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Increased risk of non-influenza respiratory virus infections associated with receipt of inactivated influenza vaccine

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Key points:

Our experimental study provides evidence consistent with temporary non-specific immunity against other respiratory viruses following influenza virus infection, a phenomenon that could explain the epidemiologic dynamics of respiratory virus epidemics described in ecologic studies.

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ABSTRACT

We randomized 115 children to trivalent inactivated influenza vaccine (TIV) or placebo. Over the following 9 months, TIV recipients had increased risk of virologically-confirmed non-influenza infections (relative risk: 4.40; 95% confidence interval: 1.31-14.8). Being protected against influenza, TIV recipients may lack temporary non-specific immunity that protected against other respiratory viruses.

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INTRODUCTION

Influenza vaccination is effective in preventing influenza virus infections and associated morbidity in school-age children [1,2]. The potential for temporary non-specific immunity between respiratory viruses after an infection, and consequent 'interference' at the population level between epidemics of these viruses, has been hypothesized with limited empirical evidence to date mainly from ecological studies [3-15]. We investigated the incidence of acute upper respiratory tract infections (URTIs) associated with virologically-confirmed respiratory virus infections in a randomized controlled trial of influenza vaccination.

METHODS

Recruitment and follow-up of participants

In a double-blind randomized controlled trial, we randomly allocated children aged 6-15 to receive 2008-09 seasonal trivalent influenza inactivated vaccine (TIV) (0.5ml Vaxigrip, Sanofi Pasteur) or placebo [16]. Serum specimens were drawn from subjects before vaccination in November–December 2008, one month after vaccination, in mid-study around April 2009, and at the end of the study in August–October 2009. Subjects were followed up for illnesses through symptom diaries and telephone calls, and illness reports in any household member triggered home visits where nasal and throat swabs (NTS) were collected from all household members. We defined the follow-up period for each subject from 14 days after receipt of TIV/placebo until collection of mid-study sera as the "winter" season and from collection of mid-study through final sera as the "summer" season.

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Proxy written informed consent was obtained for all subjects from their parents or legal guardians, with additional written assent from those 8 years of age or older. The study protocol was approved by the Institutional Review Board of Hong Kong University.

Laboratory methods

NTS were tested for 19 respiratory viruses by the ResPlex II Plus multiplex array [17-19] and for influenza A and B by reverse-transcription polymerase-chain-reaction (RT-PCR) [16,20] (Appendix Text). We refer to infections determined by these assays as 'confirmed' infections. Information on influenza serology is provided in the Appendix Text.

Statistical analysis

We defined an acute respiratory illness (ARI) determined by self-reported signs and symptoms as at least any 2 of body temperature ≥37.8°C, headache, sore throat, cough, presence of phlegm, coryza, and myalgia [16]. We defined a febrile acute respiratory illness (FARI) as body temperature ≥37.8°C plus cough or sore throat. Because duration of follow-up varied by subject, we estimated the incidence rates of ARI and FARI episodes and confirmed viral infections overall and in the winter and summer seasons, and estimated the relative risk of these episodes for subjects who received TIV versus placebo via the incidence rate ratio using Poisson regression (Appendix Text). All statistical analyses were conducted in R version 2.11.0 (R Development Core Team, Vienna, Austria). Data

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and syntax to reproduce these statistical analyses are available on the corresponding author's website.

RESULTS

Among the 115 subjects who were followed up, the median (inter-quartile range) duration of follow-up was 272 (264, 285) days with no statistically significant differences in age, sex, household size or duration of follow-up between TIV and placebo recipients (Table 1). We identified 134 ARI episodes of which 49 met the more stringent FARI case definition. Illnesses occurred throughout the study period (Appendix Figure 1). There was no statistically significant difference in the risk of ARI or FARI between subjects who received TIV or placebo, either in winter or summer 2009 (Table 2).

We were able to collect 73 NTS for testing from 65/134 (49%) of subjects' ARI episodes, which included 22/49 (45%) of the FARI episodes. The average delay between ARI onset and collection of first NTS was 1.22 days and 5% of NTS were collected >3 days after illness onset, with no statistically significant differences between TIV and placebo recipients. We detected respiratory viruses in 32/65 NTS (49%) collected during ARI episodes, which included 12/22 (55%) of the FARI episodes. We collected 85 NTS from subjects at times when one of their household contacts reported an acute URTI but the subjects were not ill, and identified viruses in 3/85 (4%) including influenza A(H3N2), coxsackie/echovirus and coronavirus 229E.

