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

Abduladeem G.M. Al-Selwi1,2,4* and Amina Barkat1,3

1Department: of Clinical epidemiology and medico-surgical sciences, Faculty of Medicine and Pharmacy, University Mohammed V, Rabat, Morocco.
2Medical Research Laboratory, Children's Hospital, Ibn Sina University Hospital, Rabat, Morocco.
3National Reference Center for Neonatology and Nutrition. Rabat Children's Hospital Ibn Sina, Rabat, Morocco.
4Taiz University in Yemen.

*Corresponding Author E-mail: abdualadeem12@gmail.com

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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 16.9%, 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 selection6. 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 resistance7.

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 pneumococcal9.

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 meningal 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 collapse10,11.

H. influenzae, called Pfeiffer’s bacillus, is a bacterium of the family: Pasteurellacae and class: Gammaproteobacteria. The cells are cocacobacilli 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 one12,13. 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 aminopenicillins, 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 cycle14.
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. 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. Controlling infections caused by antibiotic-resistant bacteria in humans requires regular monitoring of bacterial resistance and control of antibiotic use.

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.

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 for 15 articles published using GraphPad Prisma.

**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. (Figure 1). 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. (Figure 2).

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 \( S.\ pneumoniae \) 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 \( S.\ pneumoniae \)
Table 1. Summary of studies that were listed in our meta-analysis

<table>
<thead>
<tr>
<th>References</th>
<th>Year of publication</th>
<th>Region</th>
<th>N. of Samples</th>
<th>Microbe</th>
<th>Types of Antibiotics</th>
<th>Resistance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Mdaghi et al.[21]</td>
<td>2012</td>
<td>Casablanca</td>
<td>185</td>
<td>Neisseria meningitidis</td>
<td>PG</td>
<td>PG</td>
<td>In this study, the only antibiotic, penicillin G, gave significant resistance</td>
</tr>
<tr>
<td>Benbachir et al.[22]</td>
<td>2012</td>
<td>Casablanca</td>
<td>955</td>
<td>Streptococcus pneumoniae</td>
<td>PNS, AMC, CRO, CHL, ERY, TET and TSU</td>
<td>PNS, AMC, CRO, ERY</td>
<td>Antibiotic resistance rates vary considerably by geographic location at MIC&gt;2g/ml</td>
</tr>
<tr>
<td>Diaswara et al. [23]</td>
<td>2016</td>
<td>Casablanca</td>
<td>655</td>
<td>Streptococcus pneumoniae</td>
<td>MLSB</td>
<td>MLSB</td>
<td>Multi-resistant S.pneumoniae. Strains include both (vaccine and non-vaccine) serotypes. More observationnel studies are needed</td>
</tr>
<tr>
<td>Diaswara et al.[24]</td>
<td>2017</td>
<td>Casablanca</td>
<td>361</td>
<td>Streptococcus pneumoniae</td>
<td>PG and AMP</td>
<td>PG</td>
<td>The ratio was 22.2% overall for PG resistance in the research</td>
</tr>
<tr>
<td>Ghita Y et al. [25]</td>
<td>2017</td>
<td>Fes</td>
<td>123</td>
<td>Haemophilus influenzae</td>
<td>No resistance sensitive</td>
<td>sensible</td>
<td>H.influenzae, plays a major role in lower respiratory infections, these infections are a real public health problem.</td>
</tr>
<tr>
<td>Moumni M B et al [26]</td>
<td>2018</td>
<td>Fes</td>
<td>277</td>
<td>Neisseria meningitidis</td>
<td>CET</td>
<td>sensible</td>
<td>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.</td>
</tr>
<tr>
<td>EL Amin Get al.,[27]</td>
<td>2019</td>
<td>Rabat</td>
<td>2436</td>
<td>Streptococcus pneumoniae and Neisseria meningitidis</td>
<td>PG</td>
<td>PG</td>
<td>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. The need to adapt probabilistic treatment regimens to the local epidemiology.</td>
</tr>
<tr>
<td>Rhars A et al. [28]</td>
<td>2019</td>
<td>Rabat</td>
<td>100</td>
<td>Staphylococcus aureus</td>
<td>PEN, CIP et ERY</td>
<td>PEN, CIP</td>
<td>This class of antibiotics still retains its place in the treatment of staphylococci</td>
</tr>
<tr>
<td>Kouara S et al. [29]</td>
<td>2019</td>
<td>Fes</td>
<td>46</td>
<td>Staphylococcus aureus</td>
<td>PEN, CIP et ERY</td>
<td>PEN, CIP, ERY</td>
<td>The data from this study on adult MS show variability in serotypes and provide information on the antibiotic susceptibility status of pneumococcus in adults.</td>
</tr>
<tr>
<td>Nzoykorera N et al [30]</td>
<td>2019</td>
<td>Casablanca</td>
<td>74</td>
<td>Streptococcus pneumoniae</td>
<td>PG</td>
<td>PG</td>
<td>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</td>
</tr>
<tr>
<td>Raghani A et al. [31]</td>
<td>2019</td>
<td>Rabat</td>
<td>4232</td>
<td>Streptococcus pneumoniae</td>
<td>PG</td>
<td>PG</td>
<td>All precribed antibiotics were resisted by S. aureus</td>
</tr>
<tr>
<td>Saoud M Z et al. [32],</td>
<td>2019</td>
<td>Rabat</td>
<td>119</td>
<td>Staphylococcus aureus</td>
<td>PEN, CIP et ERY</td>
<td>PEN, CIP et ERY</td>
<td>All isolated strains are sensitive to third generation cephalosporin.</td>
</tr>
<tr>
<td>Ait Mousse et al. [33]</td>
<td>2020</td>
<td>Casablanca</td>
<td>245</td>
<td>Neisseria meningitidis</td>
<td>PG et 3GCs</td>
<td>PG</td>
<td>In Morocco and neighboring countries, the problem of antibiotic resistance is recognized and well documented.</td>
</tr>
<tr>
<td>Ousaid et al. [3]</td>
<td>2020</td>
<td>Casablanca</td>
<td>115</td>
<td>Staphylococcus aureus</td>
<td>OXA, AMP, AMX, CTX, SEF et ERY</td>
<td>OXA, AMP, AMX, CTX et SEF</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Epidemiological profile of invasive germs in the pediatric**

