Pneumococcal Disease in Older Adults- An Overview

V Ramasubramanian[1]

Pneumococcal disease is a group of illnesses caused by a gram positive bacterium *Streptococcus pneumoniae* (also known as "*Pneumococcus*").[1] Although more than 90 different pneumococcal serotypes are known, only a few of them are responsible for a major burden of pneumococcal disease.[2,3]

Clinical Manifestations

Pneumococcal disease can be classified as invasive or non-invasive[1-4], as is explained in the Figure 1.

Non-invasive disease is caused by infection of mucosal tissue such as respiratory tract and sinuses. This can lead to pneumonia or other mucosal infections like sinusitis, acute otitis media and other respiratory tract infections.[1-4] Pneumonia is the commonest clinical presentation of pneumococcal disease in adults.[2]

Invasive pneumococcal disease (IPD) is caused when the organism invades the mucosa, and infects the normally sterile sites of the body (like blood or CSF).[1,2] IPD includes diseases like meningitis, bacteremia, and bacteremic pneumonia.[1,2]

Risk Factors for Developing Pneumococcal Disease[5-8]

The main risk factors for pneumococcal infections in adults are chronic pulmonary disease, chronic cardiomyopathy, smoking, alcoholism, liver disease, chronic nephropathy, diabetes mellitus, and disorders associated with immunocompromised status. Thus, elderly people are a major high-risk group for pneumococcal infections because a certain degree of immunosenescence occurs in the elderly and the prevalence of chronic conditions increases with age. Living conditions can also increase the individual risk of pneumococcal disease, particularly residence in a nursing home or other long-term care facility.

These risk factors are depicted in Table 1.

The incidence of pneumococcal disease increases with co-morbidities.[5]

Adjusted relative risks for age, race, and the other medical conditions evaluated. Adapted from Kyaw et al.[7]

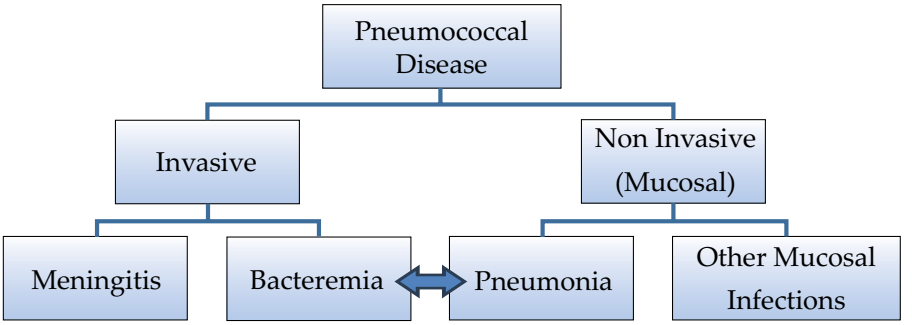

Fig. 1: Pneumococcal disease manifestations

Table 1: Risk factors for pneumococcal disease

Chronic lung disease (including asthma)	Chronic alcoholism or smoking	Living conditions such as long term care residency
Chronic heart disease	Diabetes	Asplenia (functional or anatomic)
Chronic renal disease	Immunocompromized conditions	Transplant recipients
Chronic liver disease	Cochlear implants	CSF leaks
Cancer		

Table 2: Increased risk of invasive pneumococcal disease in diseased conditions

Disease category	Fold increase
Diabetes mellitus	3.4
Chronic lung disease	5.6
Chronic heart disease	6.4
Alcoholism	11.4
Solid cancers	22.9
Hematological cancers	38.3
Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome	48.4

Burden of Pneumococcal Disease

Streptococcus pneumonia affects children and adults worldwide. Pneumococcal disease is known as the old man's friend and children's foe.[9] This is because the burden of

[1]Senior Consultant Infectious Diseases Apollo Hospital, Adjunct Professor of Infectious Diseases SRMC and MGR Medical University

