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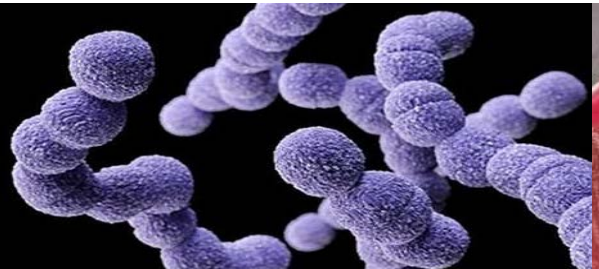
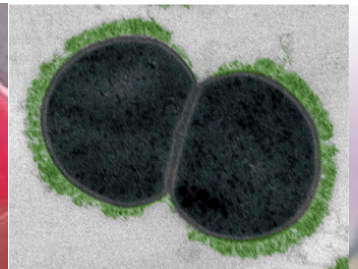
Brussels, Belgium

Molecular Bacteriology Laboratory,
Free University of Brussels, Belgium

Increase of invasive group A Streptococcus *(GAS - Strep A)* infections

Pierre Smeesters



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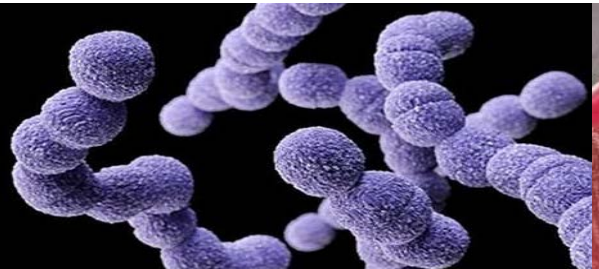
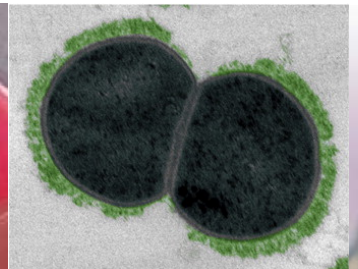
Increase of invasive group A Streptococcus *(GAS - Strep A)* infections … in the context of Strep A disease burden

