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Household transmission of influenza A and B in a school-based study of non-pharmaceutical interventions

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ABSTRACT

The effect of school-based non-pharmaceutical interventions (NPIs) on influenza A and B transmission in children's households has not been estimated in published literature. We use data from a large school-based cluster randomized trial of improved hand and respiratory hygiene measures to explore the secondary transmission of influenza A and B in households of laboratory confirmed influenza cases. Data were taken from the Pittsburgh Influenza Prevention Project, a cluster-randomized trial of NPIs conducted in ten Pittsburgh, PA elementary schools during the 2007–2008 influenza season. We estimated two measures of influenza transmissibility in households; the susceptible infectious transmission probability, using variants of the Reed–Frost chain binomial model, and the secondary attack rate. We identified predictors of ILI using a logistic generalized estimating equation model. We estimate the secondary attack rates in intervention households to be 0.26 (95% confidence interval (CI) 0.19–0.34) compared to 0.30 (95% CI 0.23–0.38) in control households. Race and age were significant risk factors for secondary ILI acquisition in this study. We found no significant differences between the transmission probabilities for infectious individuals in intervention (0.19, 95% CI 0.14–0.25), and control households (0.22, 95% CI 0.16–0.29). Similarly, estimates for secondary attack rates and transmission probabilities for households with confirmed influenza A (0.31 and 0.22) were not significantly different from estimates from households with confirmed influenza B (0.25 and 0.20). While influenza A and B are thought to have different transmission characteristics, we find no significant differences in their transmissibility within households. Though our results suggest a potential effect, we found no statistically significant effect of school-based non-pharmaceutical interventions on transmission in symptomatic children's homes.

Introduction

Non-pharmaceutical interventions (NPIs) have been proposed as a primary intervention for influenza in the absence of an effective vaccine, and as a cost-effective supplement to vaccination and antiviral medications. However, few studies have actually investigated the efficacy of these interventions on transmission of influenza A, and fewer have considered influenza B. Here we examine the effect of a school-based NPI on secondary transmission within homes, where up to 30% of influenza transmission is thought to occur (Ferguson et al., 2006; Chao et al., 2010).

School-aged children play a significant role in the introduction and spread of influenza in households. A number of studies have identified exposure to school-aged children as a significant risk factor for influenza acquisition (Viboud et al., 2004; Cauchemez et al., 2011; Frank et al., 1983). Thus, interventions targeted at this group may be effective in slowing both transmission between children and from children to others. This has been shown both theoretically and in a handful of trials (Jordan et al., 2006; Reichert et al., 2001; Piedra et al., 2005; Loeb et al., 2010; Weycker et al., 2005).

We previously found that a 5-layer educational program focused on hand and respiratory hygiene along with the provision of hand sanitizer in schools reduced laboratory confirmed influenza A related absences by 53% (Stebbins et al., 2011). A similar study from Egypt demonstrated comparable effects of improved hand hygiene on both influenza A and B (Talaat et al., 2011). While promising, these results may not capture the total effect of this type of intervention. Changes in school children's hygiene behavior resulting from this program may influence secondary influenza

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transmission within their homes, by modifying their hygiene behavior while sick.

Designing effective interventions against influenza requires an understanding of transmission dynamics of circulating strains. To date, many have focused on modeling transmission of seasonal or pandemic influenza A leaving a deficit of information around influenza B (Cauchemez et al., 2009). A and B are generally thought to have different transmission dynamics with A being more transmissible, and B primarily affecting young children (Fox et al., 1982; Frank et al., 1983; Longini et al., 1982). With the advent of a quadrivalent influenza vaccine including two strains of influenza B, additional data on the burden and dynamics of influenza B is needed to aid policy makers and regulators (Block et al., 2011).

