The relationship between school holidays and transmission of influenza in England and Wales

Charlotte Jackson*[1,2,3] BA MSc PhD, Emilia Vynnycky[2,3] BA MSc PhD, Punam Mangtani[2] MBBS MRCP MSc MD

[1] Research Department of Infection and Population Health, University College London, London, United Kingdom

[2] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

[3] Statistics, Modelling and Economics Department, Public Health England, Colindale, London, United Kingdom

*Corresponding author.

Email c.r.jackson@ucl.ac.uk

Phone +44 (0)20 3108 2375.

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Abbreviations

CI confidence interval

GP general practitioner

ILI influenza-like illness

RCGP Royal College of General Practitioners

Keywords

Epidemiology

Disease transmission, infectious

Influenza, human

Schools

Abstract

School closure is often considered as an influenza control measure, but its effects on transmission are poorly understood. We used two approaches to estimate how school holidays affect the contact parameter (per capita rate of contact sufficient for infection transmission) for influenza using primary care data (England and Wales, 1967-2000). Firstly, an age-structured susceptible-infectious-recovered model was fitted to each year's data to estimate the proportional change in the contact parameter during school holidays compared to termtime. Secondly, we calculated the percentage difference in the contact parameter between holidays and termtime from weekly values of the contact parameter, estimated directly from simple mass action models. Estimates were combined using random effects meta-analysis, where appropriate. From fitting to the data, the difference in the contact parameter amongst 5-14 year-olds during holidays compared to termtime ranged from a 36% reduction to a 17% increase; estimates were too heterogeneous for meta-analysis. Based on the simple mass action model, the contact parameter was 17% (95% confidence interval 9-25%) lower during holidays than termtime. Results were robust to the assumed proportions of infections that are reported and individuals who were susceptible when the influenza season starts. School closure may reduce transmission during influenza outbreaks.

Influenza-like illness (ILI) causes an estimated 420,000 excess general practitioner (GP) consultations in England and Wales annually (1); pandemic influenza can cause extensive morbidity and disruption. School closure may reduce cumulative and peak influenza attack rates (2, 3). However, its effects on transmission remain unclear (2, 3), partly because data on how it affects contact patterns are limited (4-7). Mathematical models can provide estimates of how contact rates vary during the year, including during school holidays (8-10).

A modelling study of French surveillance data concluded that holidays reduce the rate of influenza transmission to children by 20-29% compared to termtime but do not affect transmission to adults (8). Other modelling studies considering hospitalisation data from The Netherlands and France (10) or French primary care data (9) also suggested that contact rates were lowest during school holidays. In this paper, we estimate weekly effective contact rates from primary care data from England and Wales, providing estimates suggesting how school closure during a pandemic might affect contact patterns.

METHODS

Datasets

Weekly age-stratified GP consultation rates per 100,000 for ILI, 1967-2008, and weekly case numbers and population denominators, were provided by the Royal College of General Practitioners (RCGP) (Web Figures 1.1 and 1.2). However, consultation rates in all seasons after 1999 were low (see below) so were excluded.

We defined an influenza year to run from week 40 (early October) to week 39. We used standard definitions of "normal seasonal activity" of influenza (11, 12) to restrict analysis to epidemic weeks (those with an overall consultation rate ≥50/100,000/week before 2003/04 or

≥30/100,000/week thereafter). We excluded seasons after 1999/2000 as, in each of these years, the epidemic threshold was never exceeded or was exceeded in only one week of holiday and/or one week of termtime. We distinguish between years in which one influenza subtype dominated and other years, identified from published reports (Web Table 1.1).

Web Appendix 1 summarises how school holidays are organised in England and Wales. We assumed that holidays fell in the same weeks each year.

Assessing the relationship between school holidays and influenza transmission: overview

We quantified influenza transmission using the contact parameter: the per capita rate of effective contact (contact sufficient to cause transmission, should it occur between a susceptible and an infectious individual (13)). We used two modelling approaches to estimate the effects of school holidays on the contact parameter. Firstly, we fitted a susceptible-infectious-recovered (SIR) model to the reported incidence data for each influenza year to estimate the relative difference between the contact parameter during termtime and school holidays. Secondly, we used the method adopted by Fine and Clarkson to analyse measles and pertussis data (14, 15), whereby the contact parameter is calculated from the estimated numbers of susceptible and infectious individuals. In both methods (described below), we analysed each influenza year individually without considering births, deaths or migration.

Estimating the difference in the contact parameter between termtime and holidays by fitting to the data

Model description. The model population was stratified into susceptible, infectious and immune individuals in two age strata, 0-14 and ≥15 years. The infectious period was assumed

to be 3.5 days (16) (2 or 4 days in sensitivity analyses). The age-specific proportions of infectious people which were reported (the reporting fraction) and both the number of infectious people and the proportion of individuals who were immune to the circulating influenza strains when the epidemic threshold was reached were estimated by fitting model predictions to the reported data (see below).

