Ambient ozone and influenza transmissibility in Hong Kong

To the Editor:

Understanding the environmental drivers of influenza transmissibility would contribute to the early intervention and long-term control strategies of seasonal influenza, a serious public health problem that causes considerable morbidity and mortality each year. Within the burgeoning literature on influenza transmission, there are conflicting lines of evidence on the role of the environment [1]. Besides meteorological factors, it is also uncertain how common air pollutants such as ozone (O_3), sulfur dioxides (SO_2), nitrogen dioxide (NO_2), nitric oxide (NO) and particulate matter may affect influenza transmission [2]. The objective of our study was to examine the relationship of influenza transmissibility in Hong Kong with common air pollutants and other environmental factors, including ultraviolet radiation and absolute humidity.

A number of earlier studies on the environmental drivers of influenza transmission used absolute counts of influenza cases as the dependent variable in statistical models. However, the number of incident influenza cases is not an ideal representation of influenza transmission intensity [3]. We estimated the daily effective reproduction number (R_t), a real-time measure of transmissibility, for each influenza type/subtype using data from the subtropical city of Hong Kong, which has excellent influenza surveillance data, near year-round circulation of influenza, and considerable variations in environmental factors and pollutant levels. We combined information on influenza-like illnesses (ILIs) in the community and laboratory surveillance data to estimate weekly incidence rates of influenza virus infections in the community, referred to as ILI$^+$ rates [4]. In theory, this time series should be a linear correlate of the incidence rate of infections in the community [4], and it was previously shown that there was a very close correlation between this measure and laboratory confirmed H1N1pdm09 hospitalisations in Hong Kong in 2009–2010 [5]. Finally, we multiplied the weekly ILI$^+$ rates by a large constant, representing the inverse of the coverage of the sentinel sites in Hong Kong, and rounded to the nearest integer to obtain a time series of weekly ILI$^+$ counts (figure 1a–d). This was then interpolated to daily ILI$^+$ counts using splines. During the study period of January 1998 to December 2013, we identified 44 distinct influenza epidemics, including 16 epidemics of seasonal influenza A(H3N2), 10 of A(H1N1), four of A(H1N1pdm09) and 14 of influenza B (figure 1a–d). Daily concentrations of major air pollutants in 10 local monitoring stations were used to calculate the territory-wide daily average concentrations for Hong Kong. Meteorological data were obtained from the Hong Kong Observatory.

Transmissibility can be measured by the effective (or instantaneous) R_t as a unit-free index of outbreak intensity, defined as the average number of secondary infections caused in the population by a typical single infectious person at time t. We estimated R_t from daily ILI$^+$ counts for each influenza type/subtype. We adopted a simple branching process model [6] to estimate daily R_t values. We assumed a Gamma distribution for the serial interval with mean±SD values of 3.08±1.39 for influenza A(H1N1pdm09), 3.26±1.93 for A(H1N1), 3.48±1.88 for A(H3N2) and 3.72±1.95 for influenza B [7].

We used regression models to explore the association between influenza transmissibility, measured by the daily estimated effective R_t for up to 8 weeks either side of each epidemic peak, and various pollutant factors with 0–7 days lag values. In nonlinear univariate regression analysis, we found that R_t had statistically significant negative association with ambient O_3 across all the types/subtypes; NO and CO had a weak positive association with influenza transmissibility, while other pollutants had no consistent patterns and the estimated effects were generally not statistically significant. The estimated nonlinear effect of ozone on influenza transmissibility is shown in figure 1f. The multivariable regression (DLM, dlmn
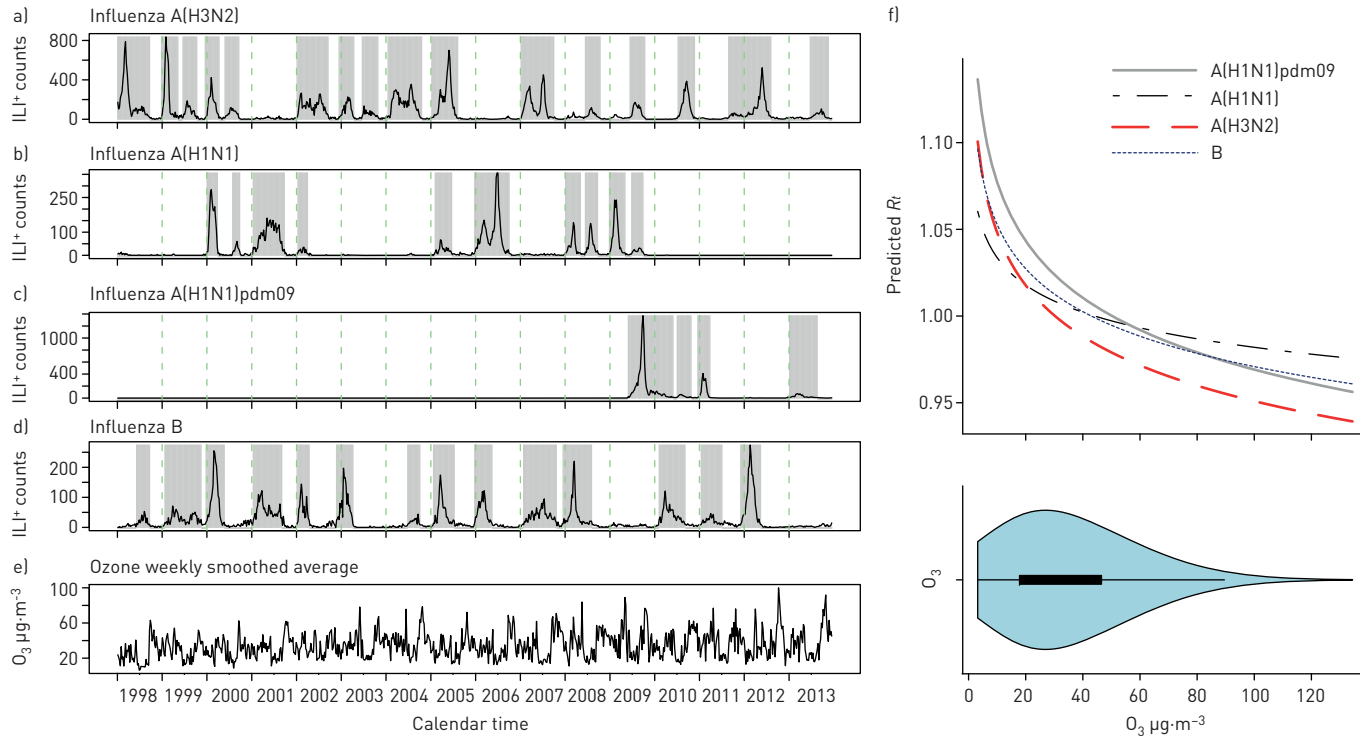
FIGURE 1 Weekly activity of influenza (influenza-like illness (ILI)+ proxy) of a) influenza A(H3N2), b) influenza A(H1N1), c) influenza A(H1N1)pdm09 and d) influenza B (black lines) along with the 44 predefined epidemics (grey bars) of these virus type and subtypes, and e) the weekly smoothed average of ozone (O_3) concentrations in Hong Kong from 1998 to 2013. f) Estimated nonlinear relationship between the effective reproduction number (R_t) and ambient daily O_3 concentrations in the regression analysis (based on the selected best-fitting lag of 5 days for A (H3N2), 6 days for A(H1N1), 7 days for A(H1N1)pdm09 and 4 days for influenza B) for influenza A(H3N2), A(H1N1) prior to 2009, A(H1N1)pdm09 from 2009 onwards and influenza B. The violin plot shown in the lower panel indicates the distribution of daily ambient ozone concentrations; the median is indicated by the white circle, the interquartile range is indicated by the black rectangle and the blue area displays a kernel density estimate of the distribution of values (i.e. a smoothed histogram).

