Effectiveness of Influenza Vaccines in the HIVE Household Cohort Over 8 Years: Is There Evidence of Indirect Protection?

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Background. The evidence that influenza vaccination programs regularly provide protection to unvaccinated individuals (ie, indirect effects) of a community is lacking. We sought to determine the direct, indirect, and total effects of influenza vaccine in the Household Influenza Vaccine Evaluation (HIVE) cohort.

Methods. Using longitudinal data from the HIVE cohort from 2010–11 through 2017–18, we estimated direct, indirect, and total influenza vaccine effectiveness (VE) and the incidence rate ratio of influenza virus infection using adjusted mixed-effect Poisson regression models. Total effectiveness was determined through comparison of vaccinated members of full or partially vaccinated households to unvaccinated individuals in completely unvaccinated households.

Results. The pooled, direct VE against any influenza was 30.2% (14.0–43.4). Direct VE was higher for influenza A/H1N1 43.9% (3.9 to 63.5) and B 46.7% (17.2 to 57.5) than A/H3N2 31.7% (10.5 to 47.8) and was higher for young children 42.4% (10.1 to 63.0) than adults 18.6% (−6.3 to 37.7). Influenza incidence was highest in completely unvaccinated households (10.6 per 100 person-seasons) and lower at all other levels of household vaccination coverage. We found little evidence of indirect VE after adjusting for potential confounders. Total VE was 56.4% (30.1–72.9) in low coverage, 43.2% (19.5–59.9) in moderate coverage, and 33.0% (12.1 to 49.0) in fully vaccinated households.

Conclusions. Influenza vaccines may have a benefit above and beyond the direct effect but that effect in this study was small. Although there may be exceptions, the goal of global vaccine recommendations should remain focused on provision of documented, direct protection to those vaccinated.

Keywords. influenza; vaccine effectiveness; cohort study; indirect protection.

Influenza vaccine is the best way to prevent influenza virus infections and their subsequent complications, including hospitalization and death. Despite a universal recommendation in the United States for annual influenza vaccination of all individuals >6 months old [1], uptake has been consistently suboptimal at approximately 45% [2]. Seasonal epidemics of influenza continue to cause substantial morbidity and mortality [3, 4] and the direct vaccine effectiveness (VE) in those vaccinated varies by season and dominant influenza subtype. On an annual basis, direct VE is most commonly estimated by test negative design studies of medically attended illnesses, which does not account for the entire benefit of influenza vaccination, including protection against mild illness and potential indirect effects through herd immunity.

The term herd immunity describes a scenario under which population level immunity to an infection is sufficiently high that epidemics become less likely or start to diminish [5, 6]. Vaccinated individuals have immunity from their vaccination and are thus protected from infection (direct VE). Unvaccinated individuals, who are not immune, receive indirect protection, primarily through reduction of the number of infectious individuals at the population level. The indirect effect is therefore distinct from the direct effect of the vaccine. The total effect of a vaccine represents the combination of direct and indirect effects [7].

A substantial amount of influenza virus transmission is thought to happen in settings with close and prolonged contact, such as households [8]. This setting is thus an ideal place to estimate indirect and total effects. There is some evidence of indirect effects from randomized studies, but these studies are limited by shorter follow-up or unique populations. A cluster randomized trial in

Hutterite communities in Canada [9] showed substantial indirect effects of inactivated influenza vaccines, surprisingly nearly as high as direct effects when 80% of children were vaccinated [9, 10]. A modeling study informed by another randomized trial in Hong Kong estimated that, for influenza B, the indirect protection for household contacts could reach 20% under certain scenarios of household transmission and vaccination coverage [11]. Additional cluster-randomized studies in India [12] and Senegal [13,14] have estimated indirect and total VE, with mixed results.

The Household Influenza Vaccine Evaluation (HIVE) Cohort has evaluated influenza vaccine effectiveness longitudinally since 2010. The prospective design of the cohort and active surveillance for acute respiratory illness (ARI) presents a unique opportunity to observe both direct and indirect impacts of vaccination. Here we estimate the direct, indirect, and total vaccine effectiveness of influenza vaccine in households with children over 8 influenza seasons.

METHODS

Study Population

We used longitudinal data from the HIVE study collected from 2010–11 through 2017–18 influenza seasons. These data include active ARI surveillance from 3909 individuals from 911 distinct households, for a total of 9371 person-seasons. Recruitment and retention of participants has been previously described [15]. The HIVE study is approved by the institutional review board at the University of Michigan Medical School.