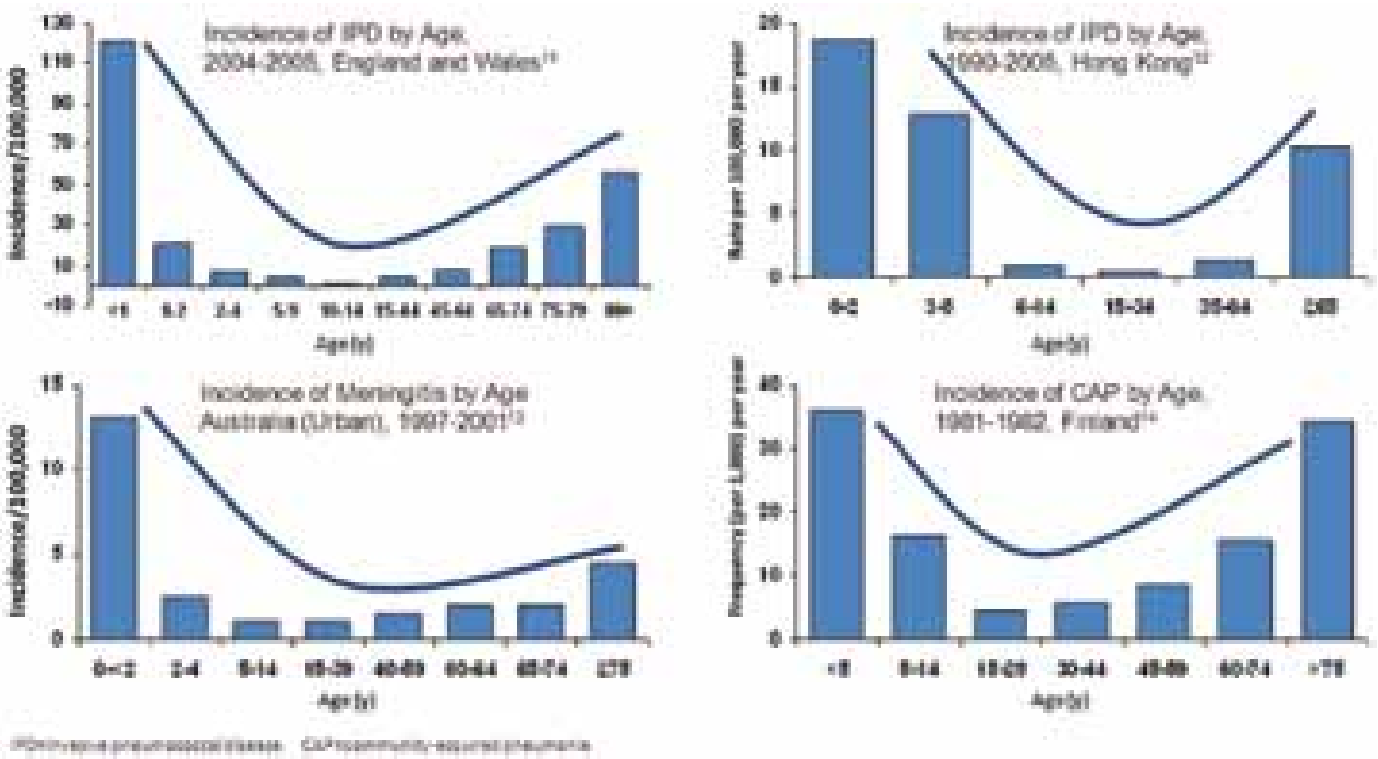

Fig. 2: Incidence of IPD and Community Acquired Pneumonia (CAP) by age across various regions

pneumococcal disease is usually found to be high in the extremes of age.[1-3,7] This is attributable to the body's immune system functioning, which is vital in protection against pneumococcal disease.[6,7] The disease burden is observed to be high in older adults, above 50 years of age.[10-11]

