

Community-based antibiotic prescribing attributable to respiratory syncytial virus and other common respiratory viruses in young children: a population-based time series study of Scottish children

Tiffany Fitzpatrick ^{1,2,3}

William Malcolm ⁴

Jim McMenamin ⁴

Arlene Reynolds ⁴

Astrid Guttman ^{2,3,5}

Pia Hardelid ¹

1 UCL Great Ormond Street Institute of Child Health; University College London
30 Guildford Street, London, UK

2 SickKids Research Institute; The Hospital for Sick Children
686 Bay Street, Toronto, Canada

3 Dalla Lana School of Public Health; University of Toronto
155 College Street, Toronto, Canada

4 Health Protection Scotland, NHS National Services Scotland
Meridian Court, 5 Cadogan Street, Glasgow, UK

5 ICES
2075 Bayview Ave, Toronto, Canada

Corresponding author contact details:

Dr. Pia Hardelid
30 Guilford Street; Holborn
London, United Kingdom WC1N 1EH
Tel: 020 7905 2979
Email p.hardelid@ucl.ac.uk

Summary

Antibiotic prescribing for viruses is inappropriate and may increase antimicrobial resistance. We estimate a large proportion of community-prescribed antibiotics in Scottish children is attributable to common respiratory viruses. The highest proportion of antibiotics were attributed to respiratory syncytial virus.

Accepted Manuscript

Abstract

Background: Inappropriate antibiotic prescribing, such as for viral illness, remains common in primary care. The objective of this study was to estimate the proportion of community-prescribed antibiotics to children aged less than five years attributable to common respiratory viruses.

Methods: We fitted time series negative binomial models to predict weekly antibiotic prescribing rates from positive viral pathogen tests for the period April 1st, 2009 through December 27th, 2017 using comprehensive, population-based administrative data for all children (<5 years) living in Scotland. Multiple respiratory viral pathogens were considered, including respiratory syncytial virus (RSV), influenza, human metapneumovirus (HMPV), rhinovirus, and human parainfluenza (HPIV) types 1-4. We estimated the proportion of antibiotic prescriptions explained by virus circulation according to type of virus, by age group, presence of high-risk chronic conditions, and antibiotic class.

Results: We included data on 6,066,492 antibiotic prescriptions among 452,877 children. The antibiotic prescribing rate among all Scottish children (<5 years) was 609.7 per 1000 child-years. Our final model included RSV, influenza, HMPV, HPIV-1 and HPIV-3. An estimated 6.9% (95% CI 5.6, 8.3), 2.4% (1.7, 3.1), and 2.3% (0.8, 3.9) of antibiotics were attributable to RSV, influenza and HMPV, respectively. RSV was consistently associated with the highest proportion of prescribed antibiotics, particularly among children without chronic conditions and for amoxicillin and macrolide prescriptions.

Conclusions: Nearly 14% of antibiotics prescribed to children in this study were estimated to be attributable to common viruses for which antibiotics are not recommended. A future RSV vaccine could substantially reduce unnecessary antibiotic prescribing among children.

Key words: Scotland; Antibiotics; Respiratory Infections; Child Health

Introduction

Antimicrobial resistance (AMR) is widely acknowledged as a serious threat to global health. The inappropriate use of antibiotics is a well-known cause of AMR. [1, 2] In recent years, numerous AMR guidelines and strategies have been introduced. [3, 4, 5] This includes 5- and 20-year strategies in the United Kingdom that call for reductions in human antibiotic use by 15% by 2024, and the development of novel vaccines to decrease the burden of infections. [6] Many AMR prevention initiatives specifically emphasize the importance of reducing unnecessary and inappropriate antibiotic prescribing, particularly for non-bacterial infections. [3, 4] However, prescribing of antibiotics for viral infections, such as otitis media, acute cough, and bronchiolitis, remains common in primary care. [1, 7, 8, 9, 10] A recent study found that 14.5% of antibiotics prescribed in primary care settings in England during 2013-5 were for upper respiratory tract infections; [11] 90-95% of which have viral aetiologies. [12, 13]

Several novel vaccines for respiratory infections, including respiratory syncytial virus (RSV), human parainfluenza (HPIV) and human metapneumovirus (HMPV), are currently under development. These may substantially reduce antibiotic prescribing once introduced. [2] Notably, influenza vaccination has been associated with a reduced risk of amoxicillin prescribing among preschool children in the UK. [14] Further, a 64% reduction in antibiotic prescribing was reported following a universal influenza vaccination program in Canada. [15]

In order to inform AMR prevention strategies and emerging vaccination programmes, a detailed understanding of the association between respiratory virus circulation and patterns of antibiotic prescribing is needed; yet accurate, population-based estimates of the proportion of antibiotics attributable to respiratory viruses are currently lacking [2, 16] In particular, it is not clear how antibiotic prescribing due to RSV and other viruses vary according to child characteristics or type of antibiotic. Thus, the objective of this study was to estimate the proportion of community-based antibiotic prescriptions attributable to common respiratory viruses among children <5 years old living in Scotland. We developed time series models using routinely collected national data from

Scotland on community-dispensed antibiotics and national laboratory surveillance data on respiratory viruses.

Methods

Data Sources

Virology Data: We extracted data on positive microbiology tests for viral respiratory pathogens in children under five years of age from the Electronic Communication of Surveillance in Scotland (ECOSS) database. [17] ECOSS is held by Health Protection Scotland (HPS), the national infection surveillance and control agency, and contains reports of positive test results reported by National Health Service (NHS) laboratories throughout Scotland. The majority of samples have been collected in hospital settings through the recommended method of nasopharyngeal swab. [18]

Antibiotic dispensing Data: Details for all community-dispensed prescriptions for antibiotics, based on the British National Formulary (BNF) classification, among children in Scotland were obtained from the Prescribing Information System (PIS) held by NHS National Services Scotland. [17, 19] The vast majority of these prescriptions were issued by NHS primary care practitioners; approximately 98% of UK citizens are registered in primary care. [20]

Hospital Data: Hospital admissions within NHS Scotland occurring before a child's fifth birthday or end of follow-up (December 27th, 2017) were identified from the Scottish Morbidity Record (SMR), specifically SMR-01 (inpatient and daycase admissions) and SMR-02 (maternity records). [17, 19] Neonatal diagnoses were identified from the Scottish Birth Records (SBR).

Population Registries: Birth date and area-level deprivation measures were identified from National Records for Scotland Birth Registrations. [19]

Study period and follow-up

Our study period covered April 1st, 2009 through December 26th, 2017 (inclusive). We included data for all children living in Scotland who were under five years of age during the study period. Follow-up time for each child was calculated until the earliest of death, 5th birthday, or end of the follow-up period.

