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Drug science, Department of Drug Sciences, University of Pavia, Pavia, Italy, Italy

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Professor Colombo is an adjunct Professor at the University of Pavia - School of Pharmacy, and brings to his work a notable combination of academic theory and analytical practice. His experience in independent consultancy has seen him perform technological assessments and economic evaluations for pharmaceutical companies and Italian governmental authorities alike, while maintaining a highly active research portfolio. Much of his recent research has focused on the economic evaluations of Drugs and Medical Device,



Dr Colombo

showcasing his ability to bring together theoretical models with their social and business applications. Since graduating from the Catholic University of Milan, Professor Colombo has authored or co-authored about 150 scientific papers and three books in the fields of health economics and pharmacoeconomics research, as well as sitting on the editorial boards of several scientific peer review journals.

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Xing Lin Feng is an Associate Professor at the School of Public Health, Peking University. Dr. Feng achieved his PhD degree in Social Medicine and Health Service Management in School of Public Health, Peking University in 2008. Dr. Feng's research area is health policy and system research, and his main research interests are to link health system strengthening efforts to the promotion of maternal and child health, and the prevention and control of non-communicable diseases.



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School of Health and Environmental Studies, Hamdan Bin Mohammed Smart University, United Arab Emirates

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Professor Samer Hamidi is a professor at Hamdan Bin Mohammed Smart University, UAE. He has 20 years of teaching and research experience in the fields of public health, health management, and online learning. He designed, developed, and delivered courses at the bachelor, master, and doctoral levels. He also led the accreditation of public health and health management programs. He is an internationally recognized scholar, an associate editor, editorial board member, and peer reviewer for several

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international journals. He co-authored 65 peer-reviewed academic papers published in well-regarded journals. His research activities focus on issues related to health systems, burden of disease, health finance, global health, and examination of quality and efficiency in the healthcare sector.



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Dean Smith is Dean of the School of Public Health at Louisiana State University Health Sciences Center in New Orleans and Professor of Health Policy and Systems Management. He is also Professor Emeritus at the University of Michigan School of Public Health where he had previously served as Senior Associate Dean for Administration and Professor of Health Management & Policy. Professor Smith was also a resident consulting economist at Pfizer, President/CEO of an HMO and a consultant to many pharmaceutical companies and health plans. Professor Smith is committed to a line of teaching, research and service that provides a better understanding of the financial aspects of



Prof. Dr. Smith

working with and working in health care delivery and financing organizations. He has published more than one hundred and thirty scientific papers and supervised more than fifty doctoral dissertations. He is editor-in-chief of the Journal of Health Administration Education and serves on the editorial boards of other journals. Professor Smith's research has been funded by the National Institutes of Health, the Robert Wood Johnson Foundation and other entities. Currently funded research includes analyses of programs to reduce the economic burden of asthma, sponsored by the MacArthur Foundation and the Merck Childhood Asthma Network. He received his bachelor's degree in economics from the University of Michigan and his doctorate in economics from Texas A&M University.

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Healthcare Costs of Potential Glucocorticoid-Associated Adverse Events in Patients with Giant Cell Arteritis

Best JH, Kong AM, Smith DM, Abbass I, Michalska M

[ClinicoEconomics and Outcomes Research 2019](#), 11:799-807

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North American cost analysis of brand name versus generic drugs for the treatment of glaucoma

Malvankar-Mehta MS, Feng L, Hutnik CML

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Canadian Medication Cost Savings Associated with Combinatorial Pharmacogenomic Guidance for Psychiatric Medications

Tanner JA, Brown LC, Yu K, Li J, Dechairo BM

[ClinicoEconomics and Outcomes Research 2019](#), 11:779-787

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Cost-Effectiveness Analysis of the Adjunctive Therapy of Ivabradine for the Treatment of Heart Failure with Reduced Ejection Fraction

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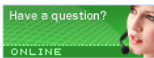
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Cevey M, Calvo-Alén J, Crespo C, Robles-Marhuenda A, Smolen L, Cortés-Hernández J

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Seetasith A, Greene M, Hartry A, Burudpakdee C

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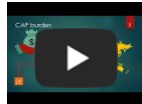
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Cost-Effectiveness Of Culture-Based Versus Empirical Antibiotic Treatment For Hospitalized Adults With Community-Acquired Pneumonia In Indonesia: A Real-World Patient-Database Study

Purba AKR, Ascobat P, Muchtar A, Wulandari L, Dik JW, d'Arqom A, Postma MJ

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Comparison Of Methods To Estimate Disease-Related Cost And Healthcare Resource Utilization For Autoimmune Diseases In Administrative Claims Databases

Schroeder KM, Gelwicks S, Naegeli AN, Heaton PC

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The Burden, Future Trends, And Economic Impact Of Lung Cancer In Saudi Arabia

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Comparative Cost Analysis Of Intravenous And Subcutaneous Administration Of Rituximab In Lymphoma Patients

Delgado Sánchez O, Gutiérrez A, do Pazo F, Ginés J, Martorell C, Boyeras B, Bento L, Garcia-Recio M, Sampol A

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Cost-Effectiveness Of Midostaurin In The Treatment Of Acute Myeloid Leukemia With The FLT3 Mutation In Spain

Arenaza A, Diez R, Esteve J, Di Nicolantonio R, Gostkorszewicz J, Martínez C, Martínez Llinàs D, Martínez-Lopez J, Montesinos P, Moure-Fernández A, Sierra J, Vinent JL

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Budget Impact Of Eltrombopag As First-Line Treatment For Severe Aplastic Anemia In The United States

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ORIGINAL RESEARCH

Budget Impact Of Including Avelumab As A Second-Line Treatment For Locally Advanced Or Metastatic Urothelial Cancer In The United States: Commercial And Medicare Payer Perspectives

Kongnakorn T, Bharmal M, Kearney M, Phatak H, Benedict A, Bhanegaonkar A, Galsky M

[ClinicoEconomics and Outcomes Research 2019](#), 11:659-672

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Alinia C, Davoodi Lahijan J

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Cost-Effectiveness Of The SQ® Grass SLIT-Tablet In Children With Allergic Rhinitis: A German Payer Perspective

Vogelberg C, Hamelmann E, Wahn U, Domdey A, Pollock RF, Grand TS

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A Cost-Effectiveness Analysis Of An Adenocarcinoma Risk Prediction Multi-Biomarker Assay For Patients With Barrett's Esophagus

Hao J, Critchley-Thorne R, Diehl DL, Snyder SR

[ClinicoEconomics and Outcomes Research 2019](#), 11:623-635

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Estimation Of The Quality Of Life Benefits Associated With Treatment For Spinal Muscular Atrophy

Lloyd AJ, Thompson R, Gallop K, Teynor M

[ClinicoEconomics and Outcomes Research 2019](#), 11:615-622

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Value For Money In The Treatment Of Patients With Type 2 Diabetes Mellitus: Assessing The Long-Term Cost-Effectiveness Of IDegLira Versus iGlarLixi In Italy

Pöhlmann J, Montagnoli R, Lastoria G, Parekh W, Markert M, Hunt B

[ClinicoEconomics and Outcomes Research 2019](#), 11:605-614

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PERSPECTIVES

Management Of Glaucoma In Developing Countries: Challenges And Opportunities For Improvement

Delgado MF, Abdelrahman AM, Terahi M, Miro Quesada Woll JJ, Gil-Carrasco F, Cook C, Benharbit M, Boisseau S, Chung E, Hadjiat Y, Gomes JAP

