Bruna Weber Scolari

MORTALIDADE E CUSTOS RELACIONADOS À INTERNAÇÃO HOSPITALAR POR DOENÇA PNEUMOCÓCICA PULMONAR EM ADULTOS NÃO VACINADOS

Dissertação apresentada à Universidade de Caxias do Sul, para obtenção do Título de Mestre em Ciências da Saúde.

Caxias do Sul

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Orientadora: Profa. Dra. Lessandra Michelin

Co-orientadora: Profa. Dra. Maria Carolina Gullo

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Banca examinadora:

Prof. Dr. Cícero Dias

Prof. Dr. Ana Paula Delamare

Prof. Dr. Emerson Rodrigues da Silva

Dedicatória

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À Direção e funcionários do Hospital Geral de Caxias do Sul.

SUMÁRIO

1 INTRODUÇÃO

Streptococcus pneumoniae, também conhecido como pneumococo, foi identificado pela primeira vez em 1881 por Louis Pasteur (1822-1895) (1, 2). Essa bactéria é classificada como Gram positiva, alfa hemolítica, capsulada, com disposição morfológica de cocos aos pares em cadeias curtas, medindo em média 0,5 a 1,25 µm de diâmetro. Assim como as demais espécies do gênero *Streptococcus*, o pneumococo é anaeróbio facultativo, catalase negativa e cresce bem em ágar sangue (3, 4).

Seu processo de identificação em laboratório é relativamente simples, porém os meios de cultura apropriados são essenciais para o sucesso do isolamento e caracterização dos pneumococos. Primeiramente, é realizada a identificação da amostra por sua aparência encapsulada típica na coloração de Gram, incluindo a morfologia das colônias em placas de ágar sangue, a suscetibilidade à optoquina, a solubilidade da bile e a reatividade com antissoros específicos para detecção do antígeno polissacarídico capsular (3, 5). A cápsula de polissacarídeo que envolve externamente o pneumococo é considerada seu mais importante fator de virulência, pois tem a função de proteger o pneumococo da fagocitose e do reconhecimento pelo sistema imunológico, contribuindo nos processos inflamatórios e gravidade da doença (6). Devido a sua capacidade de transformação genética, com intensa troca de informação celular, o pneumococo pode adquirir uma nova característica, como um polissacarídeo capsular capaz de realizar processos infecciosos ou de colonização (7). Além da importância da cápsula como fator de virulência, os polissacarídeos capsulares são os antígenos utilizados no preparo das vacinas, e servem de base para sua sorotipagem (3).

Atualmente, existem 94 sorotipos de pneumococo reconhecidos de acordo com seus perfis sorológicos e estruturas químicas únicas (1, 8). O projeto SIREVA, que busca correlacionar os sorotipos mais prevalentes na América Latina, demonstrou que para o Brasil, no período de 2000 a 2008, 13 sorotipos foram isolados com maior frequência em crianças de até cinco anos internadas em hospitais: 14, 6B, 18C, 19F, 23F, 1, 6A, 5, 19A, 9V, 3, 7F e 4 (9).

A transmissão do pneumococo ocorre através de gotículas respiratórias, podendo ser colonizador de pessoas sadias, que são consideradas assintomáticas. Ao colonizar o trato respiratório, pode ocasionar doenças invasivas e não invasivas. As doenças classificadas como não invasivas são otite, sinusite, amigdalite, bronquite e pneumonia,

já as invasivas são caracterizadas por bacteremia, meningite e pneumonia bacterêmica. A doença pneumocócica invasiva é determinada como uma infecção confirmada pelo isolamento de *S. pneumoniae* de um local normalmente estéril, tal como sangue, liquido cefalorraquidiano e fluido pleural (10-12).

A Organização Mundial da Saúde classificou, em 2015, a pneumonia adquirida na comunidade (PAC) como a terceira principal causa de morte em todo o mundo, causando 3,2 milhões de mortes/ano (13). A pneumonia pneumocócica bacterêmica (PPB) é uma forma grave de pneumonia invasiva. Aproximadamente 20% dos pacientes adultos desenvolvem infecção da corrente sanguínea e as taxas de mortalidade variam de 10% a 30% (14). Ainda em 2015, dados epidemiológicos da Europa revelaram que houve 21.118 casos confirmados de PPB, com taxa de mortalidade de 14% (1.312 pacientes) (15). Já a pneumonia pneumocócica sem bacteremia (PP) é identificada como doença não invasiva na maior parte dos consensos, com mortalidade estimada de 5 a 7% (14). Em estudo italiano, estimou-se que hospitalizações por PP tenham maior risco de complicações e mortalidade em crianças e idosos do que em adultos jovens, onde a mortalidade relacionada à pneumonia foi de 10,7%, e o custo médio por paciente hospitalizado foi de 3.090 euros (16).

Embora a pneumonia cause grande quantidade de óbitos, pouca atenção tem sido dada aos fatores que contribuem para essa mortalidade, pois uma proporção significativa de mortalidade 90 dias após a internação por pneumonia é atribuída a outras condições comórbidas (17). A presença de doenças crônicas, não apenas aumenta o risco de um indivíduo adquirir PP, mas também pode aumentar a gravidade da doença crônica (18). Em uma revisão realizada por Torres e colaboradores, observou-se que as comorbidades mais comuns em pacientes diagnosticados com PAC são: doenças respiratórias crônicas, cardiopatia crônica ou insuficiência cardíaca, diabetes mellitus, doenças cerebrovasculares, demência e doenças renais crônicas, sendo que a frequência dessas doenças crônicas é maior em pacientes com idade ≥65 anos (19).

Nos Estados Unidos (EUA), o número anual estimado de episódios de pneumonia em adultos é de 5,2 milhões, com aproximadamente 1 milhão de hospitalizações ao ano apresentando um custo médio de mais de USD 9,7 bilhões (20, 21). Na Europa, as despesas hospitalares por PAC chegam a €5.7 bilhões, sendo os custos por cada internação decorrente de PP e PPB em torno de €13.611 (22). Pacientes com idade superior a 50 anos geram maior impacto econômico em internações ao serem comparados com indivíduos de 18 anos ou menos (custo médio por episódio de €5,000 versus €2,750,

respectivamente). Isso pode ser justificado porque adultos entre 50 e 64 anos são economicamente ativos e possuem mais comorbidades relacionadas ao envelhecimento, aumentando assim os custos da internação (22, 23). Esses índices de mortalidade e custos são superiores em países em desenvolvimento, apesar de poucos dados publicados sobre PP e seu impacto para os sistemas de saúde (24).