Contact between individuals was assumed to differ between the age groups, according to the following matrix of "Who Acquires Infection From Whom":

$$\begin{pmatrix} \beta_1 & \beta_2 \\ \beta_2 & \beta_3 \end{pmatrix}$$

whereby 0-14 year-olds effectively contact each other at a rate $ß_1$, the rate at which ≥15 year-olds and 0-14 year-olds effectively contact each other equals $ß_2$ and the rate at which ≥15 year-olds contact each other equals $ß_3$. $ß_1$ was assumed to differ between termtime and school holidays. $ß_1$, $ß_2$, $ß_3$ were calculated from the corresponding elements of the Next Generation Matrix (NGM), R_{ij}, defined as the average number of secondary infectious people in age group *i* generated by an infectious person of age group *j* in a totally susceptible population (Web Appendix 2). These elements, the relative difference in the contact parameter between termtime and holidays among children, and the other unknown model parameters were estimated by fitting model predictions to the data. The basic reproduction number (R_0) was calculated as the dominant eigenvalue of the NGM (17). Web Appendix 2 provides further details of the model, including equations and parameter definitions (Web Table 2.4).

Fitting the model. The unknown parameters (elements of the NGM, used to calculate the age-dependent contact parameters, the percentage difference in $ß_1$ during termtime compared to holidays, the age-specific reporting fractions and both the number of infectious people and

the proportion of individuals who were immune when the epidemic threshold was reached), were estimated by fitting model predictions of the weekly number of reported cases to the data by maximum likelihood. The best-fit estimates were those which produced the smallest value of the log-likelihood deviance (Web Appendix 2).

The model was fitted to the data for the continuous period during which the overall consultation rate exceeded the epidemic threshold (allowing additional single weeks below the threshold during the epidemic period). The fitting was conducted separately for each year in which the number of weeks in this period exceeded the number of parameters estimated. 95% confidence intervals (CIs) for the percentage difference in the contact parameter during holidays compared to termtime (and the other estimated parameters) were calculated by bootstrapping (18). For each influenza year, 1000 bootstrap incidence curves were generated with weekly case numbers sampled from a Poisson distribution with mean equal to the reported number for that week. The 95% CI for each estimated parameter was taken as the central 95% of the distribution of estimates from the bootstrapped datasets.

In sensitivity analyses, we fitted a model without age-structure (Web Appendix 2). This model had fewer unknown parameters than the age-structured model, allowing inclusion of more years (33 versus 27) in the analyses.

Estimates of the contact parameters using simple mass action models

We also estimated the contact parameter (β_t) for each week t in each influenza year directly from the data using simple mass action models (14, 15). Weekly values of β_t were estimated using Equation 1 (Web Appendix 3):

$$\beta_t = \frac{I_{t+1}}{I_t S_t} \qquad \text{(Equation 1)}$$

S_t and I_t are the number of susceptible and infectious individuals, respectively, in week *t*, and were estimated from the data. I_t was estimated by dividing the weekly reported ILI consultation rate by the reporting fraction (see below). We used data for 5-14 year-olds only. In sensitivity analyses, we used data for all ages combined.

Assumptions about the number of susceptible individuals at the start of each influenza year. The proportion of individuals who were assumed to be susceptible to influenza at the start of each season in the simple mass action model was based on published seroprevalence data from England or the UK, for 19 influenza seasons (Figure 1, Web Table 1.1). Typically, ~30% of individuals were susceptible at the beginning of each season (Figure 1); therefore, for years for which we did not identify serological data, we assumed that 30% of individuals were susceptible. In sensitivity analyses, we assumed that 70% of individuals were susceptible at the start of each season (8, 19). Vaccination is assumed to have scarcely affected the proportion susceptible as, until 2000, it was offered in England and Wales only to individuals at high risk of complications (20).

Assumptions about the reporting fraction. We used the relationship between R_0 and the cumulative attack rate (21) to estimate the reporting fraction for each season, for all ages (Web Appendix 4, Web Figure 4.3). Based on these results, we assumed a reporting fraction of 50% for 5-14 year-olds and 30% for all ages combined (70% for both groups in sensitivity analyses).

Relationship between contact parameters and school holidays. For each influenza year, the mean value of the estimated contact parameter was calculated, separately for weeks during school holidays and termtime, for 5-14 year-olds and all ages combined. The percentage difference comparing the mean during holidays ($\bar{\beta}_{\text{holiday}}$) to termtime ($\bar{\beta}_{\text{term}}$) each year was calculated as ($100\times((\bar{\beta}_{\text{term}}-\bar{\beta}_{\text{holiday}})/\bar{\beta}_{\text{term}})$), utilising only estimates from weeks during which the epidemic threshold was exceeded. 95% CIs were calculated using the bias-corrected and accelerated bootstrapping method (22), randomly sampling with replacement 1000 estimates of β_t from weeks within strata of termtime and holidays and calculating the percentage difference as above.

