Review of antibiotic resistance in the Indian Ocean Commission: a human and animal health issue

Running headline: Antibiotic resistance in Indian Ocean

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Abstract

Antimicrobial Resistance (AMR) is a major threat to human, animal health and environment worldwide. For human, transmission occurred through a variety of routes both in health care settings and community. In animals, AMR was reported in livestock, pets and wildlife; transmission of AMR can be zoonotic with the probably most important route being food-borne transmission. The Indian Ocean Commission (IOC), composed of Comoros, Madagascar, Mauritius, Reunion (France) and Seychelles recognized the surveillance of AMR in both animal and human as a main public health priority for the region. Mayotte, French overseas territory, located in Comoros archipelago, was also included in this review.

This review summarized our best epidemiological knowledge regarding AMR in Indian Ocean. We documented the prevalence, phenotypic and genotypic profiles of prone to resistance Gram-positive and Gram-negative bacteria both in animals and humans. Our review clearly pointed out Extended-Spectrum β-Lactamase and Carbapenemase producing Enterobacteriaceae as main human and animal health issue in IOC. However, publications on AMR are scarce, particularly in Comoros, Mayotte and Seychelles. Thus, research and surveillance priorities were recommended i) estimating the volume of antimicrobial drugs used in livestock and human medicine in the different territories (mainly Third Generation Cephalosporin (3GC); ii) developing a "One Health" surveillance approach with epidemiological indicators as zoonotic foodborne pathogen (i.e. couple *Escherichia Coli*-resistance to 3GC/ Carbapenems); iii) screening travelers with a history of hospitalization and consumption of antibiotic drug returning from at risk areas (e.g. mcr-1 transmission with China or hajj pilgrims) allowing an early warning detection of the emergence for quick control measures implementation in IOC.

Keywords

Indian Ocean, Epidemiology, Antimicrobial resistance, One Health, Prevalence, Surveillance, Zoonosis

Introduction

Increasing global Antimicrobial Resistance (AMR) is a major threat to human and animal endangering decades of improvements in health care outcomes. It endangers modern human and veterinary medicine and undermines food safety (FAO, 2016).

In humans, the global burden of AMR is longer duration of illness, higher lethality, increasing costs of treatment, and inability to cure infected patient (Laxminarayan et al., 2013). In animals, antibiotic drugs use in terrestrial and aquatic animals maintains food safety, animal welfare, and protect livelihoods (Pagel and Gautier, 2012).

Transmission of AMR to human can be zoonotic taking place through a variety of routes where the food-borne route is probably the most important (Wegener, 2012). Direct transmission also occurs for specific bacteria species (e.g. methicillin-resistant *Staphylococcus aureus*).

The Indian Ocean Commission (IOC) is composed of five countries: Comoros, Madagascar, Mauritius, Reunion (France) and Seychelles. Mayotte, French overseas territory located in Comoros archipelago was also included in the study. In 2015, the IOC identified AMR surveillance in both animal and human as a main priority for territories (COI, 2015). However, AMR burden is not well evaluated but epidemiological trends in IOC should be identified.

Our systematic review objective was summarizing epidemiological knowledge and trends of AMR in prone-to-multidrug resistance bacteria species (Magiorakos et al., 2012), faecal-oral and foodborne bacteria in human and animals in IOC. We documented the prevalence, phenotypic and genotypic profiles of resistance of the selected bacteria in i) Gram-positive and ii) Gram-negative bacteria.

Material and methods

The study performed from January to March 2017 included articles and conference abstracts published from 1990 to December 2016. Bacteria species included in the different searches were those prone to develop multidrug resistance as defined by Magiorakos et al. (2012) (i.e. *Staphylococcus aureus, Enterococcus* spp., *Pseudomonas aeruginosa, Acinetobacter* spp. and the genus Enterobacteriaceae), faecal-oral and foodborne bacterial species (*Salmonella* spp., *Campylobacter* spp. and *Shigella* spp.). We used available articles obtained through match searches using Google Scholar (http://scholar.google.com), PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Web of Knowledge (http://apps.webofknowledge.com/). Relevant information was obtained for phenotypic and genotypic profiles of resistance in selected bacteria using its name combined with related terms (resistance, antimicrobial, antibiotic, Comoros, Seychelles, Reunion Island, Madagascar, Mayotte, Indian Ocean, epidemiology). Included publications were those documenting the prevalence, phenotypic and genotypic profiles of resistances of selected bacteria, others were excluded.

