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### **Smoke-free legislation and paediatric hospitalisations for acute respiratory tract infections**

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# Tobacco Control

**Smoke-free legislation and paediatric hospitalisations for acute respiratory tract infections: national quasi-experimental study with unexpected findings and important methodological implications**

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Manuscripts

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3 **Smoke-free legislation and paediatric hospitalisations for acute respiratory tract infections:**  
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5 **national quasi-experimental study with unexpected findings and important methodological**  
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7 **implications**  
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**Word count: 3738**

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3 **What this paper adds**  
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9 **What is already known on this subject**  
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12 Implementation of comprehensive smoke-free legislation is associated with significant early-life  
13 health benefits, including reductions in severe paediatric respiratory events.  
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17 Evidence on the impact of national policies typically is derived from quasi-experimental studies;  
18 given their inherent risks of bias and confounding, replication of such studies across various  
19 settings is essential.  
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26 **What this study adds**  
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28

29 We investigated if the March 2006 national implementation of comprehensive smoke-free  
30 legislation in Scotland was associated with a reduction in hospital admissions/deaths due to acute  
31 respiratory tract infections among children.  
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37 Our pre-specified interrupted time series approach suggested that implementation of smoke-free  
38 legislation in Scotland was associated with an increase in paediatric respiratory tract infection  
39 admissions/deaths.  
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45 We were concerned that this result, which contradicted published evidence, was spurious. The  
46 association was indeed reversed when accounting for an unanticipated antecedent breakpoint in  
47 the temporal trend, suggesting that the legislation may in fact be protective.  
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53 We discuss the findings from this national study and propose approaches to enhancing the  
54 methodological quality of interrupted time series studies.  
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## ABSTRACT

### Objectives

We investigated whether Scottish implementation of smoke-free legislation was associated with a reduction in unplanned hospitalisations or deaths ('events') due to respiratory tract infections (RTIs) among children.

### Design

Interrupted times series (ITS)

### Setting/participants

Children aged 0-12 years living in Scotland during 1996-2012

### Intervention

National comprehensive smoke-free legislation (March 2006)

### Main outcome measure

Acute RTI events in the Scottish Morbidity Record-01 and/or National Records of Scotland Death Records

### Results

135,134 RTI events were observed over 155 million patient-months. In our pre-specified negative binomial regression model accounting for underlying temporal trends, seasonality, sex, age group, region, urbanisation level, socioeconomic status, and seven-valent pneumococcal

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3 vaccination status, smoke-free legislation was associated with an immediate rise in RTI events  
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5 (incidence rate ratio (IRR)=1.24, 95%CI 1.20-1.28) and an additional gradual increase  
6  
7 (IRR=1.05/year, 95%CI 1.05-1.06). Given this unanticipated finding we conducted a number of  
8  
9 post-hoc exploratory analyses. Among these, automatic breakpoint detection indicated that the  
10  
11 rise in RTI events actually preceded the smoke-free law by 16 months. When accounting for this  
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13 breakpoint, smoke-free legislation was associated with a gradual decrease in acute RTI events:  
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15 IRR=0.91/year, 95%CI 0.87-0.96.  
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## 22 **Conclusions**

23  
24 Our pre-specified ITS approach suggested that implementation of smoke-free legislation in  
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26 Scotland was associated with an increase in paediatric RTI events. We were concerned that this  
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28 result, which contradicted published evidence, was spurious. The association was indeed reversed  
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30 when accounting for an unanticipated antecedent breakpoint in the temporal trend, suggesting  
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32 that the legislation may in fact be protective. ITS analyses should be subjected to comprehensive  
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34 robustness checks to assess consistency.  
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## BACKGROUND

Tobacco smoking continues to cause a considerable burden of death and disease worldwide.[1,2]

It is estimated that 40-50% of children globally are regularly exposed to second-hand smoke (SHS).[3,4] They are particularly vulnerable to the adverse effects of SHS exposure as their bodies are still undergoing development and, especially when very young, cannot influence their own degree of exposure. Among children under five years of age, exposure to SHS has been estimated to cause 165,000 deaths and almost six million disability-adjusted life years (DALYs) annually through lower respiratory tract infections (RTIs) alone.[3] Additional adverse paediatric health outcomes associated with SHS exposure include otitis media with effusion,[5] invasive meningococcal disease,[6] and wheezing disorders including asthma.[7,8]

There is a pressing need to identify effective approaches to reducing child SHS exposure and through so doing improve child health. The effectiveness of individual or family-level interventions to reduce SHS exposure has generally been disappointing.[9] At a population level, governmental policies aimed at reducing tobacco smoking and SHS exposure have the potential to also reduce child SHS exposure. Comprehensive smoke-free laws and tobacco tax increases have been shown to be associated with improved respiratory health among children.[10-13] Evaluation of the effectiveness of such policies is however complicated by the fact that they are generally not amenable to implementation in a randomised fashion.[14]

Quasi-experimental studies, such as interrupted time series (ITS) studies, are advocated as a next best alternative to randomised designs when evaluating the impact of population-level policy changes.[15] Attribution of causality is however challenging because of the inherent risks of bias



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3 and confounding. Findings are in addition sensitive to choice and specification of the statistical  
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5 modelling technique used. Pre-specification of a detailed statistical analysis plan has been  
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8 advocated to reduce the associated risk of data dredging, to encourage publication irrespective of  
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10 a study's findings, and to promote the reproducibility of science.[16,17]  
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15 We investigated whether the implementation of comprehensive smoke-free legislation in  
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17 Scotland was associated with changes in the number of unplanned paediatric hospitalisations or  
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19 deaths due to RTIs. Introduction of the Scottish smoke-free law was followed by significant  
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21 reductions in reported SHS exposure in public places and the home environment among school-  
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23 age children, along with a -40% (95%CI -47; -32,  $p < 0.001$ ) reduction in mean salivary cotinine  
24  
25 concentrations.[18] Previous studies in England, Hong Kong and the United States have  
26  
27 identified significant reductions in hospital admissions for acute RTIs among children following  
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29 introduction of smoke-free laws.[10,12,19,20] Based on these previous studies and the wider  
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31 evidence of the health impact of smoke-free legislation,[11,21-24] we hypothesised that the  
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33 Scottish smoke-free law would be associated with a reduction in acute RTI events.  
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## 43 **METHODS**

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48 This study was conducted according to a protocol developed *a priori* (National Services Scotland  
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50 reference: PAC 04/12 IR – XRB13092; Supplementary File 1). We analysed the association  
51  
52 between introduction of smoke-free legislation in Scotland and the incidence rate of unplanned  
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54 hospital admissions or deaths due to acute RTIs among children aged  $\leq 12$  years. STROBE and  
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56 RECORD statements were followed to guide reporting. Given use of fully anonymised routinely  
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3 collected health care data, we received an exemption from formal ethical assessment for this  
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5 study.  
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### 8 9 10 **Smoke-free legislation**

