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Four-strain flu vaccines coming to a pharmacy near you

Trying to decide which influenza B strain to include in the seasonal flu vaccine is enough to give anyone a headache. Manufacturing constraints limit public health officials to including only one B strain in each year's vaccine, in addition to the two strains from the A type of the virus. But because there are two distinct lineages of influenza B in circulation, public health officials have had to play a guessing game about which strain will predominate in the upcoming season—and they haven't had good luck. Predictions about which B strain will be the more prevalent have been correct only about half the time in the US in recent years.

“Our ability to predict which of these strains will circulate has not been great,” admits Ruth Karron, director of the Center for Immunization Research at the Johns Hopkins Bloomberg School of Public Health in Baltimore. “We might as well have tossed a coin.”

Starting next year, however, health officials might no longer have to gamble on that choice. On 29 February, the US Food and Drug Administration approved FluMist Quadrivalent, the first four-pronged influenza vaccine to contain both B strains, for use in people aged 2 to 49. In three clinical trials involving some 4,000 adults and children, one of which was published last November (*Vaccine* 29, 9391–9397, 2011), this quadrivalent flu vaccine promoted comparable immune responses to the existing three-strain FluMist product.

According to Tor Constantino, a spokesperson with MedImmune, the Maryland-based subsidiary of AstraZeneca behind FluMist, starting in the 2013–2014 flu season, the company plans to stop producing the current trivalent vaccine in the US and offer only the quadrivalent alternative. The company also plans to file for EU regulatory approval for the four-strain vaccine later this year.

“It's a significant advance,” says Robert Belshe, director of the Center for Vaccine Development at the Saint Louis University School of Medicine, who led the pediatric trial involving FluMist. “It takes the guessing work out of the B component.”

More four-strain vaccines could also be

on the way, although unlike MedImmune's FluMist, which uses live attenuated viruses that are sprayed into the nose, the products being developed by every other company contain killed viral particles that are administered in the arm using a needle. On 5 March, Britain's GlaxoSmithKline announced that it had submitted applications, including immunogenicity and safety data from two pivotal trials, one in children and one in adults, to both US and EU regulators for its quadrivalent flu shot. Meanwhile, France's Sanofi-Pasteur will present late-stage trial data on its four-strain flu jab at this month's Pediatric Academic Societies annual meeting in Boston, and the Swiss drugmaker Novartis reported positive phase 2 results last November with its own adjuvanted quadrivalent product (*Vaccine* 29, 8696–8704, 2011). Similar to MedImmune, some of these companies expect their products to be on the market in autumn of 2013.

On all fours

Including a second lineage of influenza B in the seasonal flu vaccine requires an increased and more stable manufacturing supply chain—something that only became possible in the US after the federal government spent billions of dollars over the past decade to modernize the country's ability to respond to public health emergencies such as the recent avian and swine flu outbreaks. “Our capacity for this has only existed in the past few years,” says Karron. “This is really a dividend of pandemic flu preparedness.”

That dividend could provide a substantial public health impact, notes Anthony Fauci, director of the US National Institute of Allergy and Infectious Disease in Bethesda, Maryland. “Influenza B strains are an important issue with regard to illness, particularly in children,” he says. “Putting two B strains in should significantly cut down the probability of having a naive population even in those who get vaccinated.”

To quantify the health benefit of including both B strains, epidemiologist Carrie Reed and her colleagues at the US Centers for Disease Control and Prevention in Atlanta modeled ten years of flu data starting from the 1999–2000



Dave Bradley Photography

To the four winds: MedImmune's FluMist.

season. Reporting earlier this year in *Vaccine* (30, 1993–1998, 2012), they found that in seasons when both B strains are circulating, a quadrivalent vaccine could help prevent up to a million cases of illness, including thousands of hospitalizations and hundreds of deaths, in the US alone. “There's going to be some impact every year on influenza-related outcomes because we're now covering four strains instead of three,” Reed says, “but the absolute impact of that is going to vary from year to year.”

Bruce Lee and Sarah Bartsch from the University of Pittsburgh School of Medicine have since taken the data of Reed's group and calculated such a vaccine's potential economic value. In unpublished results, they found that close to \$300 million in direct medical costs and another \$2.9 billion in terms of lost productivity could have been saved over the past decade had the seasonal flu vaccine contained a fourth strain. “These numbers are noteworthy,” says Lee. “A subtle change in an existing preventive measure can immediately and continuously lead to substantial cost savings for third-party payers and society.”

Elie Dolgin