In this paper we explore the indirect effects of school-based NPIs on the efficiency of influenza A and B transmission in the households of students. We also use this setting to characterize and compare household transmission properties of both circulating viruses. We aim to test two hypotheses: (1) that school-based NPI interventions reduce household transmission of influenza A and B after a primary infection of a school-aged child and (2) that influenza A and B differ in their transmissibility within household.

Methods

Study design

The Pittsburgh Influenza Prevention Project, described previously (Stebbins et al., 2011), was a cluster-randomized trial of NPIs conducted in ten Pittsburgh, PA elementary schools during the 2007–2008 influenza season (ClinicalTrials.gov number, NCT00446628 [ClinicalTrials.gov]). Five intervention schools received a set of NPIs ("WHACK the Flu") based on a program originally developed by the City of Berkeley Public Health Division (County, 2013). They received training in hand and respiratory hygiene, and a supply of hand sanitizer. Study staff conducted grade specific presentations on the 5 steps to "WHACK the Flu" and demonstrated proper hand washing techniques using soap and hand sanitizer. Study staff installed hand sanitizer dispensers filled with 62% alcohol based sanitizer in each classroom and all major common areas. Information on best practices in respiratory and hand hygiene was sent home with each child in the intervention group. The five control schools received no training. Information on the study was sent to all homes as part of the consent process.

Student absences were reported each day. When an absence was detected, study staff administered a questionnaire to a parent or guardian by telephone seeking the reason for the child's absence in addition to basic household demographic information including the race (white, black, or other), ethnicity (Hispanic/Latino or non-Hispanic/Latino), age, and sex of each individual. If the absence was due to influenza like illness (ILI), defined as fever and cough or sore throat, study staff visited the student's house within 24-h of obtaining consent, to collect laboratory specimens and additional information on both the student and other household members. Households of students who were either not absent or not absent due to ILI were not visited in this study. Study staff collected data on symptoms, dates of onset, duration of illness, year of most recent influenza vaccination, actions taken to either treat or prevent spread of illness (e.g. medical care or isolation), and activities in the days surrounding the primary illness. Home visits were conducted within a median time of three days after the onset of the student's illness. Approximately 2 weeks after the reported absence, the study team contacted the household by phone to conduct an illness investigation for the student and all secondary illnesses in the household reported since the onset of the student's symptoms. We classified secondary illnesses from this investigation through self-reported ILI. Absence surveillance and the intervention were carried out from 11/1/2007 through 4/24/2008.

During the home visit, study staff collected two nasal swabs from children with ILI to use for (1) an influenza A/B rapid test (QuickVue Influenza A&B test, Quidel Corp, San Diego, CA) and (2) RT-PCR based detection of influenza. Influenza testing was performed only during the influenza season, the start of which was determined to be 1/7/2008, based on input from the Allegheny County Health Department, Pennsylvania Department of Health and UPMC Virology Lab. Testing stopped on 4/17/2008 after no positive test results were obtained for 2 weeks and with consultation with the above mentioned agencies. This period of influenza testing corresponded precisely with the weeks when greater than 10% of specimens submitted to the US National Respiratory and Enteric Virus Surveillance System were positive for influenza.

Statistical analyses

We compared demographic characteristics of individuals and households using χ^2 tests for differences in means of categorical variables and Wilcoxon Rank sum tests for differences in means of continuous variables. We explored the effect of the intervention on household transmission and estimated transmission parameters of influenza A and B using three different approaches. First, we estimated the susceptible-infectious transmission probability (SITP), the probability that a susceptible individual will become infected due to exposure to one infectious household member. Second, we estimated the secondary attack rates (SAR) for each group of households, defined as the proportion of household members reporting ILI in the 2 weeks after the onset of symptoms in the student. Third, we used logistic generalized estimating equations (GEE) to explore the association of the intervention and key risk factors with ILI in household members. We restricted analysis to households with PCR-confirmed influenza cases and complete data unless otherwise noted. We treated the first PCR-confirmed student in each household as a primary case, and others in the same household within 2 weeks as secondary cases.

