Full Length Research Paper

Usefulness of Routine Antibacterial Susceptibility Testing Results for Resistance Surveillance in Lagos Metropolis

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ABSTRACT

The objective was to evaluate the usefulness and reliability of routine antibacterial susceptibility testing data in antibacterial resistance surveillance in Lagos Metropolis. The antibacterial susceptibility testing results of 3,961 clinical isolates of bacteria from four highly rated hospitals in Lagos metropolis were collated and evaluated. Sampling was systematically randomized over any four consecutive years between 2002-2009 for each hospital. The bacteria isolates and their respective degree of susceptibility/resistance profile among other parameters were collected using an appropriately designed and validated data collection form. Data were evaluated for conclusive identification of isolates and complete documentation of susceptibility/antibacterial resistance profile. Disk diffusion method of antibacterial susceptibility testing was used by the four hospitals. Apart from *E. coli,* only one hospital had a conclusive identification of all isolates. Reporting was similar but records were not as uniform with 4-graded and 3-graded reporting formats for susceptible and resistant isolates. None of the four hospitals has a comprehensive computerized data base of their antibacterial susceptibility results. Only one hospital; the oil company hospital, had a complete and consistent documentation in addition to a conclusive isolates identification. Documentation of resistant cases was incomplete in two hospitals and the fourth hospital had inconsistent graded reporting format. High degree of susceptibility of *E coli* isolates was exhibited to ciprofloxacin and ceftriaxone; 77.0% and 78.2% respectively. The isolates were highly resistant to amoxicillin (86.6%), tetracycline (91.0%), and cotrimoxazole (82.2%). Routine antibacterial susceptibility testing results as presently obtained in most of the hospitals are not reliable for surveillance purposes. Relevant policies and improvement in capacity building to enhance the reliability is of absolute necessity.

Keywords: Antibacterial Resistance, Infectious Diseases, Antibacterial Therapy, Antimicrobial resistance.

INTRODUCTION

The important therapeutic roles played by antibacterial agents coupled with the ongoing threat of antibacterial resistance and its attendant cost implication are compelling reasons for concern about their prudent use. There is the need for healthcare providers and governments to take proactive measures through continuous monitoring and proper surveillance activities.

Patterns of resistance to antibacterial agents are regularly monitored locally, regionally and internationally (Johnson, 2001) to ensure rational use and prolong the life span of these lifesaving agents. Pharmacists among other stakeholders by virtue of their important roles in discovery, manufacturing,

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distribution, marketing as well as in rational usage of antibacterial agents are becoming increasingly worried over the ever-growing rate of antibacterial resistance.

The problem is widely acknowledged to be pandemic and it needs urgent attention as well as sustainable inputs from all stakeholders. Unfortunately, too little an attempt is being made by most developing countries to address this ugly situation particularly in areas of rational use and surveillance (Lamikanra and Okeke, 19997).

According to World Health Organization (WHO) in 1996, "we are standing on the brink of a global crisis in infectious diseases, no country can afford to ignore their threat any longer. Most alarming of all are diseases where resistance is developing to virtually all currently available drugs, thus raising the spectre of a post antibiotic era. Trends suggest that some diseases may have no effective therapies within the next couple of years".

Antibacterial resistance is of immense cost to the health care delivery system. For instance, the National Institute of Allergy and Infectious Diseases (NIAID) estimated that, in the United States, the annual cost of treating therapeutic resistance could be as high as $30 billion (NIAID, 2001). Improvement in antibacterial therapy will achieve better quality of care, reduce health care costs and optimize healthcare system through greater cost effectiveness. This can only be achieved by sustainable surveillance of resistance and strict control of antibacterial agents use.

Continuous surveillance for antibacterial resistance exists in developed countries which are either undertaken by governments, pharmaceutical industries or for commercial purposes (Johnson, 2001). Such sentinel programmes are expensive and are lacking in most developing countries. A cost effective way of monitoring antibacterial resistance in developing countries is through the review of routine antibacterial susceptibility reports which accumulate epidemiological information of bacterial resistance profile in addition to guiding clinicians in selecting the best antibacterial agents for individual patients.

This paper seeks to evaluate the usefulness of routine antibacterial susceptibility data in antibacterial resistance surveillance in Lagos Metropolis.

