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Live Attenuated Versus Inactivated Influenza Vaccine in Hutterite Children

A Cluster Randomized Blinded Trial

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Background: Whether vaccinating children with intranasal live attenuated influenza vaccine (LAIV) is more effective than inactivated influenza vaccine (IIV) in providing both direct protection in vaccinated persons and herd protection in unvaccinated persons is uncertain. Hutterite colonies, where members live in close-knit, small rural communities in which influenza virus infection regularly occurs, offer an opportunity to address this question.

Objective: To determine whether vaccinating children and adolescents with LAIV provides better community protection than IIV.

Design: A cluster randomized blinded trial conducted between October 2012 and May 2015 over 3 influenza seasons.

Setting: 52 Hutterite colonies in Alberta and Saskatchewan, Canada.

Participants: 1186 Canadian children and adolescents aged 36 months to 15 years who received the study vaccine and 3425 community members who did not.

Intervention: Children were randomly assigned according to community in a blinded manner to receive standard dosing of either trivalent LAIV or trivalent IIV.

Measurements: The primary outcome was reverse transcriptase polymerase chain reaction–confirmed influenza A or B virus in all participants (vaccinated children and persons who did not receive the study vaccine).

Results: Mean vaccine coverage among children in the LAIV group was 76.9% versus 72.3% in the IIV group. Influenza virus infection occurred at a rate of 5.3% (295 of 5560 person-years) in the LAIV group versus 5.2% (304 of 5810 person-years) in the IIV group. The hazard ratio comparing LAIV with IIV for influenza A or B virus was 1.03 (95% CI, 0.85 to 1.24).

Limitation: The study was conducted in Hutterite communities, which may limit generalizability.

Conclusion: Immunizing children with LAIV does not provide better community protection against influenza than IIV.

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Influenza is a major cause of morbidity and mortality, resulting in excess hospitalization and death (1–3). Data from longitudinal studies suggest that children are an important source of community transmission of influenza (4–8). Vaccinating children against influenza not only protects them but can also provide indirect benefit through herd protection (that is, reducing the risk for influenza in susceptible persons by rendering immunity in others) (9–16). However, the choice of vaccine that best achieves herd protection remains uncertain (17, 18). Intranasal live attenuated influenza vaccine (LAIV) has been reported to provide 55% greater protection against influenza in children than inactivated influenza vaccine (IIV) (19, 20). Vaccinating children with LAIV compared with IIV should provide better community protection because of better direct protection of children and better indirect effects of herd protection. This question is of public health importance, particularly given differences in recommendations on preferential use of LAIV (21–23).

Most comparative influenza vaccine studies assess direct protection only (24). Understanding the comprehensive benefit of LAIV versus IIV requires evaluation of both direct and indirect effects. This is best addressed through a randomized, controlled trial; however, random assignment of the children of entire communities to vaccination with LAIV versus IIV is not possible in most settings. Hutterite colony members live communally and are relatively isolated from cities and towns, and influenza is regularly introduced into these colonies. This offers an opportunity to test the effect of vaccinating children with LAIV versus IIV on community protection in a cluster randomized trial (11). We hypothesized that a 70% or greater uptake of trivalent LAIV compared with a similar uptake of trivalent IIV among healthy children and adolescents would reduce laboratory-confirmed influenza by 50% in the LAIV versus IIV group. A 50% risk reduction was selected on the basis of a previous trial showing a 55% direct risk reduction in children who received LAIV compared with IIV (19). We also hypothesized that this would translate to a reduction in influenza-associated outcomes.

See also:

Web-Only
Supplement

METHODS

Study Colonies

Residents of Hutterite colonies within 150 km of designated cities or towns in Alberta and Saskatchewan, Canada, were enrolled and followed from 22 October 2012 through 20 May 2015. Each colony was approached annually regarding whether it would enroll for the next influenza season. Colonies were excluded if the children did not receive any routine vaccinations or if local public health policy was to offer influenza immunization to persons beyond high-risk children (for example, those with cystic fibrosis). Hutterite colonies are small communities (for example, 70 to 120 residents) with single-family dwellings and communally shared buildings, such as the kitchen, dining hall, and school. Hutterite families shop in nearby towns for supplies and clothing not available in the colony. The children attend school in the colony.

Vaccinated Children

Healthy Hutterite children aged 36 months to 15 years (ages when they attend school; age 15 years is when Hutterite children are considered to have reached maturity) were eligible to be vaccinated. Exclusion criteria included anaphylactic reaction to a previous LAIV or trivalent influenza vaccine; known IgE-mediated hypersensitivity to eggs manifested as hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock; history of asthma; medically diagnosed or treated wheezing within 42 days before enrollment; Guillain–Barré syndrome within 8 weeks of a previous influenza vaccine; anaphylactic reaction to any vaccine component; pregnancy; household contact with a severely immunocompromised person who was being cared for in a protective environment; and use of aspirin or salicylate-containing products within 30 days before enrollment.

Other Hutterite Colony Members

All other residents of Hutterite colonies were eligible to participate as nonvaccine recipients and could receive an influenza vaccine outside of the trial.

Ethics approval was obtained at McMaster University, the University of Calgary, and the University of Saskatchewan. Participants gave written consent. Participants provided consent for children, and assent was also directly sought from children aged 7 to 15 years.

Interventions

In the LAIV group, healthy children aged 36 months to 15 years received a 0.2-mL dose of intranasal LAIV (FluMist [MedImmune]) recommended for the 2012 to 2013 (influenza A/California/7/2009[H1N1]pdm09–, influenza A/Victoria/361/2011[H3N2]–, and influenza B/Wisconsin/1/2010–like viruses), 2013 to 2014 (influenza A/California/7/2009[H1N1]pdm09–, influenza A/Victoria/361/2011[H3N2]–, and influenza B/Massachusetts/2/2012–like viruses), or 2014 to 2015 influenza seasons (influenza A/California/7/2009 [H1N1]pdm09–, influenza A/Texas/50/2012[H3N2]–, and influenza B/Massachusetts/2/2012–like viruses). In the IIV group, healthy children aged 36 months to 15 years received a 0.5-mL intramuscular injection of IIV (Vaxigrip [Sanofi Pasteur]) recommended for the 3 influenza seasons. In both LAIV and IIV groups, previously unvaccinated children younger than 9 years at the time of immunization received a second dose of the vaccine 4 weeks after the first dose.