Estimating the SITP

To estimate the SITP we fit a series of models to the final outbreak size, all variants of the Reed–Frost model (Frost, 1976). The Reed–Frost model is a simple discrete time generalization of an epidemic where susceptible individuals can become infected during each generation and then remain infectious for one generation until they recover. The final outbreak size distribution predicted by this model does not rely on any details related to who infected whom (i.e. no temporal or infection chain details necessary) (Ludwig, 1975). We explored generalizations of this model (see Supplement) that allowed for heterogeneity in the infectious period, heterogeneity in transmission by household size, and community acquired infections (Longini et al., 1982; Longini and Koopman, 1982; Ball and Clancy, 1993; Fraser et al., 2011). We chose the model that best fit the data through minimizing a form of the Akaike Information Criteria (AICc) (Burnham and Anderson, 2002). We can estimate the probability of a final outbreak size (F_m^n) of m in households of size n by solving the recursive system of equations:

$$\binom{n-1}{j} = \sum_{m=0}^{j} \frac{\binom{n-1-m}{j-m} F_m^n}{logit^{-1}(q_i/n^{\alpha})^{m(n-1-j)}} \quad for\, j = 0, \ldots, n-1, \qquad (1)$$

where q_i is related to the transmission intensity in group i households (i.e. control or intervention), and α is a parameter dictating the dependence of SITP on household size, and $logit^{-1}(x) = e^x/(1+e^x)$. In this model the SITP is calculated as $logit^{-1}(q_i/n^{\alpha})$. We compared support for models with separate or

combined SITP parameters using likelihood ratio tests with a significance level of 0.05 (assuming differences in $2 \times$ log-likelihood are χ^2 distributed with degree of freedom equal to the difference in the number of parameters). Since the SITP is a function of household size, we present the SITP in all results as the SITP for the median household size of 4. All parameter estimates presented from these models are maximum likelihood estimates accompanied with 95% bootstrap confidence intervals.

Estimating the SAR

Secondary attack rates were defined as the percentage of household members, excluding the primary school-child, who reported ILI within 2 weeks of the primary school-child's absence from school. We present exact binomial 95% confidence interval estimates for all SARs.

Examining secondary ILI risk factors

We used logistic GEE models to investigate risk factors associated with reported secondary ILI while accounting for correlation of individuals within households (i.e. individuals within a household were clustered). We included covariates previously shown to have an association with ILI acquisition and potential confounders (immunization status, age, race, and household size (Cauchemez et al., 2009; France et al., 2010)). Individuals with data missing on one or more key covariates were excluded from this part of the analysis ($n = 12$), after the missing data mechanism was explored and assumed to be missing completely at random (Rubin, 1976).

Sensitivity analysis

To assess the sensitivity of our results to the definition of ILI, we estimated model parameters using two versions of the definition. The first, a common definition used by the Centers for Disease Control and the World Health Organization, specified by temperature greater than 38 °C plus sore throat or cough (United States Centers for Disease Control, 2013). The second, a less specific case definition used self-reported fever (for which no temperature) was measured with sore throat or cough. Results using the latter definition are reported throughout this paper but results from both are presented when found to be significantly different.

In our primary analysis we included all households with PCR-confirmed influenza regardless of the onset dates of households members with respect to the student.

Though the school-based intervention may have reduced family member acquisition of influenza from the community via improved cough and hand hygiene, it is more likely that the intervention reduced the family member's risk through their child's improved hand and cough hygiene. To focus on this, in a separate analysis we estimated all parameters using a set of data that excluded households where household members reported symptoms either before or on the same day as the student and report findings only when significantly different.