package in R) model that included depletion of susceptibles, interepidemic factors, absolute humidity and ambient O_3 could explain 40% of the observed variation in R_t for seasonal influenza A(H3N2), 35% for seasonal influenza A(H1N1), 60% for A(H1N1)pdm09 and 21% for influenza B. With a large proportion of the variance explained by the intrinsic factors and absolute humidity in the basic model for influenza transmissibility, the ambient O_3 contributed only marginally, explaining a further 4% of the total variance in influenza transmissibility for H3N2 and up to 1% for the other three influenza types/subtypes. A permutation analysis indicated that the association was not likely to be due to chance (data not shown). While the proportion of variance in influenza transmissibility explained by O_3 is modest, this could still correspond to a substantial effect on incidence in a single epidemic, which includes many transmission events [8]. In Hong Kong, seasonal influenza often exhibits twice-annual peaks in periods from July to August (summer) and from January to March (late winter/early spring), which generally coincide with two troughs of O_3 concentration seasonality (figure 1a–e).

The association of ambient O_3 with reduced influenza transmissibility may be related to the virucidal activity of O_3 and its effect on host defense. O_3 inactivation of influenza virus within a few hours has been reported in studies *in vitro* [9]. However, a more plausible mechanism underlying the association of O_3 with a reduction in influenza transmissibility is O_3-primed immunity against influenza virus infection. Inhalation of ambient O_3 can enhance pulmonary innate immunity that promote allergic responses in healthy human subjects and susceptible populations [10]. It is not likely that O_3 as an oxidant gas is directly recognised by a discrete receptor; O_3-induced inflammation is probably mediated by a secondary messenger. One such candidate is interleukin (IL)-33. Induced by O_3 exposure, IL-33 further activates type 2 cytokines in the lung. IL-33 appears to be the common denominator for the list of asthma triggers including allergy, viral infection and O_3 [11]. As a multifaceted cytokine, however, IL-33 not only play a pathogenic role in Th2-mediated diseases but also drives Th1 and CD8 T-cell responses that induce protective immunity against viral infections [12]. In the case of influenza, IL-33 promotes lung tissue homeostasis during viral infection [13]. Used as an adjuvant in influenza vaccines, IL-33 increases the antigen-specific CD4 and CD8 T-cell responses in preclinical settings [14].

One limitation of the present study was the interpolation of daily ILI[+] counts from the weekly data. The day-to-day variation in transmissibility might have been reduced because of this interpolation, leading to underestimated effects of the drivers for influenza. If available, using ILI[+] data at a daily scale would improve the estimates. Another limitation is that the territory-wide daily average calculation might introduce measurement errors for certain pollutants such as NO_2 and CO, which have a relatively large spatial variability. However, if the spatial variability did not change systematically with time, the aggregated exposure measurement should not bias the study findings based on territory-wide time-series data of both influenza and environmental drivers.

As a highly reactive oxidant air pollutant, O_3 may decrease host defences against bacterial and fungal infections in the airways, and aggravate pre-existing diseases such as asthma. In the case of influenza, however, ambient O_3 had not been consistently associated with hospital admissions or emergency department visits for influenza virus infections according to the review by the US Environmental Protection Agency in 2013 [10]. Our current findings of reduced influenza transmissibility associated with ambient O_3 in Hong Kong warrant further study.

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