

The burden of respiratory disease in Nigeria

M O Akanbi, C O Ukoli, G E Erhabor, F O Akanbi, and S B Gordon

Introduction

Respiratory disease is a major cause of mortality and morbidity worldwide. In most developing countries including Nigeria, the burden of respiratory disease is largely unknown; however the burden of infectious and non-infectious respiratory disease appears to be on the increase. This article aims to review current available literature on infectious and non-infectious respiratory disease among Nigerians with a view to identifying major causes of morbidity and mortality, and highlighting where gaps in knowledge exist that require new studies for their elucidation.

Nigeria is a nation of over 130 million diverse people occupying a land mass of 923 766 km². It is the fourth largest exporter of crude oil. Despite the huge gains made over the years from petroleum, the nation's people are largely impoverished. With a GDP of US\$1116 in 2007, Nigeria ranked 165 in the world (South Africa ranked 57 and Malawi 177).¹ The percentage of persons living on less than 1US\$ per day is 71.² The under-5 mortality rate was 197/1000 live births in 2007 which is still a far cry from the Millennium Development Goal target of <70/1000 by 2015.²

Methodology

A literature search was carried out using the Pubmed website and the search term 'Nigeria', with 16 799 hits. The search was redefined as 'Nigeria and Lung' (202 hits). Abstracts of these studies were read and articles that addressed the epidemiology or determinants of respiratory disease in Nigeria were reviewed. Where no relevant studies were available on Pubmed, information on the disease of interest was obtained using the 'Google scholar' search engine or grey literature.

Distribution of disease

Distribution of infectious respiratory diseases in adults *Tuberculosis*

The World Health Organization (WHO) estimates that Nigeria has the fifth highest burden of tuberculosis (TB)

in the world (see Figure 1). It is estimated that 395 000 cases of TB occurred in Nigeria in 2007 (283 cases per 100 000 population).³ The Nations' DOTS programme, which is estimated to have a coverage of 65%, has a case detection rate of 35% for smear-positive TB (the target is 70%). Despite this low case detection rate, the reported incidence of TB has been on the increase during the last 10 years as shown in Figure 2.

A survey carried out at TB referral centers in Abuja, North Central Nigeria in 2003 showed that of 1391 patients seen during the year, 21.3% were smear positive. The highest incidence of smear positive TB was found in the 21- to 30-year age group with no gender difference.⁴

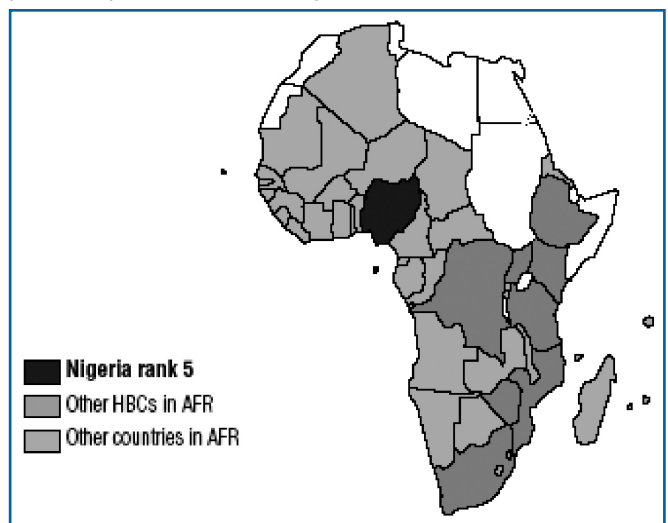
Due to a paucity of facilities for sputum culture and sensitivity, there is a paucity of data on prevalence of smear-negative TB. A 10-year review of sputum samples sent to the University College Hospital, Ibadan, Nigeria on suspicion of TB, showed that 6.9% of smear-negative sputum samples were culture positive.⁵

The burden of multidrug resistant (MDR) and extensive drug resistant (XDR) TB is largely unknown due to the absence of a national survey. The urgent need for a national survey on the prevalence of MDR TB has been recognised and preparations for the survey are in progress.