Outcomes

Our primary outcome was weekly counts of positive ECOSS detections for influenza, RSV, coronavirus, adenovirus, rhinovirus, HMPV, enterovirus, and HPIV types 1-4. Only unique weekly episodes were considered; i.e., only one positive specimen-specific test per child per week.

Admissions for acute bronchiolitis were defined as any hospitalization with an International Classification of Diseases, 10th revision (ICD-10) diagnostic code of J21.0-J21.9 identified from the discharge record. Admissions for viral pneumonia were identified according to the following ICD-10 codes: J10.0 and J11.0 (influenza pneumonia); J12.0-J12.9 (viral pneumonia not elsewhere classified); and J18.0-J18.9 (pneumonia, unspecified organism).

Covariates

Our primary independent variable of interest was weekly antibiotic prescriptions dispensed among children under five years. We examined total antibiotic prescriptions and further categorized according to common classes: amoxicillin, other penicillins, macrolides, and cephalosporins.

Birth characteristics were identified from SMR-02 and SBR. Presence of high-risk chronic medical conditions was determined from birth record and hospital discharge diagnoses occurring before the first and fifth birthdays, respectively. We used a set of ICD-10 codes (Appendix A) indicating chronic conditions associated with increased risk of severe respiratory infection based on an existing categorization of paediatric chronic conditions. [21, 22]

Area-level deprivation was determined using the Scottish Index of Multiple Deprivation (SIMD). SIMD incorporates multiple domains, including employment, health, education, housing and services, and is based on a small area of approximately 500-1000 people. [23] The SIMD version nearest to birth year, based on postal code at birth, was used. [24]

To account for national changes in antibiotic prescribing, an indicator variable was created corresponding to the publication of the UK Chief Medical Officer AMR report, which was published March 11, 2013, and precipitated 5-year AMR strategies in the UK and, specifically, Scotland. [25, 26]

All data were linked and provided by the Electronic Data Research and Innovation Service (eDRIS) to UCL researchers in pseudonymised format.

Statistical Methods

Weekly rates of antibiotic prescribing (per 1,000 children) and specimen-specific laboratory tests positives (per 100,000 children) were calculated. Weeks were calculated based on calendar date, starting with the first day of the study period (Wednesday, April 1st, 2009).

We identified a clear bi-weekly pattern in antibiotic prescribing; to account for this autocorrelation, possibly explained by pharmacies submitting claims in bi-weekly batches, we calculated a four-week moving average of prescribing rates. We also observed an increasing trend of positive weekly rhinovirus episodes. We, therefore, detrended weekly rhinovirus counts by taking the residual values (i.e., observed minus fitted values) from a linear model of weekly rhinovirus circulation.

A negative-binomial model was used to predict weekly rates of antibiotic prescribing (i.e., four-week moving averages) from weekly counts of positive respiratory viral episodes. One-week lagged counts of positive viral tests were also considered during model selection given the latency periods of the considered pathogens. [27, 28] Specifically, laboratory surveillance typically reflects illness presenting in the community at an earlier time point. We included an offset term for the logarithm of weekly follow-up person-time. Given a hypothesized additive relationship between viral episodes and antibiotic prescribing patterns, an identity link was specified. Fourier cosine-and-sine paired terms were considered to account for underlying annual, bi-annual and quarterly patterns not attributable to viral circulation; e.g. unmeasured confounding due to other secular trends, pathogens, etc. [29, 30] Similarly, indicator terms for the weeks of Christmas, New Year's, between Christmas and New Year's, and Easter were considered given holiday closures. In addition to inclusion of an indicator term for the 2013 AMR Report, we also considered an indicator for the introduction of the UK's childhood influenza vaccination program in 2013/4; i.e., Sept 1st, 2013.

A backwards stepwise model selection approach was taken to identify the most parsimonious and best-fitting model based on Akaike Information Criterion (AIC) values, [31] summarized in Table S1.

Using the final parameter set, we modelled antibiotic prescriptions by age group (i.e., <1 and 1-4 years), common antibiotic classes, and presence of chronic conditions given possible differences in antibiotic prescribing patterns and respiratory tract infection burden. We further investigated differences before versus after the 2013 AMR Report.

The attribution of antibiotic prescribing to each virus was calculated as the product of the pathogen-specific model parameter estimate and total number of positive pathogen tests. Confidence intervals (95% CI) were calculated using the standard error of the pathogen-specific parameter estimate from our negative-binomial model; i.e., lower and upper bounds of the parameter estimate were multiplied by the total number of positive pathogen-specific tests. [32] To account for autocorrelation, robust standard errors were calculated by specifying a random residual term. We further attempted to account for autocorrelation by considering various autoregressive correlation structures.

Sensitivity Analysis

We investigated the robustness of estimates to potential biases in microbiology testing practices by considering the number of prescribed antibiotics attributable to hospital admissions for bronchiolitis and viral pneumonia, respectively. Specifically, we employed the same model parameterization as the main analysis; however, weekly positive test counts were replaced with weekly counts of hospitalizations for bronchiolitis or viral pneumonia.

All analyses were performed in SAS version 9.4 (SAS Institute; Cary, NC)

Ethics

The study was approved by the Public Benefit and Privacy Panel for Health and Social Care, reference number 1617-0224.

Results

Over the approximately 8.5-year study period, 452,877 children in Scotland were prescribed antibiotics and 41,666 had positive viral respiratory laboratory tests before their fifth birthday; corresponding to 59.4% and 5.5% of the 762,357 included children, respectively (Table 1). In all,

6,066,492 antibiotic prescriptions and 87,643 positive respiratory virus tests were included. Compared to all children <5 years who lived in Scotland during the study period, children with community-based antibiotic prescriptions were more commonly male, born preterm, had high-risk chronic conditions, younger mothers and lived in deprived neighbourhoods. Many of these differences were exaggerated for children with a positive respiratory virus episode. Children with positive respiratory virus episodes were often born between September and November; thus, were of young age during peak RSV (e.g. December) and influenza (e.g. January-February) circulation. Among children diagnosed with high-risk chronic conditions, 68.9% were prescribed at least one antibiotic and 13.3% tested positive at least once for a respiratory virus before their fifth birthday (Table S2). In this cohort of Scottish children under five years of age, the overall antibiotic dispensing rate was 609.7 antibiotics per 1,000 child-years; with age-specific rates of 532.7 and 628.5 per 1,000 child-years, respectively, observed among <1 and 1-4 year olds.

