Public Health (2005) **119**, 321–327

PUBLIC HEALTH
JOURNAL OF THE ROYAL INSTITUTE OF PUBLIC HEALTH
www.elsevierhealth.com/journals/pubh

Multidrug resistance in *Salmonella enterica serovar typhi* isolated from patients with typhoid fever complications in Lagos, Nigeria

K.O. Akinyemi[a,*], S.I. Smith[b], A.O. Bola Oyefolu[a], A.O. Coker[c]

[a]*Department of Microbiology, Lagos State University, Ojo, P.M.B. 1087, Apapa, Lagos, Nigeria*
[b]*Nigerian Institute of Medical Research, Yaba, College of Medicine, University of Lagos, Idi-Araba, P.M.B. 12003 Lagos, Nigeria*
[c]*Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos, Idi-Araba, P.M.B. 12003 Lagos, Nigeria*

Received 12 August 2003; received in revised form 15 April 2004; accepted 28 April 2004

Available online 30 November 2004

KEYWORDS
Multidrug resistant; *Salmonella enterica serovar typhi*; Plasmid; Antimicrobial; Typhoid fever; Psychosis; Hepatosplenomegaly

Summary *Objective*. The aim of this study was to determine the prevalence of *Salmonella enterica serovar typhi* in patients with pyrexia of unknown origin (PUO), and antimicrobial resistance in strains isolated from patients with *S. typhi* in Lagos, Nigeria.

Study design. In total, 103 patients were included in this study, subdivided into two categories. Category A comprised 74 patients presenting with PUO, and Category B comprised 29 patients harbouring *S. typhi* who did not respond to initial treatment.

Methods. Blood samples were cultured for bacterial isolates and identified by standard procedures. Susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards. Plasmid DNA extraction was performed using the alkaline lysis method with *Escherichia coli* v517 used as the standard. Conjugation and transformation experiments were performed using standard methods. For the latter, *E. coli* K12 HB 101 (ara-14, galK2, hsd 520, lacyl, leu, mtl-1, Pro A2, rec A13, rps L20, sup E44, thii xyl-5) was used as the recipient and plasmid PBR 322 was used as the positive control.

Results. The prevalence of *S. typhi* in PUO was 16.2% (12/74). In all, 25 of 41 (61.0%) cases were multidrug resistant (MDR) with phenotypic-resistant patterns: ACoCT, ACTCeS, ACTCoCe and ACTS were commonly encountered among the strains. Interestingly, four of the strains harbouring similar plasmid DNA were isolated from patients with hepatosplenomegaly, and a strain harbouring a large transferable plasmid of 81.2 MDa was isolated from a psychosis patient.

Conclusions. Our study confirmed the circulation of MDR *S. typhi* in Lagos, Nigeria. Periodic review of antibiotics used in hospitals is essential as the efficacies of chloramphenicol, ampicillin and cotrimoxazole are now doubtful. Ciprofloxacin and ofloxacin are effective drugs for treatment of typhoid fever, but with current trends of drug abuse in Nigeria, resistance is likely to develop. These results, therefore, provide an early warning signal for the prudent use of fluoroquinolone antimicrobials to preserve their usefulness.

*Corresponding author.
E-mail address: akinyemiko@yahoo.com

0033-3506/$ - see front matter © 2004 The Royal Institute of Public Health. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.puhe.2004.04.009

Introduction

Salmonella enterica serotype typhi is the causative agent of typhoid fever, a disease that is unique to humans as the only natural hosts and reservoirs of the pathogen. The infection is transmitted by ingestion of faecally contaminated food, vegetables and/or water. Although typhoid fever does not present a distinct clinical picture, other bacterial, viral and even protozoan infections may mimic its presentation.[1–3] The disease is characterized by prolonged fever, abdominal distension, constipation, headache, apathy, rash, malaise, loss of appetite, nausea, vomiting, hepatosplenomegaly and leukopenia.[3]

Public health measures and effective antibiotic therapy have led to a decrease in typhoid fever worldwide. In developed countries such as the USA and the UK, the incidence is low and most cases are found in travellers returning from endemic areas of developing countries.[4] The situation is different in developing countries of Africa and the Indian subcontinent as this febrile disease continues to pose a threat to public health with an estimated incidence of 33 million cases each year.[5]

In Nigeria, typhoid fever is among the major widespread diseases affecting both young children and young adults in their productive years.[6] Effective treatment of patients has been based on the use of chloramphenicol, ampicillin and cotrimoxazole as soon as clinical diagnosis is made without recourse to the results of antimicrobial susceptibility tests. Chloramphenicol has been used extensively in Nigeria, as in other developing countries, since its introduction in 1948. The efficacy of this antibiotic was in doubt shortly after the extensive epidemic of typhoid fever in Mexico in the early 1970s, in which plasmid-mediated chloramphenicol-resistant *S. typhi* strains were implicated.[7] From the late 1980s to the early 1990s, the efficacy of alternative drugs such as ampicillin, trimethoprim and cotrimoxazole for typhoid fever was also questioned following the outbreaks in the Indian subcontinent, South-east Asia, South Africa and the Philippines, in which *S. typhi* strains harbouring plasmid DNA belonging to incompatibility group HI, similar to the strains isolated from Mexico, were found.[8]

In recent years, the increased number of reported cases of typhoid fever in both public and private hospitals, which often resulted in treatment failure with empirical therapy, has been a major concern. Update reports on the antimicrobial patterns of *S. typhi* strains from our environment remain a conjecture. The aim of this study was to determine the prevalence of *S. typhi* in patients with pyrexia of unknown origin (PUO), and antimicrobial resistance in strains isolated from patients with *S. typhi* in Lagos, Nigeria.

Materials and methods

Patient population and study centres

In total, 103 patients were recruited for this study. Most patients were of low and middle socioeconomic status. Between May 2000 and July 2001, the patients were admitted to: Lagos University Teaching Hospital Idi-Araba, Lagos; Ikeja General Hospital Ikeja, Lagos; Infectious Diseases Hospital Mainland, Lagos (public health institutions); and Central Bank of Nigeria Clinics, Satellite Town, Lagos (private staff clinic). Important biodata such as age, sex, history of vaccination, antimicrobial therapy, time of onset of illness etc. were recorded.

Clinical case definition and sample collection

The subjects in this study were subdivided into two categories. Category A comprised 74 patients with PUO (as diagnosed by a clinician) for up to 5 days with one or more of the following symptoms: diarrhoea, vomiting, headache, loss of appetite, malaise, and abdominal pain. Only blood samples were requested from the patients owning to purported early onset of symptoms. Category B comprised 29 patients who had been admitted for more than 3 weeks and who had initially been diagnosed for ailments such as typhoid fever and malaria. Also, complications such as hepatosplenomegaly were observed in six patients, and two patients presented with psychosis. They were later confirmed by culture to be typhoid fever, but did not respond to first-line antimicrobials.

Four millilitres of blood were collected from each patient. Of this, 1 ml of blood was transferred into a sterile EDTA bottle and kept at 4 °C until the malaria-parasite test was performed. The remaining 3 ml of blood were directly inoculated into 27 ml of brain heart infusion (BHI) broth (Oxoid, UK) for bacteriological culture.

Bacteriology

The BHI broth culture bottles were inoculated at 37 °C aerobically for 18–24 h. Subcultures were made onto solid media plates of blood agar, *Salmonella–Shigella* agar and desoxycholate