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There was no statistically significant difference in the risk of confirmed seasonal influenza infection between recipients of TIV or placebo although the point estimate was consistent with protection in TIV recipients (relative risk, RR: 0.66, 95% confidence interval, CI: 0.13, 3.27). TIV recipients had significantly lower risk of seasonal influenza infection based on serologic evidence (Appendix Text). However, subjects who received TIV had higher risk of ARI associated with confirmed non-influenza respiratory virus infections (RR: 4.40; 95% CI: 1.31, 14.8). Including 2 additional confirmed infections when subjects did not report ARI, subjects who received TIV had higher risk of confirmed non-influenza respiratory virus infections (RR: 3.46; 95% CI: 1.19, 10.1). The majority of the non-influenza respiratory virus detections were rhinoviruses and coxsackie/echoviruses and the increased risk among TIV recipients was also statistically significant for these viruses (Table 3). Most respiratory virus detections occurred in March 2009, shortly after a period of peak seasonal influenza activity in February 2009 (Figure 1).

DISCUSSION

In our study in the pre-pandemic period, we did not observe a statistically significant reduction in confirmed seasonal influenza virus infections in the TIV recipients (Table 3), although serological evidence (Appendix Text) and point estimates of vaccine efficacy based on confirmed infections were consistent with protection of TIV recipients against the seasonal influenza viruses that circulated in January-March 2009 [16]. We identified a statistically significant increased risk of non-influenza respiratory virus infections among TIV recipients (Table 3), including significant increases in the risk of rhinovirus and coxsackie/echovirus

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infections which were most frequently detected in March 2009 immediately following the peak in seasonal influenza activity in February 2009 (Figure 1).

The increased risk of non-influenza respiratory viruses among TIV recipients could be an artefactual finding, for example measurement bias could have resulted if subjects were more likely to report their first ARI episode but less likely to report subsequent episodes, while there was no real difference in rhinovirus or other non-influenza respiratory virus infections following the winter influenza season. The increased risk could also indicate a real effect. Receipt of TIV could increase influenza immunity at the expense of reduced immunity to non-influenza respiratory viruses, by some unknown biological mechanism. Alternatively, our results could be explained by temporary non-specific immunity following influenza virus infection, through the cell-mediated response or, more likely, the innate immune response to infection [21-23]. Subjects who received TIV would have been protected against influenza in February 2009 but then would not have had heightened non-specific immunity in the following weeks. They would then face a higher risk of certain other virus infections in March 2009 compared to placebo recipients (Figure 1). The duration of any temporary non-specific immunity remains uncertain [13] but could be of the order of 2-4 weeks based on these observations. It is less likely that the interference observed here could be explained by reduced community exposures during convalescence, i.e. behavioral rather than immunologic factors [14].

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The phenomenon of virus interference has been well known in virology for over 60 years [24-27]. Ecological studies have reported phenomena potentially explained by viral interference [3-11]. Non-specific immunity against non-influenza respiratory viruses was reported in children for 1-2 weeks after receipt of live attenuated influenza vaccine [28]. Interference in respiratory and gastrointestinal infections has been reported following receipt of live oral poliovirus vaccine [29-32].

Our results are limited by the small sample size and the small number of confirmed infections. Despite this limitation we were able to observe a statistically significant increased risk of confirmed non-influenza respiratory virus infections among TIV recipients (Table 3). A negative association between serologic evidence of influenza infection and confirmed non-influenza virus infection in winter 2009 was not statistically significant (odds ratio: 0.27; 95% CI: 0.01, 2.05) (Appendix text). One must be cautious in interpreting serology in children who have received TIV [2,33]. Finally, acute URTI incidence was based on self-report with regular telephone reminders and we may have failed to identify some illnesses despite rigorous prospective follow-up.

Temporary non-specific immunity leading to interference between epidemics of respiratory viruses could have important implications. First, as observed in our trial, TIV appeared to have poor efficacy against acute URTIs (Table 2) apparently because the protection against influenza virus infections conferred by TIV was offset by an increased risk of other respiratory virus infections (Table 3). Second, interference between respiratory viruses could suggest new approaches

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to mitigating epidemics [32]. Mass administration of live polio vaccine in children has been used to control enterovirus 71 epidemics [10,31]. Finally, viral interference could bias estimates of influenza vaccine effectiveness in test-negative case-control studies (Appendix text) [2,34-43]. One test-negative study reported an association between receipt of TIV and the risk of ILI associated with a non-influenza virus [38].