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Health economic evaluation of peritoneal dialysis based on cost-effectiveness in Japan: a preliminary study

Takura T, Hiramatsu M, Nakamoto H, Kuragano T, Minakuchi J, Ishida H, Nakayama M, Takahashi S, Kawanishi H

[ClinicoEconomics and Outcomes Research 2019](#), 11:579-590

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Social Return On Investment For Patient Treated By Continuous Ambulatory Peritoneal Dialysis: A Case Study In Ubon Ratchathani Province, Thailand

Lophongpanit P, Tongsiri S, Thongprasert N

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Evaluating the cost and clinical effectiveness of long-acting, injectable aripiprazole and paliperidone palmitate once a month in a real-world setting [Corrigendum]

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Overall survival of glasdegib in combination with low-dose cytarabine, azacitidine, and decitabine among adult patients with previously untreated AML: comparative effectiveness using simulated treatment comparisons

Tremblay G, Westley T, Cappelleri JC, Arondekar B, Chan G, Bell TJ, Briggs A

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ORIGINAL RESEARCH

Patient and economic burdens of postherpetic neuralgia in China

Yu SY, Fan BF, Yang F, DiBonaventura M, Chen YX, Li RY, King-Concialdi K, Kudel I, Hlavacek P, Hopps M, Udall M, Sadosky A, Cappelleri JC

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Cost-consequence analysis for human recombinant growth hormone (r-hGH) treatment administered via different devices in children with growth hormone deficiency in Italy

Foo J, Maghnie M, Colao A, Vlachaki I, Colombo G

[ClinicoEconomics and Outcomes Research 2019](#), 11:525-537

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Evaluating the cost and clinical effectiveness of long-acting, injectable aripiprazole and paliperidone palmitate once a month in a real-world setting

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HTA and innovative treatments evaluation: the case of metastatic castration-resistant prostate cancer [Corrigendum]

Bretoni A, Ferrario L, Foglia E

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Characteristics and outcome of high-cost ICU patients

Aung YN, Nur AM, Ismail A, Aljunid SM

[ClinicoEconomics and Outcomes Research 2019](#), 11:505-513

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Cost-effectiveness of adding Endocuff® to standard colonoscopies for interval colorectal cancer screening

Yu TM, Tradonsky A, Tang J, Arnold RJG

[ClinicoEconomics and Outcomes Research 2019](#), 11:487-504

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A Canadian cost-effectiveness analysis of SAPIEN 3 transcatheter aortic valve implantation compared with surgery, in intermediate and high-risk severe aortic stenosis patients

Tarride JE, Luong T, Goodall G, Burke N, Blackhouse G

[ClinicoEconomics and Outcomes Research 2019](#), 11:477-486

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ORIGINAL RESEARCH

Burden of diabetes mellitus in patients with acromegaly treated with second-line pharmacotherapy in Spain

Sánchez-Cenizo L, Aller J, Martínez-Sesmero JM, Mir N, Peral C, Rubio-Rodríguez D, Rubio-Terrés C

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Cost-effectiveness and budget impact analysis of viscosupplementation with hylan G-F 20 for knee and hip osteoarthritis

Migliore A, Integlia D, Pompilio G, Di Giuseppe F, Aru C, Brown T

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Clinical and economic burden of head and neck cancer: a nationwide retrospective cohort study from France

Schernberg A, Sagaon-Teyssier L, Schwarzingler M

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Untangling the clinical and economic burden of hospitalization for cardiac amyloidosis in the United States

Quock TP, Yan T, Tieu R, D'Souza A, Broder MS

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Cost-benefit comparison of liraglutide and sitagliptin in the treatment of type 2 diabetes in Thailand

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The added burden of depression in patients with osteoarthritis in Japan

Tsuji T, Nakata K, Vietri J, Jaffe DH

[ClinicoEconomics and Outcomes Research 2019](#), 11:411-421

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REVIEW

Abatacept: from a budget impact model to cost-effectiveness analysis – data from RCT and real life

Benucci M, Damiani A, Manfredi M, Infantino M, Grossi V, Li Gobbi F

[ClinicoEconomics and Outcomes Research 2019](#), 11:405-409

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Cost-effectiveness analysis of baricitinib versus adalimumab for the treatment of moderate-to-severe rheumatoid arthritis in Spain

Schlueter M, Finn E, Díaz S, Dilla T, Inciarte-Mundo J, Fakhouri W

[ClinicoEconomics and Outcomes Research 2019](#), 11:395-403

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Heart failure hospitalization reduction and cost savings achieved by improved delivery of effective biventricular pacing: economic implications of the OLE study under the US setting

Hernández-Madrid A, Lu X, Tsintzos SI, Fagan DH, Klepfer RN, Matía R, Chung ES

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Association of tumor location with economic outcomes and air leak complications in thoracic lobectomies: results from a national hospital billing dataset

Bhora F, Ghosh SK, Kassis E, Yoo A, Ramiseti S, Johnston SS, Rehmani S, Kalsekar I

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Treatment patterns and economic outcomes in patients with juvenile idiopathic arthritis

Marshall A, Gupta K, Pazirandeh M, Bonafede M, McMorow D

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Budget impact model of avelumab in patients with metastatic merkel cell carcinoma in the US

Bharmal M, Kearney M, Zheng Y, Phatak H

[ClinicoEconomics and Outcomes Research 2019](#), 11:349-359

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An iron triangle ROI model for health care

van der Goes DN, Edwardson N, Rayamajhee V, Hollis C, Hunter D

[ClinicoEconomics and Outcomes Research 2019](#), 11:335-348

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REVIEW

Electronic referral systems in health care: a scoping review

Azamar-Alonso A, Costa AP, Huebner LA, Tarride JE

[ClinicoEconomics and Outcomes Research 2019](#), 11:325-333

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The impact of increased post-progression survival on the cost-effectiveness of interventions in oncology

Retzler J, Davies H, Jenks M, Kiff C, Taylor M

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Bretoni A, Ferrario L, Foglia E

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Cost of achieving HbA1c and weight loss treatment targets with IDegLira vs insulin glargine U100 plus insulin aspart in the USA

Billings LK, Mocarski M, Basse A, Hunt B, Valentine WJ, Jodar E

[ClinicoEconomics and Outcomes Research 2019](#), 11:271-282

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Cost-effectiveness model for a hypothetical monotherapy vs standard of care in adult patients with treatment-resistant depression

Wang ST, Anderson IM, Mitchell D, Johnson SJ, Shiozawa A

[ClinicoEconomics and Outcomes Research 2019](#), 11:257-270

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Cost-of-illness of knee osteoarthritis: potential cost savings by not undergoing arthroplasty within the first 2 years

Ong KL, Runa M, Lau E, Altman RD

[ClinicoEconomics and Outcomes Research 2019](#), 11:245-255

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Health-related quality of life outcomes, economic burden, and associated costs among diagnosed and undiagnosed depression patients in Japan

Yamabe K, Liebert R, Flores N, Pashos CL

[ClinicoEconomics and Outcomes Research 2019](#), 11:233-243

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Health-related quality of life outcomes and economic burden of inflammatory bowel disease in Japan

Yamabe K, Liebert R, Flores N, Pashos CL

[ClinicoEconomics and Outcomes Research 2019](#), 11:221-232

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Relative value assessment: characterizing the benefit of oncology therapies through diverse survival metrics from a US perspective



