The bacterial aetiology of adult community-acquired pneumonia in Asia: a systematic review

Leon Peto\textsuperscript{a,b}, Behzad Nadjm\textsuperscript{a,b,*}, Peter Horby\textsuperscript{a,b}, Ta Thi Dieu Ngan\textsuperscript{c}, Rogier van Doorn\textsuperscript{a,b}, Nguyen Van Kinh\textsuperscript{c} and Heiman F. L. Wertheim\textsuperscript{a,b}

\textsuperscript{a}Wellcome Trust Major Overseas Programme, Oxford University Clinical Research Unit, Hanoi and Ho Chi Minh City, Vietnam; \textsuperscript{b}Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, Oxford OX3 7LJ, UK; \textsuperscript{c}National Hospital for Tropical Diseases, Hanoi, Vietnam

\textsuperscript{*}Corresponding author: Tel: +84 4 3576 4320; Fax: +84 4 3576 4319; E-mail: bnadjm@yahoo.com

Received 16 January 2014; revised 20 March 2014; accepted 20 March 2014

\textbf{Background:} Community-acquired pneumonia (CAP) is a major cause of adult mortality in Asia. Appropriate empirical treatment depends on knowledge of the pathogens commonly responsible. However, assessing the aetiological significance of identified organisms is often difficult, particularly with sputum isolates that might represent contamination with oropharyngeal flora.

\textbf{Methods:} A systematic review of all adult CAP aetiology studies from Asia, excluding the Middle East, published in English between 1 January 1990 and 1 March 2012 was conducted. Forty-eight studies reporting on 10,423 patients were included, representing data from China, India, Indonesia, Japan, Malaysia, The Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam. Data from large parts of Asia were unavailable and there was substantial heterogeneity in methodology.

\textbf{Results:} As in western studies, \textit{Streptococcus pneumoniae}, \textit{Mycoplasma pneumoniae}, \textit{Chlamydophila pneumoniae}, \textit{Legionella} spp. and \textit{Haemophilus influenzae} were all significant pathogens. However, compared with western studies, \textit{S. pneumoniae} was of less relative importance. Gram-negative bacilli and \textit{Mycobacterium tuberculosis} were more important, and in northeast Thailand \textit{Burkholderia pseudomallei} was a major pathogen.

\textbf{Conclusion:} These data have major implications for diagnostic strategies and empirical treatment. Narrow-spectrum antibiotics targeting \textit{S. pneumoniae} may be inappropriate in many Asian settings, and agents active against TB may lead to partial response and delayed TB diagnosis.

\textbf{Keywords:} Asia, Community-acquired, Microbiology, \textit{Mycobacterium tuberculosis}, Pneumonia, \textit{Streptococcus pneumoniae}

\section*{Introduction}

\textbf{Background}

Community-acquired pneumonia (CAP) is one of the most common life-threatening infections, with most deaths occurring in developing countries.\textsuperscript{1} The main burden of disease is in children, but CAP is an important cause of mortality in adults, especially the elderly and those with chronic diseases. Antibiotic treatment of CAP is usually empirical as the causative pathogen is rarely identified, even among hospitalised patients in developed countries, and almost never in time to direct immediate treatment. Appropriate selection of empirical treatment depends on the common pathogens identified in previous aetiological studies and on relevant treatment trials. The aetiology of pneumonia is well documented in developed countries (Europe, North America, Japan, Australia), with around 10 bacterial species regularly identified as pathogens in immunocompetent patients. A review of 41 European studies found that \textit{Streptococcus pneumoniae} was by far the most common bacterial cause of CAP, followed by \textit{Mycoplasma pneumoniae}, \textit{Chlamydophila pneumoniae}, \textit{Legionella pneumophila} and \textit{Haemophilus influenzae}.\textsuperscript{2}

In Asia, CAP is estimated to cause almost one million adult deaths per year. Many of these deaths occur in the elderly, but a large number occur in those with good life expectancy, including 160,000 among those aged 15–59 years.\textsuperscript{3} However, adult CAP has been poorly studied in Asia until recently. Although differences between these recent studies and European data have been noted, there has been no systematic review of CAP aetiology in Asia.
of local aetiology is critical to making rational decisions about empirical antibiotic treatment, as differences in aetiology may result in poor response to therapy chosen to cover pathogens common in western studies. Both under-use and over-use of broad-spectrum antibiotics for an infection as common as CAP could be harmful, particularly in Asia where mortality is high, resources scarce and antibiotic resistance an increasing problem.  

The aim of this systematic review was to synthesise the results of CAP aetiology studies performed among adults in Asia, focusing on bacterial pathogens. This review includes an assessment of study methodology and highlights geographical differences in aetiology, identifying areas requiring further research.

**Identifying the aetiology of pneumonia**

Identification of the pathogens responsible for pneumonia is challenging due to difficulties obtaining direct lung samples as well as the oropharyngeal contamination of expectorant. Interpreting the results of pneumonia aetiology studies requires an understanding of the limitations thereby imposed. This has been reviewed elsewhere and is discussed briefly here.9  

Taking samples directly from the lung through transthoracic needle aspiration represents a theoretic ideal diagnostic method, with high rates of positive results. Similar high-quality results can be obtained through some bronchoscopic techniques. These procedures are often considered too invasive, with costs and risks outweighing perceived benefit. Blood culture is a common procedure in clinical practice, and bacterial growth from blood is almost certainly significant, however the rate of positive culture is typically <10%.90 Pleural effusions can be tapped safely, when they are present; however, the sensitivity of pleural fluid culture is poor.  

A higher rate of positive culture is obtained from sputum, although contamination by bacteria colonising the oropharynx makes interpreting the significance of sputum isolates difficult.11 Microscopic examination of sputum for the presence of white blood cells and epithelial cells can increase the reliability of sputum culture.12 The sensitivity of all microbiological diagnostics relying on culture of living bacteria is hampered by antibiotic use prior to sampling.  

Infection by ‘atypical’ bacteria (Mycoplasma, Chlamydia and Legionella spp.) can be retrospectively assessed through serology; Legionella spp. can also be cultured. However, PCR of respiratory specimens is increasingly used. Interpretation of serology is hampered by a lack of standardised techniques and difficulty in distinguishing between current infection and past infection without acute and convalescent samples. Interpretation of PCR is complicated by oropharyngeal contamination and incidental carriage.13,14 Urine antigen testing is widely used for two organisms: S. pneumoniae, where the test performs well in adults,15,16 and L. pneumophila, where the test is specific and much quicker than culture but lacks sensitivity, especially in less severe cases.17  

Retrospective studies of CAP face problems related to uncertainty about case definition, incomplete recording of clinical information and incomplete or poor-quality microbiological investigation. Often these studies have a focus on a particular group of pathogens and rarely employ a broad, systematic approach. Increasingly it is recognised that a control group is helpful where upper airway samples are being taken and colonisation, rather than infection, is a possibility.