Os custos das internações hospitalares podem ser analisados como custos diretos que se subdividem em custos no cuidado da doença (pagamentos dos profissionais da saúde, uso das instalações físicas, materiais, medicamentos, exames, etc) e os custos não relacionados especificamente ao ambiente médico-hospitalar (recursos de deslocamento do paciente e/ou cuidadores aos serviços de saúde, alimentação, serviço de cuidadores, etc). Os custos indiretos incluem todos os outros custos causados indiretamente relacionados ao tratamento da doença, incluindo dias de licença médica no trabalho (do paciente e/ou acompanhante) e custos relacionados ao transporte, cuidados e utilização do tempo pelo paciente ou cuidador para o tratamento da doença (25, 26).

O somatório de custos diretos e indiretos é analisado como custo total relacionado à determinada doença. Os principais determinantes dos custos totais com tratamentos de saúde para pneumonias são: admissão em unidade de terapia intensiva e o tempo de internação hospitalar, presença de comorbidades específicas, o desenvolvimento de complicações e a gravidade da pneumonia. Portanto, a PAC, e especificamente a PP, impõe uma carga econômica significativa, especialmente quando associada à comorbidades (18).

Como as infecções pneumocócicas são consideradas uma grande questão de saúde pública em todo o mundo, para todas as faixas etárias, estudos que tratem de custos se tornaram ferramentas úteis e fundamentais, pois tem a finalidade de melhorar a aplicação de recursos públicos e privados, e auxiliar na tomada de decisões quanto a investimentos em saúde (16, 27). A análise do impacto econômico da saúde pode informar a relevância das perdas econômicas, melhorar a definição das prioridades de investimentos e alocação de recursos, identificando possíveis estratégias para reduzir os custos das doenças através de ações preventivas apropriadas ou estratégias de tratamento (28).

Em relação a prevenção, a imunização é a melhor maneira de reduzir a ocorrência das doenças pneumocócicas, consequentemente, hospitalizações e mortes. A vacina pneumocócica 10 valente (conjugada) foi introduzida no calendário vacinal do SUS em setembro de 2010, para ser aplicada em crianças a partir de dois meses até 15 meses de idade. Ela é composta pelos seguintes sorotipos: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F e 23F.

Trata-se de uma vacina indutora de memória imunológica T dependente com um impacto potencial de prevenção de doença pneumocócica grave de até 80% em crianças (9, 12, 29).

Além da 10 valente, há no mercado mais uma vacina conjugada 13 valente, que também induz memória T dependente e quando comparada a vacina 10 valente, os subtipos adicionais são: 3, 6A e 19A e pode ser aplicada dos dois meses aos 80 anos de idade, estando nessa vacina o sorotipo 19A o mais prevalente e mais resistente aos antibióticos. Ainda está disponível uma vacina polissacarídica 23 valente, que possui resposta T independente, não induzindo memória imunológica, apresentando uma diminuição dos anticorpos após cinco a dez anos da aplicação, que está indicada para pacientes com idade superior a 60 anos, ou pacientes com fatores de risco como: institucionalizados, com retrovirose, diabéticos, cardiopatas crônicos, nefropatas crônicos, com asplenia anatômica ou funcional, pneumopatias crônicas, asma grave a moderada, entre outros (30-32).

Tanto a vacina conjugada quanto a polissacarídica contra o pneumococo, também tem impacto na diminuição da circulação de cepas de importância clínica, evitando assim o desenvolvimento de resistência bacteriana. A variação da sensibilidade do pneumococo à penicilina tem sido observada em inúmeros estudos realizados nos Estados Unidos. Os clínicos devem ter ciência que essa resistência, tem aumentado à níveis importantes, sendo necessária mudanças na terapia empírica. Antibióticos da mesma classe utilizados previamente, são o fator de risco mais importante para a resistência de um determinado antimicrobiano. A vacina, nas faixas etárias em que foi indicada, teve efeito não só na prevenção da diminuição de casos de doença, mas também em internações por cepas multirresistentes não contidas na vacina (33, 34).

As vacinas e o conhecimento do perfil de resistência local do pneumococo aos antimicrobianos tornaram-se uma estratégia fundamental para o controle das infecções pneumocócicas e para a escolha correta dos esquemas terapêuticos efetivos. Apesar da grande disponibilidade de vacinas pneumocócicas, as taxas de vacinação permanecem muito abaixo do ideal em todo o mundo, sendo que em adultos são menos de 50% os vacinados nos grupos de alto risco. Na Europa, a taxa de imunização é considerada baixa, oscilando de 12,6% a 36,5% para pessoas do nível de risco. No Brasil, há poucas publicações sobre imunização em adultos, necessitando de trabalhos que possam avaliar adesão e resposta protetora em população de risco (23, 35-37).

Devido à escassez de dados nacionais sobre mortalidade em adultos relacionada à PP, bem como seu impacto em grupos de risco e custos hospitalares, o presente trabalho objetivou analisar os dados relacionados às internações hospitalares por PP no Hospital Geral de Caxias do Sul, no período de 01 de outubro de 2009 e 30 de abril de 2017, em pacientes adultos não vacinados previamente com vacina anti-pneumocócica, diferenciando-os em dois grupos: pacientes com idade <65 anos (considerados adultos) e ≥65 anos (considerados idosos). Para esses pacientes foram avaliados dados demográficos, fatores de risco (comorbidades), tempo de permanência hospitalar, admissão em unidade de terapia intensiva e mortalidade hospitalar. Além disso, foi avaliado o impacto econômico, através de custos diretos e indiretos, bem como custo total anual e custo ao Sistema Único de Saúde (custo total direto e custo direto por paciente). O trabalho foi aprovado pelo Comitê Editorial do Hospital Geral (COEDI) e pelo Comitê de Ética em Pesquisa da Universidade de Caxias do Sul (CEP-UCS número: 2.360.724).

