



## PRESS RELEASE

# Resistance mutations to nirsevimab are rare in respiratory syncytial virus (RSV)

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**Nirsevimab is an antibody targeting the respiratory syncytial virus (RSV). Available in France since September 2023, it is indicated in neonates and infants for the prevention of bronchiolitis caused by RSV. However, its widespread use raises the question of the emergence of resistance mutations. The POLYRES study, the largest prospective surveillance study of nirsevimab breakthrough infections to date, has just delivered its conclusions. This work, coordinated by Prof. Slim Fourati and Prof. Marie-Anne Rameix-Welti<sup>1</sup>, was funded by the ANRS MIE with the support from the French Ministry of Higher Education and Research as part of the EMERGEN Consortium.<sup>2</sup> Scientists from AP-HP (including Henri Mondor University Hospitals), Inserm, Institut Pasteur and the Universities of Paris-Est-Créteil and Versailles-Saint-Quentin-en-Yvelines, members of the ANRS MIE virology network teams, have shown that nirsevimab resistance mutations in RSV are very rare. The results of this study have just been published in the [Lancet Infectious Diseases](#) on October 15, 2024.**

Respiratory syncytial virus (RSV) is the main cause of bronchiolitis, a lower respiratory tract infection in infants. Two groups of RSV (RSV-A and RSV-B) circulate alternately or together. Every year, RSV is responsible for more than 33 million cases of bronchiolitis worldwide, leading to the deaths of 100,000 children, mainly in low-income countries. In France, the disease is responsible for around 480,000 cases a year. It is by far the most

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<sup>2</sup> Coordinated by *Santé publique France* and ANRS MIE

common cause of hospitalisation in children, leading to more than 26,000 paediatric hospitalisations every year. Nirsevimab, a new neutralising antibody\* against the virus, became available in France in September 2023. This monoclonal antibody\*\* targets a specific antigenic site (the epitope\*\*\* Ø) of the RSV surface F protein, which is involved in viral multiplication, and blocks the virus. Due to the genetically variable forms of RSV, there is a theoretical risk of the emergence of variants carrying mutations resistant to neutralisation by nirsevimab, even in the absence of selection pressure. This risk could increase with the widespread preventive use of nirsevimab. During the phase IIb/III clinical trials, only 48 RSVs infecting children treated with nirsevimab could be studied, and escape mutations# were found in two of them. The aim of the POLYRES study was to assess the risk of viral escape from nirsevimab in a large cohort using a large, multicentre, real-life observational study conducted during the 2023-2024 winter season.

The study included 695 RSV infected infants, 349 of whom had received nirsevimab prophylaxis. RSV-A was the most dominant circulating virus this season and was found in 86.6% of infected children. The teams analysed the characteristics of RSV-A and RSV-B in nasopharyngeal swabs collected as part of the children's routine care. Full-length sequencing of the viral genome was conducted to identify potential mutations in the Ø site, the nirsevimab binding site (genotypic analysis<sup>§</sup>). The ability of nirsevimab to inhibit viral multiplication in cell culture was also investigated (phenotypic analysis<sup>¥</sup>). Analysis of 472 RSV-A viruses (half from treated children) revealed no nirsevimab resistance mutation in the Ø site of the F protein. Of the 73 children infected with RSV-B, 24 had received nirsevimab prophylaxis. In these 24 children, two isolates of RSV-B had resistance mutations to the antibody. One mutation has been described before and the other is described here for the first time.

*"This study is the largest surveillance study of nirsevimab virological failures to date. It was made possible thanks to collaborative synergy with the consortium of virologists at the ANRS MIE. It is a nationwide project that will help identify the resistance phenomenon associated with the widespread use of the drug. This type of study is essential for analysing the evolutionary dynamics of viruses, in the light of existing medical solutions"* explains **Prof Marie-Anne Rameix-Welti**, head of the National Reference Centre for Respiratory Infection Viruses at the Institut Pasteur, and head of the M3P unit (Institut Pasteur, Inserm U1173).

*"The low prevalence of nirsevimab resistance mutations in treated patients is reassuring. However, escape mutations have been observed in a few RSV-Bs from treated patients, prompting caution and highlighting the importance of active molecular surveillance in the context of future wider global use of nirsevimab. These results are essential in the fight against this disease and in anticipating any form of resistance"*, adds **Prof Slim Fourati**, Head of the Virology Unit-Respiratory Viruses, CHU Henri Mondor, Inserm U955.

In conclusion, the results of the POLYRES study support the continued use of nirsevimab for RSV prophylaxis in all newborns worldwide.

\* Neutralising antibodies are specific antibodies that prevent infection by blocking the virus from entering the target cells. They do this by forming an antigen-antibody complex which inhibits the biological activity of the antigen (a substance foreign to the body capable of triggering an immune response aimed at eliminating it).

\*\* Monoclonal antibodies consist of a single type of antibody (polyclonal antibodies have several types). They are used in medicine.

\*\*\* Part of a molecule recognised by an antibody.

# Escape mutations enable the virus to thwart the action of antibodies in the human immune system.

§ Genotypic tests are based on the identification of mutations that confer resistance to the virus.