Influenza Vaccination and Household Vaccination Coverage

Influenza vaccination status was determined by a combination of self-report and documentation from electronic medical records (EMR) and the Michigan Care Improvement Registry (MCIR), as previously described [15–18]. Individuals were considered vaccinated ≥14 days after their vaccination. We calculated the proportion of vaccinated household members and the incidence of influenza virus infection each season and longitudinally (ie, pooled over 8 years). We estimated the crude incidence rate of influenza in households by level of vaccination coverage (ie, completely unvaccinated, low vaccination coverage [>0–50%], moderate vaccination coverage [51–99%], and fully vaccinated). We calculated crude incidence rate, incidence rate ratios and 95% confidence intervals (CI) using the R package *epitools*.

Influenza Infection Status

Surveillance for acute respiratory illness was carried out from October through May (2010–11 through 2014–15 seasons) or year-round (2015–16 through 2017–18 seasons), as previously described [15]. Respiratory specimens were tested for influenza by RT-PCR, including A(H3N2), A(H1N1)pdm09 subtypes and B(Yamagata) and B(Victoria) lineages, using protocols from the Centers for Disease Control and Prevention.

Influenza Incidence and Direct Effect of Influenza Vaccination

We estimated the direct effects of influenza vaccination by comparing the seasonal incidence rate among vaccinated and unvaccinated individuals. Adjusted incidence rate ratios (aIRR) were estimated from mixed-effect Poisson regression models. VE_D was calculated as 1-aIRR* 100. Vaccination was modeled as a time varying covariate, with some individuals contributing both vaccinated and unvaccinated person-time. Adjusted models included an offset term to account for person time and included potential confounders (age group, sex, and the Advisory Committee on Immunization Practices [ACIP] defined high-risk conditions [19]).

Indirect and Total Vaccine Effectiveness: Mini-Community Design

In this study we considered each household in the HIVE cohort to be a mini-community. The mini-community framework treats the household (or another small unit where contact is sufficient for transmission to occur) as the unit in which indirect and total effects of vaccination are to be estimated [20].

We fitted separate mixed-effects Poisson regression models to estimate VE_I and VE_T, with random effects for household and season. Models were adjusted for potential confounders (age group, sex, and ACIP defined high-risk conditions). To estimate VE_I we compared the incidence rate of influenza in unvaccinated individuals in completely unvaccinated households to unvaccinated members of households with higher levels of vaccination (ie, low [>0–50%] or moderate [51–99%] coverage). VE_T was estimated by comparing the incidence rate of influenza in vaccinated individuals in completely and partially vaccinated households to unvaccinated individuals in completely unvaccinated households (Figure 1).

All statistical models were run in R software, version 4.0.2. Effect estimates were considered statistically significant if 95% confidence interval (CI) did not include the null value.

RESULTS

We followed 3416 individuals from 799 distinct households, for a total of 9371 person-seasons. Each household was followed for a median of 2 seasons (range 1–8, interquartile range [IQR] 1–4). The majority of the observed person-time was in children (58.8%). School-aged children (5–17 years old) in particular, contributed 4184 (44.7%) person-seasons of follow-up. No differences in age distribution were noted by household vaccination coverage. 1753 (48.7%) individuals were female, contributing 4775 (51.0%) person-seasons of follow-up. The HIVE cohort is predominantly White, and 16% of participants were considered high risk according to the ACIP definition (Table 1).

