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## **Evolution of *Haemophilus influenzae* type b (Hib) and vaccine failure cases in France: impact of vaccination schedules**

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### **Background:**

In 2013, France modified its *Haemophilus influenzae* b (Hib) vaccination schedule to remove one dose at 3 months of age and change the age of the booster dose from 16 to 11 months. During the COVID-19 pandemic, most respiratory-transmitted diseases decreased as a result of containment measures. In this work, we aimed to provide the evolution of invasive Hib disease between the pre-and post-COVID-19 pandemic and explore the immune response of vaccine failure cases in France during the period 2017-2022.

### **Methods:**

The numbers and proportions of Hib invasive isolates during the period 2017–2022 were analyzed. The vaccine failure cases were explored by measuring the concentration of anti-polyribosyl-ribitol phosphate (PRP) IgG using specific ELISA in the sera of patients at the admission and at least one month after the onset of the disease. Anti-Hib antibodies-dependent opsonophagocytosis and complement activation assays were performed to monitor the functionality of these antibodies.

### **Results:**

During the period 2017-2022, the number of Hib invasive disease increased, particularly in children under 5 years-old, despite the measures implemented to stop COVID-19. Several cases of vaccine failure were registered with a proportion significantly higher in toddlers vaccinated according to the current scheme (2+1). The increased vaccine failure was associated with a decline in anti-PRP IgG response after the last dose to levels below the protective threshold (1 µg/ml). These levels correlated with reduced antibody-dependent opsonophagocytosis and complement activation. However, the levels of bactericidal antibodies increased significantly 1 month after the admission suggesting a secondary immune response to the Hib.

### **Conclusions :**

The simplification of the vaccination to a 2 + 1 scheme seems to reduce the level of anti PRP IgG. Hib antibodies wane rapidly after the 11 months booster and may not be enough to ensure long term protection. Surveillance of cases and monitoring of titres need to be continued to inform future vaccination Policy.