Summary measures of the relationship between school closures and influenza transmission from both approaches

We summarised the relationship between school holidays and influenza transmission using random effects meta-analysis of the estimated percentage difference in the contact parameter, separately for the estimates from fitting to the data and the simple mass action model. We used the metan command in Stata (23), which uses the method of DerSimonian and Laird (24). Heterogeneity was assessed using the I^2 statistic (25).

For the simple mass action model, influenza years were included in the meta-analysis if the estimate of the percentage difference in the contact parameter was based on at least two estimates of the contact parameter for each of termtime and holidays; we excluded years during which the contact parameter systematically increased over the year (based on visual

inspection). We analysed all years together and stratified by the number of circulating influenza strains.

Comparison of the two methods

We compared estimates from the simple mass action model to those obtained by fitting to the data using the correlation coefficient, *r*. We estimated the correlation between a) estimates of the difference in the contact parameter comparing termtime to holidays obtained from the simple mass action model for 5-14 year-olds and the age-structured model fitted to the data and b) estimates from the simple mass action model for all ages combined and the fitted model without age structure.

We also used the kappa statistic to assess the agreement between the two methods in whether the value of the contact parameter was higher or lower during school holidays than termtime.

We calculated the absolute difference between the estimates of the change in the contact parameter during holidays from the age-structured model fitted to the data and those from the simple mass action model for 5-14 year-olds, for each year, as the absolute value of $(\Delta\beta_{sm} - \Delta\beta_{fit})$, where $\Delta\beta_{sm}$ and $\Delta\beta_{fit}$ represent the percentage changes in the contact parameter during holidays from the simple mass action model and the fitted model, respectively. We converted this to a percentage difference by dividing the absolute difference by β_{sm} and multiplying by 100.

Statistical analyses were carried out using Stata 14.

RESULTS

Estimates from fitting the age-structured model to the RCGP data

The estimated percentage difference in the contact parameter during holidays compared to termtime ranged from a reduction of 36% (95% CI 31, 41%) to an increase of 17% (95% CI 15% decrease to 21% increase) (Figure 2). In 18/27 (67%) influenza years that we fitted to, the estimated contact parameter was lower during holidays than termtime, with a 95% CI excluding zero. In one year, the contact parameter was estimated to increase during holidays with a 95% CI for the change which excluded zero. Model fits are shown in Web Figure 5.4; Web Table 5.5 summarizes the best-fitting parameter estimates. Estimates were reasonably similar if the infectious period was assumed to be 2 or 4 days (Web Figure 5.5). Estimates obtained by fitting the model without age structure are presented in Web Appendix 5 (Web Figure 5.6, Web Table 5.6).

There was substantial heterogeneity between estimates (I^2>85% for both the age-structured and unstructured models). We therefore do not report summary estimates.

Estimates of the contact parameter using the simple mass action model

Weekly estimates of the contact parameter from the simple mass action model are shown in Web Figures 5.7 and 5.8.

Point estimates of the percentage difference in the contact parameter amongst 5-14 year-olds ranged from a 47% reduction to a 29% increase during holidays compared to termtime (Figure 3). In 10/33 years, the estimate was negative with a 95% CI excluding zero; in these years the estimated reduction ranged from 18% (95% CI: 7, 28%) to 47% (95% CI: 30, 58%).

The contact parameter was lower during holidays than termtime (with 95% CIs for the difference excluding zero) in 4/16 (25%) years with one dominant strain, and in 6/15 (40%) years when >1 strain circulated.

Results were robust to changing assumptions about the reporting fraction (Web Figure 5.9) and the percentage of the population that was susceptible at the start of each season (Web Figure 5.10). Results based on data for all ages combined are presented in Web Appendix 5 (Web Figure 5.11).

Excluding two years during which the estimated contact parameter increased systematically (1967/68 and 1970/71), meta-analysis suggested that the contact parameter for 5-14 year-olds was 16-17% lower during holidays than termtime (Table 1). Estimates were heterogeneous when considering all years together (I^2=49%) or years when >1 influenza strain circulated (I^2=72%), but not when restricted to years with one dominant strain (I^2=0%). Based on the latter, the contact parameter between 5-14 year-olds was 17% (95% CI: 9, 25%) lower during holidays than termtime. The estimate using data for all years was similar (17%, 95% CI: 9, 24%), despite the heterogeneity. Meta-analysis found no strong evidence of a difference in the contact parameter for all ages combined during holidays compared to termtime (Table 1), although estimates were moderately heterogeneous (25). Results were similar when restricting meta-analysis to years for which the assumed proportion of the population that was initially susceptible was based on serological data (Web Table 5.7).

Comparison of results from the different methods

The correlation coefficient (r) between the estimated difference in the contact parameter during holidays compared to termtime from the age-structured model and that for 5-14 year-

olds from the simple mass action model was 0.52 (95% CI 0.17, 0.75). The kappa statistic for the agreement between the signs of the estimates was 0.30 (p=0.05).

The estimates from fitting the model without age structure to the data were reasonably well correlated with those from the simple mass action model for all ages (r=0.67, 95% CI 0.43, 0.83). The kappa statistic for these estimates was 0.15 (p=0.20) (Table 3).