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12 On 26 March 2006, a national law came into force overnight in Scotland prohibiting smoking in  
13 enclosed public places (i.e. bars; restaurants; hotels; shops; shopping centres; libraries; archives;  
14 museums; galleries; entertainment premises (e.g. cinemas; concert halls; theatres; gaming and  
15 amusement arcades; discotheques); film studios; assembly halls; conference centres; exhibition  
16 halls; public toilets; clubs premises; educational institutions (e.g. schools); care homes and  
17 shelters; health care premises (e.g. hospitals); child care premises (e.g. nurseries); religious  
18 premises (e.g. churches); sports centres; public transportation facilities (e.g. airports) and  
19 vehicles; public telephone kiosks) and workplaces (including offshore facilities and work  
20 vehicles), with very few exemptions (i.e. residential accommodation; designated rooms in adult  
21 care homes and adult hospices; designated rooms in psychiatric hospitals and psychiatric units;  
22 designated hotel bedrooms; designated detention or interview rooms; designated laboratory  
23 rooms; Her Majesty's submarines and ships of the Royal Fleet Auxiliary; private vehicles).[25]  
24  
25 Of inspected premises, 96-99% were compliant with the law in the first year following the law's  
26 introduction, and 94-97% and 95-97% in the second and third year, respectively.[26]  
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### 48 **Study population and period**

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50 We included data from all children aged  $\leq 12$  years who were resident in Scotland at any time  
51 during the study period and had not yet experienced an RTI event before the study period.  
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53 Children aged 13 years and above were excluded in an attempt to limit potential confounding by  
54 active smoking. We included data on all first unplanned hospital admissions or deaths due to  
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3 acute RTIs (composite outcome: 'events') occurring between 1 January 1996 and 31 December  
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5 2012 (i.e. the most recent data available at the time of data extraction).  
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### 8 9 10 **Outcome definitions**

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12 Our primary outcome was the incidence rate of acute RTI events. Deaths were included to  
13 account for children that died due to an acute RTI before having reached the hospital. Secondary  
14 outcomes were the separate incidence rates of upper and lower RTI events. In these analyses,  
15 events that contained both a code for an upper and a lower RTI were counted as lower RTI  
16 events. For the purpose of this study, an event was considered to be associated with an acute RTI  
17 if this had been registered as either a primary or secondary diagnosis. The following International  
18 Classification of Diseases-10 codes were included: upper RTIs: A37, H66-67, J00-06, J09-11  
19 (not J10.0/J11.0); lower RTIs: J10.0/J11.0, J12-18, J20-22, J40-42 (Supplementary File 2). To  
20 avoid contamination of our outcome of interest with asthma exacerbations which may or may not  
21 have been due to RTIs, events where asthma was recorded as the primary diagnosis were  
22 excluded. In order to prevent dependency of data due to individual children experiencing multiple  
23 RTI events during the study period, only first events (i.e. admission or death, whichever came  
24 first) were included. For eligible children born before start of the study period (i.e. 1 January  
25 1996) a look-back period of 12 years was applied to determine whether the child previously  
26 experienced an acute RTI hospitalisation.  
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### 50 **Data sources**

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52 Data on acute RTI hospitalisations were retrieved from the Scottish Morbidity Record 01  
53 (SMR01), a national database collecting data on all hospital admissions among Scottish residents.  
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55 Deaths due to acute RTIs were identified from National Records of Scotland Death Records. Data  
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3 on individual pneumococcal conjugate vaccine (PCV) vaccination status were retrieved from the  
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5 Scottish Immunisation and Recall System database, which collects national vaccination data.  
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7 Individual-level data were linked across the different databases by electronic Data Research and  
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9 Innovation Service (eDRIS) staff at Information Services Division Scotland using the unique  
10  
11 Community Health Index (CHI) identifier before being made available to the researchers. Air  
12  
13 quality data were obtained from the UK Governmental Department for Environment Food and  
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15 Rural Affairs (DEFRA) and linked to the main data document by the researchers.[27]  
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### 22 **Data handling and covariates**

23  
24 The numbers of children at risk and those experiencing a first acute RTI event were aggregated  
25  
26 by eDRIS staff into strata based on all possible combinations of the following covariates: month;  
27  
28 year; sex (male; female); age group (<5 years; ≥5 years); region (according to health board of  
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30 residence: South-West; South-East; North); urbanisation level (according to residential post code:  
31  
32 urban; rural); socioeconomic status (quintiles of Scottish Index of Multiple Deprivation (SIMD  
33  
34 [28]; 2006 version) based on residential postcode); PCV vaccination (yes; no). On 4 September  
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36 2006, PCV was introduced into the childhood immunisations schedule at two, four, and 13  
37  
38 months of age, with a catch-up programme for children born from 5 September 2004.[29] Given  
39  
40 the close temporal proximity of PCV introduction to that of the smoke-free law in Scotland we  
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42 linked data on RTI events to PCV vaccination status at an individual level to address potential  
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44 confounding.[10]  
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53 In a post-hoc analysis we used air quality data for all Scottish monitoring sites that collected data  
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55 during the study period: carbon monoxide (CO; mg/m<sup>3</sup>); nitric oxide (NO; µg/m<sup>3</sup>); nitrogen  
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57 dioxide (NO<sub>2</sub>; µg/m<sup>3</sup>); nitrogen oxides as NO<sub>2</sub> (µg/m<sup>3</sup>); sulphur dioxide (SO<sub>2</sub>; µg/m<sup>3</sup>); ozone (O<sub>3</sub>;  
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3  $\mu\text{g}/\text{m}^3$ ); particulate matter of diameter  $<10\mu\text{m}$  (PM10;  $\mu\text{g}/\text{m}^3$ ). For each monitoring site, mean  
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5 monthly values were calculated from mean daily values and missing values were imputed using  
6  
7 linear interpolation. Availability of air quality data from fixed stations was patchy both across  
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9 time and the different monitoring sites, hampering combination of data across sites. Fairly  
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11 consistent data throughout the study period was only available for Glasgow city centre.  
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### 18 **Statistical analyses**

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20 Negative binomial regression analysis was pre-specified as our primary analysis, in which the  
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22 number of acute RTI events was the dependent variable. Predictors included: time (a continuous  
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24 variable ranging from '1' in January 1996 to '204' in December 2012, designed to account for the  
25  
26 underlying temporal trend in acute RTI events); timing of the smoke-free law (a dummy variable  
27  
28 coded '0' prior to March 2006 and '1' otherwise); an interaction variable 'time  $\times$  smoke-free law'  
29  
30 (to account for a change in temporal trend in acute RTI events following the law); month (a  
31  
32 categorical variable to account for seasonality); sex; age group; region; urbanisation level; SIMD  
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34 quintile; PCV vaccination. Akaike's information criterion (AIC) was used to select the optimal  
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36 model among three options according to the temporal change in RTI events following the smoke-  
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38 free law: immediate ('step') change; gradual ('slope') change; step + slope change. The size of  
39  
40 the population at risk was used as an offset in the models. We modelled acute RTI events using  
41  
42 three variants of negative binomial regression; NB1 (constant dispersion), NB2 (mean dispersion)  
43  
44 and NBP ("NB *rho*") which uses a second dispersion parameter that is allowed to vary freely  
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46 across the data observations.[30] The most appropriate negative binomial variant was selected  
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48 using AIC. We tested for non-linear time effects using a restricted cubic spline with four degrees  
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50 of freedom compared with one degree of freedom using the 'mvr' module in Stata.[31] In  
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3 November 2003 there was an unusually high incidence of RTI events, which was modelled using  
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5 a dummy variable.  
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#### 8 9 10 Post-hoc exploratory analyses