Clear correlations in the patterns of antibiotic prescribing and circulating respiratory virus burden were observed, as noted by co-occurring peaks (Figures 1 and 2). The final model included the following parameters: week; 2013 AMR strategy indicator; annual, biannual and quarterly sine/cosine harmonic terms; interaction terms between the AMR strategy indicator and annual harmonic terms; indicator terms for Christmas, New Year, the week between Christmas and New Year, and Easter; weekly test positives for influenza; and 1-week lagged positive test counts for RSV, HMPV, HPIV-1 and HPIV-3.

RSV was the most commonly identified respiratory virus. The observed and predicted weekly antibiotic prescribing rates are presented in Figure 3; corresponding figures for the stratified analyses by age, presence of chronic condition and antibiotic class are provided as Figures S1-3. An estimated 104,991 (95% CI: 84 758, 125 225) antibiotic prescriptions were attributable to RSV, accounting for 6.9% (5.6, 8.3) of all antibiotics prescribed to Scottish children <5 years (Table 2). Another 2.4% were attributed to influenza and 2.3% to HMPV. In the age-stratified models, 5.2% (3.9, 6.4) of antibiotics prescribed to children <1 year of age were attributed to RSV, followed by

HPIV-3 (1.6%) and HMPV (1.5%). Among children aged 1-4 years, 5.8% (4.6, 7.0) were attributed to RSV, followed by influenza (2.3%) and HMPV (1.6%).

Among children with a high-risk chronic condition recorded before their fifth birthday, 4.3% (3.2, 5.4) of antibiotics were attributable to RSV, 1.5% to influenza and 0.9% to HPIV-3 (Table 3). Among children with no high-risk conditions, 7.1%, 2.3% and 2.3% of antibiotics were attributable to RSV, HMPV and influenza, respectively. Before the AMR strategy, an estimated 5.1% of antibiotics were attributable to RSV (Table S3); 3.3%, 1.9%, 1.9%, and 0% were attributable to HPIV-3, influenza, HMPV, and HPIV-1, respectively. Following the AMR strategy, 8.8%, 2.7%, 2.3%, 1.4%, and 1.0% were attributed to RSV, HMPV, influenza, HPIV-3 and HPIV-1, respectively. Except for HPIV-3, all estimates increased post-2013.

Amoxicillin was the most commonly prescribed antibiotic, representing 61.9% of all antibiotics in this study, followed by other penicillins (23.5%) and macrolides (12.8%); cephalosporins were rarely prescribed (1.7%; Figure S3). We observed notable differences in the percent attributed to each pathogen across antibiotic categories. For example, 8.1% and 7.7% of amoxicillins and macrolides, respectively, were attributable to RSV, compared to only 2.4% of other penicillins and 1.3% of cephalosporins. Most cephalosporin prescriptions were attributed to HMPV (2.8%); HMPV was the second-most attributed pathogen for all other antibiotic categories (Table S4).

Co-occurring peaks between antibiotic prescribing and hospitalization were also observed in our sensitivity analysis of bronchiolitis and viral pneumonia (Figures S4 and S5). Approximately 9.8% (7.4, 12.1) and 2.4% (0, 5.0) of antibiotics were attributable to respiratory virus circulation indicated by hospital admissions for acute bronchiolitis and viral pneumonia, respectively.

Discussion

In this population-based study of children in Scotland, we estimated that 14% of community-based antibiotic prescriptions could be attributed to the circulation of common respiratory viruses. In all, 6.9% of antibiotic prescriptions in this study were attributed to RSV, 2.4% to influenza, 2.3% to HMPV, 1.5% to HPIV-1 and 0.6% to HPIV-3. A higher proportion of antibiotic prescriptions were

attributed to these viruses among previously healthy children without high-risk conditions, compared to children with chronic conditions. Though beyond the scope of this analysis, this might suggest stricter adherence to prescribing guidelines or prolonged use of antibiotics among children with these medical conditions. Critically, this study suggests that future vaccines might substantially reduce unnecessary antibiotic prescribing at a population-level and greater reductions may be possible within specific groups of children, such as those without chronic conditions, and for certain antibiotic classes. [33]

To our knowledge, we have provided the most comprehensive estimates to date of the proportion of antibiotics attributable to multiple respiratory viruses, along with estimates specific to key sub-groups. This study leveraged population-based health administrative data covering all children living in Scotland during the near decade-long study period. As antibiotics are not available over-the-counter in Scotland and are fully reimbursed for residents through the NHS, this study provides representative insights into community antibiotic use with minimal selection bias. It also provides novel insights into multiple laboratory-confirmed respiratory pathogens, for which reliable data are rare. The excellent data linkage infrastructure in Scotland [17] also enabled the investigation of additional factors, such as age and chronic conditions, and the consideration of hospitalizations as a secondary outcome.

Despite these major strengths, there are some limitations. Specifically, we lacked detailed, individual-level primary care data to evaluate indications for antibiotic prescribing, as this is often not recorded in prescribing databases. [14, 34] However, even when indication is available, several authors have reported that these reasons are inconsistently recorded or, worse, inaccurately recorded. [35, 36, 37] Critically, several authors have noted that prescribing physicians are aware that antibiotics should not be prescribed for viral causes and will purposefully enter another indication for prescribing, provide a non-specific indication or enter no indication at all. For example, Thompson et al. [35] reported that for children aged 0-18 years in UK primary care, “abnormal signs

and symptoms” was the second most common indication for antibiotics, after respiratory causes; with 73% of these being recorded for reasons due to a non-specific “ill-defined diagnosis”.

Further, we adopted a conservative analytical approach to reduce the possibility of over-estimating the number of antibiotics attributable to each pathogen. For example, we incorporated Fourier terms to adjust for unmeasured seasonal confounders, such as prescribing for bacterial infections; included shorter seasonal periods than traditionally considered to better reflect this seasonal variability [32, 30]; and calculated robust standard errors. While these methodological considerations reduce the possibility of over-estimation, they also increase the possibility of under-estimating the true degree to which antibiotic prescribing can be attributed to the viruses included in this study. Further, there is the potential that multicollinearity in the epidemic curves of the included pathogens may have led to an under-estimation of the true effects associated with any one pathogen. However, given the robustness of our model selection approach, goodness of the model fit, and large sample size, the effects of any multicollinearity are expected to be minimal. [38]

Finally, our study could not account for antibiotics prescribed in secondary care and viral tests not reported to ECOSS. While we assume the patterns of testing included in this analysis are representative of the circulating burden of the included pathogens, there may be biases related to health seeking behaviour and testing practices. [39] This may also be apparent from the pathogens included in the final model; i.e., the model selection process favoured pathogens that are more typically associated with severe illness (e.g., influenza, HMPV, and RSV) [40, 41], while pathogens causing mild or asymptomatic illness (e.g. rhinovirus) [40, 41] were less predictive of antibiotic prescribing patterns. Nevertheless, in the current absence of seroprevalence and routinely collected viral isolate data from primary care, the data used in this study have enabled novel insights.