The absolute value of the percentage difference in the estimates for 5-14 year-olds for each year ranged from 3 to 50 (median 14) percentage points, corresponding to percentage differences of 16-830% (median 90%).

DISCUSSION

These analyses of GP consultation data for ILI indicate that, in some years, the contact parameter was lower during school holidays than during termtime, especially for school-aged children. Estimates of the contact parameter for 5-14 year-olds from the simple mass action model were 17% (95% CI: 9, 25%) lower during holidays than termtime when a single viral strain circulated. Our results represent changes in contact estimated directly from consultation data, complementing estimates of the effects of school closures on incidence from models which make assumptions about such changes in contact patterns (26-28).

It is reassuring that the assumed reporting fraction and proportion of the population that was susceptible at the beginning of each season did not strongly influence the estimates of the relationship between school holidays and the contact parameter. There are limited data on how the proportion of cases consulting a GP varies between seasons. A household cohort

study ("FluWatch") in England (2006-2011) found that 17% (95% CI 10, 26%) of participants with PCR-confirmed influenza and 21% (95% CI 17, 25%) of those with ILI consulted a GP (29). By making assumptions about R_0, we estimated that the reporting fraction varied between seasons, but was often around 30%; this difference compared to the FluWatch estimate may reflect changes in healthcare-seeking behaviour. However, any temporal changes in consultation behaviour (or physician reporting practices) are unlikely to affect our results, given the lack of sensitivity to assumptions about the reporting fraction.

The simple mass action model assumes that the time step (one week) equals, or is a multiple of, the serial interval. Some estimates of the serial interval for influenza are approximately consistent with this, e.g. 2-3 days (30, 31), 3-4 days (32) or 5 days (33). Variation in the serial interval means that the cases recorded at each time step are not discrete generations of infection; therefore the contact parameter estimated for a given week does not exclusively reflect transmission from individuals infected in the previous week. This simplification could cause us to underestimate the change in the contact parameter associated with holidays as the timing of some transmission events would be misclassified. Geographic and temporal variation in holiday dates could also have caused underestimation of changes in the contact parameter; however, such variation was found to be limited.

Our approach involving fitting to the data required fewer assumptions than the simple mass action model, as several parameters were estimated rather than assumed and no assumptions were required about the serial interval. Sensitivity analyses found the estimates of several parameters were sensitive to model assumptions and some estimates appeared implausible (e.g. reporting fractions close to 100%). However, the estimates of the main parameter of

interest (the relative difference in the contact parameter during holidays compared to termtime) were fairly insensitive to varying the assumptions.

Unlike some influenza models (28, 34), our model did not incorporate a pre-infectious period. This is unlikely to be a major source of error in our results, given the short duration of the pre-infectious period (e.g. an incubation period of ~1.6 days (35)) and the limited viral shedding before symptoms appear (36). Similar to some other models (8), we included only two age groups in the model, to capture the influence of school holidays on contact in the age group most likely to be affected (children aged <15 years) whilst minimising computational burden and the number of parameters to be estimated (maximising the number of years which could be used in the fitting).

The estimates of the difference in the contact parameter during holidays compared to termtime from the two methods were moderately correlated. The differences between the estimates for children obtained from the two methods may result from the fact that the fitted model was explicitly structured into two age groups and fitted to consultation data for both groups, whilst the simple mass action model utilised only data for 5-14 year-olds. The latter therefore assumed that 5-14 year-olds only transmit to others in the same age group, overestimating the amount of transmission occurring between 5-14 year-olds. Conversely, the simple mass action model applied to data for 5-14 year-olds does not consider transmission from 5-14 year-olds to other age groups, so some infections which might be prevented by school holidays are not considered.

Other studies have reported some variation in the effects of school holidays on influenza transmission, although previous results appear more consistent between years than are ours.

School holidays in France were estimated to reduce transmission between children by 20-29% (8), whilst holidays were estimated to reduce R_0 by 17% in Great Britain (37) (although estimates for other countries varied), consistent with our summary estimate. A modelling study of pandemic influenza data from regions of India with different holiday timings suggested that school holidays reduced the effective reproduction number (R_n) by 14-27% (38). Other studies from France and The Netherlands also show reductions in the contact parameter during holidays compared to termtime (9, 10). However, estimates of R_n from Dutch ILI consultation data were more strongly related to absolute humidity than to Christmas holidays, although the authors noted that holidays rarely coincided with epidemics (34). This demonstrates that factors besides changes in contact patterns affect influenza transmission and may contribute to reductions in the contact parameter during holidays. Seasonal variation in transmissibility is not considered in our models, e.g. if factors such as low absolute humidity increase transmission during winter (39), then we would underestimate the change in the contact parameter during holidays.

