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Antibiotic Resistance of *Streptococcus Pneumoniae*, *Neisseria Meningitidis, Haemophilus Influenzae* and *Staphylococcus aureus* in Morocco, National Data: Meta- Analysis

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Bacterial resistance to antibiotics has a very important role because it constitutes a threat to human health, especially immunocompromised people and children, this phenomenon can lead to difficulty or even the impossibility of treating certain infections. A meta-analysis from studies in Morocco on bacteria resistant to antibiotics over the last nine years and interest of bacterial: S. pneumoniae, N. meningitidis, H. influenzae and S. aureus, also the evolution their resistance. Total 654 articles in databases (206, 162, 134, and 152 articles found in: Elsevier, PubMed, Google Scholar, and other engines, respectively). For the bacteria in which we were interested, the prevalence of resistance increases with the years. Indeed, S. pneumoniae, N. meningitidis and H. influenzae, prevalence in 2012, 2016 and 2018 was respectively around (13%, 9.7%, 5.4%), (48%, 24%, 8%) and (29%, 33%, 8%). The evolution of the resistance of S. pneumoniae, was impacted by the introduction of the vaccine, indeed, the rate of its resistance to the antibiotic erythromycin before vaccination was 76% but after the introduction of the vaccine it decreased to 61%, while the incidence of pneumonia was 17.7%, and after vaccination it decreased to 10.2%. Also, the resistance of S. pneumoniae to penicillin G increased from 2.7% in 2011 to 100% in 2020. For N. meningitidis, resistance to penicillin G increased from 11.1% to 24% between 2012 and 2019. About of H. Influenzae for Bactrim, fluoroquinolones and tetracycline (16%, 4.8%, 2.5%), S.aureus resistance increases significantly. From 2016 to 2018, the resistance of S. aureus (Penicillin G 92%, ciprofloxacin 16.5%, erythromycin 14.6%).

Keywords: Antibiotics; Bacteria resistance; *Haemophilus influenzae; Neisseria meningitidis; Streptococcus pneumoniae; Staphylococcus aureus.*

Antibiotic resistance is nowadays one of the serious problems in the field of global health. It is reaching significant proportions in all regions of the globe. Each day, new resistance mechanisms appear and spread around the world, compromising ability to treat the most common infectious diseases[1]. Antibiotic resistance is reaching high levels worldwide, including Morocco and other neighboring African countries[2], with some bacteria becoming alarmingly multi-resistant to antibiotics[3]. A bacterium is said to be resistant when it escapes the action of the supposedly active antibiotic prescribed to the patient, which is manifested by a relative or absolute clinical failure of the antibiotic therapy. In the majority of infections, a clinical failure results in the absence of improvement (fever, general condition) after approximately 72 hours of treatment and the prescription of a second antibiotic.[4,5]

There are several types of bacterial resistance, for example: natural bacterial resistance, acquired bacterial resistance, resistance by chromosomal mutation, resistance by gene acquisition, cross-resistance, co-resistance and selection[6]. Two major reasons influencing this development are the widespread use of antibiotic therapy and the epidemic spread of resistant bacteria. However, other bacterial species long spared by this phenomenon and responsible for community infections *(Streptococcus pneumoniae (S. pneumoniae), Neisseria meningitidis (N. meningitidis), Haemophilus influenzae (H. influenzae) and Staphylococcus aureus* (*S. aureus*)) have in turn evolved in the direction of resistance[7].

S. pneumoniae is a species of bacteria of the genus *Streptococcus*, it is an important pathogen. It is responsible for many infections: for example, it has increased mortality during the Spanish flu pandemic. Its original name was diplodocus *pneumoniae* in 1926, it was named *Streptococcus pneumoniae* in 1974 due to its chain-like growth in liquid media. Because of its involvement as a pathogen in pneumonia, it has long been referred to simply as pneumococcus. Pneumococcal infections are particularly dangerous and very often require hospitalization, with mortality rates ranging from 8 to 15%[8]. *S. pneumoniae,* a major cause of community acquired invasive infection for newborns and children. Invasive pneumococcal infections, including meningitis, remain worrisome with a mortality rate of over 8% and a significant risk of complications. Of more than 90 serotypes, only a limited number are responsible for pneumococcal infections. The incidence of serotype may vary depending on the age of the patient, geographic region, and time of surveillance. The advent and introduction of pneumococcal conjugate vaccines has resulted in significant progress in the prevention of pneumococcal[9].