Influenza Vaccination Coverage

Approximately 65% of the HIVE cohort is vaccinated against influenza each year. In total, 6356 (68%) person-seasons among vaccinated individuals over 8 seasons of follow-up
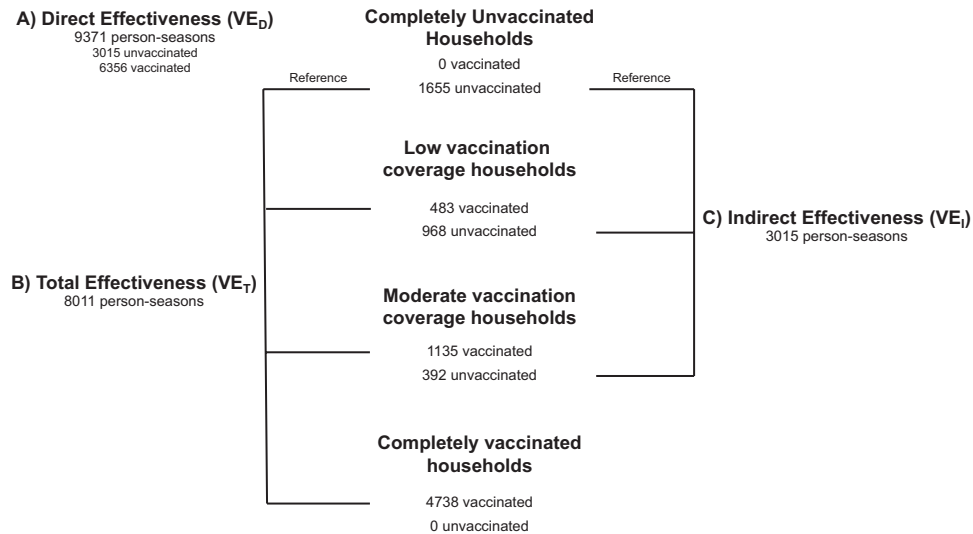
Figure 1. Person-seasons of follow-up for comparisons of influenza incidence. *A*, Direct effectiveness (VE$_D$) comparing vaccinated and unvaccinated individuals. *B*, Total effectiveness (VE$_T$) comparing vaccinated members of moderate and low vaccination coverage households to unvaccinated members of completely unvaccinated households. *C*, Indirect effectiveness (VE$_I$) comparing unvaccinated members of low and moderate vaccination coverage households to unvaccinated members of completely unvaccinated households, HIVE study, 2010–11 through 2017–18 seasons. Abbreviation: HIVE, Household Influenza Vaccine Evaluation.

were included in this analysis. At the household level, 52% households were completely vaccinated each year, on average (Figure 2). The proportion of households that were completely vaccinated ranged from 47% in 2010–11 to 60% in 2017–18. The percentage of households that were completely unvaccinated ranged from a high of 21% in 2010–11 to a low of 11% in 2017–18. On average, 17% of households were completely unvaccinated and 31% of households were partially vaccinated each season. There was little variability in vaccination coverage within households among children, pre-school aged children, or school-aged children. In most households, either all children were vaccinated, or none were (Figure S1).

Influenza Incidence and Direct Effectiveness

The incidence rate of influenza overall was 8.1 per 100 person-seasons (95% CI 7.5–8.7; Table 2). Over the 8 seasons of follow-up incidence was highest for influenza A/H3N2 infections (4.6 per 100 person-seasons, 95% CI 4.2–5.1), followed by influenza B (2.3 per 100 person-seasons, 95% CI 2.0–2.6) and influenza A/H1N1 (1.1 per 100 person-seasons, 95% CI 0.9–1.4). Incidence rates for any influenza infection were higher in both preschool (0–4 years; 10.7 per 100 person-seasons, 95% CI 9.0–12.6) and school-aged children (5–17 years; 9.1 per 100 person-seasons, 95% CI 8.2–10.1), and lower among adults (≥18 years; 6.1 per 100 person-seasons, 95% CI 5.4–6.9). Seasonal incidence of any

Table 1. Baseline Demographics of Household Influenza Vaccine Evaluation (HIVE) Study Participants and Person-time Observed by Household Vaccination Coverage, 2010–11 Through 2017–18 Seasons

