Decreasing incidence and determinants of Bacterial Pneumonia in people with HIV: The Swiss HIV Cohort Study

Suraj Balakrishna,[1,2] Aline Wolfensberger,[1] Viacheslav Kachalov,[1,2] Jan A. Roth,[3,4,5] Katharina Kusejko,[1,2] Alexandra U. Scherrer,[1,2] Hansjakob Furrer,[6] Christoph Hauser,[6] Alexandra Calmy,[7] Matthias Cavassini,[8] Patrick Schmid,[9] Enos Bernasconi,[10] Manuel Battegay,[3] Huldrych F. Günthard,[1,2] Roger D. Kouyos,[1,2] and the Swiss HIV Cohort Study (SHCS)

[1] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland.

[2] Institute of Medical Virology, University of Zurich, Zurich, Switzerland.

[3] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland.

[4] Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, University of Basel, Basel, Switzerland.

[5] Division of Research and Analytical Services, Department of Informatics, University Hospital Basel, Basel, Switzerland

[6] Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland.

[7] Division of Infectious Diseases, University Hospital Geneva, University of Geneva, Geneva, Switzerland.

[8] Division of Infectious Diseases, University Hospital Lausanne, University of Lausanne, Lausanne, Switzerland.

[9] Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland.

[10] Division of Infectious Diseases, Regional Hospital Lugano, Lugano, Switzerland.

Corresponding author: Mr. Suraj Balakrishna, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. Tel: +41432530186, E-mail suraj.balakrishna@usz.ch

Alternate corresponding author: Prof. Dr. Roger Kouyos, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. Tel: +41432553610, E-mail roger.kouyos@usz.ch

Short summary: Bacterial pneumonia in people with HIV is associated with obstructive airway disease, proton-pump inhibitors, CD4-cell-count, viral-load, smoking, and intravenous drug use. Improvements in the HIV cascade-of-care and decreased smoking may have mediated a reduction in bacterial pneumonia incidence for 2008-2018.

ABSTRACT

Background: Bacterial pneumonia is one of the leading reasons for hospitalization among people with HIV (PWH), yet there is limited evidence regarding its drivers in the era of potent antiretroviral therapy.

Methods: We assessed risk-factors for bacterial pneumonia in PWH enrolled in the Swiss HIV Cohort Study using univariable and multivariable marginal models. We further assessed the relationship between risk-factors and changes in bacterial pneumonia incidence using mediation analysis.

Results: We included 12927 PWH with follow-ups between 2008 and 2018. These patients had 985 bacterial pneumonia events during a follow-up of 100779 person-years(py). bacterial pneumonia incidence significantly decreased from 13.2 cases/1000 py in 2008 to 6.8 cases/1000 py in 2018. Older age, lower education-level, intravenous drug use, smoking, lower CD4-cell-count, higher HIV-viral load, and prior pneumonia events were significantly associated with higher bacterial pneumonia incidence. Notably, even CD4-cell-counts 350-499 were significantly associated with an increased risk compared to CD4≥500 (adjusted HR,1.39; 95% CI,1.01-1.89). Finally, we found that the decreasing incidence over the last decade can be explained by decreasing proportion of patients with CD4<500, viral-RNA>200, and smoking>one cigarette/day.

Conclusion: Improvements in cascade of care of HIV and decrease in smoking may have mediated a substantial decrease in bacterial pneumonia incidence.

Keywords: Bacterial pneumonia; HIV; incidence; risk factor; multiple mediation analysis

INTRODUCTION

Bacterial pneumonia is a threat to individual and public health, especially among the children, elderly, and individuals with immunosuppression and comorbidities [1,2]. A previous review reported an annual incidence of community-acquired bacterial pneumonia caused by *S. pneumoniae*, one of the most common pathogens causing community-acquired pneumonia, among adults in Europe to be 0.68 – 70.0 cases per 1000 individuals, differing widely across Europe [3]. Identifying the factors associated bacterial pneumonia might assist the implementation of appropriate preventive, diagnostic and therapeutic measures. Many studies over the last decades have shown that smokers, high alcohol consumers, intravenous drug users, individuals on proton-pump inhibitors, and individuals with comorbidities such as HIV, asthma and chronic obstructive pulmonary disorder (COPD) are at a higher risk of acquisition of bacterial pneumonia [4–8]. However, most studies consider only the first pneumonia cases. Also, these studies do not explicitly study the risk factors associated with bacterial pneumonia event(s) among the immunocompromised risk group such as people with HIV (PWH) in the era of potent antiretroviral therapy (ART) at large scale. In addition, it has been shown that severe non-AIDS bacterial infections, among which pneumonia, urinary tract infections and bloodstream infections were the most frequent, are the leading cause of hospital admissions among individuals with HIV in France [9].

This study aimed to estimate the incidence rate of bacterial pneumonia using time-to-event survival analysis for the years 2008 to 2018 in the Swiss HIV Cohort Study (SHCS) and to assess the risk factors associated with incidence of bacterial pneumonia using univariable and multivariable marginal models.

