This is a repository copy of *Estimation of seasonal influenza attack rates and antibody dynamics in children using cross-sectional serological data*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/162684/

Version: Accepted Version

Estimation of seasonal influenza attack rates and antibody dynamics in children using cross-sectional serological data

Amanda Minter[1], Katja Hoschler [2], Ya Jankey Jagne [3], Hadijatou Sallah [3], Edwin Armitage [3], Benjamin Lindsey [3], James A. Hay[4,5], Steven Riley[4], Thushan I. de Silva [3,6†], Adam Kucharski*[1†]

1 Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, UK
2 Respiratory Virus Reference Department, Public Health England, London, United Kingdom
3 Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, The Gambia
4 MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London, United Kingdom
5 Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States of America
6 The Florey Institute, Department of Infection, Immunity and Cardiovascular Disease, Medical School, University of Sheffield, UK

*Correspondence: A. J. Kucharski, London School of Hygiene and Tropical Medicine, Keppel Street, Bloomsbury, London WC1E 7HT (adam.kucharski@lshtm.ac.uk)
† contributed equally

Abstract

Directly measuring evidence of influenza infections is difficult, especially in low surveillance settings such as sub-Saharan Africa. Using a Bayesian model, we estimated unobserved infection times and underlying antibody responses to influenza A/H3N2 using cross-sectional serum antibody responses to four strains in children aged 24-60 months. Among the 242 individuals, we estimated a variable seasonal attack rate and found that most children had at least one infection before two years of age. Our results are consistent with previously published high attack rates in children. The modelling approach highlights how cross-sectional serological data can be used to estimate epidemiological dynamics.

Introduction

Influenza epidemics cause substantial global burden [1], with individuals infected with multiple viral strains during their lifetime [2, 3]. In sub-Saharan Africa, seasonal influenza can lead to high mortality and large burden of illness in children [4]. There is evidence early-life exposure to influenza viruses can shape both subsequent antibody responses to later strains [5] and risk of disease [6]. However, because infections may be asymptomatic or subclinical [7], it can be challenging to measure these early-life infections. Understanding of early life seasonal influenza infections in sub-Saharan Africa is further limited by the relative paucity of seroepidemiological studies of childhood populations.

We tested contemporary sera from cross-sectional samples in a childhood cohort from The Gambia against a panel of recently circulating influenza A/H3N2 strains [8]. Combining these haemagglutination inhibition (HI) assays with a Bayesian model of unobserved infections and antibody dynamics [9, 10], we estimated the frequency and timing of infections in the cohort. We then used these results to reconstruct seasonal attack rates, as well as characterise antibody responses in children following primary infections with influenza A/H3N2.

Materials and methods
Study population and serological testing

Two cohorts of unvaccinated children aged between 24 and 60 months living within a peri-urban area in The Gambia were recruited between February and April in 2017 (n=116), and between January and March in 2018 (n=126), as part of a prospective observational phase 4 study of live attenuated influenza vaccine (Figure 1a; see [8] for details), the total number included in the current study was 242. The median age of the individuals across both cohorts was 35 months (range 24-59). Pre-vaccination serum samples were taken from each participant. Each sample was tested by HI assay against a panel of three egg-cultured influenza A/H3N2 vaccine viruses: A/Texas/50/2012, A/Switzerland/9715293/2013 and A/Hong Kong/4801/2014. These were chosen to represent the main antigenically distinct A/H3N2 strains circulating during the lifetime of the children based on WHO influenza vaccine recommendations for the Northern hemisphere.

Statistical analysis

We used a Bayesian inference framework to jointly estimate infection histories and cross-reactive antibody dynamics for each participant [10]. The overall methodology is described in [9] and we detail the specific assumptions of our application in the supplementary information. For an unknown sequence of infection times from year of birth until year of sampling, a mechanistic model of antibody boosting, waning and cross-reaction generated a predicted antibody titre against each test strain for each participant. The predicted assay response (HI titre) was defined by a normally distributed random variable with mean equal to the predicted antibody response and standard deviation reflecting assay measurement error; these were interval-censored to reflect measured two-fold HI dilutions (supplementary information). The model also estimated a time-varying population-level probability of infection to account for correlation in infection risk between individuals during outbreaks. Using this framework, we estimated infection times and model parameters from the serological data.