In order to explore power of our methods to detect a statistically significant difference in SITP between groups, we conducted a number of simulations. In each simulation we generated a synthetic population of households based on the number and size distribution of households from the primary analysis. For a range of published estimates of the SITP for influenza (0.15–0.25), we generated final attack sizes based on a non-truncated, non-household-size-dependent variant of Eq. (1) (see Supplement Eq. (5), including households with zero cases), removed the households with no secondary cases (to mimic the study design), then estimated the SITP for each group (intervention and control). We conducted 1000 simulations for each set of parameters (with α, the household size dependence parameter, fixed at -0.71) and determined the percentage of time that we rejected the null in a likelihood ratio test, comparing a model with separate SITPs for each group with a null model with a single shared SITP.

All analyses were performed in the R statistical computing environment (Team, 2011; Hjsgaard et al., 2005).

Results

A total of 3360 students participated throughout the study period. We recorded 1107 absences due to illness of which 361 met the criteria for ILI. We were able to conduct home visits and influenza testing on 279 (77%) of these students. One hundred and three (103) children had PCR confirmed influenza A or B, with 52 from the control schools and 51 from the intervention schools. Of these, 89 entered our analysis as primary cases with 44 from control schools and 45 from intervention schools. Three hundred seventy three (373) household members, including the students, in these 89 households entered our analysis with 168 people (89 primary and 79 secondary cases) from 45 households reporting symptoms consistent with at least one of our definitions of ILI. When considering only households where the student reported symptoms before anyone else in the household, we included 208 individuals from 62 households.

Households from the control and intervention arms had similar reported vaccination statuses, household size, age composition, and primary child age. Despite randomization at the school level, control and intervention arms differed by race, and percentage of family members with chronic illness. Table 1 illustrates the differences between the study groups and includes a comparison of households classified by the school child's infecting influenza type.

In this analysis 49% (44) of households had a confirmed case of influenza A and 51% (45) had influenza B, however, the distribution of A and B differed between the intervention arms. The control households were primarily infected with A (61%), and the intervention households were primarily infected with B (62%). We successfully sequenced 15 influenza A/H3N2 samples from these students and sequence information can be found in GenBank (accession numbers in Table S1).

Effect of intervention

The intervention arm had a 13% lower secondary attack rate for ILI (0.26, 95% confidence interval (CI) 0.19–0.34) than the control group (0.30, 95% CI 0.23–0.38), however, the difference was not statistically significant (Table 2). When estimated separately the SITP for the intervention households is 0.19 (95% CI 0.14–0.25) with a similar estimate made for the control households of 0.22 (95% CI 0.16–0.29). When restricting analysis to households where the main study participant was the first to present symptoms (74 of 89 households), we estimate the SITP to be 0.15 (95% CI 0.09–0.21 for intervention and 0.18 (95% CI 0.10–0.26 for control households (Table S2). In both cases, we find no statistically significant difference between intervention and control groups using a likelihood ratio test. In simulations, we found that with this sample size, an intervention would have to reduce the SITP by 49–55% in order for us to have 80% power detect and a significant effect when the control group's SITP is between 0.25 and 0.20.

Age and race were significant risk factors for self reported ILI among households members in the logistic GEE model (Table 3). Compared to adults 19–50 years old, children 0–4 years old have an increased, yet not statistically significant, odds of ILI (OR 1.73, 95% CI 0.78–3.85), whereas the strongest effect is seen in children 5–18 (OR 2.03, 95% CI 1.05–3.92). The odds of ILI decreased by 19% (OR 0.81, 95% CI 0.56–1.18) per additional member of household (Fig. 1). Living in a household where at least one child attended an

Table 1
Comparison of households by study arm and PCR confirmed influenza strain of child.

	Influenza A households	Influenza B households	Control households	Intervention households
Most recent flu immunization this year	0.15	0.19	0.16	0.19
Most recent flu immunization last year	0.09	0.06	0.08	0.07
Percent <15 years old	0.52	0.51	0.51	0.52
Percent of household in full time work	0.26	0.25	0.26	0.25
Percent of household in school or childcare	0.54	0.50	0.51	0.53
Black	0.26	0.28	0.32*	0.22*
Chronic illness	0.07*	0.11*	0.05*	0.13*
Mean household size	4.02	4.36	4.25	4.13
Mean primary child age	8.26*	7.11*	8.02	7.33

* Statistical significance of χ^2 or Wilcoxan Rank Sum test at $\alpha = 0.05$.

