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Antimicrobial resistance in Madagascar: a review of the current situation and challenges

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Abstract:

Antimicrobial resistance (AMR) is a growing public health threat worldwide occurring in a wide range of pathogenic bacteria. It is encouraging that governments of countries around the world are beginning to pay attention to the issue of AMR that serves to undermine the future of modern medicine. However, each country solution approaches to this issue will differ in terms of magnitude and response capacity. Madagascar is a low-income country and one of the poorest countries in the world with poor environmental hygiene practices and easy availability of antimicrobial drugs without medical prescription. These particular contexts certainly influence the spread of multi-drug resistant bacteria. This review presents reported data on AMR from 2001 to 2018 in Madagascar among the World Health Organization (WHO) priority human pathogens, and determined the scope and magnitude of the AMR problems in the particular context of this low-income country, which could help in formulating effective response strategies for control of AMRs in Madagascar.

Key words: Antimicrobials, Madagascar, Multi-drug resistance, Prevalence

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Résistance aux antimicrobiens à Madagascar: bilan de la situation actuelle et des défis

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Abstrait:

La résistance aux antimicrobiens (RAM) est une menace croissante pour la santé publique dans le monde, qui se produit dans un large éventail de bactéries pathogènes. Il est encourageant de constater que les gouvernements des pays du monde commencent à prêter attention à la question de la RAM qui sert à saper l'avenir de la médecine moderne. Cependant, chaque approche de solution de pays à ce problème sera différente en termes d'ampleur et de capacité de réponse. Madagascar est un pays à faible revenu et l'un des pays les plus pauvres du monde avec de mauvaises pratiques d'hygiène environnementale et des médicaments antimicrobiens facilement disponibles sans prescription médicale. Ces contextes particuliers influencent certainement la propagation de bactéries multirésistantes. Cette revue présente les données rapportées sur la RAM de 2001 à 2018 à Madagascar parmi les agents pathogènes humains prioritaires de l'Organisation mondiale de la santé (OMS), et a déterminé la portée et l'ampleur des problèmes de RAM dans le contexte particulier de ce pays à faible revenu, ce qui pourrait aider à formuler des stratégies de réponse efficaces pour le contrôle des RAM à Madagascar.

Mots-clés: Antimicrobiens, Madagascar, Multi-pharmacorésistance, Prévalence

Introduction:

Antimicrobial resistance (AMR) is increasing worldwide and represents a major threat to public health (1). Indeed, in the European Union and the United States, antibiotic resistance is reported to cause over 25,000 and 23,000 deaths per year respect-

ively (2). In India, over 58,000 babies were reported to have died in one year as a result of infection caused by resistant bacteria passed from the mothers to babies (3). Thus, AMR is a worldwide concern and governments around the world are beginning to pay attention to this colossal issue.

Madagascar is the fourth largest island in the world located in the Indian Ocean (IO) off the eastern coast of southern Africa and east of Mozambique. Malagasy population is estimated around 25 million with various and mixed culture demise by Malayo-Indonesian, African and Arab ancestry. Living on an isolated island, Malagasy people are not sheltered from this AMR threat. Although no study has shown evidence that linked infectious disease death and antibiotic resistance, several studies report the presence of multi-drug resistant (MDR) bacteria in Malagasy community (4-7).

Recently, Gay et al., (4) reviewed the antimicrobial resistance in IO including Madagascar and pointed out the threatening presence of AMR in IO, although the report was to be interpreted with caution. However, particular context of each country that may constitute main factors contributing to the development of antibiotic resistance have not been addressed. For instance, Madagascar is a low-income country and one of the poorest countries in the world with poor environmental hygiene practices and high availability of antimicrobial drugs without medical prescription.

Tackling AMR progression surely represents a big challenge that needs deep context analysis and concerted efforts of local authorities and large panel of researchers in different areas of expertise. This review summarizes epidemiological knowledge and trends of AMR in Madagascar from 2001 to 2018 focusing on WHO antibiotic-resistant "priority pathogens" for research and development (R & D) for new antibiotics (8). The particular socio-economic background of the country and the management of bacterial infections are also discussed.