We considered infections on a quarterly timescale, (i.e. individuals could be infected once per 3-month window), where quarters were defined as follows: Q1: 1st January to 31st March; Q2: 1st April to 30th June; Q3: 1st July to 30th September; and Q4: 1st October to 31st December. We assumed that the antigenic distance between strains increased linearly with time, reflecting the locally linear average path of A/H3N2 antigenic evolution observed in antigenic maps of cross-reactive responses to A/H3N2 derived from naive ferret antisera [2, 11]. A Euclidean distance of one unit on the antigenic map corresponds to a two-fold reduction in HI titre between the strain that generated the antisera and the cross-reactive strain being measured. We assumed that there was no detectable antigenic change within a specific calendar year and that strains circulated according to the periods of time they were selected as vaccine components (Figure 1a).

We incorporated prior information about dynamic antibody dynamic in the model. Specifically, the level of short-term rise in titre following infection, the rate of waning of this short-term response, and subsequent persistent level of titre were informed by previous analysis of HI data using the same model [10]. In the absence of any surveillance data from The Gambia, we incorporated prior knowledge about the times of infection based on epidemiological data from neighbouring Senegal [12]: we assumed that infection was most likely to occur in the third quarter of the year, with a very low probability of infection in the remaining quarters. In 2013, there was also very little H3N2 influenza infection reported in Senegal [12]; we therefore assumed very little infection probability in all quarters in 2013 (see supplementary information for more detail). Incorporating these prior assumptions in our model, we inferred the cross-reactive antibody dynamics and individual-level times of infections for children in the cohort using the 'serosolver' package [9]. From these estimates we calculated the attack rate, as well as frequency of individual-level infections, predicted antibody responses and predicted assay response (HI titre) against different A/H3N2 strains.

Results

We estimated that influenza A/H3N2 attack rates varied considerably over the study time period. The 2017 attack rate in cohort 2 was highest, with 47% (95% credible interval (CrI): 40-52%) of children infected. The second highest attack rate was in 2016, with 24% (19-29%) of cohort 2 and 33% (31-36%) of cohort 1 infected. There were lower attack rates in 2014 and little evidence of infections in 2013 and 2015 (Figure 1b). It was not possible to estimate the attack rate with any confidence in 2012, because few individuals were born at this point.

Fig 1. a) the number of individuals in each cohort with their respective birth and sampling month. Grey filled circles indicate the frequency of A/H3N2 infections that were observed in Senegal from 2013 to 2015 (obtained from [12]). b) the estimated attack rate for the Gambia cohorts with 95% quantile interval, c) the estimated number of infections per age in months, d) the estimated age at first infection in months.

As well as estimating population-level dynamics, we could compare individual-level infection histories. We estimated that 45% of children sampled had one infection in their lifetime. Of those who had been infected, the age at first infection ranged from 0-5 years (i.e. the age range of the entire cohort), with a median age of 21 months (Figure 1d). Of 242 individuals sampled, we estimated 33% had more than one infection, with only one individual having evidence of three infections. We found that the individuals with more past infections tended to be older (Figure S1). The estimated time between infections for the individuals with more than one infection ranged from one quarter to four years (with 61% individuals having two years between infections).

Fig 2. Characteristic antibody profiles for different infection histories. The predicted antibody titres were calculated for each individual using 200 different draws from the posterior densities of the antibody parameters. Points indicate median and solid lines indicate 95% quantile intervals. Plots are the observed (black dots), predicted antibody response (no observation error) (yellow squares) and predicted assay response (with observation error) (green triangles) to the test strains when individuals were estimated to have had only one infection with a) A/Texas/50/2012 or b) A/Hong Kong/4801/2014 within a year of sampling. Plot c) shows the predicted antibody responses for hypothetical individuals sampled in 2018, that were infected either with A/Texas/50/2012 (infection in 2013) , A/Hong Kong/4801/2014 within 18 months of the sampling date or A/Hong Kong/4801/2014 within 6 months of the sampling date.