<table>
<thead>
<tr>
<th>References</th>
<th>Years</th>
<th>Regions</th>
<th>N. of samples</th>
<th>S. pneumoniae</th>
<th>N. meningitidis</th>
<th>H. influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mdaghri N, <em>et al</em> 2012</td>
<td>2012</td>
<td>Casablanca</td>
<td>185</td>
<td>13%</td>
<td>9.7%</td>
<td>5.4%</td>
</tr>
<tr>
<td>EL Amin G <em>et al</em> 2019</td>
<td>2016</td>
<td>Rabat</td>
<td>25</td>
<td>48%</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Moumni M B,<em>et al</em> 2018</td>
<td>2018</td>
<td>Fes</td>
<td>277</td>
<td>29%</td>
<td>33%</td>
<td>8%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>References</th>
<th>Resistance %</th>
<th>Resistance %</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N. of Samples</td>
<td>Total</td>
<td>N. of Samples</td>
</tr>
<tr>
<td>Benbachir <em>et al</em>, 2012</td>
<td>25</td>
<td>100</td>
<td>31</td>
</tr>
<tr>
<td>Diawara <em>et al</em>, 2016</td>
<td>15</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>References</th>
<th>Years</th>
<th>Regions</th>
<th>N. of samples</th>
<th>S. pneumoniae</th>
<th>RPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouskraoui <em>et al</em>, 2011</td>
<td>2011</td>
<td>Marrakech</td>
<td>302</td>
<td>45.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Raghani <em>et al</em>, 2019</td>
<td>2012-2018</td>
<td>Rabat</td>
<td>4232</td>
<td>1%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Diawara <em>et al</em>, 2017</td>
<td>2014</td>
<td>Casablanca</td>
<td>361</td>
<td>100%</td>
<td>22.2%</td>
</tr>
<tr>
<td>Nzoyikorera <em>et al</em>, 2019</td>
<td>2016-2018</td>
<td>Casablanca</td>
<td>74</td>
<td>32%</td>
<td>18.75</td>
</tr>
<tr>
<td>Ousaid <em>et al</em>, 2020</td>
<td>2020</td>
<td>Casablanca</td>
<td>101</td>
<td>86%</td>
<td>100%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>References</th>
<th>Years</th>
<th>N. of samples</th>
<th>Regions</th>
<th>RPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Mdaghri, <em>et al</em> 2012</td>
<td>2012</td>
<td>180/18</td>
<td>Casablanca</td>
<td>11.1%</td>
</tr>
<tr>
<td>EL Amin G <em>et al</em> 2019</td>
<td>2016</td>
<td>600/6</td>
<td>Fes</td>
<td>16.6%</td>
</tr>
<tr>
<td>K. Ait Mouss <em>et al</em> 2020</td>
<td>2019</td>
<td>245</td>
<td>Casablanca</td>
<td>24%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>References</th>
<th>Years</th>
<th>Region</th>
<th>N. of Samples</th>
<th>RAMX</th>
<th>RTRM &amp; RSU</th>
<th>RFLQ</th>
<th>RTET</th>
<th>C 3 G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghita <em>et al</em>, 2017</td>
<td>2011-2016</td>
<td>Fes</td>
<td>123</td>
<td>S:AMC28%</td>
<td>16%</td>
<td>4.8%</td>
<td>2.5%</td>
<td>S</td>
</tr>
</tbody>
</table>

*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.**

<table>
<thead>
<tr>
<th>References</th>
<th>Years</th>
<th>Regions</th>
<th>N. of Samples</th>
<th><em>H. influenzae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>El amin G <em>et al</em> 2019</td>
<td>2016 - 2018</td>
<td>Rabat</td>
<td>600</td>
<td>8%</td>
</tr>
<tr>
<td>Moumni M B, <em>et al</em> 2018</td>
<td>2018</td>
<td>Fes</td>
<td>277</td>
<td>8%</td>
</tr>
</tbody>
</table>

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

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

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 longer34. 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 problem15. The usage of antibiotics has a massive effect on these parameters, which has been extensively proven in Morocco36.

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 Spain35, in Algeria, Egypt, Morocco and Senegal3. 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 Germany37.

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 Europe41,42. 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 PEN A gene (encoding penicillin binding protein 2) are reported, in 2016, a penicillin resistant clade of isolates MENW: CC11 with altered PEN A gene was identified in Australia. Most recently recently, increase in penicillin resistant invasive isolates of MENW:CC11 has been noted in England43. 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 G44.

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, respectively 17.4%, 43.6%, 34% and 35.7% 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 aminopenicillins and C3Gs to varying degrees, oral and injectable cephalosporins in Morocco, in France, in the United Kingdom and Germany the antibiotic resistance is often multiple.

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.

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, tetracycline or vancomycin. In USA today, more than 95% S. aureus is resistant to penicillin. Additionally, ampicillin and anti-pseudomonal penicillins.

The recommended treatment is generally beta-lactam (aminopenicillin or penicillin G) or a macrolide in case of allergy to penicillin in France, and in Belgium, 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. In China, very low rates of resistance to penicillin G have been noted (11%) in 2018-2019.

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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