

Effect of Influenza Vaccination of Children on Infection Rates in Hutterite Communities

A Randomized Trial

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INFLUENZA IS A MAJOR CAUSE OF MORBIDITY and mortality, resulting in an estimated 200 000 hospitalizations and 36 000 deaths annually in the United States alone.¹⁻⁴ During pandemics, the burden of influenza illness increases substantially.⁵ Current vaccine policy focuses on immunizing those at high risk of complications of influenza.⁶ As a component of a broader policy to prevent the spread of influenza and reduce its complications, using immunization to interrupt community-wide transmission of influenza may be effective for protecting the entire population, including those at high risk.⁷

Children and adolescents appear to play an important role in the transmission of influenza.⁸⁻¹⁰ Preferential immunization of healthy youngsters has been investigated in school-based trials

Context Children and adolescents appear to play an important role in the transmission of influenza. Selectively vaccinating youngsters against influenza may interrupt virus transmission and protect those not immunized.

Objective To assess whether vaccinating children and adolescents with inactivated influenza vaccine could prevent influenza in other community members.

Design, Setting, and Participants A cluster randomized trial involving 947 Canadian children and adolescents aged 36 months to 15 years who received study vaccine and 2326 community members who did not receive the study vaccine in 49 Hutterite colonies in Alberta, Saskatchewan, and Manitoba. Follow-up began December 28, 2008, and ended June 23, 2009.

Intervention Children were randomly assigned according to community and in a blinded manner to receive standard dosing of either inactivated trivalent influenza vaccine or hepatitis A vaccine, which was used as a control.

Main Outcome Measures Confirmed influenza A and B infection using a real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay and by measuring serum hemagglutination inhibition titers.

Results The mean rate of study vaccine coverage among eligible participants was 83% (range, 53%-100%) for the influenza vaccine colonies and 79% (range, 50%-100%) for the hepatitis A vaccine colonies. Among nonrecipients, 39 of 1271 (3.1%) in the influenza vaccine colonies and 80 of 1055 (7.6%) in the hepatitis A vaccine colonies had influenza illness confirmed by RT-PCR, for a protective effectiveness of 61% (95% confidence interval [CI], 8%-83%; $P = .03$). Among all study participants (those who were and those who were not vaccinated), 80 of 1773 (4.5%) in the influenza vaccine colonies and 159 of 1500 (10.6%) in the hepatitis A vaccine colonies had influenza illness confirmed by RT-PCR for an overall protective effectiveness of 59% (95% CI, 5%-82%; $P = .04$). No serious vaccine adverse events were observed.

Conclusion Immunizing children and adolescents with inactivated influenza vaccine significantly protected unimmunized residents of rural communities against influenza.

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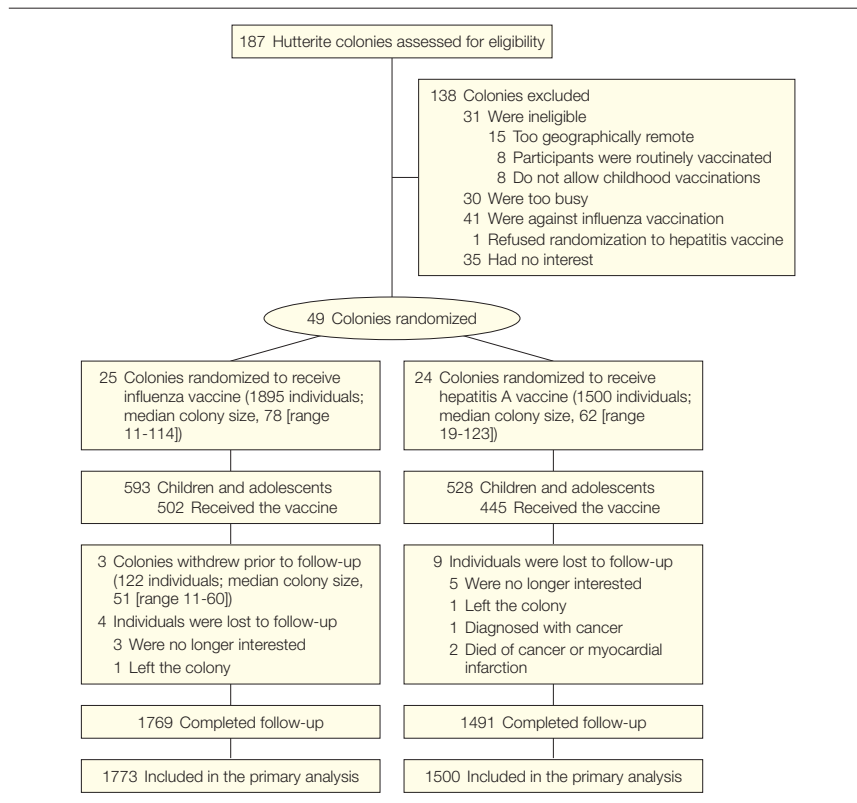
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and observational studies and may be of benefit in reducing influenza transmission.¹¹⁻¹⁸ Nonrandomized designs, unblinded studies, or lack of laboratory confirmation of influenza limit the ability to draw conclusions,¹²⁻¹⁸ particularly the potential for inactivated in-

fluenza vaccine to achieve a herd effect. A systematic review concluded that although evidence exists that vaccinat-