Results and discussion

A total of 42 articles were considered relevant for the review.

a. Gram-positive bacteria

Staphylococcus aureus

Staphylococcus aureus is one of the most common causes of nosocomial and community infections (von Eiff et al., 2001). Since 1960s, methicillin-resistant *S. aureus* (MRSA) were isolated (McCaig et al., 2006) and became a major nosocomial pathogen (Mulligan et al., 1993).

In Madagascar, MRSA was increasing from 2001 to 2014 as observed in table 1 with rising rate of resistance to oxacillin and cefoxitin. MRSA nasal carriage in community was observed with a prevalence of 14.8% in 2011 (Rasamiravaka et al., 2013, 2016). Overall resistances were higher for widely available drugs (Randrianirina et al., 2007a). Moreover, 9.0% of veterinary students were asymptomatic MRSA carriers (Rasamiravaka et al., 2016). Increasing rate of resistance to gentamicin (42.9%) and vancomycin (7.1%) was observed in MRSA isolates (Rasamiravaka et al., 2016). Nonetheless, vancomycin and tigecycline are the last drugs demonstrating therapeutic efficacy for MRSA and are compromised by the reduced susceptibility in *S. aureus* (Hu et al., 2016). Phenotypic resistance observed in Madagascar was of concern (Rasamiravaka et al., 2016), confirmation by a antimicrobial reference laboratory for genotyping should be considered.

In Mauritius, in May 2010, among all *S. aureus* isolated in hospitalized patients infections 37.8% were MRSA (Issack et al., 2011) and 39% were MRSA in July 2014 (Issack, 2016a). All *S. aureus* tested were susceptible to vancomycin (Issack et al., 2011; Issack, 2016a).

In Reunion, MRSA increased from 16.0% in 1997 to 23.0% in 2000 and decreased to less than 15.0% in 2006/07 (Belmonte et al., 2008). *S. aureus* rate of resistance to all antibiotic drugs decreased from 1997 to 2007, with the exception of the fusidic acid (16.0% in

2007). Since 1998, *S. aureus* susceptibility profile changed tending to be more resistant to aminoglycosides and quinolones (Belmonte et al., 2008).

In the other territories, literature remains absent and no publication was found regarding prevalence and antibiotic resistance profiles of *S. aureus* in humans, livestock and pets.

MRSA epidemiological trends should be better addressed in Comoros, Mayotte, Reunion and Seychelles. Rates of resistances for widely available oral agents observed in Madagascar could point out a drug overuse in this territory as well as in Mauritius.
Burden of MRSA in livestock and pets should be addressed particularly as they can directly contaminate veterinary, breeders or other animals (Moodley et al., 2008).

***Enterococcus* spp.**

Enterococcus spp. are opportunistic bacteria often involved in nosocomial infections, mainly urinary tract infections, endocarditis, wounds and bacteremia (Murray, 2000). Discovered end of 1980's (Woodford et al., 1995), vancomycin-resistant enterococci (VRE) represents a major problem in healthcare settings worldwide.

In Madagascar, in 2006-2008, rate of resistance to vancomycin in *Enterococcus* spp. was 3.3% and was high for lincomycin (90.0%) (Randrianirina et al., 2010). In 2011-2013, one *E. faecalis* resistant to vancomycin (5.6%) was isolated during an uropathogenic survey (Rasamiravaka et al., 2015).

In Mauritius, in May 2010 and July 2014, all *Enterococcus* spp. isolated in hospitalized patients were susceptible to vancomycin (Issack et al., 2011; Issack, 2016a).

In Reunion, Picot et al. (2010) did not detect any VRE in 2005 (Picot et al., 2010). In other territories, no publication was found for both humans and animals.