**Methods**

**Search strategy and selection criteria**

To minimise bias associated with retrospective studies, only prospective studies have been included, except as discussed below. The aetiology of CAP varies with clinical setting, therefore studies were grouped into outpatient studies, hospital admissions and studies of severe CAP. These categories are also typically used to decide empirical treatment. Few prospective studies were found for severe CAP, therefore retrospective studies were included for this category.  

The search consisted of three components: 1. ‘pneumonia’ or ‘respiratory tract infection’ in the title; 2. geographical terms anywhere in the citation using names of all countries along with ‘Asia’ and MeSH terms for Central, Southeast and East Asia (Siberia and the Middle East, including Iran, were not included in the review); and 3. limits specifying a publication date after 31 December 1989 up to 1 March 2012. The title and abstract of all retrieved citations were reviewed, and the full text was retrieved if the abstract suggested the article contained data on CAP aetiology in Asia. Case reports, laboratory-based studies and studies on children or other selected subgroups of CAP patients were not reviewed.  

The reference lists of all retrieved papers were searched for additional relevant studies. Where necessary, study authors were contacted for further information, including data disaggregated by country from multinational studies. Articles were included in the quantitative review if they were published in English and 1. reported on a prospective cohort of CAP patients or a retrospective cohort of severe CAP patients; 2. had consistent investigation of aetiology and 3. included a clearly selected sample of chest radiography-confirmed CAP, without exclusions that would make the sample non-comparable with other studies. Structured data extraction was performed for all studies included in the quantitative analysis, including patient selection criteria, demographics and scheme of microbiological investigation.

**Results**

**Study selection**

In total, 3562 citations were retrieved and 114 relevant English language articles were identified after screening the title and abstract. The full text of these were reviewed, identifying a further three articles from reference searching. Of the 117 articles, 48 were included in the quantitative review and 69 were excluded, either because they contained no data or duplicate data or did not fulfill the selection criteria (Figure 1).

**Study characteristics**

The 48 articles included reports on 50 cohorts of chest radiography-confirmed CAP in 10 423 patients. Of these, four were prospective outpatient cohorts,18–21 38 were prospective inpatient cohorts20–57 and eight were cohorts of patients with severe CAP (six retrospective, and defined either as admission to intensive care unit, presence of acute respiratory distress syndrome or meeting the American Thoracic Society criteria for severe).58–65 Two large inpatient studies were multinational44,55 and for these studies data from each country were treated
separately. Study size ranged from 22 to 1193 patients, with a median of 106 enrolled patients.

Most studies specified some exclusion criteria, usually related to recent hospital admission, nursing home residence, immunosuppression, lung cancer or terminal illness. The mean age was between 50–70 years for inpatient studies and 30–50 years for outpatient studies. The median proportion of males in the studies was 58%. In most inpatient studies more than one-half of participants had some co-morbidity, the commonest being chronic respiratory disease or diabetes.

Many countries had no eligible studies, including Bangladesh, Pakistan and the whole of Central Asia, and there was minimal data from Indonesia and Vietnam (Figure 2). Five studies relied only on sputum and blood culture, five tested only for atypical pathogens and the others used a range of methods. Most studies that used sputum culture also reported using some quality criteria to improve reliability, although the criteria used were varied. No studies systematically used transthoracic needle aspiration. The frequency of antibiotic use before admission was reported in 11 studies, ranging from 20 to 64%.

