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TITLE:
Increased Risk of Noninfluenza Respiratory Virus Infections Associated With Receipt of Inactivated Influenza Vaccine

ABSTRACT:
We randomized 115 children to trivalent inactivated influenza vaccine (TIV) or placebo. Over the following 9 months, TIV recipients had an 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.

Recruitment and Follow-up of Participants ::: METHODS:
In a double-blind randomized controlled trial, we randomly allocated children aged 6–15 years to receive 2008–2009 seasonal trivalent influenza inactivated vaccine (TIV; 0.5 mL Vaxigrip; Sanofi Pasteur) or placebo [16]. Serum specimens were obtained from participants before vaccination from November through December 2008, a month after vaccination, in midstudy around April 2009, and at the end of the study from August through October 2009. Participants were followed up for illnesses through symptom diaries and telephone calls, and illness reports in any household member triggered home visits during which nasal and throat swab specimens (NTSs) were collected from all household members. We defined the follow-up period for each participant from 14 days after receipt of TIV or placebo to collection of midstudy serum samples as the winter season and from collection of midstudy samples through final serum sample obtainment as the summer season.
Proxy written informed consent was obtained for all participants from their parents or legal guardians, with additional written assent from those ≥8 years of age. The study protocol was approved by the Institutional Review Board of Hong Kong University.

Laboratory Methods ::: METHODS:
NTSs 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] (Supplementary Appendix). We refer to infections determined by these assays as “confirmed” infections. Information on influenza serology is provided in the Supplementary Appendix .

Statistical Analysis ::: METHODS:
We defined an acute respiratory illness (ARI) determined by self-reported signs and symptoms as ≥2 of the following signs or symptoms: body temperature ≥37.8°C, headache, sore throat, cough, presence of phlegm, coryza, and myalgia [16]. We defined febrile acute respiratory illness (FARI) as body temperature ≥37.8°C plus cough or sore throat. Because duration of follow-up varied by participant, we estimated the incidence rates of ARI and FARI episodes and confirmed viral infections overall and during the winter and summer seasons and estimated the relative risk of these episodes for participants who received TIV versus placebo with use of the incidence rate ratio using Poisson regression (Supplementary Appendix). All statistical analyses were conducted using R, version 2.11.0 (R Development Core Team, Vienna, Austria). Data and syntax to reproduce these statistical analyses are available on the corresponding author's Web site.

RESULTS:
Among the 115 participants who were followed up, the median duration of follow-up was 272 days (interquartile range, 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 (Supplementary Appendix Figure 1). There was no statistically significant difference in the risk of ARI or FARI between participants who received TIV and those who received placebo, either during winter or summer 2009 (Table 2).

We were able to collect 73 NTSs for testing from participants for 65 of 134 (49%) ARI episodes, which included 22 of 49 (45%) FARI episodes. The mean delay between ARI onset and collection of first NTS was 1.22 days, and 5% of NTSs were collected >3 days after illness onset, with no

statistically significant differences between TIV and placebo recipients. We detected respiratory viruses in 32 of 65 NTSs (49%) collected during ARI episodes, which included 12 of 22 (55%) FARI episodes. We collected 85 NTSs from participants at times when one of their household contacts reported an acute URTI but the participants were not ill, and identified viruses in 3 of the specimens (4%), including influenza A (H3N2), coxsackie/echovirus, and coronavirus 229E.
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], .13–3.27). TIV recipients had significantly lower risk of seasonal influenza infection based on serologic evidence (Supplementary Appendix). However, participants who received TIV had higher risk of ARI associated with confirmed noninfluenza respiratory virus infection (RR, 4.40; 95% CI, 1.31–14.8). Including 2 additional confirmed infections when participants did not report ARI, TIV recipients had higher risk of confirmed noninfluenza respiratory virus infection (RR, 3.46; 95% CI, 1.19–10.1). The majority of the noninfluenza 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 the prepandemic period of our study, we did not observe a statistically significant reduction in confirmed seasonal influenza virus infections in the TIV recipients (Table 3), although serological evidence (Supplementary Appendix) and point estimates of vaccine efficacy based on confirmed infections were consistent with protection of TIV recipients against the seasonal influenza viruses that circulated from January through March 2009 [16]. We identified a statistically significant increased risk of noninfluenza respiratory virus infection among TIV recipients (Table 3), including significant increases in the risk of rhinovirus and coxsackie/echovirus infection, which were most frequently detected in March 2009, immediately after the peak in seasonal influenza activity in February 2009 (Figure 1).
The increased risk of noninfluenza respiratory virus infection among TIV recipients could be an artefactual finding; for example, measurement bias could have resulted if participants were more likely to report their first ARI episode but less likely to report subsequent episodes, whereas there was no real difference in rhinovirus or other noninfluenza respiratory virus infections after 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 noninfluenza respiratory viruses, by some unknown biological mechanism. Alternatively, our results could be explained by temporary nonspecific immunity after influenza virus infection, through the cell-mediated response or, more likely, the innate immune response to infection [21–23]. Participants who received TIV would have been protected against influenza in February 2009 but then would not have had heightened nonspecific immunity in the following weeks. They would then face a higher risk of certain other virus infections in March 2009, compared with placebo recipients (Figure 1). The duration of any temporary nonspecific 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 (ie, behavioral rather than immunologic factors) [14].
The phenomenon of virus interference has been well known in virology for >60 years [24–27]. Ecological studies have reported phenomena potentially explained by viral interference [3–11]. Nonspecific immunity against noninfluenza 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 after 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 noninfluenza respiratory virus infection among TIV recipients (Table 3). A negative association between serologic evidence of influenza infection and confirmed noninfluenza virus infection in winter 2009 was not statistically significant (odds ratio, 0.27; 95% CI, .01–2.05) (Supplementary Appendix). 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 nonspecific 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 infection conferred by TIV was offset by an increased risk of other respiratory virus infection (Table 3). Second, interference between respiratory viruses could suggest new approaches 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 (Supplementary Appendix) [2, 34–43]. One test-negative study reported an association between receipt of TIV and the risk of influenza-like illness associated with a noninfluenza virus [38].

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