan, Thailand, Malaysia, Singapore, Indonesia[57]	2001–02	1756	12·2	4·7	6·6
Taiwan[58]	2001–02	168	14·3	7·1	1·2
South Korea[59]	2001–02	126	6·3	7·1	2·4
South Korea, China, Taiwan, Hong Kong, India, Singapore, Vietnam, Philippines[60]	2002–04	955	11	13·4	1·1
Europe					
Netherlands[61]	1991–93	334	6	3	2
Spain[62]	1996–97	395	2·3	2·3	3·5
Slovenia[63]	1996–97	211	5·7	18·0	2·8
Switzerland[64]	1997–99	318	7·5	2·5	5·3
UK[65]	1998–99	267	3	13	3
Spain[66]	1999–2001	493	7·7	3·0	4·3
North America					
USA[51]	1986–87	359	2·0	6·1	6·7
USA[67]	1991	2776	32·5	8·9	3·0
Canada[68]	1991–94	149	22·8	10·7	0·7
South America					
Argentina[69]	1997–98	343	5·5	3·5	1·2
Chile[70]	2000–01	200	3·4	16·9	5·1
Chile[71]	2003–05	176	2·8	3·4	2·3
Africa					
South Africa[72]	1987–88	113	1·1	20·7	8·7
Kenya[73]	1994–96	281	2·5	0	0
Australasia					
New Zealand[74]	1992–93	255	16·1	3·1	10·6
New Zealand[75]	1999–2000	474	2·7	0·6	4·0
Australia[76]	2004–06	885	8·8	1·2	3·4
Worldwide[77]	2001–06	4337	12	7	5

Table: **Prevalence of *M pneumoniae*, *C pneumoniae*, and *Legionella* spp in studies of adult community-acquired pneumonia**

(SARS), 79 of 302 (26%) used this term to refer to pneumonia caused by *M pneumoniae*, *Legionella* spp, and *Chlamydophila* spp only, and the remainder used the term in reference to a non-specific atypical pneumonia syndrome. An additional 187 articles over the same period referred to "atypical pathogens", usually in reference to *M pneumoniae*, *Legionella* spp, and *Chlamydophila* spp only.

Throughout its history, the use of the term atypical pneumonia has not been uniformly accepted and has even been actively discouraged by several authors. Even Reimann,[44-47] whose 1938 article popularised the adjective atypical, consistently substituted "viral" for "atypical" in subsequent years, because he believed the former was more accurate. J D Adamson and R E Beamish[48] in 1947 deplored reference to atypical pneumonia, and highlighted the protean nature of the syndrome. They also suggested how primary atypical pneumonia could be further divided into nine subclassifications: common cold pneumonitis, influenzal pneumonitis, contamination pneumonitis, exacerbation pneumonitis, atelectatic pneumonitis, allergic pneumonitis, pneumonitis due to known viruses and rickettsias, pneumonitis due to unknown viruses, and miscellaneous. In the early 1950s, S P Bedson[49] and Philip Robertson and Forgan Morle[50] emphasised the inconsistent clinical picture and diverse causes as reasons to discourage use of the term. The latter authors went as far as to state that they "wish to dispel much of the mysticism associated with this group of conditions and to destroy the concept of atypical pneumonia as at present described".[50] Unable to distinguish atypical from typical pneumonia on the basis of clinical or radiographic features in the late 1980s, Guo-Dong Fang and colleagues[51] believed that the usefulness of this classification had been rendered obsolete, and recommended abandoning the term atypical pneumonia and focusing instead on the specific cause. More recently, George Sarosi[52] submitted in a monograph dedicated to this topic that atypical pneumonia "has no meaning in current medical practice and that we should get rid of it".

How common is atypical pneumonia?

With the common aetiological definition of the term (ie, pneumonia caused by *M pneumoniae*, *Legionella* spp, or *C pneumoniae*), there is little reason to classify atypical pneumonia as unusual or abnormal. As such, the adjective atypical is inappropriate and inaccurate. *M pneumoniae*, *Legionella* spp, and *C pneumoniae* are not uncommon causes of community-acquired pneumonia in adults. The table shows the prevalence of infection with these bacteria from some recent studies of community-acquired pneumonia in adults from locations around the world. Even though comparison of the findings of the studies is hampered by differences in entry criteria and diagnostic testing, infection with these organisms clearly represents a substantial burden of disease. This is even more evident when you consider that the causative organism was not identified in 19–63% of patients in these studies. For many of these studies, the so-called atypical pathogens were the most common causes after *S pneumoniae*.