MATERIALS AND METHODS

This retrospective study involved the use of antibacterial susceptibility testing results of four hospitals in Lagos, Nigeria. Lagos is the most populous city in Nigeria with a population of about 10million people. Four hospitals were chosen based on perceived high quality of their antibacterial susceptibility testing results. These were Lagos University Teaching Hospital (LUTH); a 764 bed tertiary health institution with about 10,000 patients turnover per month. Reference Hospital Lagos (RHL) belonging to Ministry of Defense with both Out-patient and In-patient facilities, St Nicholas Hospital Lagos (STNH); a private hospital, one of the most recognised by national and international agencies in Nigeria with both General and Specialized services and a well-equipped Oil Company Hospital (CNLH), with both Specialized and General Outpatient services for its staff and their dependents. All categories of health staff including consultants, other physicians, pharmacists, medical laboratory scientists, nurses among others are present in all the hospital. In each of these hospitals the antibacterial susceptibility testing results (ASTR) were made available and access to them was officially granted.

Sample size, Sampling and Data Collection
The antibacterial susceptibility testing results of 3,961 clinical isolates of bacteria were collated and evaluated. An average of 248 clinical isolates per year over any four years between 2002-2009 were sampled (TAH, 2004). In the Oil company hospital where ASTR were not too many there was complete enumeration. Sampling was systematically randomised in the other three hospitals. The various parameters such as sex of patient, age, source of isolates, isolated organisms and respective degree of susceptibility/resistance were collected using an appropriately designed and validated data collection form.

Data Analysis
Data was analysed using Epi info version 6.The four most frequently encountered bacteria isolates were further analysed in detail with respect to their susceptibility patterns. The degree of susceptibility classified for isolates as either very susceptible (+++), moderately susceptible (++), mildly susceptible (+), or resistant (R) were analysed accordingly. Both mildly susceptible (+) and (R) were categorized as resistant in the 4-graded reporting format.

Moderately susceptible bacteria isolates (++) were regarded as intermediate equivalent of Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee of Clinical Laboratory Standards or NCCLS) (CLSI, 2009). The proportion (%) of each susceptibility category for each bacteria species was calculated and compared using Chi square (χ^2) test. At 95% confidence interval, a 2-tailed *p*-value less than 0.05 was considered significant.

RESULTS

General
Disk diffusion method of antibacterial susceptibility testing was used by the four hospitals. All the hospital had a record of the various parameters such as sex of patient, age, source of isolates, isolated organisms and respective degree of susceptibility/resistance. Each isolate had been tested against an average of eleven antibacterial agents giving about 43,571 observations. Reporting format was similar but records were not as uniform. All records were in hard copies. None of the four hospitals has a comprehensive computerized data base of their antibacterial susceptibility results. However, individual patient results were computerized as an integral part of a computerized patient medical/medication profile in CNHL, the oil company.

As regard identity of bacteria isolates, only CNLH, the oil company hospital had a conclusive identification of all isolates to strain level. For example most of the records indicated just the species name such as *Staphylicoccus* sp, *Klebsiella* sp in three of the hospitals. It was only in CNLH where the strain such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus* could be established. Only *E. coli* was conclusively described by all the hospitals hence its usage as a case study for this paper. In two of the hospitals (CNLH and LUTH), there was a complete record of drugs to which the bacteria isolates resists designated as "R" in addition to those drugs the isolates were considered susceptible designated as (S) to varying degrees.

Three of the four hospitals used a 4-graded reporting format designated as very susceptible (+++), moderately susceptible (++), mildly susceptible (+), or resistant (R). These hospitals were CNLH, RHL, and STNH. In LUTH, the reporting format was predominantly a 3-graded reporting format designated as susceptible (++), intermediately susceptible (+), or resistant (R) but with pockets of 4-graded format reporting interpreted as earlier explained.

The ASTR of the oil company hospital (CNLH) is the most reliable for epidemiological studies of which resistance surveillance and a rough guide to empirical therapy are the most important. This is based not only on its conclusive identification of bacterial isolates but also due to a complete record of drugs (antibacterial disks) to which the isolates were subjected. Inconclusive identification of isolates and/or incomplete record of "R"-the drugs to which the organisms were resistant makes other hospital less useful for surveillance. In other words there was no standardization as regard interpretation and record of data.
Therefore their results cannot be pooled together.