2 REFERÊNCIAS

1. Gamez G, Castro A, Gomez-Mejia A, Gallego M, Bedoya A, Camargo M, et al. The variome of pneumococcal virulence factors and regulators. BMC Genomics. 2018;19(1):10.
2. Lopez R. Streptococcus pneumoniae and its bacteriophages: one long argument. Int Microbiol. 2004;7(3):163-71.
3. Warren L. Microbiologia e imunologia médicas ; tradução: Danielle Soares de Oliveira Daian; tradução e revisão técnica: Flávio Guimarães da Fonseca. – 13. ed. – Porto Alegre : AMGH Editora, 2016.
4. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med. 2014;371(17):1619-28.
5. Dias CA, Agnes G, Frazzon AP, Kruger FD, d'Azevedo PA, Carvalho Mda G, et al. Diversity of mutations in the atpC gene coding for the c Subunit of F0F1 ATPase in clinical isolates of optochin-resistant Streptococcus pneumoniae from Brazil. J Clin Microbiol. 2007;45(9):3065-7.
6. Calix JJ, Nahm MH. A new pneumococcal serotype, 11E, has a variably inactivated wcjE gene. J Infect Dis. 2010;202(1):29-38.
7. Obert C, Sublett J, Kaushal D, Hinojosa E, Barton T, Tuomanen EI, et al. Identification of a Candidate Streptococcus pneumoniae core genome and regions of diversity correlated with invasive pneumococcal disease. Infect Immun. 2006;74(8):4766-77.
8. Medeiros MIC, Almeida SCG, Guerra M, da Silva P, Carneiro AMM, de Andrade D. Distribution of Streptococcus pneumoniae serotypes in the northeast macro-region of Sao Paulo state/Brazil after the introduction of conjugate vaccine. BMC Infect Dis. 2017;17(1):590.
9. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Coordenação-Geral do Programa Nacional de I. Manual dos Centros de Referência para Imunobiológicos Especiais.
10. Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect. 2014;20 Suppl 5:45-51.
11. (WHO) World Health Organization. Weekly epidemiological record.6 APRIL 2012, 87th:[129–44 pp.]. Available from: http://www.who.int/wer.
12. Lucarevschi BR, Escobar AMdU, Grisi S. Custos hospitalares da meningite causada por Streptococcus pneumoniae na cidade de São José dos Campos, São Paulo, Brasil. Cadernos de Saúde Pública. 2012;28:740-8.
13. (WHO) World Health Organization. The top 10 causes of death.January 2017. Available from: http://who.int/mediacentre/factsheets/fs310/en/.
14. Cilloniz C, Torres A. Understanding mortality in bacteremic pneumococcal pneumonia. J Bras Pneumol. 2012;38(4):419-21.
15. European Centre for Disease Prevention and Control. Invasive pneumococcal disease. ECDC. Annual epidemiological report for 2015 ed: Access in Feb 2, 2018; 2015.
16. Baldo V, Cocchio S, Baldovin T, Buja A, Furlan P, Bertoncello C, et al. A population-based study on the impact of hospitalization for pneumonia in different age groups. BMC Infect Dis. 2014;14:485.
17. Perry TW, Pugh MJ, Waterer GW, Nakashima B, Orihuela CJ, Copeland LA, et al. Incidence of cardiovascular events after hospital admission for pneumonia. Am J Med. 2011;124(3):244-51.

18. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax. 2015;70(10):984-9.
19. 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):1057-65.
20. Rozenbaum MH, Mangen MJ, Huijts SM, van der Werf TS, Postma MJ. Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: A nationwide retrospective claims database analysis. Vaccine. 2015;33(28):3193-9.
21. Adamuz J, Viasus D, Camprecios-Rodriguez P, Canavate-Jurado O, Jimenez-Martinez E, Isla P, et al. A prospective cohort study of healthcare visits and rehospitalizations after discharge of patients with community-acquired pneumonia. Respirology. 2011;16(7):1119-26.
22. Vissink CE, Huijts SM, de Wit GA, Bonten MJ, Mangen MJ. Hospitalization costs for community-acquired pneumonia in Dutch elderly: an observational study. BMC Infect Dis. 2016;16:466.
23. Song JY, Choi JY, Lee JS, Bae I-G, Kim YK, Sohn JW, et al. Clinical and economic burden of invasive pneumococcal disease in adults: a multicenter hospital-based study. BMC Infectious Diseases. 2013;13(1):202.
24. Giglio N, Micone P, Gentile A. The pharmacoeconomics of pneumococcal conjugate vaccines in Latin America. Vaccine. 2011;29 Suppl 3:C35-42.
25. Brasil. Ministério da Saúde. Diretrizes Metodológicas.Diretriz de Avaliação Econômica. Secretaria de Ciência, Tecnologia e Insumos Estratégicos Departamento de Ciência e Tecnologia. 2ª edição. Brasília – DF 2014.
26. Graf von der Schulenburg JM, Greiner W, Jost F, Klusen N, Kubin M, Leidl R, et al. German recommendations on health economic evaluation: third and updated version of the Hanover Consensus. Value Health. 2008;11(4):539-44.
27. Nunes SEA. Estimativa dos custos da doença pneumocócica e estudo de custo-efetividade da introdução universal da vacina anti-pneumocócica 10 valente no Brasil. Universidade Federal de Goiás. 2014.
28. (WHO) World Health Organization. Guide to identifying the econimic consequences of disease and injury. Department of Health Systems Financing Health Systems and Services World Health Organization Geneva, Switzerland. 2009.
29. Moreira M, Cintra O, Harriague J, Hausdorff WP, Hoet B. Impact of the introduction of the pneumococcal conjugate vaccine in the Brazilian routine childhood national immunization program. Vaccine. 2016;34(25):2766-78.
30. Kaplan SL, Barson WJ, Lin PL, Romero JR, Bradley JS, Tan TQ, et al. Early trends for invasive pneumococcal infections in children after the introduction of the 13-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2013;32(3):203-7.
31. Esposito S, Tansey S, Thompson A, Razmpour A, Liang J, Jones TR, et al. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine compared to those of a 7-valent pneumococcal conjugate vaccine given as a three-dose series with routine vaccines in healthy infants and toddlers. Clin Vaccine Immunol. 2010;17(6):1017-26.
32. Jose RJ, Brown JS. Adult pneumococcal vaccination: advances, impact, and unmet needs. Curr Opin Pulm Med. 2017;23(3):225-30.
33. Andam CP, Worby CJ, Gierke R, McGee L, Pilishvili T, Hanage WP. Penicillin Resistance of Nonvaccine Type Pneumococcus before and after PCV13 Introduction, United States. Emerg Infect Dis. 2017;23(6):1012-5.

34. Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A. Predicting antimicrobial resistance in invasive pneumococcal infections. Clin Infect Dis. 2005;40(9):1288-97.
35. Silva SRd, Mello LMd, Silva ASd, Nunes AA. Impact of the pneumococcal 10-valent vaccine on reducing hospitalization for community-acquired pneumonia in children. Revista Paulista de Pediatria. 2016;34:418-24.
36. Hammitt LL, Bulkow LR, Singleton RJ, Nuorti JP, Hummel KB, Miernyk KM, et al. Repeat revaccination with 23-valent pneumococcal polysaccharide vaccine among adults aged 55-74 years living in Alaska: no evidence of hyporesponsiveness. Vaccine. 2011;29(12):2287-95.
37. Kyaw MH, Rose CE, Jr., Fry AM, Singleton JA, Moore Z, Zell ER, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis. 2005;192(3):377-86.

3 ARTIGO

How bad is the pneumococcus to adults? A cross-sectional study of mortality and costs related to pneumococcal pneumonia in adults

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ABSTRACT

Background: *Streptococcus pneumoniae* is the main pathogen identified in community-acquired pneumonia. Studies evaluating in-hospital mortality related to pneumococcal pneumonia in adults and the economic impact of direct and indirect costs are scarce.

Methods: Cross-sectional study on medical records of adult patients with pneumococcal pneumonia hospitalized in a university hospital in Brazil, from October 2009 to April 2017. All pneumococcal vaccine-naïve inpatient aged ≥ 18 years diagnosed with pneumococcal pneumonia were included, and risk factors, UCI admission, hospital length of stay, in-hospital mortality, direct and indirect costs were analyzed.

