Temporal Association in Hospitalizations for Tuberculosis, Invasive Pneumococcal Disease and Influenza Virus Illness in South African Children

Ziyaad Dangor1,2, Alane Izu1,3, David P. Moore1,3, Marta C. Nunes1,3, Fatima Solomon1,3, Natalie Beylis4, Anne von Gottberg5, Johanna M. McAnerney5, Shabir A. Madhi1,3,5*

1 Medical Research Council, Respiratory and Meningeal Pathogens Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 2 Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 3 Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Johannesburg, South Africa, 4 Mycobacteriology Referral Laboratory, National Health Laboratory Service, Johannesburg, South Africa, 5 Center for Respiratory and Meningitis Diseases, National Institute for Communicable Diseases: A Division of National Health Laboratory Service, Sandringham, South Africa

Abstract

Introduction: The seasonal variability in hospitalization for tuberculosis may in part relate to super-imposed bacterial or predisposing respiratory viral infections. We aimed to study the temporal association between hospitalization for culture-confirmed pulmonary tuberculosis (PTB), invasive pneumococcal disease (IPD) and influenza virus epidemics in South African children.

Methods: We undertook a retrospective analysis which examined seasonal trends, from 2005 to 2008, for hospitalization for culture-confirmed PTB and IPD among children in relation to the influenza epidemics in Soweto, South Africa. Original time-series of the influenza virus epidemics and hospitalization rates for PTB and IPD were decomposed into three components: a trend cycle component, a seasonal component and an irregular component using the X-11 seasonal adjustment method. To compare the seasonality amongst the three series, the trend and irregular components were removed and only seasonal components examined.

Results: Across the study period, the influenza virus epidemics peaked during May to July (winter) months, which was closely followed by an increase in the incidence of hospitalization for IPD (August to October) and PTB (August to November).

Discussion: Within- and between-year temporal changes associated with childhood TB hospitalization may in part be driven by factors which influence temporal changes in pneumococcal disease, including potential variability in the severity of influenza virus epidemics in temperate climates. The dynamics of the interplay between the host and these infectious agents appears to be complex and multifactorial.

Citation: Dangor Z, Izu A, Moore DP, Nunes MC, Solomon F, et al. (2014) Temporal Association in Hospitalizations for Tuberculosis, Invasive Pneumococcal Disease and Influenza Virus Illness in South African Children. PLoS ONE 9(3): e91464. doi:10.1371/journal.pone.0091464

Editor: Cécile Viboud, National Institutes of Health, United States of America

Received November 7, 2013; Accepted February 11, 2014; Published March 11, 2014

Copyright: © 2014 Dangor et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors acknowledge financial support from the Medical Research Council: Respiratory and Meningeal Pathogens Unit and the Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases South African Research Chair Initiative. ZD is funded in part by the Carnegie Corporation of New York. SAM is funded in part by National Research Foundation/Department of Science and Technology: South African Research Chair Initiative Program. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.*

* E-mail: shabirm@nicd.ac.za

Introduction

We have previously reported seasonal variability in hospitalization for culture-confirmed tuberculosis (TB) in South African children [1]. This temporal variability in incidence of culture-confirmed TB between and within study years, may in part relate to hospitalization for TB being precipitated by concurrent infections, including due to pneumococcus or due to increased immunological susceptibility following influenza virus [2–5]. Consequently, the within- and between-year temporal changes associated with childhood TB hospitalization may in part be driven by factors which influence temporal changes in pneumococcal disease, including potential variability in the severity of influenza virus epidemics in temperate climates.

A number of experimental models have studied the interaction between TB and invasive pneumococcal disease (IPD) [6–8], as well as influenza and IPD [9–11]. The interactions between these pathogens may relate to changes in the host epithelial barriers and failure of the innate or adaptive immune systems through dysregulation of chemical modulators, resulting in a window period of vulnerability in the exposed host [12]. This interaction has also been examined epidemiologically, [2,3,13,14] including in the context of mortality observed during the influenza pandemics.
To date, no population-based study has interrogated the possible interaction between these three pathogens in children.