Global Burden

Despite numerous studies reporting incidence data on bacteremic pneumococcal pneumonias or IPD in distinct populations and geographical settings, the global burden of pneumococcal disease (including community-acquired pneumococcal pneumonia) is not well known because of the difficulties in characterizing nonbacteremic infections. In adults, pneumonia is the most common presentation of pneumococcal infections, and bacteremic pneumococcal pneumonias account for approximately 80–90 % of overall IPD cases. The true incidence of nonbacteremic pneumococcal pneumonia is unknown, but it is considerably higher than bacteremic pneumonia given that only approximately 20–30 % of pneumococcal pneumonias happen with bacteremia.[16-19]

If only IPD is considered (bacteremic pneumococcal pneumonia), incidence rates reported in the literature have varied widely in numerous studies. These differences could reflect true epidemiological differences between distinct geographical areas, but it is believed that they largely reflect differences in rates of obtaining blood cultures from patients with pneumonia. In developed countries, the estimated incidence of IPD is around 10–20 episodes per 100,000 all-age inhabitants per year, being greatest among young infants and elderly people (approximately 50 episodes per 100,000 population-years). These figures could even be an underestimate because they do not take into account persons from whom blood cultures were never obtained or those where the culture was performed after the start of antibiotic therapy.[16-18]

In North America, where PPV23 has been used for over 30 years, decreasing rates of IPD have been reported over this time period, although a confounding effect has occurred in the last decade after the introduction of the protein conjugate vaccine for children. Currently, in the USA, the estimated annual public health burden of pneumococcal disease involves approximately 50,000 cases of pneumococcal bacteremia (case-fatality rate around 20%), approximately 3,000–6,000 cases of pneumococcal meningitis (case-fatality rate about 30%), and approximately 175,000 hospitalized cases of pneumococcal pneumonia (case-fatality rate about 5–7%).[19]

S. pneumoniae is most frequently identified among patients with community acquired pneumonia (28%).[20] In a study involving 388,406 German patients with hospitalized CAP, Ewig et al. reported a global incidence rate of 2.9 cases per 1,000 person-years (7.6 cases per 1,000 elderly person-

Table 3: Incidence rates of invasive pneumococcal disease (IPD) reported in people over 65 years old

Country	Period	Incidence Rate
Canada (Calgary)[22]	2003–2007	23.9
USA[23]	2007	37.9
Norway[24]	2008	64.6
Netherlands[25]	2006–2008	60.2
Spain (Barcelona)[26]	2005–2007	56.2
Spain (Tarragona)[27]	2006–2009	59.6
USA[28]	2010	36.4
European countries[29]	2009	9.84
Australia (Sydney)[30]	2006–2010	24
UK[31]	2009	16.4

years) with an overall mortality rate of approximately 14%, illustrating the fact that hospitalized CAP is a condition of the elderly associated with high incidence and mortality.[21]

The incidence rates of pneumococcal infections in people over 65 years old in distinct geographical settings is depicted in Table 3. As can be seen, IPD rates range from 10 to 65 cases per 100,000 population- years.[22-31]

In the USA, considering all age groups, the overall incidence of IPD was 12.8 cases per 100,000 population in 2010.[28] The incidence was almost double in adults over 65 years of age (36.4 per 100,000) than in children under 5 years of age (19 per 100,000) during this year; the mortality rate by IPD was 1.6 per 100,000 all-age population[28]. The mean incidence rate of IPD in 24 European countries was 4.3 cases per 100,000 all-age population during 2009 (6 cases per 100,000 among children under 5 years and 9.8 per 100,000 among adults over 65 years).[29]

Given differences in developing compared to developed countries (e.g., serotype distribution, disparities in laboratory testing, access to care and antibiotic use), it is possible that both the true and estimated burden of pneumococcal disease might differ in developing countries.