METHODS

Study design and study population

The Swiss HIV Cohort Study (SHCS), established in 1988, is an ongoing, nationwide, multicenter, clinic-based prospective cohort study for people with HIV (PWH) in Switzerland with continuous enrolment and semi-annual follow-up. Socio-demographic, clinical, and laboratory data are recorded in detail. The SHCS is covers about 60% of the PWH in Switzerland [10]. Until November 2019, 20684 patients have been enrolled, 5140 have died during the follow-up, and 5830 were lost to follow-up. All participants have provided written informed consent and the SHCS was approved by the local ethics committees of the participating centers [11].

As the documentation of bacterial pneumonia as a non-AIDS defining event among PWH enrolled in the SHCS started in August 2008, we restricted our study population to PWH with a follow-up between August 1, 2008 and December 31, 2018 to estimate the incidence rate of pneumonia in the SHCS. We further restricted our study population to those enrolled between January 1, 2015 and December 31, 2018 to assess risk factors associated with pneumonia due to lack of data on medication other than antiretroviral therapy prior to 2015 (Figure S1).

Outcome measures

The primary outcome of our analysis was either presumptive or definitive incident/first and recurrent/subsequent event(s) of bacterial pneumonia occurring during the observation period as defined in the SHCS. A presumptive event was defined as ‘signs and symptoms suggestive of bacterial pneumonia plus documented abnormality in chest x-ray or CT scan of lung compatible with bacterial pneumonia’ and a definitive event was defined as presumptive event plus ‘identification of a bacterial pathogen by blood culture, bronchoalveolar lavage or detection of *Legionella* or pneumococcal antigen in urine’.

Statistical analysis

We estimated the yearly incidence rate of pneumonia using time-to-event-survival analysis for the years between August 2008 and December 2018. We fitted univariable and multivariable semi-parametric marginal models, an extension of the Cox proportional-hazard model, to assess the risk factors associated with bacterial pneumonia event(s) [12]. Based on previous studies and clinical opinion, we evaluated the following variables in the univariable and multivariable analysis: variables obtained/defined at the time of SHCS enrolment – ethnicity (white or non-white), education level (with or without higher than higher education), likely source of HIV infection (men-who-have-sex-with-men (MSM), male heterosexuals, female heterosexuals, male intravenous drug users (IDUs), female IDUs, or unknown), and pack-years of smoking (<5, 5-10, or ≥10 pack-years) and time-updated variables – age, smoking status (<1 or ≥1 cigarette/day), CD4 cell counts (≥500, 350-499, 200-349, 50-199, or <50 cells/μL), viral RNA (<200 or ≥200 copies/mL), any prior pneumonia event, use of proton pump inhibitors (PPIs), use of Angiotensin-converting enzyme (ACE) inhibitors, obstructive airway diseases (inferred based on the medication for obstructive airway diseases, Table S1), kidney disease (defined as either clinically diagnosed kidney failures or with estimated glomerular filtration rate (eGFR) of <60 ml/minute for three or more months), non-conjugated pneumococcal vaccination, and conjugated pneumococcal vaccination (see supplementary section 1). We used complete-case analyses in the fitted models. We further corrected for multiple testing using Benjamini-Hochberg procedure.

We tested for possible high correlations between the risk factors using Cramer's V. We tested the proportional hazards assumption of the models based on the scaled Schoenfeld residuals, examined for influential observations using respective dfbeta residuals, and assessed for non-linearity in continuous variables using martingale residuals. Based on these model diagnostics, the chosen model was adequate to assess the risk factors associated with pneumonia (Figure S2-S5).

We further examined the possible association between calendar year and incidence of bacterial pneumonia. We assessed if this association is mediated through changing trends in CD4 cell counts, viral load, and smoking behaviour in the study population with calendar year using multiple mediation analysis (Figure 1). Figure 1.a indicates the total effect between calendar year and bacterial pneumonia. Figure 1.b indicates the direct effect of calendar year and the indirect effect of calendar year mediated through the assessed mediators. Both these models were adjusted for the following covariates: time-updated age, ethnicity, education level, and prior pneumonia event.

We performed all analyses in R, version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) [13]. We used the *survival* package in R to perform time-to-event survival analysis, fit marginal models, and to perform model diagnostics, the *survminer* package for visualizing the model diagnostics, the *mice* package to perform multiple imputations, and the *mma* package to perform multiple mediation analysis.

Sensitivity analysis

To test the robustness of the model, we fitted models in the following ways. Firstly, we fitted models for the entire period between August 2008 to December 2018 but without adjusting for medication data. Secondly, we restricted the study population to only incident/first case of pneumonia and fitted cox proportional-hazards models. Thirdly, we restricted our study population to virally suppressed patients and fitted marginal models by assessing only the follow-up time of patients with viral RNA less than 200 copies/mL during the observation time. Fourthly, we repeated the third sensitivity analysis for the entire period between August 2008 to December 2018 but without adjusting for medication data. Fifthly, instead of adjusting for the any prior pneumonia event as a time-updated variable, we adjusted for any pneumonia event that occurred prior to 2015. Sixthly, we adjusted for a stratified effect of time-updated treating physician. Seventhly, we defined our outcome variable as definitive bacterial pneumonia events (which were in addition confirmed by identification of bacterial pathogen) and fitted marginal model for the entire period between August 2008 to December 2018.