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Figure 1. Flow Diagram of Trial



ing healthy children and adolescents has the potential for reducing the effect of influenza epidemics, further data are needed because limitations in study design or execution make community benefits difficult to quantify.¹⁹

Randomizing entire communities to test the indirect benefit of vaccinating children and adolescents against influenza is not feasible in most settings. Hutterite colonies are Anabaptist rural communities found mostly in western Canada. These tightly knit communities resemble extended families but are composed of single families each residing in their own house, where children and adolescents between the ages of 3 years and 15 years attend school. Approximately 60 to 120 people reside on each colony.

Although relatively isolated from cities and towns, influenza is nevertheless regularly introduced into these communities, offering a unique oppor-

tunity to test the indirect benefit of immunizing children and adolescents.

Based on results from modeling, we hypothesized that if 70% or more of healthy children and adolescents in intervention colonies were immunized with inactivated influenza vaccine, laboratory-confirmed influenza in other residents of these colonies would be reduced.^{11,20-24} To address this question, we conducted a cluster randomized trial.

METHODS

Study Colonies

Residents of Hutterite colonies from 8 health regions in the provinces of Alberta, Saskatchewan, and Manitoba were enrolled in the trial from September 22 to December 23, 2008 (FIGURE 1). Prior to enrollment, the Hutterite boss or minister in each colony was contacted about his colony’s potential interest in the study. Research nurses surveyed colonies

that were potentially interested, determining the numbers of healthy children, adolescent, and adult colony members at high risk of complications of influenza. For ease of implementation, eligible colonies were required to be within 150 km of designated cities or towns and had to have 10 or more members at high risk of complications of influenza. Colonies were excluded if children or adolescents did not receive any routine childhood vaccinations or if local public health policy routinely offered influenza immunization to all residents of a colony, not just high-risk children (eg, cystic fibrosis) and their household members. The research protocol was approved by McMaster University Research Ethics Review Board.

Immunized Children

Healthy children and adolescents (ie, with no underlying chronic medical conditions) aged 36 months to 15 years were eligible to be immunized because in Hutterite colonies they attend school. Those between the ages of 6 months and 23 months—considered to be at high risk and eligible for routine influenza vaccination—were not offered study vaccine. Exclusion criteria included anaphylactic reaction to a previous dose of influenza vaccine; anaphylactic reaction to hepatitis A vaccine; anaphylactic reaction to neomycin; known IgE-mediated hypersensitivity to eggs manifested as hives, swelling of the mouth and throat, difficulty in breathing, hypotension, or shock; or Guillain-Barré syndrome within 8 weeks of a previous influenza vaccine.

Other Hutterite Colony Members

Other colony members were enrolled to assess the indirect effect of immunizing school-going children and adolescents. There were no exclusion criteria for this group, which included both individuals with no known chronic medical conditions and those known to be at high risk of influenza complications, including individuals

with chronic medical conditions, persons 65 years or older, children 23 months or younger, and pregnant women.⁵ Influenza vaccination status was recorded.

Interventions

Hutterite colonies were randomized to receive either immunization with inactivated seasonal influenza vaccine recommended for the 2008-2009 influenza season (A/Brisbane/59/2007 [H1N1]-like virus, A/Brisbane/10/2007 [H3N2]-like virus, B/Florida/4/2006-like virus; Vaxigrip, Sanofi Pasteur, Lyon, France) or immunization with hepatitis A vaccine (Avaxim-Pediatric, Sanofi Pasteur) as the control. This vaccine was selected as the control because it is well tolerated and provides a potential health benefit given reported outbreaks of hepatitis A on Hutterite colonies.

Vaccines

Healthy children and adolescents in colonies randomized to the influenza vaccination received 0.5-mL dose of the study vaccine intramuscularly. Those younger than 9 years who were previously unvaccinated at the time of immunization received a second 0.5-mL dose of the influenza vaccine 4 weeks after the first vaccine pursuant to influenza immunization recommendations.^{5,25}

In colonies receiving the hepatitis A vaccine, healthy children and adolescents were immunized in a manner that mimicked the influenza immunization schedule to maintain blinding. That is, those younger than 9 years who were previously unvaccinated for influenza also received 2 injections 4 weeks apart. A 0.5-mL dose of the vaccine was administered intramuscularly initially followed 4 weeks later by a second 0.5-mL injection of sterile saline. To complete the hepatitis A immunization schedule, participants received a second 0.5-mL dose 12 months after the first vaccine. Participants 9 years or older received a dose of hepatitis A vaccine and another 12 months later, at the same time as those in the influenza vaccine group received the study influenza vaccine.