Moreover, our sensitivity analysis of hospital admissions reached similar conclusions; assuming 80% of bronchiolitis is due to RSV infection, an estimated 7.8% of antibiotics would be attributable to RSV. [42] This further supports our conclusion that a substantial proportion of community-based antibiotic prescribing among children is attributable to the circulation of common respiratory

viruses. There is also the potential for unmeasured confounding, particularly due to the introduction of the UK's influenza vaccination program in 2013/4; however, inclusion of this indicator term was not found to not improve model fit. Future studies should examine the impact of the gradual introduction of routine childhood influenza vaccination in targeted age groups.

In recent years, several AMR guidelines have been published by leading international organizations; [4, 43, 44] many highlight that antibiotic prescribing for viral illness is both unnecessary and potentially dangerous and, further, that existing prescribing guidelines are being ignored. [45, 35] Rates of antibiotic prescribing noticeably declined post-2013, yet we found the percent of antibiotics attributable to respiratory viruses increased. It is possible that inappropriate prescribing for milder upper respiratory infections, for example, declined following the strategy, causing the relative percent attributed to these pathogens to increase. [46] Concurrent changes to microbiology testing practices are also possible, particularly considering testing rates for some pathogens appear low in the early study years. A recent evaluation observed a significant reduction of 14.1% in antibiotic prescribing in England following the 2013 AMR strategy but did not examine prescribing indication. [47] Further, we estimated prescribing for amoxicillin and macrolides was more closely associated with respiratory virus circulation than other antibiotics. Given the indications for these antibiotics, this is not unexpected. For example, the BNF and guidance organizations, such as the National Institute for Health and Clinical Excellence (NICE), recommend amoxicillin and certain macrolides as first-line antibiotics for children with symptoms of community acquired pneumonia and severe symptoms of otitis media; whereas, cephalosporins are generally not considered first-line treatments. [43, 48]

This study adds to a growing body of literature showing that antibiotics are commonly prescribed to children for viral illnesses. [49, 39] For example, a 2019 study of Australian primary care physicians reported that 56% of antibiotics were prescribed for respiratory infections; 84% of these were upper respiratory tract infections. [34] Another recent study reported that a third of children visiting emergency departments in the United States for bronchiolitis were prescribed antibiotics. [50] The

current literature is overwhelmingly focused on hospitalized populations. [32, 30] To our knowledge, this is the first population-based study of community-based antibiotic prescribing attributable to multiple laboratory-confirmed viruses.

The population-based data on antibiotic dispensing and respiratory viral detections used for this study is internationally unique. The authors were only able to identify two comparable studies in the literature, both specific to UK populations. [51, 52] A recent study of children in England reported that during 1995-2009 approximately 19.7%, 14.6%, and 13.6% of antibiotics prescribed among children <6 months, 6-23 months and 2-4 years of age, respectively, were attributable to RSV, controlling for influenza circulation. [51] These are considerably higher than our estimates; however, the authors acknowledge they likely overestimated the proportion due to RSV because they could not adequately adjust for several seasonal confounders, such as other winter pathogens. This difference may also be partly explained by changes in testing and prescribing practices over time and across the UK. [47, 44] Another study of English children (<18 years) estimated that approximately 2% of antibiotics over 1997-2009 were attributable to influenza, controlling for RSV circulation; [52] this is comparable to our estimate of 2.4% among Scottish children under five. Unlike these studies, we simultaneously considered more viral pathogens, allowing for richer adjustment of seasonal confounders. However, this underscores the importance of additional research to ascertain whether a similar proportion of antibiotics can be attributed to common respiratory viruses among children in other regions. This proportion will be impacted by regional differences in prescribing practices, which may also vary by prescriber types (e.g. general practitioner, paediatrician, direct-to-consumer prescribers, etc.), as suggested by a recent study of outpatient prescriptions in the United States. [53, 54] This relationship may be further impacted by differences in patient and provider expectations and knowledge around antibiotic use; for example, prescribing for antibiotics may be lower in areas with effective “Choosing Wisely” campaigns. [55] Given the relatively low antibiotic prescription rates in children in Scotland compared to in the United States [53], for example, our

results provide a likely lower bound estimate of the proportion of antibiotics prescribed for respiratory viruses in higher prescription settings.

Conclusions

Over one in ten antibiotic prescriptions among Scottish children in primary care can be attributed to circulating respiratory viruses. Given that 7% of prescriptions are due to RSV, the emergence of an RSV vaccine in the next 5-10 years is expected to contribute substantially to reducing antibiotic prescribing, especially amoxicillin and macrolides, and particularly among previously healthy children. In the meantime, these results highlight critical targets for improving primary care practice and reducing unnecessary antibiotic use.

Accepted Manuscript

Acknowledgements

We gratefully acknowledge Diane Rennie at eDRIS for her help and the ECOSS team at Health Protection Scotland for extracting the ECOSS data for linkage. This work uses data provided by patients and collected by the Scottish National Health Service (NHS) as part of their care and support. We would also like to thank Dr Linda Wijlaars at UCL for her support with preparing the data for analysis.

Disclaimer

Research at UCL Great Ormond Street Institute of Child Health supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre. This article represents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not those of the NHS, the NIHR or the Department of Health.

