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A systematic review of antibiotic-resistant *Escherichia coli* and *Salmonella* data obtained from Tanzanian healthcare settings (2004-2014)

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Antibiotic-resistant *Escherichia coli* and *Salmonella* are an increasing challenge to global health. In Tanzania reliable data is limited for trends of resistance in major hospital-acquired pathogens. Data on the prevalence of antibiotic-resistant *E. coli* and *Salmonella* from Tanzanian sources (2004-2014) was extracted from PubMed and Google Scholar databases (April-June, 2015). Descriptive statistics and logistic-regression analysis were used to estimate the prevalence and trends for resistant *E. coli* and *Salmonell*a to selected antibiotics using R software. A total of 24 articles were availablefor review, of which 21/24 (87.5%) and 7/24 (29.2%) reported the prevalence of antibiotic-resistant *E. coli* and *Salmonella*, respectively. Across all studies the average prevalence of resistance to ampicillin and co-trimoxazole was higher for *E. coli* (81.6 and 77.7%, respectively) than for *Salmonella* (64.7and 59.3%, respectively). Both groups of pathogens were also resistant to ciprofloxacin (20-22%) and 3rd-generation cephalosporins (2.5-27.8%). A logistic-regression model for published data (2004-2014) indicated that during this period of time there has been a significant increase to amoxicillin/clavulanate, ceftazidime, ciprofloxacin and gentamicin in *E. coli* (*P*< 0.001), and a significant increase in resistance to ampicillin for *Salmonella* (*P* < 0.05).Decreased *E. coli* and *Salmonella* susceptibility to critical antibiotics threatens the effective treatment of these infections in Tanzania. Proactive strategies are needed to preserve these antibiotics that remain largely active against bacterial pathogens in Tanzania.

Key words: Antibiotic resistance, trends, nosocomial *E. coli*, *Salmonella*, Tanzania.

INTRODUCTION

Antibiotic resistance (AMR) is one of the major global- health challenges of the 21st Century (Huttner et al.,

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2013). Bacteria that are resistant to ≥ 3 antibiotic classes are conventionally referred to as “multidrug-resistant” andsuch microbes challenge existing treatment regimens for bacterial infections (Laxminarayan and Heymann, 2012; Thu et al., 2012). Multidrug-resistant bacteria often cause chronic diseases in people leading to long-term hospitalization, high morbidity and mortality (Feasey et al., 2012). *Escherichia coli* and *Salmonella* sp. (*S. enterica* subspecies *enterica*) commonly cause septicemic infections in Africa (Feasey et al., 2012; Anago et al., 2015). Multidrug-resistant *E. coli* and *Salmonella* often express extended spectrum beta-lactamases (ESBLs) that favour increased resistance to broad-spectrum beta-lactam antibiotics. These genetically encoded traits are usually located on plasmids that are transferable between bacterial strains and species (Sweta Gupta et al., 2013; Anago et al., 2015). Data on antibiotic resistance for pathogens is generally limited in sub-Saharan Africa (Leopold et al., 2014). In Tanzania, a situational analysis report by Global Antibiotic Resistance Partnership Working Group (GARP) called for a coordinated response to AMR problem and reveals baseline data for presence of antibiotic-resistant *E. coli* and *Salmonella* sp.in nosocomial infections (GARP-Tanzania, 2015), but there is no systematic mechanism for tracking trends in major hospital-acquired pathogens (WHO, 2014). This review focused on the prevalence and trends of antibiotic resistance for nosocomial *E. coli* and *Salmonella* as reported in the literature between 2004 and 2014. The analysis focused on antibiotics that are considered critical to Tanzanian healthcare settings by the WHO- Advisory Group on Integrated Surveillance of Antibiotic Resistance (AGISAR, 2011).

According to AGISAR, a critically important antibiotic (CIA) is the sole, or only one of limited available therapies to treat serious human disease such as pneumonia. Antibiotics are also considered critical when they are important for treating diseases caused by either (1) organisms that may be transmitted to people from non-human sources or, (2) human diseases caused by organisms that may acquire resistance genes from non-human sources. Antibiotics that meet criterion 1 or criterion 2 are referred to as highly important antibiotics (HIA) (WHO-AGSAR, 2011).

Results from this review focus on these important antibiotics with the goal of improvingtreatment guidelines for hospital-acquired infections and address the need for enhanced antibiotic stewardship strategies in Tanzania.