The aim of this study was to evaluate whether there is seasonal pattern between influenza epidemics and hospitalization for IPD and TB in South African children.

**Methods**

**Study setting**

We undertook a retrospective study, to compare the incidence of culture-confirmed pulmonary TB (PTB) and culture-confirmed IPD among children hospitalized from 2005 to 2008 in Soweto, Gauteng, South Africa in relation to background surveillance data on influenza epidemics in the study-setting. The population of Soweto in 2005 included approximately 1.12 million mainly black urban South Africans, including 120,000 children under five years of age [18]. An estimated 90% of individuals in Soweto requiring hospitalization are admitted to Chris Hani-Baragwanath Academic Hospital (CHBAH), the only public-hospital in the study setting. All public-based health care, including hospitalization of children, is provided free-of-charge by the State.

**PTB in study population**

The standard-of-care for investigating for TB in children hospitalized for pneumonia or with other clinical signs and symptoms of TB, at CHBAH included a low threshold for performing 2–3 gastric washings or induced-sputum sample collections for *Mycobacterium tuberculosis* (MTB) culture. Identification of MTB was undertaken by the National Health Laboratory Service (NHLS), which used the WHO recommended method of specimen processing using N-acetyl-L-cysteine-NaOH, for culture of MTB from sputum. These samples were incubated in the MGIT (Mycobacterium Growth Indicator Tube) 960™ TB System (Becton Dickinson, Sparks, Maryland). Details of the study procedures have been described [1].

**Invasive pneumococcal disease in the study population**

An IPD episode was defined as identification of pneumococcus from a normally sterile site (e.g., blood, cerebrospinal fluid [CSF], pleural fluid or joint fluid). The standard culture methods at the hospital included blood cultured for pneumococcal growth with the BacT/Alert microbial detection system (Organon Teknika, Durham, NC). Blood culture specimens which flagged positive but were bacterial culture negative, and that were macroscopically and three were to 5 years of age, with an overall median age of 1.70 years. The highest burden of PTB was in children <2 years of age, with an overall median age of 1.72 years (Range: 0.25–14.25 years), Table 1. During the same period, 636 children were admitted to IPD, of whom 567 (57.7%) were HIV-infected. The majority (53.6%) of IPD cases also occurred in children <2 years of age, at a median age of 1.70 years (Range: 0.25–14.68 years), Table 1. Twelve children, nine of whom were HIV-infected, were hospitalized for IPD and PTB within two weeks of either diagnosis. Six of these children were in the 3 month to <2 year age group, three were 2 to <5 years of age and three were 5 to <15 years of age.

Six-hundred and sixty-seven children <15 years old were hospitalized with culture-confirmed PTB from 2005 to 2008, among whom the prevalence of HIV remained consistent (53–59%), although the frequency of HIV testing increased over time. Most children were underweight for age with a median weight-for-age Z-score of −2.80 (Range: −8.99–1.87). The highest burden of PTB was in children <2 years of age, with an overall median age of 1.72 years (Range: 0.25–14.25 years), Table 1. During the same period, 636 children were admitted for IPD, of whom 367 (79%) were Culture-confirmed among the three diseases.

The study was approved by the Medical Advisory Committee at CHBAH and by the by the Human Research Ethics Committee (HREC), University of Witwatersrand. Parental consent was waivered by the HREC for this retrospective study.