Methodology:

We conducted a bibliographic search for relevant available articles obtained through match searches using Google Scholar and PubMed. Relevant information was obtained for phenotypic and genotypic profiles (if available) of resistance in bacteria defined as 'critical', 'high' and 'medium priority' by the WHO (Table 1). Related terms such as 'prevalence', 'resistance', 'antimicrobial', 'antibiotic', 'epidemiology', 'Madagascar', 'African', and 'Indian Ocean' were also used to search for additional data.

We considered only strains isolated from humans and excluded strains from animals, food and food products. Considering the low rate of publication by Malagasy researchers, unpublished results presented in international congresses and seminars were included. However, data reported through national doctorate and/or master defenses (n=10) which were also referenced in Google results and/or Malagasy University websites were excluded. In total, 24 published articles and international congresses and seminars reports were included in the review.

Table 1: WHO priority pathogens list for Research and Development (R & D) of new antibiotics (5)

Priority	Pathogen
1: Critical	*Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
	Acinetobacter baumannii, carbapenem-resistant
	Pseudomonas aeruginosa, carbapenem-resistant
2: High	*Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
	Enterococcus faecium, vancomycin-resistant
	Helicobacter pylori, clarithromycin-resistant
	Campylobacter spp., fluoroquinolone-resistant
	Salmonellae, fluoroquinolone-resistant
	Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant
3: Medium	*Shigella* spp., fluoroquinolone-resistant
	Streptococcus pneumoniae, penicillin-non-susceptible
	Haemophilus influenzae, ampicillin-resistant

WHO 'critical priority' pathogens in Madagascar:

Enterobacteriaceae: carbapenem - resistant; ESBL-producing

The primary cause of resistance among members of the family Entero-bacteriaceae is β-lactamase production. In recent years, β-lactamases have extensively diversified due to the extensive use of β-lactams in hospitals (9). One of the most threatening β-lactamase is the extended-spectrum β-lactamase (ESBL) which confers resistance in Enterobacteriaceae to β-lactam antibiotics and carbapenems, except to cephamycin, but inhibited by clavulanic acid (10).

In Madagascar, ESBL producing Enterobacteriaceae (ESBL-PE) was first isolated in urinary tract infections between 2004 and 2006 (11). Following that period, high fecal carriage of ESBL-PE was identified in both community (Table 2) and hospitals (Table 3). For instance, a prevalence of 21.3% was reported in two hospitals of Antananarivo from 2006 to 2008 (12). The same trend (21.2%) was reported in a pediatric hospital in 2008 (5) whereas 10.1% was reported by Herindrainy et al., (6) in community setting investigation in 2009. Between 2013 and 2014, 18.5% of rectal colonization by ESBL-PE was estimated among pregnant women at delivery (7). Another study conducted among patients, healthcare workers and students reported 7.1% of Enterobacteriaceae nasal carriage resistance to third generation cephalosporin (3GC) in patients at admission (13). A study conducted in neonatal units of two different hospitals in Antananarivo from 2012 to 2013 reported the presence of ESBL-PE in early neonatal infection (12.9%). Due to the lack of carbapenems, these infections were treated with extended spectrum cephalo-sporins resulting in high mortality rate of 45% (14).

ESBL-PE in Madagascar mostly belong to the CTX-M-15 type (12,15) which is widely distributed worldwide (16), followed by SHV-12 type, whereas one New Delhi metallo-β-lactamase-1 (NDM-1)-producing Entero-bacteriaceae (*Klebsiella pneumoniae*) was isolated among pregnant women in the community (12). Additionally, the first carbapenem resistant Enterobacteriaceae (CRE) was reported in a community survey of uropathogens implemented in 2011–2013 (17). Imipenem resistance rate was 40% for *K. pneumoniae*, 15% for *Enterobacter cloacae* and 2.3% for *Escherichia coli*. However, the small sample size for this study could not reflect global resistance patterns. Overall, 5.7% (871/15,100) of the population studied had ESBL-PE isolated.