The differences in our estimates between years in the changes in the contact parameter could be related to variation in factors such as viral transmissibility, patterns of age-specific attack rates, and weather. They may also be related to co-circulation of other pathogens causing ILI. In the 2005/06 to 2008/09 seasons, 27-33% of patients consulting with ILI in RCGP practices have had laboratory confirmation of influenza infection (40-45). This percentage is highest (~40%) during the peak weeks for ILI consultations (45). The effects of this relatively low specificity on the estimates of the contact parameter, and their relationship with school holidays, are difficult to predict, but will depend upon the timing and size of the outbreaks caused by the co-circulating pathogens.

School holidays were associated with a reduction in the contact parameter for influenza in some years, particularly in school-aged children. Overall, the contact parameter for 5-14 year-olds was estimated to be approximately 17% lower during school holidays than termtime. The results suggest that school closure may reduce transmission during influenza outbreaks.

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Author affiliations: Research Department of Infection and Population Health, University College London, London, United Kingdom (C. Jackson); Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom (C. Jackson, P. Mangtani, E. Vynnycky); Statistics, Modelling and Economics Department, Public Health England, London, United Kingdom (C. Jackson, E. Vynnycky).

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REFERENCES

1. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. *Commun Dis Public Health* 2000;3(1):32-8.
2. Cauchemez S, Ferguson NM, Wachtel C, et al. Closure of schools during an influenza pandemic. *The Lancet Infectious Diseases* 2009;9(8):473-81.
3. Jackson C, Vynnycky E, Hawker J, et al. School closures and influenza: systematic review of epidemiological studies. *BMJ open* 2013;3(2).
4. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS medicine* 2008;5(3):e74.
5. Hens N, Goeyvaerts N, Aerts M, et al. Mining social mixing patterns for infectious disease models based on a two-day population survey in Belgium. *BMC infectious diseases* 2009;9:5.
6. Mikolajczyk RT, Akmatov MK, Rastin S, et al. Social contacts of school children and the transmission of respiratory-spread pathogens. *Epidemiology and infection* 2008;136(6):813-22.
7. Jackson C, Mangtani P, Vynnycky E, et al. School Closures and Student Contact Patterns. *Emerg Infect Dis* 2011;17(2):245-7.
8. Cauchemez S, Valleron AJ, Boelle PY, et al. Estimating the impact of school closure on influenza transmission from Sentinel data. *Nature* 2008;452(7188):750-4.
9. Finkenstadt BF, Morton A, Rand DA. Modelling antigenic drift in weekly flu incidence. *Statistics in Medicine* 2005;24(22):3447-61.
10. Xia Y, Gog JR, Grenfell BT. Semiparametric estimation of the duration of immunity from infectious disease time series: influenza as a case-study. *Applied Statistics* 2005;54(3):659-72.

11. Dedman DJ, Watson JM. The use of thresholds to describe levels of influenza activity. *PHLS Microbiology Digest* 1997;14(4):206-8.
12. Goddard NL, Kyncl J, Watson JM. Appropriateness of thresholds currently used to describe influenza activity in England. *Commun Dis Public Health* 2003;6(3):238-45.
13. Abbey H. An examination of the Reed-Frost theory of epidemics. *Hum Biol* 1952;24(3):201-33.
14. Fine PE, Clarkson JA. Seasonal influences on pertussis. *Int J Epidemiol* 1986;15(2):237-47.
15. Fine PE, Clarkson JA. Measles in England and Wales--I: An analysis of factors underlying seasonal patterns. *International journal of epidemiology* 1982;11(1):5-14.
16. Cauchemez S, Carrat F, Viboud C, et al. A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. *Statistics in medicine* 2004;23(22):3469-87.
17. Diekmann O, Heesterbeek JA, Metz JA. On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *Journal of mathematical biology* 1990;28(4):365-82.
18. Chowell G, Ammon CE, Hengartner NW, et al. Estimating the reproduction number from the initial phase of the Spanish flu pandemic waves in Geneva, Switzerland. *Mathematical biosciences and engineering : MBE* 2007;4(3):457-70.
19. Longini IM, Jr., Koopman JS, Haber M, et al. Statistical inference for infectious diseases. Risk-specific household and community transmission parameters. *Am J Epidemiol* 1988;128(4):845-59.
20. Department of Health. Influenza: the green book, chapter 19. *Green Book*, 2013.
21. Diekmann O, Heesterbeek JAP. *Mathematical epidemiology of infectious diseases: model building, analysis and interpretation*. Chichester: Wiley; 2000.

22. Carpenter J, Bithell J. Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. *Stat Med* 2000;19(9):1141-64.

23. Harris R, Bradburn M, Deeks J, et al. metan: fixed- and random-effects meta-analysis. *Stata Journal* 2008;8(1):3-28.

24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7(3):177-88.

25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60.

26. Fung IC, Gambhir M, Glasser JW, et al. Modeling the effect of school closures in a pandemic scenario: exploring two different contact matrices. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2015;60 Suppl 1:S58-63.

27. Ferguson NM, Cummings DA, Fraser C, et al. Strategies for mitigating an influenza pandemic. *Nature* 2006;442(7101):448-52.