**Results**

The influenza epidemic in South Africa generally prevails in the winter (May to September). Influenza surveillance data is collated by the Viral Watch Program (VWP), a division of the National Institute for Communicable Diseases [19]. The VWP monitors influenza patterns in more than 170 sites country-wide, predominantly (89–92%) in primary health care settings, and the methods used to test for influenza virus have been described [19]. Between 2005 and 2008, 5424 samples were received (Ages: 1 month to 84 years), 29% in children under 15 years of age [19]. The dominant influenza strains in the four years were: 2005, A(H1N1) 317/564 (56%) detections; 2006, A(H3N2) 369/491 (79%) detections; 2007, A(H3N2) 240/556 (43%) (the remainder split more or less evenly between A(H1N1) and B); 2008, A(H1N1) 310/390 (80%) detections [20].
Seasonality

The seasonality of influenza virus illness and hospitalization for IPD and PTB are depicted in Figure 1. Although the X-11 method allows for evolving seasonal components, the seasonality factors were similar from year to year. The pattern of influenza virus infections peaked mainly in May to September of each year. Influenza peaks were followed by increases in the number of children hospitalized with IPD and subsequently PTB. There was a time lag from the influenza virus peaks to the peak in hospitalization for IPD (3 months) and PTB (2–3 months). Influenza activity peaked in June, IPD in September, whilst PTB peaked during August (in 2005) and September in 2006–2008. Notably, a lesser peak in IPD occurred in April which subsequently waned over the influenza period before peaking again three months after the peak of the influenza season. The peaks in hospitalization of IPD and PTB tended to occur at similar time points.

The peaks in IPD and PTB relative to the influenza peak occurred in October (4 months later) and November (5 months later), respectively, in HIV-infected children, Figure 2. In contrast, the peak in hospitalization for IPD in HIV-uninfected children occurred prior to the peak in influenza, Figure 3.

Furthermore, we analysed the lagged month-by-month correlations between the raw data on influenza, IPD and PTB rates. We found the highest correlations between influenza and IPD or PTB, when the rate of influenza in June coincided with the rate of IPD in August and with PTB in September/October. The correlation between IPD and PTB was highest when PTB was lagged by 1 month.

Discussion

We observed a seasonal pattern in a time-sequenced manner of influenza virus activity, followed by a peak in IPD and PTB. This sequential risk of pneumococcal disease following influenza illness was first hypothesized in reference to the 1918/19 pandemic, in which deaths during the influenza pandemic occurred 7–10 days following the influenza illness and was attributed to secondary bacterial infection [23]. The vulnerability of the host to pneumococcal disease following influenza virus during this “window period” is likely to be multifactorial, and include host local and systemic immune factors [12]. In our study, however, we report a peak in IPD three months following the peak in influenza virus activity, making it less likely that the susceptibility to IPD was...
mainly precipitated by influenza virus infection. In contrast, the peak observed in hospitalization for culture-confirmed PTB, which followed 2–3 months following the peak in influenza virus circulation, could be explained in children less than 5 years of age being due to primary infection by *Mycobacterium tuberculosis* (MTB), following which it takes 6 weeks to three months for primary PTB to manifest [24]. This was corroborated partly in animal-model studies in which mice inoculated with influenza virus and then with MTB three weeks following influenza exposure, were at increased risk of developing TB [5]. We speculate that children living in close proximity to adults with infectious PTB may be at enhanced risk of primary infection with MTB when the adult source case is co-infected with a respiratory virus (e.g., influenza) and so more likely to be aerosolizing tubercle bacilli.

In older individuals, PTB may be due to reactivation of underlying latent TB infection because of immunosuppression induced by influenza virus infection, [25] with the influenza-virus induced immune suppression increasing the susceptibility of individuals with underlying TB to developing acute pneumonia [2].

The prolonged time-lag in peak of influenza virus activity and subsequent IPD in our study is not consistent with observations of others (<1 month), or that indicated by animal-model-studies [2,15,23,26,27]. It is, however, possible that influenza virus epidemics increased susceptibility to nasopharyngeal acquisition of new pneumococcal serotypes, for which the risk of disease is greatest up to two months post-acquisition [28]. Alternately, other factors may contribute to this temporal association between the peak in influenza virus activity and IPD in settings such as South Africa. In particular, the possible increased susceptibility to developing TB following influenza epidemics, may lend itself to underlying immune suppression which subsequently increases the susceptibility to developing IPD in the South African context, especially with its high burden of HIV and TB co-infection. Previous studies conducted in high HIV prevalent settings have reported an increased burden of IPD and PTB disease in HIV-infected children [1,29]. Furthermore, almost two thirds of