N. meningitidis, known as meningococcus, is a gram-negative diplococcal bacterium known for its role in meningitis. Meningococci are germs found only in humans, in the nasopharynx, where they can cause mild nasopharyngitis or an asymptomatic carrier state. One can remain a carrier for several months or even years. In a normal population, 5-10% of carriers are found, but this rate can reach 50-75% in certain dense communities (barracks, boarding schools). Out of approximately 400 carriers, only one person becomes a victim of a serious meningococcal infection, this is most often presented as acute purulent meningitis. The meningococcus could move from the nasopharynx to the meninges by following the path of the olfactory nerves. However, the meningococcus reaches central nervous system (CNS) through bloodstream. Indeed, meningococcal disease almost always present at the beginning of meningitis. This sepsis may be asymptomatic, or it may add to the meningeal syndrome a purpuric eruption (found, depending on the epidemic, in 10 to 50% of cases of meningitis), or in 5 to 10% of cases, it may present as purpura fulminans, rapidly fatal, even before meningitis develops. These superacute forms are referred to as Waterhouse-Friderichsen syndrome. In these cases, the endotoxin, by contracting the intrahepatic veins, causes the accumulation of blood upstream of these veins, resulting in capillary hemorrhages (in the adrenals among others), intravascular thrombosis and circulatory collapse[10,11].

H. influenzae, called Pfeiffer's bacillus, is a bacterium of the family: *Pasteurellacae* and class: *Gammaproteobacteria.* The cells are coccobacilli or small immobile Gram-negative rods. Richard Pfeiffer (1858-1945) was the first to describe them in 1892 from the influenza pandemic of 1889-1892. For a long time, he was believed to be responsible for influenza, until 1931, when Richard Shope isolated a virus from filtrates of pig lung shreds during a swine influenza similar to the human one[12,13]. *H. influenzae* is a species sensitive to many families of antibiotics, and has not been spared the evolution of antibiotic resistance. The level of acquired resistance for aminpenicillins, tetracycline and trimethoprim places *H. influenzae* in the species inconsistently susceptible to these antibiotics, this species is naturally resistant to lincosamides and is classified as resistant to macrolides with a 16 atom cycle[14].

S. aureus is most pathogenic species of the genus *Staphylococcus*. It is responsible for localized suppurative infections, food poisoning, and in some extreme cases, infections that could be fatal (immunocompromised patients, cardiac prostheses). *S.aureus* presents itself as a clustered shell (Grape clusters), Gram positive and catalase positive. Its name derives from the golden tint that its carotenoid concentration provides it[15]. The *S. aureus* species is commensal to humans (it is present in 15 - 30% of individuals known as healthy carriers in whom it has an ecological protection role), is an opportunistic pathogen in certain locations, under certain circumstances. *S.aureus* a good resistance to natural purification mechanisms (oxidation, desiccation, which explains its direct but also indirect transmission). *S.aureus* is a germ that has developed a remarkable level of resistance against multiple antibiotics, complicating treatment. Historically, *S. aureus* resistance appeared within two years after introduction penicillin[3]. Controlling infections caused by antibiotic-resistant bacteria in humans requires regular monitoring of bacterial resistance and control of antibiotic use[16].

The frequency of the appearance of resistance and multi-resistance is most often conditioned by an increased use of antibiotics. The pressure of these molecules on the bacterial flora seems to be at the origin of the emergence of bacterial resistance. Therefore, on the recommendation of the World Health Organization (WHO), structures for monitoring antibiotic resistance and committees on the proper use of these molecules have been set up in most countries of the world. The objective of these structures is to periodically take stock of bacterial resistance in order to better adapt antibiotic therapy[17,18].

This paper aim is to make a meta-analysis from the studies done in Morocco on antibiotic resistant bacteria during the last nine years (2011-2020). We were interested in the following bacteria: (*S. pneumoniae, N. meningitidis, H. influenzae* and *S. aureus*) and the evolution this resistance.

MATERIALS AND METHODS

A thorough meta-analysis of past studies on the topic of bacterial resistance to antibiotics was carried out using national data in Morocco, for relatively common pathogens occasionally responsible for most infectious pathologies (*S. pneumoniae, N. meningitidis, H. influenzae and S. aureus*).

Type and period of the study

This Meta-analysis on antibiotic resistance in Morocco, national data on studies conducted in the last nine years (2011-2020).