All participants or their parents provided written informed consent. Children and adolescents between the ages of 7 and 15 years provided written assent. Vaccine administration start dates ranged from October 30, 2008, for colonies in Alberta to November 13, 2008, for colonies in Manitoba.

Blinding and Allocation

A statistician independent of the study assigned colonies at random, using a standard computer pseudorandom number generator, within each of the 7 health regions in which the colonies were located. Allocation was made in a 1:1 ratio. For each stratum (health region), random permutations were generated. Colonies within these strata were randomized to one of the treatment groups. To reduce the possibility of enrollment bias, the allocation of intervention or control status to communities occurred after study participants (ie, both vaccinated and nonrecipient colony members) were enrolled in the study.

Arrangements for shipment of vaccines were made by an intermediary clinical trials research organization that received the randomization code from the statistician. Because the influenza vaccine was provided in multidose vials and the hepatitis A in single-dose vials, the nursing teams used to vaccinate children differed from the team that assessed outcomes. Vaccination nurses used the communal dining room on the Hutterite colony as the set up area and administered the vaccines in a separate room. Surveillance nurses, who assessed outcomes, were not involved in the immunization process and were blind to allocation status. Investigators, study coordinators, study monitors, trial statistician, and the data and safety monitoring board were blinded.

Follow-up

Vaccinated children and nonrecipients of study vaccine were assessed for signs and symptoms of influenza over the follow-up period, defined by the start date (>1 laboratory-confirmed in-

fluenza case in 2 consecutive weeks from sentinel sites) and stop date (no laboratory-confirmed influenza cases for 2 consecutive weeks on colonies in the health region). This period extended from December 28, 2008, until June 23, 2009. Surveillance was started at least 2 weeks after the last child in the health region's study colonies had been immunized.

Research nurses assessed all study participants twice weekly using a standardized checklist of self-reported symptoms or signs from study participants or parents. One representative from each household (eg, the mother) was designated to complete the checklist for all family members and provide this when the research nurse made a site visit. The nurse would review the checklist. If anyone reported new symptoms, the nurse interviewed the study participant to confirm their symptoms and date of onset and to obtain nasopharyngeal specimens if 2 or more of the following symptoms were present: fever ($\geq 38^{\circ}\text{C}$), cough, nasal congestion, sore throat, headache, sinus problems, muscle aches, fatigue, ear ache or infection, or chills. Research nurses would also contact the household representative if the self-reported checklists were incomplete to follow-up on missing data. We purchased identical thermometers for all study participants and provided instruction on thermometer use.

Outcomes

The primary outcome of this study was laboratory-confirmed influenza A and B in nonrecipients of study vaccine. Influenza was confirmed in participants—those who did or did not receive the vaccine—with at least 2 symptoms by detection of viral RNA in respiratory samples using the Centers for Disease Control and Prevention Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel, which targets the matrix gene for influenza A and nonstructural gene for influenza B.²⁶ Influenza was confirmed with real-time reverse transcriptase polymerase chain reaction (RT-PCR) in study par-

participants, including study vaccinated children and adolescents and nonrecipients of study vaccine at high risk of complications. Influenza titers to the seasonal subtypes determined by the hemagglutination inhibition assay in nonrecipients were also obtained. Infection was defined by a 4-fold or more increase in titer between baseline and postseason serum samples using turkey erythrocytes and the antigens circulating (A/Brisbane/59/2007 [H1N1]-like virus, A/Brisbane/10/2007 [H3N2]-like virus, B/Brisbane/60/2008-like virus).²⁵

We also assessed physician visits for respiratory illness, influenzalike illness (defined as temperature $\geq 38.0^{\circ}\text{C}$

and cough),²⁷ any school or work related absenteeism, physician-diagnosed otitis media (children ≤ 5 years), courses of antimicrobial prescriptions, lower respiratory tract infection or pneumonia, hospitalization for lower respiratory tract infection or pneumonia, deaths due to lower respiratory infection or pneumonia, and deaths due to all causes.

Adverse Reactions

All study vaccinated children and adolescents 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

Based on a pilot study conducted in Hutterite colonies, we assumed that the influenza attack rate in the control group would be from approximately 8% to 10% and that the intracluster correlation coefficient could range from 0.01 to 0.03. We calculated that 2 groups, each with approximately 1200 participants and 23 clusters, would be sufficient to detect a risk reduction of at least 50% with a power of 80% at a 2-sided significance level of .05.