Aetiology results

The results for individual studies are shown in Tables 1–3. In most studies, between 35 and 70% of participants had no pathogen identified.
| Country       | Year          | Site             | No. of patients | % Streptococcus pneumoniae | % Haemophilus influenzae | % Staphylococcus aureus | % Klebsiella pneumoniae | % Other GNB* | % Mycoplasma pneumoniae | % Chlamydophila pneumoniae | % Legionella spp. | % Viruses | % Mycobacterium tuberculosis |
|--------------|---------------|------------------|-----------------|-----------------------------|------------------------|------------------------|------------------------|--------------|------------------------|---------------------------|----------------------|-----------|----------------------------|
| Japan        | 1994–1997     | Kurashiki        | 326             | 23                          | 7                      | 2                      | 4                      | 3                        | 5                      | 3                      | 1                    | 4                    | 2^b                    |
| Japan        | 1998–2003     | Kurashiki        | 600             | 26                          | 13                     | 3                      | 2                      | 2                        | 9                      | 7                      | 2                    | 3                    |                       |
| Japan        | 1999–2000     | Multicentre      | 232             | 25                          | 19                     | 3                      | 1                      | 0                        | 5                      | 6                      | 4                    | 16                   |                       |
| Japan        | 1999–2002     | Fukuoka          | 227             | 20                          | 9                      | 7                      | 2                      | 7                        | 7                      | 4                      | 0                    | 4                    |                       |
| Japan        | 2001–2004     | Kurashiki        | 349             | 24/39^c                      | 6                      | 1                      | 1                      | 2                        | 11                     | 3                      | 1                    | 1                    | 2^b                    |
| Japan        | 2004–2006     | Nagasaki         | 88              | –/18^c                      | 16                     | 7                      | 0                      | 0                        | 5^d                    | –                      | 0                    | –                    |                       |
| Japan        | 2007–2008     | Tokyo            | 102             | 22/30^c                      | 8                      | 0                      | 2                      | 4                        | 1                      | 1                     | –                    | –                    |                       |
| Japan        | 2008–2010     | Osaka            | 170             | –/18^c                      | 4                      | 5                      | 4                      | 14                       | 9                      | 6                      | 0                    | 2^b                   |                       |
| Japan weighted average |           |                 | 1894            | 24/26^c                      | 10                     | 3                      | 2                      | 4                        | 8                      | 5                      | 1                    | 5                    |                       |
| South Korea  | 1999–2000     | Churchon         | 81              | –                           | –                      | –                      | –                      | –                        | –                      | 9                     | 12                   | 0                    |                       |
| South Korea  | 2001–2002     | Multicentre      | 126             | 13                          | 1                      | 1                      | 3                      | 10                       | 6                      | 7                      | 2                    | –                    |                       |
| South Korea  | 2002–2004     | Multicentre      | 338             | 14                          | 1                      | 1                      | 3                      | –                        | –                      | –                     | –                    | –                    |                       |
| South Korea weighted average |       |                 | 545             | 14                          | 1                      | –                      | 3                      | –                        | –                      | 7                     | 9                    | 1                    |                       |
| Taiwan       | 2001–2002     | Multicentre      | 168             | 10/24^c                      | 5                      | 2                      | 5                      | 2                        | 14                     | 7                      | 1                    | 10                   | 1^b                    |
| Taiwan       | 2001–2002     | Taipei           | 85              | –                           | –                      | –                      | –                      | –                        | –                      | 5                     | 6                    | 4                    | –                    |
| Taiwan       | 2001–2002     | Kaohsiung        | 100             | 22/26^c                      | 9                      | 1                      | 5                      | 2                        | 20                     | 13                    | 3                    | 1^b                   | 2                     |
| Taiwan weighted average |       |                 | 618             | 14/23^c                      | 5                      | 1                      | 7                      | 2                        | 14                     | 8                    | 2                    | –                    |                       |
| China        | 1988          | Hong Kong        | 90              | 9/12^e                       | 4                      | 4                      | 1                      | 3                        | 3                      | 6                    | 0                    | 6                    | 12                     |
| China        | 2001–2002     | Hong Kong        | 62              | –                           | –                      | –                      | –                      | –                        | –                      | 2                     | 3                    | 2                    | –                    |
| China        | 2001–2003     | Shanghai         | 314             | 2                            | 24                     | 2                      | 5                      | 3                        | 12                     | 5                    | 1                    | –                    |                       |
| China        | 2002–2004     | Multicentre      | 225             | 11                          | 9                      | –                      | 5                      | –                        | –                     | –                    | –                    | –                    |                       |
| China        | 2003–2004     | Multicentre      | 610             | 10                          | 9                      | 4                      | 6                      | 3                        | 21                     | 7                    | 5                    | 19^e                 |                       |
| China weighted average |       |                 | 2494            | 8/9^e                        | 9                      | 2                      | 3                      | 3                        | 11                     | 5                    | 3                    | 11                   |                       |
| Vietnam      | 2002–2004     | Ho Chi Minh      | 72              | 11                          | 11                     | –                      | 3                      | –                        | –                      | –                    | –                    | –                    |                       |
| Thailand     | 1987–1988     | Khon Kaen        | 113             | 7                            | 0                      | 6                      | 7                      | 3/17^e                   | 2                      | –                    | –                    | –                    |                       |
| Thailand     | 1998–2001     | Bangkok          | 147             | –/22^c                      | 3                      | 3                      | 10                     | 4/1^e                    | 7                      | 16                   | 5                    | –                    |                       |
| Thailand     | 2001–2002     | Bangkok          | 47              | –                            | –                      | –                      | –                      | –                        | –                      | 15                   | 9                    | 4                    | –                    |
| Thailand     | 2001–2002     | Khon Kaen        | 254             | 11                          | 4                      | 4                      | 10                     | 5/11^e                   | 4                      | 9                    | 4                    | –                    |                       |
| Thailand     | 2003–2005     | Two provinces    | 1033            | –/7^e                       | –                      | –                      | –                      | –                        | –                      | 5^e                   | 4^e                   | 23                   | 8^e                   |
| Thailand     | 2006–2008     | Chiang Mai       | 90              | 1                            | 6                      | 3                      | 4                      | 10/1^e                   | –                      | –                    | –                    | 10                   | 2                     |
| Thailand weighted average |       |                 | 1674            | 8/12^e                       | 3                      | 4                      | 9                      | 5                        | 2                      | 7                    | 4                    | 22                   |                       |
| Malaysia     | 1997–1999     | Kuala Lumpur     | 127             | 6                            | 6                      | 2                      | 10                     | 7/12^e                   | 3                      | –                    | –                    | –                    |                       |
| Malaysia     | 1999–2000     | Penang           | 98              | 3/5^e                        | 1                      | 5                      | 7                      | 12                     | 1                    | –                    | 0                    | –                    | 15                    |
| Malaysia     | 2000–2002     | Kuala Lumpur     | 346             | 4                            | 3                      | 4                      | 11                     | 8/1^e                    | 9                      | 4                    | 6                    | –                    | 5                     |
| Malaysia     | 2001–2002     | Kuala Lumpur     | 112             | –                            | –                      | –                      | –                      | –                        | 12                    | 11                   | 4                    | –                    |                       |
| Malaysia     | 2002–2003     | Seremban         | 108             | –                            | –                      | –                      | 12                     | 6                    | –                    | –                    | –                    | 10^b                  |                       |
| Malaysia weighted average |       |                 | 791             | 4/6^e                        | 4                      | 4                      | 10                     | 9                      | 7                    | 6                    | 4                    | 7                    |                       |
| Singapore    | 1991–1991     | Singapore        | 96              | 4                            | 5                      | 4                      | 3                      | 4/2^e                   | 5                      | –                    | 0                    | 2                    | 21                    |
| Singapore    | 2001–2002     | Singapore        | 73              | –                            | –                      | –                      | –                      | –                        | 10                    | 0                    | 3                    | –                    |                       |
| Singapore    | 2002–2004     | Singapore        | 96              | 6                            | 3                      | –                      | 0                      | –                        | –                    | –                    | –                    | –                    |                       |
| Singapore weighted average |       |                 | 265             | 5                            | 4                      | –                      | 2                      | –                        | 7                    | –                    | 1                    | –                    |                       |

Continued
| Country          | Year      | Site          | No. of patients | % Streptococcus pneumoniae | % Haemophilus influenzae | % Staphylococcus aureus | % Klebsiella pneumoniae | % Other GNB a | % Mycoplasma pneumoniae | % Chlamydia pneumoniae | % Legionella spp. | % Viruses | % Mycobacterium tuberculosis |
|------------------|-----------|---------------|-----------------|-----------------------------|-------------------------|------------------------|------------------------|----------------|------------------------|-----------------------|------------------|-----------|---------------------------|
| Indonesia        | 2001–2002 | Jakarta/Surabaya | 37              | -                           | -                       | -                      | -                      | -              | 3                      | 0                     | 3                | -         | -                         |
| Philippines      |           |               | 48              | 13                          | 19                      | 0                      | 0                      | 8              | -                      | -                     | -                | 0         | -                         |
| Philippines      | 2001–2002 | Manila        | 136             | -                           | -                       | -                      | -                      | -              | 7                      | 6                     | 17               | -         | -                         |
| Philippines      | 2002–2004 | Manila        | 55              | 11                          | 20                      | -                      | 11                     | -              | -                      | -                     | -                | -         | -                         |
| Philippines      |            |               | 239             | 12                          | 19                      | -                      | 6                      | -              | -                      | -                     | -                | -         | -                         |
| India            | 1987–1988 | Delhi         | 46              | 2                           | 10                      | 12                     | 17                     | 22             | 15                     | -                     | -                | -         | 2                         |
| India            | 1997–1998 | New Delhi     | 60              | -                           | -                       | -                      | -                      | -              | -                      | -                     | -                | 15        | -                         |
| India            | 1998–2000 | New Delhi     | 42              | 14                          | 10                      | 12                     | 17                     | 19             | 24                     | -                     | -                | -         | -                         |
| India            | 2001       | Srinagar      | 100             | 1                           | -                       | 7                      | 3                      | 17             | -                      | -                     | -                | -         | 0                         |
| India            | 2000–2001 | Shimla        | 70              | 27                          | -                       | -                      | 13                     | 17             | 16                     | 11                    | -                | -         | -                         |
| India            | 2002–2004 | Vellore       | 304             | 10                          | 2                       | 8                      | -                      | -              | -                      | -                     | -                | -         | -                         |
| India            | 2006–2007 | Ludhiana      | 233             | 9                            | 0                       | 3                      | 3                      | 15             | 16                     | 18                    | -                | -         | 5                         |
| India            | 2006–2007 | Vellore       | 80              | -                            | -                       | -                      | -                      | -              | 6                      | -                     | -                | -         | -                         |
| India            | 2004–2006 | Chennai       | 75              | 0                            | 0                       | 8                      | 15                     | 0              | 3                      | -                     | -                | -         | -                         |
| India            | 2005–2008 | New Delhi     | 113             | -                            | -                       | -                      | -                      | -              | -                      | -                     | 2                | -         | -                         |
| India weighted average | 923       |               | 9                | 1                            | 6                       | 9                      | 14                     | 14             | 15                     | 6                     | 10               | 3         | 7                         |
| All studies unweighted average | 9352      |               | 12               | 7                            | 4                       | 6                      | 4                      | 8              | 7                      | 3                     | 10               | 7         | -                         |