Table 2
Secondary attack rates (SAR) and susceptible infectious transmission probabilities for a household size of 4 (SITP).

	n	ILI[a]	SAR (95% CI[b])	SITP (95% CI[c])
Control	143	43	0.30 (0.23, 0.38)	0.22 (0.16, 0.29)
Intervention	141	36	0.26 (0.19, 0.34)	0.19 (0.14, 0.25)
Influenza A	133	41	0.31 (0.23, 0.39)	0.22 (0.17, 0.28)
Influenza B	151	37	0.25 (0.18, 0.32)	0.20 (0.13, 0.26)

[a] The number of ILI positive individuals using the definition of fever and cough or sore throat.
[b] Exact binomial confidence interval.
[c] Bootstrap confidence interval.

intervention school was not significantly associated with the odds of reporting ILI within 2 weeks of the child becoming symptomatic.

We stratified both on intervention arm and influenza type and re-estimated the SITPs to investigate different effects of the intervention by influenza type (Tables S2 and S3). Among households with influenza B, intervention households had statistically significantly less efficient transmission with an SITP of 0.14 (95% CI 0.07–0.21) compared to 0.25 (95% CI 0.11–0.37) for the control households when restricted to households where the school child was first to present in their household ($p = 0.04$). We find no significant differences between the SITP for intervention 0.18, 95% CI 0.05–0.29) and control (0.12, 95% CI 0.04–0.19) households with influenza A.

Transmission of influenza A and B

Forty-five (45) students had PCR confirmed influenza B and 44 had influenza A, including both H1N1, H3N2. We estimated the secondary attack rate of ILI for households with a PCR^+ influenza A infected child to be 0.31 (95% CI 0.23–0.39), and estimated the SAR for influenza B households to be 0.25 (95% CI 0.18–0.32) (Fig. 1). When restricting to only households where the child was the index case, these estimates are nearly identical for A (0.21 95% CI 0.15–0.29) and B households (0.21 95% CI 0.15–0.28).

The SITP for households with influenza A was 0.22 (95% CI 0.17–0.28) compared to 0.20 (95% CI 0.13–0.26) for influenza B households. The likelihood ratio (1.3) comparing models with separate SITPs for A and B to a common SITP provides little support for a difference between the SITP within influenza A and B households.

Table 3
Odds ratios of secondary ILI from mulitvariable logistic generalized estimating equation model.

Variable	OR (95% CI)
Household size	0.81 (0.56, 1.18)
Intervention	0.71 (0.33, 1.51)
Reported current immunization	0.51 (0.22, 1.16)
Black	0.45 (0.2, 0.99)
Only residence	2.23 (0.3, 16.5)
Influenza B	0.79 (0.38, 1.66)
Age of household member	
0–4 y/o	1.73 (0.78, 3.85)
5–18 y/o	2.03 (1.05, 3.92)
19–50 y/o	Ref
≥51 y/o	1.09 (0.4, 3.02)

Discussion

This analysis from the Pittsburgh Influenza Prevention Project provides estimates of key parameters associated with transmission of influenza A and B in households of primary school children and highlights significant risk factors for secondary ILI acquisition. Though our results suggest a protective effect of the intervention, these results were not statistically significant, except for one stratified analysis where we considered the transmission of influenza B only.

We found that point estimates for the SITP are higher in the control group than the intervention suggesting that there may be a difference that simply could not be captured with the observed sample size. We conducted simulations using the same number of households and size distribution to determine the approximate minimum effect size we could detect. Our simulations suggest that if the point estimate of the baseline group is within the range of previously reported values (Longini et al., 1982; Longini and Koopman, 1982; Cauchemez et al., 2004), we would need at least a 42% reduction in SITPs to classify it as statistically significant with the methods used in this paper.