Table 2: Evolution of antibiotic resistance of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolated from the community between 2001 and 2018 in Madagascar

Town, location	Population (sex, age or mean age)	Date	Population number	Study design	Sample type	ESBL strains	CRE strains	CRP	CRA	Resistant to CIPRO	References
Antananarivo	M/F (Mean age 33 years old)	2004-2006	6884	Laboratory surveillance	urine	29	NI	NI	NI	120	23
Multi-location[a]	M/F (under 5 years old)	2008-2009	2692	Cross-sectional study	stool	7	NI	Ni	NI	7[b]	24
Antananarivo	M/F (Mean age 28 years old)	2009	484	Cross-sectional study	stool	53	0	NI	NI	31	6
Antananarivo	M/F (1 to 89 years old)	2011-2013	335	Laboratory surveillance	urine	79	15	NI	0	154	17
Antananarivo	M/F (Age not communicated)	2006-2007	79	Laboratory surveillance	Various bacteriological specimens	NI[d]	0	0	0	NI	15
Antananarivo (Moramanga)	Pregnant women (mean age 26 years old)	2013-2014	356	Cohort study	Stool	66	1[c]	NI	NI	24[b]	7
Antananarivo	M/F students, health care workers and patients (15 to 84 years old)	2015	1710	Cohort study	nasal	50	0	0	0	12[b]	13
Antananarivo	Pregnant women 17 to 38 years old	2015	146	Cross-sectional study	Urine	11	1	0	NI	NI	46

[a]14 locations: Antananarivo, Mahajanga, Tulear, Moramanga, Ihosy, Maeva Ambatondra, sambava, fianara, Antsirannna, Tsiroanomandiy, Morondava, Tolangaro, Toamasina, [b]among ESBL strains only, [c]NDM-1 producing Enterobacteriaceae (*Klebsiella pneumoniae*), [d]Rakotonirina *et al.* (2013) conducted a study in both community and hospital population, however the number of ESBL patient in community have not been communicated see Table 3 for global number of ESBL carriage; M/F: male and female; NI: not identified; ESBL: Extended spectrum -lactamase; CRE: carbapenem resistant Enterobacteriaceae; CRP: Carbapenem Resistant *Pseudomonas aeruginosa*; CRA: Carbapenem Resistant *Acinetobacter baumannii*; CIPRO: Ciprofloxacin

***Acinetobacter baumannii*; carbapenem-resistant**

In Madagascar, the epidemiological situation of resistance of *A. baumannii* is difficult to estimate due to limited samples. In the first decade of this century (2006–2008), a prevalence of *A. baumannii* of 8.8% was reported in infections diagnosed at hospital; the resistance to ceftazidime (62.0%) and imipenem was particularly high (45.7%) (9).

A study conducted by Andriamanantena et al., (18) among patients from four hospitals (three public and one private) in Antananarivo reported that 44% of collected strains between 2006 and 2009 were resistant to imipenem and 94.3% to ceftazidime, with multi-drug resistant OXA-23-producing *A. baumannii* phenotype, while no resistance to carbapenem was reported by Rasamiravaka et al., (17) among ten uropathogenic isolates in the community between 2011 and 2013.

***Pseudomonas aeruginosa:* carbapenem-resistant**

Data in regard of *Pseudomonas* is very rare as this strain is not commonly isolated from infected patients. In 2006-2008, *P. aeruginosa* isolates showed moderate resistance to penicillins (piperacillin 12.8% and ticarcillin 31.9%) but still susceptible to ceftazidime and imipenem (9).

WHO 'high and medium priority' pathogens in Madagascar:

***Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant**

In Madagascar, the prevalence of MRSA increased from 2001 to 2014 as shown in Table 4 and 5. Beginning from rates of 0 to 6% in year 2000 and through the first decade of the twenty first century, nasal carriage rate of MRSA in the community increased to 14.8% in 2011 (19, 20). Data collected by Andrianarivelo et al., (21) seems to corroborate the trend in community acquired as well as hospital acquired strains (13.8% and 15.7% respectively). In most of the studies, risk factors analysis revealed that history of hospitalization, recent antibiotic intake and frequent contact with animals and livestock workers/veterinarians increase the risk of MRSA nasal carriage.

Indeed, populations constantly in contact with animals are the most MRSA carriers and this is particularly relevant among Malagasy pig and poultry farmers (25% of MRSA carrier, 45/180) (22). Overall, resistance rates were higher for widely available drugs (23). Increasing rate of resistance to gentamicin (42.9%) and vancomycin (7.1%) was observed in MRSA isolates (20). In the same line, an increase resistance rates to fluoroquinolones have been noticed (19-22). Considering all collected data, 3.1% (317/10,191) of studied populations have been in contact with MRSA strains.

***Enterococcus faecium*, vancomycin-resistant**

In Madagascar, reported data of Enterococcus-vancomycin resistant (EVR) are very poor. In 2006–2008, rate of resistance to vancomycin in *Enterococcus* spp. was 3.3% (9) whereas in 2011–2013, one *E. faecalis* resistant to vancomycin (5.6%) was isolated during an uropathogenic survey (17).

Table 3: Evolution of antibiotic resistance of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolated from hospitals between 2001 and 2018 in Madagascar

Town, location	Population (sex, age or mean age)	Date	Population number	Study design	Sample type	ESBL strains	CRE strains	CRP	CRA	Resistant strain to CIPRO	References
Antananarivo	M/F (mean age 37 years old)	2006-2008	651	Laboratory surveillance	Various bacteriological samples	53	4	2	22	139	12
Antananarivo	M/F children (mean age 53 months) and medical staff	2008	474	Cohort study	stool	215	0	NI	NI	NI	5
Antananarivo	M/F (Age not communicated)	2006-2007	830	Laboratory surveillance	Various bacteriological samples	239[a]	0	0	0	NI	15
Antananarivo	Newborn (0 to 2 days)	2012-2013	303	Cross-sectional study	Blood and gastric samples	51	0	0	0	8[b]	14
Antananarivo	M/F Children (age not communicated)	2015	55	Cross-sectional study	Rectal swab	4	NI	NI	NI	4[b]	47
Antananarivo	M/F Newborns and Children (1months to 15 years)	2016	101	Cross-sectional study	Rectal swab	14	NI	NI	NI	NI	48

[a]global number of ESBL carriage among hospital and community population, [b] among ESBL strains only; M/F: male and female; NI: not identified; ESBL: Extended Spectrum -lactamase; CRE: Carbapenem Resistant Enterobacteriaceae; CRP: Carbapenem Resistant *Pseudomonas aeruginosa*; CRA: Carbapenem Resistant *Acinetobacter baumannii*; CIPRO: ciprofloxacin

Table 4: Evolution of Methicillin Resistant *Staphylococcus aureus* isolated from community between 2001 and 2018 in Madagascar

Town, locality	Population (sex, age or mean age)	Dates	Population number	Study design	Sample type	Number of MRSA carrier (%)	Resistance rates to other antibiotics (%)					References
							ERY	LIN	GEN	VAN	FLUO	
Antananarivo	M/F (mean age 34 years old)	2001–2005	506	Laboratory surveillance	Various bacteriological samples	33 (6.5)	33.3	19.4	11.1	0	13.9	23
Antananarivo	M/F (Mean age 33 years old)	2004-2006	6884	Laboratory surveillance	Urine	2 (0.02)	NI	NI	NI	0	100	11
Antananarivo	M/F (Mean age 33 years old)	2011	304	Cross-sectional study	Nasal swabs	45 (14.80)	66.67	31.11	4.4	NI	53.3	19
Antananarivo	Pregnant women (mean age 26 years old)	2015	146	Cross-sectional study	Urine	3 (6)	NI	NI	NI	0	NI	46
Antananarivo	M/F (1 to 89 years)	2011-2013	335	Laboratory surveillance	Urine	4 (1.2)	NI	NI	NI	0	NI	17
Antananarivo	M/F Veterinarian student (mean age 23 years old)	2013-2014	155	Cross-sectional study	Nasal swabs	14 (9.08)	64.28	NI	42.85	7.14	57.14	20
Antananarivo	M/F Farmer (mean age 23 years old)	2013-2014	180	Cross-sectional study	Nasal swabs	45 (25)	63.5	NI	30.5	0	47.5	22
Antananarivo	M/F (1 to 81 years)	2005- 2014	282	Cross-sectional study	Various bacteriological samples	39 (13.83)	14.89	7.50	5.67	0	24.11	21

ERY: erythromycin; VAN: Vancomycin; FLUO: Fluoroquinolone; GEN: Gentamycin; LIN: Lincomycin; NI: not identified

Table 5: Evolution of Methicillin Resistant *Staphylococcus aureus* isolated from hospital between 2001 and 2018 in Madagascar

Town, locality	Population (sex, age or mean age)	Dates	Population number	Study design	Sample type	Number of MRSA carrier (%)	Resistance rates to other antibiotics (%)					References
							ERY	LIN	GEN	VAN	FLUO	
Antananarivo	M/F mean age 34 years old	2001–2005	68	Laboratory surveillance	Various bacteriological samples	3 (4.4)	33.3	19.4	11.1	0	13.9	23
Antananarivo	M/F mean age 27 years old	2006-2008	651	Laboratory surveillance	Various bacteriological samples	14 (2.1)	NI	NI	3.9	0	NI	9
Antananarivo	M/F 5 to 15 years	2016	156	Cross-sectional study	Nasal swabs	17 (13.49)	NI	NI	NI	0	59.02	22
Antananarivo	M/F 1 to 81 years	2005-2014	624	Cross-sectional study	Various bacteriological samples	98 (15.70)	14.13	9.15	6.57	0	22.44	21

ERY: erythromycin; VAN: Vancomycin; FLUO: Fluoroquinolone; GEN: Gentamycin; LIN: Lincomycin; NI: not identified

***Salmonella* spp., fluoroquinolone resistant**

Salmonella spp. are major fecal–oral food-borne pathogens found worldwide. Most human salmonellosis is associated with eating contaminated raw or undercooked chicken, eggs, pork, and contaminated water. In Madagascar, resistance rates of community associated *Salmonella* spp. among children in 2008–2009 was 0% for quinolones, low for 3GC (1.2% for ceftazidime and cefotaxime) and moderate for ampicillin (35.7%) and ticarcillin (35.7%) (24).

***Campylobacter* spp., fluoroquinolone resistant**

Campylobacter spp. are responsible for both gastro-enteritis and extra-intestinal diseases in which *C. jejuni* and *C. coli* are the most isolated species from patients with diarrhea, as reported by Randremanana et al., (25) in their studies conducted between 2010–2012 (70.1% and 23.6% respectively). The main source of infection in humans is cross-contamination from the environment including livestock animal contact and contamination from undercooked chicken, raw or unpasteurized milk (26). The rate of resistance in *Campylobacter* spp. was low in community children (from study conducted between 2008 and 2009) with overall resistance rate of 2.2% to ciprofloxacin (24) while *Campylobacter* spp. collected in 2005–2006 from chicken neck skin presented 5.5% resistance rate to ciprofloxacin (27).

***Shigella* spp., fluoroquinolone resistant**

Shigella spp. are commonly isolated from stool of dysenteric patients, particularly in developing countries (28). In Madagascar, resistance in *S. dysenteriae* started being reported by the end of the 1980s (29).

Indeed, 5 resistant strains to ampicillin, carbenicillin, streptomycin, chloramphenicol, tetracycline, sulphonamides and trimethoprim were isolated from Malagasy children in Tananarive and on the east coast of Madagascar between 1988 and 1989. In the first decade of the 21st century, high rates of resistance were reported for widely used drugs (for example 79.9% for trimethoprim-sulfamethoxazole, 62.8% for amoxicillin and 62.2% for ticarcillin) among strains isolated from community children but no resistance to ciprofloxacin was reported (24).

Resistance in *Neisseria gonorrhoeae, Haemophilus influenzae, Helicobacter pylori* and *Streptococcus pneumoniae*

A multicenter study conducted between 2004 and 2006 reported 125 cases of *Neisseria gonorrhoeae* infection in Antananarivo (30). All tested strains were susceptible to cephalosporins and fluoro-quinolones. In the same way, a study conducted in three pediatric hospitals of Antananarivo from 1998 to 2000 assessing the role of *Haemophilus influenzae* meningitis in Antananarivo reported that among 160 cases of meningitis, *H. influenzae* type b were isolated from 27 cases. Antimicrobial susceptibility testing revealed that 42%, 29% and 22% of *H. influenzae* strains were resistant to chloramphenicol, amoxicillin and gentamicin respectively with no resistance to 3GC (31). Another study reported a prevalence of *H. influenzae* B to be 43% among 119 children with meningitis in the main hospitals of Antananarivo and no resistance to 3GC was observed (32).

Resistance to other high priority pathogens such as clarithromycin-resistance in *Helicobacter pylori* have not yet been reported probably due to the lack of isolated bacteria as they require special culture media and environmental conditions for growth. However, this is contrasting with the high seroprevalence of *H. pylori* infection of 36.2% and 82% among children and adult Malagasy population respectively (33,34). A case report communicated that patient infected by *H. pylori* present refractory profile to metronidazole and clarithromycin treatment, the first and second-line therapy against *H. pylori* infection. Authors underlined that susceptibility testing is overpriced for the concerned population (36). Likewise, only one study carried out in the main hospital in Antananarivo from 1998 to 2000 reported that all *Streptococcus pneumoniae* isolated from children with meningitis were sensitive to penicillin G (32) while *S. pneumoniae* was the first isolated bacteria pathogen (34-52%) responsible for meningitis in Madagascar (31, 36).

Discussion:

A glance at bacterial resistance in countries surrounding Madagascar revealed that MRSA rates are lower in Malagasy community compared to that of Mauritius and La reunion (38% and 13% respectively). Similarly, ESBL rate is estimated to be lower compared to Mauritius and La reunion (50% and 5.6% respectively) (4). However, the main AMR issues identified for Madagascar were ESBL and MRSA which is in agreement with their increase worldwide over the past decade (37). Nevertheless, the collected data should be interpreted with caution. Indeed, due to the diversity of study designs (diagnostic isolates versus systematic detection), antibiogram panels, different periods of time and sample collection, comparison of AMR patterns between territories may be difficult. This is one of the reasons we did not present meta-analysis and estimate the evolution of AMR in Malagasy community from 2001 to 2018.

Additionally, the studies were generally fractionated to limited population, for instance, all MRSA surveys were conducted in Antananarivo suggesting that the major population were natives of this town. However, healthcare facilities are very restricted in some regions such that people from rural areas go to urban city for care, suggesting that the studied populations may actually be from different areas of Madagascar. In any case, it is important to point out that data are concentrated in capital town of Madagascar. Indeed, if prevalence rate is lower in Antananarivo, it may be actually higher in the suburb and scrubland where access to water and healthcare facilities are lacking.

Only one study conducted in 14 districts of Madagascar by Institute Pasteur of Madagascar investigated the presence of ESBL-PE in stool samples from pediatric population (24). A longitudinal survey that take account of the native town of investigated population and cover at least the capital town of each Malagasy region will be necessary to really appreciate the magnitude of AMR among Malagasy population. Another critical limitation of studies carried out in Madagascar is the lack of molecular typing. Only few studies, principally carried out by Institute Pasteur of Madagascar reported molecular data in a multicenter study. In most studies, the presence of *mec*A gene in isolated MRSA strains was not verified. This is also valid for ESBL-PEs where very few studies investigated their molecular typing. This limitation is principally due to high cost of molecular analysis and the implementation

of PCR platform is difficult even in urban laboratory.

According to our academic experience, it is important to note that there are studies conducted by academic researchers which focused on AMR prevalence with phenotypic and genotypic profiles presented at doctorate and master defense. Regrettably, they have not yet been published in peer reviewed journals or communicated in international conferences due to the inability of local researchers to cover the publication fees (personal communication). Generally, they are able to publish their work only in association with international funders or academic institutes. This fact may explain the gaps in information on pathogens of major public health importance in Madagascar. However, it is encouraging to remark that some peer-review journals propose to waive the charge for publication in low-income countries for the promotion of research.

Socio-economic factors in relation to AMR in Madagascar

Madagascar is one of the poorest countries in the World. Indeed, more than three out of every four citizens of the country lived on less than $1.90 a day in 2019 (38). There is poor access to water, and sanitation and hygiene facilities are totally absent in some areas and only about 35% of the population has access to clean water. Access to sufficient and safe sanitation facilities is vital for hygiene, disease prevention, and human health. Although Madagascar has rainfall and water resources, they are under-exploited and access to good drinking water is difficult even in the capital town of Madagascar (39,40).

The lack of access to water supply and sanitation has significant health impacts especially in propagation of infectious diseases and MDR organisms. In the same line, access to healthcare facility is difficult particularly in rural areas, where citizens have to walk over 20 miles on foot of rugged roads to reach the simplest healthcare facility where inadequate services are offered.

Antibiotic consumption and AMR infections in Madagascar

A direct relationship between antibiotic consumption, emergence, and dissemination of AMR has been demonstrated (41). A study conducted by Padget et al., (42) reported that children population estimates for antibiotic consumption were 29.3% in Antananarivo and 24.6% in Moramanga (a town 200 km from Antananarivo). In all investigated sites, the large majority of antibiotics were taken with prescription (92.2% and 87.0% for Antananarivo and Moramanga respectively) and purchased in pharmacies (89.4% and 73.5% for Antananarivo and Moramanga respectively). Moreover, living in houses without modern toilets and age between 6 to 18 months were significantly associated with antibiotic consumption after adjusting for sites, and a higher density of public health structures was associated with lower antibiotic consumption levels, while a higher density of private pharmacies was associated with higher levels across sites. Importantly, most of the antibiotics can be purchased without medical prescription and regulations on the prohibition of dispensing non-prescription drugs exist only for particular cases (certain antibiotics) and particular period (e g. plague epidemic of 2017) (43).

With regards to medical prescription, the physician role is based on the correct prescription of antibiotics although it is sometimes difficult to make an accurate diagnosis in low-income countries where diagnostic tools for bacterial infections are limited and only present in major cities. Furthermore, the risk of superinfection is high in localities where hygiene is very precarious and this context brings doctors to immediately establish antibiotic therapy even if they are aware of the viral origin of infection. Moreover, in rural localities, patients often travel more than 10 miles to reach a healthcare facility suggesting that patient who has received medication from the doctor will no longer return for follow up check as far as his condition does not really get worse. Aware of these different parameters and constraints, physicians generally opt for empirical antibiotic coverage.

The monitoring system for MDR bacteria is less well developed in Madagascar, mainly due to limited diagnostic infra-structures. Bacterial cultures are only taken after failure of empirical antibiotic therapy and the number of hospital infections is undoubtedly underestimated. This empiric antibiotic approach is dependent on local prevalence of bacteria species. Due to the lack of microbiological analysis, there is no national database for bacterial profiles of UTI or vaginal infections such that the European, and particularly French database, are used as guide for empirical therapy. Intriguingly, a study conducted by Rasamiravaka et al., (17) demonstrated that the bacterial profiles of UTI in Madagascar is not the same as presented by French recommendation. Indeed, there is an increase rate of Gram-positive cocci of up to 34% causing UTI while it is usually in the range of 10% in the French database. This point may lead to failure of empiric antibiotic therapy approach by using inappropriate antibiotics. Meanwhile, it can

also lead to increase antimicrobial resistance by selecting persistent or resistant bacteria. It is also important to note that although bacteriological analysis of UTI is important for diagnosis of bacterial infection and surveillance of bacterial susceptibility to common antibiotics, its systematic use is difficult to install because of high costs of reagents and consumables.

Conclusion:

This review highlights the prevalence of resistant strains, particularly the ESBL producers, which is far from negligible in Madagascar although the overall estimation is low. It seems necessary to set up strategy to monitor antibiotic resistance of greater magnitude. It is obvious that AMR spread is connected to the local socio-economic context indicating that tackling AMR spread does not fall only on physicians, pharmacists and microbiologists, but requires a high commitment of government with private partners in order to regulate antibiotic consumption, and improve healthcare facilities and hygiene access. Without radical improvement of accessibility and quality of healthcare as well as water, sanitation and hygiene facilities, the successful reduction of antibiotic resistance spread will remain utopian.