Thus, epidemiological situation of VRE is not clear in IOC but doesn't seem being a main issue both in animals and humans. Identifying drug uses in livestock remains necessary as glycopeptide (e.g avoparcin) use in livestock was correlated with VRE incidence in human populations (van den Bogaard and Stobberingh, 2000).

b. Gram-negative bacteria

Pseudomonas aeruginosa

Pseudomonas aeruginosa is an opportunistic pathogen causing nosocomial infections (Zhanel et al., 2010). Some strains have been found to be resistant to nearly all antibiotics (Ventola, 2015).

In Madagascar, in 2006-2008, *P. aeruginosa* isolates showed a moderate resistance to penicillin (piperacillin 12.8% and ticarcillin 31.9%) but were susceptible to ceftazidime and imipenem (Randrianirina et al., 2010).

In Mauritius, in May 2010, *P. aeruginosa* isolated in hospitalized patients showed high rate of resistance to antibiotic tested with 51.5% to aminoglycosides (52% gentamicin and 51% amikacin), 47% for ceftazidime, 73% for ciprofloxacin and 40% for meropenem (Issack et al., 2011). In July 2014, a similar survey pointed a decrease of all resistance tested

(42% for gentamicin, 29% for amikacin, 30% for ceftazidime, 47% for ciprofloxacin and 27% for meropenem) (Issack, 2016a)

In Reunion, rates of resistance to imipenem increased from 1997 to 2005 (5.9% to 6.1%) (Picot et al., 2010). Outbreaks of *P. aeruginosa* were reported in a neonatal care unit (Gérardin et al., 2006; Naze et al., 2010) but susceptibility testing of strain was not performed. In Reunion, between 2010-2012, OXA-221 was identified in *P. aeruginosa* associated with β-lactamases and carbapenemase production (Jeannot et al., 2012). The Extended-spectrum β-lactamase OXA-145 was describe in 2011 in *P. aeruginosa* and conferred resistance to 3GC and monolactams (Hocquet et al., 2011).

Trends regarding *P. aeruginosa* in IOC are not clear but acquisition of new gene of resistance to β-lactams is of concern. Rate of resistance to carbapenems identified in Mauritius are high even if decreasing. Identifying its burden in nosocomial infection is needed as well as aminoglycoside resistance. Recommended treatment for pseudomonas infection usually includes β-lactams and aminoglycosides.

Acinetobacter spp.

Acinetobacter baumannii is a troublesome pathogens for health care institutions, its ability to acquire resistance determinants, is making it threatening the current antibiotic era (Peleg et al., 2008).

In Madagascar, in 2006-2008, a prevalence of *A. baumannii* of 8.8% was identified in infections diagnosed at hospital, the resistance to ceftazidime (62.0%) and imipenem was high (45.7%) (Randrianirina et al., 2010).Among strains collected between 2006-2009 92.5% were resistant to imipenem and 94.3% to ceftazidime (Andriamanantena et al., 2010). No resistance to carbapenems was reported among ten uropathogenic isolates in community (2011-2013) (Rasamiravaka et al., 2015) but this restricted sample could not reflect the epidemiological situation. The dissemination of multidrug-resistant OXA-23-producing *A. baumannii* in hospitals of Antananarivo (Andriamanantena et al., 2010) could emphasize issues regarding failures of infection control in hospitals (Randrianirina et al., 2010).

In Mauritius, in May 2010, *Acinetobacter* spp. isolated in hospitalized patients showed high rate of resistance to antibiotic tested with 86% for gentamicin and 50% for amikacin (both aminoglycosides), 95% for cefotaxime, 85% for ciprofloxacin and 68% for Meropenem (Issack et al., 2011). In July 2014, a similar survey pointed a decreasing rate of resistance for gentamicin, cefotaxime and ciprofloxacin (respectively 79%, 94% and 82%) and increasing for amikacin (58%) and meropenem (74%) (Issack, 2016a).

In Reunion, from 1997-2005, *A. baumannii* rate of resistance decreased to all antibiotic tested (e.g. ceftazidime (74.3% to 68.1%), imipenem (12.9% to 8.3%), and ciprofloxacin (72.9% to 59.7%) (Picot et al., 2010). In 2006, an outbreak of multi-resistant *A. baumannii* phenotype 5 occurred at the hospital, strains were resistant to all β-lactams (Belmonte et al., 2010). A wide variety of *A. baumannii* sequence types was identified at the hospital and could be related to community-acquired infections; one isolate carrying the $bla_{\text{OXA-23}}^{-}$ gene was identified (Pailhoriès et al., 2015).

