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# Haemophilus influenzae resistance to beta lactams in France

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## Background

*Haemophilus influenzae* has become the dominant bacterial cause in acute otitis media (AOM). Beta-lactams are still recommended to treat AOM when children are unwell or are at risk. However, *H. influenzae* isolates are increasingly reported to be resistant to beta-lactams. The objective of this work was to describe and analyze antibiotic resistance of *H. influenzae* to inform new guidelines for appropriate antibiotic use.

## Methods

We conducted a retrospective study based on the French National Reference Center for meningococci and *H. influenzae* (NRCMHi) database.

Amino acid deduced Sequences of *fsl* genes were loaded on Phyre2 databases ([www.sbg.bio.ic.ac.uk/phyre2/](http://www.sbg.bio.ic.ac.uk/phyre2/)) that used known structure of similar proteins to model the structure of submitted proteins using Protein Homology/analogy Recognition Engine V 2.0. When building the structure, the modelling considers the conserved helices and sheets but not the type of the residue and only spatial proximities of residues is scored with iterations of refitting the structures (Pettersen et al., *J Comput Chem* 2004, 25, (13), 1605-12)

## Results

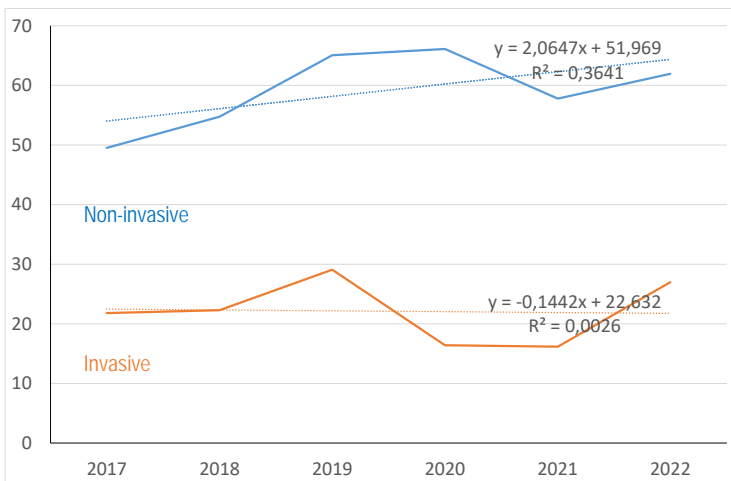
A total of 1535 *H. influenzae* were analyzed during the period 2017-2021 among which 816 were invasive (isolated from a normally sterile site) and 719 non-invasive sites.

Most of the non-invasive isolates (98%) were non-typeable while this percentage was 67% among invasive isolates.

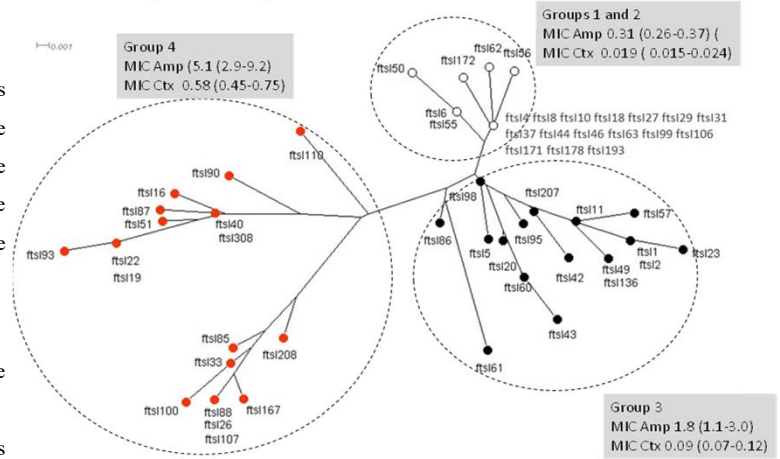
Overall, 40% of all isolates were resistant to ampicillin with almost half of these isolates producing a beta-lactamase but this percentage was significantly higher among non-invasive isolates (23% versus 60%, among invasive and non-invasive isolates respectively  $p < 0.001$ ).