Common bacteria isolate at CNL hospital.
The most commonly encountered bacteria isolates at CNL hospital were as follows;
E coli- 458 (33.0%), *S.aureus*- 177 (12.7%), *P aeruginosa*- 104 (7.5%), *K. pneumoniae*-75 (5.4%), *E. faecalis*-70 (5.0%), *S. haemolyticus*-67 (4.8%), *P. mirabilis*-52 (3.7%), *E. cloacae*-34 (2.4%), *S. typhi*-31 (2.2%), *S. pyogen*-18 (1.3%), *S. pneumoniae*- 9 (0.7) and others. Urine constituted the highest source for *E coli* (51.3%), *S aureus* (33.9%) and *K. pneumoniae* (44.0%). Ear swab was the highest source of *P. aeruginosa* (45.2%) followed by urine (20.2%).

Antibacterial Susceptibility Results for *E coli* at CNLH
Record was complete including drugs to which the isolates were resistant. High degree of sensitivity of *E coli* isolates was exhibited to ciprofloxacin and ceftriaxone; 77.0% and 78.2% respectively. The isolates were highly resistant to amoxicillin, tetracycline, cotrimoxazole and co-amoxiclav (Table 1)

Table 1:
Antibacterial Susceptibility Results for *E coli* at CNLH

S/N	Drug Class	Drug	R N (%)	S1 N(%)	S2 N(%)	S3 N (%)	Total N (%)
1	Quinolones	Ciprofloxacin	60 (13.9)	6 (1.3)	34 (7.9)	331(77.0)	431 (100.0)
2	Penicllins	Coamoxiclav	132 (32.2)	146(35.6)	111(27.1)	21(5.1)	410 (100.0)
3		Amoxicillin	225 (82.2)	17 (4.4)	43 (11.0)	8 (2.1)	390 (100.0)
4	Cephalosporins	Ceftriaxone	18(4.5)	17(4.1)	53 (13.1)	316(78.2)	404 (100.0)
5		Cefuroxime	32 (7.7)	63 (15.1)	256 (61.2)	67(16.5)	418(100.0)
6	Tetracyclines	Tetracycline	366 (84.3)	29 (6.7)	35 (8.1)	4 (0.9)	434 (100.0)
7	Aminoglycosides	Gentamicin	38 (9.3)	33 (8.7)	288 (70.4)	50 (12.2)	409 (100.0)
8	Sulphonamides	Cotrimoxazole	240 (79.5)	8 (2.7)	21(7.0)	33 (10.9)	302 (100.0)
9	Others	Nitrofurantion	12 (14.9)	40 (16.4)	70 (28.7)	126 (51.6)	244 (100.0)

Assumptions: S3 (+++) = Sensitive, S2 (++) = Intermediate, S1 (+) and R = Resistant

Table 2:
Antibacterial Susceptibility Results for *E coli* at STNH

S/N	Drug Class	Drug	R N (%)	S1 N (%)	S2 N (%)	S3 N (%)	Unknown	Total N (%)
1	Quinolones	Ciprofloxacin	5*	9	31	28	114	187
2	Penicillins	Coamoxiclav	4*	20	33	29	98	187
3		Amoxicillin	12*	6	12	3	154	187
4	Cephalosporins	Ceftriaxone	9*	26	25	28	96	187
5		Cefuroxime	5*	12	27	28	112	187
6	Tetracyclines	Tetracycline	21*	18	4	1	143	187
7	Aminoglycosides	Gentamicin	14*	52	37	4	77	187
8	Sulphonamides	Cotrimoxazole	23*	6	4	1	153	187
9	Others	Nitrofurantion	0*	12	18	4	153	187

Assumptions: S3 (+++) = Sensitive, S2 (++) = Intermediate, S1 (+) and R = Resistant, Unknown is either not tested or 'R' but not recorded.
*Conversion to percentages would be misleading

Table 3:
Antibacterial Susceptibility Results for *E coli* at RHL

S/N	Drug Class	Drug	R N (%)	S1 N(%)	S2 N(%)	S3 N (%)	Unknown	Total N (%)
1	Quinolones	Ciprofloxacin	1*	0	38	148	18	206
2	Penicillins	Coamoxiclav	49*	4	22	4	127	206
3		Amoxicillin	29*	0	0	0	177	206
4	Cephalosporins	Ceftriaxone	3*	2	2	1	198	206
5		Cefuroxime	15*	0	3	3	184	206
6	Tetracyclines	Tetracycline	0*	126	2	0	78	206
7	Aminoglycosides	Gentamicin	10	13	76	47	60	206
8	Sulphonamides	Cotrimoxazole	128*	0	0	0	78	206
9	Others	Nitrofurantion	11*	1	4	4	186	206

Assumptions: S3 (+++) = Sensitive, S2 (++) = Intermediate, S1 (+) and R = Resistant Unknown is either not tested or 'R' but not recorded.
*Conversion to percentages would be misleading.