In Comoros, the $bla_{\text{OXA-23}}^{-}$ gene in *A. baumannii* was identified in 2011 (Bonnin et al., 2013).

Pets can be reservoir of *A. baumannii* (Belmonte et al., 2014). In Reunion the prevalence in pets was 8.5% but no isolates were resistant to carbapenems (Pailhoriès et al., 2015). In cattle, the first case of OXA-24^{-} producing *A. baumannii* was recently identified (Pailhoriès et al., 2016).

Resistance to carbapenems in *A. baumannii* was observed in Comoros, Madagascar, Reunion and Mauritius. It is of concern for IOC as *A. baumannii* have an affinity with vulnerable patients (Gootz and Marra, 2008). Producing-carbapenemase *A. baumannii*, with the dissemination of OXA-23 enzymes, should be thoroughly monitored, keeping in mind the possible clonal spread of multi-resistant strains in hospital, community and pets.

Enterobacteriaceae

β-lactamases production are the primary cause of resistance among members of the family Enterobacteriaceae. In recent years, β-Lactamases have extensively diversified in response to clinical use of β-Lactams (Liakopoulos et al., 2016).

i) Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae (ESBLE)

ESBLE confer resistance to β-lactam antibiotics except cephamycins and carbapenems and are inhibited by clavulanic acid (Kliebe et al., 1985).

ESBLE was first isolated in Madagascar between 2004-2006 in urinary tract infections (Randrianirina et al., 2007b) as observed in table 2. High fecal carriage of ESBLE was identified in both hospital and community with prevalence of 21.3% in two hospitals from 2006-2008 (Randrianirina et al., 2010), 21.2% in a pediatric hospital in 2008 (Andriatahina et al., 2010) and 10.1% in community in 2009 (Herindrainy et al., 2011). Between 2013 and 2014, 18.5% of rectal colonization was estimated among pregnant women at delivery (Chereau et al., 2015). Another study (2015) pointed out 7.1% of Enterobacteriaceae nasal carriage resistance to Third Generation Cephalosporin (3GC) in patients at admission (Micheel et al., 2015). A study conducted from 2012 to 2013 pointed out the burden of ESBLE in early neonatal infection (12.9%); infections were treated with expanded spectrum cephalosporins due to the lack of carbapenems, and resulted in a high lethality (45 %) (Naas et al., 2016). In Madagascar, ESBLE mostly belong to the CTX-M-15 type (Rakotonirina et al., 2013; Naas et al., 2016), widely distributed worldwide (Coque et al., 2008).

In Mauritius, in 2005, rate of resistance to 3GC in Enterobacteriaceae from urine of patients with presumed community-acquired infection was about 9.0% for cefotaxime and 14.7% for cefixime (table 2). Isolates also showed high rates of resistance to fluoroquinolones (26.4% to ciprofloxacin) (Issack et al., 2007). Between 2010 and 2014, an increase of resistance in Enterobacteriaceae isolated in hospitalized patients was observed (46.7% to 50.7% for cefotaxime and 39.2% to 56.1% for ciprofloxacin) (Issack et al., 2011; Issack, 2016a).

In Reunion, prevalence of ESBLE was increasing at hospital with 2.0% in 1997 and 5.8% in 2007 (Belmonte et al., 2010). Broad-spectrum antibiotics use in hospitals was likely correlated with this evolution (Belmonte et al., 2010). In 2013, main ESBLE involved in infections where *Klebsiella pneumoniae* (38.0%), *Escherichia coli* (37.0%) and *Enterobacter cloacae* (24.0%) with 75.0% of the CTX-M-15 type (Robin et al., 2014).

A prevalence of 14.5% ESBLE was estimated among dogs and cats from veterinary clinics of Reunion Island (Belmonte et al., 2013).

In livestock from Comoros, Madagascar, Mauritius and Mayotte, overall 22.7% of livestock sampled were ESBLE carriers. The highest prevalence was observed among pigs (42.0%) and poultry (26%); Main contaminated farms were located in Madagascar (40.5%), Mayotte (26.9%) followed by Mauritius (13.5%) and Comoros (6.7%) (Miltgen et al., 2014).