Pneumonia

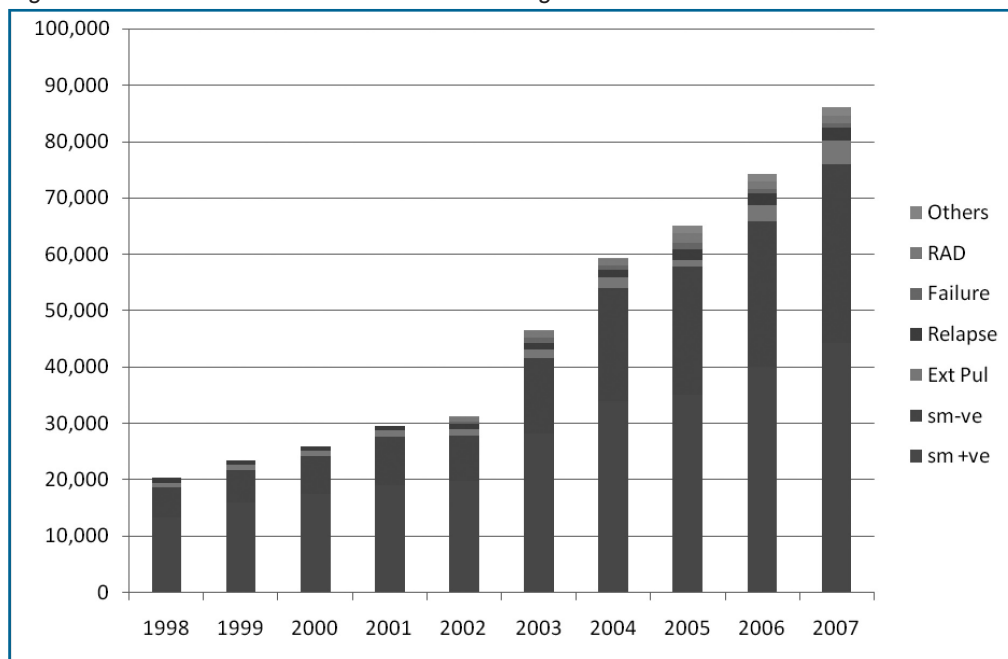
Acute lower respiratory tract infection is a common cause of hospital admission in Nigeria; however no

Figure 1 Burden of TB in Africa. WHO Africa region (AFR): rank based on estimated number of incident cases (all forms) in 2006. HBC, high-burden countries



M O Akanbi and C O Ukoli, Department of Medicine, JUTH, Jos, Nigeria; G E Erhabor, Department of Medicine, Obafemi Awolowo University, Ife-Ife, Nigeria; F O Akanbi, Evangel Hospital Jos; and S B Gordon, Liverpool School of Tropical Medicine, University of Liverpool, UK.
Correspondence to: M O Akanbi, Department of Medicine, Jos University Teaching Hospital, PM Bag 2076, Jos, Plateau State Nigeria. Email: maxwell_akanbi@yahoo.com

Figure 2 Case notification for tuberculosis in Nigeria



comprehensive study on the prevalence of pneumonia in adults is readily available. Among patients attending a TB clinic in South Western Nigeria, 6.4% had streptococcal pneumonia;⁶ unfortunately there are no other studies to corroborate this finding. Few studies have also investigated the aetiology of pneumonia in Nigerian adults. A study of 74 patients with pneumonia in Zaria, Northern Nigeria, however, showed that 50% had positive pneumococcal polysaccharide antigen and 16.2% had *Mycoplasma pneumoniae*.⁷