28. Vynnycky E, Edmunds WJ. Analyses of the 1957 (Asian) influenza pandemic in the United Kingdom and the impact of school closures. *Epidemiology and infection* 2008;136(2):166-79.

29. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *The Lancet Respiratory medicine* 2014;2(6):445-54.

30. Ferguson NM, Cummings DA, Cauchemez S, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 2005;437(7056):209-14.

31. Viboud C, Boelle PY, Cauchemez S, et al. Risk factors of influenza transmission in households. *Br J Gen Pract* 2004;54(506):684-9.

32. Cowling BJ, Fang VJ, Riley S, et al. Estimation of the serial interval of influenza. *Epidemiology* 2009;20(3):344-7.

33. Richardson M, Elliman D, Maguire H, et al. Evidence base of incubation periods, periods of infectiousness and exclusion policies for the control of communicable diseases in schools and preschools. *Pediatr Infect Dis J* 2001;20(4):380-91.

34. te Beest DE, van Boven M, Hooiveld M, et al. Driving factors of influenza transmission in the Netherlands. *American journal of epidemiology* 2013;178(9):1469-77.

35. Lessler J, Reich NG, Brookmeyer R, et al. Incubation periods of acute respiratory viral infections: a systematic review. *The Lancet infectious diseases* 2009;9(5):291-300.

36. Hayden FG, Fritz R, Lobo MC, et al. Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *The Journal of clinical investigation* 1998;101(3):643-9.

37. Hens N, Ayele GM, Goeyvaerts N, et al. Estimating the impact of school closure on social mixing behaviour and the transmission of close contact infections in eight European countries. *BMC infectious diseases* 2009;9:187.

38. Ali ST, Kadi AS, Ferguson NM. Transmission dynamics of the 2009 influenza A (H1N1) pandemic in India: the impact of holiday-related school closure. *Epidemics* 2013;5(4):157-63.

39. Shaman J, Pitzer VE, Viboud C, et al. Absolute humidity and the seasonal onset of influenza in the continental United States. *PLoS biology* 2010;8(2):e1000316.

40. Fleming DM, Chakraverty P, Sadler C, et al. Combined clinical and virological surveillance of influenza in winters of 1992 and 1993-4. *BMJ* 1995;311(7000):290-1.

41. Zambon MC, Stockton JD, Clewley JP, et al. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001;358(9291):1410-6.

42. Royal College of General Practitioners. Weekly Returns Service Annual Report 2009. 2009.

43. Royal College of General Practitioners Birmingham Research Unit. Weekly Returns Service Annual Report 2007. 2008.

44. Royal College of General Practitioners Birmingham Research Unit. Weekly Returns Service Annual Report 2006. 2006.

45. Royal College of General Practitioners Birmingham Research Unit. Weekly Returns Service Annual Report 2008. 2009.

FIGURES AND TABLES

Figure 1. Proportion of the population susceptible to infection at the start of each influenza year, 1967/68 to 2007/08, based on season-specific serological data where available (where data were not available, 30% of individuals were assumed to be susceptible at the start of each season). Error bars show 95% confidence intervals for datasets which provided denominators.