We hypothesized that the largest effect would occur in households where the child presented symptoms first, since the child is the main target of the behavior change campaign. We believed that some effect on household transmission would be seen due to the child's altered hygiene behavior with possible spill-over effects to other household members. Supporting this hypothesis, we find a larger difference in point estimates of the secondary attack rates and the SITP when using only households where the school child presented symptoms before anyone else in the household.

Although we found no significant effect of the intervention, our study design only allowed us to estimate the effect of reduced transmission in households with symptomatic children. We hypothesize that the intervention would improve the child's hygiene behavior even when ill and at home. Previous results from this study, showed that absences due to influenza A were reduced in the intervention

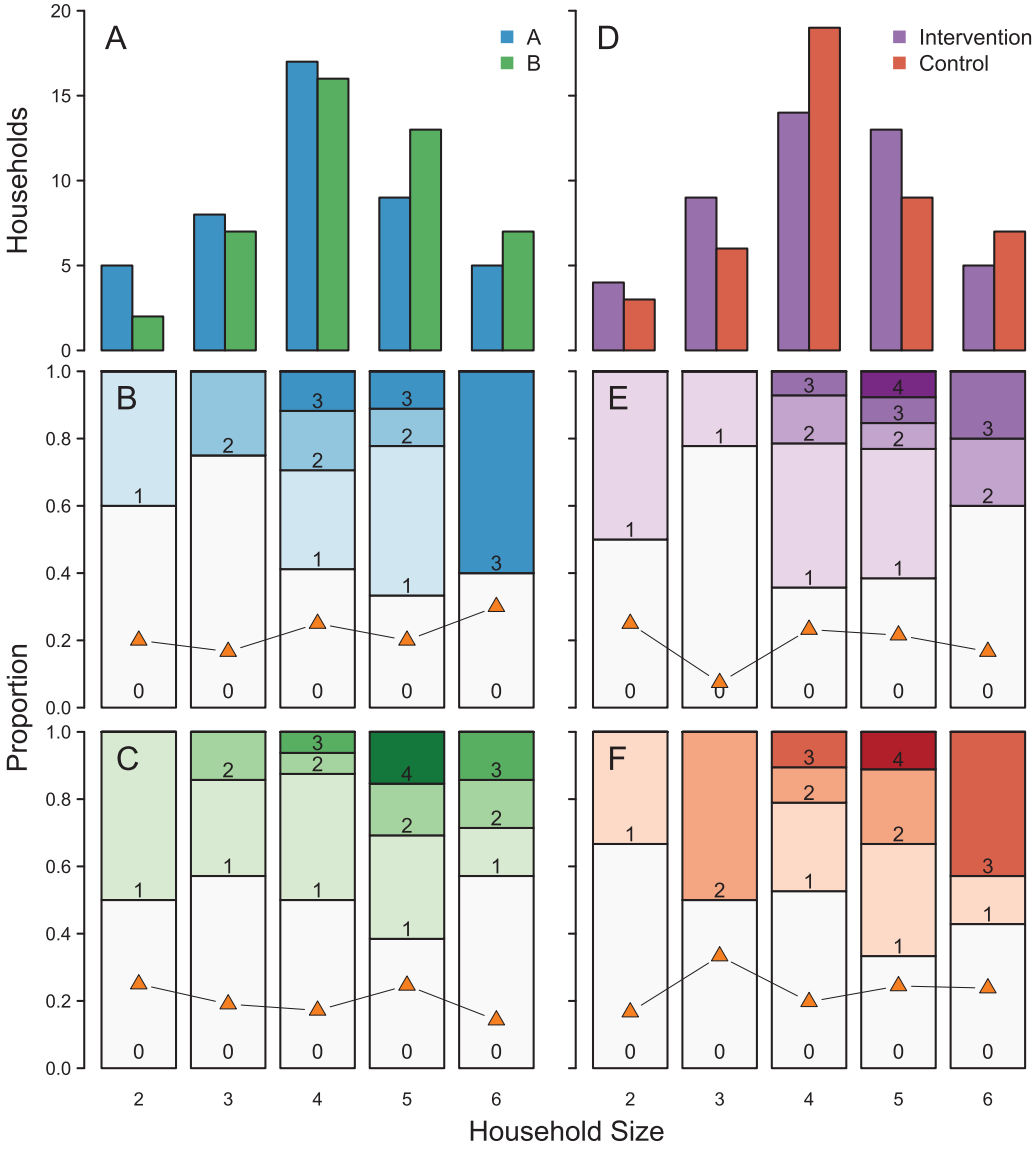

Fig. 1. Household size distribution and secondary attack rates (orange triangles) by influenza type and intervention arm. The top row (a and b) shows the household size distribution. Panels c–f show the secondary attack rate (orange triangles and line) by household size for households by influenza type (influenza A in panel c and influenza B in panel d) and intervention arm (intervention in panel e and control in panel f). For example, the first entry in panel e shows two intervention households of size two, one with one secondary case and the second with no secondary cases. The average secondary attack rate shown by the orange triangle is therefore $0.5 \times 0 + 0.5 \times 0.5 = 0.25$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

group (Stebbins et al., 2011). These averted symptomatic infections could result in fewer households having at least one case of ILI. Additionally, it is possible that many households had at least one ILI case in them without the school-aged child becoming sick enough to miss school. This analysis would not capture the impact of the interventions in these cases.

We observed differences in the influenza type between control and intervention households, where 61% (27) of control households and only 38% (17) of intervention had confirmed influenza A. Previous studies suggest that influenza B is seen less frequently in adults than in children 5–14 years of age (Philip et al., 1961; Monto and Kioumehr, 1975). Influenza A is also observed with reduced frequency in adults compared to children, but this reduction has been observed to be less (Philip et al., 1961). Our results indicate