COMMUNITY ACQUIRED PNEUMOCOCCAL PNEUMONIA IN NORTHWESTERN NIGERIA:
EPIDEMIOLOGY, ANTIMICROBIAL RESISTANCE AND OUTCOME

Garba Iliyasu[1*], Farouq Dayyab Mohammad[2], Abdulrazaq Garba Habib[3]

[1]Department of medicine, College of Health Sciences, Bayero University Kano. Kano, Nigeria. [2]Department of Medicine, Aminu Kano Teaching Hospital. Kano, Nigeria. [3]Department of medicine, College of Health Sciences, Bayero University Kano. Kano, Nigeria.

Corresponding Author Email: ilyasug@yahoo.com

Abstract

Background: Pneumococcus is the leading cause of community acquired pneumonia (CAP) worldwide, and the leading cause of mortality. Pneumococcal pneumonia is poorly studied in Nigeria. We describe the epidemiology including associated co-morbidities and outcome of pneumococcal pneumonia in North-western Nigeria.
Material and methods: We conducted a prospective, hospital based study on patients with community acquired pneumococcal pneumonia. Detailed clinical evaluation and relevant laboratory investigations were carried out. Susceptibility test to commonly used antibiotics was carried out on all confirmed pneumococcal isolates. In hospital mortality was recorded. Analysis was carried out using descriptive statistics with differences and relationships were determined using Chi square and Fisher's exact tests as appropriate, with $p < 0.05$ regarded as significant.
Results: Of the one hundred and twenty-five (125) patients with pneumococcal pneumonia were studied. The mean age of the patients was 41.3years ($\pm$ 16.84), and 69/125(55.2%) were males. Co-morbidities were observed in 63/125 (53.8%) of the patients. Resistance to commonly used antibiotics was observed. Overall in-hospital mortality was 9/117(7.8%). HIV (OR=2.081; 95%CI 1.651-3.237), age $\geq$65years (OR=5.947; 95%CI3.581-17.643), and CURB-65 score of $\geq$ 3 (OR=2.317; 95%CI1.734-4.719) were independent predictors of mortality.
Conclusion: Pneumococcal pneumonia is the commonest cause of CAP in North-western Nigeria with relatively high mortality. There is need to strengthened the vaccination policy targeting at risk adult population in Nigeria.

Key words: Pneumococcal pneumonia; Epidemiology; Antimicrobial resistance; Out come

Introduction

Streptococcus pneumoniae (the pneumococcus) is the major cause of community-acquired pneumonia (CAP) and a large contributor to morbidity and mortality worldwide (Ortqvist et al., 2005). It is an important public health concern throughout the world and a leading cause of morbidity and mortality (WHO, 2005). Africa and Asia are among the ten (10) countries with the highest numbers of pneumococcal infection globally, and combined together they account for 66% of cases (O'Brien et al, 2009). Nigeria accounts for 5% of the total burden at the third place after India and China (WHO, 2014). Studies from different part of Nigeria have shown that pneumococcus accounts for 50%, 54.5%, and 60% of CAP (Macfarlane et al., 1979; Nwosu et al., 1991; Musa et al., 2008). No population-based data on pneumococcal disease in adults in developing countries are available; estimates of disease burden are based on small clinical studies, vaccine trials, extrapolation from data in developed countries, and studies of persons at high risk for disease. Community acquired pneumonia has been studied in detail in Nigeria; however, there is a paucity of data on pneumococcal pneumonia. The Human Immunodeficiency Virus (HIV) pandemic and emergence of pneumococcal resistance has furthered the need to study pneumococcal pneumonia in the context of co-morbidities and outcome. This study is set to describe the epidemiology co-morbidities and clinical outcome associated with community acquired pneumococcal pneumonia in North-western Nigeria.

Materials and Methods

The study was a prospective study among 125 patients with community acquired pneumococcal pneumonia. The study was conducted in one of the major tertiary referral centres in north-western Nigeria over the period June 2009 to January 2011. The hospital has 550 beds and offers specialist inpatient and outpatient care, across various specialties.

All adult patients who were admitted over the study period with features compatible with CAP were initially screened, and those with microbiologically confirmed pneumococcal pneumonia were finally recruited. A sputum specimen was collected in a clean, sterile container from all the patients. In addition, blood samples were also collected, and inoculated directly into each of Brain-Heart infusion and thioglycolate culture media, with the use of standard aseptic procedures for aerobic and anaerobic cultures, respectively. All Samples were taken before administering antibiotic whenever feasible and transported to the laboratory immediately.