Results: A total of 186 patients were selected. The mean in-hospital mortality rate was 18% for adults (<65 years) and 23% for the elderly (≥ 65 years). Bacteremic

pneumococcal pneumonia affected 20% of patients in both groups, mainly with chronic respiratory disease (adjusted OR 3.07, 95%CI 1.23-7.65, p <0.01). During the 7-year period, annual total direct and indirect costs were USD 28,188 for adults (USD 1,746 per capita) and USD 16,350 for the elderly (USD 2,119 per capita).

Conclusion: Pneumococcal pneumonia remains an important cause of morbidity and mortality in the adult population, having a significant impact on direct and indirect costs. These results suggest that prevention strategies should be performed for all adults aged 18 and older, mainly for patients with chronic respiratory diseases.

Key-words: Pneumococcus; pneumococcal disease; pneumonia, hospital costs; mortality.

Key Messages:

- What is already known on this subject?

Community-acquired pneumonia caused by *Streptococcus pneumoniae* is one of the major causes of morbidity and mortality in children and the elderly worldwide. However, mortality rate and the economic impact of this disease in pneumococcal vaccine-naïve adults are rare.

- What does this study add?

Pneumococcal vaccine-naïve adults and elderly patients have a similar in-hospital mortality rate. Invasive pneumonia affected 20% of both studied groups and patients with the chronic respiratory disease were at higher risk. The costs per patient hospitalized, considering direct and indirect costs, were USD 1,746 for adults and USD 2,119 for the elderly.

INTRODUCTION

Pneumococcal infection is an important cause of morbidity and mortality worldwide. In Europe and the United States (US), *Streptococcus pneumoniae*, or pneumococcus, is the main etiologic agent of community-acquired pneumonia (CAP).[1-3] Elderly people, patients with chronic conditions (chronic obstructive pulmonary disease, bronchial asthma, chronic cardiovascular disease, cerebrovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus) and immunosuppressed persons are at risk for pneumococcal pneumonia (PP), and bacteremic pneumococcal pneumonia (BPP).[4-6] The incidence of pneumococcal invasive disease in adults ranges from 10-100 cases per 100,000 inhabitants.[7-9] In the 2015 US surveillance report, the highest rates of cases and deaths from the pneumococcal disease occurred in patients over 65 years (18.2% of cases and 1.53% of deaths).[10] Ruiz et al. carried out a study published in 2017, comparing adults (18-64 years) with elderly patients (≥ 65 years) who were diagnosed with PP and patients ≥ 65 years had higher 30-day mortality, however, were less admitted to the intensive care unit (ICU) and had a shorter hospital stay.[11]

Epidemiological data from Europe revealed 21,118 confirmed cases of the pneumococcal disease in 2015 with a mortality rate of 14% (1,312 patients) and hospital costs per PP and BPP around € 13,611 per hospitalized patient.[12] Patients over 50 years of age have a greater economic impact on hospitalizations when compared with individuals aged 18 years or less (average cost per episode of € 5,000 versus € 2,750, respectively).[13-14] These rates of mortality and costs are higher in developing countries, and scarce data is published on PP in adults and its impact on health systems.[15-16] The present study adds to the literature the in-hospital mortality impact of pneumococcal pneumonia in adults and related direct and indirect costs, comparing them to elderly patients.

METHODOLOGY

Study design and population

Cross-sectional study of medical records of adult patients diagnosed with pneumococcal pneumonia hospitalized at the General Hospital – University of Caxias do Sul, Brazil. The study period spanned from October 2009 to April 2017 and enrolled all pneumococcal vaccine-naïve inpatient aged ≥ 18 years diagnosed with PP or BPP.

Clinical and microbiological diagnosis of PP and BPP

CAP was diagnosed based on radiographic findings (new infiltrates compatible with a diagnosis of pneumonia on chest x-ray, tomography or magnetic resonance imaging) and clinical findings (acute-onset clinical symptoms suggestive of a lower respiratory tract infection, such as cough, sputum production, fever, pleural chest pain, or dyspnea). PP was defined as at least one positive result for *Streptococcus pneumoniae* in sputum, tracheal bronchial aspirate and/or bronchoalveolar lavage associated with clinical and radiographic features of CAP. Sputum specimens with >25 leucocytes per field were considered of sufficient quality for diagnosis. BPP was diagnosed based on isolating *S. pneumoniae* from blood cultures obtained before the parenteral administration of antibiotics in a patient with CAP.

Variables analyzed and covariates:

The impact of mortality associated with pneumococcal pneumonia in the adult age groups <65 years and ≥65 years was evaluated according to demographic aspects (gender, age, occupation and average income) and clinical characteristics. It was considered a dependent patient who declared not to work, students, and people that live with relatives; low income which declared monthly earn up to USD 1,190; average income that receives up to USD 2,975; and above this value was considered high income). Clinical covariates analyzed were: diagnosis of bacteremic and non-bacteremic pneumonia; admission and length of hospitalization for treatment in the intensive care unit (ICU), total hospital length of stay and related deaths, as well as comorbidities described as chronic cardiovascular disease (ischemic heart disease, coronary disease, heart failure, arrhythmia); chronic respiratory disease (chronic obstructive pulmonary disease, bronchial asthma); chronic liver disease (cirrhosis, chronic viral hepatitis); chronic renal failure (acute kidney injury and chronic kidney disease); chronic neurological disease (stroke, dementia); HIV (patient living with acquired immunodeficiency syndrome virus/AIDS and CD4 ≤ 200 cells/mm3); immunosuppression (change in immunity caused by medication or non-AIDS disease); diabetes mellitus; smoking and alcoholism.

Direct and indirect cost analysis

The cost per hospital stay was analyzed as direct costs [DC] to the Brazilian Health System/SUS defined as hospital length of stay, medicines, laboratory and imaging exams, surgical procedures and bronchoscopy, daily ICU cost, medical and other healthcare costs; and indirect costs [IC] were the patient and/or caregivers cost of the absence from

work and associated impact. Therefore, the total cost [TC] was defined as follows: TC = DC + IC

Data of direct per-patient cost of hospitalization were provided by the hospital's financial sector and were adjusted for 2017 payment rate. Indirect costs were calculated considering the cost of patient and/or caregiver productivity loss, multiplying the number of days by the average job salary. The mean national salary rate for jobs was obtained from the General Register of Employees and Unemployment (GREU - CAGED) of the Brazilian Ministry of Labor and Employment. The amounts in Brazilian Real (BRL) were converted into US dollars (USD), being 1USD = 3.18 BRL.

