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. Selectively vaccinating youngsters against influenza may interrupt virus transmission and protect those not immunized.8-10 Preferential immunization of healthy youngsters has been investigated in school-based trials 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 influenza vaccine to achieve a herd effect. A systematic review concluded that although evidence exists that vaccination...
Figure 1. Flow Diagram of Trial

- **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.

**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. 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.3,25

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 influenza 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 (≥38°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).

We also assessed physician visits for respiratory illness, influenza-like illness (defined as temperature ≥38.0°C and cough), 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. For the analysis of vaccine protective effectiveness, we used a Cox proportional hazards regression model, using robust sandwich variance estimates to account for the effect of clustering. 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) × 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
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, 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 main 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 A                                      | Hepatitis A                                      |                                               |
| Influenza detected by PCR, No. (%)               | 39 (2.1)                                         | 80 (7.6)                                      |       |
| Person-day of follow-up, No. (%)                 | 182 866                                          | 151 902                                       |       |
| No. of cases/10 000 person-days                  | 2.13                                             | 5.27                                          | .03   |
| Relative Risk (95% CI)                           | Simple, 61 (8-83)b                               | Adjusted, 61 (8-83)b                          | .03   |

Abbreviations: CI, confidence interval; HAI, hemagglutination inhibition titers; RT-PCR, real-time polymerase chain reaction.

#### 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

<table>
<thead>
<tr>
<th>Vaccine Colony</th>
<th>Study Group</th>
<th>Protective Effectiveness of Influenza Vaccine (95% CI), %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of all participants</td>
<td>1773</td>
<td>1500</td>
<td></td>
</tr>
<tr>
<td>Participants with influenza detected by RT-PCR, No. (%)</td>
<td>80 (4.5)</td>
<td>159 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Person-days of follow up, No.</td>
<td>253 243</td>
<td>210 856</td>
<td></td>
</tr>
<tr>
<td>Incidence of influenza, No. of cases/10 000 person-days</td>
<td>3.16</td>
<td>7.54</td>
<td>.04</td>
</tr>
<tr>
<td>Simple, 59 (5 to 82)b</td>
<td>Adjusted, 59 (4 to 82)c</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 | .11   |
| Simple, 55 (CI 21 to 84)b |       |        |        |

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 | .15   |
| Simple, 49 (27 to 80)b | Adjusted, 49 (27 to 80)c |       |        |

Abbreviations: CI, confidence interval; RT-PCR, real-time polymerase chain reaction.

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level of indirect vaccine protective-ness was 61% (95% CI, 5%-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, 5%-84%) and 49% (95% CI, 27%-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 influenza-like 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/
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 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 studies 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 of 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 empirical proof to support selective influenza immunization of school aged children with inactivated influenza vaccine to interrupt 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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