Antibacterial Susceptibility Results for *E coli* at STNH

Record was incomplete. Drugs to which the isolates were resistant were not recorded most time. Some degree of sensitivity of *E coli* isolates exhibited to ciprofloxacin, cefuroxime ceftriaxone and co amoxiclav was noted. The isolates were highly resistant to amoxicillin, tetracycline, cotrimoxazole as evident from record of S3 (Table 2).

Antibacterial Susceptibility Results for *E coli* at RHL

Record was incomplete. Drugs to which the isolates were resistant were not recorded most time. High degree of sensitivity of *E coli* isolates exhibited to ciprofloxacin, gentamicin was also noted. The isolates were highly resistant to amoxicillin, tetracycline, cotrimoxazole as evident from record of S3 (Table 3)

Antibacterial Susceptibility Results for *E coli* at LUTH

Record was complete but with inconsistent reporting format as either 3 or 4-graded. Drugs to which the isolates were resistant were completely recorded. High degree of sensitivity of *E coli* isolates exhibited to ciprofloxacin, gentamicin, ceftriaxone and nitrofurantoin was noted.

The isolates were highly resistant to amoxicillin, tetracycline, cotrimoxazole as evident from record of R (Table 4).

Table 4:
Antibacterial Susceptibility Results for *E coli* at LUTH

S/N	Drug Class	Drug	R N (%)	S1 N(%)	S2 N(%)	S3 N (%)	Unknown	Total N (%)
1	Quinolones	Ciprofloxacin	11	2*	31*	1*	42	87
2	Penicillins	Coamoxiclav	14	4*	4*	-	65	87
3		Amoxicillin	17	0*	1*	-	69	87
4	Cephalosporins	Ceftriaxone	8	5*	29*	1*	44	87
5		Cefuroxime	10	6*	8*	0	63	87
6	Tetracyclines	Tetracycline	70	8*	4*	0	5	87
7	Aminoglycosides	Gentamicin	34	13*	29*	0	11	87
8	Sulphonamides	Cotrimoxazole	14	2*	3*	0	68	87
9	Others	Nitrofurantion	9	6*	46*	1*	25	87

Assumptions: S3 (+++) = Sensitive, S2 (++) = Intermediate, S1 (+) and R = Resistant, Unknown = Not tested.
*Inconsistent reporting format as either 4 or 3-graded makes conversion to percentages misleading.

Antibacterial Susceptibility Results for *E coli* at LUTH

Record was complete but with inconsistent reporting format as either 3 or 4-graded. Drugs to which the isolates were resistant were completely recorded. High degree of sensitivity of *E coli* isolates exhibited to ciprofloxacin, gentamicin, ceftriaxone and nitrofurantoin was noted.

The isolates were highly resistant to amoxicillin, tetracycline, cotrimoxazole as evident from record of R (Table 4).

DISCUSSION

Surveillance of antibacterial resistance can be carried out using routinely generated susceptibility testing results from diagnostic microbiology laboratories among other sources (Henwood et al 2000). Lack of standardization as regard procedure, interpretation and record of data obtained for the routinely generated antibacterial susceptibility testing is a major limitation towards the usefulness of these data for epidemiological purposes. This could have been very cost effective for developing countries like ours where sentinel programs for that purpose are lacking. Inconclusive identification of bacteria isolate by most of the recognized hospital in the metropolis gives an insight into what could be obtained in other less rated hospitals and facilities. However, this may not necessarily affect treatment effectiveness as sensitivity pattern obtained are still being used for treatment. Its implication is less reliability of such results for surveillance purposes. Inadequate facilities may be responsible hence the need for improved capacity building and facility provision at all level of health care. The limitations highlighted above are indications for National Standard Guidelines on methods, interpretation and recording format. Methods such as those of Bauer-Kirby (1966) modified National Committee for Clinical Laboratory Standards (NCCLS) (2001) may be adopted. Pooling of local, state, regional or national records could be made possible with standardization of relevant procedures. The fact that no standard of surveillance exists in developing countries has been raised (NCID, 2005) and calls for urgent attention as the problem is enormous and the consequences are grave.