The sputum specimens were inoculated onto 5% sheep blood agar and incubated at $37^{o}C$. Inoculated plates were incubated in a candle jar so as to create a reduced oxygen tension (5%-10% additional CO2 tension). Inoculated blood culture bottles were incubated in the laboratory at $37^{0}C$ and observed for bacterial growth within 24 to 72hours and then until day 7 if there was no bacterial growth. Subcultures of inoculated media were done twice, on days 2 and 3 after incubation, and were inoculated onto blood agar plates and incubated as far sputum. Plates were examined after incubation for bacterial pathogens, by the use of standard procedures. Samples of all typical pneumococcal colonies obtained from the plates were subjected to pneumococcal identification methods of α-haemolysis, colony morphology and ethylhydrocupreine hydrochloride (optochin) sensitivity. (CLSI, 2006) All those with microbiologically proven pneumococcal infection were finally selected for the study.

Microbial susceptibility tests were carried out on all confirmed pneumococcal isolate to Penicillin G, Amoxycillin, Cefuroxime, Azithromycin, Ceftriaxone and Trimethoprim/sulfamethoxazole(TPM/SMX), using Etest strips (Manufactured by AB BIODISK, Sweden). Minimum inhibitory concentrations (MICs) were measured and strains were divided into resistant, intermediate or sensitive according to the CLSI guidelines (CLSI, 2006).
All the patients who consented were screen for HIV infection using double Enzyme Link Immunosorbent Assay (ELISA). (Rehle et al., 1997).

Pneumococcal pneumonia was defined based on clinical findings plus a chest radiograph consistent with pneumonia, in addition to Gram positive diplococci on microscopy and positive culture of *pneumococcus* from an ideal sputum specimen defined as the presence of more than 25 white cells and less than 10 squamous epithelial cells per low power field.

The following clinical data of all patients with bacteriologically proven pneumococcal pneumonia were collected and analyzed: demographic data, clinical presentation, co morbidities, HIV sero-status for those who consented, antibiotic susceptibility result and in-hospital mortality. All patients were managed according to the hospital's standard protocol for CAP. (AKTH, 2009)

Analysis was carried out using descriptive statistics with differences and relationships determined using Chi squared and Fisher's exact tests as appropriate, with $p < 0.05$ regarded as significant. Predictors were explored using univariate and multivariable analysis with unadjusted (crude) odds ratio (OR) and logistic regression adjusted, respectively. Statistical Package for Social Sciences version 16.0 was used.

Ethical clearance was obtained from the research and ethics committee of AKTH in 2009. Informed consent was obtained from the patient or a legal representative.

Results

Out of the 232 cases of bacteriologically proven community acquired pneumonia screened, 125/232(53.9%) had microbiologically proven pneumococcal pneumonia. Out of the 125 patients; 7/125(5.6%) had bacteraemic pneumonia, while the remaining 118 had primary pneumococcal pneumonia. The ages of the patients ranged from 18-79 years, with a mean age of 41.3years (± 16.84). As indicated in Table 1. The peak age groups were 55-64 years and ≥65 years. There were 69/125(55.2%) males and 56/125(44.8%) females with a male to female ratio of 1.23. The highest number of cases seen 20/125 (16.0%) was in January; the lowest was in August through September which constitutes the peak of the rainy season while November to January is within the harmattan period.

Sixty-three (53.8%) of the patients were found to have co-morbidity: chronic pulmonary disease (CPD) 22 (34.9%), HIV 9 (14.2%), sickle cell anaemia 12 (19.4%), chronic liver disease (CLD) 5 (7.9%) and chronic heart disease (CHD) 10 (15.9%). Table 1 Of the 125 patients, 71/125(56.8%) consented for HIV screening, out of which 9/71 (12.7%) tested positive. Out of the 125 patients, 20(16%) were smokers.

Only 5 (3.8%) of the isolates were sensitive to TPM/SMX, while 19 (15.2%) and 121(96.8%) were fully sensitive to penicillin and ceftriaxone respectively. (Table 2)
Eight patients were lost to follow-up and the overall mortality in the remaining 117patients was 9/117(7.8%). The highest mortality was in those aged ≥65years. Table 3: shows mortality by co-morbidities. Higher CURB-65 score was significantly associated with increased mortality. (Table 4) On multiple logistic regression analysis the only factors

predictive of mortality were HIV (OR=2.081; 95%CI 1.651-3.237), age ≥65years (OR=5.947; 95%CI3.581-17.643), and CURB-65 score of equal or more than 3 (OR=2.317; 95%CI1.734-4.719)

Discussion

Pneumococci are major contributors to community acquired pneumonia and mortality worldwide; however, more knowledge is needed, especially in developing countries like Nigeria Where data is lacking. In this cohort study we described the epidemiology, associated co-morbidities and outcome of community acquired pneumococcal pneumonia as seen in a tertiary hospital in North-western Nigeria. The large sample size of 125 obtained over a two-year period including only microbiologically confirmed pneumococcal CAP argues in favor of the strength of our study.