Blinding and Allocation

A statistician assigned colonies, using a random-number generator, within each of 5 geographic regions where participating Hutterite colonies were located to control for regional differences in influenza circulation. Allocation was to 1 of the 2 study groups (LAIV or IIV) in a 1:1 ratio. To minimize bias, we gave precedence to achieving a balance of colonies within strata or health regions as opposed to balancing overall cluster numbers between groups. We reduced the possibility of enrollment bias by allocating LAIV or IIV status to colonies after participant enrollment. Colonies were not randomly assigned again in the second and third year of the trial so that vaccine allocation remained the same over the entire study. In the event of a colony withdrawal, another colony from the same study region that met eligibility criteria was selected as a replacement and allocated to the same group as the colony that had withdrawn. Arrangements for vaccine shipment from the manufacturer to depots were made by an intermediary clinical trials research organization that received the randomization code from the statistician.

To maintain blinding, children allocated to LAIV received a concurrent 0.5-mL saline injection to mimic IIV. Those allocated to IIV received a 0.2-mL dose of intranasal saline. Among children younger than 9 years who had never previously received seasonal influenza vaccine, those allocated to LAIV received a concurrent 0.5-mL intramuscular injection of sterile saline with the first and second dose of intranasal LAIV. Those in the IIV group received concurrent 0.2-mL doses of intranasal saline administered 4 weeks apart. For blinding purposes, different teams were used to vaccinate children or assess outcomes. Vaccines were prepared by nurses behind a privacy screen in the preparation room in the Hutterite colony. Surveillance staff, who assessed outcomes, were not involved in vaccination and were blinded to allocation status. Investigators, study coordinators, study monitors, and the data and safety monitoring board were all blinded.

Follow-up

The start date of the surveillance period for influenza was defined as 1 or more cases of laboratory-confirmed influenza in 2 consecutive weeks from public health surveillance regions that occurred at least 2 weeks after completion of study vaccination in a study colony; the stop date was defined as no cases of laboratory-confirmed influenza for 2 consecutive weeks in colonies within the health region. Participants were assessed twice weekly by using a standardized checklist of self- or parent-reported symptoms or signs. If any new symptoms were reported, the participant was contacted directly by research staff, who confirmed the symptoms and obtained flocked nasal swabs if 2 or

more of the following symptoms were present: fever (temperature ≥38 °C), cough, nasal congestion, sore throat, headache, sinus problems, muscle aches, fatigue, ear ache or infection, or chills. We provided thermometers for study participants.

Outcomes

The primary outcome was laboratory-confirmed influenza A or B in all participants, the assessment of which began 2 weeks after vaccination to ensure adequate time for development of an immune response. For participants with 2 or more signs and symptoms, influenza was confirmed on the basis of detecting viral RNA in respiratory samples through duplex real-time reverse transcriptase polymerase chain reaction (RT-PCR). This test targeted the matrix gene for influenza A virus and the nonstructural gene for influenza B virus (25). All specimens with positive results on RT-PCR were then tested by using Centers for Disease Control and Prevention primers capable of differentiating wild-type from vaccine strains.

We also assessed antimicrobial prescriptions, influenza-like illness (defined as a temperature ≥38.0 °C and cough) (26), medically attended visits for respiratory illness, school- or work-related absenteeism, emergency department visits, hospital admissions, and deaths. Although we had originally planned to capture hospitalizations, we decided before data collection to consider emergency department visits as a separate outcome from hospital admission. Further, we initially planned to analyze outcomes, including physician-diagnosed otitis media, lower respiratory tract infection, and pneumonia, but a reduction in resources limited our ability to validate these outcomes. We captured all hospitalizations and deaths and reported the number of events in each study group, but because of low numbers, we did not conduct analyses.

Adverse Reactions

All vaccinated participants were observed for 15 minutes immediately after vaccination. They were also assessed for adverse events for 5 days after vaccination. Passive surveillance for adverse reactions to the vaccine was implemented throughout the study period.

Statistical Analysis

The primary comparison was the effect of LAIV on the incidence of laboratory-confirmed influenza A or B virus compared with IIV over the 3-year study period. Using a method for clustered survival times (27), we first calculated the number of events required for a hazard ratio (HR) of 0.5 and adjusted for a mean cluster size of 70. We then determined that for 90% power, a 2-sided α of 0.05, and an intracluster correlation coefficient of 0.004 (13), 120 events (cases of laboratory-confirmed influenza) would be needed within a single season. Effect size was informed by our previous trial in Hutterite colonies (11) in which we detected a larger effect (HR, 0.40) when comparing IIV with hepatitis A vaccine (control) in a similar sample size. Using rates of 4.5% for participants in the IIV group and 2.25% for those in the LAIV group who did not remain event-free by the end of follow-up, we estimated that having 1800 participants in each group would give more than 90% power to detect a HR of 0.50 (11).

Given that most participants were enrolled for 1 or more years, we used a nested frailty Cox proportional hazards regression model to account for clustering within colonies and within individuals for laboratory-confirmed influenza over the entire study period. For the primary survival outcome of any type of laboratory-confirmed influenza and secondary survival outcomes of laboratory-confirmed influenza A or B only, we fitted the nested survival model using all participants' data. In this model, we used the "frailtyPenal" function of the "frailtypack" package (version 2.7.6) in R (version 3.2.2) where the cluster-level vaccination variable (LAIV or IIV) was the only covariate included. Colonies were treated as clusters, and individual children (with data from a maximum of 3 seasons) were treated as subclusters. For the analysis of survival data within each season, we used PROC PHREG in SAS (version 9.2) and accounted for clustering by colonies via the sandwich variance estimator. These analyses were repeated for vaccinated children and nonvaccinated persons separately. For each of the secondary dichotomous outcomes, we used nested generalized estimating equations with the identity-link function to estimate the absolute risk difference of the vaccine effect (vaccination was the only covariate) (PROC GENMOD in SAS). In the analysis, we accounted for membership in the randomized clusters and repeated individual data over 3 seasons using exchangeable correlation structure.