Search strategy and criteria for choosing studies

The databases were used including: Elsevier, PubMed, Google Scholar, other engines. Search words: (Bacteria* or resistance *or Antibiotics* or *S. pneumoniae** or *N. meningitidis** or *H. influenzae* * or *S. aureus**) and (Antibiotic therapy* or resistance*). Published studies in all languages were included in the searches. A search options in Scopus database were "title, abstract, and keywords." Found a total 654 articles in databases (206, 162, 134, and 152 articles found in Elsevier, PubMed, Google Scholar, and other engines). For our analysis of the national data, 431 of the studies were excluded (see Figure 1 which includes the reasons for elimination). And following information processing, finally, we chose 15 studies.

Exploitation standards

Collecting articles for our meta-analysis using keywords: bacteria, antibiotic, resistance, *S. pneumoniae, N. meningitidis, H. influenzae, and S. aureus*. Searched for articles and studies in the literature regarding bacterial resistance to antibiotics carried out in Morocco between 2010 and 2020, and we made no distinction regarding the publication's language.

Elimination standards

Published data on bacterial resistance to antibiotics, articles or studies that are on animals, outside the selected period, connected to our study but in different directions, and that are not on national data, were excluded. A meta-analysis was performed A meta-analysis was performed for 15 articles published using GraphPad Prisma[19].

Statistical analysis

For the statistical analysis, we used three different programs including: GraphPad Prisma 9 Review Manager 5.4 and Microsoft Excel, each of which has its own benefits and traits.

• GraphPad Prisma 9: for repeat and elimination criteria, and to graph years and regions of publication. A *p value* ≤ 0.05 was regarded as significant for statistical analyzes with a 95% confidence interval (95% CI)

• Review Manager 5.4: to compare similar studies.

• Microsoft Excel to create tables, collect and compare data.

RESULTS AND DISCUSSIONS

Studies published in the period of (2010-2020) in Moroccan regions on antibiotic resistance

We have graphically represented the number of studies published in the selected period (2011-2020), the most of studies took place in 2019, followed: 2012, 2017 and 2020. (Figure1). The number of studies published in different Moroccan cities in the same period where we found, seven in Casablanca, four in Rabat, three in Fes, and one in Marrakech. (Figure2).

Studies characteristics that were considered in our meta-analysis

The 15 studies' primary characteristics (in four Moroccan regions) within scope of this systematic review. Essentially all of these were based on laboratory controls, analytical research and diagnostic surveys as illustrated in (Figure 3).

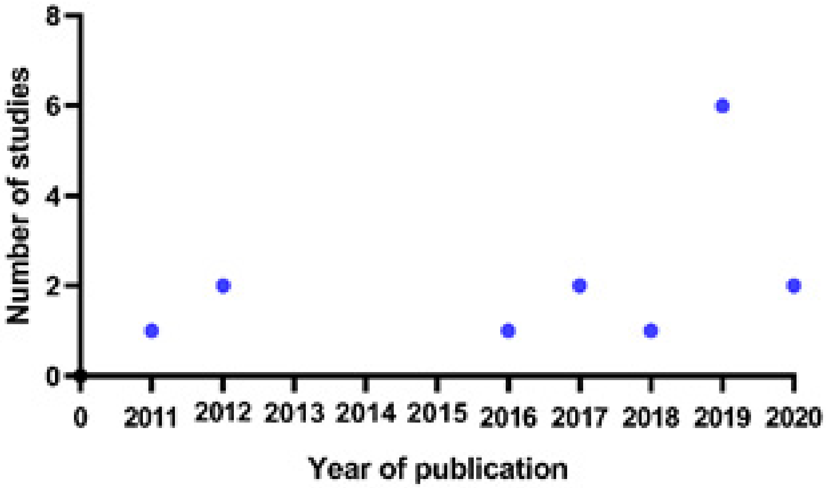

Fig. 1. Number of studies published in Morocco in period of (2011-2020) on bacterial resistance to antibiotic

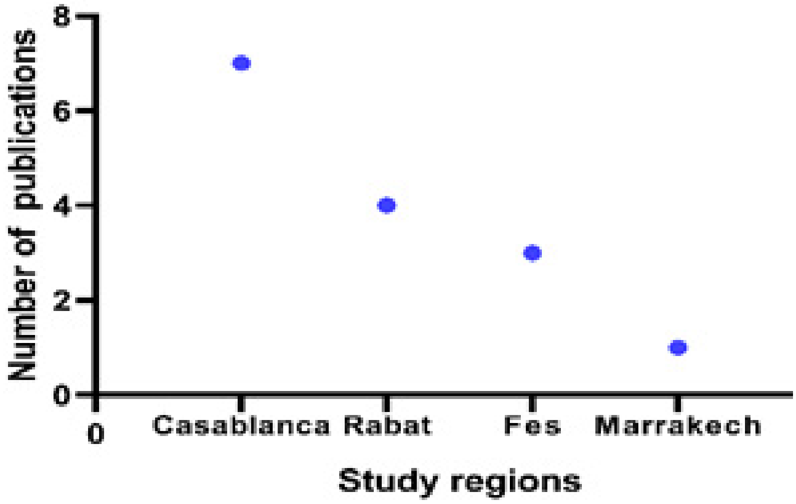

Fig. 2. Number of studies published in Moroccan cities on bacterial resistance to antibiotic in period of (2011-2020)

