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First human efficacy study of a plant-derived influenza vaccine

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In *The Lancet*, Brian Ward and colleagues report two efficacy studies that are, to the best of my knowledge, the first randomised phase 3 trials of a plant-derived quadrivalent influenza vaccine.[1] The vaccine material was generated in *Nicotiana benthamiana*, a relative of the tobacco plant. The plants were transfected with an attenuated plant viral vector (*Agrobacterium tumefaciens*) expressing influenza haemagglutinin genes and the vaccine was recovered from the transfected plants in the form of virus-like particles.

The first study was a placebo-controlled randomised trial with 10 160 adults (aged 18–64 years), done in the 2017–18 northern hemisphere influenza season. 10 136 participants (4051 [40·0%] men and 6085 [60·0%] women; mean age 44·6 years [SD 13·72]) received their assigned vaccine and were included in the analyses. The plant-derived vaccine was immunogenic, but only the H3N2 component induced a greater than four-fold change in the haemagglutination inhibition titre. The absolute vaccine efficacy for prevention of respiratory illness caused by vaccine-matched strains was 35·1% (95% CI 17·9–48·7), meaning the study did not meet its primary endpoint (70% efficacy). By comparison, the influenza vaccine efficacy for the 2017–18 season was 15%[2] in the UK, with very low efficacy for H3N2, which was the major circulating strain.

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The second study was a non-inferiority study comparing the plant-derived vaccine with a chicken egg-derived quadrivalent inactivated vaccine. It was done in 12 794 older adults (aged ≥65 years) in the 2018–19 northern hemisphere influenza season. 12 718 participants (5605 [44·1%] men and 7113 [55·9%] women; mean age 72·2 years [SD 5·7]) received their assigned vaccine and were included in the analyses. The plant-derived vaccine had an 8·8% (95% CI −16·7 to 28·7) relative vaccine efficacy for prevention of influenza-like illness compared with the comparator; though the absolute vaccine efficacy for either vaccine was not reported. Notably, although the plant-derived vaccine was equally protective, it induced a lower antibody response, measured by haemagglutination inhibition and microneutralisation.

Why is there a need for a new influenza vaccine manufactured in plants? One problem is a mismatch between vaccine and circulating strains of influenza, particularly for H3N2 strains. Circulating H3N2 viruses have become increasingly humanised (better adapted to infect human cells), which becomes an issue when the virus for the vaccine is grown in embryonated chicken eggs. During cultivation of the virus in eggs, it can adapt to attach better to the cell receptors on chicken cells, subtly shifting the sequence of the haemagglutinin antigen used for entry. Thus, the egg-derived haemagglutinin can be different to the haemagglutinin expressed by circulating H3N2 virus and antibodies raised against the vaccine strain are less able to neutralise the virus. Alternative manufacturing processes might circumvent problems of antigen mismatch caused by growth in eggs. Two alternative approaches have been licensed to date: using insect cells to make a recombinant protein (Flublok; Protein Sciences–Sanofi) and mammalian cell lines to grow virus (Flucelvax; Sequirus). The effect of changing the influenza vaccine manufacturing platform on efficacy is variable. In one study, the recombinant-based vaccine was reported to have better efficacy than a cell-derived vaccine,[3] but in another study no difference was seen.[4] The absence of a difference in the second study was potentially because the seed virus was initially cultured

in eggs, so mutations might have occurred before cell culture expansion.[5]

Alternative vaccine manufacturing processes might also be important during an influenza pandemic. Many of the potentially pandemic strains of influenza come from birds, which could have a significant effect on the production of a vaccine: if the hens required to lay the eggs are infected there might be fewer eggs or if the virus is lethal in chicken embryos it might affect how much antigen can be generated. Platforms that do not require eggs might be more resistant to these problems. One issue with the use of plants for pandemics is the speed at which material can be generated, both generating the *Agrobacterium* vector and then growing enough plants to transfect. However, these barriers can be overcome, and the use of a plant-derived pandemic vaccine is being investigated: Medicago, the funder of Ward and colleagues' studies described here, is conducting a phase 1 trial of a plant-derived virus-like particle vaccine for COVID-19 (NCT04450004).

The field of plant-derived vaccines has grown a lot in the past 28 years, since it was first shown that viral proteins could be expressed in plants.[6] There is one licensed plant-derived human therapeutic for Gaucher's disease, but this is the first time a plant vaccine has been tested in a clinical trial. It is a milestone for this technology and sows the seeds for other plant-based vaccines and therapeutics.

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Global growth trends in school-aged children and adolescents

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Despite declining rates over the past few decades, stunting continues to affect over 30% of children younger than 5 years in many countries in sub-Saharan Africa, south Asia, and the Pacific.[1] The extent to which stunting and underweight in early childhood are associated with premature death and disease explains why global nutrition policy, practice, and research have overwhelmingly focused on very young children. Yet, the rapid expansion of obesogenic environments, including in resource-poor countries, requires policy responses to address a more complex and dynamic nutritional landscape. Research that informs the scope—and timing—of interventions is needed.

In *The Lancet*, a study by the NCD Risk Factor Collaboration (NCD-RisC)[2] shifts attention to growth in older children and adolescents. The study reports the first comparable estimates of height and body-mass index (BMI) in 5–19-year-olds for all countries, using height data from 1971 to 2019 and BMI data from 1985 to 2019, obtained from 2181 sources for 193 countries (totalling measurements of 50 million 5–19 year-olds and 15 million people aged 20–30 years). Bayesian hierarchical models were used to estimate mean height and mean BMI by country, year, sex, and age, attempting to account for dimorphic pubertal timing and non-linear changes during puberty that confound the interpretation of growth in adolescence.

The authors found major changes in the height of school-aged children by country and over time, reporting a difference of 20 cm or higher between countries with the tallest and shortest heights. In 2019, the average tallest 19-year-old boys lived in the Netherlands (mean height 183·8 cm, 95% credible