Pierre Smeesters



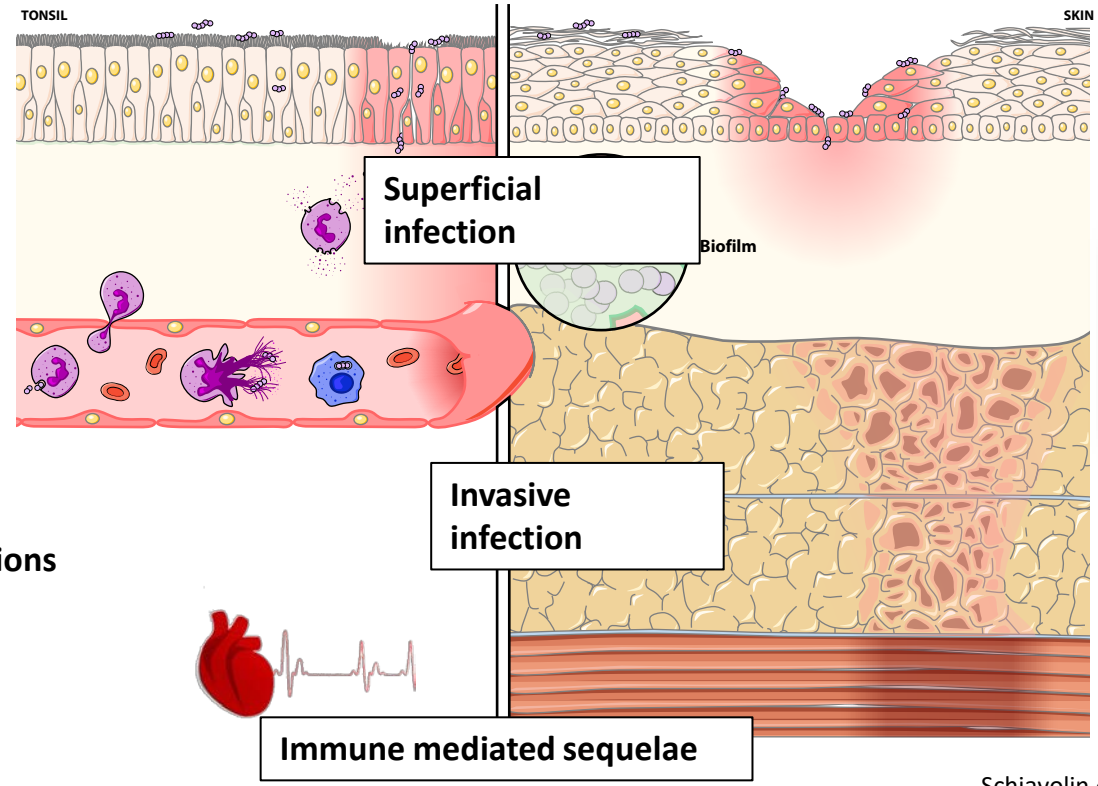


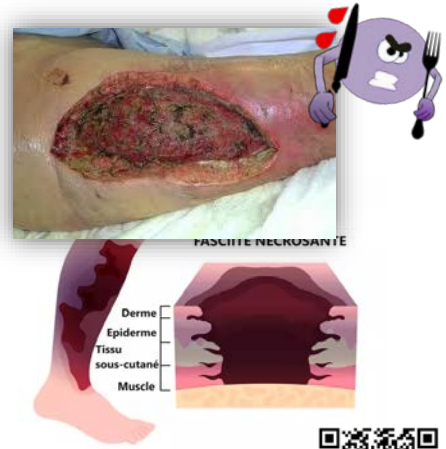

Strep A diseases

Toxin mediated infections

Colonisation

Carriage **Carriage**





Schiavolin *et al*, Critical Reviews in Microbiology, 2024

21. Global Disease Burden of *Streptococcus pyogenes*

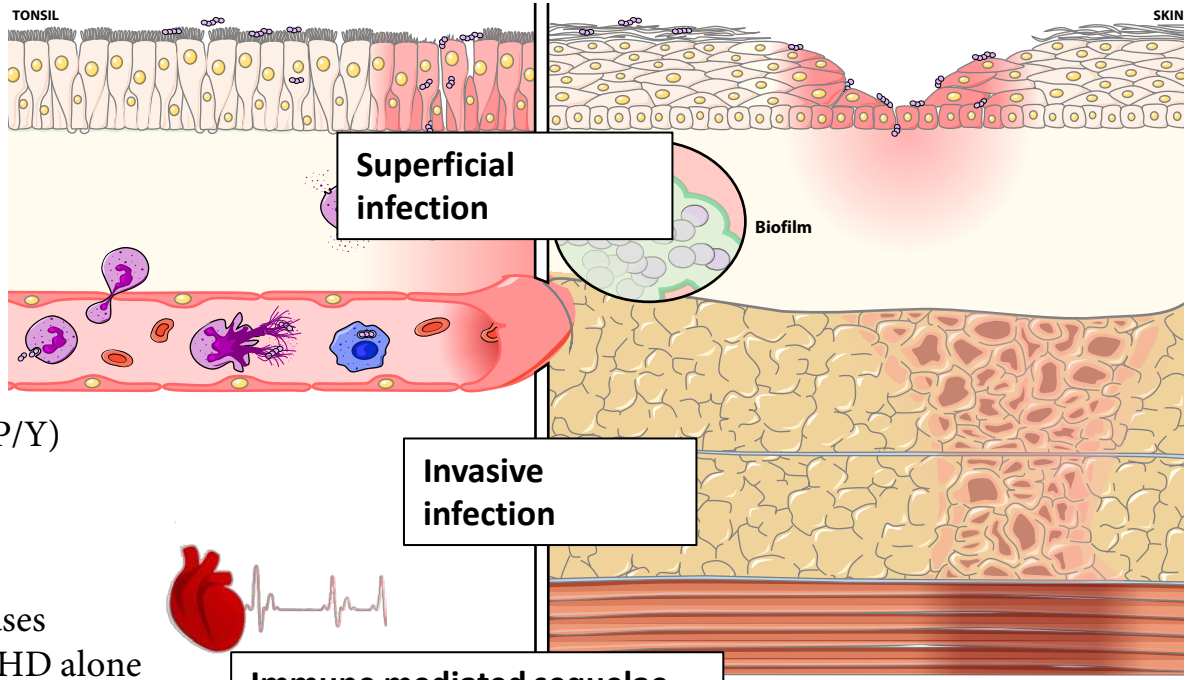
Natalie Craik, MD,[1] Thel Hla, MBBS,[2] Jeffery Cannon, PhD,[3] Hannah Moore, GradDipClinEpi, PhD,[4] Jonathan R. Carapetis, MBBS, PhD, BMedSc, FRACP, FAFPHM, FAHMS,[5] and Amy Sanyahumbi, MD[1]