|	N Individuals (%)	Person-Seasons of Follow-up N (%)			
		Completely Unvaccinated	Low Vaccination Coverage	Moderate Vaccination Coverage	Fully Vaccinated
Total	3416 (100)	1655	1451	1527	4738
Female	1753 (49)	855 (49)	737 (49)	755 (51)	2428 (49)
Age group, y					
0–5	748 (22)	208 (13)	166 (11)	241 (16)	710 (15)
5–17	1251 (37)	813 (49)	686 (47)	645 (42)	2040 (43)
18–49	1310 (38)	588 (36)	539 (37)	571 (37)	1760 (37)
≥50	107 (3)	46 (3)	60 (4)	70 (5)	228 (5)
Race					
White	2496 (73)	1184 (72)	1073 (74)	1065 (70)	695 (78)
Black	291 (9)	163 (10)	122 (8)	124 (8)	251 (5)
Asian	279 (8)	85 (5)	93 (7)	177 (12)	444 (9)
Other	350 (10)	169 (10)	115 (8)	144 (10)	303 (6)
High-risk condition	537 (16)	192 (12)	252 (17)	270 (18)	807 (17)
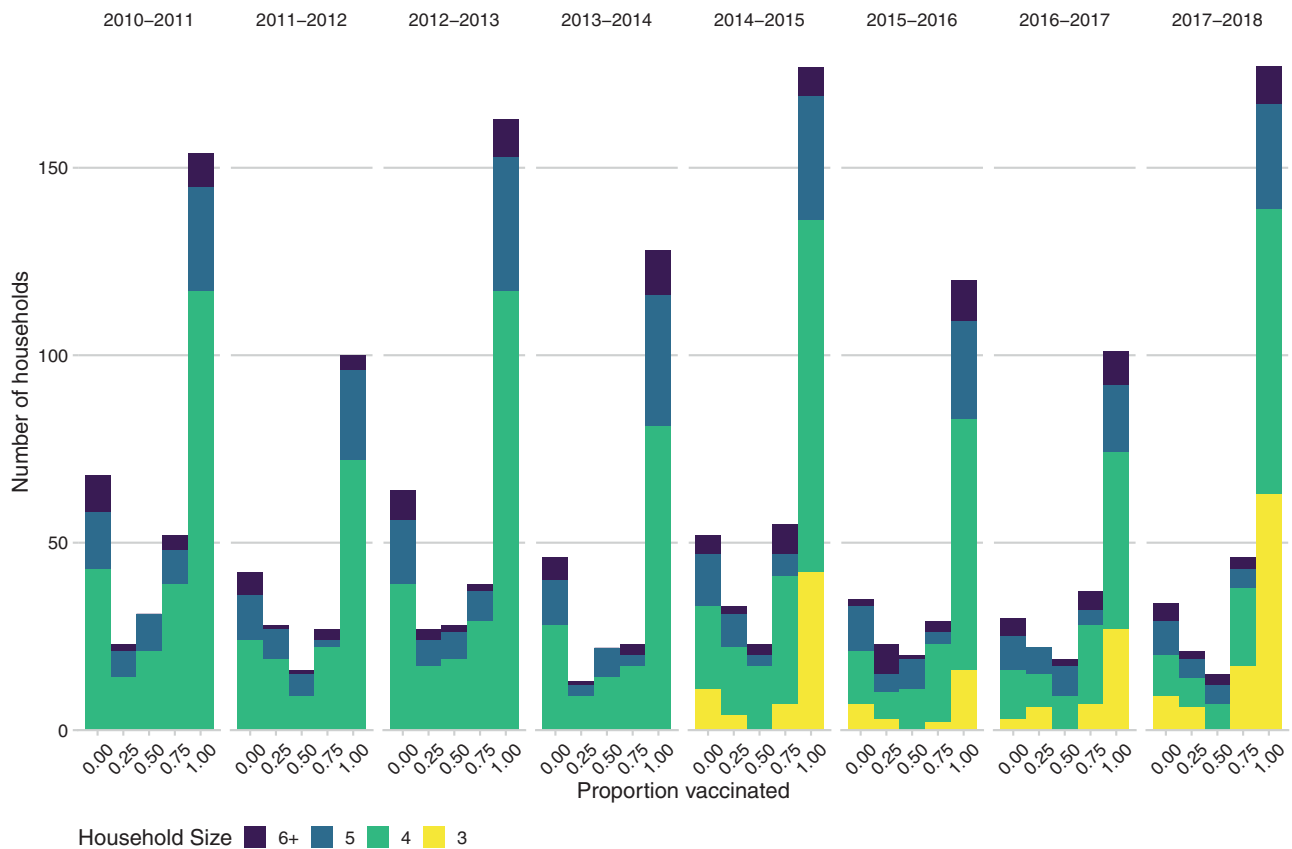
Figure 2. Distribution of household vaccination coverage by household size and season, 2010–11 through 2017–18 seasons.

influenza virus infection (Table 2) was higher among unvaccinated individuals (10.0 per 100 person-seasons, 95% CI 8.9–11.2) than vaccinated individuals (7.2 per 100 person-seasons, 95% CI 6.6–7.9). For influenza B, age stratified incidence rates (Supplementary Table 1) showed substantially higher incidence in preschool (3.1 per 100 person-seasons) and school-aged children (2.9 per 100 person-seasons) than among adults (1.4 per 100 person-seasons).

The overall adjusted VE_D was 30.2% (95% CI 14.0–43.4) with limited variation by type 40.7% (95% CI 3.9–63.5); 31.7% (95% CI 10.5 to 47.8); 46.7% (95% CI 17.2 to 57.5) for A/H1N1, A/H3N2, and influenza B, respectively). In age-group stratified models, we observed higher levels of protection for preschool (0–4 years; VE_D 42.4%, 95% CI 10.1 to 63.0) and school-aged children (5–17 years; VE_D 28.7%, 95% CI 10.4 to 43.3) than we did for adults (≥ 18 years; VE_D 18.6, 95% CI −6.3 to 37.7).