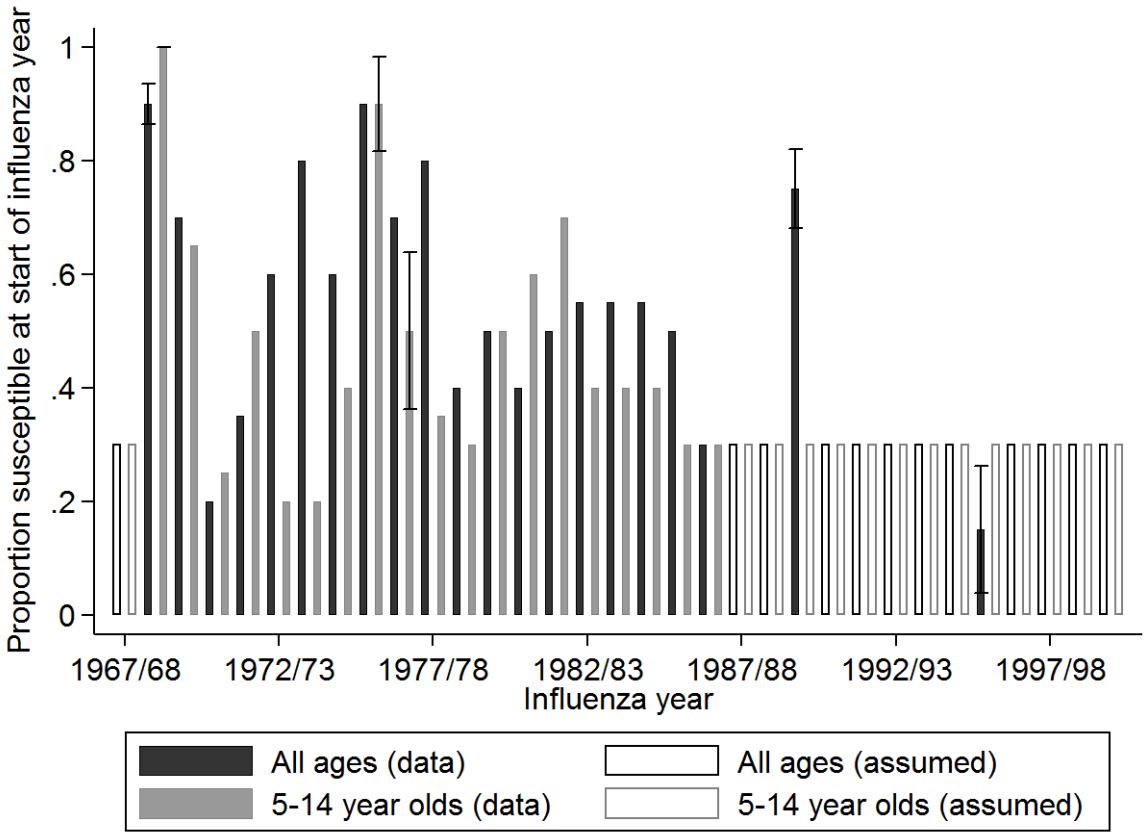

Figure 2: Estimated percentage difference in the contact parameter (amongst 0-14 year-olds) for influenza during holidays compared to termtime based on fitting the age-structured model to ILI consultation data. Crosses: single dominant subtype; Circles: more than one subtype circulating. Error bars show 95% confidence intervals.

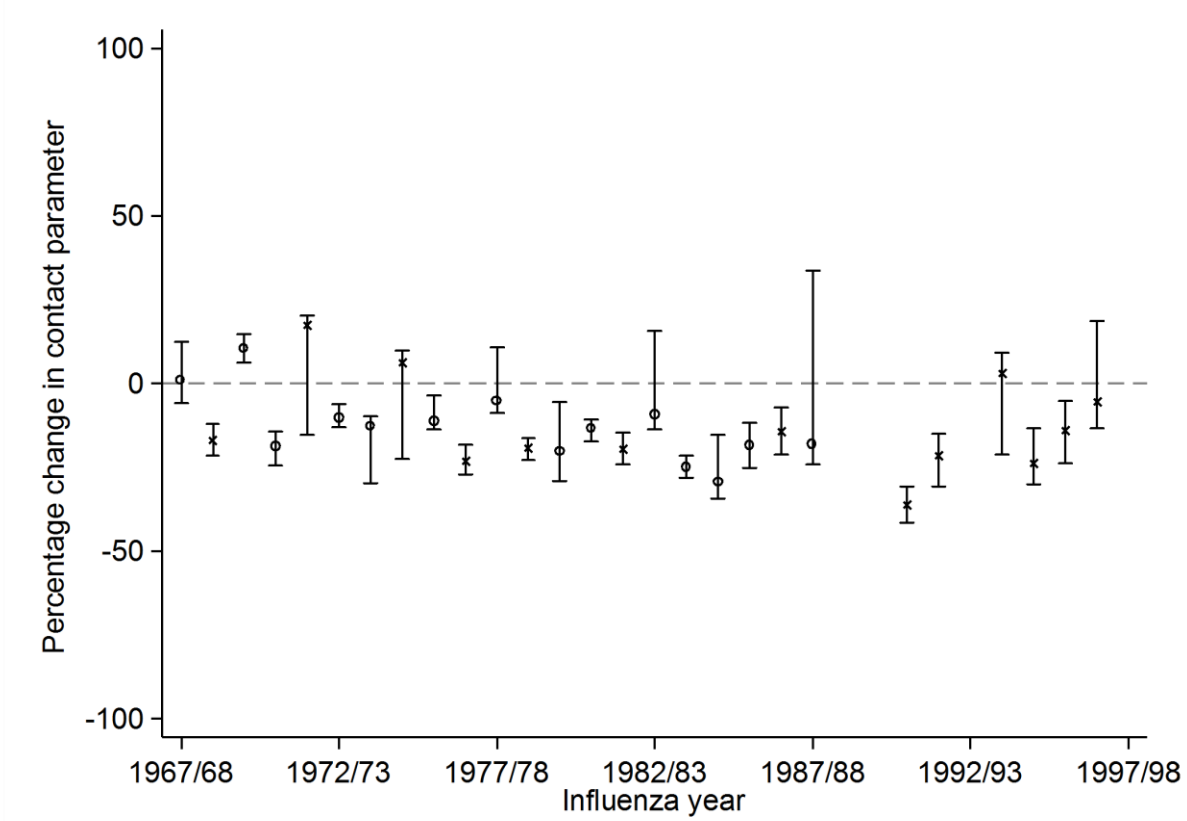

Figure 3. Estimated percentage changes in the value of the contact parameter for influenza during school holidays based on the simple mass action model applied to ILI consultation data for 5-14 year-olds (reporting fraction assumed to be 50%). Crosses: single dominant subtype; Circles: more than one subtype circulating; Squares: unknown number of subtypes circulating. Error bars show 95% confidence intervals; dotted lines indicate years in which there were ≤2 estimates of the contact parameter during termtime and / or holidays.