HIV-related pulmonary infections

The lungs remain the most common site of infection in persons living with HIV infection.^{8,9} In Nigeria, TB remains the most common pulmonary infection in persons with HIV/AIDS with incidence of TB increasing with decreasing level of immunity. In Jos, North Central Nigeria, an audit showed that 45% of HIV-infected patients admitted to the medical ward of a referral hospital had pulmonary TB.¹⁰

Acute lower respiratory infections are also very common. Salami et al¹¹ in a prospective study of HIV-infected patients attending clinic in Ilorin, Nigeria over a 16-month period found that 22.6% of the subjects developed community-acquired pneumonia, with the most common organism being *Streptococcus pneumoniae*. This is similar to findings from other African countries.^{12,13}

Distribution of infectious respiratory diseases in children

Acute respiratory infections

Acute respiratory infections are a major cause of hospital admission and death in Nigerian children. Between the years 2000 and 2003 it was estimated that pneumonia

accounted for 20% of deaths in children under the age of 5 years in Nigeria.²

In a prospective cohort study in Ilorin, the rate of acute respiratory infection was three episodes per child per year with pneumonia being responsible for 1.3 episodes per child per year.¹⁴ In another hospital-based study in Ibadan, 28.4% of children admitted to the hospital with acute lower respiratory tract infection had acute bronchiolitis with respiratory syncytial virus being the most common viral aetiological agent.¹⁵ There are scanty data on the bacterial aetiology of pneumonia in Nigerian children.

There is a seasonal variation in acute respiratory infections in Nigerian children with more episodes occurring during the rainy season.^{14,15} Pneumonia is also associated with measles infection, and this has been recognised as the major cause of death from measles in sub-Saharan Africa.¹⁶⁻¹⁸

Tuberculosis

There are sparse data on the prevalence of TB in Nigerian children. The disease burden is however likely to be high. Infection with TB in children usually follows contact with adults with smear-positive TB.^{19,20} Contact tracing for TB is not routinely carried out in Nigeria and this has been observed in other parts of sub-Saharan Africa.²¹ A survey carried out in Abuja showed that 70% of children who had close contact with adults with smear-positive TB were infected compared to 10% of the control.²²

HIV-related pulmonary infections

WHO estimates that in 2004, 5% of deaths in under-5-year-old children in Nigeria was due to HIV infection.²³ Similar figures were obtained from hospital surveys.^{24,25} Infection in most cases is through vertical transmission.^{24,25} This underscores the need for intensifying Prevention of Mother-to-Child Transmission (PMTCT) programmes within the country.

Oniyangi and colleagues in Abuja studied the pattern of paediatric HIV/AIDS and observed that pneumonia was the admitting diagnosis in 60% of their subjects and the cause of death in 71.4%.²⁴ In Ilorin, Adejuyigbe and colleagues found that 46.3% of deaths in HIV-infected children was due to pneumonia.²⁵ None of these studies looked at the aetiology of pneumonia in these children, which is an important area of study for preventive interventions.

Daniel and colleagues in Western Nigeria found an HIV seroprevalence of 10% among children with TB.²⁶ There are limited data on the prevalence of TB in HIV-infected children. This may be compounded by the challenges in diagnosing TB in children. New diagnostic tools for TB are long overdue.

Distribution of non-infectious respiratory diseases in adults

Chronic obstructive pulmonary disease (COPD)

A nationwide survey of non-communicable diseases has been carried out in Nigeria;²⁷ this unfortunately excluded respiratory diseases. There are no national data on the prevalence of COPD.

Risk factors for COPD, however, abound. National surveys on smoking patterns show an increase in the number of smokers, with the age of onset of smoking progressively falling.^{27,28} Smoking among females, though still culturally unacceptable, is also on the increase.²⁷

A more important risk factor for COPD, especially among women, is the exposure to biomass smoke. Wood remains an important cooking fuel in many homes in Nigeria. COPD resulting from such exposures has been reported in some parts of the continent.^{21,29}

Asthma

The prevalence of asthma is feared to be on the increase in developing countries with great economic and humanitarian effects.²⁸ There are, however, no longitudinal studies from Nigeria to support this. Data from developed countries clearly demonstrate this time trend.²⁸

Efforts have been made to find asthma prevalence among various populations in Nigeria. In a recent survey among university undergraduates aged 15–35 years in Ife, Western Nigeria, 10.4% of males and 17.9% of females had probable asthma.³⁰

There is an urgent need for a national survey on asthma prevalence and determinants in developing countries.