METHODS

Article search strategy and selection criteria

Search words “resistance” or “antibiotic resistance” or “multidrug resistance” and/or “*Salmonella* “or “*Escherichia*”, or “antibiotic susceptibility”, or “antibiotics”, or “antibiotic” or “bacteraemia” or “bacteriuria” and *Tanzania* were used with PubMed and Google Scholar electronic databases. Boolean operators, proximity search and mapping techniques (Boell and Cecez-Kecmanovic., 2010); Boell and Cecez-Kecmanovic, 2014) were employed to identify relevant articles. All articles published between 2004 and early 2015 that reported prevalence of antibiotic-resistant*E. coli* and *Salmonella* isolates from Tanzanian clinical specimens in healthcare settings were retrieved and analysed if antibiotic resistance data was reported based on Kirby-Bauer disc diffusion assays.

Statistical analysis

Extracted data were entered into a spreadsheet (Excel 2013, Microsoft Corp., Redmond, WA, USA). Tables and descriptive statistics were used to summarize data. Average prevalence (Number of resistant/total number isolates tested) for a 10-year period (2004-20014)and the proportion of antibiotic-resistant *E. coli* and *Salmonell*a [number of resistant/(number of sensitive +number of resistant isolates)]was computed for each antibiotic across all studies. Logistic-regression was used to assess trends in resistance for *E.coli* and *Salmonell*a to selected antibiotics for the data, published between 2004and 2014, using R software (v3.2.5, stats package). All results at $P< 0.05$ were considered statistically significant.

RESULTS

Description of search results

A total of 1,136 articles was retrieved and screened from PubMed (n=616) and Google Scholar (n=520) electronic databases between April and June, 2015 (Figure 1). Twenty-four articles (n=24) passed inclusion criteria set for this review (Table 1). The majority of the articles (16/24; 67%) consisted of cross-sectional, hospital-based studies (Table 1).

A hospital-based infection was defined as(1) an infection that was acquired by neonates within 10 days of birth in a hospital, or (2) inpatients showing symptoms of new infection >48 h following admission, or (3) community-acquired infections involving septicemic infection with the growth of pathogenic bacteria in a blood-culture that was obtained within the first 48 h of admission. Only one study by Blomberg et al.(2007), examined data from both community- and hospital-based infections. For cross-sectional studies the presence of bacterial pathogens (exposure) and antibiotic resistant infections (disease) were determined at the same point in time in a given population and the prevalence of exposure and/or diseases was assessed. A few studies (8/24; 33%) were either retrospective or prospective cohort studies (Table 1).

For retrospective studies bacteria were isolated from a cohort of individuals prior to the onset of the study and assessed for antibiotic resistance.prospective studies are rare in the field of antibiotic resistance, but typically involve a cohort of individuals that are identified and examined for the presence ofantibiotic-resistant bacteria relative to risk factors for carriage of antibiotic-resistant strains during a defined study period (Euser et al., 2009).