Eighthly, we used multiple imputation technique to impute missing values in the assessed risk factors and fitted marginal models. Finally, we tested in an exploratory analysis the effect of statin use and flu vaccination in the past year on bacterial pneumonia.

Role of the funding source: The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

RESULTS

Of the 20684 participants enrolled in the SHCS, 12927 had at least one follow-up between August 1, 2008 and December 31, 2018 (Figure S1). These patients had 985 pneumonia events during the follow-up time of 100779 person-years (py) corresponding to a crude incidence rate (IR) of 9.8 cases per 1000 py (95% confidence interval (CI): 9.2 to 10.4 cases per 1000 py). Of these 985 events, 702 were presumptive (symptoms plus radiological confirmation), while the remaining 273 events were definitive events (confirmed by identification of bacterial pathogen). 10993 out of 12927 (85.0%) patients had at least one follow-up between 2015 and 2018. Further, 9213 out of 10993 (83.8%) patients had no missing values for any of the assessed risk factors and were included in univariable and multivariable marginal models. Of the 9213 patients included in the analysis, 233 (2.5%) patients had at least one bacterial pneumonia event between 2015 and 2018. Further, 22 (9.4%) of 233 patients had more than one bacterial pneumonia events. Overall, there were 272 bacterial pneumonia events among these patients, of which 202 were presumptive, while the remaining 70 were definitive events. Table 1 lists the characteristics and exposures to potential risk factors in patients with and without pneumonia.

In univariable analysis, age, male IDUs and female IDUs compared to MSM, CD4 cell counts <500 cells/µL, HIV viral RNA ≥200 copies/mL, ≥10 pack-years of smoking at enrolment compared to <5

pack-years of smoking at enrolment, smoking ≥1 cigarette per day, use of PPIs, use of ACE inhibitors, obstructive airway diseases (inferred based on the medication for obstructive airway diseases), and any previous pneumonia event were significantly associated with higher incidence of a pneumonia event. By contrast, white ethnicity and education equal to or above bachelor level were significantly associated with lower incidence of a pneumonia event. Most effects identified in the univariable analysis were robust towards adjustment in the multivariable analysis (Figure 2). Corresponding P-values of univariable and multivariable analysis are shown in table S2. Ethnicity, ≥10 pack-years of smoking, male IDUs, and ACE inhibitors were no longer significantly associated with incidence of pneumonia in the multivariable analysis.

Overall, our analysis thus identified several risk factors for pneumonia. Most notably, association between incidence of pneumonia became stronger (higher HR) with decrease in CD4 cell count and even the CD4 cell counts of 350 to 499 cells/μL was significantly associated with higher incidence of pneumonia compared to CD4 cell counts of more than 500 cells/μL (adjusted HR, 1.39; 95% CI, 1.01 to 1.89). The strongest increased risk was observed for CD4 cell counts of less than 50 cells/μL (adjusted HR, 7.68; 95% CI, 2.46 to 23.98). Also, use of PPIs (adjusted HR, 1.65; 95% CI, 1.20 to 2.27) and prior pneumonia event (adjusted HR, 4.82; 95% CI, 3.51 to 6.61) were significantly associated with higher incidence of pneumonia.

When considering the entire follow up time from August 2008 to December 2018, the incidence rate of pneumonia significantly decreased from 13.2 cases/1000 py (95% CI: 9.8 to 17.8 cases/1000 py) in 2008 to 6.8 cases/1000 py (95% CI: 5.4 to 8.7 cases/1000 py) in 2018 (Figure 3). Furthermore, we found that the risk factors for which data were available for this period had a similar association with bacterial pneumonia as found in the main model (sensitivity analysis). In addition, we found that calendar year (total effect: log(HR), -0.087; 95% CI, -0.143 to -0.031) was significantly associated with decrease in incidence of bacterial pneumonia. However, calendar year (direct effect: log(HR), -0.032; 95% CI, -0.092 to 0.027) was no longer significantly associated with bacterial pneumonia upon adjustment for CD4 cell count, viral RNA, and smoking status. Hence, we hypothesized an indirect

effect of calendar year on bacterial pneumonia through mediators (CD4 cell count, viral RNA, and smoking status). The proportion of individuals with CD4 cell counts less than 500 cells/μL, with viral RNA more than 200 copies/mL, and smoking ≥1 cigarette per day significantly decreased with calendar year (Figure S6). Using multiple mediation analysis, we estimated significant indirect effects of calendar year (total indirect effect: log(HR), -0.055; 95% CI, -0.067 to -0.042) through hypothesized mediators (Figure 4).