Occupational lung diseases

Lung diseases following occupational exposures among Nigerians have been extensively studied. These include wood workers,³¹ cement workers,³² stone cutters,³³ and coal miners.³⁴ This database has, however, not translated into improved respiratory health among workers exposed to dust. Education on the ill-effects of occupational exposure to dust is still low with suboptimal use of protective devices.³⁵

Sarcoidosis

This is thought to be rare among Africans, but there have been several reported cases in Nigeria. Awotedu and colleagues³⁶ in Ibadan, diagnosed 12 patients with sarcoidosis over a 2-year period. There was another report of four cases over an 8-month period.³⁷ A study of lymph node histology over a 20-year period in Benin, showed that sarcoidosis was present in 0.2% of the samples.³⁸ Sarcoidosis may not be as rare as we think.

Pulmonary malignancies

Kaposi's sarcoma (KS) is fast becoming the most important pulmonary malignancy in Nigerian adults due to the HIV/AIDS epidemics. Atypical African KS has been shown to be associated with AIDS.³⁹ Among HIV-infected patients in Malawi, pulmonary KS is associated with palatal KS and blood-stained pleural effusion, or persistent pulmonary symptoms not responsive to antibiotic and anti-tuberculous therapy.²¹ This is a finding that requires validation as facilities for diagnosis of pulmonary KS are largely unavailable.

Distribution of non-infectious respiratory diseases in children

Asthma

Asthma is one of the most common chronic illnesses afflicting the paediatric age group.⁴⁰ Despite recent advances in knowledge of the aetiology and management of asthma, this has not reduced mortality and morbidity resulting from it.⁴¹

Data obtained from the International Study of Asthma and Allergies in Childhood (ISAAC, <http://isaac.auckland.ac.nz>) showed the prevalence of asthma as 13.1% in Nigerian children aged 6 to 7 years.⁴² Prevalence values from African countries were generally lower than those obtained from developed nations with only the South African prevalence being close to that obtained in the United Kingdom. A longitudinal study carried out in Ghana, showed an increasing prevalence of childhood asthma over a 10-year period.⁴³ Similar studies from other African nations are needed to understand the trend and possible emerging risk factors for childhood asthma on the continent.

Cystic fibrosis

There is no indexed report of cystic fibrosis in a Nigerian. There are however a few cases among South African Blacks with an estimated prevalence range of 1 in 784 to 1 in 13 924.⁴⁴

HIV-associated non-infective pulmonary disease

Kaposi's sarcoma

HIV-associated KS is believed to be common in African children but data on its prevalence are scanty. A study of causes of peripheral lymphadenopathy in Nigerian children over a 20-year period showed that 2% was due to KS.⁴⁵ The burden of pulmonary KS in Nigerian children is largely unknown.

Non-Hodgkin's lymphoma

Incidence of non-Hodgkin's lymphoma is high in non-HIV-infected and HIV-infected African children. Incidence among non-HIV-infected Nigerian children is 76.2/million, compared to 0.3/million in US black children and 2/million in US white children; while the extrapolated incidence in HIV-infected Nigerian children is 4400/million.⁴⁶ We need national studies to verify these figures.

Determinants of respiratory disease in Nigerians

The prevalence of infectious and non-infectious diseases tends to be on the increase. This is probably due to an interaction of several factors; biological, environmental, and behavioural.