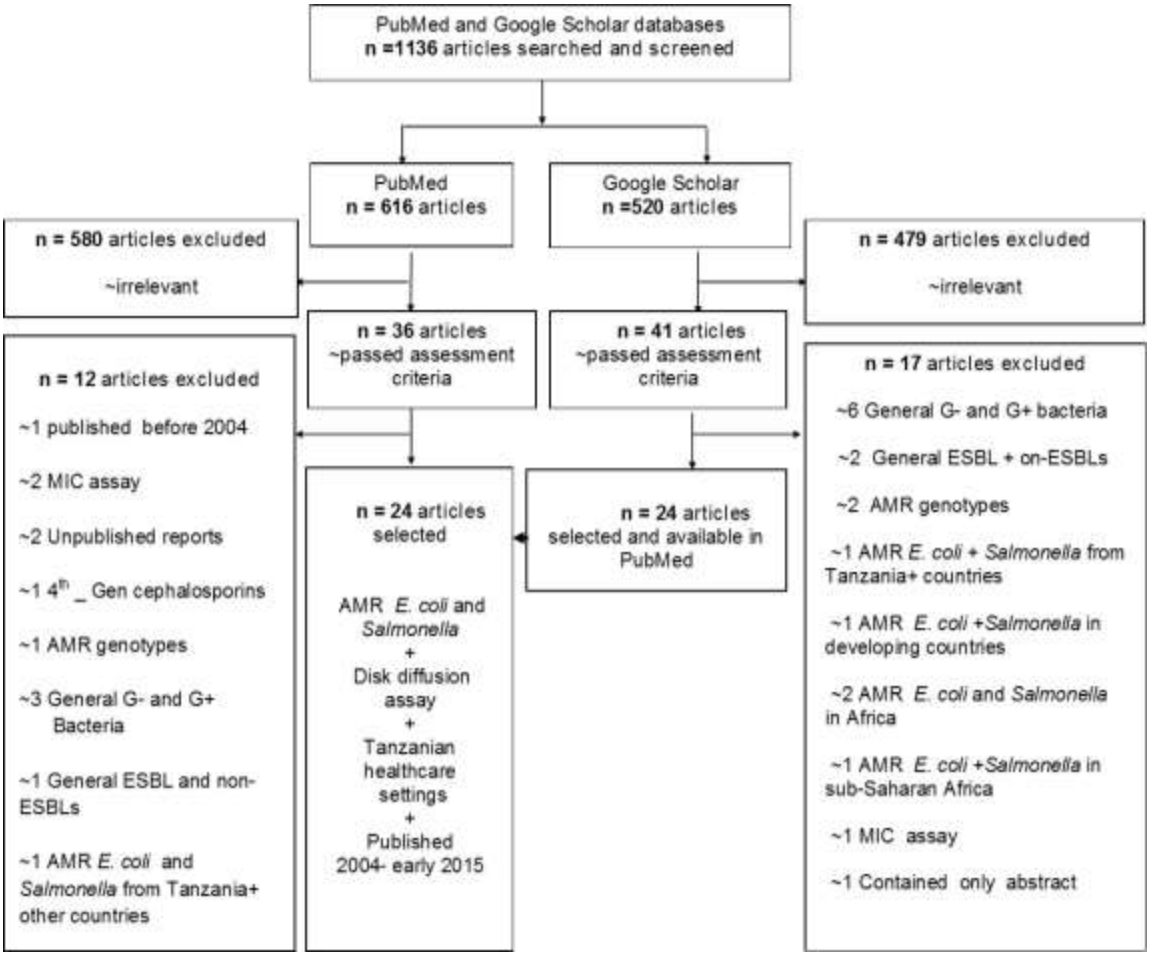

Figure 1. Flow diagram indicating an inclusion assessment of selected articles for systematic review.

Description of microbiological analysis

In the studies considered, clinical samples were collected directly from patients of varying age (neonates; 0-26 days; children; >5 and >18 years; adults, >65 years) and from stored samples (bio-bank). Blood was the main clinical type of sample (13/24; 54.2%) (Blomberg et al., 2004, 2007); Ndugulile et al., 2005; Mshana et al., 2009; Kayange et al., 2010; Moyo et al., 2010; Crump et al., 2011; Meremo et al., 2012; Mhada et al., 2012; Msaki et al., 2012; Christopher et al., 2013; Mushi et al., 2014). Other samples included urine (9/24; 37.5%), pus (6/24; 25%), and other body fluids (6/24; 25%. All studies employed disc diffusion assays for antibiotic susceptibility testing and *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were commonly used as quality control organisms. For selected studies, the susceptibility assays for critically important antibiotics (CIA) included ampicillin, amoxicillin/clavulanate, ciprofloxacin, ceftazidime, gentamicin, and meropenem and for highly important antibiotics (HIA), the assays were performed to co- trimoxazole, chloramphenicol and tetracycline.

Prevalence of antibiotic-resistant *E. coli*

In the last two decades there has been an increasing number of reports about antibiotic-resistant *E. coli* isolates from tertiary hospitals. In the selected studies, antibiotic-resistant *E. coli* from septicaemia (BSI) and urinary tract infections (UTI) was reported in seventeen studies (17/24; 70.8%), while four studies (4/24; 16.7%) reported other *E. coli*-associated infections such as surgical site infections (SSI) and diarrhoea (Table 1). When data were pooled from the 21 published reports, *E. coli* indicated high resistance to ampicillin (81.6%), tetracycline (74.9%) and co-trimoxazole (77.7%) (Table 2).

Prevalence of antibiotic-resistant *Salmonella*

Non-typhoidal *Salmonella enteric* serovar typhimurium

Table 1. Synopsis of studies included in systematic review (n=24 articles).