Created: August 21, 2022; Updated: October 4, 2022.

High-income, each year:
- 15% school children
- 4–10% of adults

- 8,400,750 cases of **impetigo** each year
- 1-20% among children in less-developed countries
- Up to 40–90% in some areas

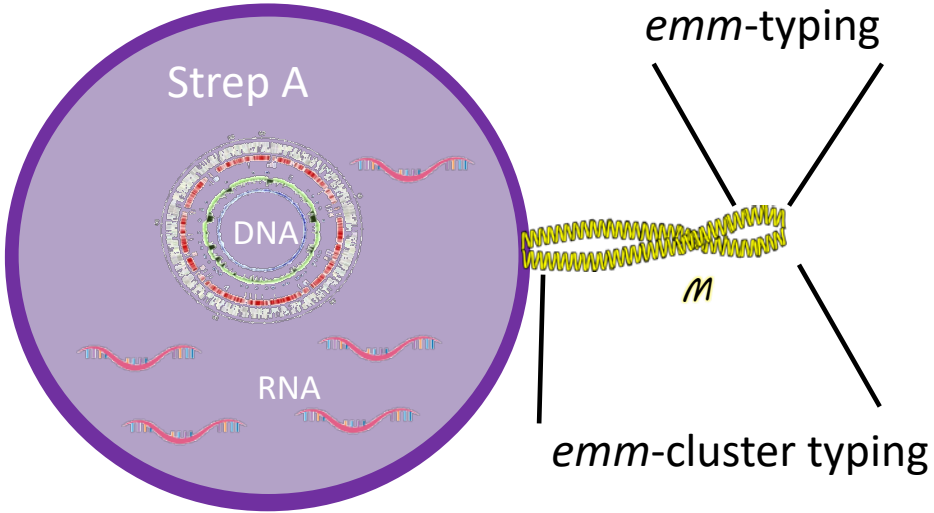
Strep A **pharyngitis**



- 663,000 cases each year
- 163,000 deaths
- Increase over time
- Incidence from 2-100 (100K P/Y)

In 2019
- 40 million RHD cases
- 2,789,443 new RHD cases
- 305,651 deaths from RHD alone

Strep A microbiology



Strain diversity

No vaccine

1) The main “**killer**”: **A**cute **R**heumatic **F**ever and **R**heumatic **H**eart **D**iseases