As diagnostics improve, we are likely to gain a better knowledge of the burden of the various pneumonia pathogens. With use of nucleic acid detection methods we now have a better appreciation of the importance of viruses in both adult and childhood pneumonia.[78] Respiratory viruses (panel), often thought of as causes of atypical pneumonia syndrome, can be detected in about one-third of adults[79] and in over a half of children[80–84] admitted with community-acquired pneumonia. The situation is complicated further by the common finding

of mixed infections with viruses and bacteria[79,85,86] and the abundance of evidence supporting an interaction between respiratory viruses and bacteria in the pathogenesis of pneumonia.[87] As a result, defining atypical pneumonia by type of pathogen alone is problematic.

Does an atypical pneumonia syndrome exist?

Some epidemiological and clinical features are more strongly associated with specific causes of pneumonia. For example, mycoplasma pneumonia is commonly associated with young adults, headache, and epidemics.[88] However, there is substantial overlap of epidemiological, clinical, laboratory, and radiographic features between pneumonia caused by the so-called atypical pathogens and pneumonia due to other microorganisms.[89–97] The similarities are more notable than the differences and have become increasingly evident over time, as we recognise that the features of each infection are broader than was once thought. Although some clinicians believe that pneumonia caused by the so-called atypical pathogens as a group can be reliably differentiated clinically from pneumonia caused by other microorganisms, largely by supposed characteristic patterns of extrapulmonary involvement with the former,[98,99] this view is an oversimplification and is unsubstantiated. These claims need to be supported by evidence.

The Japanese Respiratory Society has written guidelines for the management of community-acquired pneumonia[100,101] that include a protocol for identification of atypical pneumonia. The original algorithm incorporated nine different variables that were refined in 2005 to six variables: patient older than 60 years, no or minor underlying diseases, persistent cough, limited chest auscultatory findings, no sputum or no identified causative organism by rapid diagnosis, and peripheral white-cell count of fewer than 10 000 cells per μL.[100] This protocol was designed to focus on the identification of mycoplasma and chlamydia pneumonia, as there is a low incidence of documented legionella pneumonia in Japan. Therefore, the finding that the protocols are sensitive and reasonably specific for detecting mycoplasma pneumonia is unsurprising.[100,101] The protocol performed poorly for mixed infections[101] and has not been assessed for the detection of legionnaires' disease. It would be more correct to refer to these as protocols for distinguishing mycoplasma pneumonia, rather than for atypical pneumonia.

The clinical differentiation of legionnaires' disease from other pneumonias has received particular attention given the disease's public health importance and the limitations of current diagnostic tests for legionellosis.[102] Although some presenting features might help with the recognition of legionnaires' disease, a reliable algorithm with adequate sensitivity and specificity is hard to devise.[90,103] Cunha[99] devised a weighted point scale system for diagnosing legionnaires' disease at the Winthrop-University Hospital. Despite being widely promoted, the system has yet to be rigorously assessed in a prospective study. The only published assessment of the system[104] used case–control study methods to compare 37 patients with legionnaires' disease with 31 adults with bacteraemic pneumococcal pneumonia, and incorrectly attempted to estimate predictive values that cannot be calculated with this study design. The sensitivity was 78–87% for detecting legionella pneumonia, but the specificity was only 50–65%. There are many problems with this type of study. The use of highly selected comparators (bacteraemic pneumococcal pneumonia in this situation), and the failure to account for pneumonia caused by several pathogens or no identifiable pathogen, makes it difficult to interpret these findings in clinical practice.

As a minimum, any diagnostic algorithm for atypical pneumonia should be tested prospectively on an unselected sizeable population of adults with community-acquired pneumonia, although there will still be difficulties interpreting results in view of the large proportion of patients (usually greater than 50%) for whom no pathogen can be identified. A randomised trial comparing an algorithm with existing clinical practice would help to determine whether differences exist in clinical outcomes and antimicrobial use. Furthermore, the robustness of any algorithm should be tested in various different geographical locations.

Panel: Viral pathogens associated with pneumonia

- Influenza A and B viruses
- Respiratory syncytial virus
- Parainfluenzaviruses 1–4
- Adenoviruses
- Human metapneumovirus
- Rhinoviruses
- Coronaviruses (including 229E, OC43, NL63, HKU1, and severe acute respiratory syndrome)
- Measles virus
- Enteroviruses
- Hantaviruses
- Bocavirus