Study design	Healthcare setting[#]	Source of infection	Study population	Patient (n)	Reference
Cross-sectional	HLH	UTI	Resistant *E. coli*	5153	Blomberg et al. (2005) [1]
Prospective-cross-sectional	MNH	BSI	Resistant *S. tyhi, S. enteritidis, S. tyhimurium, S. newport*	1787	Blomberg et al. (2007) [2]
Cross-sectional	MNH	Bacterial infection	Resistant *E. coli*	7617	Blomberg et al. (2004) [3]
Prospective-cross-sectional	BMC	BSI	Resistant *E. coli Salmonella* spp.	634	Christopher et al. (2013) [4]
Prospective-cross-sectional	KCMC	BSI	Resistant *S. typhi*	403	Crump et al. (2011) [5]
Cross-sectional	MNH	UTI	Resistant *E. coli*	382	Fredrick et al. (2013) [6]
Cross-sectional	MNH	UTI	Resistant *E. coli Salmonella* Typhi	300	Lyamuya et al. (2011) [7]
Cross-sectional	MNH	SSI	Multidrug resistant *E. coli*	100	Manyahi et al. (2014) [8]
Cross-sectional	BMC	BSI	Resistant *E. coli*	945	Marwa et al. (2015) [9]
Cross-sectional	BMC	UTI	Resistant *E. coli*	247	Masinde et al. (2009) [10]
Prospective-cross-sectional	BMC	BSI	Resistant *E. coli Salmonella* sp.	346	Meremo et al. (2012) [11]
Cross-sectional	MNH	BSI	Resistant *E. coli*	330	Mhada et al. (2012) [12]
Cross-sectional	BMC	Lower limb ulcer	Multidrug resistant *E. coli*	300	Moremi et al. (2014) [13]
Retrospective	MNH	BSI	Resistant *E.coli Salmonella* sp.	13,886	Moyo et al. (2010) [14]
Cross-sectional	MNH	Diarrhoea	Resistant *S.* typhi, S. typhimurium, Enteritidis	280	Moyo et al. (2011) [15]
Prospective-cross-sectional	BMC	SSI	Resistant *E. coli*	250	Mawalla et al. (2011) [16]
Prospective cohort	KCMC	BSI	Resistant *E. coli*	181	Morpeth et al. (2008) [17]
Cross-sectional	MHC	UTI	Resistant *E. coli*	231	Msaki et al. (2012) [18]
Cross-sectional	BMC	Hospital infections	Multidrug resistant *E. coli*	800	Mshana et al. (2009) [19]
Prospective-cross-sectional	BMC	BSI	Resistant *E. coli*	770	Kayange et al. (2010) [20]
Cross-sectional	MNH	UTI	Multidrug resistant *E. coli*	50	Ndugulile et al. (2005) [21]
Cross-sectional	BMC	Hospital infections	Multidrug resistant *E. coli*	227	Mushi et al. (2014) [22]
Cross-sectional	MRH	Diarrhoea	Resistant *E. coli* 0157	275	Raji at al. (2008) [23]
Cross-sectional	BMC	UTI	Resistant *E. coli*	370	Festo et al. (2011) [24]

[#]HLH, Hydom Lutheran Hospital; MNH, Muhimbili National Hospital; BMC, Bugando Medical Center; KCMC, Kilimanjaro Christian Medical Center; MRH, Morogoro Regional Hospital; MHC, Makongoro, Health Center.

Table 2. Summary of antibiotic resistance prevalence among *Escherichia coli* in healthcare settings, Tanzania (2004-2014); (Ref: [1, 3, 4, 6 - 14, 16 - 24] (21 studies)).

Antibiotic [a] (*N)[b]	Prevalence range (%) of resistant *E. coli* in various studies	Average prevalence n[c]/*N (%)
Ampicillin[13] (2073)	53 - 100	1692/2073 (81.6)
Amoxicillin/clavulanate[10](1572)	38 - 100	551/1572 (35.1)
Cefotaxime[5] (151)	5 - 92	42/151 (27.8)
Ceftazidime[6] (1403)	5 - 50	161/1403 (11.5)
Tetracycline[10] (1570)	59 - 100	1177/1570 (74.9)
Gentamicin[14] (2098)	8 - 92	313/2098 (14.9)
Co-trimoxazole[18] (1881)	50 - 100	1462/1881 (77.7)
Chloramphenical[8] (407)	45 - 100	210/407 (51.6)
Ciprofloxacin[11] (899)	5 - 46	181/899 (20)
Nitrofuratoin[7] (1674)	4 - 32	350/1674 (20.9)
Meropenem[3] (271)	5 - 19	53/271 (19.6)

[a] superscripts (3-18) indicate the number of reviewed studies; [b] *N=Total number of tested *E. coli* isolates; [c] n= number of antibiotic-resistant isolates.

has emerged as a predominant cause of invasive bacterial infection among African HIV-infected individuals

Table 3. Summary of antibiotic resistance prevalence among *Salmonella* sp., in healthcare settings, Tanzania (2004-2014) (Ref: [2, 4, 5, 7, 11, 14, 15], (7 studies))

Antibiotic [a] (*N)[b]	Prevalence range (%) of resistant *Salmonella* in various studies	Average prevalence n[c]/*N (%)
Ampicillin[6] (136)	41 - 100	88/136 (64.7)
Amoxicillin/clavulanate[5] (67)	0 - 100	27/67 (40.3)
cefotaxime[2] (46)	0 - 3	1/46 (2.2)
Ceftazidime[2] (40)	0 - 3	1/40 (2.5)
Tetracycline[4] (59)	0 - 42	17/59 (28.8)
Gentamicin[4] (44)	0 - 29	7/44 (15.9)
Co-trimoxazole[7] (108)	0 - 100	64/108 (59.3)
Chloramphenical[4] (100)	21 - 85	29/100 (29)
Ciprofloxacin[4] (18)	0 - 100	4/18 (22.2)
Nitrofuratoin[2] (10)	0 - 20	2/10 (20)