Funding

This work was supported by a competitive training award from Mitacs; Mitacs Globalink Research Award. Additional financial support was provided by the SickKids Research Institute and UCL's Global Engagement Fund. We also acknowledge support from the National Institute for Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital for Children National Health Service (NHS) Foundation Trust.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

References

- [1] M. Ashworth, R. Latinovic, J. Charlton, K. Cox, G. Rowlands and M. Gulliford, "Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database," *J Public Health*, vol. 26, no. 3, pp. 268-74, 2004.
- [2] K. E. Atkins and M. Lipsitch, "Can antibiotic resistance be reduced by vaccinating against respiratory disease?," *Lancet*, vol. 6, no. 11, pp. 820-1, 2018.
- [3] S. C. Davies, "Annual Report of the Chief Medical Officer. Volume Two, 2011: Infections and the rise of antimicrobial resistance," Department of Health, London, 2013.
- [4] World Health Organization, "Global action plan on antimicrobial resistance," WHO Press, Geneva, 2015.
- [5] S. Rogers Van Katwyk, J. M. Gromshaw, M. Nkangu, R. Nagi, M. Mendelson, M. Taljaard and S. J. Hoffman, "Government policy interventions to reduce human antimicrobial use: A systematic review and evidence map," *PLoS Med*, vol. 16, no. 6, p. e1002819, 2019.
- [6] Global and Public Health Group, Emergency Preparedness and Health Protection Policy, "Contained and controlled: The UK's 20-year vision for antimicrobial resistance," United Kingdom Government, 2019.
- [7] H. B. M. Otters, J. C. van der Wouden, F. G. Schellevis, L. W. A. van Suijlekom-Smit and B. W. Koes, "Trends in prescribing antibiotics for children in Dutch general practice," *J Antimicrob Chemother*, vol. 53, no. 2, pp. 361-6, 2004.
- [8] J. Holstiege, T. Schink, M. Molohkia, G. Mazzaglia, F. Innocenti, A. Oteri, I. Bezermer, E. Poluzzi, A. Puccini, S. Pilgaard Ulrichsen, M. C. Sturkenboom, G. Trifirò and E. Garbe, "Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study," *BMC Pediatrics*, vol. 14, p. 174, 2014.
- [9] A. Majeed and K. Moser, "Age- and sex-specific antibiotic prescribing patterns in general practice in England and Wales in 1996," *British J Gen Pract*, vol. 49, no. 446, pp. 735-6, 1999.
- [10] M. H. Ebell and T. Radke, "Antibiotic use for viral acute respiratory tract infections remains common," *Am J Manag Care*, vol. 21, no. 10, pp. e567-75, 2015.
- [11] F. C. K. Dolk, K. B. Pouwels, D. R. M. Smith, J. V. Robotham and T. Smieszek, "Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions?," *J Antimicrob Chemother*, vol. 73, no. 2, pp. ii2-10, 2018.
- [12] A. W. Chow, M. S. Benninger, I. Brook, J. L. Brozek, E. J. Goldstein, L. A. Hicks, G. A. Pankey, M. Seleznick, G. Volturo, E. R. Wald and T. M. File Jr., "IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults.," *Clin Infect Dis*, vol. 54, no. 8, pp. e72-112, 2012.
- [13] T. Jartti, P. Lehtinen, T. Vuorinen and O. Ruuskanen, "Bronchiolitis: age and previous wheezing episodes are linked to viral etiology and atopic characteristics.," *Pediatr Infect Dis J*, vol. 28, no.

- 4, pp. 311-7, 2009.
- [14] P. Hardelid, Y. Ghebremichael-Weldeselassie, H. Whitaker, G. rait, R. Gilbert and I. Petersen, "Effectiveness of live attenuated influenza vaccine in preventing amoxicillin prescribing in preschool children: a self-controlled case series study," *J Antimicrob Chemother*, vol. 73, no. 3, pp. 779-86, 2018.
- [15] J. C. Kwong, S. Maaten, R. E. G. Upshur, D. M. Patrick and F. Marra, "The Effect of Universal Influenza Immunization on Antibiotic Prescriptions: An Ecological Study," *Clin Infect Dis*, vol. 49, no. 5, pp. 750-6, 2009.
- [16] R. Farley, G. Spurling, L. Eriksson and C. Del Mar, "Antibiotics for bronchiolitis in children under two years of age (Review)," *Cochrane Database of Systematic Reviews*, vol. 10, p. DOI: 10.1002/14651858.CD005189.pub4, 2014.
- [17] M. Bennie, W. Malcolm, C. A. Marwick, K. Kavanagh, J. Sneddon and D. Nathwani, "Building a national Infection Intelligence Platform to improve antimicrobial stewardship and drive better patient outcomes: the Scottish experience," *J Antimicrob Chemother*, vol. 72, no. 10, pp. 2938-42, 2017.
- [18] P. Hardelid, M. Verfuerden, J. McMenemy and R. Gilbert, "Risk factors for admission to hospital with laboratory-confirmed influenza in young children: birth cohort study," *Eur Respir J*, vol. 50, p. 1700489, 2017.
- [19] Health Protection Scotland, "Data and surveillance," 2019. [Online]. Available: <https://hps-beta.azurewebsites.net/data/>. [Accessed 27 08 2019].
- [20] M. R. Lis Y, "The VAMP Research multi-purpose database in the U.K.," *J Clin Epidemiol.*, vol. 48, no. 3, pp. 431-43, 1995.
- [21] C. Feudtner, J. Feinstein, W. Zhong, M. Hall and D. Dai, "Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation," *BMC Pediatrics*, vol. 14, p. 199, 2014.
- [22] M. L. Verfuerden, T. Fitzpatrick, L. Holder, A. Zylbersztejn, L. Rosella, R. Gilbert, A. Guttmann and P. Hardelid, "Respiratory tract infection mortality: burden and risk factors in three high-income jurisdictions," *Under Review*, 2019.
- [23] Scottish Government, "The Scottish Index of Multiple Deprivation," 22 08 2019. [Online]. Available: <https://www2.gov.scot/Topics/Statistics/SIMD>. [Accessed 27 08 2019].
- [24] NHS Scotland, Public Health and Intelligence, "Deprivation Guidance for Analysts," [Online]. Available: https://www.isdscotland.org/Products-and-services/Gpd-support/Deprivation/_docs/PHI-Deprivation-Guidance-version-3-2.pdf. [Accessed 8 Oct 2019].
- [25] Department of Health and the Department for Environment, Food and Rural Affairs, "UK Five Year Antimicrobial Resistance Strategy 2013 to 2018," Department of Health, London, 2013.
- [26] Scottish Medicines Consortium and Scottish Antimicrobial Prescribing Group, "Scottish Management of Antimicrobial resistance Action Plan 2014 – 18 (ScotMARAP 2)," 2014. [Online]. Available: <https://www.gov.scot/publications/scottish-management-antimicrobial-resistance->

action-plan-2014-18-scotmarap2/.