Statistical analysis

Statistical analysis was performed for demographic and clinical variables and results were presented as frequencies and percentages, means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Patient characteristics were compared between the two groups (adults vs elderly patients), as were variables related to pneumococcal pneumonia, comorbidities, hospital length of stay, ICU admission and outcomes. The Kaplan-Meier method was used to determine associations between age groups and survival. Comparisons were performed with chi-square or Fisher's exact tests for qualitative variables, and Student's t-test for quantitative variables. Multivariate analyses were reported as odds ratios (ORs) and 95% confidence intervals (CIs), considering the younger patients (age < 65 years) as the reference group. The creation of the statistical model was performed through logistic regression with the Backward for Wald method. The final model was created with the categorization of the individuals for in-hospital death and pneumococcal bacteremia, being observed the evaluation on the general performance, that is, the variation occurred in the odds ratio log of the model independent variables by the values of Cox & Snell R square (R-adjusted). A P value <0.05 was considered statistically significant. All the statistical analysis was performed using the R software version 3.3.3 for Windows.

RESULTS

During the study period, 186 patients with PP or BPP criteria were included. Of these, 127 (between 18 and 64 years old) were adults and 59 were elderly (65 years or older). Mean age for adults was 46 ± 11.5 years, and for the elderly 70 ± 4.8 years, mainly

dependent or low-income patients. Table 1 summarizes the baseline characteristics of all patients stratified by age.

The BPP affected 20% of the selected patients, with no difference between the two groups ($p = 0.86$). Comorbidities such as chronic heart, respiratory diseases, and immunosuppression were more prevalent in the elderly population ($p < 0.01$), while chronic liver or renal diseases and presence of HIV infection were more frequent in the adult population ($p < 0.01$). Chronic neurological disease, diabetes mellitus, smoking, and alcoholism had no impact among age groups.

A total of 25.6% patients younger than 65 years and 28.8% of elderly patients were admitted to the ICU and the mean length of stay was 3 days for both groups. The mean total hospital length of stay was 10 days for adults and 14 days for the elderly. During the study period, 37 patients died (19.9%), being 18.1% adults and 23.7% elderly. The Kaplan-Meier curve (Figure 1) shows the patient's survival curve according to age and length of hospital stay. Both groups have similar results until the twentieth day of hospitalization, after which there was a decrease in survival of elderly.

Regarding the risk of in-hospital death due to pneumococcal pneumonia, ICU admission contributed to higher mortality rate (OR 156.3, 95% CI 34.1-715.9, $p < 0.001$) with no difference in mortality between groups (OR 1.41, 95% CI 0.66-2.98, $p = 0.40$), as shown in table 2. Among comorbidities evaluated for bacteremic pneumococcal pneumonia, only chronic respiratory disease had an impact (adjusted OR 3.07, 95% CI 1.23-7.65, $p < 0.01$) in both age groups (table 3).

The costs related to PP and BPP are described in table 4. The average amount spent annually on direct and indirect costs was USD 28,188 for the population aged <65 years and USD 16,350 for the population ≥ 65 years. During the 7- year period, the total annual direct cost for pneumococcal pneumonia was of USD 24,458 for adults and USD 14,676 for the elderly. The costs per patient hospitalized, considering direct and indirect costs, were USD 1,746 for adults and USD 2,119 for the elderly. Finally, the Brazilian Ministry of Health spent on direct costs for pneumococcal pneumonia USD 1,515 for each hospitalized adult and USD 1,902 per patient aged ≥ 65 years.

Table 1 - Characteristics of patients with pneumococcal pneumonia

Characteristic	Age <65 yrs (n= 127)	Age ≥65 yrs (n= 59)	*P value*
Male sex, n (%)	78 (62,4)	40 (67,8)	0,40
Age (years), mean (SD)	46 (36-55)	70 (67-72)	0,001
Average income, n (%)			0,30
Dependent	38 (30)	17 (29)	
Low	80 (63)	42 (71)	
Intermediate	9 (7)	0 (0)	
High	0 (0)	0 (0)	
Pneumonia, n (%)			0,86
Pneumococcal pneumonia	102 (80)	48 (81)	
Bacteremic Pneumococcal Pneumonia	25 (20)	11 (19)	
Comorbidities, n (%)			
Chronic Heart Disease	36 (28,3)	31 (52,5)	<0,01
Chronic Respiratory Disease	47 (37,0)	35 (59,3)	<0,01
Chronic Liver Disease	11 (8,6)	0 (0)	<0,01
Chronic Renal Disease	11 (8,6)	3 (5,0)	<0,01
HIV	29 (22,8)	0 (0)	<0,01
Chronic Neurological Disease	8 (6,3)	5 (8,5)	0,60
Immunosuppressed Disease	19 (14,9)	17 (28,8)	0,02
Diabetes Mellitus	6 (4,7)	4 (6,7)	0,50
Smoking	46 (36,2)	24 (40,6)	0,60
Alcoholism	25 (19,7)	10 (16,9)	0,60
ICU admission, n (%)	33 (25,6)	17 (28,8)	0,10
Mean Leigh of Stay (days)			
Total	10 (7-15)	14 (5-22)	0,46
ICU	3 (0-5)	2 (0-3)	0,40
Death, n (%)	23 (18,1)	14 (23,7)	0,34

SD: Standard deviation, HIV: Human Immunodeficiency Virus, ICU: Intensive care unit

Table 2 - Multivariate logistic regression analysis to predict hospital mortality associated with pneumococcal pneumonia.

Risk factors	OR	95% CI	*P value*
Age ≥ 65 yrs	1,41	0,66-2,98	0,40
Chronic respiratory disease	0,40	0,18-0,88	0,02
Chronic heart disease	1,10	0,52-2,32	0,80
Chronic liver disease	1,56	0,39-6,20	0,50
Chronic renal disease	2,43	0,76-7,74	0,15
HIV	0,60	0,20-1,85	0,35
Chronic neurological disease	1,89	0,55-6,50	0,31
Immunosuppression	0,97	0,39-2,52	0,94
Smoking	1,17	0,56-2,43	0,70
Alcoholism	1,52	0,60-3,60	0,35
Diabetes Mellitus	0,43	0,05-3,52	0,40
Bacteremic Pneumonia	0,57	0,25-1,32	0,20
ICU Mortality	156,3	34,1 – 715,9	<0.001

HIV: Human Immunodeficiency Virus, ICU: Intensive care unit

Table 3 - Multivariate logistic regression analysis to predict risk factors associated bacteremic pneumococcal pneumonia

Risk factors	adj. OR	95% CI	*P value*
Age ≥ 65 yrs	0,77	0,32-1,90	0,58
Chronic respiratory disease	3,07	1,23-7,65	0,01
Chronic heart disease	0,88	0,36-2,16	0,77
Chronic liver disease	0,76	0,16-3,23	0,68
HIV	1,16	0,37-3,64	0,80
Chronic neurological disease	1,87	0,35-9,89	0,43
Immunosuppression	2,55	0,80-8,18	0,09
Diabetes Melittus	0,60	0,13-2,81	0,53

HIV: Human Immunodeficiency Virus

Table 4 - Costs related to hospitalization for pneumococcal pneumonia

Costs	Age < 65 yrs	Age ≥ 65 yrs
Direct cost *per capita*	USD 1,515	USD 1,902
Indirect cost *per capita*	USD 231	USD 216
Total cost *per capita*	USD 1,746	USD 2,119
Total Annual Cost	USD 28,188	USD 16,350

DISCUSSION

The pneumococcal disease has a high incidence in both the adult and the elderly population, with a significant impact on direct and indirect costs to the public health system. Although PP mainly affects the population with comorbidities, there was no observed difference in mortality between the two groups. Patients with chronic respiratory disease were at higher risk for bacteremic pneumonia, however with no higher mortality.

