Systematic Review and Meta-analysis of Indirect Protection Afforded by Vaccinating Children Against Seasonal Influenza: Implications for Policy

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Background. Universal childhood vaccination is a potential solution to reduce seasonal influenza burden.

Methods. We reviewed systematically the literature on “herd”/indirect protection from vaccinating children aged 6 months to 17 years against influenza.

Results. Of 30 studies included, 14 (including 1 cluster randomized controlled trial [cRCT]) used live attenuated influenza vaccine, 11 (7 cRCTs) used inactivated influenza vaccine, and 5 (1 cRCT) compared both vaccine types. Twenty of 30 studies reported statistically significant indirect protection effectiveness (IPE) with point estimates ranging from 4% to 66%. Meta-regression suggests that studies with high quality and/or sufficiently large sample size are more likely to report significant IPE. In meta-analyses of 6 cRCTs with full randomization (rated as moderate quality overall), significant IPE was found in 1 cRCT in closely connected communities where school-aged children were vaccinated: 60% (95% confidence interval [CI], 41%–72%; I² = 0%; N = 2326) against laboratory-confirmed influenza, and 3 household cRCTs in which preschool-aged children were vaccinated: 22% (95% CI, 1%–38%; I² = 0%; N = 1903) against acute respiratory infections or influenza-like illness. Significant IPE was also reported in a large-scale cRCT (N = 8510) that was not fully randomized, and 3 ecological studies (N > 10000) of moderate quality including 36% reduction in influenza-related mortality among the elderly in a Japanese school-based program. Data on IPE in other settings are heterogeneous and lacked power to draw a firm conclusion.

Conclusions. The available evidence suggests that influenza vaccination of children confers indirect protection in some but not all settings. Robust, large-scaled studies are required to better quantify the indirect protection from vaccinating children for different settings/endpoints.

Keywords. seasonal influenza; influenza vaccine; indirect protection; children; immunization policy.

Influenza is an important cause of excess morbidity and mortality with substantial economic costs [1]. The World Health Organization (WHO) recommends annual vaccination against influenza with inactivated influenza vaccines (IIVs) or live attenuated influenza vaccines (LAIVs) [1]. In most countries where influenza vaccination programs exist [2–5], the target population is primarily people with high risk of complications such as the chronically ill or frail, paradoxically those in whom the vaccine is less effective [1].

Children have the highest influenza attack rate and prolonged viral shedding [6]. Routine childhood influenza immunization protects children directly and is postulated to reduce influenza transmission within the community, which indirectly protects susceptible contacts [7].

Introducing new vaccines into national immunization programs requires complex pragmatic and cost-effectiveness considerations [8, 9]. One key consideration is potential indirect protection. We conducted a systematic review to determine whether and to what extent vaccinating children aged 6 months to 17 years against influenza protects other individuals, either in the same community, schools, or household.

METHODS

We followed a prospective protocol (PROSPERO CRD42012003449 [10]) and reported according to the Preferred Reporting Items for Systematic Reviews and

Search Strategy and Selection Criteria

The literature search was conducted by a medical librarian (C. K.) in multiple key biomedical bibliographic databases; the last search was done on 10 August 2016. Hand searching or personal communication with authors, where necessary, was performed by J. K. Y. A detailed search strategy is in Supplementary Appendix 2. Three authors (J. K. Y., A. H., M. G.) independently reviewed all titles and abstracts from the search results.

Inclusion and Exclusion Criteria

We included original research studies conducted in any context and of any study design where the intervention was immunization of children (6 months to 17 years of age) against influenza using seasonal LAIV and/or IV of any valency, ie, monovalent, bivalent, trivalent, or quadrivalent. We included observational studies because many relevant studies were likely to have observational design.

Among randomized or nonrandomized interventional studies, the comparator included either no vaccine, a placebo, or an alternative (noninfluenza) vaccine. Studies were included if outcome measures related to influenza infection after intervention periods were measured among the people living in the same community in which the vaccinated children dwell (“wider community”), students in the same school with the vaccinated children (“school students”), or members of the same household of the vaccinated children (“household contacts”). In anticipation of a wide range of endpoints used in eligible studies, we predefined and examined 6 endpoints: laboratory-confirmed influenza (LCI), influenza-like illness (ILI), acute respiratory tract infection (ARTI), medically attended acute respiratory infection, influenza and pneumonia hospitalization, and influenza mortality. We considered LCI as the primary endpoint with others as secondary measures. We did not extract and examine strain-specific data.

Based on the unit of random assignment, we categorized cluster randomized controlled trials (cRCTs) into community, school, or household cRCTs. No restriction on the language or year of publication was applied. Mathematical modeling studies and economic evaluations that did not provide primary measures of indirect protection effect were excluded.

Study Selection and Data Extraction

Studies with uncertain eligibility had the full text reviewed by coauthors. Any disagreement regarding eligibility was resolved by discussion among coauthors.

Quality Appraisal

Three authors (J. K. Y., A. H., M. G.) independently assessed the quality of the body of evidence following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [12]. Results of risk of bias assessments, using the Cochrane approach [13], were also incorporated under the GRADE framework. Any disagreements regarding quality appraisal were resolved by the review supervisor (K. M.).

Statistical Analysis

We obtained or calculated indirect protection effectiveness (IPE) from studies where relevant data could be extracted. The formula to calculate IPE was [1 − relative risk] or [1 − incidence ratio], expressed as a percentage [14, 15].

For cRCTs where we were able to extract relevant data, we performed meta-analyses to generate pooled estimate of IPE by settings according to the categories of vaccinees and contacts and also the types of vaccine and study design. We used Review Manager software version 5.3 (RevMan, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark, 2014), and chose the Mantel-Haenszel method and random-effects model in anticipation of high heterogeneity among included studies; we also compared these pooled estimates with those generated from fixed-effects models [16]. The assessment of publication bias, including generating funnel plots and using the Begg and Mazumdar adjusted rank correlation test [17], was conducted for meta-analysis with ≥10 studies. For this assessment, we used Comprehensive Meta-Analysis software version 2.2.064 (Biostat, Englewood, New Jersey).

Heterogeneity, the variation among the results of individual studies beyond that expected from chance, was tested with the $I^2$ statistic for each overall estimate using RevMan. We considered heterogeneity to be mild if $I^2$ <30%, moderate if $I^2$ = 30%–50%, and notable if $I^2$ >50% [18, 19]. We performed a series of meta-regression analyses to explore the potential sources of heterogeneity using comprehensive meta-analysis. The covariates investigated included the type of cRCT (ie, community/school/household cRCT), the extent of randomization (fully randomized or not), location, publication year, disease endpoint (LCI or others), coverage in vaccinees, study sample size, the extent of predominant strain(s) matching those in the vaccine, the quality of individual cRCTs (<2 or ≥2 domains with high/unclear risk of bias according to the Cochrane approach [13]).

RESULTS

Study Selection and Characteristics

Of 4506 studies retrieved, 30 met our inclusion criteria (Figure 1) [20–49]. Nine studies were cRCTs [22, 25, 28, 29, 36, 41–44], 1 [28] of which was not fully randomized. In King et al [28], among the 28 participating (intervention/control) schools, 4 intervention schools were not randomly selected. Because this only covered a small proportion (14%) of participating schools and the authors stated that “similar results were obtained when the analysis of data from the questionnaires was restricted to the randomized schools,” we included this study as a cRCT but conducted subgroup analyses without including it. Table 1 and
Supplementary Appendix 3 summarized the characteristics and results of cRCTs and non-cRCT studies, respectively, stratified by settings. Thirteen studies reported on IPE with trivalent LAIV (LAIV3) [21, 24, 26–28, 33, 34, 39, 40, 45, 47–49]; another 11 studies used IIV (monovalent IIV1 [30] or trivalent IIV3 [20, 22, 23, 25, 29, 36, 37, 42–44]). Two studies [38, 41] used bivalent LAIV (LAIV2) and bivalent IIV (IIV2) in parallel, and 3 examined both LAIV3 and IIV3 [31, 35, 46]. Only 1 study [32] used quadrivalent LAIV (LAIV4). No study of quadrivalent IIV met the inclusion criteria. All 30 studies were conducted in high-income [20–22, 24–37, 39–49] or upper-middle-income [23, 38] economies. Only 3 studies provided information on power calculations underpinning examination of IPE from vaccinating children [29, 31, 49].

Quality Appraisal
Using the GRADE approach, the overall quality of 7 cRCTs in the meta-analysis [22, 25, 28, 29, 36, 41, 43] and 2 other cRCTs [42, 44] was rated as moderate (Supplementary Appendix 4). Results of risk of bias assessment for individual cRCTs are shown in Supplementary Appendix 5. There are 10 types of settings in the 21 non-cRCT studies; studies in 9 settings had either low or very low quality (Supplementary Appendix 3) except for 1 study (moderate quality), in which 3 ecological studies examined IPE to the wider community when 50%–85% of school-aged children were vaccinated with IIV [20, 23, 37].

Overall Results of All Studies
Statistically significant IPE was reported by 20 [20–39] of the 30 studies, with the point estimates ranging from 4% to 66% for various endpoints (Table 1; Figure 2; Appendices 3 and 4).

Meta-analysis and Meta-regression of CRCTs
Seven [22, 25, 28, 29, 36, 41, 43] of the 9 cRCTs [22, 25, 28, 29, 36, 41–44] provided relevant data for meta-analysis by settings. While statistically significant IPE was found in all the settings...
### Table 1. Summary of Study Characteristics and Results of Cluster Randomized Controlled Trials, by Category of Vaccinees, Category of Contacts of Vaccinees, Vaccine Type, and Study Design

| Category of Vaccinees | Category of Contacts of Vaccinees | Vaccine Type | Study Design | Study, First Author | Country, Duration, y | Vaccine coverage of Intervention Vaccine | Vaccine coverage of Control Arm | Vaccine Target Contacts | Comparable Group of Vaccine Target Contacts | Comparable Contacts | Vaccine Match | Outcome Measures | Profile of Vaccinees | Contacts of Vaccinees | Profile of Comparison Group | Main Results |
|-----------------------|----------------------------------|-------------|-------------|---------------------|----------------------|------------------------------------------|---------------------------------|-------------------------------|------------------------------------------|-------------------|---------------|-----------------|---------------------|----------------|----------------------|----------------------|----------------|
| **School-aged vaccines** |                                   |             |             |                     |                      |                                          |                                 |                               |                                          |                   |               |                  |                      |                 |                      |                      |                |
| Wider community       | Household contacts                | IIV         | School cRCT | King 2006 [28]      | USA, 1 y, 2004-05   | 47% NS                     | 0 (assumed) NS                     | Good mismatch                 | (1) anything or ILL: 100%        | (2) any fever plus cough or sore throat | 24 primary schools (age ≥5 y): 4 schools to grade 8 | All-age all adults in the households | Household members in control schools | Adjusted absolute difference: (1) 11% (95% CI, 8%–14%); (2) 4% (95% CI, 2%–5%) |
| Household contacts    | IIV                               | LAIV        | Household cRCT | Cowling 2010 [40]  | Hong Kong, 1 y, 2009 | 100% NS                     | 0 (assumed) NS                     | Good laboratory-confirmed influenza | Children at school 6-15 y         | All-age household contacts        | | | |
| Household contacts    | Both                              | IIV         | Household cRCT | Gruber 1990 [44]   | USA, 1 y, 1985-86   | 100% NS                     | 0 (assumed) NS                     | Poor culture or serologically confirmed influenza | Children at school or day care 3-18 y | All-age all family members | | | |
| **Pre-school-age vaccines** |                                   |             |             |                     |                      |                                          |                                 |                               |                                          |                   |               |                  |                      |                 |                      |                      |                |
| Household contacts    | IIV                               | Household   | Colombo 2001 [42]   | Italy, 1 y, 1995-96 | 100% NS                     | 0 (assumed) NS                     | NR influenza-like illness           | Children 1-6 y                     | All-age all household members  | Household members in control schools | | | |
| Household contacts    |                                    | LAIV        | Hurwitz 2000 [25]   | USA, 1 y, 1999-97   | 100% ~30% NS             | 0 (assumed) ~30% NS             | Respiratory illness: (1) any; (2) with fever; (3) temp >38°C | Children 2-5 y                     | All-age all household members  | Household members in control schools | Indirect protection against respiratory illness, (1) any: 16% (P = .1), (2) with fever: 42% (P = .04), (3) temp >38°C: 47% (P = .04) (1-sided P value) |
in the forest plot in Figure 3A, multivariate meta-regression found that the major sources of heterogeneity were study randomization (ie, whether fully randomized; coefficient = -0.559; \( P = .005 \)) and study sample size (ie, whether <1000 participants; coefficient = 0.708; \( P = .002 \)) (adjusted \( R^2 = 0.94 \)).

After excluding the study that was not fully randomized (Figure 3B) [28], IPE estimates remained significant in the members of closely connected communities where school-aged children were vaccinated (IPE, 60% [95% confidence interval [CI], 41%–72%] against LCI; 1 cRCT), and also household members of preschool-aged vaccinees (IPE, 22% [95% CI, 1%–38%] against ARTI/ILI; \( F = 0 \); 3 cRCTs). In multivariate meta-regression, study sample size was the only significant source of heterogeneity (coefficient = 0.709; \( P = .001 \); adjusted \( R^2 = 1.00 \)).

Meta-analyses using fixed-effects models revealed largely similar estimates compared with those from random-effects models (Supplementary Appendix 7). We did not assess setting-specific publication bias due to the small number of comparisons. When combining all the comparisons derived from the 7 cRCTs, no significant publication bias was found (Supplementary Appendix 7).

**Key Findings of Individual cRCTs**

One cRCT (highest quality) assessed IPE of vaccinating school-aged children with IIV3 (3–15 years old) among Hutterite colonies in rural Canada during 2008–2009 (Table 1) [29]. In the influenza vaccination colonies, 502 children (83%) were vaccinated and 1271 colony members were not. In the control arm, 445 children (79%) were given hepatitis A vaccine and 1055 colony members were not vaccinated. Among nonvaccinated subjects, 3% (39/1271) in the influenza vaccination colonies and 8% (80/1055) in the control colonies developed LCI (adjusted IPE, 61% [95% CI, 8%–83%]).

Four cRCTs [28, 41, 43, 44] examined IPE of vaccinating school-aged children among all-age household members. Only the largest study [28] (N = 8510) reported significant results (Table 1); this study used LAIV3 (moderate quality; conducted in 2004–2005 season with vaccine mismatched) and consisted of 11 intervention schools (3022 households) and 17 control schools (5488 households) across 4 US states. Compared with control schools, adult household contacts of intervention schools had significantly lower disease rate (absolute difference: 3.7% for fever/ILI; 10.8% for fever plus cough/sore throat; no IPE was reported). One small cRCT included 119 children (71 given IIV3; 48 received placebo) from 119 households and was conducted in 2008 in Hong Kong [43]. This study did not show significant IPE against laboratory-confirmed influenza. Similarly, another small cRCT (N = 191) from the United States did not show significant IPE among household contacts of schoolchildren receiving IIV3 [44]. The fourth cRCT was conducted among 192 preschool-aged children in the United States during 1996–1997; participants received LAIV2/IIV2/placebo
The study reported a nonsignificant IPE (5% [95% CI, –87% to 51%]) against LCI among household contacts.

The remaining 4 cRCTs addressed the IPE among all-age household contacts from IIV administration in preschool-aged children (Table 1) [22, 25, 36, 42]; significant IPE was shown in 3 studies [22, 25, 36]. In a cRCT conducted in Italy during 2000–2001 (unknown vaccine match) among children aged 6 months to 9 years with recurrent ARTI [22], IIV3 vaccination significantly reduced ARTIs among household contacts. Another cRCT by the same authors was conducted in the following influenza season (202 children received IIV3 and 101 got placebo) [36]; IPE in household contacts was 30% for ARTIs and 32% for medical visits associated with ARTI.

A US cRCT of IIV3 recruited daycare children during 1996–1997 [25]. The study reported 42% significantly fewer ILIs in unvaccinated household contacts (n = 120) of vaccinated children vs controls. One cRCT of IIV3, conducted among preschool-aged children aged 1–6 years (177 vaccinees only) during 2005–2006 (unknown vaccine match), did not report significant IPE [42].
Overall Results of Non-cRCT Studies

The data from 10 settings (based on categories of vaccinees/contact/vaccine/study design) derived from 21 non-cRCT studies with heterogeneous characteristics are inconclusive (Appendices 3 and 4). Only four of the 10 reports showed statistically significant results, including one with moderate quality (which consisted of three large-scale ecological studies [20, 23, 37]). Two ecological studies examined the national IIV3 program for school-aged children in Japan [20, 37]; one of them [20] (reappraisal of the prior one [37]) assessed age-specific influenza-related mortality in Japanese seniors (65–90 years old) during and after the program. Mortality data in the United States (prior to recommendation of school-based vaccination) were used as the control. The school-based vaccination program resulted in a 36% (95%
CI, 17%–51%) reduction of influenza-related mortality among Japanese elderly, with no reduction in the United States for the same period. The third ecological study was conducted during 2001–2002 in Moscow, which assessed the rates of ILI in children and the reduction of morbidity among noninstitutionalized elderly [23]. Coverage was 57%–72% of approximately 40,000 among the targeted children, compared with <1% of approximately 61,000 children in the 2 control regions. Significantly fewer ILIs were reported among the elderly in the intervention regions (0.07%) compared with the control regions (0.24%).

DISCUSSION

In our systematic review, studies with high quality and/or sufficiently large sample size support that influenza vaccination in children affords indirect protection to (1) members of closely connected communities against LCI, (2) household members against ARTI or ILI, and (3) the elderly in wider communities against influenza-related mortality. For other settings and/or disease endpoints, the current evidence is heterogeneous and has insufficient power to draw conclusions regarding the indirect protection of vaccinating children.

The available data of heterogeneous nature preclude a meaningful comparison of IPE between LAIV and IIV. Similar IPE of LAIV and IIV was seen in a recent cRCT including approximately 4,600 participants that directly compared LAIV3 with IIV3 among the Hutterite colonies in Canada during 2012–2015 [50]. That study found a nonsignificant hazard ratio of developing LCI (1.0 [95% CI, 0.9–1.2]) between unvaccinated colony members of LAIV and IIV clusters.

Our findings expand upon, but remain largely consistent with, a narrative review in 2005 which concluded that “overall results are suggestive of indirect protection” from vaccinating children [51]. Importantly, we have included 19 additional studies with primary data on indirect protection of influenza vaccination in children [20, 21, 23, 24, 26–29, 31, 32, 34, 35, 39, 43, 45–49], and have been able to perform meta-analyses. Several modeling studies in the United Kingdom and the United States also support our findings [52–55]. For example, a stochastic simulation model estimated that vaccinating 20% of children aged 6 months to 18 years in the United States would reduce influenza cases by 46% nationwide [55]. Despite variations in model design, parameters and assumptions across these modeling studies, the key elements to achieving indirect protection consistently appear to be good vaccine efficacy and relatively high coverage among targeted children.

Our systematic review was preregistered [10], conducted, and reported according to the PRISMA guidelines [11], with quality appraisal performed using a recognized approach [12]. However, there are some limitations of the currently available evidence. The overall quality of identified studies is relatively low, with many ecological studies and nonrandomized community-based trials.

We found substantial heterogeneity in the results across settings and among studies within each context. In addition, while it is intuitive to expect that a coverage “threshold” may be required to reduce virus transmission and thus confer indirect protection, the small number of cRCTs in the meta-regression and the heterogeneous nature of non-cRCT studies in this review did not allow for a robust assessment of a “level” of coverage required to achieve indirect protection. One modeling analysis reports a positive linear relationship between the extent of indirect protection and the effective coverage range (vaccine efficacy combined with coverage) if ≥20% of targeted children are vaccinated [56].

All studies included in this review were conducted in high-income countries with preexisting influenza vaccination of high-risk individuals, particularly the elderly, and those with chronic medical conditions, although coverage in contact populations was usually not reported. Therefore, these results may not be directly generalizable to other settings, particularly low- or middle-income countries. Social mixing patterns within communities also differ and may have a considerable impact on influenza transmission [57]. For example, in the Michigan study by Monto et al, indirect protection was greater in younger adults who were more likely to be parents and, therefore, in direct contact with children [30]. Other factors, such as variability in the immune status of vaccinees and contacts, for example from comorbidities or previously acquired natural immunity, likely also affect the extent of indirect protection, but are difficult to assess.

An important insight from our review is that school-based vaccination of school-aged children, the population group that has been recognized to play a key role in the transmission of influenza, appears to provide indirect as well as direct protection [57, 58]. School-based influenza vaccination programs have been feasible in certain contexts, but are highly resource intensive [59–61]. The phased rollout of school-based LAIV in the United Kingdom achieved higher coverage than delivery via primary care providers [32, 48]. The likelihood of attaining high coverage is an important component of decision making regarding introduction of influenza vaccination programs.

Epidemiological studies are required to better examine the ideal target age group for a childhood vaccination program. Modeling studies in the United Kingdom suggest that vaccinating both primary and secondary schoolchildren, but not by vaccinating only one group, is required to eliminate influenza transmission for a particular season [62]. In addition, more robust interventional studies with large sample sizes are needed to better quantify indirect protection for a range of different settings and disease endpoints, particularly in lower- and middle-income countries. The cRCT is the optimal epidemiological design for assessing indirect protection, although it is resource intensive [14]. Additional evidence could be derived from studying the contacts of vaccinees in individual RCTs, where there are suitable geographic clusters and variations in vaccine coverage [14, 15]. Another approach is to use simulation models that...
are appropriately designed and parameterized, such as the one informing the policy change in the United Kingdom [58].

In conclusion, our findings can inform decision making regarding the introduction and implementation of childhood influenza vaccination programs. However, unvaccinated contacts will still remain more susceptible than vaccinees; indirect protection cannot replace annual vaccination as the most effective way to prevent influenza at an individual level [1].

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
Author contributions. J. K. Y., A. E. H., D. I., and K. K. M. conceived of the study. C. K. conducted the literature search. J. K. Y., A. E. H., and M. G. independently screened search records. J. K. Y., A. E. H., and M. G. independently extracted data from individual studies and assessed study quality. C. C., D. I., and K. K. M. oversaw the study and provided important guidance. J. K. Y. performed all statistical analyses and wrote the first draft of the manuscript. All authors contributed to the interpretation of data analyses, participated in drafting and revising the manuscript critically for intellectual content, and gave final approval to the version for submission.

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