Individual-level log-titres predicted by the model corresponded well with observed log-titres (Figure 2a-b). Because the model separately accounted for antibody dynamics and measurement error, it was possible to generate predictions for antibody response (true serum antibody levels) and assay response (the observed antibody titre) separately. The observed and predicted antibody titres for those individuals infected with A/Texas/50/2012 (Figure 2a) decrease with increasing strain circulation time.

By modelling the underlying antibody dynamics, the model was capable to capture the variation in observed log-titre according to when participants would have been infected. Participants with an inferred recent infection with A/Hong Kong/4801/2014 (n=62) (Figure 2b) had higher antibody titres than those infected with A/Texas/50/2012 (n=8). Although very few individuals were estimated to have been infected with A/Switzerland/9715293/2013, log-titres of at least 3 (equivalent to a raw titre of 1:40) were observed for the majority of participants estimated to have had one previous infection, which in the model was explained by a high estimated level of cross-reaction.

The effect of time-since-infection on predicted measurements is illustrated in Figure 2c. For the predicted antibody response, the level of response to an A/Hong Kong/4801/2014 infection 18 months from the sampling date and an A/Texas/50/2012 infection, was lower than a more recent infection with A/Hong Kong/4801/2014 within 6 months of the sampling date. Our model was able to capture the process of antibody waning with time after infection.

Discussion

By testing contemporary serum against strains antigenically similar to those circulating during the lifetime of a paediatric cohort, and adjusting for cross-reactive antibody dynamics and assay uncertainty using a Bayesian model, we estimated the epidemiology of childhood influenza A/H3N2 infections in The Gambia. We found high seasonal attack rates in several years, with almost half the population infected in the peak year. Most children had a primary A/H3N2 infection by two years of age. Our range of attack rate estimates was broadly consistent with previously published estimates of infection risk in children from observed data; a systematic review of vaccine randomised controlled trials from 32 countries estimated a combined symptomatic and asymptomatic attack rate of 22.5% (95 %CI(9.0%, 46.0%)) [13].

There are some limitations to our study. We imposed a quarterly timescale in our model due to the observation that neighbouring Senegal has a high-risk influenza season focused on a single quarter. As our data is cross-sectional, without this prior on timing of infection, we would not be able to infer differences between quarters. Though we had strong priors on the timing of infection, we did not enforce a strong prior on the magnitude of infection in the third quarter. Higher resolution estimates could be possible if multiple serological samples were collected within each year. In addition, infection in this study is measured as HI response, there are other assays and forms of testing which may confirm infection in individuals which we have reported as negative.

We also assumed that circulating influenza viruses corresponded to the vaccine strain at the time, and that for A/Texas/50/2012 and A/Hong Kong/ 4801/2014, the same strain circulated for two consecutive years. Although seasonal influenza viruses can emerge many months ahead of the vaccine strain selection, epidemics were concentrated in a small portion of the year in our model and so the broad sequence of antigenic change observed in A/H3N2 viruses in The Gambia during 2011–18 is unlikely to be substantially different to that assumed. For viruses which had well described egg-adaptations, including A/Switzerland/9715293/2013 and A/Hong Kong/4801/2014, we anticipate HI titres would be smaller in magnitude compared to if the viruses tested were more similar to the actual circulating virus. This would mean that our inferred attack rates are lower than the true attack rates.

Previous studies have found longitudinal data is required to reliably estimate waning antibody responses [3]. We therefore incorporated prior information on the relative magnitudes of short- and long-term antibody responses, with a strong prior on the rate of waning. However, our final estimates for the boost in titre following infection were generally higher than the prior estimate, suggesting sufficient information in the data to estimate child-specific magnitudes of response (Figure S2). We assumed a common waning rate for both adults and children. In reality, this rate may be different in children and adults, but in the absence of a robust estimate for children only, we chose to use an inferred waning rate from a mixed age cohort. Previous studies have shown that in mixed age cohorts that the waning rate is close to a year, hence it is likely that within the timescales we are using that any differences in waning rate would not make a substantial difference to inferred attack rates. Our attack rates estimates were robust to prior information on waning only (Figure S4). We also incorporated prior information about the timing of infection within a year, with the low attack estimated