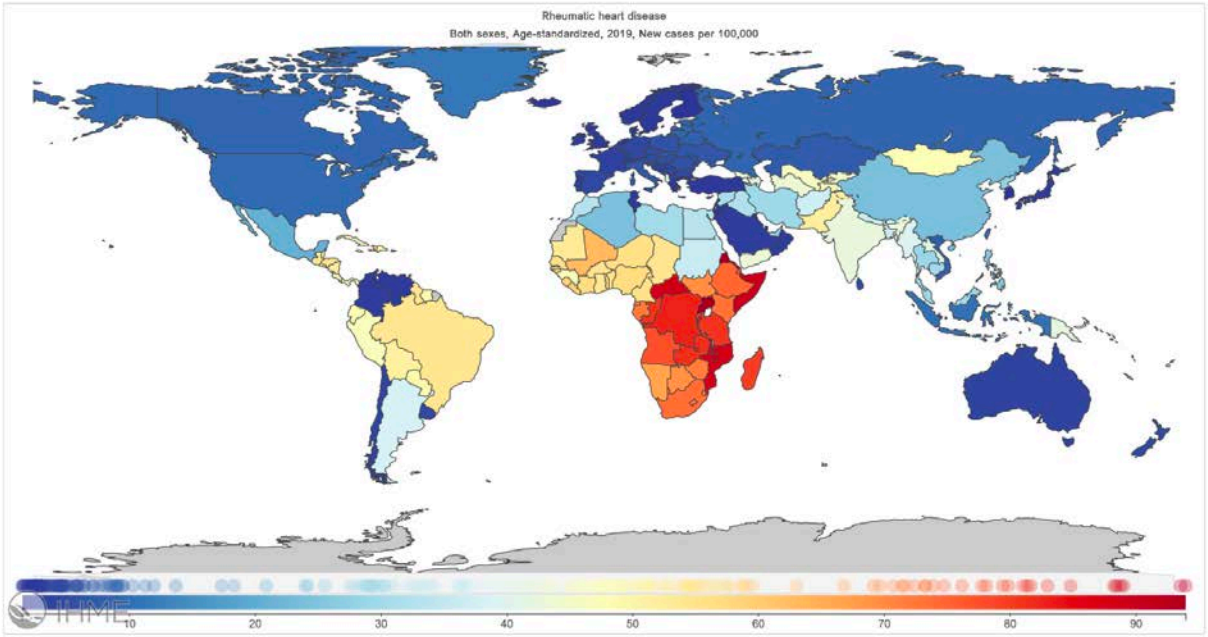


Figure 1. Global incidence of rheumatic heart disease 2019, age-standardized new cases per 100,000 population (Institute for Health Metrics and Evaluation, 2022).

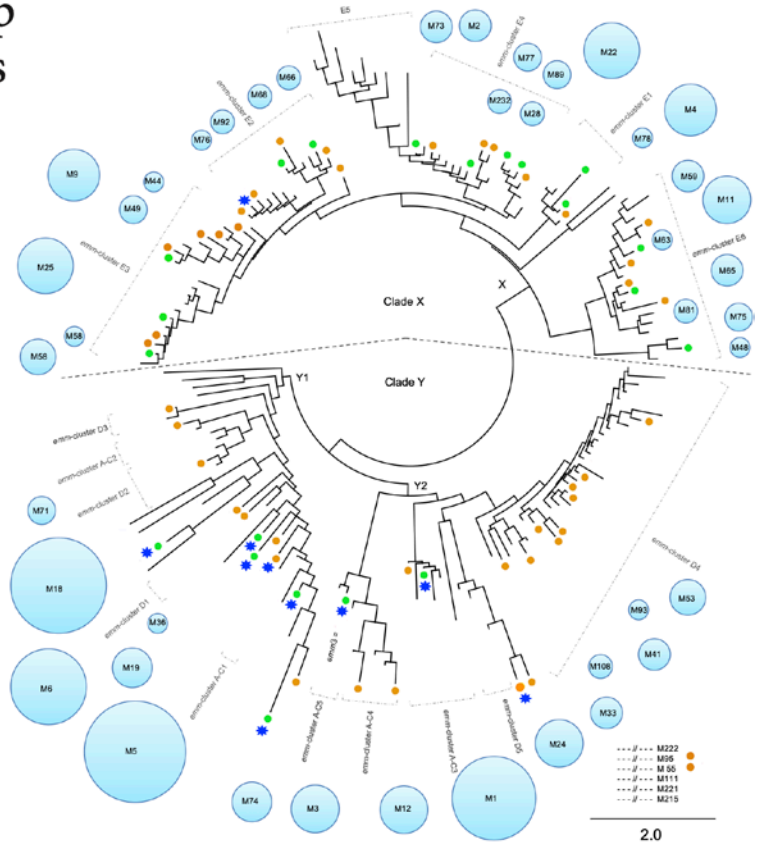
Clinical Infectious Diseases
MAJOR ARTICLE