Macaulay R, Ahuja A, Ademisoye E, Juarez-Garcia A, Shaw JW

[ClinicoEconomics and Outcomes Research 2019](#), 11:199-219

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Reduction of direct costs in high-risk lumbar discectomy patients during the 90-day post-operative period through annular closure

Thaci B, McGirt MJ, Ammerman JM, Thomé C, Kim KD, Ament JD

[ClinicoEconomics and Outcomes Research 2019](#), 11:191-197

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Health care utilization and costs following amplified versus non-amplified molecular probe testing for symptomatic patients with suspected vulvovaginitis: a US commercial payer population

Ackerman SJ, Knight T, Wahl PM, Cartwright CP

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A cost-consequence analysis of parecoxib and opioids vs opioids alone for postoperative pain: Chinese perspective

Barra M, Remák E, Liu DD, Xie L, Abraham L, Sadosky AB

[ClinicoEconomics and Outcomes Research 2019](#), 11:169-177

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Cost-effectiveness of secukinumab compared to other biologics in the treatment of ankylosing spondylitis in Finland

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CORRIGENDUM 

Budget impact analysis of sarilumab for the treatment of rheumatoid arthritis in patients with an inadequate response to conventional synthetic DMARD or TNF inhibitor therapies [Corrigendum]

Ferrufino CP, Munakata J, Wei W, Proudfoot C, Kuznik A, Boklage SH, Chen C

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Cost-Effectiveness Of Culture-Based Versus Empirical Antibiotic Treatment For Hospitalized Adults With Community-Acquired Pneumonia In Indonesia: A Real-World Patient-Database Study

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Objective: This study analyzes the cost-effectiveness of culture-based treatment (CBT) versus empirical treatment (ET) as a guide to antibiotic selection and use in hospitalized patients with community-acquired pneumonia (CAP).

Patients and methods: A model was developed from the individual patient data of adults with CAP hospitalized at an academic hospital in Indonesia between 2014 and 2017 (ICD-10 J.18x). The directed antibiotic was assessed based on microbiological culture results in terms of the impact on hospital costs and life expectancy (LE). We conducted subgroup analyses for implementing CBT and ET in adults under 60 years, elderly patients (≥ 60 years), moderate-severe CAP (PSI class III-V) cases, and ICU patients. The model was designed with a lifetime horizon and adjusted patients' ages to the average LE of the Indonesian population with a 3% discount each for cost and LE. We applied a sensitivity analyses on 1,000 simulation cohorts to examine the economic acceptability of CBT in practice. Willingness to pay (WTP) was defined as 1 or 3 times the Indonesian GDP per capita (US\$ 3,570).

Results: CBT would effectively increase the patients' LE and be cost-saving (dominant) as well. The ET group's hospitalization cost had the greatest influence on economic outcomes. Subgroup analyses showed that CBT's dominance remained for Indonesian patients aged under 60 years or older, patients with moderate-severe CAP, and patients in the ICU. Acceptability rates of CBT over ET were 74.9% for 1xWTP and 82.8% for 3xWTP in the base case.

Conclusion: Both sputum and blood cultures provide advantages for cost-saving and LE gains for hospitalized patients with CAP. CBT is cost-effective in patients all ages, PSI class III or above patients, and ICU patients.

Keywords: microbiological culture, empirical treatment, life expectancy, cost-effectiveness, community-acquired pneumonia

Introduction

Community-acquired pneumonia (CAP) is an infectious disease with a clinical severity ranging from mild to life-threatening. CAP has high mortality rates and is costly to treat.¹ In the US in 2012, the total direct medical costs related to CAP were estimated at US\$ 7,220 to US\$ 11,443.² In European countries, the cost was estimated to be between €1,201 and €1,586 per patient. These high costs have been partially attributed to multiple antibiotic resistance.³

Established international guidelines of the British Thoracic Society (BTS), American Thoracic Society (ATS), and National Institute for Health and Care Excellence (NICE) concur that empirical treatment of CAP with antibiotics is urgent considering the elevated mortality rates, the culture timing, and unspecified results from clinical and radiology methods for determining bacterial infections.⁴⁻⁶ Additionally, abstaining from microbiological evaluation in clinical practices for empirical treatment of CAP patients potentially leads to antibiotic resistance and overuse, which indirectly contributes to hospitalization costs.⁷⁻⁹ At present, the implementation of rapid, advanced molecular microbiology methods for CAP diagnostics has largely been developed.¹⁰ The extended use of these promising novel approaches, however, remains unavailable and costly in low-middle income countries (LMICs), which carry higher burdens of the disease. Controversies surrounding the recommendation for the use of microbiology tests in mild-moderate hospitalized cases and outpatient CAP management have been described by previous research since clinical improvement could be achieved by empirical antibiotics alone.^{11,12} The evaluation of sputum cultures from respiratory samples is recommended for inpatient CAP treatment, aiming to select appropriate antibiotics and prevent further antibiotic resistance.^{4,6,13}

When immediately employed, early directed therapy after evaluating culture results is an essential strategy to prevent high rates of antibiotic resistance. The implementation of culture analysis in developing countries with a high prevalence of CAP, such as Indonesia, should be considered alongside the assessment of culture analysis impact on costs and patient life expectancy (LE). Since 2014, Indonesia has employed a new universal health coverage program, which the health ministry contracted to a single public insurance company (Badan Penyelenggara Jaminan Sosial or BPJS). The universal health coverage also involves the implementation of a national social security system in managing expenditure related to reimbursement and costing in the national healthcare system, inclusive of cost-effectiveness considerations. Hitherto, the lack of evidence for cost-effectiveness has hampered the implementation of culture analysis as a diagnostic tool guiding the management of CAP. Therefore, the culture analysis approach has rarely been adopted in hospitals or in communities. Considering the current limitations of the evidence regarding the value of culture analysis prior to empirical-based antibiotic administration in CAP patients, we performed a cost-effectiveness

analyses on the implementation of culture-based treatment (CBT) compared to empirical treatment only (ET) in hospitalized CAP patients.

Materials And Methods

Decision-Tree Model Overview

A decision-tree model was designed from individual patient data of hospitalized CAP patients in Indonesia. The model is shown in Figure 1. We built the model based on a payer perspective. The decision-tree compared two options: i) patients with empirical antibiotic treatment (ET) during hospitalization and ii) patients with CBT for whom medications were adjusted based on microbiological evaluation in terms of the culture and antimicrobial susceptibility tests. The culture analysis was conducted on samples from respiratory tracts (sputum) and blood draws. One package was produced for positive cultures demonstrating antimicrobial susceptibility after identification of the microorganisms. We assumed that the level of competencies and advances of the laboratory staff were equal in handling the specimens and reporting the results. The CBT group were treated with empirical antibiotics based on the Indonesian guidelines at 24 hrs post-admission. Thereafter, culture results were provided, and the patients were treated with the directed therapy involving a second round of antibiotics.¹⁴ The second round of antibiotics could be different from the previous empirical treatment (antibiotic change or AC) or be the same as (no antibiotic change or NC). We included in the AC group patients with negative cultures with no microorganism growth, for whom the physicians subsequently stopped the use of antibiotics. In the ET group, we assumed that the treatment using antibiotics was empirical during hospitalization. The termination states of the decision-tree for both CBT and ET were presented as recovery or death. Patients with no sputum available for culture tests were assumed to undergo empirical therapy during hospitalization, and we included such patients in the ET group. As there was no specific indication to the physician examining the culture of

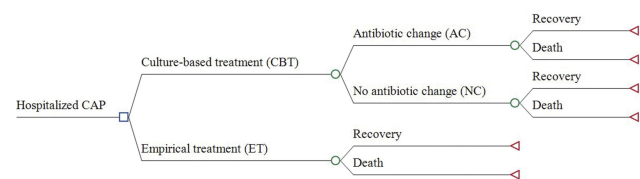


Figure 1 Decision-tree model of the culture-based treatment (CBT) and empirical treatment (ET) groups in the management of CAP.

patients' sputum, we assumed that the decision to perform ET or CBT was random.