Characteristics of the studies included in our analysis on antibiotic resistance

In each article, indicated the region and year of the study, the germs studied, the antibiotics, the most resistant bacteria, the number of references on which each research was based and the number of samples in each study. And we added comments for each reference.

The most of studies were conducted in 2019, 2012, 2017, and 2020, with fewer studies conducted in 2012, 2016, and 2018. Among the studies analyzed in our evaluation, seven studies were conducted and published in Casablanca, four in Rabat, three in Fes, and one study in Marrakech. (Table 1).

Epidemiological profile of invasive germs in the pediatric

Bacterial meningitis in the pediatric population remains a worrying pathology due to its frequency and severity, studies made on the antimicrobial resistance of the most frequent bacteria in hospitals in Morocco, and these studies have concluded that the most frequent bacteria: *S. pneumoniae; N. meningitidis and H. influenzae.*

According to these studies, which are presented in the table below, the prevalence of *S. pneumonia*e was 13%, *N. meningitidis* was 9.7%, and *H. influenzae* was 5.4% in Casablanca in 2012 (based on 185 samples).

In 2018, in Morocco, (out of 277 samples), *S. pneumoniae* infection was confirmed 29%, *N. meningitidis* infection was 33% and *H. influenzae* infection was 8%.

In 2016, a study was conducted in Rabat on 25 samples, half of the samples were infected with *S. pneumoniae* at 48%, *N. meningitidis* at 24% and *H. influenzae* at 8%.

According which studies (2012, 2018), ceftriaxone was used in the treatment in both studies and the outcome was favorable in all patients. Both studies concluded that C3Gs are the most effective treatment for bacterial meningitis and suggested that the vaccination program against *H. Influenzae* b should be strengthened.

Evolution of *S. pneumoniae* resistance to antibiotics

The period of realization of the two studies is about seven years, where the resistance of bacteria was studied on both penicillin and erythromycin, at the beginning of the two studies the rate of bacterial resistance to penicillin was 25% and after about seven years was 31%.The rate of resistance to erythromycin was 15% and after seven years was 21%, therefore, there is a remarkable increase in bacterial resistance to the aforementioned antibiotics, which imposes attention to the use antibiotic in treatment *S.*

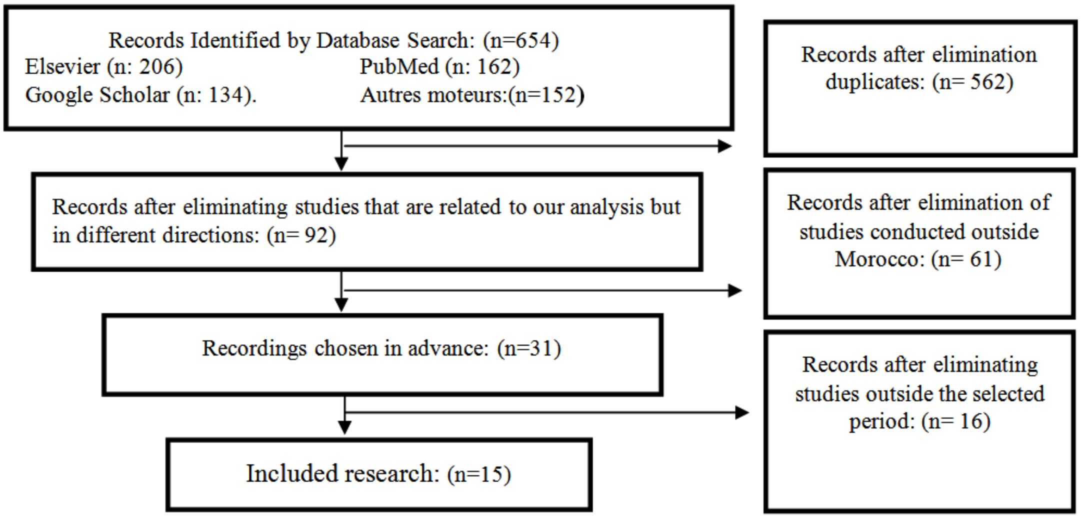

Fig. 3. PRISMA Graph for the selection of studies: shows the number of researches or studies included in our search of literature on bacterial resistance to antibiotic, the processing of the data, and the elimination criteria, which led to the selection of 15 studies for our meta-analysis