- [27] C. Chiavenna, A. M. Presanis, A. Charlett, S. de Lusignan, S. Ladhani, R. G. Pebody and D. De Angelis, "Estimating age-stratified influenza-associated invasive pneumococcal disease in England: A time-series model based on population surveillance data," *PLoS Med*, vol. 16, no. 6, p. e1002829, 2019.
- [28] R. Blackburn, H. Zhao, R. Pebody, A. Hayward and C. Warren-Gash, "Laboratory-Confirmed Respiratory Infections as Predictors of Hospital Admission for Myocardial Infarction and Stroke: Time-Series Analysis of English Data for 2004–2015," *Clin Infect Dis*, vol. 67, no. 1, pp. 8-17, 2018.
- [29] K. Cassell, P. Gacek, T. Rabatsky-Ehr, S. Petit, M. Cartter and D. M. Weinberger, "Estimating the True Burden of Legionnaires' Disease," *Am J Epidemiol*, vol. 188, no. 9, pp. 1686-94, 2019.
- [30] H. Zhou, W. W. Thompson, C. G. Viboud, C. M. Ringholz, P. Y. Cheng, C. Steiner, G. R. Abedi, L. J. Anderson, L. Brammer and D. K. Shay, "Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008," *Clin Infect Dis*, vol. 54, no. 10, pp. 1427-36, 2012.
- [31] C. Chatfield, *The Analysis of Time Series: An Introduction*, London: Chapman & Hall/ CRC, 2003.
- [32] R. M. Reeves, P. Hardelid, R. Gilbert, F. Warburton, J. Ellis and R. G. Pebody, "Estimating the burden of respiratory syncytial virus (RSV) on respiratory hospital admissions in children less than five years of age in England, 2007-2012," *Influenza Other Respir Viruses*, vol. 11, no. 2, pp. 122-9, 2017.
- [33] M. C. Kneyber and J. L. Kimpen, "Antibiotics in RSV bronchiolitis: still no evidence of effect," *Eur Respir J*, vol. 29, no. 6, p. 1285, 2007.
- [34] J. Yan, L. Hawes, L. Turner, D. Mazza, C. Pearce and J. Buttery, "Antimicrobial prescribing for children in primary care," *J Paediatr Child Health*, vol. 55, no. 1, pp. 54-8, 2019.
- [35] P. L. Thompson, N. Spyridis, M. Sharland, R. E. Gilbert, S. Saxena, P. F. Long, A. P. Johnson and I. C. K. Wong, "Changes in clinical indications for community antibiotic prescribing for children in the UK from 1996 to 2006: will the new NICE prescribing guidance on upper respiratory tract infections just be ignored?," *Arch Dis Child*, vol. 94, no. 5, pp. 337-40, 2009.
- [36] I. Petersen, R. Gilbert, S. Evans, A. Ridolifi and I. Nazareth, "Oral antibiotic prescribing during pregnancy in primary care: UK population-based study," *J Antimicrob Chemother*, vol. 65, no. 10, pp. 2238-46, 2010.
- [37] R. Mangione-Smith, E. A. McGlynn, M. N. Elliot, P. Krogstad and R. H. Brook, "The Relationship Between Perceived Parental Expectations and Pediatrician Antimicrobial Prescribing Behavior," *Pediatrics*, vol. 103, no. 4, pp. 711-8, 1999.
- [38] M. R. Lavery, P. Acharya, S. A. Sivo and L. Xu, "Number of predictors and multicollinearity: What are their effects on error and bias in regression?," *Communications in Statistics - Simulation and Computation*, vol. 1, pp. 27-38, 2019.

- [39] A. Köchling, C. Löffler, S. Reinsch, A. Hornung, F. Böhmer, A. Altiner and J. F. Chenot, "Reduction of antibiotic prescriptions for acute respiratory tract infections in primary care: a systematic review," *Implement Sci*, vol. 13, no. 1, p. 47, 2018.
- [40] S. Rhedin, A. Lindstrand, A. Hjelmgren, M. Ryd-Rinder, L. Öhrmalm, T. Tolfvenstam, A. Örtqvist, M. Rotzén-Östlund, B. Zweyberg-Wirgart, K. Broliden and P. Naucner, "Respiratory viruses associated with community-acquired pneumonia in children: matched case-control study," *Thorax*, vol. 70, no. 9, pp. 847-53, 2015.
- [41] J. M. Uitti, P. A. Tähtinen, M. K. Laine, P. Huovinen, O. Ruuskanen and A. Ruohola, "Role of Nasopharyngeal Bacteria and Respiratory Viruses in Acute Symptoms of Young Children.," *Pediatr Infect Dis J.*, vol. 34, no. 10, pp. 1056-62, 2015.
- [42] R. J. Pickles and J. DeVincenzo, "RSV and its propensity for causing bronchiolitis," *J Pathol*, vol. 235, no. 2, pp. 266-76, 2015.
- [43] NICE, "Antimicrobial prescribing guidelines," 2019. [Online]. Available: <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/antimicrobial-prescribing-guidelines>. [Accessed 27 08 2019].
- [44] European Commission, "A European One Health Action Plan against Antimicrobial Resistance (AMR)," 06 2017. [Online]. Available: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf. [Accessed 27 08 2019].
- [45] C. Costelloe, C. Metcalfe, A. Lovering, D. Mant and A. D. Hay, "Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis," *BMJ*, vol. 340, p. c2096, 2010.
- [46] T. Fahey, N. Stocks and T. Thomas, "Systematic review of the treatment of upper respiratory tract infection," *Arch Dis Child*, vol. 79, no. 3, pp. 225-30, 1998.
- [47] A. J. Walker, H. J. Curtis and B. Goldacre, "Impact of Chief Medical Officer activity on prescribing of antibiotics in England: an interrupted time series analysis," *J Antimicrob Chemother*, vol. 74, pp. 1133-6, 2019.
- [48] Joint Formulary Committee, BNF 74: September 2017, London: Pharmaceutical Press, 2017.
- [49] W. F. Holmes, J. T. Macfarlane, R. M. Macfarlane and R. Hubbard, "Symptoms, signs, and prescribing for acute lower respiratory tract illness," *Br J Gen Pract*, vol. 51, no. 464, pp. 177-81, 2001.
- [50] J. Papenburg, P. S. Fontela, R. R. Freitas and B. Burstein, "Inappropriate Antibiotic Prescribing for Acute Bronchiolitis in US Emergency Departments, 2007–2015," *J Pediatr Inf Dis Soc*, vol. in press, p. doi: 10.1093/jpids/piy131, 2019.
- [51] S. Taylor, R. J. Taylor, R. L. Lustig, C. Schuck-Paim, F. Haguinet, D. J. Webb, J. Logie, G. Matias and D. M. Fleming, "Modelling estimates of the burden of respiratory syncytial virus infection in children in the UK," *BMJ Open*, no. e009337, p. 6, 2016.