GNB: Gram-negative bacilli; - indicates data not available.
Percentages refer to the proportion with a specific pathogen identified. Patients may have more than one pathogen identified.
Country totals are given for hospitalised CAP and are a weighted average of those studies that report data for each organism.
Averages given for all studies (outpatient, hospitalised or severe) are unweighted as variation between countries is likely to be greater than variation due to random error.
a Includes Enterobacteriaceae and non-fermenters but not Haemophilus influenzae, Moraxella catarrhalis or atypical pathogens. Isolates of Burkholderia pseudomallei, when present, are not included in the total but are given separately after a forward slash, and are not included in averages as incidence is geographically variable.
b Cases reported but protocol did not indicate systematic testing. Not included in averages.
c Excluding/including urine antigen testing. If only one value is given, antigen testing was not performed.
d Country-specific data from a multinational study.
e Study used urine antigen testing alone with no culture.
f Period of study not available, therefore publication date given.
The aggregated results from all Asian studies of hospitalised patients are compared with a review of European studies of CAP in Table 4. As most of the data are from hospitalised patients, the results discussed below refer to this group unless otherwise stated.

**Streptococcus pneumoniae**

*Streptococcus pneumoniae* was the most commonly identified pathogen (13.3% with urine antigen testing included) (Table 1). The proportion of CAP attributed to *S. pneumoniae* showed great variation between countries, with average rates of 24% in Japan, 14% in South Korea and Taiwan, 12% in The Philippines, 8–9% in Thailand, China and India and 4–5% in Malaysia and Singapore. Seven inpatient studies used urine pneumococcal antigen testing, with positive rates of 0–3% using the Wellcogen test and 7–33% using the BinaxNOW test. The proportion of *S. pneumoniae* isolated from a sterile site was 2.7% in the 14 studies that reported these data versus 10.4% in those who had positive cultures from any site in these studies.

**Haemophilus influenzae**

The overall rate for Asia was 6.9%, with variation between Asian countries (Table 1). The highest rates were in The Philippines (19%), followed by Japan (10%) and China (9%). The lowest rates were found in India and South Korea (both 1%). In The Philippines, *H. influenzae* was found more commonly than *S. pneumoniae*. The proportion with *H. influenzae* isolated from a sterile site was 0.1% in the 12 studies that reported these data versus 4.5% in those who had positive cultures from any site in these studies.

**Mycoplasma pneumoniae and Chlamydophila pneumoniae**

Twenty-nine studies included diagnostics for these organisms; all used serology and four also used PCR. *Mycoplasma pneumoniae* and *C. pneumoniae* were common CAP pathogens (identified in 8.3% and 6.9% of all hospitalised patients, respectively) (Table 1), with higher rates in outpatient cohorts (22.9% for *M. pneumoniae* and 23.6% for *C. pneumoniae*) (Table 2).

**Legionella spp**

The proportion of patients diagnosed with *Legionella spp* was low (3.0%). One multicentre study described a particularly high rate of infection at a study site in Manila (17%), but there are no other data from The Philippines to corroborate this. In one study, the proportion with *L. pneumophila* detected was 2.7% by urine antigen, rising to 6.2% with serology. Another study found no *L. pneumophila* urine antigen-positive cases among 373 patients, but detected *Legionella longbeachae* infection in 3.8% using serology and PCR.

**Gram-negative bacilli (GNB)**

GNB were identified in 13.0% of hospitalised patients when averaging all Asian studies (Table 1; see footnote for definition). The lowest proportions were seen in East Asia, with a higher number reported in Southeast Asia and India. The most common GNB...
Table 3. Aetiology of community-acquired pneumonia (CAP) in those with severe disease (includes retrospective studies)

| Country     | Year       | Site      | No. of patients | % Streptococcus pneumonia | % Haemophilus influenzae | % Staphylococcus aureus | % Klebsiella pneumoniae | % Other GNB\(^a\) | % Mycoplasma pneumoniae | % Chlamydaphila pneumoniae | % Legionella spp. | % Viruses | % Mycobacterium tuberculosis |
|-------------|------------|-----------|-----------------|----------------------------|-------------------------|-------------------------|-------------------------|------------------------|-------------------------|--------------------------|----------------------|----------|-----------------------------|
| Japan\(^b\) | 1995–2002  | Toyama    | 72              | 14                         | 3                       | 3                       | 7                       | 11                     | –                       | –                       | 3\(^c\)              | –        | 3\(^c\)                     |
| Taiwan\(^b\) | 2001      | N Taiwan  | 169             | 2                          | 3                       | 4                       | 11                      | 21                     | –                       | –                       | –                    | –        | –                           |
| Taiwan\(^b\) | 2001–2003 | Taipei    | 62              | 15                         | 3                       | 10                      | 8                       | 16                     | 2\(^c\)                 | –                       | 2\(^c\)              | 2\(^c\)  | –                           |
| Taiwan\(^b\) | 2002–2003 | Taichung  | 22              | 14                         | 5                       | 5                       | 18                      | 0                      | 5                      | 0                       | –                    | –        | –                           |
| Thailand\(^b\) | 1999–2001 | Khon Kaen | 105             | 13                         | 8                       | 4                       | 11                      | 3/19\(^f\)            | –                       | –                       | 1\(^c\)              | –        | –                           |
| Singapore\(^b\) | 1989–1993 | Singapore | 57              | 7                          | 0                       | 9                       | 9                       | 5/18\(^h\)            | 7\(^c\)                 | –                       | 4\(^c\)              | –        | 16\(^c\)                    |
| Singapore\(^b\) | 1991–1993 | Singapore | 59              | 5                          | 8                       | 7                       | 15                      | 17/7\(^m\)            | 2\(^c\)                 | –                       | 3\(^c\)              | –        | –                           |
| Singapore\(^b\) | 2003–2005 | Singapore | 80              | 13                         | 1                       | 1                       | 5                       | 5                      | –                       | –                       | 1\(^c\)              | –        | 4\(^c\)                     |
| All studies unweighted average | 626 | 10 | 4 | 5 | 9 | 12 | – | – | – | – | – | – | – | – |