To avoid the lack of independence associated with counting multiple outcomes, we counted each specific outcome within a season in a participant only once in our analyses. Therefore, participants could contribute data for more than 1 year in the nested frailty analysis, but within a particular season they contributed only up to their first infection with influenza. In the generalized estimating equation analysis, only the first event in a season was counted. Outcomes for vaccinated and nonvaccinated persons were analyzed on the basis of their original assignment to a vaccine by colony. All *P* values and 95% CIs were calculated as 2-sided. Differences with *P* values less than 0.05 were considered statistically significant.

Role of the Funding Source

The study was funded by the Canadian Institutes of Health Research, Public Health Agency of Canada, and Canadian Institutes of Health Research Influenza Research Network. Funding organizations played no role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to approve publication of the finished manuscript.

RESULTS

Participants

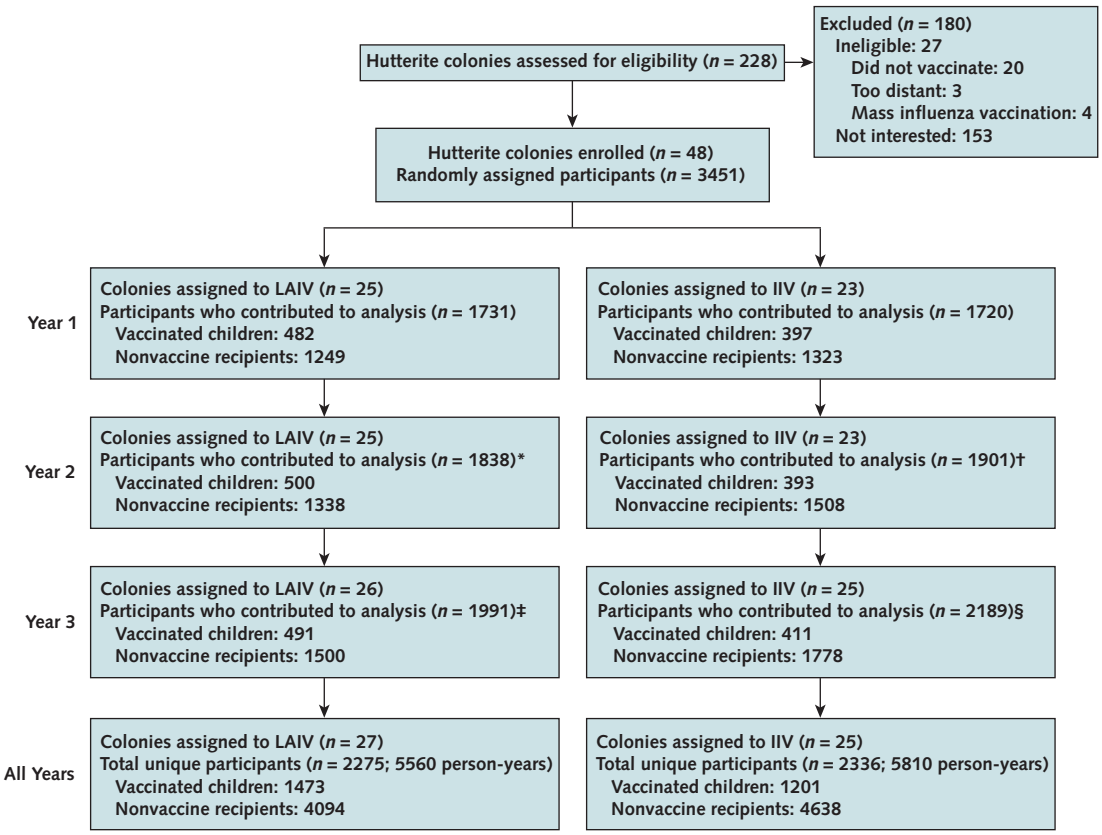
A total of 4611 unique participants from 52 colonies (27 and 25 assigned to the LAIV and IIV groups, respectively) were enrolled over the 3-year trial. Char-

Table 1. Characteristics of All Study Participants in 52 Colonies at First Entry to Study and Vaccination Status by Year*

Variable	LAIV	IIV
Colonies, *n*	27	25
Participants, *n*	2275	2336
Median per colony (range), *n*†		
Total residents	95 (66–135)	106 (68–146)
Enrolled participants	88.5 (31–123)	89.0 (56–130)
Households	21 (15–32)	22 (16–35)
Vaccinated children		
Total, *n*	654	532
Median per colony (range), *n*†	24 (4–41)	20 (5–42)
Receipt of vaccine by noneligible participants, *n (%)*‡	107 (7.0)	129 (7.6)
Influenza vaccination status, *n/N (%)*§		
Year 1		
Received study vaccine	482/621 (77.6)	397/514 (77.2)
Received vaccine outside of study	23/621 (3.7)	2/514 (0.4)
Did not receive vaccine	116/621 (18.7)	115/514 (22.4)
Year 2		
Received study vaccine	500/638 (78.4)	393/546 (72.0)
Received vaccine outside of study	18/638 (2.8)	23/546 (4.2)
Did not receive vaccine	120/638 (18.8)	130/546 (23.8)
Year 3		
Received study vaccine	491/657 (74.7)	411/601 (68.4)
Received vaccine outside of study	22/657 (3.3)	23/601 (3.8)
Did not receive vaccine	144/657 (21.9)	167/601 (27.8)
Median participants per colony by region (range), *n*†		
Alberta		
Calgary	99 (93–111)	99 (72–101)
Central	74 (50–123)	84 (80–124)
South	81 (55–109)	99 (73–124)
Saskatchewan		
South	77 (45–98)	82 (79–113)
North	98.5 (31–109)	83 (56–130)
Age		
Median age (range), *y*	20 (<1–85)	22 (<1–94)
Participants, *n*		
0–<3 y	231	226
3–<9 y	357	293
9–<16 y	379	333
16–<25 y	311	423
25–<65 y	876	928
≥65 y	121	133
Female, *n (%)*	1249 (54.9)	1282 (54.9)
Participants with coexisting conditions, *n (%)*		
≥1 coexisting condition	179 (7.9)	204 (8.7)
Asthma	72 (3.2)	76 (3.3)
Blood disorders	5 (0.2)	3 (0.1)
Cardiovascular disease	32 (1.4)	32 (1.4)
Diabetes	55 (2.4)	68 (2.9)
Kidney or liver disease	9 (0.4)	10 (0.4)
Swallowing and choking problems	15 (0.7)	10 (0.4)
Immunocompromised‖	18 (0.8)	29 (1.2)
Pregnancies	105 (4.6)	109 (4.7)
Other¶	9 (0.4)	8 (0.3)