The Limitations of the Rheumatogenic Concept for Group A Streptococcus: Systematic Review and Genetic Analysis

Gabrielle de Crombrugghe,[1,2] Noemie Baroux,[3] Anne Botteaux,[2] Nicole J. Moreland,[4] Deborah A. Williamson,[5] Andrew C. Steer,[3,6] and Pierre R. Smeesters[1,2,3,6]

CID 2020:70 (1 April)

Gabrielle de Crombrugghe



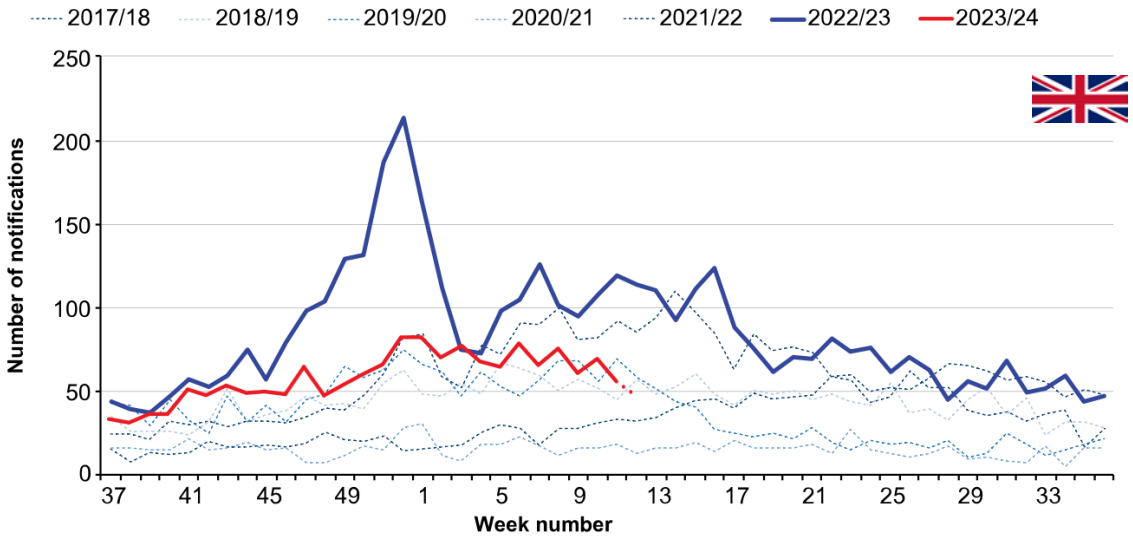
- So-called ‘classic rheumatogenic *emm* types’ are not so classic if you take a broader view beyond mid-century US outbreaks and look to endemic settings.
- Is “rheumatogenicity” even a useful concept? Can all GAS strains cause ARF?