GNB: Gram-negative bacilli; – indicates data not available.
Percentages refer to the proportion with a specific pathogen identified. Patients may have more than one pathogen identified.
Country totals are given for hospitalised CAP and are a weighted average of those studies that report data for each organism.
Averages given for all studies (outpatient, hospitalised or severe) are unweighted as variation between countries is likely to be greater than variation due to random error.
\(^a\) Includes Enterobacteriaceae and non-fermenters but not Haemophilus influenzae, Moraxella catarrhalis or atypical pathogens. Isolates of Burkholderia pseudomallei are not included but are given separately after a forward slash, and are not included in averages as incidence is geographically variable.
\(^b\) Retrospective study of severe CAP.
\(^c\) Cases reported but protocol did not indicate systematic testing. Not included in averages.
isolated was Klebsiella pneumoniae (6.3%), largely from sputum, but the proportion with K. pneumoniae bacteraemia averaged 2.0% in the 17 studies where this was reported, with an overall isolation rate of 6.2% in these studies. A comparison of studies performed in different settings revealed higher rates of GNB with increasing severity (Table 5). Among patients with severe CAP, GNB were the most common pathogens identified (21.5%).

In two studies carried out in northeast Thailand, Burkholderia pseudomallei was the most common pathogen identified in CAP and was cultured in 15% of 367 cases. Studies of patients hospitalised with CAP in Malaysia and Singapore identified B. pseudomallei in 1–2%, although the proportion was much higher among patients admitted to the intensive care unit in Singapore (9.2%) (Table 3). A prospective Cambodian study of inpatient CAP found B. pseudomallei in 1.6% of patients (not included in the quantitative review as there were no data for other pathogens).

Staphylococcus aureus

Staphylococcus aureus was isolated in 4.0% of patients, increasing to 5.1% in patients with severe CAP (Table 5). The proportion with S. aureus isolated from a sterile site was 1.9% in the 14 studies that reported these data versus 4.5% in those who had positive cultures from any site in these studies.

Mycobacterium tuberculosis

Ten studies included TB diagnostics in their protocol; all used microscopy and four also performed culture. Rates of M. tuberculosis in patients presenting with CAP were >10% in three of these studies (Table 1). Six other studies reported some cases with TB but did not test systematically.

Moraxella catarrhalis

Moraxella catarrhalis was isolated in <1% of hospitalised patients on average (data not shown).

**Discussion**

This review represents a synthesis of published Asian CAP aetiology studies and reveals several important patterns. In the West, GNB and S. aureus are uncommon causes of CAP and are usually found in the context of hospital-acquired pneumonia (Table 4). In Asia these organisms were identified in a higher proportion of patients. Conversely, although S. pneumoniae was commonly identified, it was relatively less important than in most European studies. Also, a substantial proportion of patients presenting with CAP in Asian countries were found to have TB, which is often considered to cause only more chronic pulmonary disease. Finally, B. pseudomallei was a major cause of CAP in northeast Thailand and was also reported in other Southeast Asian countries.

**Limitations**

There were several challenges in conducting this review, resulting in some limitations to the data. First, there were limitations in determining aetiology using currently available methods. With the exception of B. pseudomallei, interpretation of the clinical relevance of GNB such as K. pneumoniae is problematic as most are isolated from sputum culture and could therefore represent colonisation rather than infection. While this is also true for Gram-positive pathogens such as S. pneumoniae and S. aureus, pre-sampling antibiotic use favours colonisation by GNB. Obtaining reliable results from sputum culture is difficult, even in well-resourced hospitals. A lack of rigorous microbiological isolation...
standards, for example, specimen collection following antibiotic use, delays in specimen transport, or culture of specimens with inadequate microscopic screening for white blood cells, might be expected to reduce isolation of more fastidious bacteria such as *S. pneumoniae* and *H. influenzae* and to increase isolation of Enterobacteriaceae and *S. aureus*.9 The most common GNB isolated from sputum in most studies is *K. pneumoniae*, and while this is a well-recognised CAP pathogen, the high rate of isolation of *K. pneumoniae* could also relate to the issues outlined above. In some cases, isolation of GNB almost certainly represented colonisation rather than infection. One such example is an Indian study of 46 patients that reported Gram-negative pneumonia in 37% based on sputum culture, most of whom responded to penicillin despite the organisms being intrinsically resistant to this antibiotic.45 Without routine collection of invasive respiratory specimens it is difficult to have full confidence in the clinical relevance of culture results. For example, we are aware of only one large study in the past 20 years, performed in Kenya, which used routine transthoracic needle aspiration for bacteriological diagnosis of CAP.69 In this study of hospitalised patients, only 0.7% of HIV-negative patients had a GNB isolated compared with an average of 7.9% in three other comparable African studies that used sputum culture.70–72 It is notable that where data were available, comparison of samples positive from sterile sites with samples positive by any means was similar for *S. aureus* (1.9% vs. 4.5%), *S. pneumoniae* (2.7% vs. 10.4%) and *K. pneumoniae* (2.0% vs. 6.2%), while *H. influenzae* was less commonly isolated from sterile sites (0.1% vs. 4.5%). However, whether this reflects that this bacterium was more commonly a contaminant of sputum or differences in pathogenesis or virulence is difficult to determine.

A second limitation is the absence of data from large parts of Asia (Figure 2). The data included in this review largely come from patients admitted to large urban hospitals in relatively wealthy countries. Consequently, there are few data from areas where the highest burden of disease is expected. A limitation of the methodology is that only studies published in English were included and therefore relevant studies in other languages will have been missed. There were seven studies identified from the database and reference searches that might have been included if published in English, but these were all from Japan, China or South Korea, countries that already have 19 studies included here.

**Gram-negative bacilli**

Despite these issues, the higher isolation rate of GNB in CAP cannot be discounted. Many studies that reported high rates of GNB in sputum have no apparent methodological deficiencies compared with Japanese or western studies describing much lower rates. Furthermore, the proportion of patients with bacteraemic *K. pneumoniae* pneumonia, where there can be little doubt of its clinical relevance, was 1.7% in the studies that reported it compared with only 0.1% in two large western studies.71,72

The underlying cause of the higher rate of GNB in Asian studies is unclear; importantly, those studies that quantified prior antibiotic use provided no evidence to suggest that this was responsible for the higher rates of sputum isolation of *K. pneumoniae*. Although there are few data comparing GNB carriage internationally, two studies report high rates (36–57%) of GNB nasopharyngeal carriage in developing countries and lower rates of 4–9% in developed countries.75,76 If confirmed, geographical differences in the nasopharyngeal microbiome might account for higher rates of Gram-negative CAP in Asia, although this could also cause more Gram-negative contamination of sputum samples. Other explanations for the high rates of Gram-negative CAP described could relate to underlying diseases, with the unequivocally high rates of Gram-negative pneumonia seen in malnourished children as an extreme example.77 A syndrome of invasive *K. pneumoniae* infection, which can include pneumonia and liver abscess, is well described in Taiwan and several other Asian countries, although the cause for this geographic distribution is unknown.78–82