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12 We performed a number of exploratory post-hoc analyses to assess the robustness of the findings  
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14 from our primary analyses, which were felt to be implausible (discussed below).  
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18  
19 First, we performed stratified analyses according to age group and sex to explore whether the  
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21 association between smoke-free legislation and acute RTI events differed across categories of  
22  
23 these variables. Young age and male sex are important risk factors for RTIs in childhood.  
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27  
28 Second, we explored whether the association between smoke-free legislation and RTI events was  
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30 robust to accounting for temporal trends in air quality. Given the patchiness of air quality  
31  
32 availability, we performed an exploratory analysis adding Glasgow city centre air quality data as  
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34 parameters to the model, using data on acute RTI events occurring in South-West Scotland only.  
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38 Backward selection of air quality indicators was based on AIC.  
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43 Third, we ran time series regressions on the acute RTI events with seasonal autoregressive  
44  
45 integrated moving average ((S)ARIMA) errors to account for regular and seasonal autoregression  
46  
47 in the data. The models contained an underlying trend, a dummy variable for the post-ban period  
48  
49 and a post-ban temporal trend, allowing a number of intervention effects to be tested. Again, we  
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51 tested for non-linear time effects using Stata's 'mvars' module.[31] Candidate error models were  
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53 identified from autocorrelation and partial autocorrelation plots. The most appropriate model was  
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57 selected using the AIC statistic and was subjected to standard diagnostic tests for white noise  
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3 residuals using the Ljung-Box Portmanteau statistic as well as graphically using auto-correlation  
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5 plots and correlograms.[32]  
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10 Fourth, we tested for structural breaks in the time series data using Stata's 'estat sbsingle'  
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12 command. The procedure searches for a possible trend break over a stipulated range of dates by  
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14 calculating the value of the test statistic (Wald or likelihood ratio) at each date and then using the  
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16 maximum value of the test statistic to identify the potential break.[33] For the test to work, the  
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18 series needed to be trimmed prior to the search so as to avoid using dates too close to the end or  
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20 beginning of the series which would result in breakdown of the procedure. After 20% trimming  
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22 we tested for a break in the intercept (step change) as well as a break in the trend (slope change).  
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25 As a test of robustness we used the econometrics software EViews to also check for a structural  
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27 break using its comprehensive suite of breakpoint detection options with 20% trimming of the  
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29 data. The selected breakpoint and its form (step and/or slope) was then included as an additional  
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31 regressor in the negative binomial model and the models re-estimated.  
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39 All analyses were performed within the National Services Scotland's Safe Haven environment  
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41 using Stata MP version 14 except for the (S)ARIMA models. These were analysed separately on  
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43 aggregated data which were supplied to the authors by the NSS Safe Haven after statistical  
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45 disclosure control. The (S)ARIMA models and the structural break analysis were developed  
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47 using Stata SE version 14 with the structural break point further corroborated using EViews 9.5.  
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## 55 RESULTS

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3 During 155 million patient-months of observation, 135,134 acute RTI events were recorded:  
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5 79,153 upper RTI events and 56,011 lower RTI events. There was substantial variation in the  
6  
7 incidence rate of acute RTI events over time (Figure 1) and across demographic subgroups (Table  
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**Table 1. Demographic characteristics of children experiencing an acute respiratory tract infection event**

Characteristic	Acute RTI events (n)			Mean monthly acute upper RTI event rate (per 1000 children)		
	Upper RTIs (n=79,153)	Lower RTIs (n=56,011)	All RTIs (n=135,134)	Upper RTIs (0.51)	Lower RTIs (0.36)	All RTIs (0.87)
Sex						
Male	46,116	31,912	78,028	0.58	0.40	0.98
Female	33,007	24,099	57,106	0.43	0.32	0.76
Age						
0-4 years	67,462	51,109	118,571	1.16	0.88	2.05
5-12 years	11,661	4,902	16,563	0.12	0.05	0.17
Region						
North	28,074	18,257	46,332	0.57	0.37	0.93
South-West	34,496	23,759	58,255	0.50	0.34	0.84
South-East	16,553	13,994	30,547	0.46	0.39	0.86
Urbanisation level						
Urban	64,939	46,739	111,678	0.51	0.37	0.89
Rural	14,184	9,272	23,456	0.49	0.32	0.81
Socio-economic status						
Quintile 1 (most affluent)	12,508	8,928	21,436	0.41	0.30	0.71
Quintile 2	14,507	9,693	24,200	0.48	0.32	0.81
Quintile 3	14,808	10,043	24,851	0.50	0.34	0.84
Quintile 4	16,849	11,658	28,507	0.57	0.39	0.96
Quintile 5 (most deprived)	20,451	15,689	36,140	0.58	0.45	1.03
PCV vaccination status						
PCV received	13,324	5,619	18,943	0.69	0.19	0.88
PCV not received	65,799	50,392	116,191	0.47	0.39	0.86

PCV = pneumococcal conjugate vaccine; RTI = respiratory tract infection

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3 In our primary analysis, introduction of smoke-free legislation was associated with an immediate  
4 rise in acute RTI events (incidence rate ratio (IRR) 1.24, 95% confidence interval (CI) 1.20-1.28)  
5 and an additional gradual increase over time (IRR 1.06 per year, 95%CI 1.05-1.06; Table 2). This  
6 finding was consistent when upper and lower RTI events were considered separately (Table 1 and  
7 Supplementary File 3).  
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17 Post-hoc subgroup analyses to assess whether the unanticipated findings were confined to certain  
18 subgroups demonstrated consistency across sex and age subgroups (Supplementary File 4 and 5).  
19 In an analysis of data from South-West Scotland only, addition of mean monthly air quality  
20 indicators measured in Glasgow improved model performance (Supplementary File 6). This did  
21 not have a major bearing on the association between smoke-free legislation and acute RTI events:  
22 immediate change IRR 1.25, 95%CI 1.19-1.32; gradual change IRR 1.08 per year, 95%CI 1.06-  
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36 In further post-hoc analyses, the strength of association between timing of smoke-free legislation  
37 and acute RTI events was very similar when evaluated using a reg(S)ARIMA model of order  
38 AR(1,7) MAR(3,12): IRR 1.15, 95%CI 1.02-1.28. However, automatic breakpoint detection  
39 suggested that the increase in acute RTI events started well before introduction of smoke-free  
40 legislation – i.e. in November 2004 (Supplementary File 7). Using this breakpoint rather than  
41 timing of smoke-free legislation in the primary negative binomial regression analysis indeed  
42 improved model performance as compared to the primary model (Supplementary File 8). When  
43 timing of smoke-free legislation was then added to the model that included the November 2004  
44 breakpoint, smoke free legislation was associated with a gradual decrease in acute RTI events  
45 (IRR 0.91 per year, 95%CI 0.87-0.96), with no evidence of a ‘step’ change at that time (Table 2).  
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**Table 2. Multivariable negative binomial regression model for acute respiratory tract infection events**