rate in 2013 (median 0 in both cohorts) informed by Senegal surveillance data [12]. In the absence of this prior information in 2013, there was little difference in the estimated attack rates (Figure S5).
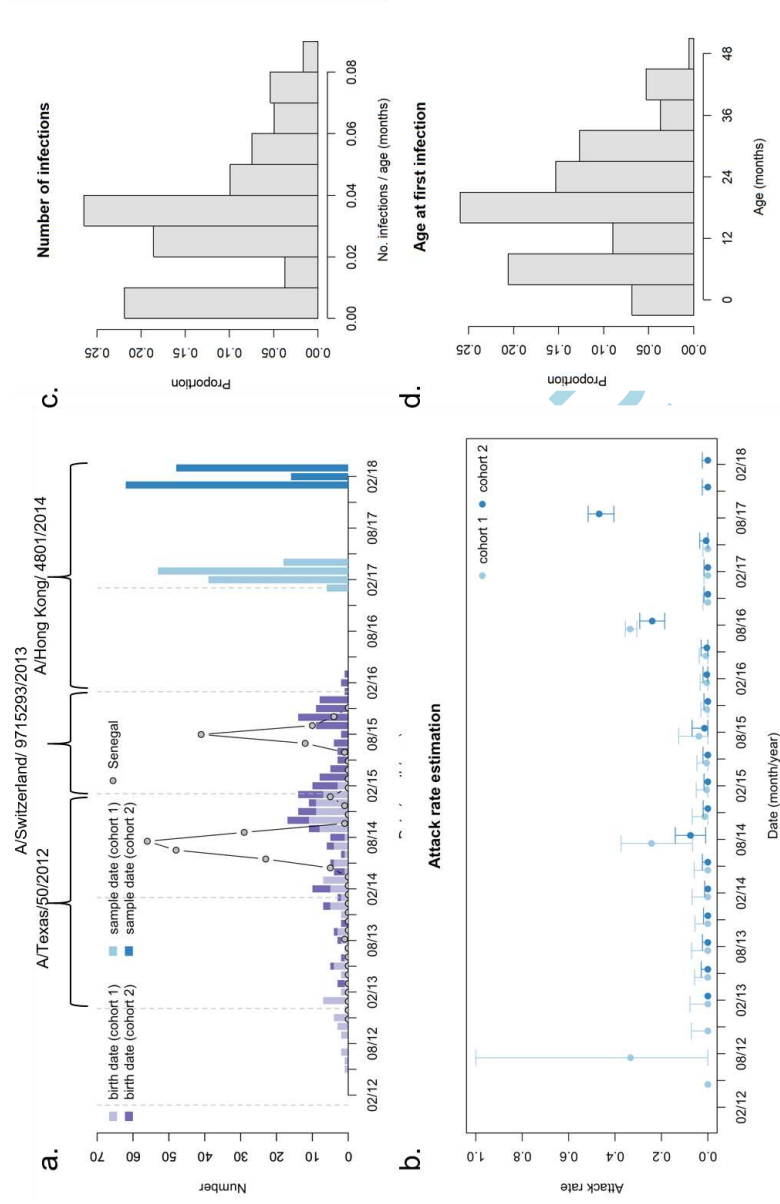
Early-life infections are important for influenza, but have been historically challenging to measure. Applying modelling frameworks to data generated by testing contemporary sera tested against multiple historical strains opens up the possibility of estimating epidemiological dynamics in a wide variety of settings. Using our methods, this could be achieved either through new serological surveys or secondary analysis of existing serum banks [14]. This may be especially important in countries where there is a paucity of influenza surveillance and incidence data, yet where details of influenza attack rates are vital for planning public health policy around influenza prevention. In addition to providing insight into population- and individual-level risk, knowledge of unobserved prior infections could be a useful predictor variable in analysis of subsequent infection risk, disease risk, or responses to vaccination, given the increasing evidence for immune imprinting during childhood on these parameters [6].
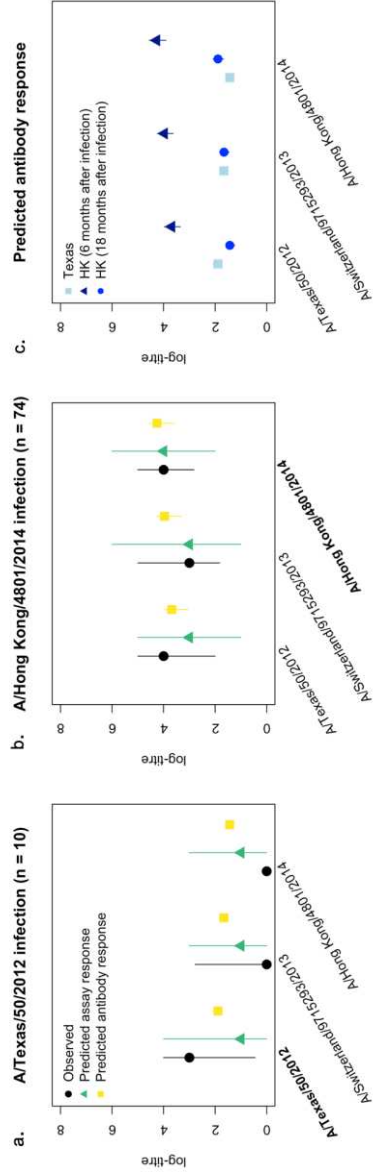
References