Comparison with previous studies

Studies report the elderly as a risk group for PP mortality. Our study population was stratified into the adult group (18 to 64 years old) and the elderly group (≥65 years) and no statistical difference for in-hospital mortality between the two groups was observed, demonstrating the importance of this disease in all age groups of adult patients, which differs from the 2015 US surveillance report that describes higher cases and deaths from pneumococcal disease in patients over 65 years, with progressive increase of mortality in patients over 75 years of age.[10] In a study conducted in 2017, elderly patients had higher 30-day mortality (OR 6.83; CI 95% 1.22-38.22; p = 0.028) and this outcome may be related to immunosenescence, since they were healthy and functional elderly people. [17] The presence of chronic diseases influences both the chance of acquiring the infection due to changes in immune response, as well as the severity of the disease and its outcome. Patients with comorbidities have a high mortality rate related to pneumococcal disease in the short (30 days) and long-term (1 year) period. The comorbidities associated with PP are chronic heart, respiratory and liver diseases, acute or chronic renal failure, immunodepression, institutionalized patients with chronic neurological diseases, patients living with HIV, diabetes mellitus, smoking, and alcoholism. [18-20]

Pneumonia increases the body's oxygen demand and the release of inflammatory cytokines, causing increased thrombogenesis and heart disease. These factors may predispose to acute cardiac events concomitant with infection, increasing mortality. In the present study, heart disease occurred in 52.5% of elderly patients (p <0.01) and did not have an impact on mortality in both groups (OR 1.1, CI 95% 0.52-2.32, p = 0.8). Musher et al. demonstrated that 19.4% of patients admitted with PP had more than one cardiac event during hospitalization.[21] According to Corrales-Medina et al., patients with heart disease account for a quarter of patients with CAP and have 60% risk for 30-day

mortality, especially if there is heart failure (OR 4.3), arrhythmias (OR 1.8) or coronary disease (OR 1.5).[22]

Torres and colleagues, in their review of risk factors for pneumococcal disease, showed that chronic lung disease was an independent risk factor for the pneumococcal CAP, especially in the elderly. [18] COPD and bronchial asthma were the most prevalent comorbidities found in both groups of our studied population with increased risk for bacteremic pneumonia (adjusted OR 3.07, 95% CI 1.23-7.65, p <0.01). Patients with COPD have lung architecture changes that predispose respiratory infections, and adults with asthma have a 12-17% attributable risk of acquiring invasive pneumococcal infections, especially if there are frequent disease exacerbations. [23-24]

The pneumococcal disease has been an important cause of morbidity in cirrhotic patients. However, in our study, only 11 patients aged <65 years had liver disease and there was no impact on mortality (OR 1.56: 95% CI 0.39-6.20, p = 0.5). A study published in 2011, showed that cirrhotic patients had a higher risk for PAC (46.3% vs. 33%, p = 0.007).[25] In a Spanish study, patients aged between 18-64 years with liver disease had an index for PP of 541/100,000 (OR 56.3, 95% CI 49.1-64.6) and patients ≥ 65 years had a PP index of 1,263/100,000 (OR 15.0, 95% CI 13.1-17.2).[26]

The chronic renal disease is an important cause of mortality worldwide, and the incidence of pneumonia in dialysis patients is 27.9/100 persons/year, with a 1-year survival rate of 0.51. [27] In our study, chronic renal failure was more prevalent in the population aged ≤64 years (p <0.01), with no impact on mortality (p = 0.15). Several studies suggest a relationship between chronic renal disease and PP, although the pathophysiological mechanisms involved are not well understood. [28]

Several studies suggest a high risk for pneumococcal disease associated with primary immunodeficiency due to B cell defects. [29] Solid tumors and hematological malignancies also predispose to infections, especially by gram-positive bacteria. [30] In the population studied, immunosuppression was more prevalent in the elderly (p <0.01). HIV infection also showed relevance as a risk factor for pneumococcal pneumonia (p <0.01) on this population. The risk of invasive pneumococcal disease is increased in patients living with HIV, especially in those with CD4 <200 cells/mm3, even with the adequate use of antiretroviral therapy. [31-32] The American rate of invasive pneumococcal disease in patients living with HIV aged 18-64 years was equivalent to 173/100,000 in 2010. [6]

There are few studies evaluating the relationship between smoking and pneumococcal disease in adults. Chun et al. published a study in 2015 on the association between passive smoking and invasive pneumococcal disease in 171 children and found no association to PP.[33] Another study conducted in 2000 found that active smoking would be a strong risk factor for invasive disease in immunocompetent adults (OR 4.1, 95% CI, 2.4 - 7.3).[34] In an Australian study, smokers were 3.7 times more likely to have an invasive disease. Despite this, tobacco use had no impact on PP or BPP among the age groups evaluated in our study.

Alcoholism has been linked to the independent risk of acquiring CAP and PP.[35] In a study of 19,000 subjects were followed for 10 years, the overall mortality attributed to PP in alcohol users was 30%, compared to non-users (17 %).[36] In our study, 25 (19.7%) adults and 10 (16.9%) elderly patients were alcohol users, with no impact on mortality during hospital stay ($p = 0.35$). Chronic neurological diseases and diabetes mellitus also had no impact on mortality. While chronic neurological diseases have a higher incidence in the elderly, diabetes mellitus has been related to PP in patients <40 years old, with an increased risk for bacteremic pneumonia (OR 1.4 to 4.6). [18]

We observed that the BPP affected 20% of the selected patients, with no difference between the age groups ($p = 0.86$), no impact on length of stay or in-hospital mortality. This incidence of BPP corresponded to previously published data in which 25-30% of patients with PP had concomitant bacteremia, and approximately 75% of all pneumococcal diseases are non-bacteremic pneumococcal pneumonia. [37] The hospital length of stay due to PP and BPP was higher for elderly patients (mean of 14 days), as well as the rate of admission to the ICU (28.8% vs. 25.6 % in adults). A study conducted in the Netherlands in 2016 had similar results, with an average length of hospital stay of 12 days. [12] Ruiz et al. identified a mortality risk in ICU of 4.2 ($p = 0.10$), however, in our study the in-hospital mortality was higher (OR of 156.3) since all 37 patients died in the ICU.