Table 1. Summary of studies that were listed in our meta-analysis

References	Year of publication	Region	N. of Samples	Microbe	Types of Antibiotics	Resistance	Comments
Bouskraoui et al [20]	2011	Marrakech	302	Streptococcus pneumoniae	PG	PG	penicillin resistance of carrier strains in children under 2 years old
N. Mdaghri et al.[21]	2012	Casablanca	185	Neisseria meningitidis	PG	PG	In this study, the only antibiotic, penicillin G, gave significant resistance
Benbachir et al.[22]	2012	Casablanca	955	Streptococcus pneumoniae	PNS, AMC, CRO, CHL, ERY, TET and TSU	PNS, AMC, CRO, ERY	Antibiotic resistance rates vary considerably by geographic location at MIC>2?g/ml
Diawara et al. [23]	2016	Casablanca	655	Streptococcus pneumoniae	MLSB	MLSB	Multi-resistant S.pneumoniae. Strains include both (vaccine and non-vaccine) serotypes. More observationnel studies are needed
Diawara et al.[24]	2017	Casablanca	361	Streptococcus pneumoniae	PGand AMP	PG	The ratio was 22.2% overall for PG resistance in the research
Ghita Y et al. [25]	2017	Fes	123	Haemophilus influenzae	No resistance sensitive	sensible	H.influenzae, plays a major role in lower respiratory infections, these infections are a real public health problem.
Moumni M B et al.[26]	2018	Fes	277	Neisseria meningitidis	CET	sensible	Following this study, we can conclude that the therapeutic regimens using 3rd generation cephalosporins in the treatment of community meningitis are effective. We also suggest the reinforcement of the vaccination program against H. influenzae b.
EL Amin G et al.,[27]	2019	Rabat	2436	Streptococcus pneumoniae and Neisseria meningitidis	PG	PG	Nosocomial meningitis represents 73.8% of documented meningitis in this series. Many of them are related to neurosurgery or consecutive to the placement of a CSF shunt.
Rhars A et al. [28]	2019	Rabat	100	Staphylococcus aureus	PEN, CIP et ERY	PEN, CIP	The need to adapt probabilistic treatment regimens to the local epidemiology.
Kouara S et al. [29]	2019	Fes	46	Staphylococcus aureus	PEN, CIP et ERY	PEN, CIP, ERY	This class of antibiotics still retains its place in the treatment of staphylococci
Nzoyikorera N et al [30]	2019	Casablanca	74	Streptococcus pneumoniae	PG	PG	The data from this study on adult MS show variability in serotypes and provide information on the antibiotic susceptibility status of pneumococcus in adults
Raghani A et al. [31]	2019	Rabat	4232	Streptococcus pneumoniae	PG	PG	The importance of the frequency of pneumopathies as well as the isolation of resistant germs incites us to improve the hygiene conditions, the means of prevention and the reasoned prescription of antibiotics
Saoud M Z et al. [32],	2019	Rabat	119	Staphylococcus aureus	PEN, CIP et ERY	PEN, CIP et ERY	All prescribed antibiotics were resisted by S. aureus
Ait Mouss et al. [33]	2020	Casablanca	245	Neisseria meningitidis	PG et 3GCs	PG	All isolated strains are sensitive to third generation cephalosporin.
Ousaid et al. [3]	2020	Casablanca	115	Staphylococcus aureus	OXA, AMP, AMX, CTX, SEF et ERY	OXA, AMP, AMX, CTX et SEF	In Morocco and neighboring countries, the problem of antibiotic resistance is recognized and well documented.

Abbreviations: PEN : penicillin, PG : Penicillin G, SEF : Cefpodoxime, CHL : Chloramphenicol, ERY : erythromycin, TET : Tetracyclin, OXA : Oxacillin, AMP : ampicillin, CIP : Ciprofloxacin, CTX : Cefotaxime, AMX : amoxicillin, CET : Ceftriaxon, MLSB : macrolide, lincosamides , streptogramin B et C3G : cephalosporins 3rd generation.