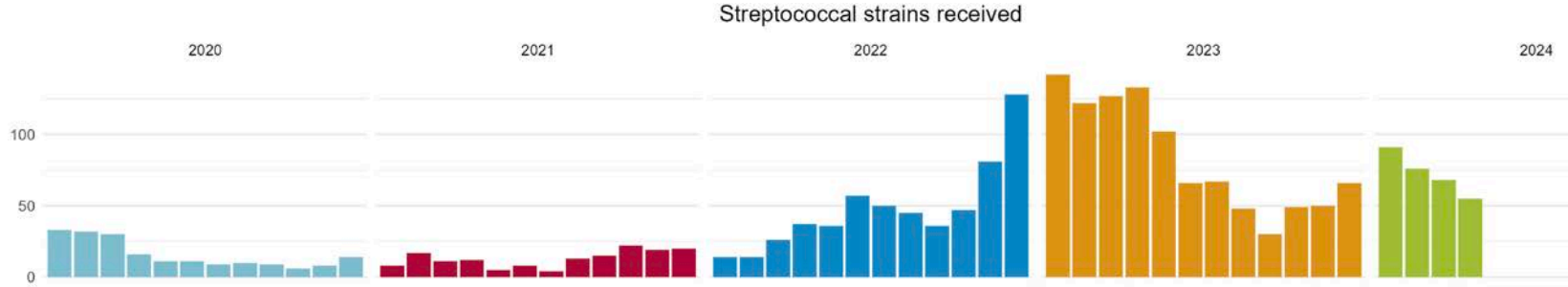
2) Another important killer: Invasive Strep A infections

Research and analysis

Group A streptococcal infections: fourth update on seasonal activity in England, 2023 to 2024

Updated 4 April 2024





Courtesy of Prof Veerle Matheeussen

Emergence of dominant toxigenic M1T1 *Streptococcus pyogenes* clone during increased scarlet fever activity in England: a population-based molecular epidemiological study

Nicola N Lynskey, Elita Jauneikaite*, Ho Kwong Li, Xiangyun Zhi, Claire E Turner, Mia Mosavie, Max Pearson, Masanori Asai, Ludmila Lobkowicz, J Yimmy Chow, Julian Parkhill, Theresa Lamagni, Victoria J Chalker, Shiranee Sriskandan*

Lancet Infect Dis 2019;

Present since 2008

nature communications

Article

https://doi.org/10.1038/s41467-023-36717-4

Detection of *Streptococcus pyogenes* $M1_{UK}$ in Australia and characterization of the mutation driving enhanced expression of superantigen SpeA

Received: 21 September 2022

Accepted: 13 February 2023

Published online: 24 February 2023

Check for updates

Mark R. Davies[1,13], Nadia Keller[2,13], Stephan Brouwer[2,13], Magnus G. Jespersen[1,13], Amanda J. Cork[2], Andrew J. Hayes[1], Miranda E. Pitt[1], David M. P. De Oliveira[2], Nichaela Harbison-Price[2], Olivia M. Bertolla[2], Daniel G. Mediati[3], Bodie F. Curren[2], George Taiaroa[1], Jake A. Lacey[4], Helen V. Smith[5], Ning-Xia Fang[5], Lachlan J. M. Coin[1], Kerrie Stevens[6], Steven Y. C. Tong[4,7], Martina Sanderson-Smith[8], Jai J. Tree[3], Adam D. Irwin[9,10], Keith Grimwood[11,12], Benjamin P. Howden[6], Amy V. Jennison[5] & Mark J. Walker[2]

RAPID COMMUNICATION

Increase in invasive group A streptococcal infections and emergence of novel, rapidly expanding sub-lineage of the virulent *Streptococcus pyogenes* M1 clone, Denmark, 2023

Thor Bech Johannesen[1], Charlotte Munkstrup[2], Sofie Marie Edslev[1], Sharmin Baig[1], Stine Nielsen[2], Tjede Funk[2], Dennis Karsten Kristensen[3], Lars Hervig Jacobsen[3], Signe Fischer Ravn[3], Niels Bindslev[3], Sophie Gubbels[3], Marianne Voldstedlund[3], Pikka Jokelainen[4], Søren Hallstrøm[1], Astrid Rasmussen[1], Karl Gústaf Kristinsson[5,6], David Fuglsang-Damgaard[7], Ram B Dessau[8,9], Agnieszka Barbara Olsén[10], Christian Salgaard Jensen[11], Annette Skovby[12], Svend Ellermann-Eriksen[13], Thøger Gorm Jensen[14], Esad Dzajic[15], Claus Østergaard[16], Steen Lomborg Andersen[17], Steen Hoffmann[1], Peter Henrik Andersen[2], Marc Stegger[1,18]