Table 4: Age association and % *S. pneumonia* in community acquired pneumonia for adults in India

Study	Place	Age	% S. pneumonia (microbiologically diagnosed cases)
Dey AB et al[32]	Delhi	Mean age 50.6 (60% cases > 50 years)	55% (Sputum + Blood)
Bansal S et al[33]	Shimla	Mean age 52.8 + 18.1 years	35.8% (Sputum + Blood + Pleural fluid)
Oberoi A et al[34]	Ludhiana	Mean age 40 years	32.6% (Sputum); 14.6% (Blood)
Capoor MR et al[35]	Delhi	Mean age 48 years	35.3% (Sputum + Blood + Pleural fluid)
Abdullah BB et al[36]	Bijapur	Mean age 72.2 + 6.1 years (study in 65+ years)	30.8% (Sputum)

% pneumococcal etiology was calculated considering only the cases in which microbiological diagnosis was possible

Indian Burden

Some of the factors which influence the local epidemiology of pneumococcal disease include geographical distribution, seasonal trends, cyclic variation, trends of antibiotic use and childhood immunization.

In India, across various studies that have identified etiology of community acquired pneumonia in adults, *S pneumoniae* has been identified as the commonest pathogen, accounting for about 30-55% of cases (where microbiological diagnosis was possible).[32-36]

In a 10 year retrospective study on community-acquired acute bacterial meningitis in India, *S pneumoniae* accounted for >60% of cases in adults.[37] Case-fatality rate in invasive disease has been found to be highest, in adults above 50 years of age (28%), in India.[38] The Invasive Bacterial Infections Surveillance (IBIS) study group carried out a prospective, hospital-based surveillance for IPD in adults, over a period of 15 years, across 7 hospitals in India.[39] IPD has been identified as an inadequately addressed problem in Indian adults. In the study, 37.2% of IPD cases showed clinical worsening or death. IPD was associated with an overall case fatality of 26.4% in adults, even in the hospital setting. Meningitis, sepsis and invasive pneumonia were associated with case fatality rates of 36.9% and 36.6% and 20.8% respectively.[39] In the IBIS study, resistance to antibiotics was observed to be low, with only 2.7% of isolates being non-susceptible to penicillin. Resistance to cotrimoxazole was observed to be high, to an extent of 85.2% in 2008.[39]

The prevalence of antibiotic resistant pneumococci has been increasing globally,[3] including in India.[40] A multi-drug resistant clone of pneumococcal serotype 19A (ST320 clone), has recently shown a high prevalence in Asian countries, and has also been isolated from India.[41]

Difficulties in Laboratory Diagnosis

Barriers do exist in estimating the true burden of pneumococcal disease in the community; the major one being pertinent to the laboratory diagnosis of *Streptococcus pneumonia*. Despite the huge burden of this disease, microbiological diagnosis has always been rather difficult.

In recent times, there has been a decline in the quality of laboratory diagnosis of pulmonary infections.[42,43] This is evident by the huge proportion of cases of unidentified microbial etiology. Pneumococci are less frequently diagnosed. One possibility could be that other organisms could

have gained prominence, but this possibility remains unproven, as few studies identify any likely causative organism in over a half of the cases.[42] Considering this observation, Barlett has made an interesting remark that 'either pneumococcus is disappearing or microbiology is disappearing'.[43]

An important reason is, in today's times, we pay less attention to obtaining appropriate samples, and place a higher importance to the performance of microbiological tests. Because of the characteristic of intermittent appearance in the bloodstream, it is difficult to make the diagnosis of pneumococcal infection with a single sample. Obtaining a set of adequate volume of blood samples for culture, good quality of sputum or nasopharyngeal samples, ensuring timely transportation and appropriate processing to avoid contamination, appropriate and timely performance of subcultures and serotyping are some of the essential criteria for a good laboratory diagnosis of *S. pneumoniae*, the significance of which is not being realized sufficiently in the recent times.