---

**Figure 1. Seasonality of FLU, IPD and PTB in All children.** Seasonal factors of influenza (FLU) virus overall circulation and association to hospitalization for invasive pneumococcal disease (IPD) and culture-confirmed pulmonary tuberculosis (PTB) in children. The axis for seasonal factors for influenza is on the left and for IPD and PTB is on the right.

doi:10.1371/journal.pone.0091464.g001

**Figure 2. Seasonality of FLU, IPD and PTB in HIV-infected children.** Seasonal factors of influenza (FLU) virus overall circulation and association to hospitalization for invasive pneumococcal disease (IPD) and culture-confirmed pulmonary tuberculosis (PTB) in HIV-infected children. The axis for seasonal factors for influenza is on the left and for IPD and PTB is on the right.

doi:10.1371/journal.pone.0091464.g002
hospitaled PTB and IPD cases with a known HIV status were HIV-infected in our study period.

To our knowledge, this is the first study to describe the seasonality among all three of these pathogens, the plausibility of which is corroborated by experimental models, vaccine probe studies and epidemiological observations during influenza pandemics. The possible mechanisms supporting an increased host susceptibility to IPD following influenza virus infection are evident from experimental animal-model studies, which have been reviewed in detail [9–11]. The dynamics of the interplay between the host and the infectious agent is complex and multifactorial and include disruptions in the physical barriers and an imbalance in the pro-inflammatory (interleukin [IL]-1, IL6, tumor necrosis factor [TNF] and gamma-interferon [INFγ]) and anti-inflammatory (IL10, IL17) cytokine/chemokine pathways which disrupt the recruitment of cellular elements of the innate immune response, including macrophages and neutrophils. Although this process may be beneficial to the host in establishing long-term immunity at the time of the pneumococcal infection, it may increase susceptibility to TB.

Specifically, idiosyncrasies in the regulation of Toll-like receptors (TLRs) and INFγ are common to influenza illness, pneumococcal disease and TB. TLRs are pattern recognition receptors expressed by macrophages, dendritic cells and lymphocytes. Certain TLRs are down-regulated by influenza virus, thus resulting in a failure of macrophages to activate NF-kB and chemokines which in turn result in less neutrophil recruitment [9,10]. TLRs, particularly TLR-2, are also important in the host response to TB [6]. Studies have demonstrated that an increased predisposition to TB can occur by altering the encoding proteins that signal TLR activity [7]. Neutrophils have also been shown to protect mice against TB [8], so it is plausible that perturbations in TLR functioning with its effect on neutrophil recruitment, may play a role in predisposition to MTB disease. On the other hand, INFγ produced by lymphocytes is an important component of the host defense to viruses as well as intracellular pathogens such as MTB. Bronchiolar lavage on mice with influenza and subsequently infected with pneumococcus had increased levels of INFγ as opposed to mice with human metapneumovirus (hMPV) and subsequently infected with pneumococcus [26]. INFγ produced in response to viral infections results in inadequate bacterial clearance from the lung by macrophages in-vivo and in-vitro [30]. Furthermore, high concentrations of INFγ disrupted macrophage clearance in the alveolus [10].

Our clinical understanding of the association between influenza epidemics and susceptibility to bacterial infections at a population level arise from ecological studies. It is reported that most deaths during the influenza pandemic of 1918/19 were related to secondary bacterial infection, including pneumococcus [23,31] with a median time of death of 7–10 days [23]. In 14 studies addressing fatal bacterial pneumonia in the 1918/1919 pandemic, pneumococci was identified in 81% of 249 positive cultures [15]. Furthermore, pneumococcus was identified in 24% of postmortem lung biopsies [31]. During the 2009 H1N1 influenza pandemic, 36 fatalities were reported in children in the United States, 10 (43%) of whom had bacterial co-infection, three with pneumococcus [16]. In countries where pneumococcal conjugate vaccine (PCV) was not routinely given to children, pneumococcal bacteraemia was highest in children <4 years of age [32]. An increase in the number of TB-related deaths was also noted during the 1918/19 pandemic [4,33]. In South Africa, where the burden of TB continues to remain high, 10% of fatalities associated with the 2009 H1N1 influenza virus pandemic had concurrent TB [17].