We performed various sensitivity analyses to test the robustness of the model. Overall, we estimated similar effects for the assessed risk factors indicating the robustness of the assessed models (Figure S7-S17). Notably, by restricting our study population to virally suppressed patients, we observed only a trend of association (P-value between 0.05 and 0.1) for the association of CD4 cell counts of 350 to 499 cells/μL and CD4 cell counts of 200 to 349 cells/μL compared to CD4 cell counts of more than 500 cells/μL with higher incidence of pneumonia (Figure S9). However, fitting marginal models to the entire data from 2008 to 2018 without medication data and restricting our study population to virally suppressed patients, we observed a significant association of CD4 cell counts of 350 to 499 cells/μL and CD4 cell counts of 200 to 349 cells/μL compared to CD4 cell counts of more than 500 cells/μL with higher incidence of pneumonia (Figure S10). Hence, a non-significant association in the former case might be due to lack of power. We further assessed the association between nadir CD4 cell counts and bacterial pneumonia for the entire data from 2008 to 2018. However, we did not find an independent significant effect of nadir CD4 cell counts when adjusted for other variables (Figure S11).

Prior pneumonia events in an individual might depend on the length of follow-up of that patient. Therefore, we applied alternative approaches less dependent on the follow-up time. Instead of adjusting for time-updated prior pneumonia event, we adjusted for at least one pneumonia event in 2014 (Figure S12) and for any pneumonia event that occurred in the last 5 years prior to observation time (between 2010 and 2014) (Figure S13). In both approaches, the prior pneumonia event was significantly associated with higher incidence of pneumonia. By adjusting for treating physician (as a stratified effect), we estimated a significant association of conjugated vaccination (adjusted HR, 0.56;

95% CI, 0.38 to 0.83) and non-conjugated vaccination (adjusted HR, 0.64; 95% CI, 0.46 to 0.9) (Figure S14). Some of the presumptive (symptoms plus radiological confirmation) bacterial pneumonia events could be due to misdiagnosis of viral pneumonia events. Therefore, as a sensitivity analysis, we defined outcome variable as definitive (confirmed by identification of bacterial pathogen) bacterial pneumonia events. We found similar effect sizes of that obtained in the main model for the entire time frame (August 2008 to December 2018) (Figure S15). However, several estimates were no longer significant, possibly due to lack of power.

DISCUSSION

In the SHCS, the incidence rate of bacterial pneumonia has significantly decreased from 13.2 cases per 1000 py in 2008 to 6.8 cases per 1000 py in 2018. Older age, IDUs, smoking status, HIV-related factors such as lower CD4 cell counts and higher viral RNA, use of PPIs, comorbidities such as obstructive airway diseases, and prior pneumonia events were significantly associated with a higher incidence of bacterial pneumonia. Further, mediation analysis indicated that decrease in incidence of bacterial pneumonia over the last decade was mediated to a large extent through a decreasing proportion of individuals with CD4 cell counts less than 500 cells/µL, with viral RNA more than 200 copies/mL, and smoking ≥1 cigarette per day.

In our study, risk associated with pneumonia increases with decrease in CD4 cell counts. Our results were similar to a study in Danish HIV-positive persons where the authors estimated an increase in crude incidence rate of pneumonia and bacteremia with decrease in CD4 cell counts [14]. The strongest increased risk was observed for CD4 cell counts less than 50 cells/µL (HR, 7.98) compared to CD4 cell counts more than 500 cells/µL. This is most likely due to the severe immunosuppression among patients with low CD4 cell counts making them more susceptible not only for the common AIDS defining illnesses but also for bacterial pneumonias. In a sensitivity analysis, we restricted our study population to virally suppressed individuals and assessed the robustness of associated risk-factors with pneumonia. CD4 cell counts lower than 200 remained significantly associated with higher

incidence of bacterial pneumonia. We then considered the entire follow-up period (August 2008 to December 2018) and restricted to virally suppressed individuals to increase the statistical power. Even CD4 cell counts of 350 to 499 cells/µL remained significantly associated with higher incidence of pneumonia. This suggests that already subtle immunosuppression is one of the key risk-factors associated with pneumonia even in virally suppressed patients. Moreover, we found that viral suppression is associated with lower incidence of bacterial pneumonia even after adjusting for CD4 levels. This is consistent with [15] who found that ART protects against community acquired pneumonia. Taken together our findings on the impact of CD4 levels and viral suppression further support the current strategy of treating all PWH as early as possible as only those treated earlier (higher baseline CD4) would recover to nearly normal CD4 cell counts after treatment [16].

Proton pump inhibitors (PPIs) are among the most prescribed drugs in the world and are used for the management of gastrointestinal disorders [17]. PPIs may reduce the acidity of the upper aerodigestive tract, thereby causing an increase in bacterial colonization of the larynx, esophagus and lungs, causing an increased incidence of pneumonia [18]. In our study, we found a significant association between proton pump inhibitors (PPIs) and higher incidence of bacterial pneumonia as shown in several studies [19–22]. Despite this evidence, there is an argument that early symptoms due to pneumonia, such as cough or chest discomfort, might be mistaken for acid-related symptoms and treated empirically with PPIs shortly before the eventual clinical diagnosis of pneumonia thereby biasing the risk associated with PPIs [23]. However, in our study, the median time to pneumonia event while on PPIs was 1.80 years and the earliest pneumonia event occurred 27 days after being on PPIs (Figure S18). As studies have shown overuse of PPIs, PWH might benefit from a cautious use of PPI, especially among those with other risk factors such as obstructive airway disease [17,22].