The empirical use of antibiotics may also impair the laboratory diagnosis by conventional culture-based methods. This is because the culture-based methods can detect only multiplying and growing organisms, unlike the newer methods like polymerase chain reaction (PCR) and antigen detection, which can detect even dead remains of the bacteria.

S.pneumoniae displays an intrinsic property of autolysis, and can destroy itself in culture or outside the human body. This is a major factor which impairs its laboratory diagnosis. Apart from this, *S. pneumoniae* is a fastidious organism, and requires 5% sheep blood agar for good growth. Human or horse blood does not serve as a good culture medium for pneumococcus. For a good growth, 5% CO_2 is recommended, and the conventional candle jar is not the best instrument to serve this purpose. These requirements pose logistic challenges for many laboratories in India.

There is no gold standard test for the laboratory diagnosis of *S. pneumoniae*, particularly the noninvasive pneumonia. Also, sputum is not the best sample, as *S. pneumoniae* is a part of the normal nasopharyngeal flora, which can confound the diagnosis of lower respiratory infections. In fact, even with the best quality of respiratory tract samples examined by microscopy or culture, the diagnosis can only be presumed (presumptive diagnosis), unless it is confirmed by isolation of the organism from sterile sites like blood or pleural fluid. This is possible in only a few cases, as majority of the cases of pneumococcal pneumonia are confined to the respiratory tract only.

The different tests used for pneumococcal diagnosis have their own limitations.[44] Conventional culture-based methods have a low yield. Moreover, these are compounded by problems of autolysis and extracting requirements of the organism. These can identify only live organisms. However, these are the ones mostly relied upon for diagnosis.

Serotyping is not routinely done in our country, which is another barrier in the surveillance of sero-epidemiology of pneumococcal disease.

The newer methods of antigen detection, polymerase chain reaction (PCR) as well as the conventional and real-time polymerase chain reaction (PCR) should be used to supplement the conventional methods. One advantage of these tests is that these do not require replicating bacteria for detection, and can increase the yield. However, these are expensive, require technical expertise, and not commonly available in the Indian setting.

Urinary antigen detection may demonstrate falsely positive result in the presence of nasopharyngeal carriage, which is a common problem in children and also to an extent in adults. Also, this test can remain positive for a long time after a previous episode of infection or vaccination, which may result in a false positive result during the subsequent episode. Moreover, the test has been observed to show negative results in presence of positive blood/sputum cultures, and hence, should be used in conjunction with the culture-based methods only.

Inspite of all these challenges and limitations, the problem of pneumococcal disease is significant all over the world, but especially so in developing countries like India. Better awareness and surveillance will help us address the issue more comprehensively and save more lives.

Disclosure

Have received Honorariums / research grants / Advisory Board member / from Pfizer, MSD, Sanofi.

References

1. Goldblatt D, O'Brien KL. Chapter 134. Pneumococcal Infections. In: Longo DL, Fauci AS, Kasper DL et al, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9120169. Accessed June 23, 2012.
2. CDC. Chapter 16. Pneumococcal Disease. In: Anonymous. Pink Book. 12th ed. (2nd printing). Maryland: Public Health Foundation. http://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html. Accessed June 20, 2012.
3. Goldblatt D, O'Brien KL. Chapter 134. Pneumococcal Infections. In: Longo DL, Fauci AS, Kasper DL et al, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9120169. Accessed June 23, 2012.
4. CDC. Chapter 16. Pneumococcal Disease. In: Anonymous. Pink Book. 12th ed.

(2nd printing). Maryland: Public Health Foundation. http://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html. Accessed June 20, 2012.

5. World Health Organization. 23-valent pneumococcal polysaccharide vaccine: WHO position paper. *Wkly Epidemiol Rec* 2008;83:373-84.
6. Watson DA, Musher DM, Jacobson JW et al. A brief history of the pneumococcus in biomedical research: a panoply of scientific discovery. *Clin Infect Dis* 1993;17:913-24.
7. Kyaw MH, Rose CE, Jr, Fry AM et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. *J Infect Dis* 2005;192;377-86.
8. Weinberger B, Heindler-Brandstetter D, Schwanninger A, et al. Biology of immune responses to vaccines in elderly persons. *Clin Infect Dis* 2008;46:1078-84.
9. CDC. Prevention of Pneumococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-08):1-24.
10. Prevenar 13 prescribing information. Wyeth limited, India. LPDPRV042013 dated March 2014
11. Finn A, Jenkinson HF. The pneumococcus: 'old man's friend' and children's foe. *Microbiology* 2006;152:281-83.
12. Maggi S. Vaccination and healthy ageing. *Expert Rev Vaccines* 2010;9(3Suppl):3-6.
13. VRBPAC. Adult Indication Briefing Document. Prevenar 13. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/vaccines andrelatedbiologicalproductsadvisorycommittee/ucm279680.pdf. Accessed September 22, 2014, 2012.
14. Adapted from Health Protection Agency. Invasive pneumococcal disease incidence rate per 100,000 population by age grouping England and Wales, 1996-2005. http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733823380?p=1203409671876. Accessed 23 Jun 2012.
15. Adapted from Ho PL, Chiu SS, Cheung CH et al. Invasive pneumococcal disease burden in Hong Kong children. *Pediatr Infect Dis J* 2006;25:454-5.
16. Ortqvist A, Hedlund J, Kalin M. Streptococcus pneumoniae: epidemiology, risk factors, and clinical features. *Semin Respir Crit Care Med* 2005;26:563–74.
17. Lynch JP, Zhanel GG. Streptococcus pneumoniae: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. *Curr Opin Pulm Med* 2010;16:217–25.
18. Fedson DS, Scott JA. The burden of pneumococcal disease among adults in developed and developing countries: what is and is not known. *Vaccine* 1999;17(Suppl.1):S11–8.
19. Atkinson W, Wolfe S, Hamborsky J, eds. Epidemiology and prevention of vaccine-preventable diseases. 12th ed. CDC. Washington, DC: Public Health Foundation, 2011.
20. Said MA, Johnson HL, Nonyane BAS, Deloria-Knoll M, O'Brien KL, AGEDD Adult Pneumococcal Burden Study Team. In: Estimating the burden of non-bacteremic pneumococcal pneumonia among adults: results from a meta-analysis. [Poster no 52.] In: 8th International pneumococci and pneumococcal diseases; 2012 March 11–15; Brazil.
21. Ewig S, Birkner N, Strauss R, Schaefer E, Pauletzki J, Bischoff H, Schraeder P, Welte T, Hoeffken G. New perspectives on community-acquired pneumonia in 388406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009;64:1062–9.
22. Kellner JD, Vanderkooi OG, MacDonald J, Church DL, Tyrrell GJ, Scheifele DW. Changing epidemiology of invasive pneumococcal disease in Canada, 1998–2007: update from the Calgary- area Streptococcus pneumoniae research (CASPER) study. *Clin Infect Dis* 2009;49:205–12.
23. Pilishvili T, Lexau C, Farley MM, et al. Active Bacterial Core Surveillance/Emerging Infections Program Network. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010;201:32–41.
24. Vestrheim DF, Høiby EA, Aaberge IS, Caugant DA. Impact of a pneumococcal conjugate vaccination program on carriage among children in Norway. *Clin Vaccine Immunol* 2010;17:325–34.
25. Rodennburg GD, de Greeff SC, Jansen AG, et al. Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. *Emerg Infect Dis* 2010;16:816–23.
26. Ardanuy C, Tubau F, Pallares R, et al. Epidemiology of invasive pneumococcal disease among adult patients in Barcelona before and after pediatric 7-valent pneumococcal conjugate vaccine introduction, 1997–2007. *Clin Infect Dis* 2009;48:57–64.
27. Vila-Corcoles A, Ochoa-Gondar O, Gomez-Bertomeu F. Raga- Luria X; EPIVAC Study Group. Invasive pneumococcal disease in Catalonian elderly people, 2002–2009: serotype coverage for different anti-pneumococcal vaccine formulations at the beginning of the new conjugate vaccines era. *Vaccine* 2011;29:7430–4.
28. Centers for Disease Control and Prevention. 2012. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae, 2010. http://www.cdc. gov/abcs/reports-findings/survreports/spneu10.pdf. Accessed 7 Oct 2014.
29. European Centre for Disease Prevention and Control. Annual epidemiological report 2011. Reporting on 2009 surveillance data and 2010 epidemic intelligence data. Stockholm: ECDC; 2011.
30. Flego KL, Truman G, Sheppeard V, Gilmour RE. Invasive pneumococcal disease in western Sydney, 2002–2010. *NSW Public Health Bull* 2011;22:219–21.
31. Elston JW, Santaniello-Newton A, Meigh JA, et al. Increasing incidence of invasive pneumococcal disease and pneumonia despite improved vaccination uptake: surveillance in Hull and East Yorkshire, UK, 2002–2009. *Epidemiol Infect* 2012;140:1252–66.
32. Dey AB, Nagarkar KM, Kumar V. Clinical presentation and predictors of outcome in adult patients with community-acquired pneumonia. *The National Medical Journal of India* 1997;10:169-72.
33. 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.
34. Oberoi A, Aggarwal A. Bacteriological Profile, Serology and Antibiotic Sensitivity Pattern of Micro-organisms from Community Acquired Pneumonia. *JK Science* 2006;8:79-82.
35. Capoor MR, Nair D, Aggarwal P et al. Rapid diagnosis of community-acquired pneumonia using the Bac T/ alert 3D system. *Braz J Infect Dis* 2006;10:352-6.
36. Abdulla BB, Zoheb M, Ashraf SM et al. A Study of Community-Acquired Pneumonias in Elderly Individuals in Bijapur, India. ISRN Pulmonology. vol. 2012, Article ID 936790, 10 pages, 2012. doi:10.5402/2012/936790. Accessed Jun 23, 2012.
37. Mani R, Pradhan S, Nagarathna S et al. Bacterial profile of community acquired acute bacterial meningitis: A ten year retrospective study in a tertiary neurocare centre in South India. *Indian Journal of Medical Microbiology* 2007;25:108-14.
38. IBIS. Prospective multicentre hospital surveillance of Streptococcus pneumoniae disease in India. Invasive Bacterial Infection Surveillance (IBIS) Group, International Clinical Epidemiology Network (INCLEN). *Lancet* 1999;353:1216-21.
39. Thomas K, Mukkai Kesavan L, Veeraraghavan B, Jasmine S, Jude J, Shubankar M et al. Invasive pneumococcal disease associated with high case fatality in India. *Journal of Clinical Epidemiology* 2013;66:36-43

40. Kim SH, Song JH, Chung DR et al. Changing trends in antimicrobial resistance and serotypes of Streptococcus pneumoniae isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrob Agents Chemother* 2012;56:1418-26.

41. Shin J, Baek JY, Kim SH et al. Predominance of ST320 among Streptococcus pneumoniae serotype 19A isolates from 10 Asian countries. *J Antimicrob Chemother* 2011;66:1001-4.

42. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. *Clin Infect Dis* 2011;52Suppl4:S296-304.

43. Bartlett JG. Decline in microbial studies for patients with pulmonary infections. *Clin Infect Dis* 2004;39:170-2.

44. Schaar V, Nordström T, Mörgelin M, Riesbeck K. Moraxella catarrhalis outer membrane vesicles carry β-lactamase and promote survival of *Streptococcus pneumoniae* and *Haemophilus influenzae* by inactivating amoxicillin. *Antimicrob Agents Chemother* 2011;55:3845-53.