*Burkholderia pseudomallei* is well recognised as a major cause of community-acquired sepsicaemia and pneumonia in northeast Thailand. Although less common, it is also important in other Southeast Asian countries because of the high mortality rate and implications for antibiotic selection. No infection was identified in studies outside Southeast Asia, although it has been described in case series from other Asian countries such as India and Taiwan, and it can be overlooked if unexpected.83

**Gram-positive cocci**

The proportion of CAP with *S. aureus* followed a similar, although less marked, geographical pattern to that of GNB and the same uncertainties apply. With the exception of Japan, the proportion of CAP patients diagnosed with *S. pneumoniae* was lower than in western studies. Issues of microbiological technique may have some impact but this should not affect urine antigen positivity, which is substantially different between one large Thai study (7%) compared with similarly well-designed Japanese (33%) and Spanish (31%) studies.15,35,48 While higher rates of infection with other pathogens would lower the proportion attributable to *S. pneumoniae*, this seems insufficient to explain the observed differences.

**Mycobacterium tuberculosis**

Many studies found that TB was common among patients presenting with CAP, which is also the case among high-prevalence populations in Africa, the Middle East and the USA.69,70,84–86 However, because of the inconsistent approach to TB diagnosis the data are incomplete, making comparisons between countries difficult. Despite these uncertainties, these data show that *M. tuberculosis* is an important cause of lower respiratory infection in many parts of Asia. Decisions about the choice of routine investigations performed for CAP and the choice of empirical treatment should reflect this. In particular, care should be taken with the empirical use of antibiotics with antituberculous activity, such as quinolones, which may lead to a partial response, mask diagnosis and ultimately promote the development of drug-resistant TB.

**Atypical bacteria**

The number of *M. pneumoniae, C. pneumoniae* and Legionella infections varied greatly. This may have related to geographical variation or to changes in incidence during different study periods, as studies typically lasted only 1–2 years (shorter than the classic epidemic cycle of *M. pneumoniae*). Furthermore, there was wide variation in diagnostic techniques, with different methods and diagnostic criteria in almost every study. Use of a simultaneous
control group was rarely performed. The gold standard for serologic diagnosis of a rise in antibody titre between acute and convalescent serum specimens was widely used in East Asia, although diagnoses were also often made on single high IgM titres. Repeat specimens were not used at all in most of the Indian studies, presumably as it was not practical to obtain them.

Conclusions

Appropriate selection of diagnostic tests and empirical treatment for CAP is crucial and depends both on knowledge of the common pathogens identified in aetiology studies and on the results of therapeutic trials. The available aetiology data from Asia are limited but suggest that use of empirical guidelines based on Western data may be inappropriate due to the higher proportion of CAP associated with GNB and TB. Insufficiently broad antibiotic coverage when treating Gram-negative pneumonia may result in avoidable morbidity and mortality, whereas excessive use of broad-spectrum antibiotics increases healthcare costs for those least able to afford it and is already contributing to an unprecedented problem of antibiotic resistance in Asia. 87

Future aetiology studies should be large, have rigorous microbiological methodology (including routine testing for M. tuberculosis) and include less developed or rural areas with little existing data. Interpretation of results is difficult without the routine collection of invasive specimens, such as transthoracic needle aspiration, and the inclusion of a control group. The multicentre Pneumonia Etiology Research for Child Health care–control study includes all of these elements and will make a major contribution to understanding childhood pneumonia. 88 A similarly rigorous study is needed in adults. An additional approach to inform treatment is via randomised comparisons of different empirical treatment strategies. Until now there have been relatively few trials comparing therapeutic regimens for adult CAP in Asia. By avoiding the need for non-routine diagnostics, perhaps other than a sputum sample for TB, it may be possible for a trial to extend to areas where aetiology studies are less practical. Such trials could provide reliable data to guide the empirical treatment of CAP across Asia, home to one-half of the world’s population.

Authors’ disclaimer: The funders had no role in the design, analysis or interpretation of the study.

Authors’ contributions: LP was involved in study design, wrote the first draft of the manuscript, conducted the literature search, reviewed the abstracts, performed the analysis and contributed to the final draft; BN wrote the final draft and contributed to the analysis; PH, TTDN, RVd, NVK and HFLW were involved in study design, reviewed the abstracts, contributed to the analysis and contributed to the final draft. All authors have read and approved the final manuscript. BN is the guarantor of the study.

Funding: This work was supported by the European Union FP7 project ‘European Management Platform for Emerging and Re-emerging Infectious Disease Entities (EMPERIE)’ [grant code 223498] and the Wellcome Trust Major Overseas Programme.

Competing interests: None declared.

Ethical approval: Not required.

References

1. Lozano R, Naghavi M, Foreman K et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2013;380:2095–128.
2. Woodhead M. Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. Eur Respir J Suppl 2002;36:20s–27s.
3. World Health Organization. Global burden of disease (GBD). Geneva: World Health Organization; 2008. http://www.who.int/healthinfo/global_burden_disease/gbd/en/ [accessed 1 August 2012].
4. Liam CK, Pang YK, Poosparajah S et al. Community-acquired pneumonia: an Asia Pacific perspective. Respiriology 2007;12:162–4.
5. Brown JS. Geography and the aetiology of community-acquired pneumonia. Respiriology 2009;14:1068–71.
6. Song JH, Thamlilikul V, Hsieh PR. Clinical and economic burden of community-acquired pneumonia amongst adults in the Asia-Pacific region. Int J Antimicrob Agents 2011;38:108–17.
7. Kumarasamy KK, Taleman MA, Walsh TR et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis 2010;10:597–602.
8. Jean SS, Hsieh PR. High burden of antimicrobial resistance in Asia. Int J Antimicrob Agents 2011;37:291–5.
9. Bortlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis 2011;52(Suppl 4):S296–304.
10. Campbell SG, Marrie TJ, Anstey R et al. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: a prospective study. Chest 2003;123:1142–50.
11. Mobbbs KJ, van Saene HK, Sunderland D et al. Oropharyngeal Gram-negative bacillary carriage: a survey of 120 healthy individuals. Chest 1999;115:1570–5.
12. Heineman HS, Chawla JK, Lofton WM. Misinformation from sputum cultures without microscopic examination. J Clin Microbiol 1977;6:518–27.
13. Daxboeck F, Krause R, Wenisch C. Laboratory diagnosis of Mycoplasma pneumoniae infection. Clin Microbiol Infect 2003;9:263–7.
14. Kumar S, Hammerschlag MR. Acute respiratory infection due to Chlamydia pneumoniae: current status of diagnostic methods. Clin Infect Dis 2007;44:568–76.
15. Briones ML, Blanquer J, Ferrando D et al. Assessment of analysis of urinary pneumococcal antigen by immunochromatography for etiologic diagnosis of community-acquired pneumonia in adults. Clin Vaccine Immunol 2006;13:1092–7.
16. Turner P, Turner C, Kaewcharernnet N et al. A prospective study of urinary pneumococcal antigen detection in healthy Karen mothers with high rates of pneumococcal nasopharyngeal carriage. BMC Infect Dis 2011;11:108.
17. Svarer CW, Luck C, Elverdal P et al. Immunochromatitic kits Xpert Legionella and BinaxNOW Legionella for detection of Legionella pneumophila urinary antigen have low sensitivities for the diagnosis of Legionnaires’ disease. J Med Microbiol 2012;61:213–7.
18. Cao B, Ren LL, Zhao F et al. Viral and Mycoplasma pneumoniae community-acquired pneumonia and novel clinical outcome evaluation in ambulatory adult patients in China. Eur J Clin Microbiol Infect Dis 2010;29:1443–8.
Community-acquired pneumonia in Japan: a prospective ambulatory and hospitalized patient study. J Med Microbiol 2005;54:395–400.