We used generalized estimating equations to adjust for membership in the randomized clusters with the logit-link function for dichotomous variables.²⁸ For the analysis of vaccine protectiveness, we used a Cox proportional hazards regression model, using robust sandwich variance estimates to account for the effect of clustering.²⁹ We conducted an adjusted analysis for which a baseline covariate for influenza immunization of nonrecipients was included. To avoid lack of independence associated with counting multiple outcomes, each specific outcome in a study participant was only counted once in the analysis. If study vaccine children wished to be vaccinated with a study vaccine that differed from that to which they had been assigned, their data were analyzed according to the vaccine to which they had been allocated.

All *P* values and 95% confidence intervals (CIs) were calculated with 2-tailed tests. Differences with *P* < .05 for 2-tailed tests were considered significant. The protective effectiveness of the vaccine was estimated using the hazard ratio (HR) [(1-HR) \times 100]. Statistical analyses were conducted using SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Participants

One hundred eighty-seven colonies in Alberta, Manitoba, and Saskatchewan were approached about the study. Of

Table 1. Baseline Characteristics of All Study Participants and Colony Characteristics^a

Variable	Influenza Vaccine		24 Hepatitis A Vaccine Colonies (n = 1500)
	25 Colonies (n = 1895)	22 Colonies (n = 1773)	
Age, mean (SD), y	26.1 (20.0)	25.9 (19.9)	26.0 (20.0)
Age groups, y, No. (%)			
<3	100 (5.3)	96 (5.4)	86 (5.7)
3-15	672 (35.5)	633 (35.7)	553 (36.9)
16-49	852 (45.0)	793 (44.7)	650 (43.3)
50-64	177 (9.3)	166 (9.4)	136 (9.1)
>64	94 (5.0)	85 (4.8)	75 (5.0)
Female sex, No. (%)	1077 (56.8)	1010 (60.0)	848 (56.5)
Vaccinated against influenza, No. (%) ^b	172 (12.4)	172 (9.7)	122 (11.6)
≥ 1 Coexisting condition, No. (%)	176 (8.1)	170 (9.6)	133 (7.2)
Asthma	70 (3.7)	69 (3.9)	45 (3.0)
Congestive heart failure	8 (0.4)	8 (0.5)	4 (0.3)
Blood disorders	15 (0.8)	15 (0.8)	11 (0.7)
Compromised management of respiratory secretions	8 (0.4)	8 (0.4)	6 (0.4)
Diabetes	46 (2.4)	42 (2.4)	40 (2.7)
Immunocompromised ^c	13 (0.7)	12 (0.7)	13 (0.9)
Pregnancy ^d	31/451 (6.9)	31/421 (7.4)	23/354 (6.5)
Other ^e	3 (0.2)	3 (0.2)	3 (0.2)
Clusters, mean (SD), No.			
All residents per colony	86.0 (22.9)	89.7 (22.7)	76.6 (24.6)
Enrolled participants per colony	75.8 (25.4)	80.6 (21.7)	62.5 (25.6)
Households per colony	21.1 (9.0)	22.2 (8.4)	18.3 (7.0)
Age 3-15 y given study vaccine	21.0 (8.7)	22.8 (7.6)	18.5 (8.7)
Age <2 y	3.5 (2.3)	3.7 (2.3)	3.1 (1.6)
Age ≥ 65 , No.	4.3 (2.3)	4.3 (2.2)	4.4 (2.8)
Total at high risk of complications	16.0 (6.5)	16.4 (6.5)	14.0 (7.6)

^aPercentages may not sum to 100 due to rounding.

^bThis refers to individuals with high-risk conditions who received influenza vaccine at baseline. The denominator excludes children who were immunized as part of the intervention.

^cSolid organ tumor (n = 17), lymphoma (n = 1), immunosuppressive agents (n = 3), autoimmune disorders (n = 5).

^dFrequency of pregnant women is calculated among women of child bearing age: 16 to 45 years.

^eThere was 1 participant with liver disease, 1 with kidney disease, and 1 with chronic obstructive lung disease in each study group.

these, 49 (26.2%) met eligibility criteria and agreed to participate in the study (Figure 1). After being randomized but prior to immunization and follow-up, 3 of 49 colonies (each in a different health region) withdrew from the study. Therefore, 46 colonies, 22 in the influenza group and 24 in the hepatitis A group were followed up (Figure 1). Thirty-eight of 409 families (9.3%) in the 22 influenza vaccine colonies and 34 of 510 families (6.7%) in the 24 hepatitis A colonies, refused to participate. Of the 3 colonies that dropped out after randomization, 67 of the members (54.9%) were female; 5 (4.1%) were younger than 3 years, 38 (31.4%) were between 3 and 15 years, 59 (48.8%) were between 16 and 49 years, 11 (9.1%) were between 50 and 64 years, and 9 (7.4%) were older than 64 years.