Analyzing costs related to PP and BPP, the average amount spent annually on direct and indirect costs was higher in the population aged <65 years (USD 28,188 vs USD 16,350), justified by the number of adults enrolled and the related indirect costs (economically active population). In the per capita analysis, however, the cost was higher in the elderly population (USD 2,119 vs USD 1,746), due to direct costs of prolonged hospitalization and incidence of comorbidities. A European study showed an average of direct costs community-acquired pneumonia (CAP) treatment of € 196 in the outpatient setting and €

1,553 in the hospital setting, and a Japanese study demonstrated an average inpatient treatment of USD 4,851. [38-39]

In conclusion, strategies should be encouraged to reduce PP incidence, avoiding the high total cost and in-hospital mortality associated with pneumococcal disease in the adult population. Thus, vaccines appear as an important and effective intervention to be performed in the adult population with comorbidities. [40] Future studies on cost-effectiveness and cost-benefit models are necessary to infer the economic impact that the immunization of the entire adult population with pneumococcal conjugate vaccine 13 (PCV13) and pneumococcal polysaccharide vaccine 23 (PPV23) could represent for the public or private health systems.

Our study had limitations such as lack of data on 30-day outpatient mortality, association with antimicrobial resistance and pneumococcal serotypes, and information related to influenza vaccine status. Despite being a monocentric study, the results point out costs impact and mortality in the adult population. Preventive measures should be encouraged in different age groups, and cost-effectiveness studies should be conducted to assess the actual impact on the public health system of anti-pneumococcal vaccination for the adult population, regardless of comorbidities.

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- Competing interests:

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- Ethical approval:

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REFERENCES

1. Quan TP, Fawcett NJ, Wrightson JM, et al. Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998–2014. *Thorax* 2016;71(6):535-42.
2. Medeiros MIC, Almeida SCG, Guerra MLLS, et al. Distribution of *Streptococcus pneumoniae* serotypes in the northeast macro-region of São Paulo state/Brazil after the introduction of conjugate vaccine. *BMC Infect Dis* 2017;17:590.
3. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med* 2014; 371:1619-28.
4. Kyaw MH, Rose CE Jr, Fry AM, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. *J Infect Dis* 2005;192: 377-86.
5. Soárez PC, Sartori AMC, Freitas AC, et al. Cost-Effectiveness Analysis of Universal Vaccination of Adults Aged 60 Years with 23-Valent Pneumococcal Polysaccharide Vaccine versus Current Practice in Brazil. *Plos one* 2015;10(6): e0130217.
6. Lynch JP III, Zhanel GG. *Streptococcus pneumoniae*: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. *Curr Opin Pulm Med* 2010;16:217–25.
7. Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. *Thorax* 2013;68:171-6.
8. Rozenbaum MH, Mangen MJ, Huijts SM, et al. Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: A nationwide retrospective claims database analysis. *Vaccine* 2015;33(28):3193-9.
9. Adamuz J, Viasus D, Campreciós-Rodríguez P, et al. A prospective cohort study of healthcare visits and rehospitalizations after discharge of patients with community-acquired pneumonia. *Respirology* 2011;16(7):1119–26.
10. Centers for Disease Control and Prevention. 2015. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, *Streptococcus pneumoniae.* http://www.cdc.gov/abcs/reports-findings/survreports/spneu15.pdf (accessed 09 Apr 2018)
11. Ruiz LA, España PP, Gómez A, et al. Age-related differences in management and outcomes in hospitalized healthy and well-functioning bacteremic pneumococcal pneumonia patients: a cohort study. *BMC Geriatrics* 2017;17:130.
12. European Centre for Disease Prevention and Control. Invasive pneumococcal disease. In: ECDC. Annual epidemiological report for 2015. Stockholm: ECDC;

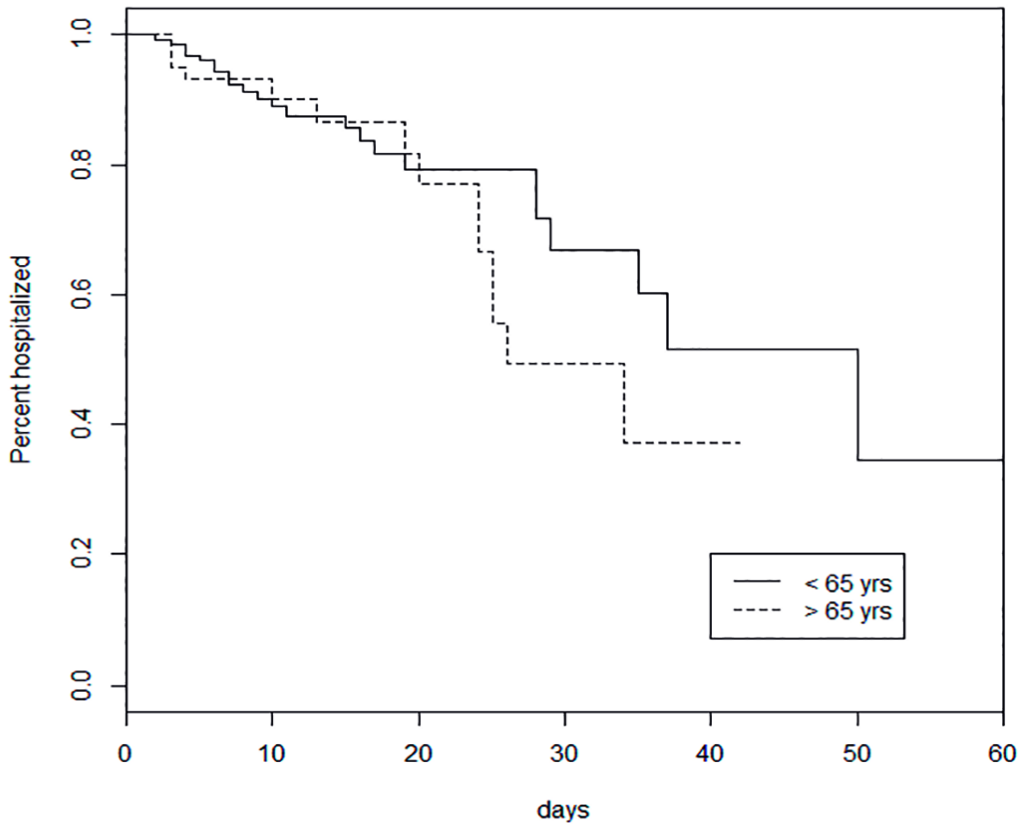
https://ecdc.europa.eu/en/publications-data/invasive-pneumococcal-disease-annual-epidemiological-report-2015 (accessed 09 Apr 2018)