Immunisation remains a cost-effective way of preventing disease. The WHO-expanded programme on immunisation in Nigeria includes BCG (Bacillus Calmette-Guéri), diphtheria, pertussis, measles, tetanus, and more recently monovalent hepatitis B vaccine (2004).⁴⁷ Immunisation coverage in Nigeria is largely dependent on political commitment. Figure 3 is a graph showing the pattern of BCG vaccine coverage in Nigeria from 1980 to 2006.

Poverty and malnutrition are important contributors to preventable infectious diseases in Nigeria. The recent HIV/AIDS scourge has also impacted negatively on morbidity and mortality due to TB and pneumonia.

Behavioural factors contributing to the increasing burden of respiratory disease in Nigeria include the increasing prevalence of cigarette smoking, particularly among the youth. Smoking in women is also on the increase. More importantly, the persistent exposure to biomass smoke, particularly from cooking fuel, may make this the most important risk factor for COPD in Nigeria.

Other important factors include the increasing globalisation and its impact on respiratory disease. Could exposure to refined food and reduced exposure to parasites early in life ('The hygiene hypothesis') explain the rising incidence of non-communicable diseases (particularly asthma)? These are areas requiring investigation.

Conclusion

The burden of respiratory disease in Nigeria is high (see Table 1). Respiratory infections, particularly TB and bacterial pneumonia, are the major causes of death in adults and children, with morbidity and mortality due to these diseases rising sharply in HIV-infected persons. The impact of biomass exposure and cigarette smoking

Table 1 Classification of respiratory disease burden in Nigeria

Infectious respiratory disease	Adults	Tuberculosis Pneumonia HIV-related infection
	Children	Acute respiratory infection Tuberculosis HIV-related infection
Non-infectious respiratory disease	Adults	COPD Asthma Occupational lung disease Pulmonary malignancies Sarcoidosis
	Children	Asthma HIV-related malignancies

on respiratory health is largely unknown.

The paucity of data is apparent. This is compounded by the absence of reliable population based denominators to rightly assess the burden of disease.⁴⁸

With a belated national prevalence study for MDR TB underway, other pressing questions needing answers are the prevalence of bronchial asthma among adult Nigerians and more importantly, the prevalence of COPD and the etiological role of biomass exposure (particularly cooking fuel).