Characteristics of the colonies were similar in the 2 groups (TABLE 1). There were 1271 nonrecipients in the influenza vaccine colonies and 1055 nonrecipients in the hepatitis vaccine colonies. Of those vaccinated, 502 were in the influenza group and 445 were in the hepatitis A group. The mean vaccine coverage among healthy children (study vaccinated children/total number of healthy children aged 3 to 15 years) of clusters assigned to the influenza vaccine was 83% (range, 53%-100%). This was similar to the mean vaccine coverage among colonies assigned to hepatitis A vaccine, 79% (range, 50%-100%). Of the 294 nonrecipients (12.6%) who received influenza vaccination outside of the study, 24 (8.2%) were younger than 3 years, 2 (0.7%) were between the ages of 3 and 15 years (both of whom had asthma), and the 268 (91.2%) were adolescents and adults older than 15 years.

Outcomes

Laboratory-confirmed influenza was detected in 119 nonrecipients: 39 (3.1%) in the colonies assigned to influenza immunization (23, influenza A and 16, influenza B by RT-PCR) and 80 (7.6%; 60, influenza A and 20 influenza B by PCR) in colonies assigned to hepatitis A. The

Table 2. Protective Effectiveness on Nonrecipients of Immunizing Children and Adolescents With Influenza Vaccine

Study Group	Nonrecipients in Vaccine Colony		Protective Effectiveness of Influenza Vaccine (95% CI), %	P Value
	Influenza (n = 1271)	Hepatitis (n = 1055)		
Influenza detected by PCR, No. (%)	39 (3.1)	80 (7.6)		
Person-day of follow-up, No. (%)	182 866	151 902		
No. of cases/10 000 person-days	2.13	5.27	Simple, 61 (8-83) ^a	.03
			Adjusted, 61 (8-83) ^b	.03
Vaccine Tested by HAI^c			Relative Risk (95% CI)	
No. of nonrecipients	714	603		
≥4-Fold increase in serum titers, No. (%)				
A/Brisbane/59/2007, H1N1	66 (9.2)	81 (13.4)	Simple, 0.59 (0.33-1.01) ^d	.06
A/Brisbane/10/2007, H3N2	256 (35.9)	259 (42.3)	Simple, 0.74 (0.47-1.10) ^d	.15
B/Brisbane/60/2008	24 (3.4)	38 (6.3)	Simple, 0.54 (0.29-1.00) ^d	.05

Abbreviations: CI, confidence interval; HAI, hemagglutination inhibition titers; PCR, polymerase chain reaction.
^aA robust sandwich variance estimator was used with Cox proportional hazards to adjust for membership in the randomized colonies.
^bProtective effectiveness was adjusted for baseline influenza vaccination in all participants outside of those immunized as part of the study, such as those at high risk for complications of influenza.
^cNonrecipients of study vaccine who were vaccinated at baseline were not included because of difficulty in interpretation.
^dGeneralized estimating equations were used to adjust for membership in the randomized clusters with the logit-link function for dichotomous variables.

Table 3. Protective Effectiveness of Immunizing Children and Adolescents With Influenza Vaccine on All Participants, Healthy Children and Adolescents, and Those at High Risk of Complications

Study Group	Vaccine Colony		Protective Effectiveness of Influenza Vaccine (95% CI), % ^a	P Value
	Influenza	Hepatitis A		
No. of all participants	1773	1500		
Participants with influenza detected by RT-PCR, No. (%) ^a	80 (4.5)	159 (10.6)		
Person-days of follow up, No.	253 243	210 856		
Incidence of influenza, No. of cases/10 000 person-days	3.16	7.54	Simple, 59 (5 to 82) ^b	.04
			Adjusted, 59 (4 to 82) ^c	
Subgroups				
Healthy participants who received vaccine, No.	502	445		
Influenza detected by PCR, No. (%)	41 (8.2)	79 (17.8)		
Person-days of follow up, No.	70 377	58 954		
Incidence of influenza, No. of cases/10 000 person-days	5.83	13.40	Simple, 55 (CI -21 to 84) ^b	.11
High risk of complications, No.	363	321		
Participants with influenza detected by PCR, No. (%)	16 (4.41)	27 (8.41)		
Person-days of follow up, No.	52 303	46 693		
Incidence of influenza, No. of cases/10 000 person-days	3.06	5.78	Simple, 49 (-27 to 80) ^b	.15
			Adjusted, 49 (-27 to 80) ^c	.15

Abbreviations: CI confidence interval; RT-PCR, real-time polymerase chain reaction.
^aNegative CIs for vaccine protective effectiveness refer to an increase in risk associated with vaccine.
^bA robust sandwich variance estimator was used with Cox proportional hazards to adjust for membership in the randomized colony.
^cProtective effectiveness was adjusted for baseline influenza vaccination in all participants outside of those immunized as part of the study, such as those at high risk of complications of influenza.

level of indirect vaccine protective-ness was 61% (95% CI, 8%-83%; $P = .03$) in an adjusted model (TABLE 2). The intracluster correlation coefficient was 0.004. Of the 1317 nonrecipients (56.6%) from whom serum specimens were obtained, fewer participants in influenza immunized colonies showed a 4-fold or more increase in serum hemagglutination titers to each of the 3 seasonal vaccine strains; however, differences were not statistically significant (Table 2).