- [52] D. M. Fleming, R. J. Taylor, F. Haguinet, C. Schuck-Paim, J. Logie, D. J. Webb, R. L. Lustig and G. Matias, "Influenza-attributable burden in United Kingdom primary care," *Epidemiol Infect*, vol. 144, no. 3, pp. 537-47, 2016.
- [53] L. M. King, M. Bartoces, K. E. Fleming-Dutra, R. M. Roberts and L. A. Hicks, "Changes in US Outpatient Antibiotic Prescriptions From 2011-2016," *Clin Infect Dis*, vol. 70, no. 3, pp. 370-7, 2020.
- [54] C. B. Foster, K. A. Martinez, C. Sabella, G. P. Weaver and M. B. Rothberg, "Patient Satisfaction and Antibiotic Prescribing for Respiratory Infections by Telemedicine," *Pediatrics*, vol. 144, no. 3, p. e20190844, 2019.
- [55] Choosing Wisely Canada, "Using Antibiotics Wisely," [Online]. Available: <https://choosingwiselycanada.org/campaign/antibiotics/>. [Accessed 03 Feb 2020].
- [56] J. A. Finkelstein, J. P. Metlay, R. L. Davis, S. L. Rifas-Shiman, S. F. Dowell and R. Platt, "Antimicrobial use in defined populations of infants and young children.," *Arch Pediatr Adolesc Med*, vol. 154, no. 4, pp. 395-400, 2000.
- [57] A. D. Hay, J. Heron and A. Ness, "The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study.," *Fam Pract*, vol. 22, no. 4, pp. 367-74, 2005.
- [58] G. Ryan, M. Singh and K. Dwan, "Inhaled antibiotics for long-term therapy in cystic fibrosis.," *Cochrane Database Syst Rev*, vol. 3, p. CD001021, 2011.
- [59] V. Palin, A. Molter, M. Belmonte, D. M. Ashcroft, A. White, W. Welfare and T. van Staa, "Antibiotic prescribing for common infections in UK general practice: variability and drivers," *J Antimicrob Chemother*, vol. 74, no. 8, pp. 2440-50, 2019.
- [60] NHS National Services Scotland, "Joint SMVN/SHPN Public Health Microbiology advisory Statement for Influenza Point of Care Tests," 2018. [Online]. Available: <https://www.smvn.scot.nhs.uk/wp-content/uploads/2018/11/SMVN-PHMicro-Influenza-POCT.pdf>. [Accessed 26 Nov 2019].

Figure 1. Weekly rates of antibiotic prescribing and positive viral specimen tests for influenza and respiratory syncytial virus (RSV), among Scottish children under 5 years of age

Figure 2. Weekly rates of antibiotic prescribing (per 1,000; gray) and positive viral specimen tests* (per 100,000 children; black) for other common respiratory viral pathogens, among Scottish children under 5 years of age.

* Y-axis scales vary.

Figure 3. Observed and predicted (95% CI) rates of weekly antibiotic prescribing (smoothed four-week moving average), among Scottish children under 5 years of age

Accepted Manuscript

Table 1. Characteristics of Scottish children born Apr 2, 2004 – Dec 27, 2017; overall study cohort and according to having any antibiotic prescribed or positive viral respiratory specimen test recorded before their 5th birthday

Characteristic, N (%)	All Children Included in the Study	Children Prescribed Antibiotics in the Community ¹	Children with Positive Respiratory ² Viral Tests ¹ Detected in Hospital Settings
	N = 762,357	N = 452,877	N = 41,666
Birth Season			
Winter (Dec – Feb)	184,798 (24.24)	108,310 (23.92)	9,478 (22.75)
Spring (Mar – May)	185,929 (24.39)	112,785 (24.90)	9,103 (21.85)
Summer (Jun – Aug)	198,669 (26.06)	117,844 (26.02)	10,787 (25.89)
Fall (Sept – Nov)	192,961 (25.31)	113,938 (25.16)	12,298 (29.52)
Sex			
Male	385,889 (50.62)	237,965 (52.55)	23,808 (57.14)
Female or missing*	376,468 (49.38)	214,912 (47.45)	17,858 (42.86)
Gestational age (weeks)			
Preterm (<34)	15,826 (2.08)	9,627 (2.13)	2,421 (5.81)
Late Preterm (34-36)	40,331 (5.29)	24,628 (5.44)	3,454 (8.29)
Early term (37-38)	136,707 (17.93)	82,598 (18.24)	8,811 (21.15)
Term (39-40)	384,007 (50.37)	231,272 (51.07)	19,549 (46.92)
Late term (41+)	171,705 (22.52)	103,940 (22.95)	7,323 (17.58)
Missing	13,781 (1.81)	812 (0.18)	108 (0.26)
High risk chronic condition			
Recorded Before 1 st birthday	46,027 (6.04)	29,810 (6.58)	5,737 (13.77)
Recorded before 5 th birthday	66,153 (8.68)	44,903 (9.92)	8,794 (21.11)
Maternal age at birth (years)			
<19	25,945 (3.40)	15,909 (3.51)	1,399 (3.36)
19-24	150,306 (19.72)	94,464 (20.86)	9,172 (22.01)
25-29	201,097 (26.38)	123,645 (27.30)	11,408 (27.38)
30-34	220,287 (28.90)	130,218 (28.75)	11,666 (28.00)
35-39	125,341 (16.44)	72,761 (16.07)	6,556 (15.73)
40+	27,280 (3.58)	15,880 (3.50)	1,465 (3.52)
Missing	66,153 (8.68)	**	**

Mean (SD)	29.22 (5.98)	29.06 (5.97)	29.95 (5.97)
Area-level deprivation quintile			
1 st (Least deprived)	128,745 (16.89)	67,574 (14.92)	6,237 (14.97)
2 nd	129,484 (16.98)	75,166 (16.60)	6,588 (15.81)
3 rd	136,054 (17.85)	81,258 (17.94)	7,218 (17.32)
4 th	153,427 (20.13)	94,960 (20.97)	8,769 (21.05)
5 th (Most deprived)	176,213 (23.11)	111,740 (24.67)	10,002 (24.01)
Missing	38,434 (5.04)	22,179 (4.90)	2,852 (6.84)

¹At least once before 5th birthday. ²Including influenza, respiratory syncytial virus, human parainfluenza, coronavirus, enterovirus, rhinovirus or human metapneumovirus.