¥ Phenotyping, carried out using phenotypic tests, makes it possible to define the sensitive or resistant nature of the virus. This is done by culturing the virus in the presence of the antiviral being studied.

## Reference:

### ***Genotypic and Phenotypic Characterisation of RSV after Nirsevimab Breakthrough Infections in a Large Multicentre Observational Real-world Study.***

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**About:**

**About ANRS MIE:** ANRS Emerging Infectious Diseases is an autonomous agency of Inserm (the French National Institute for Health and Medical Research). Its mission is to facilitate, evaluate, coordinate and fund research into HIV/AIDS, viral hepatitis, sexually transmitted infections, tuberculosis and emerging and re-emerging infectious diseases.

For more information: <https://anrs.fr/en/>

**About AP-HP:** Europe's leading university hospital centre (CHU), AP-HP and its 38 hospitals are organised into six university hospital groups (AP-HP. Centre – Université Paris Cité; AP-HP. Sorbonne University; AP-HP. Nord – Université Paris Cité; AP-HP. Université Paris-Saclay; AP-HP. Henri-Mondor University Hospitals and AP-HP. Hôpitaux Universitaires Paris Seine-Saint-Denis) and are structured around five Paris Region universities. In close collaboration with major research organisations, AP-HP has eight world-class university hospital institutes (ICM, ICAN, IMAGINE, FOReSIGHT, PROMETHEUS, InovAND, Re-Connect, THEMA) and France's largest healthcare data warehouse (EDS). A major player in applied research and innovation in healthcare, AP-HP holds a portfolio of 810 active patents, its clinician-researchers produce more than 11,000 scientific publications every year and nearly 4,400 research projects are currently under development, all sponsors included. In 2020, AP-HP obtained the Carnot Institute label, which rewards the quality of its partnership research: Carnot@AP-HP offers applied and clinical research solutions in the field of healthcare to industrial players. In 2015, AP-HP also set up the *Fondation de l'AP-HP*, which works directly with healthcare professionals to support the organisation of care, hospital staff and research within AP-HP.

For more information: <http://www.aphp.fr>

**About the Institut Pasteur:** The Institut Pasteur, a non-profit foundation with recognized charitable status set up by Louis Pasteur in 1887, is today an internationally renowned center for biomedical research. In the pursuit of its mission to tackle diseases in France and throughout the world, the Institut Pasteur operates in four main areas: research, public health, training, and development of research applications. The Institut Pasteur is a globally recognized leader in infectious diseases, microbiology, and immunology, with research focusing on the

biology of living systems. Among its areas of investigation are emerging infectious diseases, antimicrobial resistance, certain cancers, neurodegenerative diseases, and brain connectivity disorders. The Institut Pasteur's outstanding research is facilitated by the development of a technological environment of the highest standard, with core facilities for nanoimaging, computational biology and artificial intelligence. Since its inception, 10 Institut Pasteur scientists have been awarded the Nobel Prize for Medicine, including two in 2008 for the 1983 discovery of the human immunodeficiency virus (HIV) that causes AIDS. The Institut Pasteur is part of the Pasteur Network a worldwide network of 33 members on five continents, united by Pasteurian values, which contribute to global health. Since July 1, 2021, the Institut Pasteur is a research partner organization of Université Paris Cité.

For more information: <https://www.pasteur.fr/en>

**About Inserm:** Founded in 1964, Inserm is a public scientific and technological institute dedicated to biomedical research and human health, and is involved in the entire range of activities from the laboratory to the patient's bedside. It also partners with the most prestigious research institutions in the world that are committed to scientific challenges and progress in these fields.

For more information: <https://www.inserm.fr/en/home/>

**About université Paris-Est Créteil:** With 14 faculties, schools and institutes, 1 observatory and 32 research laboratories, Université Paris-Est Créteil has been active in all fields of knowledge since 1970. Each year, UPEC trains over 42,000 students and working professionals of all ages.

A major player in the dissemination of academic, scientific and technological knowledge, the university offers more than 500 training courses in all disciplines and at all levels. UPEC offers personalized support for all successes, thanks to undergraduate and graduate training, recognition of prior learning and lifelong learning opportunities. Furthermore, the university runs a growing number of apprenticeship programs in order to stimulate entrepreneurship and ease professional integration.

Université Paris-Est Créteil has built its strategic plan around three strategic orientations: UPEC is an engaged university that aims to match academic excellence with societal relevance. It encourages and supports all paths of students' success with dedicated programs. UPEC masters its trajectory and is a university open to the world and its diversity.

For more information: <https://www.en.u-pec.fr/>

**About the UVSQ:** University of Versailles Saint-Quentin-en-Yvelines (UVSQ) is a leading multidisciplinary higher education and research institution. The quality of UVSQ's undergraduate and graduate programs (master's programs, doctorates, post-doctoral fellowships) is backed by the compelling research programs conducted in UVSQ research centers and laboratories. UVSQ is a medium size university (20 000 students) located in the Southwestern suburb of Paris, where internationally known businesses are established (such as Renault, PSA, Dassault...) as well as renowned French research institutes (CNRS,CEA...).

For more information: <https://www.uvsq.fr/english>