13. Vissink CE, Huijts SM, Argine de Vit G, et al. Hospitalization costs for community acquired pneumonia in Dutch elderly: an observational study. *BMC Infect Dis* 2016; 16:466.
14. Spoorenberg S, Bos WJ, Heijligenberg R, et al. Microbial aetiology, outcomes, and costs of hospitalisation for community-acquired pneumonia; an observational analysis. *BMC Infect Dis* 2014;14(1): 335.
15. Song JY, Choi JY, Lee JS, et al. Clinical and economic burden of invasive pneumococcal disease in adults: a multicenter hospital-based study. *BMC Infect Dis*. 2013;13:202.
16. Giglioa N, Miconeb P, Gentilea A. The pharmacoeconomics of pneumococcal conjugate vaccines in Latin America. *Vaccine* 2011;14;29(3):C35-42.
17. Corrêa RA, José BPS, Malta DC, et al. Carga de doença por infecções do trato respiratório inferior no Brasil, 1990 a 2015: estimativas do estudo Global Burden of Disease 2015. *Rev. bras. epidemiol* 2017; 20(1):171-81.
18. Torres A, Blasi F, Dartois N, et al. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax* 2015;70(10):984-9.
19. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013;68:1057-65.
20. Adamuz J, Viasus D, Jimenez-Martinez E, et al. Incidence, timing and risk factors associated with 1-year mortality after hospitalization for community-acquired pneumonia. *J Infect* 2014;68:534-41.
21. Musher DM, Rueda AM, Kaka AS, et al. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis* 2007; 45:158.
22. Corrales-Medina VF, Musher DM, Wells GA, et al. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation* 2012;125: 773–81.
23. Froes F, Roche N, Blasi F. Pneumococcal vaccination and chronic respiratory diseases. *Int J Chron Obstruct Pulmon Dis* 2017;12:3457-68.
24. Dodd KE, Mazurek JM. Pneumococcal Vaccination Among Adults With Work-related Asthma. *Am J Prev Med.* 2017; 53(6): 799-809.

25. Viasus D, Garcia-Vidal C, Castellote J, Community-acquired pneumonia in patients with liver cirrhosis: clinical features, outcomes, and usefulness of severity scores. *Medicine*, 2011; 90(2):110-18.
26. Gil-Prieto R, Pascual-Garcia R, Walter S, et al. Risk of hospitalization due to pneumococcal disease in adults in Spain. The CORIENNE study. *Human Vaccines & Immunotherapeutics*. 2016;12(7):1900-05.
27. Vandecasteele SJ, Ombelet S, Blumental S, et al. The ABC of pneumococcal infections and vaccination in patients with chronic kidney disease. *Clinical Kidney Journal* 2015;8(3):318-24.
28. Huang ST, Lin CL, Chang YJ, et al. Pneumococcal pneumonia infection is associated with end-stage renal disease in adult hospitalized patients. *Kidney International* 2014;86(5):1023-30.
29. Picard C, Puel A, Bustamante J, et al. Primary immunodeficiencies associated with pneumococcal disease. *Curr Opin Allergy Clin Immunol* 2003;3:451.
30. Cardoso NT, Santos BA, Barbosa AV, et al. Serotypes, antimicrobial resistance and genotypes of *Streptococcus pneumoniae* associated with infections in cancer patients in Brazil. *Diagn Microbiol Infect Dis* 2017;87(3):281-5.
31. Marcus JL, Baxter R, Leyden WA, et al. Invasive Pneumococcal Disease Among HIV-Infected and HIV-Uninfected Adults in a Large Integrated Healthcare System. *AIDS Patient Care STDS* 2016;30:463.
32. Munier AL, de Lastours V, Porcher R, et al. Risk factors for invasive pneumococcal disease in HIV infected adults in France in the highly active antiretroviral therapy era. *Int J STD AIDS* 2014; 25:1022.
33. Chun CS, Weinmann S, Riedlinger K, et al. Passive Cigarette Smoke Exposure and Other Risk Factors for Invasive Pneumococcal Disease in Children: A Case-Control Study. *The Permanente Journal* 2015;19(1): 38-43.
34. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. *N Engl J Med* 2000;342(10):681-9.
35. de Roux A, Cavalcanti M, Marcos MA, et al. Impact of alcohol abuse in the etiology and severity of community acquired pneumonia. *Chest* 2006; 129(5):1219-25.

36. Bhatty M, Pruett SB, Swiatlo E, et al. Alcohol abuse and *Streptococcus pneumoniae* infections: Consideration of Virulence Factors and Impaired Immune Responses. *Alcohol (Fayetteville, NY)* 2011;45(6):523-39.
37. Isturiz RE, Hall-Murray C, McLaughlin JM, et al. Pneumococcal conjugate vaccine use for the prevention of pneumococcal disease in adults <50 Years of Age. *Expert Review of Vaccines* 2017; 17: 45-55.
38. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012; 67:71-9.
39. Konomura K, Nagai H, Akazawa M. Economic burden of community-acquired pneumonia among elderly patients: a Japanese perspective. *Pneumonia* 2017;9:19.
40. Morton JB, Morrill HJ, La Plante KL, et al. Risk stacking of pneumococcal vaccination indications increases mortality in unvaccinated adults with Streptococcus pneumoniae infections. *Vaccine* 2017; 23;35(13):1692-97.

Figure 1. Kaplan-Meier curve on hospital survival analysis of adult (<65 years) and elderly (≥ 65 years) patients with pneumococcal pneumonia.



4 CONSIDERAÇÕES FINAIS E PERSPECTIVAS

A doença pneumocócica tem alta incidência tanto na população adulta, quanto idosa, com impacto expressivo em custos diretos e indiretos para o sistema público de saúde brasileiro. Apesar de incidir principalmente na população com comorbidades, não houve diferença de mortalidade entre os grupos de pacientes estudados. Na análise de sobrevida hospitalar, ambas as faixas etárias possuem resultados semelhantes até o vigésimo dia de internação, sendo que após esse período, há uma diminuição da sobrevida em idosos. Não houve diferença em mortalidade hospitalar por doença pneumocócica quando há apenas pneumonia ou se associada à bacteremia, porém, houve mais pneumonia bacterêmica em pacientes com pneumopatia crônica. Assim, medidas preventivas devem ser incentivadas em pacientes pneumopatas, e estudos de custo-efetividade devem ser realizados para avaliar o real impacto no sistema público de saúde da vacinação anti-pneumocócica para toda a população adulta, independente de comorbidades e de faixa etária.

Perspectivas futuras:

- Avaliar o impacto da doença pneumocócica em população adulta vacinada;
- Identificar as comorbidades associadas a internações hospitalares e mortalidade na população de crianças e adolescentes com doença pneumocócica bacterêmica e que foram vacinados;
- Analisar a custo-efetividade da vacina anti-pneumocócica conjugada 13 (VCP 13) na população adulta através de modelos matemáticos.