Characteristic	Event rate ratio (ERR (95%CI))	
	Primary model (pre-specified)	Post-hoc analysis
Time (per year increase)	1.01 (1.01-1.01)	0.99 (0.99-1.00)
Smoke-free legislation	1.24 (1.20-1.28)*	Dropped from model based on AIC
Time since smoke-free legislation (per year increase)	1.06 (1.05-1.06)*	0.91 (0.87-0.96)*
November 2004 breakpoint	Not in model	1.13 (1.08-1.19)
Time since November 2004 breakpoint (per year increase)	Not in model	1.16 (1.12-1.20)
Month (reference = January)		
February	0.83 (0.80-0.86)	0.83 (0.80-0.86)
March	0.78 (0.75-0.81)	0.78 (0.75-0.81)
April	0.54 (0.52-0.56)	0.54 (0.52-0.57)
May	0.52 (0.50-0.54)	0.52 (0.50-0.54)
June	0.46 (0.44-0.48)	0.46 (0.44-0.48)
July	0.33 (0.32-0.30)	0.33 (0.32-0.35)
August	0.29 (0.28-0.48)	0.29 (0.28-0.31)
September	0.47 (0.45-0.34)	0.47 (0.45-0.49)
October	0.57 (0.55-0.59)	0.57 (0.55-0.60)
November	0.84 (0.81-0.88)	0.85 (0.82-0.88)
December	1.26 (1.22-1.31)	1.27 (1.23-1.32)
Male sex (reference = female)	1.31 (1.28-1.33)	1.31 (1.28-1.33)
Age 5-12 years (reference = 0-4 years)	0.07 (0.07-0.08)	0.07 (0.07-0.08)
Region (reference = North)		
South-West	0.87 (0.85-0.89)	0.87 (0.85-0.89)
South-East	0.90 (0.89-0.92)	0.90 (0.89-0.92)
Living in urban area (reference = rural)	0.99 (0.97-1.01)	0.99 (0.98-1.01)
Socio-economic status (reference = Quintile 1; most affluent)		
Quintile 2	1.11 (1.09-1.14)	1.11 (1.08-1.14)
Quintile 3	1.14 (1.11-1.17)	1.14 (1.11-1.17)
Quintile 4	1.25 (1.22-1.29)	1.25 (1.22-1.29)
Quintile 5 (most deprived)	1.35 (1.32-1.39)	1.35 (1.31-1.39)
PCV vaccination received (reference = not received)	0.45 (0.43-0.46)	0.45 (0.43-0.46)

November 2003 (outlier)	1.48 (1.37-1.60)	1.61 (1.49-1.74)
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AIC = Akaike's Information Criterion; PCV = pneumococcal conjugate vaccine

The post-hoc analysis includes adjustment for an additional breakpoint in November 2004;

\* $p < 0.001$  (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine; RTI = respiratory tract infection

## DISCUSSION

In this large national ITS study conducted according to a pre-specified analysis plan, introduction of comprehensive smoke-free legislation in Scotland was associated with a significant increase in paediatric RTI events. Findings from our exploratory post-hoc analyses, which were undertaken to further investigate this unexpected finding, however indicated that the increase in RTI events most likely preceded the legislation by 16 months, making a direct causal link between the legislation and increased risk of RTIs implausible.

Our study has a number of strengths. It was conducted according to a pre-defined protocol, including a detailed statistical analysis plan, which was developed *a priori* in an attempt to promote scientific transparency and reproducibility.[17] We used over 10 million patient-years of high-quality data routinely collected over a 17-year period. Virtual universal availability of the CHI number minimises risks of incorrect data linkage across the datasets. We accounted for underlying temporal trends in RTI events as well as changes in population size and demographic structure. We applied a look-back period to reduce bias from RTI events occurring prior to the

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3 study period. Our modelling approach is widely applied in the evaluation of national public  
4 health interventions, including national smoke-free laws.[11,20,22,23]  
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10 Given these strengths, the implausible findings are of considerable concern. It is important to  
11 consider the limitations of the study to see if these may have contributed to the observed findings.  
12 Allocation of a nationwide intervention cannot be randomised, and a quasi-experimental  
13 approach is considered a potentially valid method to evaluate impact such interventions.[15] Re-  
14 analyses of cluster randomised controlled trials using an ITS approach have demonstrated that  
15 their findings can in fact be highly similar.[34-36] Whilst residual bias could possibly have  
16 influenced our findings,[14] we consider it unlikely that this would explain the implausible  
17 results of our primary analysis.  
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31 Results of our pre-specified primary analysis were unanticipated and contradicted prior evidence  
32 on the topic.[10,12,19] Studies in other countries, including in the UK, previously identified  
33 consistent associations between comprehensive smoke-free legislation and subsequent reductions  
34 in paediatric RTI hospitalisations.[10,12,19] In line with these studies, there is consistent  
35 evidence for reductions in severe asthma exacerbations among children and in respiratory  
36 admissions among adults following implementation of smoke-free laws.[11,20,22] Post-hoc  
37 analyses showed that our findings were consistent across demographic subgroups and unlikely to  
38 have resulted from residual confounding by air pollution. As findings from ITS studies have  
39 previously been reported to be sensitive to choice of the modelling approach,[37] we performed  
40 additional aggregate-level times series analyses, again confirming the findings of our primary  
41 analysis. Automatic breakpoint detection is a method to explore whether a change in the  
42 incidence of the outcome under study indeed co-occurred with the known timing of the  
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3 intervention, and its use has been promoted as a routine validity test in single-group ITS  
4 analyses.[38] Using such an approach in a previous study, Kabir and colleagues were able to  
5 pinpoint timing of the observed reduction in small-for-gestational-age births to introduction of  
6 comprehensive smoke-free legislation in Ireland.[39] Using two different approaches and  
7 software packages to perform automatic breakpoint detection in our time series, the unanticipated  
8 increase in RTI events was shown to have preceded the smoke-free law by 16 months. This  
9 earlier breakpoint corresponds quite closely with temporal trends in paediatric RTI  
10 hospitalisations in England, which rose consistently from 2003 onwards.[40] In a previous  
11 study, implementation of English comprehensive smoke-free legislation in 2007 was associated  
12 with a reduction in paediatric RTI admissions when accounting for this rising underlying  
13 trend.[10] This closely corresponds to the findings of our post-hoc analysis in Scotland, where  
14 RTI events were shown to increase consistently from 2004 onwards, this rise being attenuated  
15 after implementation of smoke-free legislation. Whereas an exploration of the underlying causes  
16 of the increasing trend in RTI events in Scotland was outside the scope of our study, several  
17 potential explanations for the corresponding rise in England have been postulated at the levels of  
18 the carer (e.g. decreasing threshold to take children to primary care or straight into hospital for  
19 evaluation), the health professional (e.g. decrease in threshold for referral by primary care doctors  
20 or for hospital admission), and the health care system (e.g. introduction of four-hour waiting  
21 target at emergency departments, unintended financial incentives for admission).[40]

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51 Perhaps the main value of this study therefore is that it uncovers a number of important  
52 methodological challenges, which have not previously received adequate attention in the applied  
53 ITS literature. We used advanced methods and followed a pre-specified analytical approach –  
54 including a detailed statistical analysis plan – in an attempt to promote transparency.[16,17,41]

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3 Despite this, our study yielded findings which were implausible and highly likely to be spurious.  
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5 We therefore conducted a number of exploratory post-hoc analyses, which added weight to our  
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7 assessment that the findings of our primary analysis were indeed spurious. It is important to  
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9 acknowledge that these post-hoc analyses were unlikely to have been conducted should the  
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11 findings from our primary analysis have confirmed our initial hypothesis. In such a scenario, our  
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13 study would still have biased the literature on the topic.  
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20 At present, most public policy interventions remain unevaluated. ITS studies are arguably the  
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22 most robust approaches we have at our disposal to evaluate the public health impact of these  
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24 major experiments, which are seldom amenable to being implemented in a randomised  
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26 fashion.[14] Despite their limitations, there is thus a need for many more ITS studies to be  
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28 undertaken to continue to inform policy making at national, regional and global levels. To  
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30 address the issues highlighted by our study, we propose that future ITS studies evaluating public  
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32 health interventions should analyse the association under study using a number of different  
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34 modelling approaches; ideally these should be pre-specified and include approaches based on  
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36 both individual and aggregate level data (i.e. formal time series approaches). Also, we  
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38 recommend that automatic breakpoint detection approaches are included to validate temporal co-  
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40 occurrence of the intervention and the change in the outcome under study. This and other  
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42 machine learning approaches are likely to become increasingly applicable in discerning unusual  
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44 patterns in time series data over and above variations due to natural changes and those explained  
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46 by temporal, environmental, and individual-level confounding.[38] Confidence in the results  
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48 from individual ITS studies can be further increased by reproducing findings in other settings,  
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50 and interpreting findings from individual studies in the light of the totality of evidence on the  
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52 topic.  
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Going back to the primary hypothesis under investigation, we are reluctant to draw firm conclusions on the impact of Scotland's smoke-free legislation on paediatric RTIs given the inconsistent findings of the various analyses. Building on the existing evidence base on the topic,[20-24] we feel it is highly unlikely that smoke-free legislation was indeed responsible for a rise in paediatric RTI events, as our primary analyses seemed to suggest. On the other hand, given these findings it is also difficult to be confident that the result of our additional exploratory analyses – which were post hoc – provides a more valid representation of the actual impact of the legislation.