The overall influenza vaccine protective effectiveness measured by RT-PCR to diagnose influenza among all study participants was 59% (95% CI, 5%-82%; $P = .04$) in the adjusted analysis (TABLE 3). Protective effectiveness for healthy children and adolescents was 55% (95% CI, -21% to 84%) and 49% (95% CI, -27% to 80%) for participants of all ages at high risk of complications. Of the 80 PCR-confirmed influenza cases from influenza vaccine colonies, 72 (90%) were outbreak-related (defined by ≥ 2 specimens that tested positive for influenza within 5 days). Of the 159 from hepatitis vaccine colonies, 158 (99%) were outbreak-related (FIGURE 2). There were 6 outbreaks in influenza-vaccine colonies (median cases, 12; range, 3-16) and 13 outbreaks in hepatitis A vaccine

colonies (median cases, 9; range, 4-26). In addition to these outbreaks of seasonal influenza, we detected 15 cases of 2009 H1N1 from May 22 to June 4, 2009. These were all observed in an outbreak on 1 influenza vaccine colony.

In adjusted models, the HR was 0.58 (95% CI, 0.34-0.99; $P = .046$) for antimicrobial prescriptions, 0.63 (95% CI, 0.37-1.06; $P = .08$) for physician visits for respiratory illness, 0.57 (95% CI, 0.28-1.16; $P = .12$) for influenzalike illness, and 0.41 (95% CI, 0.12-1.42; $P = .159$) for otitis media. The relative risk of absenteeism was 0.56 (95% CI, 0.31-1.20; $P = .14$). Three participants were hospitalized for lower respiratory infection in each study group; there were no other cases of lower respiratory infection or pneumonia and no deaths due to these infections. Two deaths occurred, 1 due to myocardial infarction and 1 due to cancer; both occurred in study colonies prior to circulation of influenza.

Adverse Events

When comparing 502 healthy children and adolescents who received influenza vaccine with 445 of those who received hepatitis A vaccine, there were no significant differences respectively in children who experienced pain at the injection site (43 [8.6%] vs 29 [6.5%],

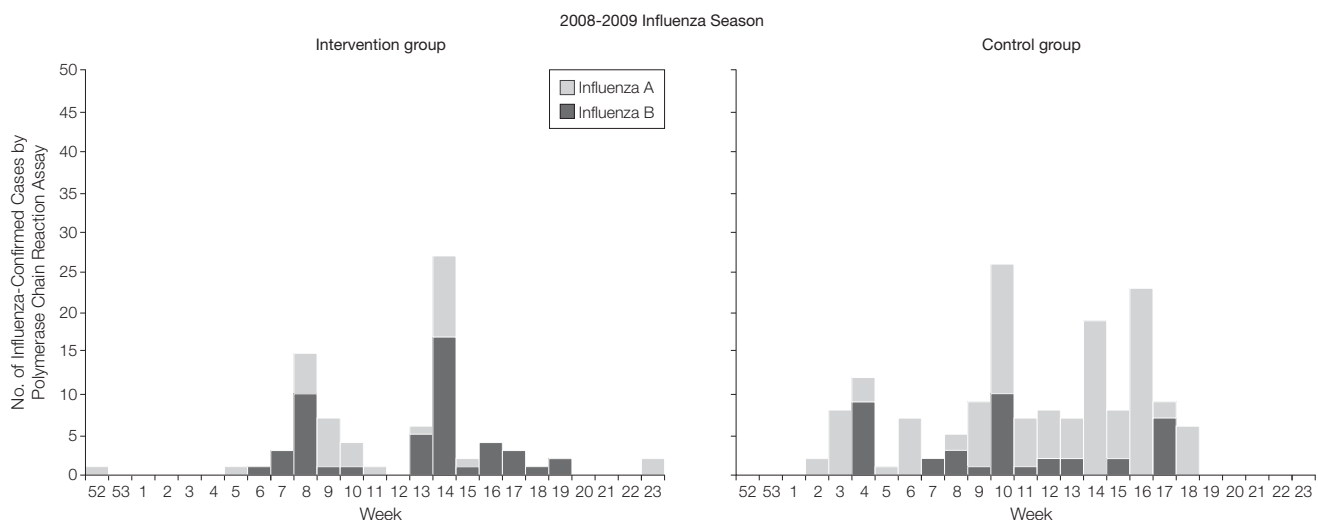
$P = .24$), redness (1 [0.20%] vs 6 [1.3%], $P = .06$), swelling (6 [1.1%] vs 2 [0.45%], $P = .21$), chills (3 [0.60%] vs 1 [0.22%], $P = .62$), and limitation of movement (18 [3.6%] vs 8 [1.8%], $P = .09$). However, more children and adolescents vaccinated with influenza vaccine reported muscle ache (11 [2.2%] vs 6 [1.3%], $P = .03$).