In the main model, conjugated and non-conjugated vaccination were not significantly associated with bacterial pneumonia. However, when adjusted for the stratified effect of treating physician in the model, conjugated and non-conjugated pneumococcal vaccination were significantly associated with a lower incidence of pneumonia. This could be because the patient population treated by a particular

physician may have similar risk-profile which in turn may influence treatment and vaccination regimes in the patients. Although pneumococcal vaccine is recommended for PWH enrolled in the SHCS, only 40-50% have been vaccinated. Pneumococcal vaccination may have benefited the individuals at risk for pneumonia. Education level equal to or above bachelor level was significantly associated with lower incidence of pneumonia as shown in previous studies [24]. Higher education may serve as a proxy for higher income, better standard of living, and better nutrition, thereby reducing the risk of infections such as pneumonia.

Any previous bacterial pneumonia event increased the risk of pneumonia by 4.82 folds even after adjusting for some of the most common risk factors associated with recurrent pneumonia such as immunosuppression (lower CD4 cell counts) and obstructive airway diseases. 'Prior pneumonia events' was significantly associated with higher incidence of pneumonia and was robust in these models. This association could be due to unadjusted risk factors of bacterial pneumonia such as neurological disorders associated with dysphagia, chronic lung disease other than COPD like bronchiectasis, diabetes mellitus and malnutrition [25–29].

One of the limitations of our study is the possible bias in the model estimates due to the uncertainty in missing values. However, we found similar estimates when we performed multiple imputation techniques to impute the missing values (Figure S16). Due to the lack of medication data prior to 2015, we had to restrict the data from 2015 to 2018 reducing the power of the study. However, in the sensitivity analysis, we used the data from 2008 till 2018 and found similar estimates further indicating the robustness of our model. There was lack of data for airway diseases as they were not directly reported in the SHCS dataset. However, we inferred the comorbidity such as obstructive airway diseases based on the medication data using the ATC codes. Finally, most bacterial pneumonia events were presumptive and hence it cannot be excluded that a part of those were caused by viral pathogens. It should be noted however that these presumptive bacterial pneumonia events were identified by infectious disease specialists based on both symptoms and radiology, and that effect sizes were robust even when restricting the analyses to bacterial pneumonia cases confirmed by

identification of bacterial pathogen (even though significance was lost for some factors, possibly due to the reduced statistical power).

Despite these limitations, our models were robust to various sensitivity analyses and assessed the risk factors associated with pneumonia events in a well-defined population over a long observation period – with a high retention proportion among participants. Also, our statistical models accounted for recurrent events and changes in risk behaviour over time; this allowed us to longitudinally estimate the impact of risk factors associated with bacterial pneumonia.

CONCLUSION

Incidence of bacterial pneumonia is significantly associated with comorbidities (obstructive airway disease), medication (PPIs), HIV-related (lower CD4 and higher viral RNA), and lifestyle related (smoking and IDU) risk factors. Improvements in cascade of care of HIV (higher CD4 cell counts and lower viral RNA) and decrease in smoking may have mediated a substantial decrease in bacterial pneumonia incidence.

Funding: This work was support by the Swiss National Science Foundation within the framework of the Swiss HIV Cohort Study, under SHCS project #862 and by the SHCS research foundation. The data is gathered by the five Swiss university hospitals, two cantonal hospitals, 15 affiliated hospitals, and 36 private physicians (listed in www.shcs.ch/180-health-care-providers). AW is supported by the academic career program "Filling the gap" of the Medical Faculty of the University of Zurich.

Acknowledgements: We thank the patients for participating in the SHCS, the study nurses, physicians, data managers, and the administrative assistants. The members of the SHCS are Anagnostopoulos A, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert CR (Chairman of the Mother and Child Substudy), Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Rudin C, Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, and Yerly S.

Author contributions: SB, RDK, and AW developed the study protocol and drafted the manuscript. Remaining authors critically reviewed the study protocol and the manuscript. SB and RDK performed the statistical analyses. SB was the principal investigator. All authors contributed to the design of the study and approved the final version of the manuscript.

Conflict of interests: HFG, outside of this study, report grants from Swiss HIV Cohort Study, grants from Swiss National Science Foundation, grants from NIH, grants from Gilead unrestricted research grant, personal fees from Advisor/consultant for Merck, ViiV healthcare and Gilead Sciences and member of DSMB for Merck, grants from Yvonne Jacob Foundation. The institution of HF has received educational grants not related to this work from Gilead, ViiV, MSD, Abbvie, Pfizer, and

Sandoz. The institution of MC received research grants from Gilead, ViiV and MSD. RDK received grants from Gilead. All other coauthors declare no conflict of interests.