[a] superscripts (2-7) indicate the number of reviewed studies; [b] *N=Total number of tested *Salmonella* isolates; [c] n= number of antibiotic-resistant isolates. For Meropenem no resistant *Salmonella* was detected.

and malnourished children with case fatality rates of 20 to 25% (Crump et al., 2011; Feasey et al., 2012). In sub-Saharan Africa, presence of invasive non-typhoidal *Salmonella* (NTS) has been reported by several authors (Mshana, Matee and Rweyemamu, 2013; Carden et al., 2015). Antibiotic-resistant *Salmonella* data from Tanzanian sources was reported in seven studies (7/24; 29%; Table1).*S. enterica* subsp *enteric* serovars Typhi, Typhimurium, Enteritidis and Newport were reported in four studies (4/7; 57.1%) (Blomberg et al., 2007); Crump et al., 2011; Lyamuya et al., 2011); Moyo et al., 2011). Three studies (3/7; 42.1%) reported *Salmonella* at the genus level (Moyo et al., 2010; Meremo et al., 2012; Christopher et al., 2013). Pooling data across studies demonstrated relatively high average resistance to ampicillin (64.7%) and co-trimoxazole(59.3%) (Table 3).

Prevalence of extended spectrum beta-lactamase producers (ESBLs)

Multidrug-resistant *Escherichia coli* and *Salmonella* that produce ESBLs are increasingly reported worldwide (Rogers, Sidjabat and Paterson, 2011; Manyahi et al., 2014; Rezai et al., 2015). For Tanzania occurrence of globally distributed *E. coli* ST 131 clone with β-lactamase and fluoroquinolone resistance was first reported in 2011 (Mshana et al., 2011). For this review ESBL producing *E. coli* were reported in five studies (5/24; 20.8%) (Ndugulile et al., 2005); Mshana et al., 2009; Manyahi et al., 2014; Moremi et al., 2014; Mushi et al., 2014). Pooling data across studies indicated that the average prevalence of ESBL producing *E. coli* in Tanzania was 39.2%. In these studies ESBL producing strains were frequently resistant to co-trimoxazole (76.9-92%), gentamicin (30.8-93%) and ciprofloxacin (45-92%).

ESBL genes ($bla_{\text{CTX-M-15}}$, $bla_{\text{SHV-12 and}}$ $bla_{\text{OXA\_48}}$) were identified in *E. coli* by PCR for two studies (Ndugulile et al., 2005; Mushi et al., 2014).

Trends of antibiotic resistance

Between 2004 and 2014 there was asignificantly increasing trend ($P< 0.001$) for *E. coli* resistance to critically important antibiotics [amoxicillin/clavulanate (38 to 100%);ceftazidime (5 to 50%); ciprofloxacin (5 to 46%) and gentamicin (8 to 92%)] and an insignificant change for ampicillin resistance (53 to 100%;$P>0.05$). For highly important antibiotics [co-trimoxazole (50 to 100%) and tetracycline (59 to 100%)], the trend of increasing resistancewas insignificant ($P> 0.05$)(Table 4). For *Salmonella*the trend of increasing resistance was significant ($P < 0.05$) for ampicillin (41 to 100%) but no significant trend was detected for co-trimoxazole, amoxicillin/clavulanate, ceftazidime, ciprofloxacin, gentamicin and tetracycline (Table5).

DISCUSSION

Published data (2004-2014) aboutthe prevalence of antibiotic-resistant *E. coli* and *Salmonella* from hospital-acquired infections in Tanzania suggests thatthere was a high average prevalence of resistanceto ampicillin (81.6 versus 64.7%, *E. coli* and *Salmonella*, respectively) and co-trimoxazole (77.7 versus 59.3%) (Tables 2 and 3). Comparable results were reported for *E. coli* in Kenya (ampicillin, 95%; co-trimoxazole, 95%) (Sang et al., 2012), Ethiopia (ampicillin, 100%; co-trimoxazole, 62.9%) (Beyene and Tsegaye, 2011; Kibret and Abera, 2011), Zimbabwe (ampicillin, 84.5%; co-trimoxazole, 68.5%) (Mbanga et al., 2010) Ghana (ampicillin; 66.7%; co-trimoxazole, 68.2) (Hackman et al., 2014), Nigeria

Table 4. The odds ratio of antibiotic-resistant *Escherichia coli* in healthcare settings, Tanzania (2004-2014)[a].

