Clinical pathology selected abstracts

written by CAP TODAY
September 18, 2025

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Genomewide association study of long COVID

September 2025—Severe acute respiratory syndrome coronavirus 2 infection can lead to post-acute sequelae, or a condition known as long COVID. The World Health Organization defines long COVID as any symptoms that typically present within three months of acquiring COVID-19 and that persist for at least two months. Long COVID generally manifests as fatigue, pulmonary symptoms, and cognitive dysfunction. The biological mechanisms of long COVID are not well understood. Changes in the serotonin system may lead to cognitive changes, while mitochondrial changes may lead to fatigue, and complement and platelet activation to vascular disease. Long COVID is more common in people who have been hospitalized, especially those treated for COVID-19 in the intensive care unit. However, it can occur in people with mild COVID-19 symptoms. The authors performed a genomewide association study of long COVID as part of the COVID-19 Host Genetics Initiative (COVID-19 HGI) to discover the biological mechanisms behind the chronic condition. They conducted the genomewide association study and replication studies using 6,450 long COVID cases and 1,093,995 population controls from 24 studies across 16 countries. The authors used a strict long COVID case definition that required having an earlier test-verified SARS-CoV-2 infection (strict case definition) and a broader long COVID case definition that included self-reported or clinician-diagnosed SARS-CoV-2 infection (broad case definition). The broad definition included all contributed studies, whereas the strict definition included only 11 studies. Controls were either population controls or participants who had recovered from COVID-19 without having experienced long COVID. The data from the 16 countries represent populations from six genetic ancestries. The most common symptoms reported in the questionnaire-based studies were fatigue, shortness of breath, and problems with memory and concentration. The results showed heterogeneity in the frequency of symptoms. They also showed an association between *FOXP4* and long COVID, independent of the previously described association between *FOXP4* and severe COVID-19. The *FOXP4* signal was replicated in 9,500 long COVID cases and 798,835 population controls. The authors concluded that since *FOXP4* is a transcription factor in lung physiology and pathology, these results highlight the importance of lung function in the biological mechanism of long COVID. They also found that COVID-19 severity was a causal risk factor for long COVID. The authors noted that additional research is needed to understand the full extent of long COVID since such symptoms as fatigue and cognitive dysfunction are also symptoms of conditions that do not involve the lung.

Lammi V, Nakanishi T, Jones SE, et al. Genome-wide association study of long COVID. *Nat Genet*. 2025;57:1402–1417.

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Modeling the re-emergence of infectious diseases with declining U.S. vaccination rates

Widespread adoption of childhood vaccination has eliminated many infectious diseases in the United States. However, concern about declining vaccination rates among pediatric patients is mounting as ongoing policy debates and other factors have reduced the number of childhood vaccinations. High rates of childhood vaccination in the United States eliminated (defined as cessation of sustained local transmission) such infectious diseases as measles, rubella, diphtheria, poliomyelitis, and smallpox nationwide. Maintaining population immunity above a critical threshold is necessary to prevent the re-emergence of these infectious diseases. Cases of such infectious diseases sporadically surface in the United States, the majority of which are linked to underimmunized U.S. travelers returning from endemic countries. Consequently, the United States is susceptible to the re-introduction or re-emergence of infectious diseases previously eliminated through vaccination programs. Declining vaccination rates for infectious diseases started during the COVID-19 pandemic and were attributed, in part, to such factors as personal beliefs, misinformation, and distrust. The growing antivaccine movement has coincided with a number of recorded outbreaks of vaccine-preventable diseases in the United States. For example, the number of measle cases has increased since 2024, leading to a significant number of pediatric hospitalizations. The current U.S. policy debate has centered on revising the long-standing vaccination schedule, in part by eliminating various vaccination recommendations and public school-based vaccination mandates. The concern among medical professionals is that this will lead to significantly lower vaccine coverage and immunity. The authors conducted a modeling study to demonstrate the potential long-term effects of reducing or ceasing routine childhood vaccination for measles, rubella, diphtheria, and poliomyelitis. Their study estimated the risk of re-emergence of previously eliminated infectious diseases and their major infection-related complications. The authors designed a simulation model to assess the importation and dynamic spread of vaccine-preventable infectious diseases across the 50 states and District of Columbia. The model accounted for state-level variation in demography, population immunity, and infectious disease importation risk. It was also used to evaluate differences in vaccination rates over a 25 year period using various scenarios. The inputs for the model were childhood vaccination rates based on 2004 to 2023 data. The primary outcomes were estimated U.S. cases of measles, rubella, poliomyelitis, and diphtheria. The secondary outcome was infection-related complications, including post-measles neurological sequelae, congenital rubella syndrome, paralytic poliomyelitis, hospitalization, and death. The analysis also included the probability and timing for an infection to re-establish endemicity. The results from the simulation model showed that, at current state-level vaccination rates, measles may re-establish endemicity (83 percent of simulations; mean time, 20.9 years) with an estimated 851,300 cases (95 percent uncertainty interval [UI], 381,300–1.3 million cases) over a 25-year period. In a scenario with a 10 percent decline in measles-mumps-rubella (MMR) vaccination, the model estimated 11.1 million (95 percent UI, 10.1–12.1 million) cases of measles over 25 years. Of interest, an increase of five percent in MMR vaccination produced estimates of only 5,800 new cases (95 percent UI, 3,100–19,400 cases). A decline of 50 percent in routine childhood vaccinations would also impact cases of measles, rubella, poliomyelitis, and diphtheria, with the model predicting 51.2 million (95 percent UI, 49.7–52.5 million) measles cases over 25 years; 9.9 million (95 percent UI, 6.4–13.0 million) rubella cases; 4.3 million (95 percent UI, 4–21.5 million) poliomyelitis cases; and 197 (95 percent UI, 1–1,000) diphtheria cases. Under this scenario, complications would increase and could include 51,200 cases (95 percent UI, 49,600–52,600 cases) of postmeasles neurological sequelae, 10,700 cases (95 percent UI, 6,700–14,600 cases) of congenital rubella syndrome, and 5,400 cases (95 percent UI, 0–26,300 cases) of paralytic poliomyelitis. In addition, measles would be expected to become endemic at a mean of 4.9 years in 99.8 percent of simulations (95 percent UI, 4.3–5.6 years), rubella at a mean of 18.1 years in 100 percent of simulations (95 percent UI, 17.0–19.6 years), and polio at a mean of 19.6 years in 55.6 percent of simulations (95 percent UI, 14.0–24.7 years). Diphtheria returned to epidemic levels in less than one percent of simulations, and it took more than two decades. The disease did become endemic with a larger vaccine decline. However, the authors noted a large variation in model output across U.S. populations. They concluded that declining childhood vaccination rates would increase the frequency and size of outbreaks of previously eliminated vaccine-preventable infections, which would eventually create a return to endemic levels. The timing and critical threshold would vary based on the type of infectious disease. Measles would most likely be the first to return without improved vaccination coverage and public health response. Furthermore, the authors concluded that this study supports the need to continue routine childhood vaccination coverage to prevent resurgence of these infectious diseases in the United States.

Kiang MV, Bubar KM, Maldonado Y, et al. Modeling reemergence of vaccine-eliminated infectious diseases under declining vaccination in the US. *JAMA*. 2025. doi.org/10.1001/jama.2025.6495

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