This difference remained significant if only non-typeable isolates (invasive versus non-invasive) were considered. The percentage of Beta-lactamase negative ampicillin resistant (BLNAR) was significantly higher among non-invasive isolates than that among invasive isolates (57% versus 30% respectively,  $p < 0.001$ ).

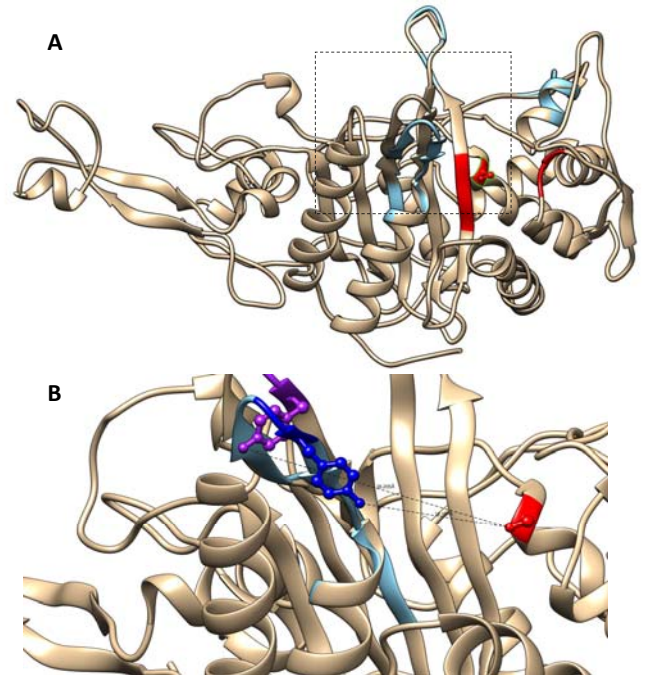
The year-by-year evolution of ampicillin-resistant isolates is shown in Fig. 1.



**Figure 1.** The evolution of the percentages of *H. influenzae* resistant to ampicillin between 2017-2022 showed a stable trend among invasive isolates but an increasing trend among non-invasive isolates. This trend was delayed during the COVID-19 pandemic.



**Figure 2.** Phylogenetic tree of *fsl* based on the sequence multiple alignment of amino-acid sequences deduced from the DNA sequences of all *fsl* alleles defined among the 107  $\beta$ -lactamase negative isolates. The tree was visualized by SplitsTree4, with individual alleles in each group that were indicated by different colors. The grey boxes indicate each group and the geometric means of minimum inhibitory concentrations (MICs) of the isolates of each group of ampicillin and cefotaxime, and the 95% confidence intervals of geometric means are in brackets.



**Figure 3.** Representation of PBP3 modeled structure. (A) Ribbon representation of the wild-type PBP3 (allele *fsl14*) and a modified PBP3 (allele *fsl140*). The segments that differed between the two proteins are shown in cyan. The active site is shown in red with the active Ser327 in red as balls and sticks. SxN and KTG motifs are shown in red. (B) The two Tyr557 residues on both proteins are shown as well as their distance from the active Ser327. The modified PBP3 has an OH- group protruding in the active site reducing access to this site of negatively charged beta-lactams

## Conclusion

- *H. influenzae* resistance to ampicillin seems to be more prevalent among non-invasive isolates.
- This resistance shows an increasing trend that may have been delayed during the COVID-19 pandemic but re-increased in 2022.
- BLNAR isolates are associated with modification in PBP3 that may reduce the access of beta-lactams to the active site of PBP3.
- The choice of using the amoxicillin/clavulanic acid combination as the first-line antibiotic in cases of suspected *H. influenzae* AOM may not be supported by the data and needs to be considered.