Table 2. Epidemiological profile of invasive germs in the pediatric

References	Years	Regions	N. of samples	*S. pneumoniae*	*N. meningitidis*	*H. influenzae*
Mdaghri N, *et al* 2012	2012	Casablanca	185	13%	9.7%	5.4%
EL Amin G *et al 2019*	2016	Rabat	25	48%	24%	8%
Moumni M B,*et al* 2018	2018	Fes	277	29%	33%	8%

Table 3. Resistance of *S.pneumoniae* to antibiotics

References	Resistance %		Resistance % After 7 years		
	N. of Samples	Total	N. of Samples	Total	Total %
Benbachir *et al,* 2012	25	100	31	100	56.6
Diawara *et al,* 2016	15	100	21	100	43.4
Total		200		200	

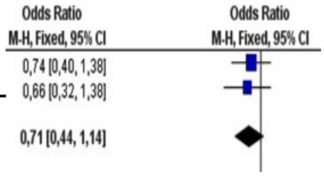

Table 4. Resistance of *S. pneumoniae* to penicillin G: (SPRPG)

References	Years	Regions	N. of samples	*S. pneumoniae*	RPG
Bouskraoui M*et al 2011*	2011	Marrakech	302	45.8%	2.7%
Raghani A *et al*.2019	2012-2018	Rabat	4232	1%	10.6%
Diawara *et al*, 2017	2014	Casablanca	361	100%	22.2%
Nzoyikorera N *et al*.2019	2016-2018	Casablanca	74	32%	18.75
Ousaid *et al*, 2020	2020	Casablanca	101	86%	100%

Table 5. Resistance of *N. meningitidis* to penicillin G:)NMRPG)

References	Years	N. of samples	Regions	RPG
N. Mdaghri, *et al* 2012	2012	180/18	Casablanca	11.1%
EL Amin G *et al* 2019	2016	600/6	Fes	16.6%
K. Ait Mouss *et al* 2020	2019	245	Casablanca	24%

Table 6. Epidemiological profile of lower respiratory infections with *H. influenzae*

References	Years	Region	N. of Samples	RAMX	RTRM & RSU	RFLQ	RTET	C 3 G
Ghita Y *et al* 2017	2011-2016	Fes	123	S:AMC28 %	16%	4,8%	2,5%	S

Abbreviations: R: Resistance, S: Sensibles, AMX: amoxicillin, SU: sulfamethoxazole, FLQ: fluoroquinolones, TET: Tetracyclin, AMC: amoxicillin-clavulanic and TRM: The resistance of trimethoprim *pneumoniae* infection and evaluation effectiveness treatment and antibiotic resistance heterogeneity.

Resistance of *S. pneumoniae* to penicillin G

Through previous studies carried out from 2011 until 2020 on 302 samples, *S. pneumoniae* was the most resistant to Penicillin G, in 2011 the percentage of resistance to Penicillin G was at 2.7%, and in the second study carried out on 101 samples this resistance evolved to 100% in 2020.

Evolution of *N.meningitidis* resistance to penicillin G

Three studies on non-tuberculous bacterial meningitis in pediatric in two Moroccan regions (Casablanca and Fes), found that resistance of *N. meningitidis* to penicillin G was 4.3 in 2000, 11.1% in 2012, 16.6% in 2016, and 24% in 2019.

Evolution of *H. Influenzae* resistance to antibiotics

Epidemiological profile of lower respiratory infections with *H. influenzae*

A study carried out in the period 2011-2016 on 123 strains of *H. influenzae* responsible for lower respiratory infections, this study showed that the strains that are resistant to amoxicillin are sensitive to the combination amoxicillin-clavulanic acid 28% of cases, and the resistance to other antibiotics 16% to trimethoprim -sulfamethoxazole, 4.8% to fluoroquinolones 2.5% to tetracyclins, and no resistance to 3rd generation cephalosporins was observed.

Epidemiological profile meningitis of *H. influenzae* bacterial

The data of the retrospective studies carried out in Rabat over a period of three years based on CSF analysis of 95 positive cases were documented (59 adults and 36 children) of which the percentage of *H. Influenzae* cases was 8% (2 cases) and the antibiotic resistance was not documented, and in the second study carried out in Fes, showed that CSF analysis of 24 positive cases, of which the percentage of *H. Influenzae* cases was 8%, and the antibiotic resistance was not documented. It can be concluded that there is a lack of study of the resistance of *H. Influenzae* to antibiotics in these two studies Table 7.

Evolution of *S. aureus* resistance to antibiotics

S. aureus is the main cause of nosocomial infections and can affect several parts of the body and the emergence of resistant strains is a major problem in the public health of all the world that continues to increase according to the data of previous studies.