Atypical pneumonia and antimicrobial therapy

A substantial amount of recent published work on empirical antimicrobial therapy for community-acquired pneumonia has focused on "atypical coverage"—ie, the inclusion of antimicrobials (usually macrolides or fluoroquinolones) with activity against *M pneumoniae*, *C pneumoniae*, and *Legionella* spp.[105–108] These pathogens are all resistant to β-lactam antibiotics, the class of antibiotic most commonly used as empirical treatment for pneumonia, and the importance of atypical coverage features prominently in guidelines for the management of community-acquired pneumonia.[109–111] Whereas this term might serve as a reminder that some major

pneumonia pathogens are resistant to β-lactams, this is hardly justification for the continued use of an inaccurate term. Perhaps more importantly, reference to atypical coverage assumes that any perceived benefit of this therapy is because of treatment of atypical pathogens, despite the lack of microbiological evidence to support this concept. This obscures the fact that benefits might result from the antibiotics themselves rather than the involvement of specific pneumonia pathogens.[112,113] Recent data from a mouse study suggest that improved outcomes for pneumonia treated with protein synthesis inhibitors over pneumonia treated with β-lactams might be related to suppression of the inflammatory response.[114]

The problems in the use of the adjective atypical are illustrated by the various guidelines on management of community-acquired pneumonia published in Europe and North America.[109–111] There is general agreement that the term "atypical pneumonia" has outgrown its historical usefulness and its use is not recommended because "it implies, incorrectly, a distinctive clinical pattern".[110] However, the term "atypical pathogens" is retained by the British Thoracic Society for infections caused by *M pneumoniae*, *C pneumoniae*, *C psittaci*, and *Coxiella burnetii*, but not *Legionella* spp or viruses, since those included are "difficult to diagnose early in the illness and are sensitive to antibiotics other than β-lactams such as macrolides, tetracyclines, or fluoroquinolones".[110] The European guidelines seem to use the term "atypical pathogens" to include *Mycoplasma* spp, *Chlamydia* spp, *Legionella* spp, and *Bordetella pertussis*,[111] and The Infectious Diseases Society of America (IDSA)–American Thoracic Society (ATS) guideline uses the term for organisms that are "not detectable on Gram stain or cultivatable on standard bacteriological media, including *M pneumoniae, C pneumoniae, Legionella* spp, and respiratory viruses", and then expands on the nature of the relevant respiratory viruses.[109] The problems of definition reappear in treatment sections of guidelines. For example, the IDSA–ATS guidelines refer to macrolides as treatment for atypical organisms, but this class of antibiotic obviously has no activity against viruses. Nevertheless, the British Thoracic Society guidelines conclude that the term "atypical pathogens" remains useful to clinicians in guiding discussion about infectious cause and management of community-acquired pneumonia.[110] As a consequence the adjective atypical, for which there is no agreed definition, is retained and remains linked to pneumonia by association tending to perpetuate the notion of atypical pneumonia.

Conclusions

As most commonly used today, atypical pneumonia is a tired, inaccurate, and confusing term. Should we abolish the term altogether as some have suggested? We believe that the original description of atypical pneumonia as an unusual entity is potentially helpful and has clear meaning and purpose. Therefore, we should restrict its use to describe pneumonia that is truly out of the ordinary in clinical presentation and epidemiology. The recognition of new and unusual forms of pneumonia can have immense public health importance, and recent history provides many such examples. The outbreak of pneumonia at the Legionnaires' convention in Philadelphia in 1976 could rightly be described as atypical at the time.[39] The cluster of cases of pneumocystis pneumonia in San Francisco, USA, in 1981 was a key event in the recognition of HIV infection and, once recognised, became a sentinel diagnosis for AIDS.[115,116] The rapid response to the SARS outbreak in 2003 followed the early recognition of an unusual respiratory disease;[117–119] SARS is an excellent recent example of a genuine atypical pneumonia. In each case the recognition of an atypical type of pneumonia by clinicians led to important discoveries, intensive efforts to determine the pathogen, and public health responses.

We should stop referring to *M pneumoniae*, *C pneumoniae*, and *Legionella* spp as atypical pathogens. These are common pneumonia pathogens that have their own characteristic features, and we should cease trying to convince ourselves that unrelated pathogens cause a unified and distinct pneumonia syndrome. We should recognise that the term atypical pathogen has provided a useful shorthand for a diagnostic approach based on Gram stains and culture on agar plates, but this does not justify its continued use when diagnostic techniques have moved beyond these methods. The term might seem useful to clinicians for discussions on treatment and cause, but, because no agreement exists on a definition of the causative organism, this use will cause ongoing confusion. Writers of textbooks and reviews should abandon the current popular use of atypical pneumonia, which is largely still included through tradition only and refrain from using the term atypical pathogens as it lacks definition. Appropriate use would avoid some of the current confusion and misconceptions around a potentially useful term.

Contributors

DRM conceived the idea and wrote the first draft. DRM and STC contributed to the writing and revision of the paper. Both authors have seen and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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