Indirect Effectiveness of Influenza Vaccines

Influenza incidence was generally highest among individuals in completely unvaccinated households (Figure 3). Overall, there appears to be a decline in influenza incidence with increasing proportion of household vaccinated. However, in some seasons, such as 2014–15, when the estimates of VE_D in this cohort were essentially zero, the incidence rate was higher than in other seasons, and no decline was observed with increasing household vaccination coverage.

For indirect effect estimates we included a total of 3015 person-seasons of observation in unvaccinated individuals (Figure 1). We observed a lower incidence of influenza among unvaccinated individuals in moderately vaccinated households (8.9 infections per 100 person-seasons [95% CI 6.2–12.4]) compared to those in completely unvaccinated households (10.6 infections per 100 person-seasons [95% CI 9.1–12.3]). Point estimates for crude indirect vaccine effectiveness (VE_I) comparing unvaccinated individuals in moderate vaccination coverage households to those in completely unvaccinated households suggest low levels of protection but were not statistically different from zero (VE_I 15.6 95% CI −21.4 to 41.3). The observed crude VE_I in low vaccination coverage households was 2.4% (95% CI −24.9 to 24.6; Table 3).

In both unadjusted and adjusted models there was no significant reduction in influenza incidence comparing unvaccinated individuals in low or moderately vaccinated households to those in completely unvaccinated households (Table 3). Age-group stratified models (Supplementary Table 2) demonstrate that school-aged children had lower indirect effect estimates in low (−3.4% 95% CI −52.9 to 30.0) and in moderate (−69.8% 95% CI −216.9 to 9.0) coverage households than either pre-school aged

Table 2. Seasonal Incidence Rate (95% CI) of Influenza Infection and Direct Vaccine Effect (VED) Overall and Stratified by Type/Subtype and Age Group From the Household Influenza Vaccine Evaluation (HIVE) Study, Pooled Over 8 Seasons (2010–11 Through 2017–18 Seasons)

	Influenza Infections	Person-seasons	Incidence Rate per 100 person-seasons (95% CI)	Crude VE$_D$ [a]	Unadjusted VE$_D$ With Random Effects [b]	Adjusted VE$_D$ With Random Effects [c]
Any influenza	760	9371	8.1 (7.5–8.7)			
Unvaccinated	300	3007	10.0 (8.9–11.2)	Ref	Ref	Ref
Vaccinated	460	6364	7.2 (6.6–7.9)	27.5 (16.2–37.4)	32.6 (19.8–43.7)	30.2 (14.0–43.4)
Influenza type/subtype [b]						
Influenza A	546	9371	5.8 (5.3–6.3)			
Unvaccinated	209	3007	7.0 (6.0–8.0)	Ref	Ref	Ref
Vaccinated	337	6364	5.3 (4.7–5.9)	23.8 (9.5–35.9)	28.5 (13.0–41.2)	29.0 (10.0–44.0)
Influenza A/H3N2	431	9371	4.6 (4.2–5.1)			
Unvaccinated	161	3007	5.4 (4.6–6.2)	Ref	Ref	Ref
Vaccinated	270	6364	4.2 (3.8–4.8)	20.8 (3.7–34.8)	27.1 (9.9–41.1)	31.7 (10.5–47.8)
Influenza A/H1N1	107	9371	1.1 (0.9–1.4)			
Unvaccinated	48	3007	1.6 (1.2–2.1)	Ref	Ref	Ref
Vaccinated	59	6364	0.9 (0.7–1.2)	41.9 (15.0–60.3)	38.7 (0.4–62.3)	40.7 (3.9–63.5)
Influenza B	216	9371	2.3 (2.0–2.6)			
Unvaccinated	91	3007	3.0 (2.4–3.7)	Ref	Ref	Ref
Vaccinated	125	6364	2.0 (1.6–2.3)	35.1 (15.0–50.5)	37.9 (13.8–55.2)	46.7 (17.2–57.5)
Age group						
0–4 y	142	1325	10.7 (9.0–12.6)			
Unvaccinated	55	325	16.9 (12.7–22.0)	Ref	Ref	Ref
Vaccinated	87	1000	8.7 (7.0–10.7)	48.6 (28.1–63.3)	49.7 (26.3–65.7)	42.4 (10.1–63.0)
5–17 y	382	4184	9.1 (8.2–10.1)			
Unvaccinated	163	1433	11.4 (9.7–13.3)	Ref	Ref	Ref
Vaccinated	219	2751	8.0 (6.9–9.1)	30.0 (14.3–42.9)	33.3 (16.3–46.8)	28.7 (10.4–43.3)
≥18 y	236	3862	6.1 (5.4–6.9)			
Unvaccinated	92	1257	7.3 (5.9–9.0)	Ref	Ref	Ref
Vaccinated	144	2605	5.5 (4.7–6.5)	24.5 (1.9–41.9)	26.5 (4.5–43.4)	18.6 (-6.3–37.7)

Abbreviations: CI, confidence interval; Ref, reference.