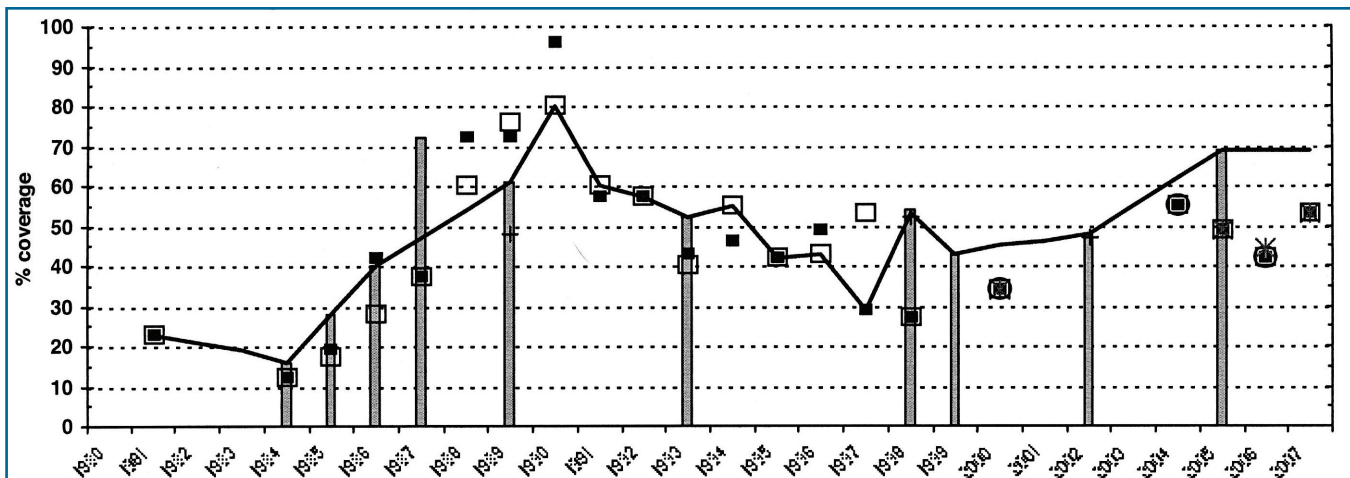
Acknowledgement

This work was supported by the Pan African Thoracic Society – MECOR grant – and the Royal College of Physicians (UK) Travel Bursary.

References

1. International Monetary Fund. World Economic Outlook Database. International Monetary Fund, 2007.
2. World Health Organization. *Public Health and the Environment*. Geneva: WHO, 2007.
3. World Health Organization. *Global Tuberculosis Control: Surveillance, Planning and Financing*. WHO Report 2007. Geneva: WHO, 2007.
4. Bassey EB, Momoh MA, Imadiyi SO, et al. The trend of pulmonary tuberculosis in patients seen at DOTS clinics in the Federal Capital Territory, Abuja, Nigeria. *Public Health* 2005; 119: 465–8.
5. Kehinde OA, Ige OM, Dada-Adegoke HO, Obaseki FA, Ishola OC. Pulmonary tuberculosis in Ibadan: a ten year review of laboratory reports. *Afr J Med Sci* 2006; 35: 475–8.
6. Agwu E, Ohinion AA, Agba MI. Incidence of Streptococcus Pneumoniae among patients attending tuberculosis clinics in Ekpoma, Nigeria. *Shiraz E-Medicine J* 2006; 1–7.
7. Macfarlane JT, Adegboye DS, Warrell MJ. Mycoplasma pneumonia and the aetiology of lobar pneumonia in Northern Nigeria. *Thorax* 1979; 34: 713–19.
8. Back JM, Rosen MJ, Peavy HH. Pulmonary complications of HIV infection. Report of the fourth NHLBI workshop. *Am J Respir Crit Care Med* 2001; 164: 2120–6.
9. Murray JF, Felton CP, Garay SM, et al. Pulmonary complications of the acquired immunodeficiency syndrome: report of a National Heart, Lung and Blood Institute workshop. *N Engl J Med* 1984; 310: 1682–8.
10. Idoko JA, Anteyi E. HIV associated tuberculosis in Jos. *Niger Med Pract* 1994; 28: 49–54.
11. Salami AK, Olatunji PO, Oluboyi PO, Akanbi AA, Fawise EA. Bacterial pneumonia in the AIDS patients. *West Afr J Med* 2006; 25: 1–5.
12. Koulla-Shiro S, Kuaban C, Belec L. Acute community acquired bacterial pneumonia in human immunodeficiency virus (HIV) infected and non-HIV infected adults in Cameroon: aetiology and outcome. *Tuber Lung Dis* 1996; 77: 47–51.
13. van Oosterhout JJ, Laufer MK, Graham SM, et al. A Community-based study of the incidence of trimethoprim-sulfamethoxazole-preventable infections in Malawian adults living with HIV. *J Acquir Immune Defic Syndr* 2005; 39: 626–31.
14. Fabule D, Parakoyi DB, Spiegel R. Acute respiratory infections in Nigerian children: prospective cohort study of incidence and case management. *J Trop Pediatr* 1994; 40: 279–84.
15. Johnson AW, Aderele WI, Osinusi K, et al. Acute bronchiolitis in Tropical Africa: a hospital based perspective in Ibadan, Nigeria. *Pediatr Pulmonol* 1996; 24: 236–47.
16. De Buse PJ, Jones G, Nairdo A. A comparison of penicillin and tetracycline in pulmonary complications of measles; a clinical and radiological assessment. *East Afr Med J* 1969; 46: 46–54.
17. Wesley AG, Sutton JB, Widrich AJ. The aetiology of pneumonia associated with measles in Bantu children. *S Afr Med* 1971; 45: 1402–4.
18. Morton R, Mee J. Measles pneumonia: lung puncture findings in 56 cases related to chest X-ray changes and clinical features. *Ann Trop Paediatr* 1986; 6: 41–5.
19. Grzybowski S, Barnett GD, Styblo K. Contacts of adults with active Pulmonary Tuberculosis. *Bull Int Union Tuberc* 1975; 50: 90–106.
20. Loudon RG, Williamson, Johnson JM. An analysis of 3,485