Further work is required to more fully characterize temporary non-specific immunity overall and within specific groups such as children. Animal studies [44-50] and volunteer adult human challenge studies [51] could provide useful evidence. Further community-based observational cohort studies, and community-based experimental studies such as our vaccine trial, may be particularly suitable for investigating temporary non-specific immunity since most acute URTIs do not require medical attention.

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CONFLICTS OF INTEREST

BJC has received research funding from MedImmune Inc., a manufacturer of influenza vaccines. DKMI has received research funding from Roche. JSMP receives research funding from Crucell MV. The authors report no other potential conflicts of interest.

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Table 1. Characteristics of subjects and duration of follow-up.

	TIV (n=69)		Placebo (n=46)	
	n	(%)	n	(%)
Age group				
6-8 years	19	(28%)	16	(35%)
9-11 years	41	(59%)	27	(59%)
12-15 years	9	(13%)	3	(7%)
Female	30	(43%)	23	(50%)
Median duration of follow-up (days)	272		272	
Mean number of individuals per household	3.7		3.6	

Abbreviations: TIV = trivalent inactivated influenza vaccine.

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Table 2. Incidence rates of acute upper respiratory tract infections among 115 subjects aged 6-15 years who received trivalent inactivated influenza vaccine (TIV) or placebo.

	TIV (n=69)		Placebo (n=46)		Relative risk (95% CI)		p-value
	Rate*	(95% CI)	Rate*	(95% CI)			
Winter 2009							
ARI† episodes	2080	(1530, 2830)	2260	(1550, 3300)	0.92	(0.57, 1.50)	0.74
FARI† episodes	609	(346, 1070)	753	(392, 1450)	0.81	(0.34, 1.92)	0.63
Summer 2009							
ARI† episodes	1510	(1130, 2020)	1160	(757, 1780)	1.30	(0.78, 2.18)	0.31
FARI† episodes	658	(424, 1020)	442	(221, 884)	1.49	(0.65, 3.38)	0.33

* Incidence rates estimated as the number of ARI or FARI episodes per 1,000 person-years of follow-up.

† ARI defined as at least two of body temperature ≥37.8°C, cough, sore throat, headache, runny nose, phlegm and myalgia; FARI defined as body temperature ≥37.8°C plus cough or sore throat.

Abbreviations: TIV = trivalent inactivated influenza vaccine; CI = confidence interval; ARI = acute respiratory illness; FARI = febrile acute respiratory illness.

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Table 3. Incidence rates of respiratory virus detections by RT-PCR and multiplex assay in respiratory specimens collected from 115 subjects aged 6-15 years who received trivalent influenza vaccine (TIV) or placebo, during 134 acute respiratory illness (ARI) episodes.

	TIV (n=69)			Placebo (n=46)			p-value
	n	Rate*	(95% CI)	n	Rate*	(95% CI)	
Any seasonal influenza	3	58	(19, 180)	3	88	(28, 270)	0.61
Seasonal influenza A(H1N1)	2	39	(10, 160)	2	59	(15, 240)	0.68
Seasonal influenza A(H3N2)	1	19	(3, 140)	0	0	(0, 88)	0.31
Seasonal influenza B	0	0	(0, 58)	1	29	(4, 210)	0.17
Pandemic influenza A(H1N1)	3	58	(19, 180)	0	0	(0, 88)	0.08
Any non-influenza virus†	20	390	(250, 600)	3	88	(28, 270)	<0.01
Rhinovirus	12	230	(130, 410)	2	59	(15, 240)	0.04
Coxsackie/echovirus	8	160	(78, 310)	0	0	(0, 88)	<0.01
Other respiratory virus‡	5	97	(40, 230)	1	29	(4, 210)	0.22

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ARI episode with specimen collected but no virus detected	19	369	(235, 578)	14	412	(244, 696)	0.75
ARI episode with no specimen collected	41	796	(586, 1080)	28	824	(569, 1190)	0.89

* Incidence rates estimated as the number of virus detections or illness episodes per 1,000 person-years of follow-up. Acute respiratory illness (ARI) defined as at least two of body temperature ≥37.8°C, cough, sore throat, headache, runny nose, phlegm and myalgia.

† In TIV recipients there were 4 detections with both rhinovirus and coxsackie/echovirus, and 1 detection with both coxsackie/echovirus and coronavirus NL63.

‡ including positive detections of coronavirus, human metapneumovirus, parainfluenza, RSV. The ResPlex II multiplex array tested for 19 virus targets including influenza types A and B (including 2009-H1N1), RSV types A and B, parainfluenza types 1-4, metapneumovirus, rhinovirus, coxsackievirus/echovirus, adenovirus types B and E, bocavirus, coronavirus types NL63, HKU1, 229E and OC43.