Antibiotic [b]	Odds ratio	95% Confidence interval
Critically important		
Ampicillin	1.08[ns]	0.90 -1.28
Amoxacillin/clavulanate	2.13***[c]	1.86 - 2.45
Ceftazidime	0.61***	0.49 - 0.76
Ciprofloxacin	0.59***	0.49 - 0.70
Gentamicin	0.73 **	0.61 - 0.88
Highly important		
Co-trimoxazole	1.12[ns]	0.95 - 1.32
Tetracycline	1.09[ns]	0.89 - 1.31

[a] Odds ratios as estimated by logistic-regression analysis. Chloramphenicol, Nitrofuratoin and Meropenem were not analysed due to insufficient data; [b] Categories according to WHO advisory group on integrated surveillance of antibiotic resistance (AGISAR, 2011); [c] * $P < 0.05$ ** $P < 0.01$;*** $P < 0.001$; ns, non-significant ($P > 0.05$).

Table 5. The odds ratio of antibiotic-resistant *Salmonella* sp., in healthcare settings, Tanzania (2004-2014)[a].

Antibiotic[b]	Odds ratio	95% Confidence interval
Critically important		
Ampicillin	1.77*[c]	1.16 - 2.68
Amoxicillin/clavulanate	1.00[ns]	0.70 - 1.43
Ceftazidime	1.00[ns]	0.61 - 1.68
Ciprofloxacin	1.24[ns]	0.79 - 1.96
Gentamicin	1.13[ns]	0.71 - 1.78
Highly important		
Co-trimoxazole	1.49[ns]	0.45 - 5.51
Tetracycline	0.20[ns]	0.02 - 1.39

[a] Odds ratios as estimated by logistic-regression analysis. Chloramphenicol, Nitrofuratoin and Meropenem were not analysed due to insufficient dat; [b] Categories according to WHO advisory group on integrated surveillance of antibiotic resistance (AGISAR, 2011); [c] * $P < 0.05$; ns, non-significant ($P > 0.05$).

(ampicillin, 100%; co-trimoxazole 75.6%) (Yah et al., 2007) and South India (ampicillin, 99%; co-trimoxazole, 68.7%) (Razak and Gurushantappa, 2012). High resistance to ampicillin and co-trimoxazole is a challenge for treatment of bacterial infections in Tanzania where ampicillin is used as an empirical therapy and co-trimoxazole is used as a prophylaxis to prevent opportunistic infections among HIV-infected individuals (Hamel et al., 2008; Marwa et al., 2015).The use of robust and affordable diagnostic tools for bacterial infections in Tanzanian hospitals in accordance is highly recommended to restrict ineffectiveadministration of these antibiotics. Resistance to these “older” antibiotics is particularly unfortunate because alternatives will be increasingly expensive in a country that can ill-afford increased medical expenses.

Relatively high resistance of *E. coli* and *Salmonella* to critical antibiotics such as ciprofloxacin (20 versus 22.2%, respectively) was evident (Table 2 and 3).Over the course of the review period, there was a statistically significant increase in *E. coli* resistance to amoxacillin/clavulanate ($P < 0.001$), ceftazidime ($P < 0.001$), ciprofloxacin ($P < 0.001$) and gentamicin ($P < 0.01$), whereas no significant trend was observed for *Salmonella* (Table 4 and 5). This disparity in trends suggests that there is a greater need to scrutinize treatment decisions for *E.coli* infections. Reduced susceptibility of nosocomial *E. coli* pathogens to critical antibiotics was also reported by others in Nigeria (ciprofloxacin, 15.4%) and Iran (ciprofloxacin, 16.8%) (Khameneh and Afshar, 2009; Akinkunmi et al., 2014). Conversely, the rapid spread of ciprofloxacin resistance in a widely disseminated *S.typhi* strain (haplotype H58) both in Africa and Southeast Asia (Berkley et al., 2001; Chiou et al., 2014) alerts for the possible emergence of