No publication was found for Seychelles but prevalence of ESBLE (mainly represented by *E. coli, K. pneumoniae* and *E. cloacae*) in IOC seems increasing both in humans and animals. Broad-spectrum antibiotics overuse is likely correlated with this evolution (Belmonte et al., 2010).

ii) Carbapenemase producing Enterobacteriaceae (CPE)

In Madagascar first CPE was reported in a community survey of uropathogens implemented in 2011-2013 (Rasamiravaka et al., 2015). Imipenem rate of resistance was 40.0% for *K. pneumoniae,* 15.0% for *E. cloacae* and 2.3% for *E. coli* (Rasamiravaka et al., 2015). The reduced sample size for this study could not reflect global resistances patterns.

In Mauritius, rate of resistance to meropenem in Enterobacteriacae increased from 0.51% in 2010 to 5.32% in 2014 among hospitalized patients (Issack et al., 2011; Issack, 2016a).

In Reunion, in 2007, resistance to imipenem in Enterobactericeae was low (1 to 2 cases by year) (Belmonte et al., 2008).

First detection of New Delhi Methallo-β-Lactamase-1 (NDM-1) gene in *K. pneumoniae* in IOC occurred in a Mauritius patient in 2009 (Poirel et al., 2012), in 2011 in Reunion (Cabanes et al., 2012), in 2013-2014 in Madagascar (Chereau et al., 2015).

In Mayotte, an outbreak of CPE involving *E. cloacae* of IMI-1 type occurred at the hospital (Miltgen al., 2016). First investigations tend to highlight a community source of contamination but further investigations should confirm it (Miltgen et al., 2016).

In animal, no publication was found regarding CPE.

CPE are endangering the ability to cure infectious diseases. NDM-1 fast propagation in IOC is pointing the need of AMR surveillance and alert system. Mauritius seems particularly affected by CPE, their spread could constitute an issue for other territories as few therapeutic alternatives are available to treat infected patients.

iii) Foodborne and faecal-oral origin Enterobacteriaceae

1. Non-typhoidal *Salmonella* spp.

Salmonella is a major foodborne pathogen found worldwide. Most human salmonellosis is associated with eating contaminated raw or undercooked chicken, eggs, pork and contaminated water.

In Madagascar, in 2008-2009, *Salmonella* spp. rate of resistance in community-children was low for 3GC (1.2% for ceftazidime and cefotaxime), absent for quinolones and moderated for ampicillin (35.7%) and ticarcillin (35.7%) (Randrianirina et al., 2014).

In Mauritius, in 2009, *Salmonella enterica* serovar Enteritidis was isolated in humans without resistance identified for all antibiotic tested; transmission by chicken consumption was suspected (Issack et al., 2014). In 2014, *Salmonella* spp. isolated in stools of patients with gastroenteritis were all sensitive to Ampicillin and Ciprofloxacin and presented low resistance to Trimethoprim-sulfamethoxazole (2%) and Nalidixic Acid (1%) (Issack, 2016b).

In Reunion, between 2007-2009, rates of resistance among *Salmonella* spp. isolated in broiler chicken flocks were of 38.3% to streptomycin, 31.8% to tetracycline and 16.8% to ampicillin (Henry et al., 2013) but no resistance to 3GC was identified. *S. Hadar* displayed reduced susceptibility to fluoroquinolones (80.8% to enrofloxacin) (Henry et al., 2013).

In Comoros, no resistance in *Salmonella* spp. was identified between 1987-1988 (Petat et al., 1990).

Publications regarding AMR among *Salmonella* spp. are scarce in IOC. Resistances to quinolones in *Salmonella* spp. seems appearing in Reunion, probably do to its overuse, but not in Mauritius.

2. *Campylobacter* spp.

Campylobacter spp. can cause both gastroenteritis and extra-intestinal disease. *C. jejuni* and *C. coli* are the most often isolated from patients with diarrhea as confirmed in Madagascar in 2010-2012 (70.1% and 23.6% respectively) (Randremanana et al., 2014). Main infection source in humans is undercooked chicken, raw or unpasteurized milk, and cross-contamination from the environment (Humphrey et al., 2007).

In Madagascar, rate of resistance in *Campylobacter* spp. was moderate in community children in 2008-2009, with overall resistance of 24.8% for amoxicillin, 2.2% for ciprofloxacin, 1.8% for erythromycin and 1.1% for tetracycline (Randrianirina et al., 2014). Rate of resistance was higher for *C. coli* (Randrianirina et al., 2014).

In animals, *Campylobacter* spp. collected in 2005-2006 from chicken neck-skin in Madagascar presented 35.8% of resistance to ampicillin, 18.3% to erythromycin, 5.5% to ciprofloxacin and 3.7% to nalidixic acid (Garin et al., 2012).

In Mauritius, in 2014, *Campylobacter* spp. isolated in gastroenteritis cases presented high resistance to Quinolones with 51% of resistance to ciprofloxacin and 4% to erythromycin (Issack, 2016b). High quinolone resistance in *Campylobacter* spp. is probably due to antibiotic overuse in veterinary medicine (Issack, 2016b).

Publications regarding AMR among *Campylobacter* spp. are scarce in IOC particularly in animals. Resistance to quinolones in Mauritius could be due to its overuse in poultry industry (Issack, 2016b).

3. *Shigella* spp.

Shigella spp. is responsible for dysentery predominating in developing countries (Kahsay and Muthupandian, 2016).

In Madagascar, in 1988-1989, resistances in *S. dysenteriae* started being observed (Cassel-Béraud et al., 1990). In 2008-2009, rate of resistance in community children were high for widely used drugs (e.g. 79.9% for trimethoprim-sulfamethoxazole, 62.8% for amoxicillin, 62.2% for ticarcillin) but no resistance for ciprofloxacin was reported (Randrianirina et al., 2014).

In Comoros, *Shigella* spp. isolated between 1987-1988 did not exhibit significant resistances (Petat et al., 1990).

Few up-to-date publications regarding AMR in *Shigella* spp. were found.

Perspectives

One main challenge regarding this review was the data collection and comparison of AMR patterns between territories in the diversity of study designs (diagnosis isolates vs. systematic detection), antibiogram panels, over different periods of time and targeting various bacteria species. Thus, results should be interpreted with caution but this attempt of review was not performed before and confirmed that AMR is threatening IOC. Main issue identified for IOC was ESBL and CPE which is in agreement with their increase worldwide over the past decade (Cantón et al., 2012).

Literature was limited in Comoros, Mayotte and Seychelles confirming needs to develop AMR surveillance and research in these territories and scarce for bacterial species: *Enterococcus* spp., *Pseudomonas aeruginosa*, *Salmonella* spp., *Campylobacter* spp. and *Shigella* spp.

In IOC, the SEGA-One Health network was created in 2009 with the objective of monitoring outbreak-prone infections (Solet et al., 2014). It aims to develop a surveillance of AMR in human and animals but disparity of resources between territories and between animal and human health could be a brake in the establishment of such a system.

Thus, priorities should be established:

i) A direct relationship between antibiotic consumption, emergence and dissemination of AMR was demonstrated (The antibiotic alarm, 2013). Estimating the volume of antimicrobial drugs used, types and access (e.g. over-the-counter) is an essential step for IOC. The overuse of 3GC could have driven to selection pressures on bacterial community in both animals and humans observed (i.e. ESBLE and CPE in hospitals with carbapenems use). Drugs monitoring could help predicting risks of emergence in territories (Van Boeckel et al., 2015). Research on drug uses and habits in community, by practitioners and in livestock should be explored to adapt control measures.

ii) Integrated AMR One health approach including human, animal and environment in both surveillance and research is clearly needed (e.g. MRSA in veterinarians, *A. baumannii* in pets, humans and livestock, ESBLE in livestock and humans). Using standardized indicators (antibiotic drugs-bacteria species couple) for surveillance of AMR patterns across health care settings, countries and host species is essential. One relevant epidemiological indicator, for both animal and human, could be *E. Coli* AMR, particularly 3GC and carbapenems. Surveillance should be accompanied by further investigations regarding genetic support of resistance between hosts for source of contamination and dynamics of propagation between reservoirs identification (human, animal and environment).

iii) Spread of NDM-1-Producing Enterobacteriaceae in IOC confirms needs for strengthening the early warning surveillance system of AMR emergences. The region is connected to hotspots of AMR as Asia (12.0% of traffic) characterized by high AMR prevalence in community (e.g. ESBL in China (Quan et al., 2017), important antibiotic consumption (Van Boeckel et al., 2014), and emergence of new AMR profiles (e.g. NDM-1, mcr-1) (Liu et al., 2016)). Screening of travelers, returning from at risk AMR areas, with a history of hospitalization and consumption of antibiotic drugs abroad has been recently proposed (Armand-Lefevre et al., 2017) and could be relevant for an early emergence detection. However, screening is costly, thus, initiating reflection regarding pooling laboratory resources is essential.

Our article is the first attempt summarizing knowledge regarding AMR in both animal and human health sectors in IOC. This review clearly points out research and surveillance gaps and constitutes a tool for future activities to lead.

Author contribution

NG performed the review and collected the data from literature; NG wrote the first draft of the manuscript; EC, OB, LF revised and provided first feedback for the manuscript. All authors provided articles, have drafted and revised the work critically for important intellectual contents and approved the final version. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

This article has been funded by the Indian Ocean Health Agency and the European Regional Development Fund “Traquer les Risques Sanitaires dans l’Océan Indien avec une approche One Health”.

Acknowledgments

Félix Guyon Hospital for technical laboratory support.

Conflict of interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1. Evolution of antibiotic resistance of S. *aureus* from 2001 to 2014 in Indian Ocean Commission

Country	Population	Year	Study design	Sample type	Isolates number	OXA/CEF	PEN	ERY	LIN	SXT	GEN	Reference
Madagascar	Com	2001-2005	Laboratory surveillance	Pus, genital, urine, respiratory	68	6.5%	87.9%	14.6%	6.1%	16.8%	1.9%	(Randrianirina et al., 2007a)
Madagascar	Hosp	2001-2005	Laboratory surveillance	Surgical wounds, pus, hemoculture	506	4.4%	91.2%	10.3%	7.3%	13.2%	0.0%	(Randrianirina et al., 2007a)
Reunion	Hosp	2007	Laboratory surveillance	Unknown (diagnostic specimen)	--	13%	85.0%	18.0%	11%	0.4%	0.8%	(Belmonte et al., 2008)
Madagascar	Hosp	2010	Laboratory surveillance	Surgical wounds, pus, burn, urine, respiratory	103	13.6%	92.2%	19.4%	5,8	NI	3.9%	(Randrianirina et al., 2010)
Mauritius	Hosp	2010	Laboratory surveillance	Unknown (diagnostic specimen)	127	37.8%	95.3%	27.6%	NI	NI	NI	(Issack et al., 2011)
Madagascar	Com	2011	Cross-sectional study	Nasal swabs	45	38.8%	100.0%*	66.7%*	31.1%*	68.9%*	4.4%*	(Rasamiravaka et al., 2013)
Madagascar	Com	2011-2013	Laboratory surveillance	Urine	48	8.3%	75.0%	NI	NI	58.3%	NI	(Rasamiravaka et al., 2015)
Madagascar	Com (veterinarian)	2013-2014	Cross-sectional study	Nasal swabs	30	46.7%	100%	60.0%	NI	76.7%	20%	(Rasamiravaka et al., 2016)
Madagascar	Com (veterinarian)	2013-2014	Cross-sectional study	Nasal swabs	14	100.0%*	100%*	64.3%*	NI	71.4%*	42.9%*	(Rasamiravaka et al., 2016)
Mauritius	Hosp	2014	Laboratory surveillance	Blood culture, pus, burn, urine, swab, respiratory intravascular catheter	140	39.0%	NI	31.0%	NI	NI	NI	(Issack, 2016a)

OXA: oxacillin/CEF: cefoxitin, PEN: penicillin, ERY: erythromycin, LIN: lincomycin, SXT: trimethoprim sulfamethoxazole, GEN: gentamicin; NI: not identified; * Resistance in MRSA strains

Table 2. Evolution of antibiotic resistance of Enterobacteriaceae from 2004 to 2013 in Indian Ocean Commission

