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Bolstering influenza protection for older adults

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With its annual recurrence, influenza presents a substantial threat to global public health, causing millions of illnesses and thousands of deaths worldwide.[1] Some populations, such as older adults, children younger than 5 years, pregnant people, and people with underlying medical conditions, are at increased risk of complications. Influenza infections also cause substantial economic burden, costing the USA an estimated US$6·3–25·3 billion annually.[2] The approval of the influenza vaccine in 1945 led to numerous vaccine developments, including enhanced (eg, high dose, adjuvanted) influenza vaccines for older adults.[3] The effectiveness of influenza vaccines can vary in older adults due to factors such as health status, correct matching of vaccines with circulating strains, and overall immune response. Aging immune systems (ie, immunosenescence) can reduce vaccine effectiveness. Studies have shown that enhanced vaccines are more effective than standard (non-enhanced) vaccines in older adults.[4,5]

Multiple strategies are being implemented or tested to boost the effectiveness of influenza vaccines for older adults. The US Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices advocate the use of high-dose influenza vaccines or adjuvanted influenza vaccines for individuals aged 65 years and older as they have been found to be more effective.[6] To further enhance vaccine effectiveness, other factors are being considered, including vaccination timing and the number of doses.[7] If successful, these strategies could substantially bolster the protection provided by influenza vaccines for older adults, marking an important development in the battle against the disease.

Among the challenges posed by influenza, there is a glimmer of hope in the form of new vaccine technologies. Nanoparticle vaccines adjuvanted with Matrix-M have shown safety and increased immunogenicity in older adults in a phase 3 trial.[8] Furthermore, the potential of mRNA vaccines, which have shown remarkable effectiveness in tackling SARS-CoV-2 infections, is being harnessed for the prevention of influenza infections. Several studies are ongoing in older adults to assess the efficacy of mRNA vaccines compared with standard-dose influenza vaccines (NCT06028347, NCT06431607, NCT05823974, NCT05446740, and NCT05585632). In the pursuit of more effective vaccines, licensed influenza vaccines are being combined with other vaccine candidates that stimulate mucosal or cell-mediated immune responses, or both.

In *The Lancet Infectious Diseases*, Joseph Eiden and colleagues report a multicentre, randomised, double-blind, double-dummy, phase 1b trial of the monovalent H3N2 *M2*-deficient single-replication (M2SR) vaccine.[9] In the study, the M2SR vaccine was administered intranasally to older adults (aged 65–85 years) with or without simultaneous intramuscular administration of an enhanced inactivated influenza vaccine (Fluzone High-Dose Quadrivalent; hereafter Fluzone HD). Eiden and colleagues showed that this unique combination induced higher serological responses, mucosal immune responses, rates of seroconversion and seroprotection, and T-cell responses than Fluzone HD and M2SR vaccine given alone. The M2SR vaccine induced a two-fold or greater increase in nasal IgA titres in 43 (48%) of 89 participants when administered alone and in 33 (36%) of 91 participants when coadministered with Fluzone HD. T-cell responses were also induced in the groups that received M2SR vaccine, showing the ability of the experimental vaccine to enhance the breadth of immune responses. Future studies should investigate the durability and quality of antibody responses by assessing the differences in antibody titre, the clonotype specificities, and affinities of influenza antigen-specific antibody responses.

Although Eiden and colleagues' early preclinical and clinical trials have shown some promising results regarding dose–response, induction of mucosal immunity, and cell-mediated immune responses, as well as protection against viral challenge in people, the true efficacy and potential of M2SR as a mucosal vaccine remains uncertain. The induction of systemic and mucosal immune responses is considered to provide enhanced protection compared with systemic or mucosal response alone. Nonetheless, the planned efficacy studies will be crucial for determining whether the M2SR vaccine alone or combined with a high-dose, adjuvanted, or recombinant haemagglutinin vaccine in older adults is advantageous before this approach

can be considered a viable and an effective vaccination strategy.

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