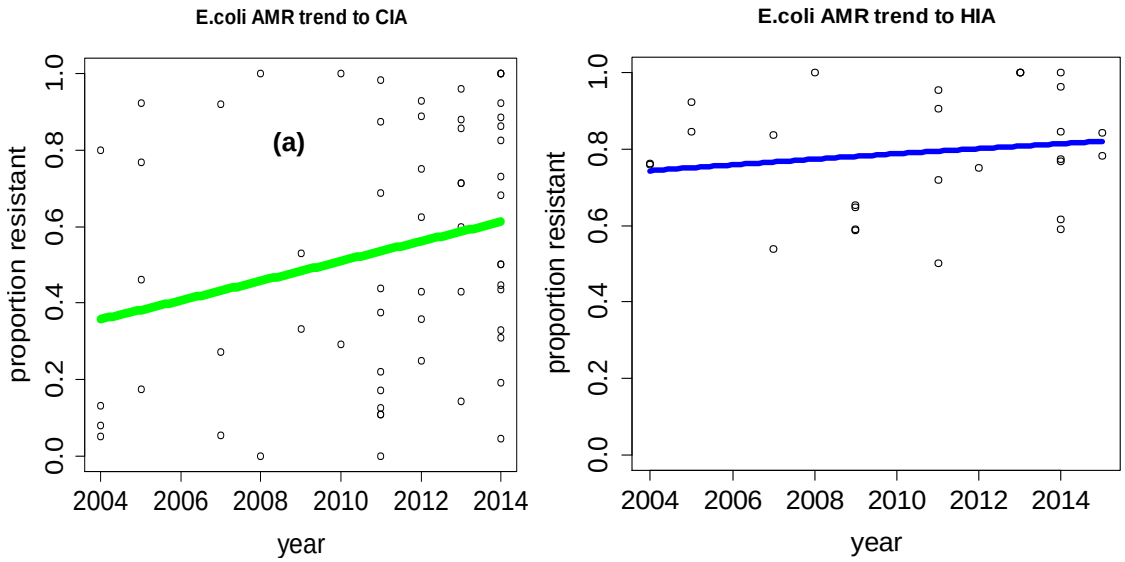

Figure 2. a: Trend in antibiotic resistance of *Escherichia coli* to critically important antibiotics (CIA, ampicillin; gentamicin; amoxicillin/clavulanate; ciprofloxacin and ceftazidime) in 10 year period (2004-2014), healthcare settings, Tanzania; b: Trend in antibiotic resistance of *E. coli* to highly important antibiotics (HIA, co-trimozazole and tetracycline) in 10 year period (2004-2014), healthcare settings, Tanzania.

this lineage of bacteria in Tanzania, particularly if there is heavy reliance of fluoroquinolones to treat Typhoid infections.

Detection of ESBL and carbapenamase-producing strains among *E.coli* isolates has been reported in several studies (Ndugulile et al., 2005; Moremi et al., 2014; Mushi et al., 2014). These isolates were highly resistant to amoxicillin/clavulanate (88.5-90.9%), ceftazidime (50-100%), ciprofloxacin (45.5-61.3%) and gentamicin (72.7-93.5%).Emerging resistance to extended beta-lactams and fluoroquinolones is an escalating public health concern for the management of infections among children and immuno-compromised individuals. Dissemination of ESBL strains in healthcare settings has been previously reported in various countries, including Kenya (Kiiru et al., 2012), Benin (Anago et al., 2015), Iran (Rezai et al., 2015), Brazil (Ferreira et al., 2011) and Bangladesh (Lina et al., 2014). Access to diagnostic tools that can detect ESBLs in local healthcare settings needs to be enhanced. In Tanzania,like many developing countries, laboratory capacity to confirm ESBL phenotypes is limited and diagnostic tools for infections are commonly unavailable or unreliable (Berkley et al., (2001).

Findings from community-acquired infections were addressed by Blomberg et al. (2007). Unexpectedly, they found that *E.coli* and *Salmonella* pathogens were more prevalent in confirmed community cases compared with hospital-acquired cases (32.9 and 17.9%, respectively). Furthermore, it was evident that *E. coli* pathogens were more susceptible ($P< 0.05$) to amoxicillin-clavulanate (75% vs 31%), cefuroxime (88% vs 54%), ceftazidime (88% vs 46%) and cefotaxime (88% vs 50%) in community-acquired infections compared with hospital-acquired cases, respectively. These results are consistent with reports from other community-level studies conducted in South Africa (McKay and Bamford, 2015), Iran (Hashemi et al., 2013), France (De Bus et al., 2013) and Spain (Junquera et al., 2005).

There is evidence of increasing numbers of *E. coli* and *Salmonella* resistance to critical antibiotics in Tanzania over the past 10 years (Figures 2a and 3a). This is probably explained in part by a high prevalence of nosocomial infections and growing rates of hospitalization reported in developing countries. This increased service demand has likely increased reliance on more potent antibiotics as initial or empirical treatment because they act against a wide range of pathogens (Laxminarayan and Heymann, 2012; Thu et al., 2012). As a consequence, this practice facilitates selection and persistence of bacterial strains resistant to critical antibiotics (Mshana et al., 2009; Meremo et al., 2012). High resistance to these antibiotics in nosocomial *E. coli* and *Salmonella* infections has been reported in Cameroon (Lonchel et al., 2012), India (GARP-India, 2011) and Latin America (Salles et al.,2013).Decreased *Salmonella* non-susceptibility to highly important antibiotics (Figure 3b) may suggest an increased proportion of susceptible isolates to this group of antibiotics for the period between 2004 and 2014. Nevertheless, a relatively high resistance (59.3%) to co-trimoxazole may be explained by its common usage as an alternative treatment for infectious diarrhoea (Casburn-Jones and Farthing, 2004) (Table 3). In