Figure 3 BCG immunisation coverage in Nigeria 1980–2006



Description of trend

Due to increased activity to reach the UCI-goal and large campaigns in the late 1980s, coverage rates increase from 16% in 1984 to 80% in 1990, supported by survey data between 1984 and 1986. Political problems lead to a reduction of coverage rates after 1990. Following a campaign in 1997, coverage increases back to a level of 53%. The estimates since 1998 are based on recent surveys.

Data presented in chart

Year	WHO/UNICEF estimate (%)	Reported to:*		Government official estimate (%)	Reported doses administered (%)**	Survey data (%)***	
		WHO (%)	UNICEF (%)			Survey 12-23 months	Survey <12 months
1980	23	23	23				
1981	21						
1982	19						
1983	16	12	12			16	
1984	28	28	42			28	
1985	40	37	37			40	
1986	47	60	72			72	
1987	54	76	72			61	48
1988	60	80	96				
1989	61	60	57				
1990	80	80	96				
1991	60	60	57				
1992	57	57	57				
1993	52	40	43			52	
1994	55	55	46				
1995	42	42	42				
1996	43	43	49				
1997	29	53	29				
1998	53	27	27			54	52
1999	43					43	
2000	45	34	34	34	34		
2001	46						
2002	48					48	47
2003	55						
2004	62	55	55	55			
2005	69	49	49		49	69	
2006	69	42	42	42	44		
2007	69	53	53		53		

*Prior to 1998 national reports to WHO/UNICEF did not specify whether information was derived from administrative records, surveys or other sources.

**Coverage based on registration of doses administered by health care providers.

***In case more than one survey was implemented in a certain year the highest value is presented. Details of all data are presented in the second section of this report.

Tuberculosis contacts in the city of Edinburgh during 1954–1955. *Am Rev Tuberc* 1954; 77: 623–47.

21. Gordon SB, Graham S. Epidemiology of respiratory diseases in Malawi. *Malawi Med J* 2006; 18: 134–46.

22. Nakaoka H, Lawson L, Squire SB, Coulter B, Ravn P. Risk of tuberculosis among children. *Emerg Infect Dis* 2006; 12: 1383–8.

23. World Health Organization. *Mortality Country Fact Sheet* 2006. Geneva: WHO, 2006.

24. Oniyangi O, Awani B, Iregbu KC. The pattern of paediatric HIV/AIDS as seen at the National Hospital, Abuja Nigeria. *Niger J Clin Pract* 2006; 9: 153–8.

25. Adejuyigbe EA, Oyelami O, Onayemi O, Durosimi MA. Paediatric HIV in Ile-Ife, Nigeria. *Cent Afri J Med* 2003; 49: 74–8.

26. Daniel OJ, Ogunfowora OB, Oladapo OT. HIV Sero-prevalence among children diagnosed with TB in Nigeria. *Trop Doct* 2007; 37: 268–9.