Wattanatham A, Chaoprasong C, Nonthapisud P et al. Community-acquired pneumonia in Southeast Asia: the microbial differences between ambulatory and hospitalized patients. Chest 2003;123:1512–9.

Bansal S, Kashyap S, Pal LS et al. Clinical and bacteriological profile of community acquired pneumonia in Shimla, Himachal Pradesh. Indian J Chest Dis Allied Sci 2004;46:17–22.

Boonsawat W, Boonma P, Tangdajahiran T et al. Community-acquired pneumonia in adults at Srinagarind Hospital. J Med Assoc Thai 1990;73:345–52.

Chan CH, Cohen M, Pang J. A prospective study of community-acquired pneumonia in Hong Kong. Chest 1992;101:442–6.

Chaudhry R, Dhawan B, Dey AB. The incidence of Legionella pneumophila: a prospective study in a tertiary care hospital in India. Trop Doc 2000;30:197–200.

Dey AB, Chaudhry R, Kumar P et al. Mycoplasma pneumoniae and community-acquired pneumonia. Natl Med J India 2000;13:66–70.

Fujiki R, Kawayama T, Ueyama T et al. The risk factors for mortality of community-acquired pneumonia in Japan. J Infect Chemother 2007;13:157–65.

Hara K, Yahara K, Gotoh K et al. Clinical study concerning the relationship between community-acquired pneumonia and viral infection in northern Thailand. Intern Med 2011;50:991–8.

Hirakata Y, Yanagihara K, Kurihara S et al. Comparison of usefulness of plasma procalcitonin and C-reactive protein measurements for estimation of severity in adults with community-acquired pneumonia. Diagn Microbiol Infect Dis 2008;61:170–4.

Hooi LN, Looi I, Ng AJ. A study on community acquired pneumonia in adults requiring hospital admission in Penang. Med J Malaysia 2001;56:275–84.

Horie M, Ugajin M, Suzuki M et al. Diagnostic and prognostic value of procalcitonin in community-acquired pneumonia. Am J Med Sci 2012;343:30–5.

Huang HH, Zhang YY, Xiu QY et al. Community-acquired pneumonia in Shanghai, China: microbial etiology and implications for empirical therapy in a prospective study of 389 patients. Eur J Clin Microbiol Infect Dis 2006;25:369–74.

Hui KP, Chin NK, Chow K et al. Prospective study of the aetiology of adult community acquired bacterial pneumonia needing hospitalisation in Singapore. Singapore Med J 1993;34:329–34.

Ishida T, Hashimoto T, Arita M et al. Etiology of community-acquired pneumonia in hospitalized patients: a 3-year prospective study in Japan. Chest 1998;114:1588–93.

Ishida T, Hashimoto T, Arita M et al. A 3-year prospective study of a urinary antigen-detection test for Streptococcus pneumoniae in community-acquired pneumonia: utility and clinical impact on the reported etiology. J Infect Chemother 2004;10:359–63.

Javed S, Chaudhry R, Passi K et al. Sero diagnosis of Legionella infection in community acquired pneumonia. Indian J Med Res 2010;131:92–6.

Kasamatsu Y, Yamaguchi T, Kawaguchi T et al. Usefulness of a semi-quantitative procalcitonin test and the A-DROP Japanese prognostic scale for predicting mortality among adults hospitalized with community-acquired pneumonia. Respir Med 2012;106:330–6.

Lauderdale TL, Chang FY, Ben RJ et al. Etiology of community acquired pneumonia among adult patients requiring hospitalization in Taiwan. Respir Med 2005;99:1079–86.

Lee SJ, Lee MG, Jeon MJ et al. Atypical pathogens in adult patients admitted with community-acquired pneumonia in Korea. Jpn J Infect Dis 2002;55:157–9.

Liam CK, Lim KH, Wong CM. Community-acquired pneumonia in patients requiring hospitalization. Respir Med 2001;95:259–64.

Liam CK, Pang YK, Poosaramaj S. Pulmonary tuberculosis presenting as community-acquired pneumonia. Respir Med 2006;11:786–92.

Liu Y, Chen M, Zhao T et al. Causative agent distribution and antibiotic therapy assessment among adult patients with community acquired pneumonia in Chinese urban population. BMC Infect Dis 2009;9:31.

Loh LC, Khoo SK, Quah SY et al. Adult community-acquired pneumonia in Malaysia: prediction of morality from severity assessment on admission. Respir Med 2004;9:379–86.

Lui G, Ip M, Lee N et al. Role of ‘atypical pathogens’ among adult hospitalized patients with community-acquired pneumonia. Respir Med 2009;14:1098–105.

Madhu SV, Gupta U, Gulera JS et al. Clinical and bacteriological profile of hospitalized community acquired pneumonias—a preliminary study. Indian J Chest Dis Allied Sci 1990;32:95–100.

Ngeow YF, Suwanjutha S, Chantarajanasiri T et al. An Asian study on the prevalence of atypical respiratory pathogens in community-acquired pneumonia. Int J Infect Dis 2005;9:144–53.

Oberai A, Aggarwal A. Bacteriological profile, serology and antibiotic sensitivity pattern of microorganisms from community acquired pneumonia. JK Sci 2006;8:79–82.

Olsen SJ, Thamthitiwat S, Chantra S et al. Incidence of respiratory pathogens in persons hospitalised with pneumonia in two provinces in Thailand. Epidemiol Infect 2010;138:1811–22.

Ong G, Antonio-Velmonte M, Mendoza MT. Etiologic agents of community-acquired pneumonia in the adult: the PGH experience. Phil J Microbiol Infect Dis 1995;24:29–32.

Reechaipichitkul W, Lulitanond V, Tantiwong P et al. Etiologies and treatment outcomes in patients hospitalized with community-acquired pneumonia (CAP) at Srinagarind Hospital, Khon Koen, Thailand. Southeast Asian J Trop Med Public Health 2005;36:156–61.