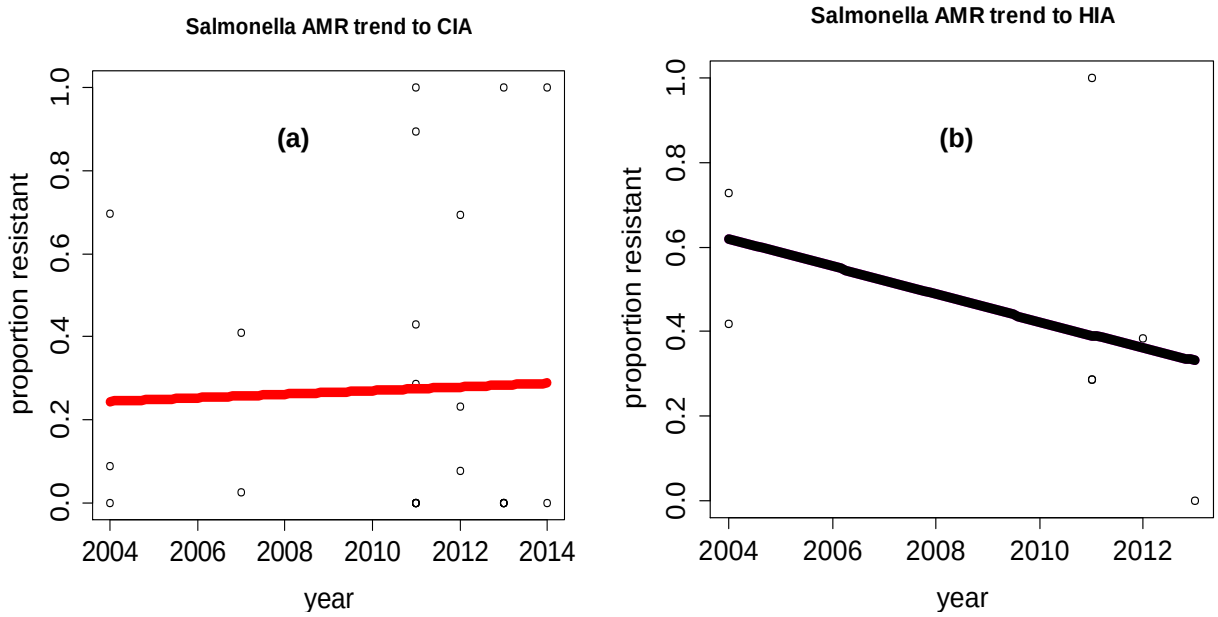

Figure 3. a: Trend in antibiotic resistance of *Salmonella* to critically important antibiotics (CIA, ampicillin; gentamicin; amoxicillin/clavulanate; ciprofloxacin and ceftazidime) in 10 year period (2004-2014), healthcare settings, Tanzania; b: Trend in antibiotic resistance of *Salmonella* to highly important antibiotics (HIA, co-trimozazole and tetracycline) in 10 year period (2004-2014), healthcare settings, Tanzania.

contrast, high *Salmonella* susceptibility to highly important antibiotics such as co-trimoxazole, has been reported in various countries like Nepal (1995-2015: co-trimoxazole, 98.8%) (Shrestha et al., 2016), Southern India (2009-2011:co-trimoxazole,95%) (Choudhary et al., 2013), and Montenegro (2005-2010: co-trimoxazole, 96.3%) (Mijovic, 2012).These findings suggest that local susceptibility testing of highly important antibiotics may be essential for timely treatment of *Salmonella* infections in low-income populations like Tanzania where access and/or options tomore potent antibiotics is generally limited (Laxminarayan et al., 2015).

It is important to note that the majority of the reviewed studies relied on data from hospital-acquired infections. Only one study included data from community- acquired infections and consequently, it is possible that the numbers reported in the literature are upwardly biased. This can happen when patients self-medicate prior to presentation at a hospital and this probably increases the possibility of isolating resistant strains. The use of Clinical and Laboratory Standard Institute (CLSI) guidelines was reported only by a subset of studies. Thus, the accuracy of any susceptibility data from studies that employed different guidelines might have caused variation in results. Finally, the lack of ESBL phenotype data in many studies might result in an underestimate of the prevalence of multidrug-resistant bacteria. Overall, high *E. coli* and *Salmonella*non-susceptibility to ampicillin and co-trimoxazole suggests that these antibiotics can be inappropriate empirical treatment for major nosocomial infections in Tanzania. Further, decreased *E. coli* and *Salmonella* susceptibility to amoxicillin/clavulanate, ceftazidime, ciprofloxacin and gentamicin threatens the effective treatment ofthese infections in Tanzania. Implementing proactive strategies in antibiotic stewardship to preserve the effectiveness of critical antibioticsthat appear to remain largely effective against bacterial pathogensin Tanzania is crucial. Applying enhanced infection control measures would limit further spread of resistant bacteria in healthcare settings and community as well.

Conflict of Interest

The authors declare that there is no conflict of interest.

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