27. Akinkugbe OO. *Non-communicable Diseases Survey*. Lagos, Nigeria: Federal Ministry of Health and Social Services, 1997.
28. Eder W, Ege MJ, Mutius EV. The asthma epidemic. *N Engl J Med* 2006; 355: 2226–35.
29. Erhabor GE, Koalwole OA. Chronic Obstructive Pulmonary Disease: a ten-year review of clinical features in OAUTHS, Ile-Ife, Nigeria. *Niger J Med* 2002; 11: 101–4.
30. Erhabor GE, Agbroko SO, Bamigboye P, Awopeju O. The prevalence of asthma symptoms among university students 15–35 years of age in Obafemi Awolowo University, Ile-Ife, Osun State. *J Asthma* 2006; 43: 161–4.
31. Ige OM, Onadeko OB. Respiratory symptoms and ventilatory functions of the Sawmillers in Ibadan, Nigeria. *Afr J Med Sci* 2000; 29: 101–4.
32. Kalaic I. Chronic non-specific lung disease in cement workers. *Arch Environ Health* 1973; 26: 78–83.
33. Warrell A, Harrison BD, Fawcett IW, et al. Silicosis among grindstone cutters in North of Nigeria. *Thorax* 1975; 30: 389–98.
34. Ogakwu MAB. Pilot health survey among Enugu coal miners. *Niger J Med* 1973; 3: 97–9.
35. Ezeonu E, Ezeonu J, Edeogu OC. Occupational health hazards in the Nigerian cement industry – workers' awareness and perception. *Afr Newslett Occup Health and Safety* 2005; 15: 73–6.
36. Awotedu AO, George PO, Oluboyo G, et al. Sarcoidosis in Africans; 12 cases with histological confirmation from Nigeria. *Trans R Soc Trop Med Hyg* 1987; 8: 1027–8.
37. Elegbeleye OO. Sarcoidosis in Africans. *Trop Geogr Med* 1978; 30: 467–71.
38. Olu-Eddo, Ohanaka CE. Peripheral lymphadenopathy in Nigerian adults. *J Pak Med Assoc* 2006; 56, 405–8.
39. Pozniak AL, Latif AS, Neill P, et al. Pulmonary Kaposi's sarcoma in Africa. *Thorax* 1992; 47: 730–2.
40. Evans R 3rd, Mullally DI, Wilson RW, et al. National trends in the morbidity and mortality of asthma in the US; Prevalence, hospitalization and deaths from asthma over two decades: 1965–1984. *Chest* 1987; 91: 655b–74S.
41. Buist AS, Vollmer VM. Reflection on the rise in asthma morbidity and mortality. *JAMA* 1990; 264, 1719–20.
42. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP. World-wide time trends in the prevalence and symptoms of asthma and allergic rhinoconjunctivitis and eczema in childhood. ISAAC Phases one and three repeat multicountry cross-sectional survey. *Lancet* 2006; 368, 733–43.
43. Addo-Yobo EOD, Woodcock A, Allotey A, Baffoe-Bonnie B, Strachan D. Increasing prevalence of asthma in Ghana (children) 1993–2003. *PLoS Med* 4:e70:doi:10.1371/journal.pmed.2008.
44. Podoac C, Golden A, Jenkins T, Ramsay M. Cystic fibrosis carrier frequencies in populations of African origin. *J Med Genetics* 1999; 36: 41–4.
45. Adesuwa Olu-Eddo N, Egbagbe EE. Peripheral lymphadenopathy in Nigerian children. *Niger J Clin Pract* 2006; 9, 134–8.
46. Centers for Disease control and prevention. AIDS among children – United States, 1996. *MMWR* 1996; 45: 1005–10.
47. WHO/UNICEF Review of National Immunization Coverage 1980–2007. Geneva: WHO, 2007.
48. Cooper RS, Oshotimehin B, Kaufman JS, Forrester T. Disease burden in sub-Saharan Africa: what should we conclude in the absence of data? *Lancet* 1998; 35: 208–10.

AJRM

The African Journal of Respiratory Medicine

Call for articles

The Editors welcome articles on respiratory medicine from all health professionals, medical and non-medical.

We publish Review Articles, Original Articles, Short Reports, Case Reports, and Letters.

Please see 'Guidance to authors' on page 32 and email your manuscript to editor@fsg.co.uk.