Furthermore, PCV probe studies also corroborated the suggestion of an interaction between pneumococcal disease and both influenza illness [14], and TB [2]. Notably, PCV-vaccinated children were less likely to be hospitalized for pneumonia attributable to respiratory viruses, including influenza virus (5% efficacy) [14,34], and had a reduced likelihood of being hospitalized for culture-confirmed PTB (43% efficacy) compared to placebo recipients [2]. These clinical observations were attributed to hospitalizations for influenza-associated pneumonia and culture-confirmed PTB possibly having been precipitated by co-infection with pneumococcus [2]. The interaction between IPD and TB is further supported by case reports in HIV-infected adults [35,36].

A limitation of our study is that it focused solely on hospitalized cases. Our study could not measure whether there may have been any changes in clinician behavior in terms of referral, admission and investigating children with TB over time. The influenza data is based on community surveillance; however, although not specific to the Soweto population, the seasonality of influenza is unlikely to be different in this region as most of the samples were collected from the broader Johannesburg region [19]. Although

Figure 3. Seasonality of FLU, IPD and PTB in HIV-uninfected children. Seasonal factors of influenza (FLU) virus overall circulation and association to hospitalization for invasive pneumococcal disease (IPD) and culture-confirmed pulmonary tuberculosis (PTB) in HIV-uninfected children. The axis for seasonal factors for influenza is on the left and for IPD and PTB is on the right.
doi:10.1371/journal.pone.0091464.g003

Seasonality of Flu, IPD and PTB

| Time | Seasonal Factors |
|------|-----------------|
| Jan '05 | FLU | IPD | PTB |
| Jan '06 | FLU | IPD | PTB |
| Jan '07 | FLU | IPD | PTB |
| Jan '08 | FLU | IPD | PTB |
| Jan '09 | FLU | IPD | PTB |

- **HIV** -
  - FLU
  - IPD
  - PTB

- **Seasonal Factors**
  - FLU
  - IPD
  - PTB

- **Time**
  - Jan '05
  - Jan '06
  - Jan '07
  - Jan '08
  - Jan '09
we could not establish the occurrence of all three disease processes in the same individual, at least twelve children had IPD and culture-confirmed PTB within two weeks of either diagnosis during their hospitalization. We observed a peak in IPD prior to the influenza season which may be explained by other respiratory viruses precipitating an increase in IPD hospitalization, particularly RSV from early March in this setting [13,37,38].

In conclusion, our study indicates a temporal association between influenza illness, pneumococcal disease and TB. Coincidentally, these peaks in hospitalization followed the influenza seasonal peaks, more so in HIV-infected children. The peaks in hospitalization for IPD and PTB were largely synchronous over the study period. It is conceivable that interventions against any one of these, e.g. vaccination against influenza virus or pneumococcal disease, may alter the epidemiology of hospitalization to another in our setting and settings such as ours (low-income, high-density with a high background HIV and TB prevalence). This has already been partly corroborated by our observations on PCV and its effect on hospitalization rates for influenza-associated pneumonia and culture-confirmed PTB [2,14].