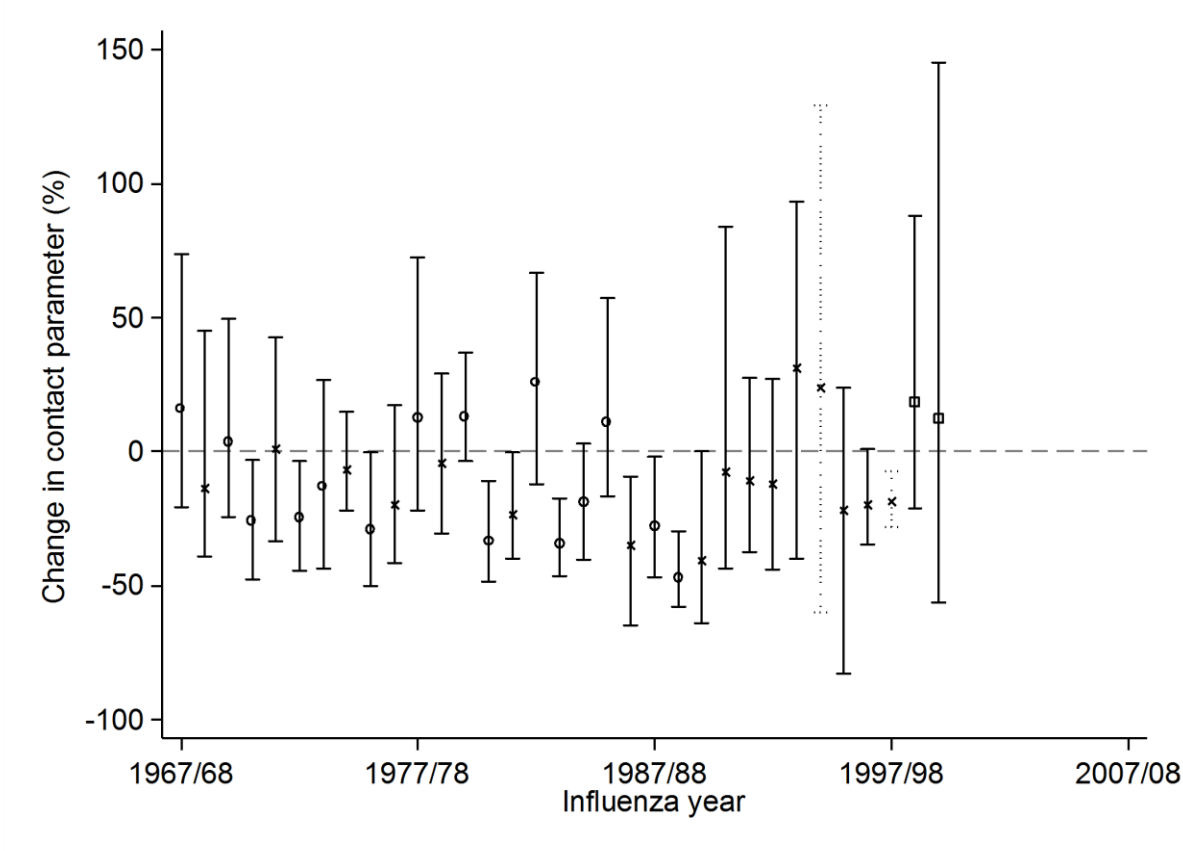

Table 1. Estimates of the Percentage Difference in the Contact Parameter Comparing School Holidays to Termtime, by Age Group and Number of Circulating Influenza Strains, Based on Random Effects Meta-Analysis of Estimates Obtained From the Simple Mass Action Model. In Two Eligible Years, the Number of Circulating Subtypes was Unknown.

	Change in contact parameter during holidays (%)	95% CI	Number of years included in estimate	I^2 (%)
5-14 year-olds				
All years	-17	-24, -9	29	49
Years with a single circulating subtype	-17	-25, -9	14	0
Years with >1 circulating subtype	-16	-29, -3	13	72
All ages				
All years	-5	-10, 0.1	29	39
Years with a single circulating subtype	-6	-13, 0.8	14	25
Years with >1 circulating subtype	-5	-12, 3	13	50

Table 2: Number of influenza years during which the contact parameter for 5-14 year-olds was estimated to decrease or increase during holidays, based on the age-structured model fitted to the data and the simple mass action model for 5-14 year-olds.

		Estimate from simple mass action model	
		Decrease during holidays	Increase during holidays
Estimate from fitting to data	Decrease during holidays	17	5
	Increase during holidays	2	3

Table 3: Number of influenza years during which the contact parameter for all ages combined was estimated to decrease or increase during holidays, based on the homogeneous mixing model fitted to the data and the simple mass action model for all ages combined.

		Estimate from simple mass action model	
		Decrease during holidays	Increase during holidays
Estimate from fitting to data	Decrease during holidays	11	6
	Increase during holidays	8	8