Given the continuing need for formal quasi-experimental evaluations of public health interventions to inform policy making, we propose additional steps to improve the robustness of such studies, including: exploring the association between the intervention and outcome using a number of different (pre-specified) modelling approaches; analysing time series using both individual- and aggregate-level approaches; assessing for potential confounding by unmeasured factors; and using automatic breakpoint detection or alternative machine learning approaches to scrutinise findings from pre-specified primary analyses, irrespective of whether these support the underlying hypothesis. We hope that the lessons drawn from this experience will increase the validity of future ITS studies in the medical and public health literature.



### **Contributor Statement**

JVB conceived the study, obtained funding, developed the methods, analysed the data, interpreted the findings, and drafted the manuscript. DFM developed the methods, analysed the data, interpreted the findings, and contributed to drafting the manuscript. CM, CPvS, and JPP developed the methods, interpreted the findings, and provided feedback on the manuscript. IS extracted data, interpreted the findings, and provided feedback on the manuscript. AS conceived the study, obtained funding, developed the methods, interpreted the findings, and supervised drafting of the manuscript.

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### **Competing interests**

The authors declare that they have no competing interests.

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8 **Figure 1. Monthly time series of acute respiratory tract infection (RTI) event rates.** Dashed  
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10 grey line indicates introduction of smoke-free legislation.  
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17 **Supplementary Files**  
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22 **Supplementary File 1:** Study protocol  
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25 **Supplementary File 2:** List of ICD-10 codes  
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29 **Supplementary File 3: Table S1.** Multivariable negative binomial regression model for acute  
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31 upper and lower respiratory tract infection events  
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35 **Supplementary File 4: Table S2.** Multivariable negative binomial regression model for acute  
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37 respiratory tract infection events stratified according to sex  
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41 **Supplementary File 5: Table S3.** Multivariable negative binomial regression model for acute  
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43 respiratory tract infection events stratified according to age group  
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47 **Supplementary File 6: Table S4.** Multivariable negative binomial regression model for acute  
48  
49 respiratory tract infection events in South-East Scotland with adjustment for air quality  
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52 **Supplementary File 7: Figure S1.** Automatic breakpoint detection in trimmed time series of  
53  
54 acute respiratory tract infection (RTI) events. The likelihood ratio (LR) test statistic  
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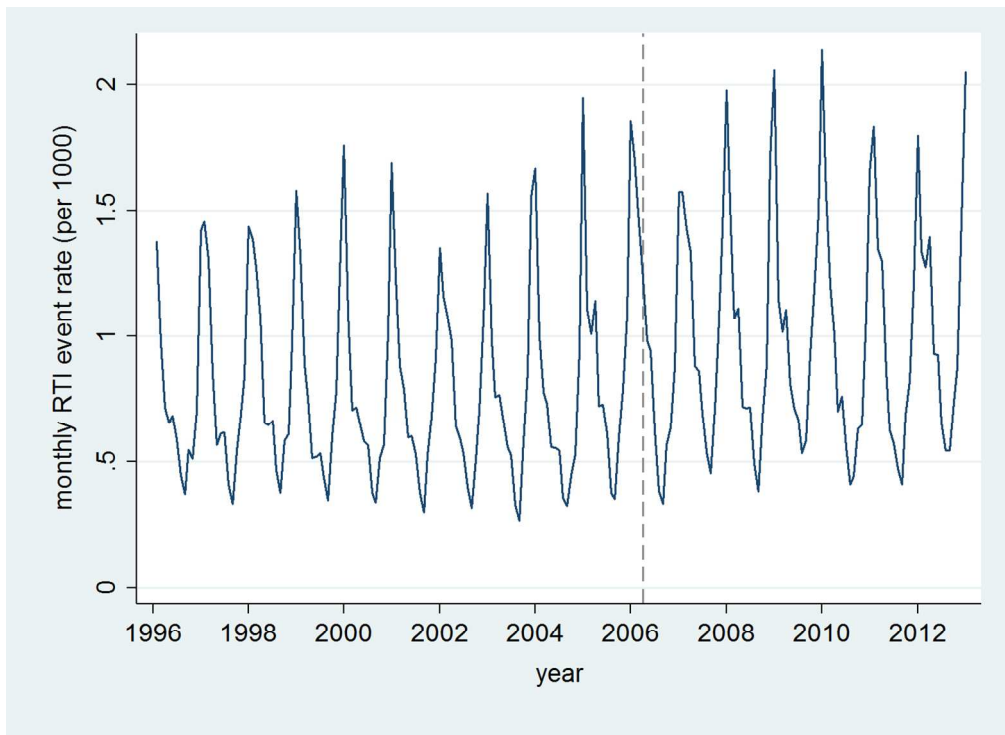
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3 maximises in November 2004, indicating the most likely breakpoint in the time series.  
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6 Dashed grey line indicates introduction of smoke-free legislation.  
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9 **Supplementary File 8: Table S5.** Multivariable negative binomial regression model for acute  
10 respiratory tract infection events with November 2004 breakpoint instead of timing of  
11 smoke-free legislation  
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Monthly time series of acute respiratory tract infection (RTI) event rates. Dashed grey line indicates introduction of smoke-free legislation.

511x371mm (72 x 72 DPI)

Review Only

### Supplementary Text S1: Study protocol

This study protocol was part of an application to the National Health Service National Services Scotland Privacy Advisory Committee (PAC 04/12 IR – XRB13092).

#### What is the background to the study?

Respiratory infections in childhood are one of the commonest reasons for hospital admission, primarily among infants. There is clear evidence that both antenatal and postnatal second-hand smoke (SHS) exposure increase the risk of respiratory infections among children. The relative contribution of SHS exposure to paediatric respiratory infections is greater than for childhood asthma, and adult lung cancer and cardiovascular disease for example. Worldwide the vast majority of the estimated 165,000 childhood deaths each year associated with SHS exposure are due to respiratory infections.

In Europe, over 50 percent of all children are regularly exposed to SHS. Particularly young children, who are most at risk of developing respiratory infections, have no means of controlling their own degree of SHS exposure and are therefore largely dependent on rules and regulations. However, despite World Health Organization (WHO) recommendations to implement smoke-free environments as part of a comprehensive approach to reduce SHS exposure, only 11% of countries had done so by 2010.