Saito A, Kohno S, Matsushima T et al. Prospective multicenter study of the causative organisms of community-acquired pneumonia in adults in Japan. J Infect Chemother 2006;12:63–9.

Shah BA, Singh G, Naik MA et al. Bacteriological and clinical profile of community acquired pneumonia in hospitalized patients. Lung India 2010;27:54–7.

Shankar EM, Kumarasamy N, Vignesh R et al. Epidemiological studies on pulmonary pathogens in HIV-positive and -negative subjects with or without community-acquired pneumonia with special emphasis on Mycoplasma pneumoniae. Jpn J Infect Dis 2007;60:337–41.

Sohn JW, Park SC, Choi YH et al. Atypical pathogens as etiologic agents in hospitalized patients with community-acquired pneumonia in Korea: a prospective multi-center study. J Korean Med Sci 2006;21:602–7.

Song JH, Oh WS, Kang CI et al. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asia Network for surveillance of resistant pathogens. Int J Antimicrob Agents 2008;31:107–14.

Warrier R, Brahmadattan KN, Muthiah AS et al. Chlamydia pneumoniae—seroprevalence among adults presenting with acute
community-acquired pneumonia (CAP). J Assoc Physicians India 2006;54:77–8.

57 Yen MY, Hu BS, Chen YS et al. A prospective etiologic study of community-acquired pneumonia in Taiwan. J Formos Med Assoc 2005;104:724–30.

58 Hu HC, Huang CC, Tsai YH et al. Outcome analysis of patients requiring mechanical ventilation with severe community-acquired pneumonia and identified bacterial pathogens. Chang Gung Med J 2005;28:229–36.

59 Lee KH, Hui KP, Tan WC et al. Severe community-acquired pneumonia in Singapore. Singapore Med J 1996;37:374–7.

60 Poulou V. Severe community-acquired pneumonia requiring intensive care: a study of 80 cases from Singapore. Singapore Med J 2008;49:458–61.

61 Reechaipichitkul W, Pispraset V. Severe community-acquired pneumonia (CAP) treated at Sirinagarind Hospital, Khon Kaen, Thailand. Southeast Asian J Trop Med Public Health 2004;35:430–3.

62 Tan YK, Khoo KL, Chin SP et al. Aetiology and outcome of severe community-acquired pneumonia in Singapore. Eur Respir J 1998;12:113–5.

63 Tseng J-S, Chan M-C, Hsu J-Y et al. Procalcitonin is a valuable prognostic marker in ARDS caused by community-acquired pneumonia. Respirrology 2008;13:505–9.

64 Wu CL, Lin FJ, Lee SY et al. Early evolution of arterial oxygenation in severe community-acquired pneumonia: a prospective observational study. J Crit Care 2007;22:129–36.

65 Yoshimoto A, Nakamura H, Fujimura M et al. Severe community-acquired pneumonia in an intensive care unit: risk factors for mortality. Intern Med 2005;44:710–6.

66 Rammaert B, Beaute J, Borand L et al. Pulmonary melioidosis in Cambodia: a prospective study. BMC Infect Dis 2011;11:126.

67 Niederman MS, Mandell LA, Anzueto A et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730–54.

68 American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.

69 Scott JA, Hall AJ, Muyodi C et al. Aetiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya. Lancet 2000;355:1225–30.

70 Nyamande K, Laloo UG, John M. TB presenting as community-acquired pneumonia in a setting of high TB incidence and high HIV prevalence. Int J Tuberc Lung Dis 2007;11:1308–13.

71 Yoshimine H, Oishi K, Mubiru F et al. Community-acquired pneumonia in Ugandan adults: short-term parenteral ampicillin therapy for bacterial pneumonia. Am J Trop Med Hyg 2001;64:172–7.

72 Koula-Shiro S, Kuaban C, Belec L. Acute community-acquired bacterial pneumonia in human immunodeficiency virus (HIV) infected and non-HIV-infected adult patients in Cameroon: aetiology and outcome. Tuber Lung Dis 1996;77:47–51.

73 Marston BJ, Plouffe JE, File TM Jr et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group. Arch Intern Med 1997;157:1709–18.

74 Falquera M, Carratala J, Ruiz-Gonzalez A et al. Risk factors and outcome of community-acquired pneumonia due to Gram-negative bacilli. Respirrology 2009;14:105–11.

75 Philpot CR, McDonald PJ, Chai KH. Significance of enteric Gram-negative bacilli in the throat. J Hyg (Lond) 1980;85:205–10.

76 Wolf B, Gama A, Rey L et al. Striking differences in the nasopharyngeal flora of healthy Angolan, Brazilian and Dutch children less than 5 years old. Ann Trop Paediatr 1999;19:287–92.

77 Chisti MJ, Tebruegge M, La Vincente S et al. Pneumonia in severely malnourished children in developing countries—mortality risk, aetiology and validity of WHO clinical signs: a systematic review. Trop Med Int Health 2009;14:1173–89.

78 Alsafi HS, Venkatesh SK, Chan DS et al. CT appearance of pyogenic liver abscesses caused by Klebsiella pneumoniae. Radiology 2011;260:129–38.

79 Chung DR, Lee SS, Lee HR et al. Emerging invasive liver abscess caused by K1 serotype Klebsiella pneumoniae in Korea. J Infect 2007;54:578–83.

80 Li J, Fu Y, Wang JY et al. Early diagnosis and therapeutic choice of Klebsiella pneumoniae liver abscess. Front Med China 2010;4:308–16.

81 Yang CC, Yen CH, Ho MW et al. Comparison of pyogenic liver abscess caused by non-Klebsiella pneumoniae and Klebsiella pneumoniae. J Microbiol Immunol Infect 2004;37:176–84.

82 Fang CT, Lai SY, Yi WC et al. Klebsiella pneumoniae genotype K1: an emerging pathogen that causes septic ocular or central nervous system complications from pyogenic liver abscess. Clin Infect Dis 2007;45:284–93.

83 Brent AJ, Matthews PC, Dance DA et al. Misdiagnosing melioidosis. Emerg Infect Dis 2007;13:349–51.

84 Alzeer A, Mashiah A, Fakim N et al. Tuberculosis is the commonest cause of pneumonia requiring hospitalization during Hajj (pilgrimage to Makkah). J Infect 1998;36:303–6.

85 Dahmash NS, Chowdhury MN. Re-evaluation of pneumonia requiring admission to an intensive care unit: a prospective study. Thorax 1998;44:49–1.

86 Park DR, Sherbin VL, Goodman MS et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. J Infect Dis 2001;184:268–77.

87 Laxminarayan R, Duse A, Wattal C et al. Antibiotic resistance—the need for global solutions. Lancet Infect Dis 2013;13:1057–98.

88 Levine OS, O’Brien KL, Deloria-Knoll M et al. The Pneumonia Etiology Research for Child Health Project: a 21st century childhood pneumonia etiology study. Clin Infect Dis 2012,54(Suppl 2):S93–101.