COMMENT

Immunization of children and adolescents aged 3 to 15 years with the trivalent influenza vaccine formulated for the 2008-2009 influenza season conferred 61% indirect protection against influenza among persons who did not receive the study vaccine. The protection conferred to all study participants was similar. Our data suggest that a significant herd immunity effect can be achieved when the uptake of vaccine is approximately 80% in clusters in which children and adolescents aged 3 to 15 years are immunized.

The effect of the indirect protection of immunizing children and adolescents on study participants was substantial, with similar results when adjusting for baseline immunization, which was low (12%) in participants other than those vaccinated as part of the intervention. A match between vaccine influenza A strains (A/Brisbane/

Figure 2. Epidemic Curve of Influenza A and B in Enrolled Colonies



59/2007 [H1N1]-like virus, A/Brisbane/10/2007 [H3N2]-like virus) and those circulating in the study colonies,²⁵ the relatively large number of children in the colonies, and the comprehensive surveillance likely facilitated this effect. Although there was a mismatch between vaccine influenza B strain (B/Florida) and the circulating strain (B/Brisbane 60/2008), the findings of the serological analysis were of borderline significance, even though they did not reach statistical significance. Although the vaccination of children is the most likely explanation for the effect observed, an alternate explanation is the overall immunization rate of 38% in the influenza vaccine colonies compared with 8% in hepatitis A vaccine colonies. One possible explanation for the lack of significant differences in serologic outcomes is that the influenza vaccination may have attenuated infection that is rendered it subclinical but without preventing infection.

The substantial indirect benefit found in this setting validates observational studies and modeling studies, offering rigorous scientific proof about the ability of inactivated vaccine to induce herd immunity. The reduction in cases of influenza appeared to be primarily due to the prevention of outbreaks, with about half as many observed in colonies receiving the influenza vaccine colonies as those receiving the hepatitis A vaccine. The efficacy of the intervention in preventing influenza in the relatively young adult population of this study is comparable with estimates of inactivated vaccine efficacy.³⁰ Although there were relatively few elderly individuals in this population, the protective effect is likely comparable with or greater than what can be achieved by direct immunization.³¹ Importantly, the vaccine was generally well tolerated, and there were no serious adverse events in the young children immunized.

The unique nature of our study population allowed for the clear demonstration of community benefit, a distinct advantage over inferences made on the basis of household contact stud-

ies or nonrandomized 2-community comparisons.^{12-14,16-18} The relatively large number of outbreaks that we observed during the study demonstrates that there is significant influenza activity in Hutterite colonies. Their relative isolation allowed us to better observe the effect of immunizing children compared with a population-dense metropolitan community with inherently more confounding factors such as travel to and from the community and variability in exposures. Considering for instance the rapid spread of influenza A(H1N1) in the 2009 pandemic, understanding whether influenza transmission can be prevented or reduced by immunizing children is of high priority so that groups such as pregnant women and aboriginal populations who are at high risk of complications may potentially be indirectly protected.^{32,33}

We acknowledge that the study had limited power to detect an effect in subgroups, including participants at high risk of complications and among vaccinated children and adolescents, as well as for other secondary outcomes. Nevertheless, the point estimates of the effect were consistent, all demonstrating protective effects with influenza immunization of children. The fact that children between the ages of 24 and 36 months were not immunized as part of the intervention is a limitation of the study. We acknowledge that this may have resulted in an underestimate of the effect size that could have been achieved. Another study limitation is that 3 colonies that were randomized dropped out of the study. However, we believe this was independent of the outcome. These 3 colonies dropped out the study because they were too busy, they withdrew prior to being immunized (so that no vaccine-related adverse reaction would have taken place), and they were blind to the intervention. Moreover, the characteristics of the residents of these colonies are similar to the 46 colonies that remained in the trial.

Our findings offer experimental proof to support selective influenza immunization of school aged children with inactivated influenza vaccine to inter-

rupt influenza transmission. Particularly, if there are constraints in quantity and delivery of vaccine, it may be advantageous to selectively immunize children in order to reduce community transmission of influenza.