Data Input

Individual patient data were derived from 351 retrospective records of adult patients admitted on referral to the academic hospital of Dr. Soetomo, Indonesia, from 2014 to 2017. This hospital is a central hospital for the eastern part of Indonesia and has roughly 1,514 beds. The Center of Research and Development of Dr. Soetomo Hospital, under the ethical committee, approved the study proposal with no. 480/Panke.KKE/X/2014. The committee decided that the study did not require a review in terms of patient consent since the study was performed with retrospective observational design. We obtained the clinical data from the Department of Medical Record and all relevant costs from the Finance Department, Dr. Soetomo Hospital. The data were anonymous and confidentially. The study met the agreement with Indonesian research conduct and the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subject version 2013).¹⁵

We included hospitalized CAP cases that had both blood and sputum culture with a pneumonia severity index (PSI) class from I to V. We input data of patients whose average age was 57.6 years (min-max: 19–91 years); they were predominantly males (78.3%). We performed subgroup analyses for the implementation of CBT on patients under 60 and aged ≥ 60 , PSI class III and above, and in the intensive care unit (ICU). We defined the age of 60 as the breakpoint for the aging population in

Indonesia, according to the United Nations Population Fund (UNFPA 2014).¹⁶ We addressed PSI class III in subgroup analyses since this cutoff increases the risk of 30-day mortality by ten times compared to class II.¹⁷

Calculation Of The Outcomes

We assessed the LE outcome in our model by adjusting the patients' ages to the average LE for the Indonesian population between 2010 and 2015 using data provided by the United Nations Department of Economic and Social Affairs, Population Division, 2017.¹⁸ The average LE for each group of these ages for men and women is separately presented in Figure 2. The model-time horizon was the lifetime where recovery patients would have LE greater than their ages. Considering the discount rate launched by the Health Ministry of Indonesia, we applied a 3% discount each for costs and LE.¹⁹

Hospitalization costs were valued in US\$ with 2016 adjustments. The conversion rate to an Indonesia Rupiah (IDR) was equal to US\$ 13,308.33 according to the Organization for Economic Cooperation and Development (OECD).²⁰ The costs from data were formulated as C, which is calculated from the average of the individual cost of administration (Ca), pharmacy costs (Cp), laboratory and radiology (Cl) expenses, cost of bed (Cb), and medical staff costs (Cm). The incremental cost-effectiveness ratio (ICER) in terms of total hospitalization costs and LE was calculated with the following Formula 1 below. Notably, in case the numerator was negative (cost-saving), and the denominator

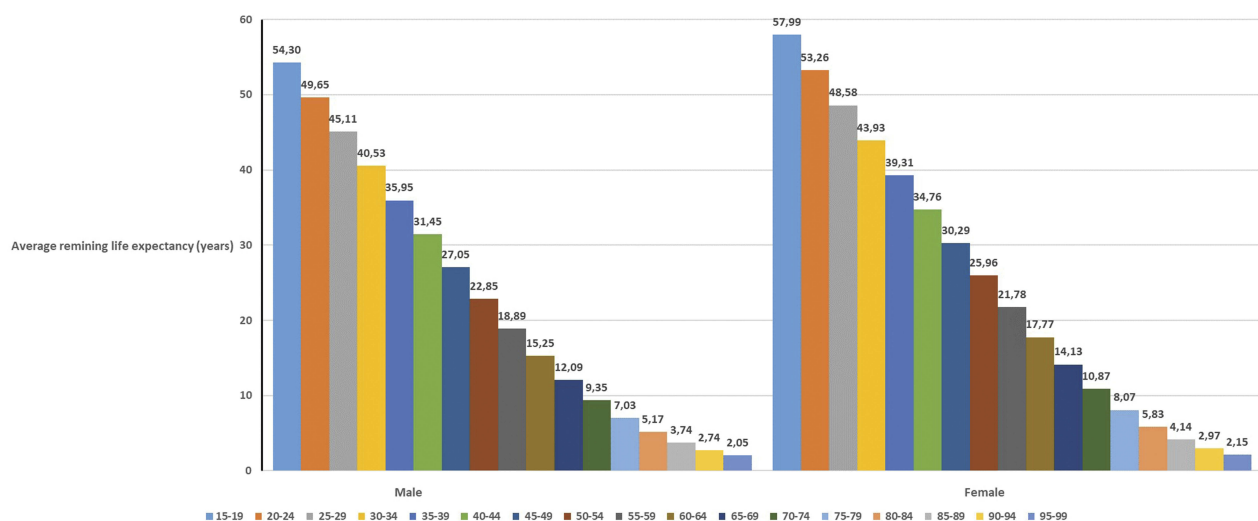


Figure 2 Average remaining life expectancy of Indonesian males and females for the patient model (calculated from the United Nations Department of Economic and Social Affairs, Population Division, 2017. World Population Prospects).¹⁷

was positive (improving LE), then the ICER indicated dominant.

Formula 1 Incremental cost-effectiveness ratio (ICER) calculation based on Ca, Cp, Cl, Cb, and Cm

$$ICER = \frac{\Delta[(\sum_i^n (C_a + C_p + C_l + C_b + C_m))P_{death\,averred}]}{\Delta[\sum_i^{n\,male} X_{LE(male)} + \sum_i^{n\,female} X_{LE(female)}]}$$

Table 1 shows the costs and LE employed gamma and exponential distribution, respectively. According to the World Health Organization – Choosing Interventions for Cost-Effectiveness criterion (WHO-CHOICE), a particular intervention is highly cost-effective when the ICER is less than the willingness-to-pay (WTP), defined as the Indonesian cost-

Table 1 The Total Hospitalization Costs And Life-Expectancy Parameters For The Decision-Tree Model