#### Why is the study needed?

Epidemiologic evaluations have shown reductions in asthma hospitalisations as well as preterm birth following the introduction of smoke-free legislation in different countries. To the best of our knowledge, the effect on respiratory tract infections has not been studied. Given the huge disease burden of

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2  
3 respiratory tract infections in childhood and the clear and important association between SHS exposure  
4  
5 and respiratory infections in childhood, smoke-free legislation may carry important health benefit in this  
6  
7 area. A better estimate of the range of effects that smoke-free legislation may have on paediatric health  
8  
9 can serve as a mandate to further enhance the enforcement of measures to protect young people  
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11 worldwide from the adverse effects of SHS exposure.  
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19 **What are the aims and objectives of the study?**

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21  
22 We aim to investigate the association between introduction of smoke-free legislation in Scotland (26  
23  
24 March 2006) and incidence changes in hospitalisations for acute respiratory infections among children  
25  
26 aged 0-12 years.  
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33 **Give a brief outline of the study design and data sources involved.**

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36  
37 *Study design*

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39 Interrupted time series

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42 *Time period*

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45 Hospitalisations or deaths associated with respiratory infections in children aged 12 years or under at  
46  
47 that time occurring between January 1, 1996 and December 31, 2012 are included in the study.  
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50  
51 *Population*

52  
53 All first unplanned hospitalisations or deaths (together: 'events') associated with acute respiratory  
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55 infections among children aged 12 years or under at that time are included in the given study period. A  
56  
57 hospitalisation or death is considered to be associated with a respiratory infection if such is recorded as  
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3 either a primary or secondary diagnosis at the event. Deaths are included to account for children that  
4  
5 died before reaching the hospital. Planned hospitalisations (e.g. for ear, nose, and throat (ENT) surgery)  
6  
7 and hospitalisations for chronic upper respiratory infections are excluded. Furthermore, to prevent  
8  
9 overlap with a previous study evaluating asthma hospitalisations (Mackay et al. NEJM 2010), all  
10  
11 hospitalisation where asthma is recorded as the primary diagnosis are excluded. Children aged 13 years  
12  
13 and above are excluded in an attempt to limit the potential confounding effect of self-smoking.  
14  
15

### 16 17 18 *Outcome*

19  
20 The primary outcome is the number of first events associated with any acute respiratory infection. All  
21  
22 hospitalisations and deaths where an acute respiratory tract infection is recorded as either a primary or a  
23  
24 secondary diagnosis are included. Secondary outcomes include the number of events associated with  
25  
26 acute upper respiratory tract infections, and the number of events associated with acute lower  
27  
28 respiratory tract infections. A list of diagnostic international classification of diseases (ICD)-codes is  
29  
30 attached as an appendix to the original protocol.  
31  
32

33  
34  
35 In order to prevent dependency of data, only first events for each child will be included in the dataset.  
36  
37 Subsequent hospitalisations or death in a child that has previously been hospitalised are thus excluded.  
38  
39 For children entering the study at the start of the study period (i.e. 1 January 1996) a look back period of  
40  
41 12 years will be applied to determine whether the child has experienced a hospitalisation for a  
42  
43 respiratory infection prior to study entry.  
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45

### 46 47 48 *Covariates*

49  
50 The following covariates will be included in the study: sex, age group, PCV immunisation status, month of  
51  
52 admission, region, urban/rural setting, socioeconomic status (SES).  
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3 On 4 September 2006 PCV was introduced into the childhood immunisations schedule. Although the  
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5 relative contribution of true pneumococcal infections to the total burden of admissions for respiratory  
6  
7 infections, the majority of which is likely to be of viral aetiology, is expected to be small, the close  
8  
9 temporal proximity of PCV introduction to that of the smoking ban necessitates adjustment for a  
10  
11 potential confounding effect of vaccine exposure. Therefore SMR01 data will be linked to SIRS on an  
12  
13 individual level and timed PCV immunisation status will be added as a potential confounder to the  
14  
15 analyses.  
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20  
21 Three regions of residence will be considered based on the following grouping of local health boards:  
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23 southwest (Ayrshire, Greater Glasgow and Clyde, Dumfries and Galloway, Lanarkshire), southeast  
24  
25 (Lothian, Borders, Forth Valley), and north (Grampian, Highland, Tayside, Fife, Island). Urban or rural  
26  
27 setting will be based on the 2006 Scottish Executive Urban Rural Classification system. SES will be  
28  
29 categorised into quintiles according to the 2006 Scottish Index of Multiple Deprivation (SIMD).  
30  
31

### 32 *Dataset and items*

34  
35 Data on emergency hospital admissions or deaths associated with respiratory infections will be extracted  
36  
37 from the Scottish Morbidity Record 01 (SMR01). The following data items will be extracted: data of birth  
38  
39 (DOB), sex (SEX), postcode (PC), hospital code (INSTCODE), admission date (ADMDATE), admission type  
40  
41 (ADMTYPE), admission/transfer from (ADMTFM), main and secondary conditions (DG1-2), discharge type  
42  
43 (DISTYPE). Data will be linked on an individual basis via the community health index (CHI) number to the  
44  
45 Scottish Immunisation and Recall System (SIRS) for ascertainment of PCV immunisation status.  
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51 Relevant data will be aggregated and provided in tabular form by ISD as follows. After data linkage on  
52  
53 individual level, strata will be formed based on combinations of the different covariates (associated  
54  
55 levels in brackets): sex (male/female); age group (<5 years/≥5 years); region  
56  
57 (southwest/southeast/north); urbanisation level (urban/rural); SES (five quintiles as per SIMD); PCV  
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3 vaccination (yes/no); month (12 levels); year (1996-2012: 17 levels). Thus,  $2 \times 2 \times 3 \times 2 \times 5 \times 2 \times 12 \times 17 = 48,960$   
4  
5 strata are formed. Event counts as well as population counts will be calculated and provided for each  
6  
7 stratum. A table demonstrating final data structure is attached as an appendix to the original study  
8  
9 protocol.

### 10 11 12 13 *Sample size*

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15 Sample size calculation for time-oriented analyses is complicated given the complexity of the models,  
16  
17 and in a way redundant given that nationwide data are being used for the current study. To the best of  
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19 our knowledge, no prior studies in any other region have evaluated changes in the number of hospital  
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21 admissions for respiratory infections among children following the introduction of smoke-free  
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23 legislation.

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28 In a previous epidemiological evaluation of the Scottish smoking ban a highly significant ( $p < 0.001$ ) annual  
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30 drop in asthma hospitalisations of 13% was found among children  $< 15$  years of age. Meta-analyses of  
31  
32 observational studies indicate that second hand smoke exposure is associated with higher risk of  
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34 respiratory tract infections in infancy (OR 1.54 (95% CI 1.40-1.69) for lower respiratory tract infections in  
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36 infancy and 1.62 (95% CI 1.33-1.97) for middle ear disease in childhood) when compared to incident and  
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38 current asthma in children (OR 1.21 (95% CI 1.08-1.36), and 1.30 (95% CI 1.22-1.39), respectively). This  
39  
40 indicates that smoke-free legislation is likely to have a larger effect on acute respiratory infections than  
41  
42 asthma. Furthermore, paediatric hospital admissions for acute respiratory infections are more common  
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44 than for asthma, and the study period for the current study is longer than compared to the previous  
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46 asthma study. Therefore, we expect the current study to have ample power to detect a significant and  
47  
48 clinically relevant drop in hospitalisations for respiratory infections, if present.

### *Statistical analyses*

#### Univariate analyses

Population-level incidence trends ('counts') will be plotted over time to identify any apparent temporal changes. Interrupted time series analysis using negative binomial regression will be used to study the association of time trends in the outcomes of interest and introduction of smoke-free legislation. The analyses will allow for a sudden ('step') and a trend ('slope') change in incidence trends of each of the outcomes following 26 March 2006 (i.e. when the smoking ban came into force). Stratum-specific mid-year population estimates will be used to define the denominator for the analyses.