[a] Direct vaccine effect (VE$_D$) calculated as 100*(1-IRR).

[b] Mixed-effects Poisson regression models with random effects for household and season.

[c] Mixed-effects Poisson regression models adjusted for age group, sex, calendar time, and high-risk condition.

[d] Two influenza illnesses were influenza A/influenza B coinfections. These illnesses are considered as one infection for incidence rate calculations of any influenza and separately for type specific incidence rate estimates.

children (low VE$_I$ 11.7% 95% CI −63.8 to 52.4 moderate VE$_I$ 10.2% 95% CI −195.3 to 72.7) or adults (low VE$_I$ 15.3% 95% CI −38.3 to 48.2; moderate VE$_I$ 21.1% 95% CI −37.6 to 54.8), suggesting that school-aged children were not as well protected by the vaccination status of their close contacts. Age-stratified VE$_I$ estimates had had broad and overlapping confidence intervals. We also estimated VE$_I$ by influenza type/subtype; VE$_I$ was lowest for influenza A/H3N2 (low VE$_I$ −32.2% 95% CI −94.4 to 10.1); moderate VE$_I$ −19.7% 95% CI −111.4 to 32.2) and highest for influenza A/H1N1 low VE$_I$ 56.3% 95% CI −9.2 to 82.5; moderate VE$_I$ 24.9% 95% CI −122.9 to 74.7), matching the VE$_D$ estimates (Supplementary Table 3).

Total Household Effect of Influenza Vaccines

The total effect of influenza vaccines compares vaccinated individuals in households with varying levels of vaccination coverage to unvaccinated individuals in completely unvaccinated households. To estimate total effect of influenza vaccine (VE$_T$)

we included 8011 person-seasons of follow-up in the analytical subset. The crude incidence rate was again highest among individuals in completely unvaccinated households (10.6 per 100 person-seasons, 95% CI 9.1–12.3) (Table 4). Among vaccinated individuals in low (5.5 per 100 person-seasons, 95% CI 3.6–8.1), moderate (6.8 per 100 person-seasons, 95% CI 5.3–8.5), and fully vaccinated (7.9 per 100 person-seasons, 95% CI 7.1–8.7) households the incidence rate was lower. Notably, there is substantial overlap in the confidence intervals of the incidence rate estimates among vaccinated individuals in households with varying levels of vaccination coverage.

We found a significant total effect of influenza vaccines. In low vaccination coverage and moderate coverage households, VE$_T$ was 56.4% (95% CI 30.1 to 72.9) and 43.2% (95% CI 19.5 to 59.9), respectively, after adjusting for potential confounders. For individuals in fully vaccinated households, VE$_T$ was also significant (VE$_T$ 33% [95% CI 12.1 to 49.0]), but this estimate was similar to overall VE$_D$.
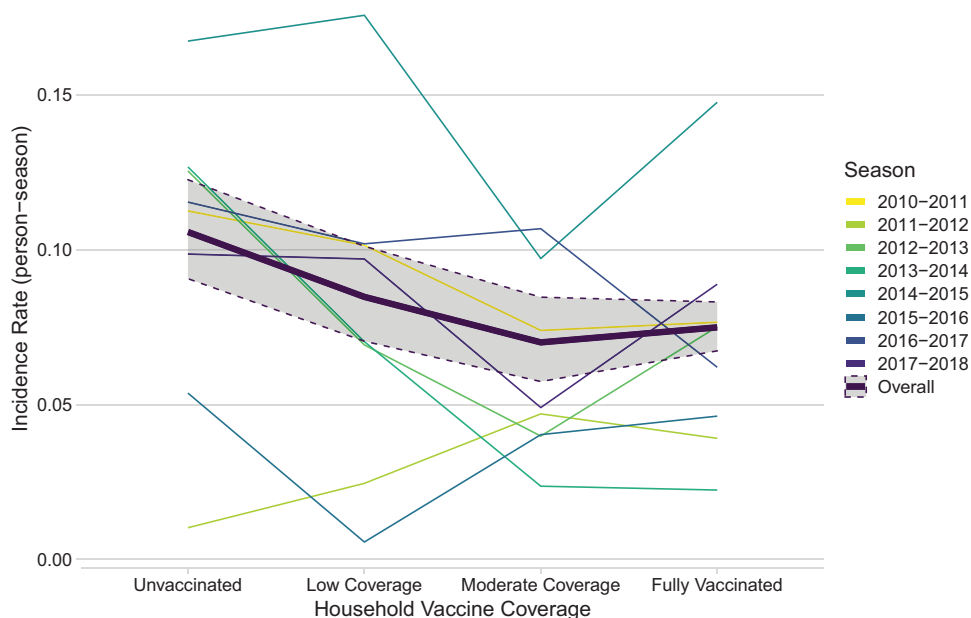
Figure 3. Incidence of influenza infection by household vaccination coverage and season, HIVE Study 2010–11 through 2017–18 seasons. Solid lines represent incidence rate estimates, dashed lines represent exact Poisson 95% confidence intervals. Abbreviation: HIVE, Household Influenza Vaccine Evaluation.