A study conducted over a period of 2016-2018 in Rabat, on 117 samples taken in consulting rooms and emergency cases with an average age of 47 years, where *S. aureus* was 92%, and tests were performed to determine its resistance to antibiotics, the percentage of resistance to penicillin G was 92%, to ciprofloxacin at 16.5%, and erythromycin at 14.6%.

Table 7. Epidemiological profile meningitis of *H. influenzae* bacterial

References	Years	Regions	N. of Samples	*H.influenzae*
El amin G *et al* 2019	2016 - 2018	Rabat	600	8%
Moumni M B, *et al* 2018	2018	Fes	277	8%

Table 8. Resistance of *S. aureus* to antibiotics

References	Years	Regions	Infectious pathologies	N. of Samples	RPENG	RCIP	RERY
Saoud M Z *et al.* 2019	2016-2018	Rabat	Surgical operations and emergencies	117	92%	16.51%	14.61%
Rhars A *et al* 2019	2017-2019	Rabat	Diabetic foot abscess and cellulitis	100	89.6	6.9%	-
Kouara S *et al* 2019	2018-2019	Fes	Intravenous catheters and urine cultures	46	2%	4%	88%

Abbreviations: PEN G: penicillin G, ERY: erythromycin CIP: ciprofloxacin.

Another study in Rabat conducted from 2017-2019 (Table 8) and the mean age of patients 49 year, and the samples were on patients with abscesses, diabetic foot and cellulitis, 29% of these samples were to *S. aureus*, and tests were performed showing that resistance to penicillin G was 89.6%, and to ciprofloxacin 6.9%, and resistance to erythromycin was not tested.

In another study conducted from 2018-2019 in Fes, on 46 samples of urine and venous catheters in people with an average age of 46 years, all samples contained *S. aureus* and were resistant to erythromycin to 88%, and ciprofloxacin 4% and penicillin G 2%.

DISCUSSION

In our analysis of national data on bacterial resistance to antibiotics, we chosen 15 articles conducted over the previous ten years in four Moroccan regions, analyzed and compared the data from these studies to learn about antibiotic-resistant germs and the kinetics of this resistance, rapid emergence of resistant bacteria is occurring global, including in Morocco and neighboring countries, jeopardizing the effectiveness of antibiotics which have revolutionized medicine and let millions of people live longer[34]. Misuse of these medications has been linked to the challenge of antibiotic resistance. In addition, paucity of development of new drugs due to weaker economic incentives and onerous regulatory requirements by the pharmaceutical industry, is a serious problem[35]. The usage of antibiotics has a massive effect on these parameters, which has been extensively proven in Morocco[36].

Based our meta-analysis on the evaluation of the evolution of resistance of *S. pneumoniae, N. meningitidis, H. influenzae,* and *S. aureus*.

According the results obtained from the studies carried out in Morocco, we can say for the different bacteria, the prevalence of resistance increases with the years, in fact, in 2012 it was (13%, 9.7%, 5.4%) respectively *S. pneumoniae, N. meningitidis and H. influenzae*, in 2016 (48%, 24%, 8%) and in 2018 (29%, 33%, 8%), and we did not find documents on the prevalence of *S.aureus.*

We noticed that the evolution of resistance regarding *S. pneumoniae* was impacted by the introduction of the vaccine, rate of resistance *S. pneumoniae* to antibiotic erythromycin before vaccination was 76% and after the introduction of the vaccine decreased to 61%, and the incidence of pneumonia was 17.7% and after vaccination decreased to 10.2%. The resistance of *S. pneumoniae* to penicillin G, increased from 2.7% in 2011 to 100% in 2020,in addition, the study documented high rates of resistant to penicillin of *S. pneumoniae* in Spain[37], in Algeria, Egypt, Morocco and Senegal[3]. Increase in antibiotic resistance for *S. pneumoniae* has been attributed to several factors, differences in regulatory practices, economic factors and including sociocultural factors in France and Germany[37].