Corresponding author: Mr. Suraj Balakrishna, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. Tel: +41432530186, E-mail suraj.balakrishna@usz.ch

Alternate corresponding author: Prof. Dr. Roger Kouyos, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. Tel: +41432553610, E-mail roger.kouyos@usz.ch

REFERENCES

1. Todar K. Streptococcus pneumoniae: Pneumococcal pneumonia. Todar's Online Textbook of Bacteriology. 2003.

2. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. Clin Microbiol Infect. **2011**; 17 Suppl 6((Suppl 6)):E1-59.

3. Torres A, Cillóniz C, Blasi F, et al. Burden of pneumococcal community-acquired pneumonia in adults across Europe: A literature review. Respir Med. **2018**; 137:6–13.

4. Franzetti F, Grassini A, Piazza M, et al. Nosocomial Bacterial Pneumonia in HIV-Infected Patients: Risk Factors for Adverse Outcome and Implications for Rational Empiric Antibiotic Therapy. Infection. **2006**; 1(34):9–16.

5. Liapikou A, Cilloniz C, Torres A. Drugs that increase the risk of community-acquired pneumonia: a narrative review. Expert Opin Drug Saf. **2018**; 17(10):991–1003.

6. Cillóniz C, García-Vidal C, Moreno A, Miro JM, Torres A. Community-acquired bacterial pneumonia in adult HIV-infected patients. Expert Rev Anti Infect Ther. **2018**; 16(7):579–588.

7. Eurich DT, Sadowski CA, Simpson SH, Marrie TJ, Majumdar SR. Recurrent Community-acquired Pneumonia in Patients Starting Acid-suppressing Drugs. Am J Med. **2010**; 123(1):47–53.

8. Dang TT, Majumdar SR, Marrie TJ, Eurich DT. Recurrent pneumonia: a review with focus on clinical epidemiology and modifiable risk factors in elderly patients. Drugs Aging. **2015**; 32(1):13–19.

9. Collin A, Le Marec F, Vandenhende M-A, et al. Incidence and Risk Factors for Severe Bacterial Infections in People Living with HIV. ANRS CO3 Aquitaine Cohort, 2000-2012. PloS One. **2016**; 11(4):e0152970.

10. Kohler P, Schmidt AJ, Cavassini M, et al. The HIV care cascade in Switzerland: reaching the UNAIDS/WHO targets for patients diagnosed with HIV. AIDS. **2015**; 29(18):2509–2515.

11. Swiss HIV Cohort Study, Schoeni-Affolter F, Ledergerber B, et al. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol. **2010**; 39(5):1179–1189.

12. Amorim LDAF, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. Int J Epidemiol. **2015**; 44(1):324–333.

13. R Core Team (2020). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

14. Søgaard OS, Reekie J, Ristola M, et al. Severe bacterial non-aids infections in HIV-positive persons: Incidence rates and risk factors. J Infect. **2013**; 66(5):439–446.

15. Madeddu G, Porqueddu EM, Cambosu F, et al. Bacterial Community Acquired Pneumonia in HIV-Infected Inpatients in the Highly Active Antiretroviral Therapy Era. Infection. **2008**; 36(3):231–236.

16. Stirrup O, Copas A, Phillips A, et al. Predictors of CD4 cell recovery following initiation of antiretroviral therapy among HIV- 1 positive patients with well- estimated dates of seroconversion. HIV Med. **2018**; 19(3):184–194.

17. Luo H, Fan Q, Xiao S, Chen K. Changes in proton pump inhibitor prescribing trend over the past decade and pharmacists' effect on prescribing practice at a tertiary hospital. BMC Health Serv Res. **2018**; 18(1):537.

18. Fohl AL, Regal RE. Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? World J Gastrointest Pharmacol Ther. **2011**; 2(3):17–26.

19. Badiola N, Alcalde V, Pujol A, et al. The proton-pump inhibitor lansoprazole enhances amyloid beta production. PloS One. **2013**; 8(3):e58837.

20. Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. BMJ. **2016**; 355:i5813.

21. Zirk- Sadowski J, Masoli JA, Delgado J, et al. Proton-Pump Inhibitors and Long-Term Risk of Community-Acquired Pneumonia in Older Adults. J Am Geriatr Soc. **2018**; 66(7):1332–1338.

22. Nehra AK, Alexander JA, Loftus CG, Nehra V. Proton Pump Inhibitors: Review of Emerging Concerns. Mayo Clin Proc. **2018**; 93(2):240–246.

23. Vaezi MF, Yang Y-X, Howden CW. Complications of Proton Pump Inhibitor Therapy. Gastroenterology. **2017**; 153(1):35–48.

24. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax. **2013**; 68(11):1057–1065.

25. Almirall J, Rofes L, Serra-Prat M, et al. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. Eur Respir J. **2013**; 41(4):923–928.

26. Sanchez-Muñoz G, López-de-Andrés A, Hernández-Barrera V, et al. Hospitalizations for Community-Acquired and Non-Ventilator-Associated Hospital-Acquired Pneumonia in Spain: Influence of the Presence of Bronchiectasis. A Retrospective Database Study. J Clin Med. **2020**; 9(8):2339.