*<7 children had missing values

**<7 children had missing values; missing category has been joined with 40+ category

Accepted Manuscript

Table 2. Estimated number and percent (95% CI) of antibiotics attributable to specific respiratory pathogens over the study period (Apr 1, 2009 – Dec 27, 2017); stratified by age

Pathogen	Under 5 years of age		Under 1 year of age		1 - 4 years of age	
	N (95% CI)	% (95% CI)	N (95% CI)	% (95% CI)	N (95% CI)	% (95% CI)
Influenza	36 138 (25 317, 46 959)	2.38 (1.67, 3.09)	1 551 (0, 3 226)	0.59 (0.00, 1.22)	29 166 (19 944, 38 388)	2.33 (1.59, 3.06)
RSV	104 991 (84 758, 125 225)	6.92 (5.59, 8.25)	13 596 (10 303, 16 888)	5.16 (3.91, 6.41)	72 670 (57 093, 88 248)	5.80 (4.55, 7.04)
HMPV	35 514 (11 681, 59 347)	2.34 (0.77, 3.91)	3 818 (714, 6 922)	1.45 (0.27, 2.63)	20 090 (2 452, 37 728)	1.60 (0.20, 3.01)
HPIV-1	9 319 (2 552, 16 085)	0.61 (0.17, 1.06)	649 (0, 1 714)	0.25 (0, 0.65)	6 609 (1 248, 11 971)	0.53 (0.10, 0.95)
HPIV-3	22 890 (7096, 38 684)	1.51 (0.47, 2.55)	1 714 (4 105, 1 832)	1.56 (0.70, 2.42)	8 772 (0, 21 611)	0.70 (0, 1.72)

RSV: Respiratory syncytial virus; HMPV: Human Metapneumovirus; HPIV-1: Human Parainfluenza virus, type 1; HPIV-3: Human Parainfluenza, type 3

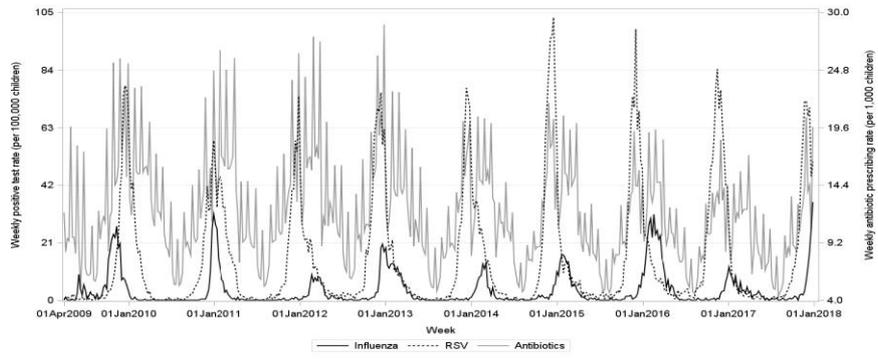
Table 3. Estimated number and percent (95% CI) of antibiotics attributable to specific respiratory pathogens (Apr 1, 2009 – Dec 27, 2017); stratified by recorded diagnosis of major chronic illness before 5th birthday

Pathogen	High-Risk Chronic Condition Recorded Before 5 th Birthday		No High-Risk Chronic Condition Recorded	
	N (95% CI)	% (95% CI)	N (95% CI)	% (95% CI)
Influenza	3 175 (1 979, 4 372)	1.51 (0.94, 2.08)	29 813 (20 290, 39 337)	2.28 (1.55, 3.01)
RSV	9 056 (6 717, 11 395)	4.30 (3.19, 5.41)	93 113 (75 290, 110 936)	7.13 (5.76, 8.49)
HMPV	1 481 (0, 3 614)	0.70 (0, 1.72)	29 867 (10 794, 48 940)	2.29 (0.83, 3.75)
HPIV-1	898 (94, 1 703)	0.43 (0.04, 0.81)	7 192 (1 423, 12 961)	0.55 (0.11, 0.99)
HPIV-3	1 840 (132, 3 549)	0.87 (0.06, 1.68)	16 850 (3 548, 30 152)	1.29 (0.27, 2.31)

RSV: Respiratory syncytial virus; HMPV: Human Metapneumovirus; HPIV-1: Human Parainfluenza virus, type 1; HPIV-3: Human Parainfluenza, type 3

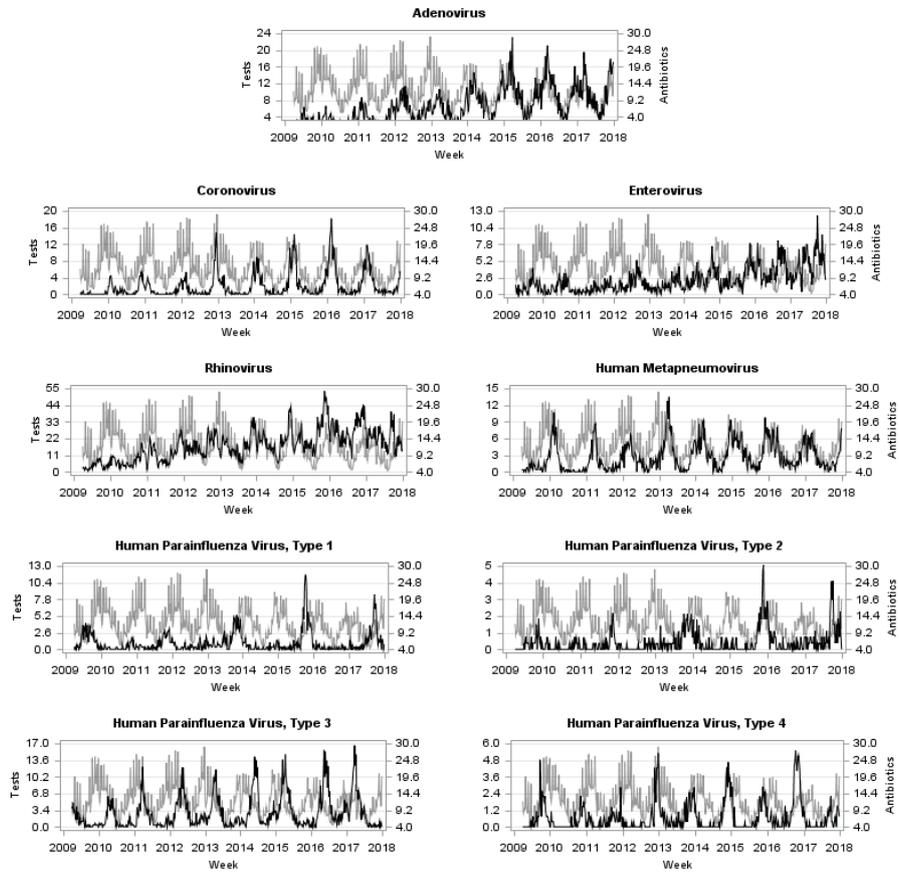
Accepted Manuscript

Figure 1



ACQ

Figure 2



ACC

Figure 3

