Emergence of multi-resistant *Salmonella* in Morocco

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***Abstract*—In Morocco, epidemiological studies show the emergence of multi-drug resistance in human, avian, aquaculture and environmental salmonellae. The misuse of antibiotics as growth factors in livestock and their uncontrolled use in human and veterinary medicine are the main cause of the multiple resistances of bacteria to antibiotics. Multi-drug resistance is reported in several serotypes, mainly S.Typhimurium, S. Kentucky and S. Newport. This resistance is mainly ensured by the production of extended spectrum Beta lactamase (ESBL) and plasmid cephalosporinase. These enzymes confer high resistance to most therapeutic beta-lactams (with the notable exception of carbapenems in humans); and their genes, especially located on plasmids, propagate very easily between bacteria. It should be noted that some serotypes such as S. kentucky developed resistance to ciprofloxacin, S. Agona resisted to ceftriaxone by producing extended-spectrum beta-lactamase with a minimum inhibitory concentration of 16 µg / ml and S. Typhimurium produced an extended-spectrum beta-lactamase TEM-3 type. This multiresistance is associated with morbidity and mortality. These results are alarming and worrying, as given that *Salmonella* has developed resistance to antibiotics (fluoroquinolones and 3rd generation cephalosporins) prescribed for severe salmonellosis in adults and children. Consequently, the widespread dissemination of multi-resistance to antibiotics in salmonellae is a real public health problem.**

Keywords : Morocco, emergence, multi-drug resistance, *Salmonella*, antibiotics, public health.

I. INTRODUCTION

The infections due to the genus *Salmonella* are a major public health risk. Thus, *Salmonella* has acquired a multiple resistance to antibiotics mainly prescribed for the population at risk infected with salmonellosis. The emergence of multidrug resistant *Salmonella* is reported worldwide (Africa [1, 2], European Union [3] and Asia [4]).

The acquisition of this multi-resistance is essentially due to the misuse of antibiotics as growth factors, prophylactic and therapeutic agents in animal husbandry; All the more, the multi-drug resistance can be attributed to strains isolated from offensive environment or to antibiotics daily used. Indeed, the uncontrolled use of antibiotics in poultry production has increased the emergence of multi-resistant bacteria [5, 6]. As a result, certain serotypes (S.Typhimurium, S. Kentucky and S. Agona) have developed resistance to antibiotics administered to adults and children for severe salmonellosis such as 3rd generation cephalosporins and fluoroquinolones [7-9].

II. EVOLUTION OF ANTIBIOTIC RESISTANCE

Recently, *Salmonella* has acquired resistance to antibiotics [10, 11]. The acquisition of this resistance gives the multiple resistant pathogen an emergent nature [12, 13]. In Morocco, Several research studies have been examined the prevalence of multidrug susceptibility in different isolated strains of *Salmonella* from different origin (food [14], avian [15] and environmental [16, 17]).

Indeed, it has been found that the isolated salmonellae exhibit a high level of resistance to the following antibiotics: tetracycline, nalidixic acid and streptomycin. In 1995, all strains isolated at the Ibnou Sina University Hospital Center in Rabat between 1980 and 1991 had a low level of resistance to antibiotics [18], whereas in 1998, S.Typhimurium produced an extended-spectrum beta-lactamase TEM-3 type was isolated at the Ibn Rochd hospital in Casablanca [19]. In addition, in 2006, the first case of S. Kentucky isolated from turkeys resistant to ciprofloxacin was reported; During the same year another strain of the same serotype with the same resistance profile was isolated in a child from an 8-month-old in the pediatric ward at the Ibn Rochd University Hospital in Casablanca for acute and febrile diarrhoea [20]. Even more, in 2008, a high level of quinolone resistance was reported in S. Kentucky with minimal inhibitory concentrations (MICs) of 4-16 µg / ml [9]. In 2010, according to Karraouan et al., 82% of the isolated strains are resistant to at least one antibiotic and 50.3% are multiresistant, but they are all sensitive to 3rd generation cephalosporins. Also, no extended spectrum beta-lactamase (ESBL) was disclosed in this study [15]. However, in 2014, the Agona serotype developed a beta-lactamase spectrum that produced a high level of resistance to ceftriaxone with a MIC of 16 µg / ml [21]. In addition, S.Kentucky had a high level of NaR and CipR resistances

[22]. Also, in 2016, 65.6% of the isolated *Salmonella* are resistant to at least one antibiotic and 25% are resistant to ciprofloxacins [23]. It should be noted that *Salmonella* resistant to ciprofloxacin are generally resistant to several antibiotics [24], and are associated to increased morbidity and mortality.

III. GENES RESPONSIBLE FOR ANTIBIOTIC RESISTANCE

Resistance to antibiotics is usually due to a gene plasmid that can be easily acquired by the bacteria [25].

Genotypic analysis of *Salmonella* resistant to ciprofloxacin showed that this resistance was due to chromosomal point mutations in quinolone targets located mainly in regions called quinolone-resistance determining region (QRDR), which encode for the active site of the protein coding respectively for Subunit A of the DNA gyrase and topoisomerase IV. Analysis of the GyrA gene sequences revealed two point mutations, respectively, S83-F and D87-N, and on the ParC T57-S and S80-I gene. Another non-coding mutation has been detected on the ParCI193-L gene in S. Albert and S. Newport [20].

In S. Typhimurium and S. Newport, respectively, the resistances to C3G-type ESBL SHV-12, carried by a conjugating plasmid (aproximately 60Kbp) replicon IncI and Cmy-2 carried by a non-conjugative plasmid (approximately 210-kb) replicon IncA/C have been reported [9].

Recently, a study showed that some strains of *Salmonella* harbored one to four plasmids, from the group IncII in S. Mbandaka, IncFIIA in S. Typhimurium, and IncL/M in S. Hadar and S. Blockley. For the first time in Morocco, a genomic island 1 of intact *Salmonella* (SGI1) carrying the resistance genes aadA2, floR, tetG, blaPSE-1 and sul1 was detected in S. Typhimurium DT104. In S. Hadar, the resistances to ampicillin, tetracycline and streptomycin was associated respectively with blaTEM-1, tetA and strA genes, whereas the resistance to nalidixic acid is due to a mutation in gyrA (Asp87Asn) and in parC (Thr54Ser) [26].

These results are alarming and worrying, and highlight the presence of multidrug-resistant *Salmonella* potentially dangerous for human health in Morocco.

IV. CONCLUSION

In the last two decades, the expansion of multiple resistant *Salmonella* to the different classes of antibiotics is probably one of the most striking facts of human and animal antimicrobial resistance. At the same time, the *Salmonella* resistant to third-generation cephalosporins (C3G) and ciprofloxacins remains a major public health issue. This is particularly true because the treatment of severe human salmonellosis is mainly based on two antibiotics (C3G and fluoroquinolones), and only one for children (C3G) [8]. In the end, it is clear that a reduction of C3G use in animals is one of the important levers in order to reduce the prevalence of these enzymes in animals *Salmonella*. Indeed, the European Commission 'Regulation No 1831/2003' in the European Union has banned the use of antibiotics as growth promoters in animal husbandry in order to limit the selection and multiplication of multi-resistant strains [6].

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