Supporting Information

Figure S1 Decomposition of the time series for influenza (FLU) virus data into the original (raw data), seasonal, trend and irregular components. (TIFF)

References

1. Danger Z, Lu A, Hillier K, Solomon F, Byrdy N, et al. (2013) Impact of the antiretroviral treatment program on the burden of hospitalization for culture-confirmed tuberculosis in South African children: a time-series analysis. Pediatr Infect Dis J 32: 922–927.
2. Moore DP, Klugman KP, Madhi SA (2010) Role of Streptococcus pneumoniae in hospitalization for acute community-acquired pneumonia associated with culture-confirmed Mycobacterium tuberculosis in children: a pneumococcal conjugate vaccine probe study. The Pediatric infectious disease journal 29: 1099–1104.
3. Noh JY, Lee J, Choi WS, Song JY, Seo YB, et al. (2013) Concurrent tuberculosis and influenza, South Korea. Emerg Infect Dis 19: 165–167.
4. Bradshaw BS, Smith DW, Blanchard S (2008) A cohort study of tuberculosis and influenza mortality in the twentieth century. Biodemography Soc Biol 54: 74–94.
5. Volker M, Pierce C, Honfi FL, Dubos RJ (1947) The enhancing effect of concurrent infection with pneumotrophic viruses on pulmonary tuberculosis in mice. J Exp Med 86: 203–214.
6. Jo EK (2008) Mycobacterial interaction with innate receptors: TLRs, C-type lectins, and NLRs. Current opinion in infectious diseases 21: 279–286.
7. Khor CC, Chapman SJ, Vannberg FO, Dunne A, Murphy C, et al. (2007) A Mal functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. Nat Genet 39: 523–528.
8. Pedrosa J, Saunders BM, Appelberg R, Orme IM, Silva MT, et al. (2008) Neutrophils play a protective nonphagocytic role in systemic Mycobacterium tuberculosis infection of mice. Infection and immunity 66: 577–583.
9. Short KR, Habets MN, Hermans PW, Dhavatopoulou DA (2012) Interactions between Streptococcus pneumoniae and influenza virus: a mutually beneficial relationship? Future Microbiol 7: 609–624.
10. Moore DP, Dagan R, Madhi SA (2012) Respiratory viral and pneumococcal coinfection of the respiratory tract: implications of pneumococcal vaccination. Expert Rev Respir Med 6: 451–463.
11. McCullers JA (2006) Insights into the interaction between influenza virus and Streptococcus pneumoniae. Clin Microbiol Rev 19: 571–582.
12. Haynes L, Szaba FM, Eaton SM, Lammer PA, et al. (2012) Immunity to the conserved influenza nucleoprotein reduces susceptibility to secondary bacterial infections. J Immunol 189: 4921–4929.
13. Stemhalle LG, Hjuler T, Andersen A, Kaltoft M, Ravn H, et al. (2008) Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study. Clinical infectious diseases - an official publication of the Infectious Diseases Society of America 46: 1165–1171.
14. Madhi SA, Klugman KP (2004) A role for Streptococcus pneumoniae in virus-associated pneumonia. Nat Med 10: 811–813.
15. Klugman KP, Chien YW, Madhi SA (2009) Pneumococcal pneumonia and influenza: a deadly combination. Vaccine 27 Suppl 3: C99–C114.
16. CDC (2009) Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) - United States, May-August 2009. MMWR Morb Mortal Wkly Rep 58: 1071–1074.
17. Archer B, Cohen C, Naidoo D, Thomas J, Makunga C, et al. (2009) Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: epidemiology and factors associated with fatal cases. Euro Surveill 14.
18. Statistics South Africa S Gauteng Sub-district Population Mid-year Estimates 2000–2009. In: Directorate Information Management DOH, editor.
19. McAnerny JM, Cohen C, Moyes J, Besselaar TG, Boys A, et al. (2012) Twenty-five years of outpatient influenza surveillance in South Africa, 1980–2008. J Infect Dis 206 Suppl 1: S135–138.
20. National Institute of Communicable Diseases Seasonal Influenza Surveillance. 2011. ASSA (March 2011) ASSA2008 Aids and Demographic model. Actuarial Society of South Africa.
21. Ladifay D, Queneville B (2001) Seasonal Adjustment With the X-11 Method: Springer. 225 p.
22. Brandtje J, Shanks GD (2000) Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis 14: 1193–1199.
23. Marais RJ, Gie RP, Schaff HS, Heseling AC, Oshhara CC, et al. (2004) The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 8: 392–402.
24. Singhania S, Bell C, Woodhead M (2010) Pneumococcal vaccination rate: report of two cases. Int J Tuberc Lung Dis 14: 1497–1498.
25. Ludekiew HP, Aerts L, Hamelin M, Boivin G (2011) Long-term impairment of Streptococcus pneumoniae lung clearance is observed after initial infection with influenza A virus but not human metapneumovirus in mice. J Gen Virol 92: 1662–1665.
26. Davis BM, Aiello AE, David S, Rohani P, Shrestha S, et al. (2012) Influenza and community-acquired pneumonia interactions: the impact of order and time of infection on population patterns. Am J Epidemiol 175: 363–367.
27. Gray RM, Dillon HC, Jr. (1989) Natural history of pneumococcal infections. Pediatr Infect Dis J 8: 823–25.
28. Nunes MC, von Gottberg A, de Gouveia L, Cohen C, Moore DP, et al. (2013) The impact of antiretroviral treatment on the burden of invasive pneumococcal disease in South African children: a time series analysis. AIDS 25: 435–462.
29. Sun K, Metzger DW (2008) Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med 14: 558–562.
30. Moore DP, Dagan R, Madhi SA (2010) Role of Streptococcus pneumoniae in the influenza season which may be explained by other respiratory viruses precipitating an increase in IPD hospitalization, particularly RSV from early March in this setting [13,37,38].