IIV = inactivated influenza vaccine; LAIV = live attenuated intranasal influenza vaccine.
* Percentages may not sum to 100 due to rounding.
† Refers to enrolled participants at entry and during follow-up.
‡ Refers to participants not aged 3–15 y who received IIV at first entry to study.
§ Refers only to children who were participants in the study and were eligible for vaccination because the data for nonparticipants were not accessible.
‖ Solid organ tumor (n = 28), leukemia (n = 2), splenectomy (n = 1), kidney transplantation (n = 4), immunosuppressive agents (n = 7), and autoimmune disorders (n = 5).
¶ Juvenile arthritis (n = 1), Cushing syndrome (n = 1), cystic fibrosis (n = 4; two per group), chronic obstructive lung disease (n = 7), and chronic heart failure (n = 6; two of these also had chronic obstructive lung disease).

Figure. Study flow of diagram of study participants.



IIV = inactivated influenza vaccine; LAIV = live attenuated influenza vaccine.
* 199 persons in a year-1 colony did not participate in year 2 and were replaced by 306 persons from a new colony.
† 178 persons in a year-1 colony did not participate in year 2 and were replaced by 359 persons from a new colony.
‡ 99 persons in a year-2 colony did not participate in year 3 and were replaced by 252 persons from a new colony.
§ 71 persons in a year-2 colony did not participate in year 3 and were replaced by 257 persons from 1 new colony and new enrollees from other colonies; 102 persons from year 1 reenrolled.

acteristics of the colonies and participants enrolled were similar between both groups (Table 1). In year 1, there were 3451 participants enrolled from 48 colonies, 25 of which were assigned to the LAIV group and 23 to the IIV group (Figure). In year 2, one colony in each group chose not to reenroll and each was replaced with a new colony. This occurred again in year 3; then, one new colony was assigned to each group and a year-1 colony was reenrolled after not participating in year 2 along with new participants enrolled from existing study colonies. Although 2 colonies in year 2 and 2 in year 3 chose not to participate, no participants withdrew during any of the influenza seasons. We enrolled 665 new participants (306 and 359 in the LAIV and IIV groups, respectively) in year 2 and 509 (252 and 257 in the LAIV and IIV groups, respectively) in year 3. Because participants were reenrolled each influenza season, the final analysis was based on the sum of those enrolled each year—5560 person-years for the LAIV group (1731, 1838, and 1991 in years 1, 2, and 3, respectively) and 5810 person-years for the IIV group (1720, 1901, and 2189 in years 1, 2, and 3, respectively) (Table 2).

Of children who received the study vaccine, 336 of 1186 (28.3%) had been previously vaccinated with IIV. The percentage of vaccinated children ranged from 74.7% to 77.6% per year in the LAIV group and from 68.4% to 77.2% per year in the IIV group. The percentage that received influenza vaccine outside of the study ranged from 2.8% to 3.7% per year in the LAIV group and from 0.4% to 4.2% per year in the IIV group. The percentage that did not receive any influenza vaccine ranged from 18.7% to 21.9% per year in the LAIV group and from 22.4% to 27.8% per year in the IIV group.

Outcomes

Over the 3-year study period, influenza A or B virus infection occurred at a rate of 5.3% (295 cases over 5560 person-years) in the LAIV group compared with 5.2% (304 cases over 5810 person-years) in the IIV group (Table 2). Of these participants, 190 (3.4%) in the LAIV group and 194 (3.3%) in the IIV group had influenza A virus, whereas 107 (1.9%) in LAIV group and 115 (2.0%) in the IIV group had influenza B virus. When we reviewed all participants with influenza A virus, 85 (44.7%) had H3N2 and 105 (55.3%) had H1N1 (from the

Table 2. Effectiveness of LAIV Compared With IIV at Preventing RT-PCR–Confirmed Influenza Virus Infection for All Study Participants*

Outcome	RT-PCR–Confirmed Influenza Virus Infection, *events/person-years (%)*		HR (95% CI)
	LAIV	IIV	
Primary outcome: all influenza virus infection†			
All years‡	295/5560 (5.3)	304/5810 (5.2)	1.03 (0.85–1.24)
Year 1	119/1731 (6.9)	74/1720 (4.3)	1.61 (0.61–4.29)
Year 2	118/1838 (6.4)	154/1901 (8.1)	0.80 (0.39–1.64)
Year 3	58/1991 (2.9)	76/2189 (3.5)	0.85 (0.36–1.99)
Secondary outcomes§			
Influenza A virus infection			
All years‡	190/5560 (3.4)	194/5810 (3.3)	1.01 (0.59–1.74)
Year 1 (H3N2)	40/1731 (2.3)	18/1720 (1.0)	2.22 (0.57–8.61)
Year 2 (H1N1)	105/1838 (5.7)	107/1901 (5.6)	1.02 (0.47–2.23)
Year 3 (H3N2)	45/1991 (2.3)	69/2189 (3.2)	0.72 (0.26–2.02)
Influenza B virus infection			
All years‡	107/5560 (1.9)	115/5810 (2.0)	1.02 (0.76–1.35)
Year 1	80/1731 (4.6)	57/1720 (3.3)	1.41 (0.47–4.19)
Year 2	14/1838 (0.8)	51/1901 (2.7)	0.28 (0.05–1.55)
Year 3	13/1991 (0.7)	7/2189 (0.3)	2.18 (0.32–14.82)