| Parameters | Mean | SD | Minimum | Maximum | Distribution |
|------------------------------|---------|---------|---------|----------|-------------------------|
| Hospitalization costs (US\$) | | | | | |
| AC group | | | | | |
| All cases | 3055.36 | 1324.61 | 1265.10 | 5879.22 | Gamma (5.320;0.002) |
| Aged < 60 | 2868.93 | 1210.45 | 1256.10 | 5612.69 | Gamma (5.618;0.002) |
| Aged ≥ 60 | 3284.81 | 1435.54 | 1270.37 | 5879.22 | Gamma (5.236;0.002) |
| PSI class ≥ III | 3125.82 | 1391.43 | 1270.37 | 5815.62 | Gamma (4.741;0.002) |
| ICU | 4180.82 | 1434.50 | 1755.12 | 5879.22 | Gamma (8.494;0.002) |
| NC group | | | | | |
| All cases | 2984.84 | 1364.44 | 1281.48 | 5725.82 | Gamma (4.786;0.002) |
| Aged < 60 | 2821.38 | 1441.64 | 1320.01 | 5679.82 | Gamma (3.830;0.001) |
| Aged ≥ 60 | 3163.16 | 1272.82 | 1281.48 | 5725.82 | Gamma (6.176;0.002) |
| PSI class ≥ III | 2932.67 | 1291.13 | 1281.48 | 5725.82 | Gamma (5.159;0.002) |
| ICU | 3392.25 | 1434.90 | 1534.96 | 5560.95 | Gamma (5.592;0.002) |
| ET group | | | | | |
| All cases | 4091.45 | 2086.94 | 1757.86 | 10723.91 | Gamma (3.844;0.001) |
| Aged < 60 | 3387.53 | 1197.75 | 1759.19 | 6661.80 | Gamma (7.999;0.002) |
| Aged ≥ 60 | 6992.35 | 1875.02 | 1770.64 | 10411.34 | Gamma (13.907;0.002) |
| PSI class ≥ III | 4092.31 | 2158.37 | 1757.86 | 10723.91 | Gamma (3.595;0.001) |
| ICU | 5666.88 | 2235.09 | 1769.25 | 10411.34 | Gamma (6.428;0.001) |
| Life-expectancy (years) | | | | | |
| AC group | | | | | |
| All cases | 22.11 | 12.07 | 3.47 | 53.26 | Exponential (0.5;22.11) |
| Aged < 60 | 28.97 | 9.34 | 18.89 | 53.26 | Exponential () |
| Aged ≥ 60 | 10.05 | 4.34 | 3.47 | 17.77 | Exponential (0.5;10.05) |
| PSI class ≥ III | 16.43 | 9.04 | 3.74 | 43.93 | Exponential (0.5;16.43) |
| ICU | 16.28 | 7.70 | 7.03 | 27.05 | Exponential (0.5;16.28) |
| NC group | | | | | |
| All cases | 22.80 | 12.33 | 3.74 | 49.65 | Exponential (0.5;22.80) |
| Aged < 60 | 29.63 | 9.60 | 18.89 | 49.65 | Exponential (0.5;29.63) |
| Aged ≥ 60 | 10.67 | 5.16 | 3.74 | 17.77 | Exponential (0.5;10.67) |
| PSI class ≥ III | 18.43 | 11.24 | 3.74 | 40.53 | Exponential (0.5;18.43) |
| ICU | 25.17 | 8.70 | 7.77 | 39.31 | Exponential (0.5;25.17) |
| ET group | | | | | |
| All cases | 20.31 | 10.71 | 3.74 | 57.99 | Exponential (0.5;20.31) |
| Aged < 60 | 27.68 | 9.23 | 18.89 | 57.99 | Exponential (0.5;27.68) |
| Aged ≥ 60 | 9.27 | 3.99 | 3.74 | 17.77 | Exponential (0.5;9.27) |
| PSI class ≥ III | 15.97 | 7.41 | 3.74 | 40.53 | Exponential (0.5;15.97) |
| ICU | 16.76 | 7.14 | 3.47 | 30.29 | Exponential (0.5;16.76) |

Abbreviations: Group AC, antibiotic change after culture; group NC, no antibiotic change after culture; group ET, empirical antibiotics only.

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effectiveness threshold of gross domestic product (GDP) per capita. If the ICER is between 1 and 3 times the GDP per capita, then the intervention is cost-effective.²¹ This definition was also applied in a previous study which was performed in Indonesia.²² For these thresholds, we applied the Indonesian GDP per capita in 2016 at US\$ 3,570.²³

Sensitivity Analyses

We performed one-way tornado sensitivity analyses using TreeAge Pro 2019 to address the robustness of the model ICERs on the changes of the upper and lower limits of the parameter values. The parameters included in the test were costs and the probability of death being averted. The outcome of LE was conclusive as it was based on the data presented by WHO for the Indonesian population.¹⁸ We also conducted random probabilistic sensitivity analyses using a Monte Carlo simulation with 1,000 random cohorts on the respective corresponding distributions. We addressed a cost-effectiveness acceptability curve to draw relationships between ICER and the Indonesian affordability threshold. Indeed a relationship between the probabilistic sensitivity analysis (PSA) and univariate analysis exists in terms of input. Notably, we used the range for the input in the PSA and in the univariate analysis.

Results

Baseline Characteristic Of The Patients

Concerning the change of antibiotics after culture analysis among patients in the CBT group, we determined that the AC and NC probabilities were 55.8% and 44.2%, respectively. The probability of antibiotic changes was based on microbiological evaluations and was not influenced by age or severity. This was subsequently analyzed with beta distributions. Patients' baseline characteristics of the patients and the probabilities of antibiotic changes and deaths being averted in the AC, NC, and ET groups are presented in Table 2.

Cost-Effectiveness Analyses

The results of cost-effectiveness analyses are shown in Table 3. The implementation of CBT over ET from a payer perspective was dominant, where CBT was cost-saving (US\$ 1,066,885) and improved LE (247 years) in all cases. In subgroup analyses, CBT was the most cost-saving, with an incremental cost of US\$ 3,828,006 for adults 60 years or older. Moreover, in the elderly group (aged ≥ 60), in terms of health effects, it was found that

Table 2 Baseline Variables And Probabilities For The Inputs On The Decision-Tree Model And Univariate Analysis From Patient Data

| Variable | Value | Distribution |
|--|------------|----------------|
| Baseline (N=351) | | |
| Age in years, mean (SD) | 57.6(15.2) | |
| Male, n (%) | 275(78.3) | |
| Aged ≥ 60 , n (%) | 109(30.1) | |
| PSI class \geq III, n (%) | 208(59.3) | |
| ICU, n (%) | 85(24.2) | |
| Probability of antibiotic changes | | |
| Probability of antibiotic change after culture (AC) | 0.558 | Beta (87, 69) |
| Probability of no-antibiotic change after culture (NC) | 0.442 | Beta (69, 87) |
| Death averted in the AC group | | |
| All cases | 0.793 | Beta (69, 18) |
| Aged < 60 | 0.917 | Beta (44, 4) |
| Aged ≥ 60 | 0.641 | Beta (25, 14) |
| PSI class \geq III | 0.769 | Beta (40, 12) |
| ICU | 0.667 | Beta (8, 4) |
| Death averted in the NC group | | |
| All cases | 0.725 | Beta (50, 19) |
| Aged < 60 | 0.889 | Beta (32, 4) |
| Aged ≥ 60 | 0.546 | Beta (18, 15) |
| PSI class \geq III | 0.718 | Beta (28, 11) |
| ICU | 0.556 | Beta (5, 4) |
| Death averted in the ET group | | |
| All cases | 0.579 | Beta (133, 82) |
| Aged < 60 | 0.577 | Beta (60, 44) |
| Aged ≥ 60 | 0.270 | Beta (10, 27) |
| PSI class \geq III | 0.581 | Beta (68, 49) |
| ICU | 0.391 | Beta (25, 39) |

Abbreviations: Group AC, antibiotic change after culture; group NC, no antibiotic change after culture; group ET, empirical antibiotics only.

637 life-years were saved by CBT versus ET. Even in the other categorizations, CBT performed better for both hospitalization costs and LE outcomes for patients with PSI class \geq III or ICU patients, and the cost-effectiveness outcomes were cost-saving (dominant) compared to ET.