DISCUSSION

In this prospective longitudinal study over 8 years, we were able to demonstrate nearly consistent moderate, direct protection against symptomatic influenza infection by vaccination. We also demonstrated significant total effectiveness that was statistically similar across households that varied in the extent of vaccination coverage. Indirect protection of unvaccinated people that live with vaccinated household contacts was not evident.

Direct protection of influenza vaccines has been demonstrated previously, but our findings include mild and moderate illnesses often missed by studies of medically attended acute respiratory illness (MAARI). This was particularly of interest for type B infections, which are more difficult to study with the MAARI design as longer duration of annual surveillance is needed to capture sufficient numbers of outcomes. In this

study, direct influenza VE was highest for influenza B and for A/H1N1. The low estimates for A/H3N2 reflect global patterns in vaccine effectiveness during this time period and are particularly driven by the 2014–15 season, when incidence was high, vaccine strain (A/Texas/50/2012) was considered a mismatch with predominant circulating viruses (genetic group 3c.2a), and vaccine effectiveness was near zero [18, 22, 23].

In this study, the total effect of household vaccination was larger than the direct VE in low and moderate coverage households. Interestingly, we observed a trend of lower total VE point estimates with increasing household coverage. In fully vaccinated households, for example, total VE (33%) was similar in magnitude to the direct VE (30%), suggesting that protection in these households is primarily driven by the direct vaccine effects rather than a combination of direct and indirect effects. It is also possible that individuals in fully vaccinated households

Table 3. Seasonal Incidence Rate (95% CI) and Indirect Vaccine Effect (VEᵢ) of Any Influenza Infection Among Unvaccinated Individuals by Household Vaccination Coverage in the Household Influenza Vaccine Evaluation (HIVE) Study population, Pooled Over 8 Seasons (2010–11 Through 2017–18 Seasons)

	Influenza Infections	Person-seasons of Follow-up	Seasonal Incidence Rate per 100 person-seasons (95% CI)	Crude VEᵢ [a]	Unadjusted VEᵢ With Random Effects [b]	Adjusted VEᵢ With Random Effects [c]
Completely unvaccinated	175	1655	10.6 (9.1–12.3)	Ref	Ref	Ref
Low vaccination coverage	100	968	10.3 (8.4–12.6)	2.4 (−24.9 to 24.6)	9.6 (−21.1 to 32.6)	8.2 (−20.6 to 30.1)
Moderate vaccination coverage	35	392	8.9 (6.2–12.4)	15.6 (−21.4 to 41.3)	16.9 (−25.2 to 44.9)	4.6 (−41.2 to 35.6)

Abbreviations: CI, confidence interval; Ref, reference.

[a]Indirect vaccine effect (VEᵢ) calculated as 100*(1-aIRR).

[b]Mixed-effects Poisson regression models with random effects for individual, household, and season.

[c]Mixed-effects Poisson regression models adjusted for age group, sex, calendar time, and high-risk condition.

Table 4. Seasonal Incidence Rate and Total Vaccine Effect (VET) of Any Influenza Infection Comparing Vaccinated Individuals in Households With Varying Levels of Vaccination Coverage to Unvaccinated Individuals in Completely Unvaccinated Households, in the Household Influenza Vaccine Evaluation (HIVE) Study Population, Pooled Over 8 Seasons (2010–11 Through 2017–18 Seasons)

	Influenza Infections	Person-seasons of Follow-up	Seasonal Incidence Rate per 100 person-seasons (95% CI)	Crude VE$_T$ [a]	Unadjusted VE$_T$ With Random Effects [b]	Adjusted VE$_T$ with Random Effects [c]
Completely unvaccinated	175	1655	10.6 (9.1–12.3)	Ref	Ref	Ref
Low vaccination coverage	26	472	5.5 (3.6–8.1)	45.0 (16.9 to 64.7)	57.7 (32.2–73.6)	56.4 (30.1–72.9)
Moderate vaccination coverage	75	1109	6.8 (5.3–8.5)	33.5 (12.4 to 49.7)	41.5 (17.0–58.7)	43.2 (19.5–59.9)
Fully vaccinated	379	4804	7.9 (7.1–8.7)	21.3 (5.5 to 44.5)	33.0 (12.1–49.0)	33.0 (12.1–49.0)

Abbreviations: CI, confidence interval; Ref, reference.

