'Original antigenic sin' at the center of researchers' model addressing age-specific influenza immunity

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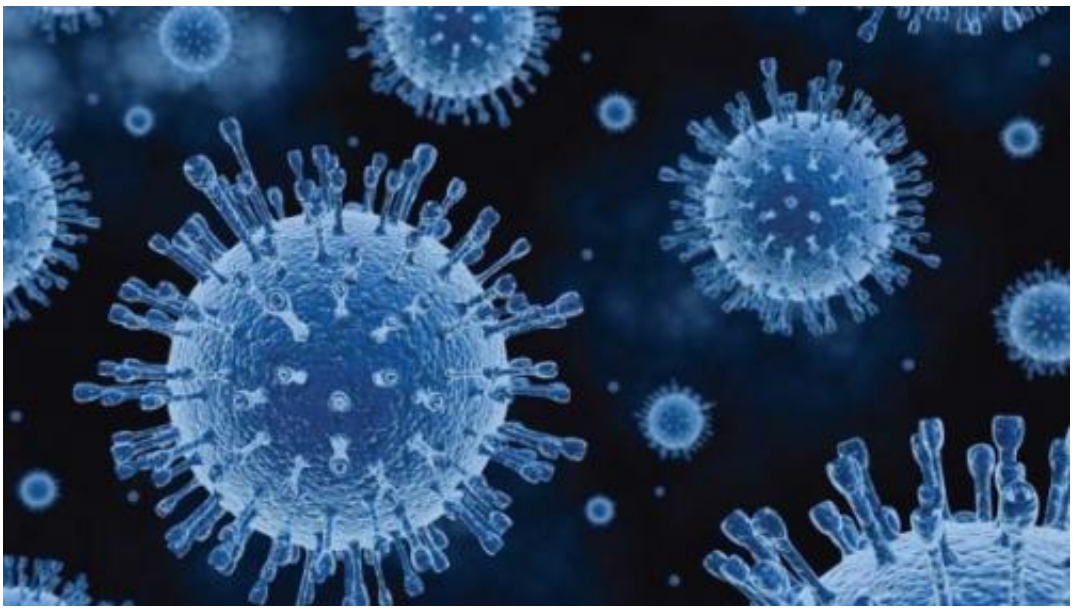

(Medical Xpress)—Mathematicians are helping to build a better picture of how populations develop immunity to flu and which groups are most at risk of getting – and transmitting – infection each year.

The adage 'what doesn't kill you makes you stronger' may ring true for certain infectious diseases – those where repeated exposure to the pathogen progressively builds population immunity – but not for

influenza. When scientists investigated age-specific immunity to influenza strains after the 2009 swine flu pandemic, a curious pattern emerged. Antibodies against seasonal flu appear to peak in school-age children, drop in middle age and rise again in the over 65s.

Now mathematicians in Cambridge have developed a model that explains this little-understood pattern, and in so-doing are helping to build a better picture of how flu might be controlled. At the heart of their model is the concept of 'original antigenic sin', a phenomenon first identified in the 1960s by American epidemiologist Thomas Francis that describes how the body's immune system, in effect, takes short cuts.

Rather than generating a specific antibody response every time a new pathogen is encountered, the immune system may instead reproduce a previous response to something similar (the 'original antigenic sin') it has seen before. What this means for immunity is that it's not just the infections we've had in the past but the order in which we've had them that could be important for how protected we are against a disease.

Dr Julia Gog and PhD student Adam Kucharski at the Department of Applied Mathematics and Theoretical Physics believe that the strikingly characteristic profile of immunity to influenza can be explained in these terms, and they've built a mathematical model to test it.

Understanding how immunity develops in a population is crucial for developing a robust public health defence, especially for a pathogen like pandemic influenza, which the UK government's latest National Risk Register has listed as the most likely risk to have the highest impact in the next five years.

Yet, modelling the dynamics of influenza on population immunity is no straightforward exercise, as Gog explained: "The evolving nature of the virus – necessitating an annual race to identify an appropriate vaccine –

means that individuals can be exposed to many different strains over a lifetime. And for every new strain that appears, the number of possible infection histories a person could have had doubles. To build a model, mathematicians need to keep track of millions, if not billions, of possible combinations of infections."

According to Gog and Kucharski's model, the trick is to reconstruct the combinations of past exposures from the probabilities of having seen each particular strain. There is a catch, however. Individuals who have been exposed to one particular strain are more likely to have been exposed to other strains; this is because individuals who have previously been exposed are more likely to be old than young. The model therefore handles each age group separately: individuals who are the same age will have lived through the same series of epidemics, which means that past exposures will be independent.

Their model has enabled them to explain the distinctive pattern of age-specific immunity for flu. Immunity increases initially, peaking in school-age children, then decreases as previous exposures prevent new antibodies being made. Only when the strain evolves 'out of reach' of the original antigenic sin are new antibodies generated in later middle age. In the elderly, complete freedom from original antigenic sin, along with vaccination programmes, leads to another increase in immunity.

But what does this mean for disease control and identifying risk? "There could be gaps in immunity because less-effective immune responses are being generated as a result of original antigenic sin," explained Kucharski. "Over time, certain age groups may develop 'blind spots' in their antibody profile. We are building 'gap maps' to understand how often this happens. Moreover, the view that severe epidemics only arise when the virus has evolved significantly may be oversimplified. They could also arise if there are individuals whose immune response is ineffective because of original antigenic sin, which would explain why

unassuming flu strains occasionally cause large outbreaks."

Provided by University of Cambridge