27. Saiz LC, Garjón J, Gorricho J, Erviti J, Gil-García MJ, Martín-Merino E. Validation and incidence of community-acquired pneumonia in patients with type 2 diabetes in the BIFAP database. Epidemiol Infect. **2017**; 145(14):3056–3064.

28. Jensen AV, Faurholt-Jepsen D, Egelund GB, et al. Undiagnosed Diabetes Mellitus in Community-Acquired Pneumonia: A Prospective Cohort Study. Clin Infect Dis. **2017**; 65(12):2091–2098.

29. Phung DT, Wang Z, Rutherford S, Huang C, Chu C. Body mass index and risk of pneumonia: a systematic review and meta-analysis. Obes Rev. **2013**; 14(10):839–857.

Table 1: Characteristics of the study population during the study period (2015-2018)

	Patients without any pneumonia event	Patients with at least one pneumonia event	All patients
Number of patients	8980	233	9213
Follow-up time (person-years)	28175.0	785.0	28960.0
Number of pneumonia events	-	272	272
Year of birth; median [IQR]	1967 [1960 - 1975]	1963 [1957 - 1969]	1967 [1960 - 1975]
Gender (male); n (%)	6537 (72.8)	159 (68.2)	6696 (72.7)
Ethnicity (white); n (%)	6878 (76.6)	203 (87.1)	7081 (76.8)
Education level (bachelor or higher level); n (%)	3190 (35.5)	43 (18.4)	3233 (35.1)
Age at HIV-diagnosis; median [IQR]	34 [27 - 42]	32 [26 - 43]	33 [27 - 42]
Nadir CD4 cell counts (cells/µL) [*]; median [IQR]	479 [341 - 638]	392.5 [235 - 548]	476 [339 - 634]
Viral RNA more than 200 copies per/ml [*]; n (%)	1597 (17.8)	45 (19.3)	1642 (17.8)
Smoked one or more than one cigarette [*]; n (%)	3993 (44.5)	159 (68.2)	4152 (45.1)
Used PPIs [*]; n (%)	1502 (16.7)	83 (35.6)	1585 (17.2)
Used ACE inhibitors [*]; n (%)	1094 (12.2)	58 (24.9)	1152 (12.5)
Kidney disease [*]; n (%)	1527 (17.0)	54 (23.2)	1581 (17.2)
Obstructive airway disease [*]; n (%)	527 (5.9)	48 (20.6)	575 (6.3)
Ever had non-conjugated pneumococcal vaccination [§]; n (%)	3788 (42.2)	128 (54.9)	3916 (42.5)
Ever had conjugated pneumococcal vaccination [§]; n (%)	4058 (45.2)	119 (51.1)	4177 (45.3)

[*] These time-updated variables proportions/median were calculated based on the study period (January 2015 to December 2018); [§] Conjugated and non-conjugated vaccination proportions were calculated based on ever vaccinated and not just during the study period; Abbreviations: IQR, Interquartile range; PPIs, Proton-pump inhibitors; ACE, Angiotensin-converting enzyme.

Figure 1: Schematic representation of multiple mediation analysis

Panel a) indicates the total effect between calendar year and bacterial pneumonia. Panel b) indicates the direct effect of calendar year and the indirect effect of calendar year mediated through the assessed mediators. Both these models were adjusted for the following covariates: time-updated age, ethnicity, education level, and prior pneumonia event.

Figure 2: Factors associated with incidence of pneumonia (with medication and comorbidities)

Abbreviations: CI, Confidence interval; HR, Hazard ratio; MSM, Men-who-have-sex-with-men; IDUs, Intravenous drug users; PPIs, Proton-pump inhibitors; ACE, Angiotensin-converting enzyme. Black and light gray error bars show point estimate of hazard ratio and 95% confidence interval for each assessed risk factors in univariable and multivariable marginal models, respectively. Note: Variables with an asterisk (*) are time-updated.

Figure 3: Yearly incidence rate of pneumonia in the SHCS

Abbreviations: SHCS, Swiss HIV Cohort Study; py, person-years; The solid line shows the point estimate for incidence rate over time and the shaded region around line indicate the 95% confidence interval. Note: incidence rate for the year 2008 is estimated based on the data from August 1, 2008 to December 31, 2008.

Figure 4: Multiple mediation analysis estimates

Black error bar shows logarithm of hazard ratio and 95% confidence interval of the association between calendar year and bacterial pneumonia along a given pathway as described in Figure 1. Abbreviations: HR, Hazard ratio.