The peak age group affected and overall male preponderance observed in this study is in keeping with most studies on CAP in Nigeria were pneumococcus was the major pathogen (Macfarlane et al., 1979; Nwosu et al., 1991; Musa et al., 2008). However, we found a slight peak among females within the reproductive age group. This could be attributed to the close proximity of these cohorts to children, whom in many studies were shown to act as reservoirs for adult infection (Hoshino et al., 2002; Muhlemann et al., 2003).

Pneumococcal pneumonia occurred preferentially during the cold dry season This phenomenon has already been described, with a clear link to external temperature (Dowell et al., 2003) which results in drying of mucosal surfaces, coupled with concomitant respiratory viral infections (Talbot et al., 2005a) and increased tendency to cytoadherence by bacteria (Hakansson et al., 1994). The number of patients seen in this study was higher during the harmattan and dry season with fewer cases seen during the rainy season. This seasonal variation is similar to what was reported by Macfarlen et al. (1979) in the 70s and Onyemelukwe et al. (1982) in the 80s in Zaria, Nigeria.

Although it is a hospital based study, high rate of HIV infection (11.5%) was observed among the patients studied when compared with Nigerian prevalence of 5% (WHO, 2009). Previous studies have shown high rate of pneumococcal infection among HIV infected patients (Gilks et al., 1996; Redd et al., 1990; Garcia-Leoni et al., 1992; Schuchat et al., 1991). In fact HIV infection has been recognized as a risk factor for recurrent IPI (Nuorti et al., 2000; Turett et al., 2001).

The comorbidities identified in our study were also reported to be risk factors for pneumococcal disease in several studies worldwide (Janoff et al., 1993; Gentile et al., 2003; Laupland et al., 2004; Talbot et al., 2005b; Lipsky et al., 1986; Chi et al., 2006). The number of patients with COPD in this study outnumbered that of smokers (a major risk factor), this is not surprising as studies in Nigeria has identified in-door pollution such as the use of fire wood for cooking as a significant risk factor for COPD (Erhabo et al., 2002), which could have accounted for the difference. Other common risk factors were not seen in this study, probably because of the limited sample size and restriction of the study to medical wards as this would have missed out some solid malignancies admitted in to surgical oncology unit.

Studies have reported that the risk of dying in patients with pneumococcal disease is dependent on host factors such as age and comorbidities as well as bacterial factors such as serotype and antibiotic resistance (Alanee et al., 2007; Harboe et al., 2009; Jansen et al., 2009; Weinberger et al., 2010). In the current study HIV, age ≥ 65 and CURB-65 score of ≥ 3 were shown to be independent risk factors for mortality, indicating that these patient groups are important vaccination targets in Nigeria for reducing mortality associated with pneumococcal infection. In a multivariate model, immunosuppression (Klemets et al., 2008) was also shown to increase mortality risk in patients with pneumococcal pneumonia. Gordon et al. (2002) showed HIV infected African patients to have higher mortality following pneumococcal infection. In addition to being at higher absolute risk for pneumococcal infection, older adults are also at much higher risk for death should they acquire the infection (Yu et al., 2003). This may be related to ageing related changes in both the innate and adaptive immune response (De Gaudio et al., 2009). In a recent study, age-related impairment of alveolar macrophages and Toll-like receptor levels were seen in mice with pneumonia caused by pneumococcus (Boyd et al., 2012). It is also known that; ageing is associated with a procoagulant state and mitochondrial damage resulting in cellular apoptosis during sepsis (Gavazzi and Krause, 2002). This is reflected in our study, where age ≥65years was the strongest predictor of mortality in a logistic regression model.