[1] Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. The Lancet. 2018;391(10127):1285 – 1300.

[2] Fonville JM, Wilks SH, James SL, Fox A, Ventresca M, Aban M, et al. Antibody landscapes after influenza virus infection or vaccination. Science. 2014;346(6212):996–1000.

[3] Kucharski AJ, Lessler J, Read JM, Zhu H, Jiang CQ, Guan Y, et al. Estimating the Life Course of Influenza A(H3N2) Antibody Responses from Cross-Sectional Data. PLoS Biol. 2015;13(3):e1002082–e1002082.

[4] Lafond KE, Nair H, Rasooly MH, Valente F, Booy R, Rahman M, et al. Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982–2012: A Systematic Analysis. PLoS Med. 2016 03;13(3):1–19. Available from: https://doi.org/10.1371/journal.pmed.1001977.

[5] Lessler J, Riley S, Read JM, Wang S, Zhu H, Smith GJD, et al. Evidence for Antigenic Seniority in Influenza A (H3N2) Antibody Responses in Southern China. PLoS Pathog. 2012 07;8:e1002802.

[6] Gostic KM, Ambrose M, Worobey M, Lloyd-Smith JO. Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting. Science. 2016;354(6313):722–726.

[7] Leung NH, Xu C, Ip DK, Cowling BJ. The fraction of influenza virus infections that are asymptomatic: a systematic review and meta-analysis. Epidemiology. 2015;26(6):862.

[8] Lindsey BB, Jagne YJ, Armitage EP, Singanayagam A, Sallah HJ, Drammeh S, et al. Effect of a Russian-backbone live-attenuated influenza vaccine with an updated pandemic H1N1 strain on shedding and immunogenicity among children in The Gambia: an open-label, observational, phase 4 study. Lancet Respir Med. 2019;7(8):665 – 676.

[9] Hay JA, Minter A, Ainslie K, Lessler J, Kucharski AJ, Riley S. Serosolver: an open source tool to infer epidemiological and immunological dynamics from serological data. bioRxiv. 2019;.

[10] Kucharski AJ, Lessler J, Cummings DAT, Riley S. Timescales of influenza A/H3N2 antibody dynamics. PLoS Biol. 2018 08;16:1–19.

[11] Smith DJ, Lapedes AS, de Jong JC, Bestebroer TM, Rimmelzwaan GF, Osterhaus ADME, et al. Mapping the Antigenic and Genetic Evolution of Influenza Virus. Science. 2004;305(5682):371–376.

[12] Niang MN, Barry MA, Talla C, Mbengue A, Sarr FD, Ba IO, et al. Estimation of the burden of flu-association influenza-like illness visits on total clinic visits through the sentinel influenza monitoring system in Senegal during the 2013 - 2015 influenza seasons. Epidemiol Infect. 2018;146(16):2049–2055.

[13] Somes MP, Turner RM, Dwyer LJ, Newall AT. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: A systematic review and meta-analysis. Vaccine. 2018;36(23):3199 – 3207.

[14] Metcalf CJE, Farrar J, Cutts FT, Basta NE, Graham AL, Lessler J, et al. Use of serological surveys to generate key insights into the changing global landscape of infectious disease. The Lancet. 2016;388(10045):728–730.

Figure 1

Figure 2