that influenza B transmission to families was comparable to influenza A despite individuals >14 making up a large proportion of the population of our households (51% in control and 52% in intervention households). When we compare households with influenza A to those with B, we find little evidence to support differences in transmissibility. Our results underscore the importance of influenza B vaccination in adults as well as children.

This analysis had a number of limitations. All secondary cases were diagnosed with a clinical definition of influenza which has lower sensitivity and specificity than laboratory-confirmation. However, we expect independent non-differential misclassification as a result of this case definition which would bias our effect estimates towards the null. Our models rely on the assumption that all transmission occurred solely within the household. We also tested models that included community transmission, but none were supported by the data (as measured by AICc). Due to the relatively low proportion of missing data we assumed that our data was missing completely at random, which may not be the case. If the missing data mechanism was strongly related to one or more observed or unobserved factors, our results could be biased. Despite the fact that this is one of the largest studies of its kind, the number of households with a confirmed influenza index case may not be

large enough to detect statistical differences in key parameters. A larger sample size would allow for more precise estimation of and detection of small differences in these parameters.

Conclusions

The results from this study demonstrate an approach for evaluating the effect of an NPI on household influenza transmission and suggest that this school-based program had little to no effect transmission beyond the classroom in households of influenza infected students. To our knowledge this is the first study to look at how school based NPIs impact transmission in the households and a larger study of this kind would help provide more evidence on the efficacy of NPIs on health based outcomes both in school and at home. This study adds to only a few previous estimates of the transmissibility of influenza B and finds no evidence supporting differences between influenza A and B.

Authors contributions

JHS, CJV, DSB, DATC, and ASA conceived and designed the study and analyses. JHS, CJV, DSB, and DATC collected the original data. ASA, DATC, and BMA analyzed the data. ASA, JHS, CJV, DSB, DATC, and BMA wrote the paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2013.09.001.

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