Figure S2 Decomposition of the time series for invasive pneumococcal disease (IPD) data into the original (raw data), seasonal, trend and irregular components. (TIFF)

Figure S3 Decomposition of the time series for culture-confirmed pulmonary tuberculosis (PTB) data into the original (raw data), seasonal, trend and irregular components. (TIFF)

Acknowledgments

We are thankful to all patients whose data were used in this study. We thank the Medical Advisory Committee and CHIHAH for allowing us to conduct our study. We would like to thank the Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA) for their efforts in collating IPD cases, the National Health Laboratory Service Central Data Warehouse for providing laboratory data and the Viral Watch Program of the National Institute for Communicable Diseases for the influenza data.

Author Contributions

Conceived and designed the experiments: ZD AI SAM. Performed the experiments: ZD AI SAM. Analyzed the data: ZD AI SAM. Contributed reagents/materials/analysis tools: DPM MCN FS NB AvG JMM. Wrote the paper: ZD AI SAM.
33. Nooyer A (2011) The 1918 influenza pandemic hastened the decline of tuberculosis in the United States: an age, period, cohort analysis. Vaccine 29 Suppl 2: B38–41.

34. Madhi SA, Ludewick H, Kivunda L, Niekerk N, Cutland C, et al. (2006) Pneumococcal coinfection with human metapneumovirus. J Infect Dis 193: 1236–1243.

35. Schleicher GK, Feldman C (2003) Dual infection with Streptococcus pneumoniae and Mycobacterium tuberculosis in HIV-seropositive patients with community acquired pneumonia. Int J Tuberc Lung Dis 7: 1207–1208.

36. Louw A, Tikly M (2007) Purulent pericarditis due to co-infection with Streptococcus pneumoniae and Mycobacterium tuberculosis in a patient with features of advanced HIV infection. BMC Infect Dis 7: 12.

37. Madhi SA, Ludewick H, Kivunda L, van Niekerk N, Cutland C, et al. (2007) Seasonality, incidence, and repeat human metapneumovirus lower respiratory tract infections in an area with a high prevalence of human immunodeficiency virus type-1 infection. The Pediatric infectious disease journal 26: 693–699.

38. Weinberger DM, Grant LR, Steiner CA, Weatherholtz R, Santosham M, et al. (2014) Seasonal drivers of pneumococcal disease incidence: impact of bacterial carriage and viral activity. Clin Infect Dis 58: 188–194.