HR = hazard ratio; IIV = inactivated influenza vaccine; LAIV = live attenuated intranasal influenza vaccine; RT-PCR = reverse transcriptase polymerase chain reaction.
* There was a vaccine match for influenza A virus in the first and second year of the trial (influenza A/Victoria/361/2011[H3N2]–like virus and influenza A/California/7/2009[H1N1]pdm09–like virus, respectively) but a mismatch between influenza A/Texas/50/2012(H3N2)–like vaccine strain and the circulating influenza A/Switzerland/9715293/2013(H3N2)–like virus. There was a lineage mismatch for influenza B virus for the first study year (influenza B/Wisconsin/1/2010–like virus vaccine strain and both influenza B/Wisconsin and influenza B/Brisbane/60/2008 circulating viruses) and the third year of the study (influenza B/Massachusetts/2/2012–like virus vaccine and both influenza B/Massachusetts/2/2012–like virus and influenza B/Brisbane/60/2008–like circulating virus) and a lineage match in the second year.
† The sum of events of influenza A and B virus infections is greater than all events of influenza virus infection when participants were co-infected with both influenza A and B viruses. All HRs were calculated using the participants' first infection with influenza virus.
‡ The denominator is the sum of persons enrolled each year. Because participants were reenrolled in the study over 3 y, 5560 LAIV person-years were included in the analysis, of which 2275 were unique persons. A total of 5810 IIV person-years was included in the analysis over 3 y, of which 2336 were unique persons. That a person could contribute for >1 y was accounted for in the analysis by using a nested frailty model. The variable colony as a random effect in the nested frailty model was significant ($P < 0.001$), but there was no effect for individual participants ($P = 0.49$).
§ Refers to RT-PCR–confirmed cases of influenza for influenza A virus subtypes alone or of influenza B virus alone.

2013 to 2014 influenza season) in the LAIV group; further, 87 (44.8%) had H3N2 and 107 (55.3%) had H1N1 in the IIV group.

For the primary outcome, we found no significant difference between LAIV and IIV (pooled HR, 1.03 [95% CI, 0.85 to 1.24]) (**Table 2**). Although the attack rates of influenza differed by region, the relationship between the 2 groups within a single region was generally similar (**Appendix Table 1**, available at www.annals.org).

For the secondary outcomes, there was no significant difference for RT-PCR–confirmed influenza A (HR, 1.01 [CI, 0.59 to 1.74]) or B (HR, 1.02 [CI, 0.76 to 1.35]) virus in all participants. We also found no significant difference in influenza A or B virus in vaccinated children (HR, 0.97 [CI, 0.71 to 1.34]) (**Appendix Table 2**, available at www.annals.org). Children vaccinated with LAIV had a significantly higher risk for influenza A virus infection (HR, 1.62 [CI, 1.02 to 2.59]) but were protected against influenza B virus (HR, 0.66 [CI, 0.46 to 0.96]). Attack rates of influenza for children younger than 6 years in the LAIV and IIV groups (6.2% vs. 6.3%) were similar to those in older children (6.2% vs. 6.4%). For indirect benefit, the HR in persons who did not receive the study vaccine was 1.03 (CI, 0.85 to 1.24) for influenza A and B viruses, and no difference for influenza A (HR, 0.95 [CI, 0.79 to 1.15]) or B (HR, 1.27 [CI, 0.88 to 1.84]) virus was found. Epidemic curves are shown in the **Appendix Figure** (available at www.annals.org).

In a pooled analysis of the 3 influenza seasons that compared LAIV with IIV in all participants, we found the following: absolute difference for influenza-like illness, 0.28% (CI, −0.59% to 1.15%); antimicrobial prescriptions, −0.33% (CI, −1.18% to 0.53%); medically attended visits for respiratory illness, 0% (CI, −0.82% to 0.81%); emergency department visits, −0.10% (CI, −0.57% to 0.37%); hospital admissions, 0.01% (CI, −0.19% to 0.22%); and school- or work-related absenteeism, 0.22% (CI, −0.92% to 1.36%). No significant difference in these outcomes between groups during the study period was found (**Appendix Table 3**, available at www.annals.org). Both groups had 11 hospital admissions, for a total of 22. Of note, 10 deaths occurred—9 unrelated to infection and 1 due to pneumonia—all in participants who did not receive the study vaccine.

More children in the IIV than LAIV group had adverse reactions to the vaccine in all 3 study years, mostly because of adverse reactions at the injection site (**Appendix Table 4**, available at www.annals.org). No serious adverse events were related to vaccination.

Discussion

Vaccination of Hutterite children aged 36 months to 15 years with LAIV had a similar effect on laboratory-confirmed influenza A and B viruses compared with vaccination with IIV. Clinically relevant outcomes, such as influenza-like illness, medically attended visits for respiratory illness, and absenteeism, were similar in both groups. We planned to detect a 50% risk reduction in laboratory-confirmed influenza A and B viruses among all study participants. The lower limit of the CI in the LAIV versus IIV comparison was 0.85, which refers to a 15% risk reduction. This ruled out our hypothesized effect along with other clinically important risk reductions. The relative attack rates between the groups in vaccinated children and nonvaccinated persons were consistent with findings of the overall effect, thus showing no overall benefit for all participants with respect to protection against influenza when LAIV is compared with IIV.