The most widely affected antibacterial agents by resistance such as amoxicillin, co-trimoxazole, tetracycline, and even co-amoxiclav are equally the most affordable thereby complicating therapy for the therapist and the poor populace. Reports have also shown that these agents are most widely abused (Fakeye et al, 1998). Efforts to prolong the life span of these agents in the country need to be improved upon. Enforcement of standard of practice at all levels is important as well as public enlightenment for the community to ensure greater rational used.

Among available susceptibility methods such as Broth dilution which has been miniaturized, Antimicrobial Gradient method such as Etest (bioMérieux AB BIODISK), Disc diffusion method and automated instruments that can generate rapid 3.5 -16 h susceptibility test results like MicroScan WalkAway (Siemens Healthcare Diagnostics, BD Phoenix Automated Microbiology System (BD Diagnostics), disk diffusion is still the cheapest (Jorgensen and Ferrraro, 2009). Therefore, there is the need to

strengthen our capacity building on this method for routine use and its applicability for antibacterial resistance surveillance.

As much as surveillance should be improved particularly through routine data, regulation on sales, and uses need to be improved upon as well. The use of updated treatment guidelines which reflect applicable pattern of resistance profiles, regularly revised drug formulary to include new agents has been stressed (Suleiman and Adepeju, 2005).

As noted from the results, no class of antibacterial agent is spared from the increasing resistance profile and is equally a cause for concern. The usage of each class should be closely monitored. Attempt at searching for new drugs is very important and should be up-graded with the array of untapped natural resources at our disposal, of course adequate political backing and improved research funding is needed. Politicians should be made to know the consequences of antibacterial resistance which has a great deal of externality for the rich and the poor as well as for international communities in order to gain the much lacking and highly needed political support. Most so-called new drugs are actually product of structural modification with similar basic properties to existing ones hence resistance easily develops to them. The difficulty in drug discovery is reflected in the absence of any novel class of antibacterial drug approved for use in the United States between 1968 and 2000 (Weber and Courvalin, 2005). Where new products are eventually available, they are not free from antimicrobial resistance development particularly if abused. In-addition new drugs are usually not available and unaffordable to majority of patients in developing countries. Examples are moxifloxacin-a relatively new quilonlone antibacterial agent used in the treatment of community acquired pneumomia (Drummond et al, 2003) and linezolid used in the treatment of methicillin resistant *staphylococcus* in some countries before the year 2003 (Li et al, 2003) but hardly in use in Nigeria and most developing countries up till now.

Wise use of available agents (which include surveillance and rational therapy) and prudent use of resources available to procure them still remain the most pragmatic option for us. Some experts have suggested that multi-modal approaches will effectively slow down and even halt the increasing trends of health care-associated antibacterial resistance, for example, aggressive infection control with effective surveillance cultures, hand hygiene and possibly antibacterial use control (Okeke el al, 1999; Ogunsola et al, 2000).

All the stakeholders need to be properly educated and be well informed on the imminent danger of irrational practices to avoid the catastrophe of emerging resistant strains of otherwise sensitive bacteria isolates. National Standard on procedures should be developed and enforced, Laboratories to be more equipped among other capacity building mechanisms.

Computerized Quarterly and Annual Antibiogram should be mandated to monitor resistance patterns. Consensus evidence-based Standard Treatment Guidelines and Formulary are necessary. In addition, formulation of appropriate and well informed policies and provision of legal frame work for relevant activities within the health sector that affects antibacterial usage as well as provision of adequate and effective monitoring and evaluation strategy are essential. Lastly, External Interdisciplinary Quality assessment committee should be set up at all levels for regular inspection, accreditation, monitoring and evaluation of relevant health care delivery service centres including government hospitals for compliance and conformance to promulgated standard.

Conclusion: Routine antibacterial susceptibility testing results as presently obtained in most of the hospitals are not very reliable for surveillance purposes. Relevant policies and improvement in capacity building in facilities, standardized reports and complete documentation among others would go a long way to promote antibacterial resistance surveillance activities in the country.

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