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Author Contributions: Dr Loeb had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

- Langley JM, Faughnan ME. Prevention of influenza in the general population. *CMAJ*. 2004;171(10):1213-1222.
- Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;292(11):1333-1340.
- Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. 2003;289(2):179-186.
- Dushoff J, Plotkin JB, Viboud C, Earn DJD, Simonsen L. Mortality due to influenza in the United States—an annualized regression approach using multiple-cause mortality data. *Am J Epidemiol*. 2006;163(2):181-187.
- Palese P. Influenza: old and new threats. *Nat Med*. 2004;10(12)(suppl):S82-S87.
- Fiore AE, Shay DK, Broder K, et al; Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009 [published correction in *MMWR Recomm Rep*. 2009;58(32):896-897]. *MMWR Recomm Rep*. 2009;58(RR-8):1-52.
- Medlock J, Galvani AP. Optimizing influenza vaccine distribution. *Science*. 2009;325(5948):1705-1708.
- Fox JP, Hall CE, Cooney MK, Foy HM. Influenza virus infections in Seattle families, 1975-1979: study design, methods and the occurrence of infections by time and age. *Am J Epidemiol*. 1982;116(2):212-227.
- Monto AS, Koopman JS, Longini IM Jr. Tecumseh study of illness, XIII: influenza infection and disease, 1976-1981. *Am J Epidemiol*. 1985;121(6):811-822.
- Brownstein JS, Kleinman KP, Mandl KD. Identifying pediatric age groups for influenza vaccination using a real-time regional surveillance system. *Am J Epidemiol*. 2005;162(7):686-693.
- Yang Y, Sugimoto JD, Halloran ME, et al. Transmissibility and control of pandemic influenza A (H1N1) virus. *Science*. 2009;326(5953):729-733.
- Monto AS, Davenport FM, Napier JA, Francis T Jr. Modification of an outbreak of influenza in Tecumseh Michigan, by vaccination of schoolchildren. *J Infect Dis*. 1970;122(1):16-25.
- Espósito S, Marchisio P, Cavagna R, et al. Effectiveness of influenza vaccination of children with recurrent respiratory tract infections in reducing respiratory-related morbidity within the households. *Vaccine*. 2003;21(23):3162-3168.
- Piedra PA, Gaglani MJ, Kozinets CA, et al. Herd immunity in adults against influenza-like illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. *Vaccine*. 2005;23(13):1540-1548.
- Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating school children against influenza. *N Engl J Med*. 2001;344(12):889-896.
- Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. *JAMA*. 2000;284(13):1677-1682.
- Rudenko LG, Slepishkin AN, Monto AS, et al. Efficacy of live attenuated and inactivated influenza vaccines in schoolchildren and their unvaccinated contacts in Novgorod, Russia. *J Infect Dis*. 1993;168(4):881-887.
- King JC Jr, Stoddard JJ, Gaglani MJ, et al. Effectiveness of school-based influenza vaccination. *N Engl J Med*. 2006;355(24):2523-2532.
- Jordon R, Connock M, Albon E, et al. Universal vaccination of children against influenza: are there indirect benefits to the community? a systematic review of the evidence. *Vaccine*. 2006;24(8):1047-1062.
- Longini IM Jr, Koopman JS, Monto AS, Fox JP. Estimating household and community transmission parameters for influenza. *Am J Epidemiol*. 1982;115(5):736-751.
- Longini IM, Ackerman E, Elveback LR. An optimization model for influenza A epidemics. *Math Biosci*. 1978;38:141-157.
- Halloran ME, Longini IM, Cowart DM, Nizam A. Community interventions and the epidemic prevention potential. *Vaccine*. 2002;20(27-28):3254-3262.
- Weycker D, Edelsberg J, Halloran ME, et al. Population-wide benefits of routine vaccination of children against influenza. *Vaccine*. 2005;23(10):1284-1293.
- Dushoff J, Plotkin J, Viboud C, Simonsen L, Miller M, Loeb M, Earn DJD. Vaccinating to protect a vulnerable subpopulation. *PLoS Med*. 2007;4(5):e174.
- Public Health Agency of Canada. Flu Watch May 31, 2009 to June 6, 2009 [Web page]. http://www.phac-aspc.gc.ca/fluwatch/08-09/w22_09/index-eng.php. Updated June 12, 2009. Accessed October 4, 2009.
- Dawood FS, Jain S, Finelli L, et al; Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans [published correction appears in *N Engl J Med*. 2009;361(1):102]. *N Engl J Med*. 2009;360(25):2605-2615.
- Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? *JAMA*. 2005;293(8):987-997.
- Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13-22.
- Wei LJ, Lin DY, Weissfeld L. Regression-analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc*. 1989;84:1065-1073.
- Jefferson TO, Rivetti D, Di Pietrantonj C, Rivetti A, Demicheli V. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev*. 2007;(2):CD001269. doi:10.1002/14651858.CD001269.pub3.
- Jefferson T, Di Pietrantonj C. Inactivated influenza vaccines in the elderly—are you sure? *Lancet*. 2007;370(9594):1199-1200.
- Jamieson DJ, Honein MA, Rasmussen SA, et al; Novel Influenza A (H1N1) Pregnancy Working Group. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet*. 2009;374(9688):451-458.
- Kermode-Scott B. Canada has world's highest rate of confirmed cases of A/H1N1, with Aboriginal people hardest hit. *BMJ*. 2009;339:b2746. doi:10.1136/bmj.b2746.