Although most vaccinated children (80%) in our study were aged 6 years or older, overall attack rates of influenza for those younger than 6 years in both groups were similar to those in older children. A previous trial showed a direct protective effect of LAIV in children younger than 19 years (28). Although one third of children who received the study vaccine had previously received IIV, priming with IIV followed by boosting with LAIV resulted in similar protective antibodies to prime-boost vaccination with LAIV–LAIV or trivalent IIV–IIV in children (29).

Observational studies in the United States using quadrivalent LAIV suggested a lack of effectiveness against H1N1 influenza A pdm09 virus in the 2013 to 2014 season (22). This vaccine was not available in Canada during that season, so we used trivalent LAIV. In contrast to the experience in the United States, we found that LAIV protection against H1N1 influenza A pdm09 virus in 2013 to 2014 was similar to that of IIV. Observational data from 2014 to 2015 in the United States seem to show no difference in direct protection between LAIV and IIV (22). Given the similar effect of LAIV and IIV on laboratory-confirmed influenza and secondary outcomes in our study, inactivated vaccines that are available at a lower cost seem to be cost-effective, although we did not formally assess this (30).

Strengths of our study were that participants, investigators, and outcome assessors were blinded; active surveillance was intense; clusters were stratified by geographic regions to balance exposure to influenza; allocation to vaccinated groups was conducted after enrollment to reduce the possibility of selection bias; the trial was conducted over 3 influenza seasons; and clinical outcomes were assessed. Estimates of these outcomes, such as medically attended influenza or visits to emergency departments, were aligned with results of laboratory-confirmed influenza. Of note, because a placebo group was not included, our study did not assess vaccine effectiveness but was designed to evaluate whether there was incremental benefit of LAIV over IIV for community protection. We acknowledge the differences between Hutterite colonies and other communities. Hutterites share certain spaces, including schools and dining halls, but they live in family homes and share many characteristics of other rural communities. Although influenza transmission networks in Hutterite communities may differ from that in other communities, there are no data to confirm this. In fact, there may be more variability in social networks between urban and rural communities—or even among various urban communities—than between Hutterite and other (rural) communities. Even if variability exists, if a clear benefit of LAIV over IIV in reducing influenza-associated illness cannot be detected in this setting it is unlikely to be seen in other communities.

Our results suggest that vaccinating children with LAIV does not confer better community protection against influenza than IIV. Although the choice of an influenza vaccine for children may depend on various factors, our data suggest no additional benefit of LAIV over IIV.

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Appendix Table 1. Laboratory-Confirmed Influenza Virus Infection, by Region*

Variable	Primary Outcome: All Influenza, *events/person-years (%)*	
	LAIV	**IIV**
All years*	295/5560 (5.3)	304/5810 (5.2)
Alberta		
Calgary	43/1016 (4.2)	51/718 (7.1)
Central	65/1064 (6.1)	67/1164 (5.8)
South	78/1493 (5.2)	79/2019 (3.9)
Saskatchewan		
South	63/762 (8.3)	61/665 (9.2)
North	46/1225 (3.8)	46/1244 (3.7)

IIV = inactivated influenza vaccine; LAIV = live attenuated intranasal influenza vaccine.
* Because participants were reenrolled in the study over 3 y, 5560 LAIV person-years were included in the analysis, of which 2275 were unique persons. A total of 5810 IIV person-years was included in the analysis over 3 y, of which 2336 were unique persons.

Appendix Table 2. Effectiveness of LAIV Versus IIV in Preventing RT-PCR–Confirmed Influenza Virus Infection in Vaccinated Children and Nonvaccinated Persons