#### Multivariate analyses

Potential confounding will be adjusted for by formation of demographic subgroups and subsequent stratified analysis. Potential confounders include: sex, age, PCV immunisation status, region, urban/rural setting, and SES. Month of admission will be added to the model to account for seasonal variation in hospital admissions for respiratory infections. Aikake's and Bayesian information criteria will be used for final model selection. A combination of Hosmer-Lemeshow statistic and receiver operating characteristic (ROC)-curves will be used to assess model performance for logistic regression models.

#### Software

All analyses will be performed using Stata 12.1.

**Supplemental File 2:****International Classification of Diseases (ICD)-10 codes used to define respiratory tract infection (RTI) events****upper RTIs:**

A37	whooping cough
H66/67	suppurative and unspecified otitis media
J00	acute nasopharyngitis
J01	acute sinusitis
J02	acute pharyngitis
J03	acute tonsillitis
J04	acute laryngitis
J05	acute tracheitis
J06	acute upper respiratory infections of multiple or unspecified sites
J09-11 (not J10.0/J11.0)	influenza

**lower RTIs:**

J10.0/J11.0	influenza with pneumonia
J12	viral pneumonia
J13	pneumococcal pneumonia
J14/15	other bacterial pneumonia
J16/17	pneumonia due to other specified organism
J18	pneumonia, organism unspecified
J20	acute bronchitis
J21	acute bronchiolitis
J22	unspecified acute lower respiratory infection
J40/41/42	bronchitis



**Supplementary Table S1. Multivariable negative binomial regression model for acute upper and lower respiratory tract infection events**

Characteristic	Event rate ratio (ERR (95%CI))	
	Acute upper RTIs	Acute lower RTIs
Time (per year increase)	1.01 (1.00-1.01)	1.02 (1.01-1.03)
Smoke-free legislation	1.22 (1.19-1.26)*	1.23 (1.18-1.30)*
Time since smoke-free legislation (per year increase)	Dropped from model based on AIC	1.12 (1.11-1.13)*
Month (reference = January)		
February	0.98 (0.94-1.02)	0.71 (0.67-0.75)
March	1.07 (1.03-1.11)	0.53 (0.51-0.56)
April	0.81 (0.78-0.84)	0.32 (0.30-0.33)
May	0.82 (0.79-0.86)	0.27 (0.25-0.28)
June	0.75 (0.72-0.79)	0.21 (0.20-0.23)
July	0.56 (0.53-0.58)	0.14 (0.13-0.15)
August	0.48 (0.46-0.50)	0.13 (0.12-0.14)
September	0.76 (0.72-0.79)	0.22 (0.21-0.24)
October	0.86 (0.82-0.89)	0.33 (0.31-0.35)
November	0.96 (0.92-1.00)	0.75 (0.71-0.79)
December	1.16 (1.11-1.20)	1.35 (1.29-1.41)
Male sex (reference = female)	1.33 (1.31-1.36)	1.25 (1.22-1.29)
Age 5-12 years (reference = 0-4 years)	0.10 (0.09-0.10)	0.05 (0.05-0.05)
Region (reference = North)		
South-West	0.85 (0.84-0.87)	0.87 (0.84-0.89)
South-East	0.81 (0.79-0.83)	1.04 (1.01-1.08)
Living in urban area (reference = rural)	1.00 (0.97-1.02)	1.00 (0.97-1.03)
Socio-economic status (reference = Quintile 1)		
Quintile 2	1.14 (1.11-1.17)	1.06 (1.02-1.11)
Quintile 3	1.16 (1.13-1.20)	1.10 (1.05-1.14)
Quintile 4	1.30 (1.26-1.34)	1.18 (1.13-1.22)
Quintile 5 (most deprived)	1.33 (1.30-1.38)	1.34 (1.28-1.39)
PCV vaccination received (reference = not received)	0.69 (0.67-0.72)	0.23 (0.22-0.24)
Nov 2003 (outlier)	1.95 (1.77-2.14)	Not in model

\*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine; RTI = respiratory tract infection

**Supplementary Table S2. Multivariable negative binomial regression model for acute respiratory tract infection events stratified according to sex**

Characteristic	Event rate ratio (ERR (95%CI))	
	Males	Females
Time (per year increase)	1.01 (1.01-1.01)	1.02 (1.01-1.02)
Smoke-free legislation	1.23 (1.18-1.28)*	1.26 (1.20-1.31)*
Time since smoke-free legislation (per year increase)	1.06 (1.05-1.07)*	1.05 (1.04-1.06)*
Month (reference = January)		
February	0.84 (0.80-0.88)	0.82 (0.78-0.87)
March	0.80 (0.76-0.84)	0.76 (0.72-0.80)
April	0.56 (0.53-0.59)	0.51 (0.49-0.54)
May	0.55 (0.52-0.58)	0.48 (0.46-0.51)
June	0.50 (0.47-0.53)	0.41 (0.39-0.44)
July	0.34 (0.33-0.36)	0.31 (0.29-0.33)
August	0.30 (0.29-0.32)	0.27 (0.25-0.29)
September	0.51 (0.48-0.54)	0.41 (0.39-0.44)
October	0.61 (0.58-0.64)	0.52 (0.49-0.55)
November	0.87 (0.82-0.92)	0.82 (0.77-0.86)
December	1.29 (1.23-1.35)	1.24 (1.17-1.30)
Age 5-12 years (reference = 0-4 years)	0.07 (0.07-0.07)	0.08 (0.08-0.08)
Region (reference = North)		
South-West	0.87 (0.85-0.89)	0.87 (0.85-0.90)
South-East	0.91 (0.89-0.94)	0.89 (0.87-0.92)
Living in urban area (reference = rural)	0.99 (0.97-1.02)	0.99 (0.96-1.02)
Socio-economic status (reference = Quintile 1)		
Quintile 2	1.12 (1.08-1.16)	1.10 (1.06-1.14)
Quintile 3	1.14 (1.11-1.18)	1.14 (1.10-1.18)
Quintile 4	1.24 (1.20-1.28)	1.27 (1.23-1.32)
Quintile 5 (most deprived)	1.32 (1.27-1.36)	1.40 (1.34-1.45)
PCV vaccination received (reference = not received)	0.43 (0.41-0.45)	0.47 (0.44-0.49)
Nov 2003 (outlier)	1.43 (1.29-1.58)	1.55 (1.39-1.73)

\*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine

**Supplementary Table S3. Multivariable negative binomial regression model for acute respiratory tract infection events stratified according to age group**