The extensive use, misuse and abuse of antibiotics have been said to be the main driving factors of drug resistance in developing countries of world, where access to drugs are poorly controlled and the level of self-medication remains high (Arikpo et al., 2011). Hence it is not surprising we found resistance to antibiotics which are commonly used as first line empirical treatment for pneumonia in Nigeria. A similar trend has been reported in previous studies in Nigeria (Habib et al., 2003; Akanbi et al., 2004; Iwalokun et al., 2012; Adeleye et al., 2008). The prophylactic usage TMP/SMX in AIDS patients has been linked to the wide spread pneumococcal resistance to TMP/SMX (Soeters et al., 2012). However, this antibiotic had been recommended by theWHO (WHO, 2005) for the treatment of pneumococcal disease in HIV/AIDS patients. The resistance rate to TMP/SMX in this study is alarming and this has implication on the use of this drug as prophylaxis for pneumococcal infection in HIV/AIDS patients in Nigeria.

Our case definition for pneumococcal pneumonia was limited to clinical findings, chest x ray features and isolation of pneumococcus from an ideal sputum specimen, rather than the gold standard lung aspirate, hence our data might not have described true invasive pneumococcal pneumonia. This is due to lack of the expertise in doing the procedure and restriction in our ethical approval. Our study highlighted the significance of pneumococcus as a leading cause of community acquired pneumonia in North-western Nigeria. With available effective pneumococcal vaccines, effort should

be geared towards popularizing vaccinating at-risk adult particularly those above 65years of age in Nigeria. Measures to curtail the emergence and spread of pneumococcal resistance such as antibiotic policy and introduction of antimicrobial stewardship program need to be implemented.

Conflict of Interest: Authors declare that there is no conflict of interests.

References

1. Adeleye, A., Uju, L., Idika, N. and Sobande, O. (2008). Cotrimoxazole Resistance in Streptococcus Pneumonia Isolated from Sputum of HIV-positive Patients. *West Indian Med J*., 57:497-499.
2. Aminu Kano Teaching Hospital (AKTH): Antibiotic guideline in common bacterial infection. 2009.
3. Akanbi, I.I., Taiwo, A.A., Babatunde, S.S., Onilke, S.K. and Abdulraheem, I.S. (2004). Antibiotic susceptibility pattern of Streptococcus pneumoniae in Ilorin, Nigeria. *Afr J Clin Exp Microbiol*., 5:173-176.
4. Alanee, S.R., McGee, L., Jackson, D., Chiou, C.C., Feldman, C., and Morris, A.J., Ortqvist, A., Rello, J., Luna, C.M., Baddour, L.M., Ip, M., Yu, V.L. and Klugman, K.P. (2007). Association of serotypes of treptococcus pneumoniae with disease severity and outcome in adults: an international study. *Clin Infect Dis*., 45:46–51.
5. Arikpo, E.A., Eja, M.E., Enyi-Idoh, K.H., Akubuenyi, F., Ngang, U., Akam, C. and Ekomabasi, I. (2011). Patterns of antibiotics drug use in southern Nigerian communities. *World J. Appl. Sci. Technol*. 3:86-92.
6. Boyd, A.R., Shivshankar, P., Jiang, S., Berton, M.T. and Orihuela, C.J. (2012). Age-related defects in TLR2 signaling diminish the cytokine response by alveolar macrophages during murine pneumococcal pneumonia. *Exp Gerontol*., 47:507–518.
7. Chi, B.A., Jackson, L.A. and Neuzil, K.M. (2006). Characteristic and outcomes of older adults with community-acquired pneumococcal bacteraemia. *J Am Geriatr Soc*., 54:115-120
8. Clinical and Laboratory Standard Institute (CLSI) (2006). *Performance Standards for Antimicrobial Susceptibility Testing: Sixteenth Informational Supplement*. CLSI document M100-S16. (ISBN 1-56238-588-7) Wayne, PA: CLSI.
9. De Gaudio, A.R., Rinaldi, S., Chelazzi, C. and Borracci, T. (2009). Pathophysiology of sepsis in the elderly: clinical impact and therapeutic considerations. *Curr Drug Targets*., 10:60–70.
10. Dowell, S.F., Whitney, C.G., Wright, C., Rose, C.E. and Schuchat, A. (2003). Seasonal patterns of invasive pneumococcal disease. *Emerg Infect Dis*., 9:573-579.
11. Erhabo, G.E. and Kolawole, O.A. (2002). Chronic obstructive pulmonary disease: a ten-year review of clinical features in O.A.U.T.H.C., Ile-Ife. *Niger J Med*., 11:101-104
12. Garcia-Leoni, M.E., Moreno, S., Rodeno, P., Cercenado, E., Vicente, T. and Bouza, F. (1992). Pneumococcal pneumonia in adult hospitalized patients infected with the human immunodeficiency virus. *Arch Intern Med*., 9:1808-1812.
13. Gavazzi, G. and Krause, K.H. (2002). Ageing and infection. *Lancet Infect Dis*., 2:659–666.
14. Gentile, J.H., Sparo, M.D., Mercapide, M.E. and Luna, C.M. (2003). Adult bacteraemic pneumococcal pneumonia acquired in the community. A prospective study on 101 patients. *Medicina (B Aires)*., 63:9-14.
15. Gilks, C.F., Ojoo, S.A., Ojoo, J.C., Brindle, R.J., Paul, J., and Batchelor, B.I.F., Kimari, J.N., Newnham, R., Bwayo, J., Plummer, F.A., Plummer, M.A., Gilks, C.F. and Warrell, D.A. (1996). Invasive pneumococcal disease in a cohort of predominantly HIV-1 infected female sex- workers in Nairobi, Kenya. *Lancet*., 347:718-23.
16. Gordon, S.B., Chaponda, M., Walsh, A.L., Whitty, C.J. and Machili, C.E. (2002). Pneumococcal disease in HIV-infected Malawian adults: acute mortality and long-term survival. *AIDS*., 16:1409-1417.
17. Habib, A.G., Nwokedi, E.E., Ihesiulor, I.U., Mohammed, A. and Habib, Z.G. (2003). Wide spread antibiotic resistance in savannah Nigeria. *Afr J Med Med Sci*., 32:303-305.
18. Hakansson, A., Kidd, A., Wadell, G., Sabharwal, H. and Svanborg, C. (1994). Adenovirus infection enhances the in vitro adherence of Streptococcus pneumoniae. *Infect Immun*., 62:2707-2714.
19. Harboe, Z.B., Thomsen, R.W., Riis, A., Valentiner-Branth, P., Christensen J, Jr., Lambertsen, L., Krogfelt, K.A., Konradsen, H.B. and Benfield, T.L. (2009). Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. *PLoSMed*., 6:e1000081.
20. Hoshino, K., Watanabe, H. and Sugita, R. (2002). High rate of transmission of penicillin-resistant *Streptococcus pneumoniae* between parents and children. *J Clin Microbiol*., 40: 4357-4359
21. Iwalokun, B.A., Fowora, M., Akinloye, O., Oluwadun, A., Antonio, M. and Adegbola, R.A. (2012). A retrospective study of clinical Streptococcus pneumonia isolates from four health facilities in South-West Nigeria. *Int J Med Med Sci*., 4:160-170.
22. Janoff, E.N., O'Brien, J., Thompson, P., Ehret, J., Meiklejohn, G., and Duvall, G. and Douglas, JM., Jr. (1993). Streptococcal pneumonia colonization, bacteraemia, and immune response among persons with human immunodeficiency virus infection. *J Infect Dis*., 167: 49-46.

23. Jansen, A.G., Rodenburg, G.D., van der Ende, A., van Alphen, L., Veenhoven, R.H., Spanjaard, L., Sanders, E.A. and Hak, E. (2009). Invasive pneumococcal disease among adults: associations among serotypes, disease characteristics, and outcome. *Clin Infect Dis*., 49:e23–9.

24. Klemets, P., Lyytikainen, O., Ruutu, P., Ollgren, J. and Nuorti, J. (2008). Invasive pneumococcal infections among persons with and without underlying medical conditions: implications for prevention strategies. *BMC Infect Dis*., 8:96.

25. Laupland, K.B., Gregson, D.B., Zygun, D.A., Doig, C.J., Mortis, G. and Church, D.L. (2004). Severe blood stream infection: a population-based assessment. *Crit Care Med*., 32:992-997.

26. Lipsky, B.A., Boyko, E.J., Inui, T.S. and Koepsell, T.D. (1986). Risk factors for acquiring pneumococcal infection. *Arch Intern Med*., 146:2179-2185

27. Macfarlane, J.T., Adeghoye, D.S. and Warrell, M.J. (1979). Mycoplasma pneumonia and the aetiology of lobar pneumonia in Northern Nigeria. *Thorax*., 34:713-719.

28. Muhlemann, K., Matter, H.C., Tauber, M.G. and Bodmer, T. (2003). Nationwide surveillance of nasopharyngeal *Streptococcus pneumoniae* isolates from children with respiratory infection, Switzerland, 1998-1999. *J Infect Dis*., 187: 589-596

29. Musa, B.M., Tijjani, B.M., Okpapi, J.U., Borodo, M.M., Babashani, M. and Shehu, Y. (2008). Bacterial isolates and Antibiotic Sensitivity in Community Acquired Pneumonia. *Niger Med J*., 49:63-66.

30. Nuorti, J.P., Butler, J.C., Gelling, L., Kool, J.L., Reingold, A.L. and Vugia, D.J. (2000). Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. *Ann Intern med.,* 132:182-190.

31. Nwosu, C.M. and Anisiuba, B.C. (1991). A hospital study of adult community acquired pneumonia: Clinical and microbiological characteristics and response to penicillin. *Orient J Med*., 3:138-141.

32. O'Brien, K.L., Wolfson, L.J., Watt, J.P., Henkle, E., Deloria-Knoll, M. and McCall, N. (2009). Burden of disease caused by Streptococcus pneumonia in children younger than 5years: Global estimates. *Lancet*., 374:893-902.

33. Onyemelukwe, G.C. and Greenwood, B.M. (1982). Pneumococcal serotypes, epidemiological factors and vaccine strategy in Nigerian patients. *J Infect*., 5: 157-63.

34. Ortqvist, A., Hedlund, J. and Kalin, M. (2005). Streptococcus pneumoniae: epidemiology, risk factors, and clinical features. *Semin Respir Crit Care Med*.,26:563–574.

35. Rehle, T.M., Mattke, P., Liomba, G.N., Krämer, S., Gershy-Damet, G.M., Konan, K., Sangare, A., Zeken,g L., Tsague, J.M., Kaptue, L., Eberle, J., Gürtler, L. (1997). Evaluation of a quantitative double ELISA strategy for confirmation and differentiation of HIV infection. *J Virol Methods*., 66(2):203-209.

36. Redd, S.C., Rutherford, G.W., Sande, M.A., Lifson, A.R., Hadley, W.K., Facklam, R.R. and Spiker, J.S. (1990). The role of human immunodeficiency virus infection in pneumococcal bacteremia in San Francisco residents. *J Infect Dis*., 162:1012-1017.

37. Schuchat, A., Broome, C.V., Hightower, A., Coster, S.J. and Parkin, W. (1991). Use of surveillance for invasive pneumococcal disease to estimate the size of the immunosuppressed HIV-infected population. *JAMA*., 265:3275-3279

38. Soeters, H.M., Gottberg, A., Cohen, C., Quan, V. and Klugman, K.P. (2012). Epidemiology and Surveillance Trimethoprim-Sulfamethoxazole Prophylaxis and Antibiotic Non-susceptibility in Invasive Pneumococcal Disease. *Antimicrob Agents Chemother*., 56:1602-1605.

39. Talbot, T.R., Hartert, T.V., Mitchel, E., Halasa, N.B., Arbogast, P.G., Poehling, K.A., Schaffner, W., Craig, A.S. and Griffin, M.R. (2005a). Asthma as a risk factor for invasive pneumococcal disease. *N Engl J Med*., 352:2082-2090.

40. Talbot, T.R., Poehling, K.A., Hartert, T.V., Arbogast, P.G., Halasa, N.B., Edwards, K.M., Schaffner, W., Craig, A.S. and Griffin, M.R. (2005b). Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. *Am J Med*., 118:285-291.

41. Turett, G.S., Blum, S. and Telzak, E.E. (2001). Recurrent pneumococcal Bacteraemia: Risk Factors and Outcomes. *Arch Intern Med*., 161:2141-2144.

42. Weinberger, D.M., Harboe, Z.B., Sanders, E.A., Ndiritu, M., Klugman, K.P., Rückinger, S., Dagan, R., Adegbola, R., Cutts, F., Johnson, H.L., O'Brien, K.L., Scott, J.A. and Lipsitch, M. (2010). Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clin Infect Dis*., 51:692–699.

43. WHO expert consultation on Cotrimoxazole pophylaxix in HIV infection. WHO technical report series, Geneva; 2005. Available from: http://www. who.int/hiv/pub/meetingreports/ctx/en [Last accessed on 22 August 2015].

44. World Health Organisation. The Global Burden of Disease: 2014Update.Geneva, Switzerland. Available from: http://www.who.int/healthinfo/global burden disease/GBD report 2014 update. [Last accessed on 29 August 2016]

45. WHO/UNAIDS; Global facts and figures. 2009.

46. Yu, V.L., Chiou, C.C. and Feldman, C. (2003). An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered and clinical outcome. *Clin Infect Dis*., 37: 230-237.