Abbreviations: TIV = trivalent inactivated influenza vaccine; ARI = acute respiratory illness; CI = confidence interval.

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FIGURE LEGENDS

Figure 1. Timing of influenza and other respiratory virus detections in 115 subjects aged 6-15 years (panels A-D) compared to local influenza surveillance data (panel E). Solid red bars indicate detections in 69 subjects who received 2008-09 trivalent inactivated influenza vaccine, black dashed bars indicate detections in 46 subjects who received placebo. The bottom panel shows local laboratory surveillance data on the proportion of influenza virus detections among specimens submitted to the Public Health Laboratory Service. Fewer than 2% of PHLS specimens were positive for influenza B throughout the year.

Footnote to Figure 1: 'Other viruses' included coronavirus, human metapneumovirus, parainfluenza, RSV.

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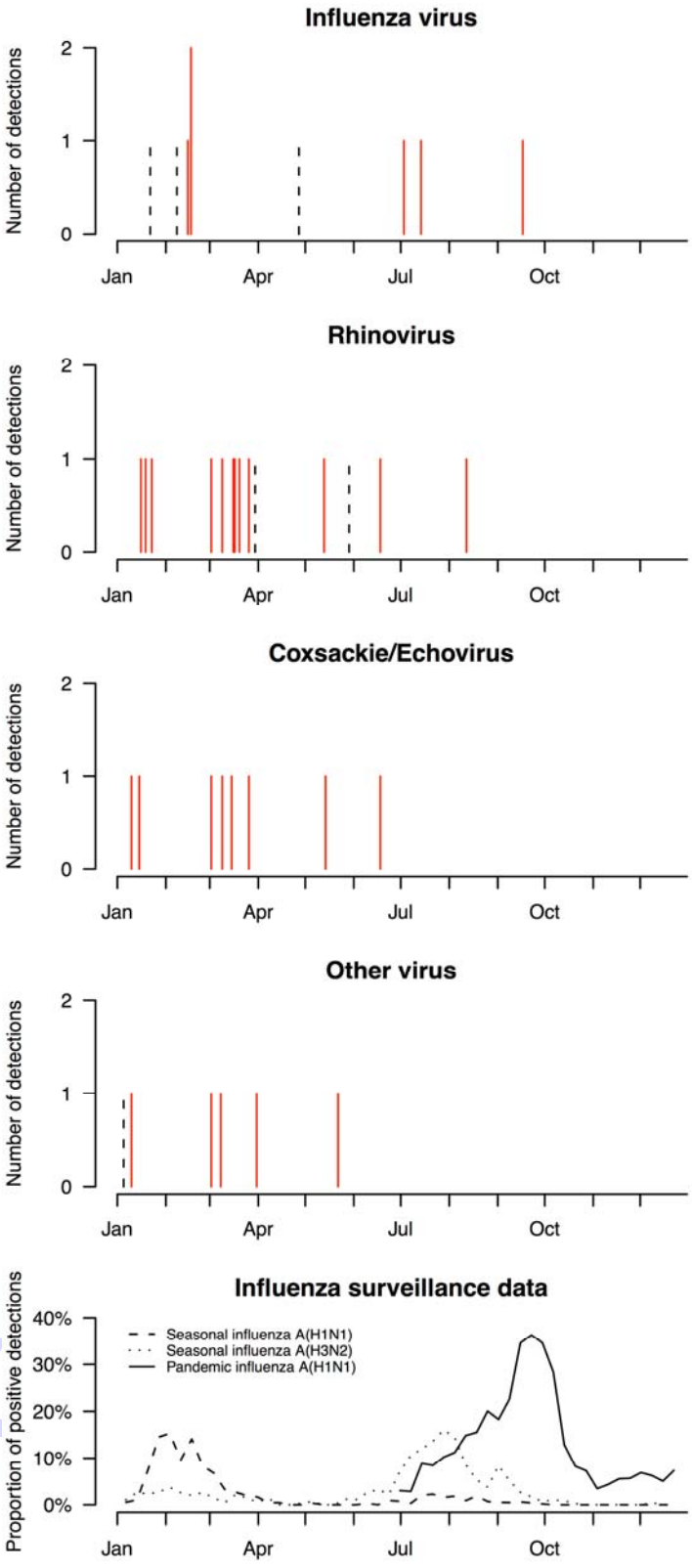

Fig. 1

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