Univariate And Probabilistic Sensitivity Analyses

Hospitalization costs for the ET group are shown on the top of the Tornado diagrams (Figure 3), which indicate that they had the strongest effect on the ICERs out of all parameters. When hospitalization costs for the ET group increased, the ICERs decrease. In contrast, when

Table 3 Cost-Effectiveness Ratio For ET Versus CBT In 1,000 Patients With CAP

| Group | Cost (US\$) | LE (Years) | Incremental Costs (US\$) | Incremental LE (Years) | CEA Outcomes |
|-----------------|-------------|------------|--------------------------|------------------------|--------------|
| All cases | | | | | |
| ET | 4,074,326 | 1,252 | Reference | Reference | Dominant |
| CBT | 3,007,441 | 1,499 | -1,066,885 | 247 | |
| Aged < 60 | | | | | |
| ET | 3,456,992 | 1,118 | Reference | Reference | Dominant |
| CBT | 2,889,390 | 1,861 | -567,602 | 742 | |
| Aged ≥ 60 | | | | | |
| ET | 7,050,151 | 554 | Reference | Reference | Dominant |
| CBT | 3,222,145 | 1,191 | -3,828,006 | 637 | |
| PSI class ≥ III | | | | | |
| ET | 4,050,898 | 1,189 | Reference | Reference | Dominant |
| CBT | 3,068,381 | 1,479 | -982,516 | 290 | |
| ICU | | | | | |
| ET | 5,635,566 | 842 | Reference | Reference | Dominant |
| CBT | 3,843,146 | 1,257 | -1,792,420 | 432 | |

Abbreviations: CEA, cost-effectiveness analyses; ET, empirical treatment; ICU, intensive care unit; LE, life expectancy; US\$, US dollar; PSI, pneumonia severity index; CBT, culture-based treatment.

hospitalization costs for AC and NC groups (CBT) increased, the ICERs correspondingly increased. The parameters of death averted in the CBT and ET groups were only slightly influential on ICER calculations, especially in patients with moderate-severe CAP (PSI class III-V). Tornado diagram evaluation is also provided in calculation results in [Supplementary Table S1](#).

The results of probabilistic sensitivity analyses on ICER values with 1,000 cohorts (Monte-Carlo simulations) between CBT and ET are shown in [Figure 4](#). Correspondingly, [Figure 5](#) shows the acceptability probabilities at varying WTP levels. In all cases, the probabilities of cost-effectiveness acceptability in 1xWTP and 3xWTP were 75% and 83%, respectively. In the subgroup analyses of patients all ages with moderate to severe CAP (PSI class ≥ III), and in the ICU, CBT would be a cost-effective or even cost-saving approach compared to 1xGDP per capita (US\$ 3,570). CBT for patients 60 years or older represented the most cost-effective option, with acceptability values between 81% for 1xWTP and 89% for 3xWTP. The results of calculations of Monte-Carlo simulations and cost-effectiveness acceptability are available in [Supplementary Table S2](#) and [S3](#), respectively.

Discussion

Our findings demonstrate that treatment based on the evaluation of cultures followed by antimicrobial susceptibility

testing (CBT) has advantages in terms of both cost and LE for CAP patients. CBT was dominant, not exceeding the GDP threshold in terms of cost-effectiveness (three times GDP) and even being cost-saving. Therefore, this method can reasonably be implemented for adults in general hospitals in Indonesia. Without culture analysis, treatments for CAP are more expensive and result in lost life-years, particularly for geriatric patient cases and high-severity classes of patients.²⁴⁻²⁸ Notably, the incidence of CAP among elderly people is high since they frequently present with pre-existing immunosuppressive conditions and comorbid conditions.^{29,30} According to ATS/BTS, the severity of CAP infection among males was higher than females.³¹ This is the reason that males need hospitalization more than females, as reflected in the input data for our study. Also, some previous prospective studies demonstrated this issue.³¹⁻³³

In non-ICU hospitalization, culture analysis is one of the procedures recommended by the Infectious Diseases Society of America (IDSA) and ATS to guide antibiotic use for CAP patients.⁴ The implementation of the guidelines with the threshold of US\$ 100,000/QALY (quality-adjusted life years) leads to cost-savings of US\$ 799 to US \$ 1,379 per patient and improved quality of life, particularly in elderly people.³⁴ In the ICU, it is essential to consider CBT implementation since the use of antibiotic is costly. A previous study conducted in an LMIC reported

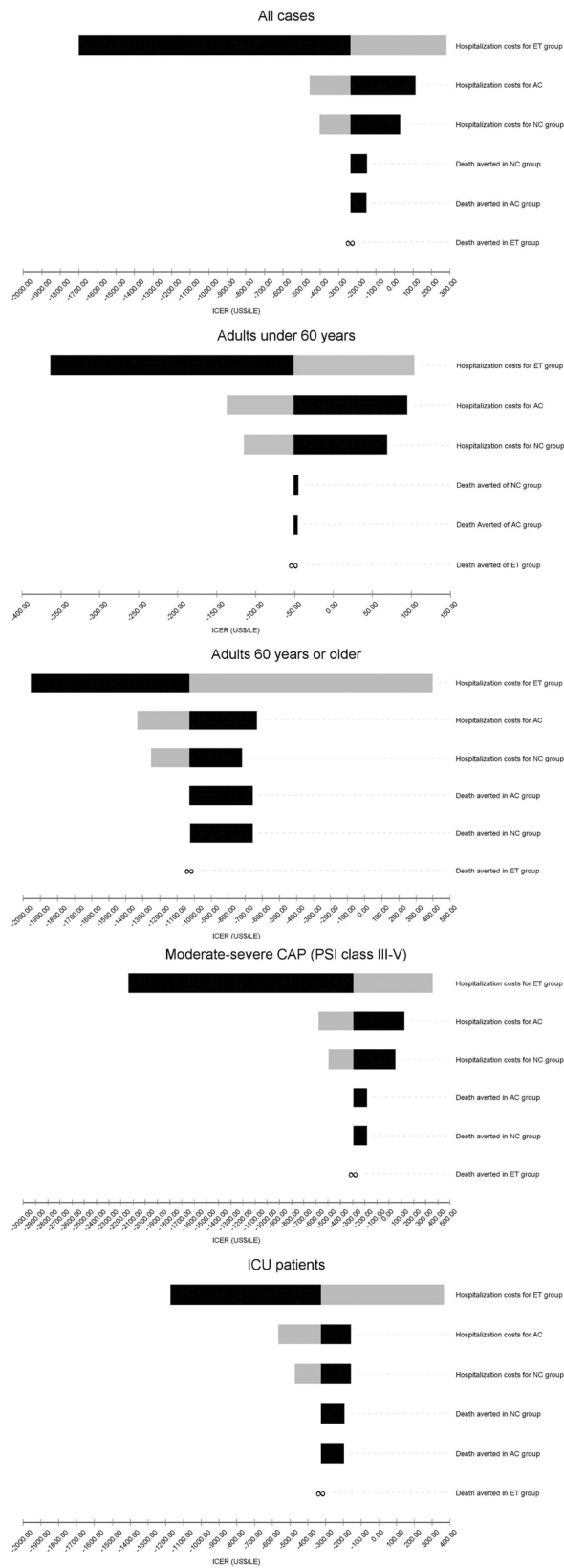


Figure 3 Tornado one-way sensitivity analyses of ICER per LE comparing CBT against ET groups.

Note: Black and grey bars indicate high and low limits, respectively.

Abbreviation: PSI, pneumonia severity index.

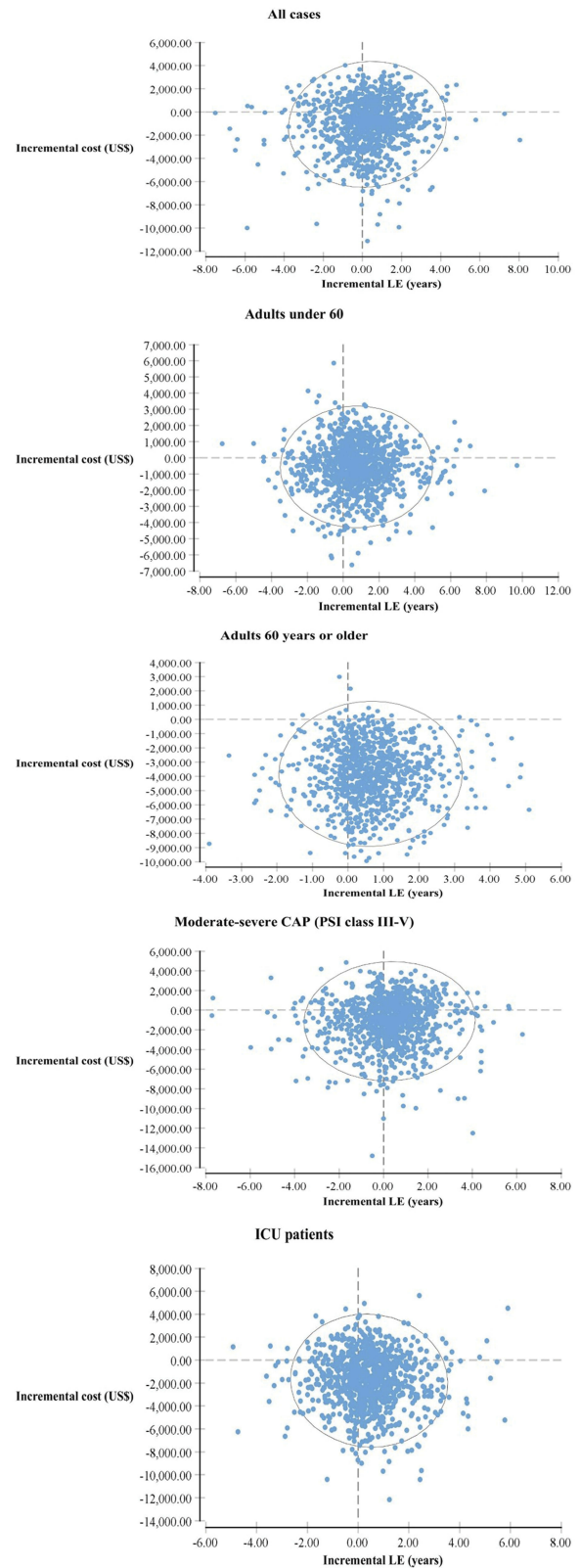


Figure 4 Monte-Carlo simulations of the cost-effectiveness analyses of CBT versus ET groups using 1,000 simulations.

Note: The circle indicates a 95% confident surface.

Abbreviations: CAP, community-acquired pneumonia; ICU, intensive care unit; LE, life expectancy; PSI, pneumonia severity index.

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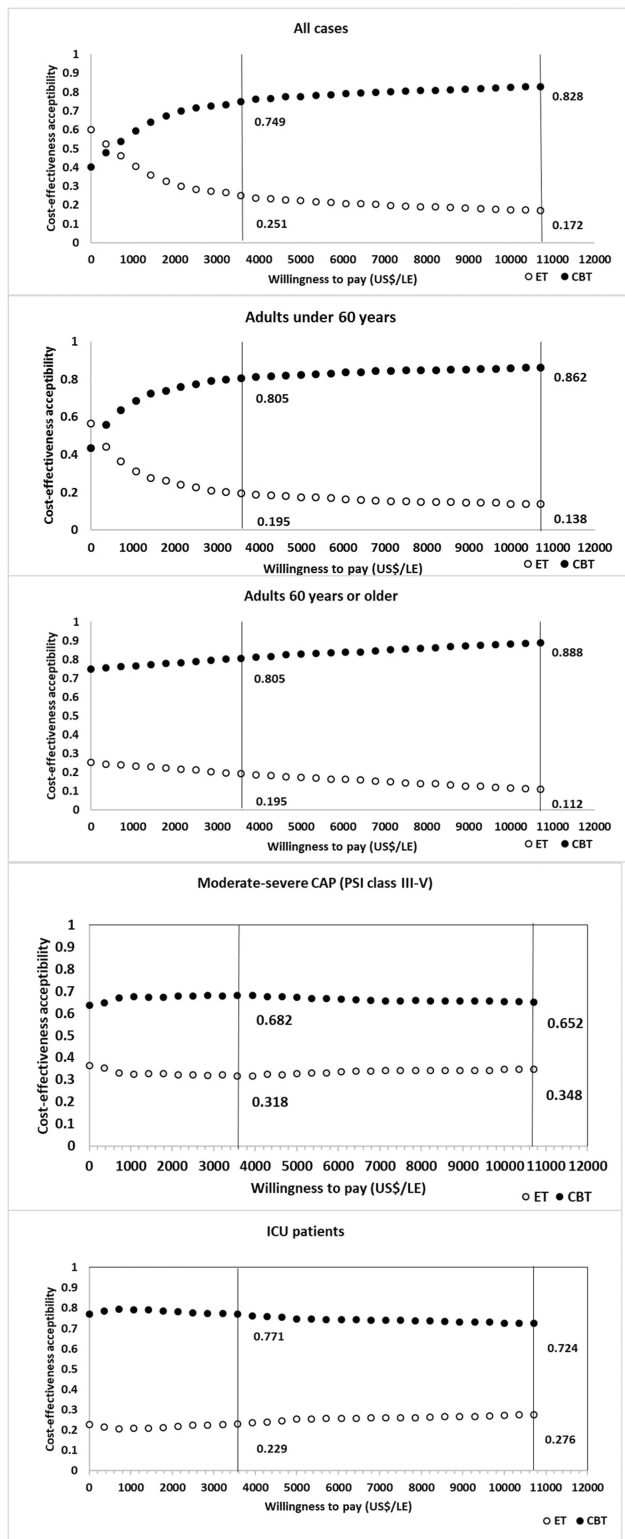


Figure 5 Cost-effectiveness acceptability curve (CEAC) labelled on the 1xWTP (US\$ 3570.28/LE) and 3xWTP (US\$ 10,710.84). **Abbreviations:** CAP, community-acquired pneumonia; ET, empirical treatment; CBT, culture-based treatment; ICU, intensive care unit, PSI, pneumonia severity index.

that antibiotic utilization for CAP patients in ICU was determined as the highest proportion (38%) of total hospitalization costs.³⁵

The assessment of severity using the PSI score resulted in higher sensitivity of sputum culture analyses. Gram staining and sputum culture procedures are very useful for inpatient treatment plans and ICU patients, guiding CAP diagnosis and antimicrobial selection.³⁶ The organisms from the microbiological culture are more likely to accurately represent respiratory tract pathogens in CAP patients.³⁷ Furthermore, the implementation of blood and sputum culture analysis should be considered in patients with moderate and severe CAP with poor clinical prognosis and who are considerably susceptible to bacteremia.^{38,39}

Culture analysis is part of diagnostic stewardship that supports antimicrobial identification and infection prevention programs. CBT should be part of such integrated management within a theragnostic approach, involving multi-disciplines, and leading personalized management, improvement of prescriptions for treatment, improved clinical outcomes, and decreasing costs.^{40,41} An issue of concern is the potential contamination of biological specimens. Contaminated blood and sputum cultures could extend costs and have adverse effects.^{42,43} The role of the clinical microbiologist is critical at this point for screening assessments of the quality of the sample. Recently, several advanced methods to reduce contaminations have been developed, such as matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) and multiplex nucleic acid amplification test (NAAT).^{44,45} However, these methods are costly.