Country/ Year	Population	Study design	Sample type	Isolates number	ESBL carriers/ individuals tested	ESBLE/ Enterobacteriaceae tested	AMX	AMC	CAZ/ CEF	GEN	NAL	CIP	SXT	Bacterial Species	References

Madagascar 2004-2006	Com	Laboratory surveillance	urine	775	NI	3.8%	76.4%	15.6%	4.0%/ -	9.2%	24.5%	15.4%	64.8%	*E. Coli, K Pneumoniae, Proteus spp., Enterobacter spp., Citrobacter spp.*	(Randrianirina et al., 2007b)
Mauritius 2005	Com	Laboratory surveillance	Urine	224	NI	12.9%	NI	1,60%	- / 9.0%	9.9%	34.0%	26.4%	49.5%	*E. Coli, Klebsiella spp., Proteus spp.*	(Issack et al., 2007)
Reunion 2006-2007	Hosp	Laboratory surveillance	Unknown (diagnostic specimen)	240*	NI	5.8%	NI	NI	NI	67.0%	NI	74.0%	75.0%	*E. Coli, E. Cloacae, K. Pneumoniae*	(Belmonte et al., 2010)
Madagascar 2006-2008	Hosp	Laboratory surveillance	Surgical wounds, pus, burn, urine, respiratory	249	NI	21.3%	91.0%	69.0%	26,0% /26.0%	31.0%	52.0%	41.0%	71.0%	*E. Coli, K. Pneumoniae, Proteus spp., Enterobacter spp., Citrobacter spp.*	(Randrianirina et al., 2010)
Madagascar 2008	Hosp	Cohort study	Stool	30*	57,10%	NI	100.0%	100.0%	86.2%	91.4%	62.0%	50.0%	96.5%	*E. Coli, K. Pneumoniae*	(Andriatahina et al., 2010)
Madagascar 2008	Com	Cohort study	Stool	58*	22,10%	NI	100.0%	100.0%	90.0%	76.7%	63.3%	46.7%	93.3%	*E. Coli, K. Pneumoniae*	(Andriatahina et al., 2010)
Madagascar 2008-2009	Com	Cross-sectional study	Stool	195	NI	3.1%	82.%1	1.0%	1.5% /3.1%	1.0%	10.8%	3.1%	84.6%	*E. Coli*	(Randrianirina et al., 2014)
Madagascar 2009	Com	Cross-sectional study	Stool	53*	NI	NI	100.0%	98.0%	NI	NI	68.6%	60.8%	90.2%	*E. Coli, K. Pneumoniae, Enterobacter spp., Citrobacter spp.*	(Herindrainy et al., 2011)
Mauritius 2010	Hosp	Laboratory surveillance	Unknown (diagnostic specimen)	195	NI	NI	NI	NI	46.7%	50.6%	NI	39.2%	NI	*E. Coli, K. Pneumoniae*	(Issack et al., 2011)
Madagascar 2011-2013	Com	Laboratory surveillance	Urine	224*	NI	33.0%	80.8%	58.0%	30.4%-30.4%	NI	NI	NI	69.2%	*E. Coli, Citrobacter spp., K pneumoniae, Proteus spp., Serratia spp.*	(Rasamiravaka et al., 2015)
Madagascar 2013-2014	Pregnant women	Cohort study	Stool	66*	18.5%	NI	NI	NI	NI	NI	NI	36.0%	NI	*E. Coli, Citrobacter freundii, K pneumoniae, Enterobacter cloaca., Morganella morganii.*	(Chereau et al., 2015)
Mauritius 2014	Hosp	Laboratory surveillance	Blood culture, pus, burn, urine, swab, respiratory intravascular catheter	301	NI	NI	NI	NI	50.7%	33.2%	NI	56.1%	NI	*E. Coli, K. Pneumoniae*	(Issack, 2016a)

689 AMX: amoxicillin, AMC: amoxicillin + claviculanic acid, CAZ: ceftazidime, SXT: trimethoprim sulfamethoxazole, GEN:
690 gentamicin, CIP: ciprofloxacin, NAL: nalidixic acid, CEF: cefotaxim; NI: not identified; *ESBL isolates only

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