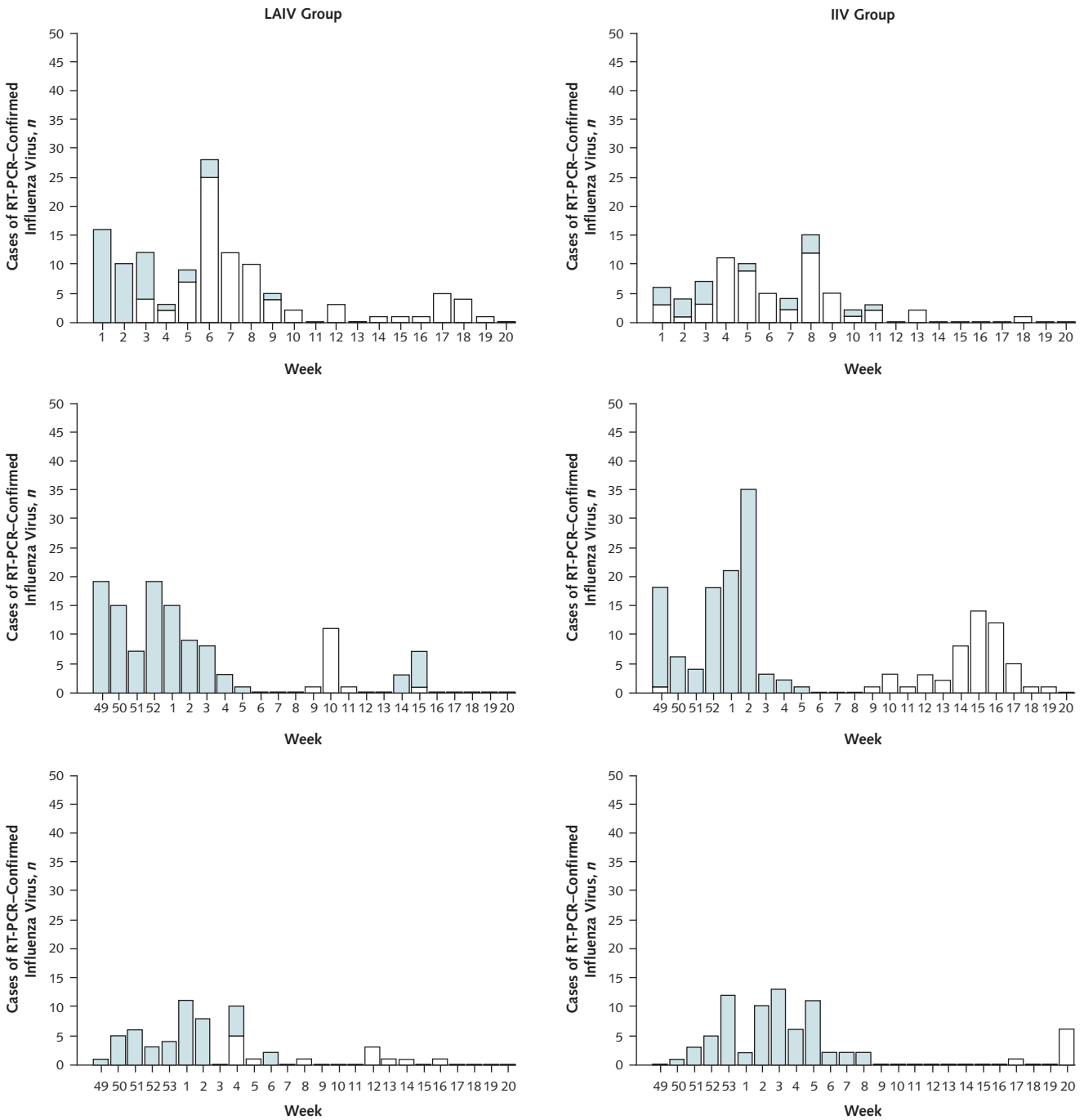
Variable	Vaccinated Children			Nonvaccinated Persons		
	Events/Person-Years (Percentage)		HR (95% CI)	Events/Person-Years (Percentage)		HR (95% CI)
	LAIV	IIV		LAIV	IIV	
All influenza virus infection*						
All years†	91/1473 (6.2)	77/1201 (6.4)	0.97 (0.71–1.34)	204/4087 (5.0)	227/4609 (4.9)	1.03 (0.85–1.24)
Year 1	46/482 (9.5)	25/397 (6.3)	1.54 (0.38–6.29)	73/1249 (5.8)	49/1323 (3.7)	1.59 (0.67–3.80)
Year 2	26/500 (5.2)	37/393 (9.4)	0.55 (0.18–1.63)	92/1338 (6.9)	117/1508 (7.8)	0.90 (0.44–1.80)
Year 3	19/491 (3.9)	15/411 (3.6)	1.10 (0.30–3.96)	39/1500 (2.6)	61/1778 (3.4)	0.76 (0.32–1.78)
Influenza A virus infection						
All years†	56/1473 (3.8)	30/1201 (2.5)	1.62 (1.02–2.59)	134/4087 (3.3)	164/4609 (3.6)	0.95 (0.79–1.15)
Year 1 (H3N2)	16/482 (3.3)	2/397 (0.5)	6.70 (1.15–39.14)	24/1249 (1.9)	16/1323 (1.2)	1.59 (0.41–6.20)
Year 2 (H1N1)	22/500 (4.4)	16/393 (4.1)	1.09 (0.34–3.49)	83/1338 (6.2)	91/1508 (6.0)	1.04 (0.48–2.24)
Year 3 (H3N2)	18/491 (3.7)	12/411 (2.9)	1.27 (0.29–5.70)	27/1500 (1.8)	57/1778 (3.2)	0.56 (0.20–1.61)
Influenza B virus infection						
All years†	36/1473 (2.4)	48/1201 (4.0)	0.66 (0.46–0.96)	71/4087 (1.7)	67/4609 (1.5)	1.27 (0.88–1.84)
Year 1	31/482 (6.4)	23/397 (5.8)	1.12 (0.25–4.97)	49/1249 (3.9)	34/1323 (2.6)	1.54 (0.55–4.33)
Year 2	4/500 (0.8)	22/393 (5.6)	0.14 (0.03–0.72)	10 (0.7)	29 (1.9)	0.39 (0.06–2.50)
Year 3	1/491 (0.2)	3/411 (0.7)	0.33 (0.03–4.31)	12/1500 (0.8)	4/1778 (0.2)	3.67 (0.59–23.00)

HR = hazard ratio; IIV = inactivated influenza vaccine; LAIV = live attenuated intranasal influenza vaccine; RT-PCR = reverse transcriptase polymerase chain reaction.

* The sum of events of influenza A and B virus infections is greater than all events of influenza virus infection when participants were co-infected with both viruses. All HRs were calculated using the participants' first infection with influenza virus.

† The denominator is the sum of persons enrolled each year. Because participants were reenrolled in the study over 3 y, 5560 LAIV person-years were included in the analysis, of which are 2275 were unique persons. A total of 5810 IIV person-years was included in the analysis over 3 y, of which 2336 were unique persons. That a person could contribute for >1 y was accounted for in the analysis by using a nested frailty model. The variable colony as a random effect in the nested frailty model was significant ($P < 0.001$), but there was no effect for individual participants ($P = 0.49$).

Appendix Figure. Epidemic curves of laboratory-confirmed influenza by week for each intervention group.



Green and white bars indicate influenza A and B viruses, respectively. IIV = inactivated influenza vaccine; LAIV = live attenuated influenza vaccine; RT-PCR = reverse transcriptase polymerase chain reaction. **Top**. Influenza season 1. **Middle**. Influenza season 2. **Bottom**. Influenza season 3.