For *N. meningitidis*, there is an increase in resistance to penicillin G in Morocco where in 2012 was 11.1% to 24% in 2019. In USA the rate of resistance was 10.3%[36]. *N. meningitidis* resistant to Penicillin G have become frequent and total resistance is increasing in Belgium to 4.8%[38,39] in Canada, 21.7%[40], and over the past 2 decades, an increase in penicillin G resistance has been observed in many parts of the world, with a higher rate in Europe [41,42]. Penicillin resistance in *N. meningitidis* due to beta-lactamase production remains relatively rare. Isolates with resistance and reduced susceptibility to penicillin G due to alterations in the PENA gene (encoding penicillin binding protein 2) are reported, in 2016, a penicillin resistant clade of isolates MENW: CC11 with altered PENA genes was identified in Australia. most recent recently, increase in penicillin resistant invasive isolates of MENW:CC11 has been noted in England[43]. Currently in France, the progressive, of the number of strains of decreased sensitivity with penicillins, the appearance of resistant strains to the penicillin G, make reconsider the problem of the sensitivity and resistance *N. meningitidis* to penicillin G[44].

Studies conducted from 2011 to 2016 in Morocco on *H. influenzae* resistance to antibiotics, we found that resistance for trimethoprim -sulfamethoxazole, fluoroquinolones, and tetracycline antibiotics is (16%, 4.8%, 2.5%) respectively, and that amoxicillin-resistant *H. influenzae* strains are susceptible to the combination of amoxicillin and clavulanic acid in 28% of cases and no resistance to C3Gs. Comparing the percentages for Qatar, Saudi Arabia and Islamic Republic of Iran, we found a high prevalence of â-lactam resistant isolates, respectively17.4%[45], 43,6 %[46], 34 %[47] and 35,7 % [48] and two studies conducted in Rabat and Fes in (2016-2018), it was noted that no antibiotic resistance was documented. Indeed, resistance to ampicillin by production of ß-lactamases Type TEM-1 (Exceptional ROB-1) concerns nearly 35% of *H. influenzae* strains in France. Decreased susceptibility by modification of the ß-lactam target is less frequent, reaching 8 to 10% of strains, but it can become a concern, affecting aminpenicillins and C3Gs to varying degrees, oral and injectable cephalosporins in Morocco[49], in France[50,51]. in the United Kingdom and Germany[52,53] the antibiotic resistance is often multiple[37,54].

H. influenzae can develop resistance to fluoroquinolones through a typical stepwise mutation process of the primary target, DNA gyrase and topoisomerase IV, using four mutations in the GYRA genes, by C and by E. Initial treatment can also lead to GYRA mutations, with additional mutations occurring in Spain and France[55].

For the resistance of *S.aureus* in Morocco, it was found that the resistance increased significantly in 2016-2018 (Penicillin G 92%, ciprofloxacin 16.5% and erythromycin 14.6%) and in 2017-2019 the resistance to penicillin G 89.6%, ciprofloxacin 6.9% and erythromycin was not tested. In 2018 - 2019, (Penicillin G 2%, ciprofloxacin 4% and erythromycin 88%). These studies showed the percentage of resistant *S.aureus*.

In Ireland a study showed that 10 strains of *S. aureus*, (71.42%) were resistant to penicillin G, no strain was resistant to meticillin, gentamycin, rifampicin, teicoplanin or vancomycin[56]. In USA today, more than 95% *S. aureus* is resistant to penicillin. Additionally, ampicillin and anti-pseudomonal penicillins[57].

The recommended treatment is generally betalactam (aminpenicillin or penicillin G) or a macrolide in case of allergy to penicillin in France, and in Belgium[58], in Canada It is noted that the incidence rate of *S. aureus* strains has gradually increased from 4.0% prior to 2000 to 5.2% in 2010-2020. It appears that this increasing rate is directly related to the increase in S. aureus infections and a change in antibiotic[59]. In China, very low rates of resistance to penicillin G have been noted (11%)[60].

The results of meta-analysis on the evolution of the resistance of *S. pneumoniae, N. meningitidis, H. influenzae,* and *S. aureus* on the latest Moroccan national studies have shown the need for the implementation of a strategy national report on antibiotic resistant bacteria and that an effective plan is needed to combat this resistance.

CONCLUSION

This meta-analysis on the studies and researches on bacterial resistance to antibiotics in the last ten years in Morocco, described the incidence and the evolution of bacterial resistance of very frequent germs such as *S. pneumoniae, N. meningitidis, H. influenzae and S. aureus* reported between 2011-2020. It can be concluded that for the bacteria that we were interested in, the percentage of resistance varies for each species and that the incidence of resistance increases with the years. This increase has been attributed to several factors, include economic factors and socio-cultural, without neglecting role of antibiotic consumption, which has been amply demonstrated to fight against this resistance it is necessary to respect systematic surveillance measures, a good management the use of antibiotic as well as to respect rules and health protocol.

Competing interests

Authors declare that they have no competing interests. The views expressed in this paper are those of the authors and do not represent the official views of their organizations.

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