[a]Total vaccine effect (VE$_t$) calculated as 100*(1-aIRR).

[b]Mixed-effects Poisson regression models with random effects for individual, household, and season.

[c]Mixed-effects Poisson regression models adjusted for age group, sex, calendar time, and high-risk condition.

are more health-conscious and are more likely to report illnesses meeting our case definition and are thus more likely to have influenza detected. Our results are consistent with cluster randomized trials from India [12], which demonstrated substantial total VE, even in the absence of indirect protection. Similar patterns of total and indirect VE were also found in Senegal [13].

Studies of total and indirect protection of influenza vaccines have, in general, been limited to ecologic studies [24–27], modeling studies, or relatively small studies with non-specific outcomes (eg, febrile respiratory illness) [28, 29]. Few have been conducted in large populations in natural communities or in communities primarily vaccinated with inactivated influenza vaccine instead of live attenuated influenza vaccine. Previous individual-based studies have demonstrated indirect effects of influenza vaccine as large as the direct VE [9, 10], but the magnitude of indirect protection has varied based on the predominant circulating viruses. We expected lower indirect protection against influenza A/H3N2 viruses for the same reason that we expected lower direct VE. Our findings (Supplementary Table 3) suggest that indirect protection, if present, may be higher for influenza A/H1N1 but the small numbers in these stratified analyses limit our ability to draw conclusions.

In previous studies indirect effects have varied by age-group [11, 13]. We explored the potential for effect modification using age-stratified models of indirect VE. We found that the lack of an observed indirect effect seems to be driven by the fact that school-aged children did not benefit from vaccination of household contacts as adults and pre-school aged children did (Supplementary Table S2). This result is consistent with findings from Hong Kong showing that vaccinating children reduced infections in adult household contacts but did not reduce the overall infection probability [11]. School-aged children are known to drive influenza epidemics [30, 31], and as a result of their contact patterns [32], they represent the group at highest risk of community-acquired influenza. We did not collect data on contact patterns or school-level vaccination, limiting our ability to explore these effects. As

shown by Tsang et al, the proportion of infections acquired in the household compared to the community has an impact on the overall indirect protection [11]. In addition, a number of recently observed issues affecting estimates of direct influenza VE may influence the indirect effects. Repeated annual vaccination, antigenic drift, mutations induced by growing vaccine viruses in chicken eggs, and waning immunity have all been linked to lower than expected direct VE in recent years [17, 18, 22, 33–37]. These mechanisms require further exploration, including individual hazard models to explore the relative contribution of community and household risk [38], as a potential explanation for the lack of indirect VE observed in this analysis.

Lack of heterogeneity in vaccine uptake is a challenge for evaluating indirect protection at the household level, as individuals share vaccination habits with others in their household. Also, most influenza infections in the HIVE study are considered community-acquired [16, 17], making identification of indirect protection resulting from reductions in household transmission risk a challenge. A more granular evaluation of indirect protection at the household level requires a situation where household members have similar risk of infection but different access to vaccination based on individual factors that are not shared by all household members. This is the situation that we are presented with given the US prioritization schemes for SARS-CoV-2 vaccine deployment. Although the household cohort was somewhat limited in the ability to evaluate potential indirect protection for unvaccinated members of partially vaccinated households, future findings in the era of COVID-19 may be quite different. Especially, as prioritization schemes will result in varied vaccination timing among household members. Similarly, the HIVE study population may not be generalizable to indirect effects observed in other settings (eg, high crowding, inadequate ventilation) with higher risk of household transmission.

We were unable to convincingly demonstrate indirect protection beyond the direct effect, but we did show that vaccine had a clear role in preventing mild disease in a cohort of families

living in their own homes. The indirect effect might have been clear if the vaccines had higher direct effects. This is in agreement with recent literature reviews [39], meta-analyses [40], and cluster-randomized trials [12], which found inconsistency in demonstration of indirect effects. The entire concept of indirect protection or herd immunity has become a focus of efforts to control COVID-19 outbreaks. It is important to remember that the primary focus with a vaccine should be good direct VE and that indirect protection should be seen as a bonus, but not a necessity.

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 copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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