Figure 1

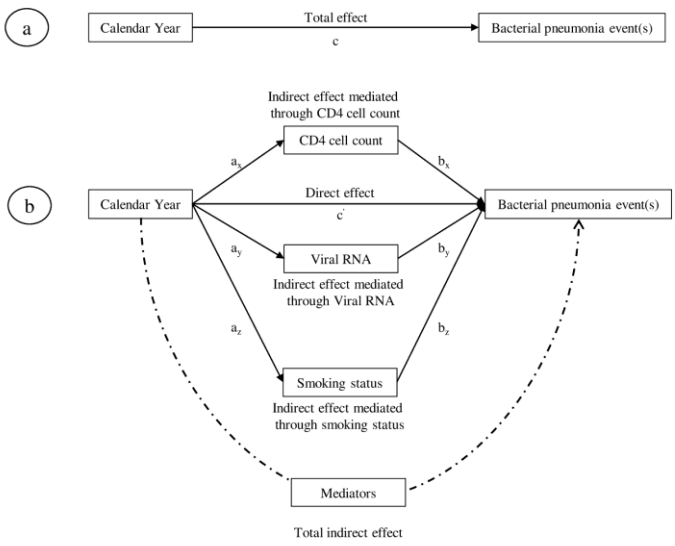

Figure 2

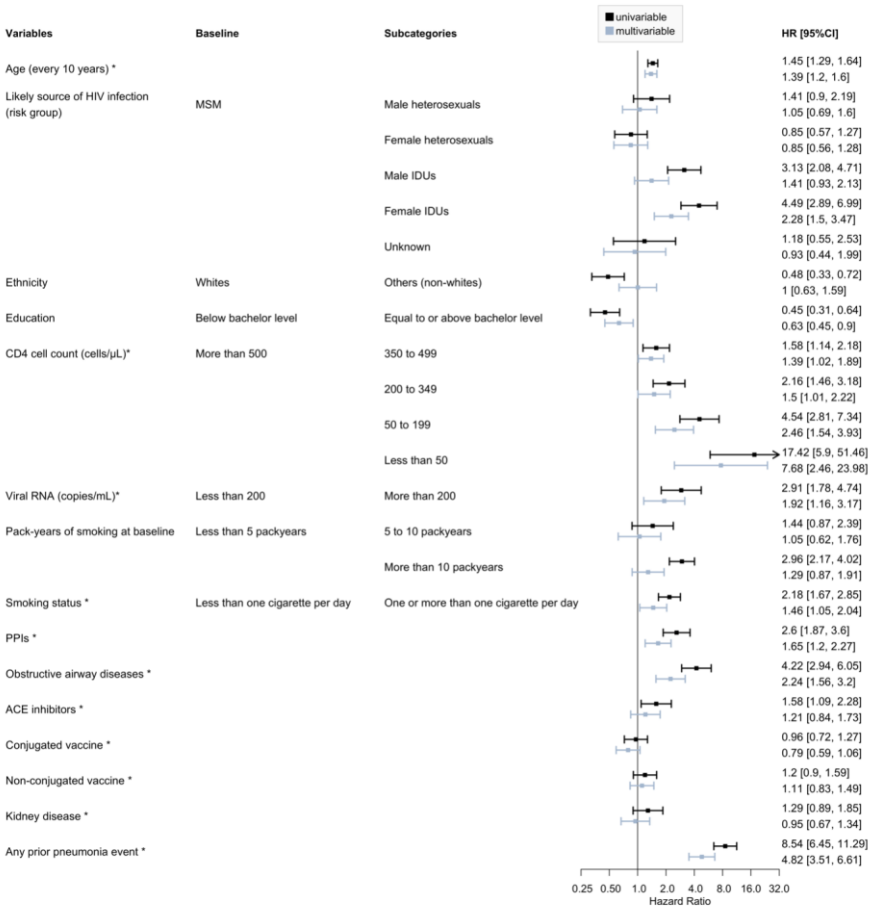

Figure 3

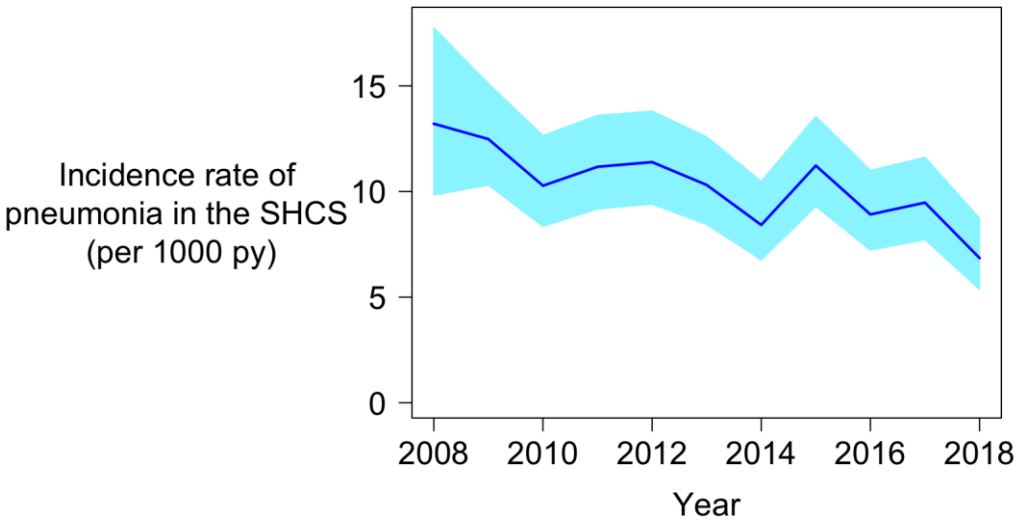

Figure 4