Characteristic	Event rate ratio (ERR (95%CI))	
	Age = 0-4 years	Age = 5-12 years
Time (per year increase)	1.01 (1.01-1.02)	1.02 (1.01-1.03)
Smoke-free legislation	1.30 (1.25-1.35)*	1.36 (1.27-1.45)*
Time since smoke-free legislation (per year increase)	1.08 (1.07-1.08)*	0.90 (0.89-0.92)*
Month (reference = January)		
February	0.79 (0.76-0.82)	1.03 (0.95-1.12)
March	0.72 (0.70-0.75)	1.11 (1.03-1.20)
April	0.51 (0.49-0.53)	0.66 (0.61-0.72)
May	0.48 (0.46-0.50)	0.70 (0.65-0.76)
June	0.41 (0.40-0.43)	0.72 (0.66-0.78)
July	0.30 (0.29-0.31)	0.50 (0.46-0.55)
August	0.26 (0.25-0.28)	0.44 (0.41-0.48)
September	0.42 (0.40-0.44)	0.74 (0.68-0.80)
October	0.53 (0.51-0.55)	0.78 (0.72-0.85)
November	0.82 (0.78-0.85)	0.98 (0.91-1.06)
December	1.27 (1.22-1.32)	1.23 (1.14-1.32)
Male sex (reference = female)	1.34 (1.32-1.35)	1.17 (1.13-1.21)
Region (reference = North)		
South-West	0.88 (0.86-0.90)	0.85 (0.82-0.89)
South-East	0.91 (0.89-0.93)	0.89 (0.85-0.93)
Living in urban area (reference = rural)	0.99 (0.87-1.02)	0.98 (0.94-1.02)
Socio-economic status (reference = Quintile 1)		
Quintile 2	1.10 (1.07-1.13)	1.15 (1.09-1.22)
Quintile 3	1.12 (1.09-1.15)	1.22 (1.15-1.29)
Quintile 4	1.23 (1.20-1.27)	1.31 (1.24-1.38)
Quintile 5 (most deprived)	1.34 (1.30-1.38)	1.36 (1.29-1.44)
PCV vaccination received (reference = not received)	0.38 (0.37-0.40)	2.14 (1.98-2.32)
Nov 2003 (outlier)	1.53 (1.40-1.66)	1.33 (1.10-1.61)

\*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine

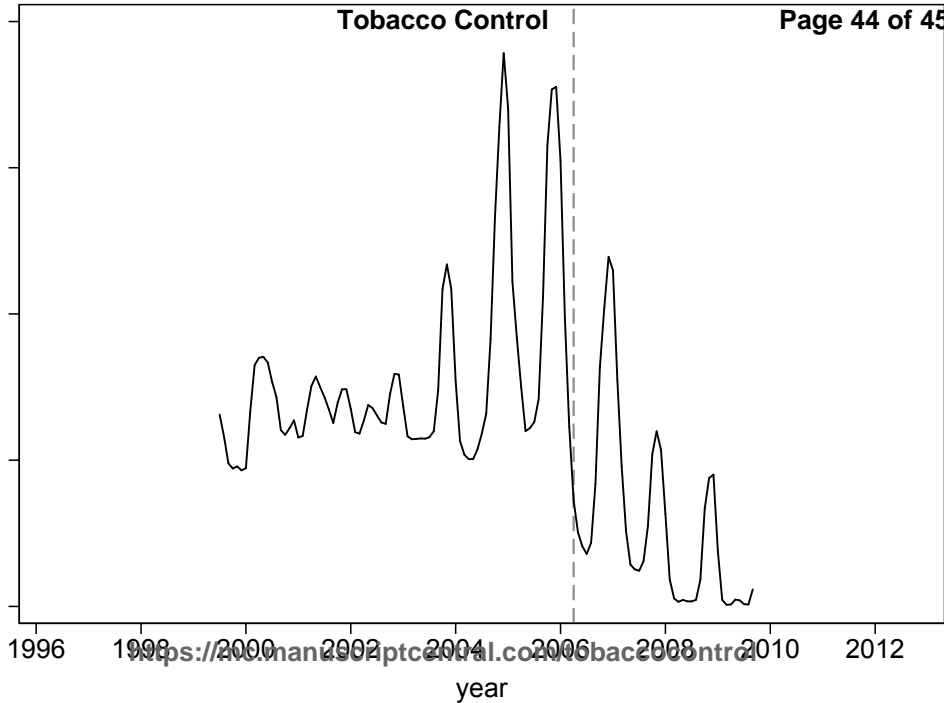
**Supplementary Table S4. Multivariable negative binomial regression model for acute respiratory tract infection events in South-East Scotland with adjustment for air quality**

Characteristic	Event rate ratio (ERR (95%CI))
Time (per year increase)	0.99 (0.98-1.01)
Smoke-free legislation	1.25 (1.19-1.32)*
Time since smoke-free legislation (per year increase)	1.08 (1.06-1.10)*
Month (reference = January)	
February	0.82 (0.76-0.87)
March	0.76 (0.71-0.82)
April	0.53 (0.49-0.58)
May	0.52 (0.48-0.57)
June	0.44 (0.40-0.48)
July	0.32 (0.29-0.35)
August	0.26 (0.24-0.29)
September	0.43 (0.39-0.46)
October	0.54 (0.50-0.58)
November	0.80 (0.74-0.86)
December	1.26 (1.18-1.36)
Male sex (reference = female)	1.30 (1.26-1.33)
Age 5-12 years (reference = 0-4 years)	0.08 (0.08-0.08)
Living in urban area (reference = rural)	0.83 (0.80-0.86)
Socio-economic status (reference = Quintile 1)	
Quintile 2	1.17 (1.12-1.23)
Quintile 3	1.29 (1.23-1.35)
Quintile 4	1.41 (1.35-1.47)
Quintile 5 (most deprived)	1.38 (1.32-1.44)
PCV vaccination received (reference = not received)	0.50 (0.48-0.54)
Air quality indicators	
Carbon monoxide (CO; per mg/m <sup>3</sup> )	0.88 (0.74-1.03)
Nitric oxide (NO; per µg/m <sup>3</sup> )	0.95 (0.93-0.97)
Nitrogen dioxide (NO <sub>2</sub> ; per µg/m <sup>3</sup> )	0.96 (0.95-0.98)
Nitrogen oxides as NO <sub>2</sub> (per µg/m <sup>3</sup> )	1.03 (1.02-1.05)
Sulphur dioxide (SO <sub>2</sub> ; per µg/m <sup>3</sup> )	0.99 (0.99-1.00)
Ozone (O <sub>3</sub> ; per µg/m <sup>3</sup> )	0.99 (0.99-1.00)
Particulate matter of diameter <10µm (PM10; per µg/m <sup>3</sup> )	1.01 (1.00-1.01)

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\*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine

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**Supplementary Table S5. Multivariable negative binomial regression model for acute respiratory tract infection events with November 2004 breakpoint instead of timing of smoke-free legislation**

Characteristic	Event rate ratio (ERR (95%CI))
Time (per year increase)	0.99 (0.99-1.00)
Smoke-free legislation	Not in model
Time since smoke-free legislation (per year increase)	Not in model
November 2004 breakpoint	1.23 (1.20-1.27)*
Time since November 2004 breakpoint (per year increase)	1.08 (1.07-1.09)*
Month (reference = January)	
February	0.83 (0.80-0.86)
March	0.78 (0.75-0.81)
April	0.54 (0.53-0.57)
May	0.52 (0.51-0.54)
June	0.46 (0.45-0.48)
July	0.33 (0.32-0.35)
August	0.29 (0.28-0.31)
September	0.47 (0.45-0.49)
October	0.58 (0.55-0.60)
November	0.85 (0.82-0.89)
December	1.27 (1.22-1.31)
Male sex (reference = female)	1.30 (1.28-1.33)
Age 5-12 years (reference = 0-4 years)	0.07 (0.07-0.08)
Region (reference = North)	
South-West	0.87 (0.85-0.89)
South-East	0.90 (0.89-0.93)
Living in urban area (reference = rural)	0.99 (0.98-1.01)
Socio-economic status (reference = Quintile 1)	
Quintile 2	1.11 (1.09-1.14)
Quintile 3	1.14 (1.11-1.17)
Quintile 4	1.25 (1.22-1.29)
Quintile 5 (most deprived)	1.35 (1.31-1.39)
PCV vaccination received (reference = not received)	0.45 (0.43-0.46)
Nov 2003 (outlier)	1.61 (1.49-1.74)

\*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine