RESEARCH ARTICLE

The role of interspecies recombination in the evolution of antibiotic-resistant pneumococci

Joshua C D'Aeth[1]*, Mark PG van der Linden[2], Lesley McGee[3], Herminia de Lencastre[4,5], Paul Turner[6,7], Jae-Hoon Song[8], Stephanie W Lo[9], Rebecca A Gladstone[9], Raquel Sá-Leão[10], Kwan Soo Ko[8], William P Hanage[11], Robert F Breiman[12], Bernard Beall[3], Stephen D Bentley[9], Nicholas J Croucher[1]*, The GPS Consortium

[1]MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, Imperial College London, London, United Kingdom; [2]Institute for Medical Microbiology, National Reference Center for Streptococci, University Hospital RWTH Aachen, Aachen, Germany; [3]Respiratory Diseases Branch, Centers for Disease Control and Prevention, Atlanta, United States; [4]Laboratory of Molecular Genetics, Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Oeiras, Portugal; [5]Laboratory of Microbiology and Infectious Diseases, The Rockefeller University, New York, United States; [6]Cambodia Oxford Medical Research Unit, Angkor Hospital for Children, Siem Reap, Cambodia; [7]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; [8]Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea; [9]Parasites & Microbes, Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, United Kingdom; [10]Laboratory of Molecular Microbiology of Human Pathogens, Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Oeiras, Portugal; [11]Center for Communicable Disease Dynamics, Harvard T.H. Chan School of Public Health, Boston, United States; [12]Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, United States

*For correspondence: j.daeth17@imperial.ac.uk (JCD'A); n.croucher@imperial.ac.uk (NJC)

Group author details: The GPSConsortium See page 27

Competing interest: See page 28

Funding: See page 28

Received: 01 February 2021
Accepted: 16 April 2021
Published: 14 July 2021

Reviewing editor: Paul B Rainey, Max Planck Institute for Evolutionary Biology, Germany

Abstract Multidrug-resistant *Streptococcus pneumoniae* emerge through the modification of core genome loci by interspecies homologous recombinations, and acquisition of gene cassettes. Both occurred in the otherwise contrasting histories of the antibiotic-resistant *S. pneumoniae* lineages PMEN3 and PMEN9. A single PMEN3 clade spread globally, evading vaccine-induced immunity through frequent serotype switching, whereas locally circulating PMEN9 clades independently gained resistance. Both lineages repeatedly integrated Tn*916*-type and Tn*1207.1*-type elements, conferring tetracycline and macrolide resistance, respectively, through homologous recombination importing sequences originating in other species. A species-wide dataset found over 100 instances of such interspecific acquisitions of resistance cassettes and flanking homologous arms. Phylodynamic analysis of the most commonly sampled Tn*1207.1*-type insertion in PMEN9, originating from a commensal and disrupting a competence gene, suggested its expansion across Germany was driven by a high ratio of macrolide-to-β-lactam consumption. Hence, selection from antibiotic consumption was sufficient for these atypically large recombinations to overcome species boundaries across the pneumococcal chromosome.