Appendix Table 3. Effect of LAIV Versus IIV on Secondary Outcomes in All Participants*

Variable	LAIV, *n (%)*	IIV, *n (%)*	Absolute Difference (95% CI), *percentage points*
Influenza-like illness			
All years	278 (5.0)	273 (4.7)	0.28 (–0.59 to 1.15)
Year 1	94 (5.4)	79 (4.6)	1.62 (–2.3 to 4.10)
Year 2	110 (6.0)	115 (6.0)	0.03 (–3.30 to 3.40)
Year 3	74 (3.7)	79 (3.6)	0.05 (–2.10 to 2.20)
Antimicrobial prescriptions			
All years	251 (4.5)	283 (4.9)	–0.33 (–1.18 to 0.53)
Year 1	95 (5.5)	80 (4.7)	0.79 (–2.40 to 3.90)
Year 2	77 (4.2)	106 (5.6)	–1.1 (–3.4 to 1.2)
Year 3	79 (4.0)	97 (4.4)	–0.42 (–2.80 to 2.00)
Medically attended visit for respiratory illness			
All years	246 (4.4)	258 (4.4)	0 (–0.82 to 0.81)
Year 1	97 (5.6)	74 (4.3)	1.3 (–1.9 to 4.4)
Year 2	70 (3.8)	92 (4.8)	–0.70 (–3.10 to 1.70)
Year 3	79 (4.0)	92 (4.2)	–0.18 (–2.50 to 2.20)
Emergency department visits			
All years	78 (1.4)	87 (1.5)	–0.10 (–0.57 to 0.37)
Year 1	25 (1.4)	20 (1.2)	0.35 (–0.69 to 1.40)
Year 2	27 (1.5)	35 (1.8)	–0.23 (–1.70 to 1.30)
Year 3	26 (1.3)	32 (1.5)	–0.05 (–1.10 to 0.98)
Hospital admissions			
All years	11 (0.20)	11 (0.19)	0.01 (–0.19 to 0.22)
Year 1	3 (0.17)	1 (0.06)	0.20 (–0.13 to 0.52)
Year 2	5 (0.27)	6 (0.31)	0 (–0.44 to 0.43)
Year 3	3 (0.15)	4 (0.18)	–0.04 (–0.31 to 0.23)
School- or work-related absenteeism			
All years	463 (8.3)	471 (8.1)	0.22 (–0.92 to 1.36)
Year 1	130 (7.5)	139 (8.1)	–0.35 (–6.10 to 5.40)
Year 2	166 (9.0)	168 (8.8)	0.07 (–5.90 to 6.00)
Year 3	167 (8.4)	164 (7.5)	0.57 (–4.30 to 5.50)

IIV = inactivated influenza vaccine; LAIV = live attenuated intranasal influenza vaccine.
* There were 1731 LAIV and 1720 IIV participants in year one, 1838 LAIV and 1901 IIV in year 2, and 1991 LAIV and 189 IIV participants in year 3. The denominator for "all years" is the total participant-years, 5560 for LAIV and 5810 for IIV.

Appendix Table 4. Adverse Events to LAIV and IIV in Children Receiving Study Vaccine for All 3 Years*

Variable	LAIV *n* = 482	IIV *n* = 397
Year 1		
One or more adverse reactions	54 (3.1)	162 (9.4)
Arm pain	12 (0.7)	121 (7.0)
Redness at injection site	4 (0.2)	12 (0.7)
Swelling at infection site	4 (0.2)	24 (1.4)
Limited arm movement	3 (0.2)	23 (1.3)
Headache	15 (0.9)	27 (1.6)
Loss of appetite	8 (0.5)	6 (0.3)
Myalgia	6 (0.3)	21 (1.2)
Chills	9 (0.5)	24 (1.4)
Nausea	13 (0.8)	8 (0.5)
Vomiting	20 (1.2)	6 (0.3)
Diarrhea	5 (0.3)	5 (0.3)
Rash	3 (0.2)	0 (0)
Fever	7 (0.4)	11 (0.6)
Eye redness	1 (0.1)	2 (0.1)
Shortness of breath	0 (0)	0 (0)
Other symptoms	7 (0.4)	4 (0.2)
	***n* = 500**	***n* = 393**
Year 2		
One or more adverse reactions	40 (2.2)	150 (7.9)
Arm pain	8 (0.4)	122 (6.4)
Redness at injection site	1 (0.1)	14 (0.7)
Swelling at infection site	0 (0)	14 (0.7)
Limited arm movement	1 (0.1)	46 (2.4)
Headache	15 (0.8)	33 (1.7)
Loss of appetite	4 (0.2)	6 (0.3)
Myalgia	3 (0.2)	39 (2.1)
Chills	9 (0.5)	16 (0.8)
Nausea	13 (0.7)	5 (0.3)
Vomiting	3 (0.2)	4 (0.2)
Diarrhea	1 (0.1)	5 (0.3)
Rash	1 (0.1)	1 (0.1)
Fever	17 (0.9)	7 (0.4)
Eye redness	1 (0.1)	3 (0.2)
Shortness of breath	1 (0.1)	0 (0)
Other symptoms	5 (0.3)	4 (0.2)
	***n* = 491**	***n* = 411**
Year 3		
One or more adverse reactions	52 (2.6)	174 (7.9)
Arm pain	18 (0.9)	152 (6.9)
Redness at injection site	2 (0.1)	10 (0.5)
Swelling at infection site	2 (0.1)	23 (1.1)
Limited arm movement	6 (0.3)	39 (1.8)
Sore throat	6 (0.3)	7 (0.3)
Runny nose	9 (0.5)	10 (0.5)
Headache	13 (0.7)	25 (1.1)
Loss of appetite	1 (0.1)	5 (0.2)
Myalgia	5 (0.3)	18 (0.8)
Chills	5 (0.3)	21 (1)
Nausea	1 (0.1)	8 (0.4)
Vomiting	1 (0.1)	8 (0.4)
Diarrhea	0 (0)	1 (0)
Rash	0 (0)	3 (0.1)
Fever	4 (0.2)	15 (0.7)
Eye redness	2 (0.1)	1 (0)
Shortness of breath	0 (0)	0 (0)
Other symptoms	2 (0.1)	4 (0.2)

IIV = inactivated influenza vaccine; LAIV = live attenuated intranasal influenza vaccine.
* Values are numbers (percentages).