To our knowledge, this study is the first cost-effectiveness analysis for culture analysis in CAP patients considering real-world data and the impact of the effect of culture analysis in terms of changes in antibiotic treatments, particularly in an LMIC setting. The utility impact was accounted for the overall population as well as relevant subgroups of patients aged ≥ 60 , with PSI class $\geq III$ and in the ICU. This approach provided the necessary level of granularity. However, this study has some limitations. First, community data from primary healthcare was not available. There is a lack of sample data related to CAP in the community since facilities for clinical diagnostics and bacterial identification remain unavailable, and these are not routine procedures, especially in remote areas. In clinical practice, we assumed randomness in the decision to do ET or CBT, as confirmed by the clinicians. However, we could not exclude that in some specific cases some aspect, may still have influential this decision and so probably introducing some bias in our analysis. Second, this study used a retrospective dataset; patients with incomplete data related to ICER outcomes could not be analyzed. In

further investigations comparing the effects of treatments, randomized controlled clinical trials are necessary to obtain additional results. As such, our study can be considered as hypothesis generating rather than providing final evidence. Lastly, we did not include costs associated with the side effects of the treatments in the present research. Common undesirable side effects of antibiotic treatment, such as diarrhea, *Clostridium difficile* infections, and allergic reactions can extend the length of hospitalization and increase costs.⁴⁶

Conclusion

In conclusion, CAP patients undergoing treatments based on culture analyses (CBT) were estimated to receive benefits in terms of cost-savings and increased LE than those with empirical treatment (ET) during their hospitalization; CBT was labeled dominant compared to ET. Notably, the implementation of CBT provides considerable advantages for patients all ages as well as for higher severity classes. Most notably in severe CAP cases, cultures can adequately guide antibiotic selection for patients with PSI class III or above or who are hospitalized in ICUs.

Abbreviations

AC, antibiotic change; ATS, American Thoracic Society; BTS, British Thoracic Society; Ca, cost of administration; CAP, Community-Acquired Pneumonia; Cb, cost for bed; CBT, Culture-based treatment; Cl, costs for laboratory and radiology; Cm, costs for medical staff; Cp, costs for pharmacy; ET, Empirical treatment; GDP, Gross Domestic Product; ICD, International Classification of Diseases; ICER, Incremental Cost Effectiveness Ratio; ICU, Intensive Care Unit; IDSA, Infectious Diseases Society of America; LE, Life Expectancy; LMICs, Low-Middle Income Countries; MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization-Time Of Flight; NAAT, Nucleic Acid Amplification Test; NC, no antibiotic change; NICE, National Institute for Health and Care Excellence; OECD, Organization for Economic Cooperation and Development; PSI, Pneumonia Severity Index; QALY, Quality-Adjusted Life Years; UNFPA, United Nations Population Fund; WHO, World Health Organization; WHO-CHOICE, World Health Organization – Choosing Interventions for Cost-Effectiveness criterion; WTP, Willingness-to-Pay.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Outside of this work, Prof. Postma reports receiving various grants and honoraria from both public (EU, WHO) and private (pharmaceutical companies) parties. Prof. Postma is also shareholder of Pharmacoeconomics Advice Groningen and Ingress Health, and advisor to Asc Academics Groningen and Health-Ecore. The other authors report no conflicts of interest in this work.

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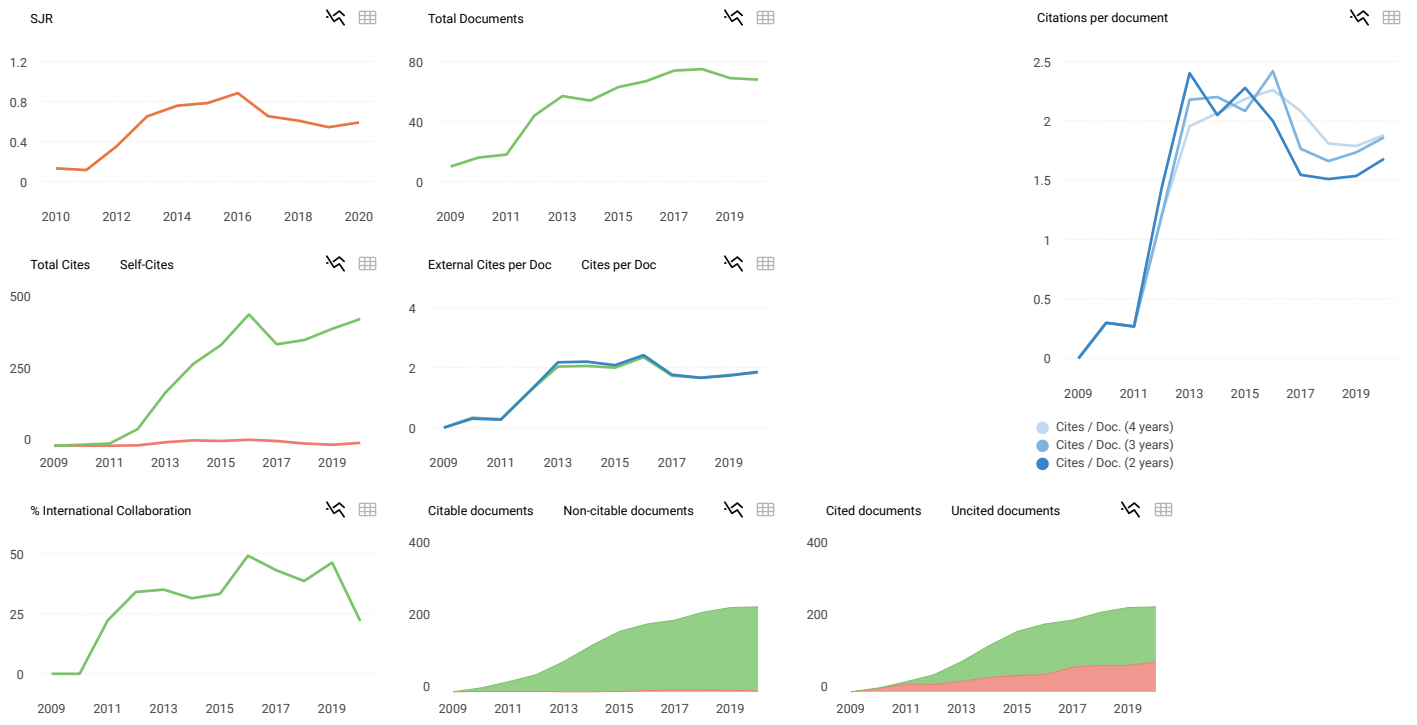
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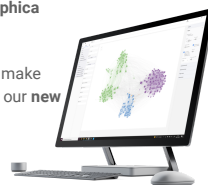
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