The main strategy should first focus on controlling the spread of resistant strains through; (i) proper use of antibiotics, (ii) training on the right prescription (national education in antibiotic use), and (iii) the fight against illicit sales. For antibiotics, they must be issued only under prescription. It is assumed that such measures will discourage self-medication which may decrease the number of customers of the pharmacists thus government supportive measures should be considered. Indeed, the government must reassure antibiotic distributors that prohibition of antibiotic delivery without prescription will have no negative impact in their business. Moreover, government should propose different measures to reduce distributors' fear such as subvention and/or drug tax reduction. These measures require the increase number of pharmacy and drug deposit to not damage the accessibility of the drug, which is virtually improved by their presence in grocery stores that are largely close to the population.

In parallel, accessibility to healthcare facilities should be improved and private pharmacies should be controlled in order to reduce antibiotic over consumption. Furthermore, control of antibiotic dispatching as well as circulation/distribution of antibiotics should be rigorous to avoid the circulation of fake and poor-quality drugs. Indeed, some drugs placed on the market, despite having the active ingredients, may be under dosed or with poor bioavailability for the body resulting in decreased antibiotic concentration on the infectious sites. Such drugs must be tracked by the sanitary authorities. The free sale of authentic or non-genuine medication in general grocery stores must be prohibited, with only pharmacists and drug stores allowed to sell them. With regards to the difficulty of most Malagasy patients to pay for overpriced microbiological analysis due to high cost of reagents/consumables in medical laboratory, one alternative is the use of homemade reagents with the help of reference strains as quality control that may reduce charge of each test. For susceptibility testing, a proposed solution is to reduce the number of first line antibiotic disk testing to those really used by physicians and those detecting AMR. Thus, laboratory can propose cheaper price accessible to most households.

Other important keys to prevent AMR are national and international network in surveillance of MDR strains. It is encouraging that the "Mérieux Foundation (MF)" supports the setting up of a laboratory network for medical microbiology analysis and infectious disease surveillance. With the support of the Ministry of Public Health, MF generates national laboratories network called RESAMED in order to standardize practices, facilitate the flow of data and knowledge, and participate in the national health strategy, particularly on antimicrobial resistance surveillance. However, this type of support should be extended to applied research such as discovery of new antimicrobial compounds and in a fundamental aspect including accurate microbiological resistance mechanisms study. In this aspect, research and development (R & D) should be more innovative in the fight against bacterial infections by finding new original antibiotic with low risk of resistance from non-cultivable and telluric bacteria or original antimicrobial compounds targeting virulence ability of bacteria instead of their viability.

This latter approach does not intend to compete with the search of new antibiotics or to replace the use of available antibiotics but rather to reduce the use of the latter (for example decrease the dose of prescribed antibiotic while maintaining its full effectiveness) which hopefully could slow down the spread of MDR bacteria. Other interesting compounds are those with antibiofilm properties. Indeed, the ability of bacteria to form biofilm is one of the key mechanisms of microbial resistance to antibiotics as the biofilm matrix protects them against antimicrobials and immune

defense (44). It is promising that natural compounds have already been isolated from African and Malagasy plants with the ability to disrupt biofilm formation of *Pseudomonas aeruginosa* PAO1 and restore tobramycin effectiveness in *in vitro* experiments (45, 46).

To conclude, Madagascar is not adequately armed to actively tackle MDR progression. It is urgent that the government adopt the minimal requirement to contain MDR progression such as increasing accessibility to health care service and prohibiting delivery of antibiotic without medical prescription. With the re-emergence of Plague in 2017 in the country, a very strong counterattack by the antimicrobial prophylaxis of mass was instituted by the health authorities (more than one million doses of antibiotic to treat 100,000 people were distributed by the WHO) so we can expect an increase in the resistance rate in the coming years. As evoked by WHO "*While more R and D is vital, alone, it cannot solve the problem. To address resistance, there must also be better prevention of infections and appropriate use of existing antibiotics in humans and animals, as well as rational use of any new antibiotics that are developed in future…..The lack of adequate surveillance in many parts of the world leaves large gaps in existing knowledge of the distribution and extent of this phenomenon*" (8).

This review article provides an update on the baseline data and enlightenment of the magnitude of AMR in Madagascar and the particular context of the country which may explain the difficulty in developing standardized public health actions. Madagascar is under threat of AMR spread which needs urgent reaction of government and non-governmental entities concerned in preservation of public health.

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