RAPID COMMUNICATION

Sustained increase of paediatric invasive *Streptococcus pyogenes* infections dominated by $M1_{UK}$ and diverse *emm*12 isolates, Portugal, September 2022 to May 2023

Catarina Gouveia[1,*], Maria Paula Bajanca-Lavado[2,*], Rafael Mamede[3], Ana Araújo Carvalho[1], Fernanda Rodrigues[4], José Melo-Cristino[3], Mario Ramirez[3], Ana Friães[3], Portuguese Group for the Study of Streptococcal Infections[5], Portuguese Study Group of Pediatric Invasive Streptococcal Disease[5]

RAPID COMMUNICATION

Increase in bloodstream infections caused by *emm1* group A *Streptococcus* correlates with emergence of toxigenic $M1_{UK}$, Belgium, May 2022 to August 2023

Juan Pablo Rodriguez-Ruiz[1,2], Qiang Lin[1,2], Christine Lammens[1,2], Pierre R Smeesters[2,4], Stefanie van Kleef-van Koeveringe[2,5], Veerle Matheeussen[1,2,5], Surbhi Malhotra-Kumar[1,2]

EPUB AMERICAN SOCIETY FOR MICROBIOLOGY | mSphere®
RESEARCH ARTICLE
March 2024 Volume 9 Issue 3 e00729-23
https://doi.org/10.1128/msphere.00729-23

Clinical, microbiological, and molecular characterization of pediatric invasive infections by *Streptococcus pyogenes* in Spain in a context of global outbreak

Eva Ramírez de Arellano[1,2], Jesús Saavedra-Lozano[2,3], Pilar Villalón[4], Ana Jové-Blanco[3], David Grandioso[5], Jared Sotelo[1,2], Anna Gamell[6], Juan José González-López[2,7], Eloísa Cervantes[8], María José Gónzalez[9], Victoria Rello-Saltor[10], Cristina Esteva[11], Francisco Sanz-Santaeufemia[12], Genoveva Yagüe[13], Ángela Manzanares[14], Patricia Brañas[15], Enrique Ruiz de Gopegui[2,16], Jaime Carrasco-Colom[17], Federico García[2,18], Emilia Cercenado[19,20], Isabel Mellado[21], Elena del Castillo[22], María Pérez-Vazquez[1,2], Jesús Oteo-Iglesias[1,2], Cristina Calvo[2,21], on behalf of the Spanish PedGAS-Net/CIBERINFEC GAS Study Group

MICROBIAL GENOMICS
SHORT COMMUNICATION
van der Putten *et al.*, *Microbial Genomics* 2023;9:001026
DOI 10.1099/mgen.0.001026
MICROBIOLOGY SOCIETY
OPEN DATA OPEN ACCESS

Novel *emm*4 lineage associated with an upsurge in invasive group A streptococcal disease in the Netherlands, 2022

Boas C.L. van der Putten[1]†, Wendy C.M. Bril-Keijzers[2], Lidewij W. Rumke[3], Stefan M.T. Vestjens[3], Linda A.M. Koster[1], Marloes Willemsen[1]‡, Marlies A. van Houten[4], Nynke Y. Rots[5], Bart J.M. Vlaminckx[6], Brechje de Gier[5] and Nina M. van Sorge[1,2,*]

$M1_{UK}$ and M12 are the current rock stars
$M1_{UK}$ known before clinical upsurge
Pathogen **and** Host **and** Environment are **important**

Expansion of Invasive Group A *Streptococcus* $M1_{UK}$ Lineage in Active Bacterial Core Surveillance, United States, 2019–2021

Yuan Li, Joy Rivers, Saundra Mathis, Zhongya Li, Sopio Chochua, Benjamin J. Metcalf, Bernard Beall, Jennifer Onukwube, Christopher J. Gregory, Lesley McGee

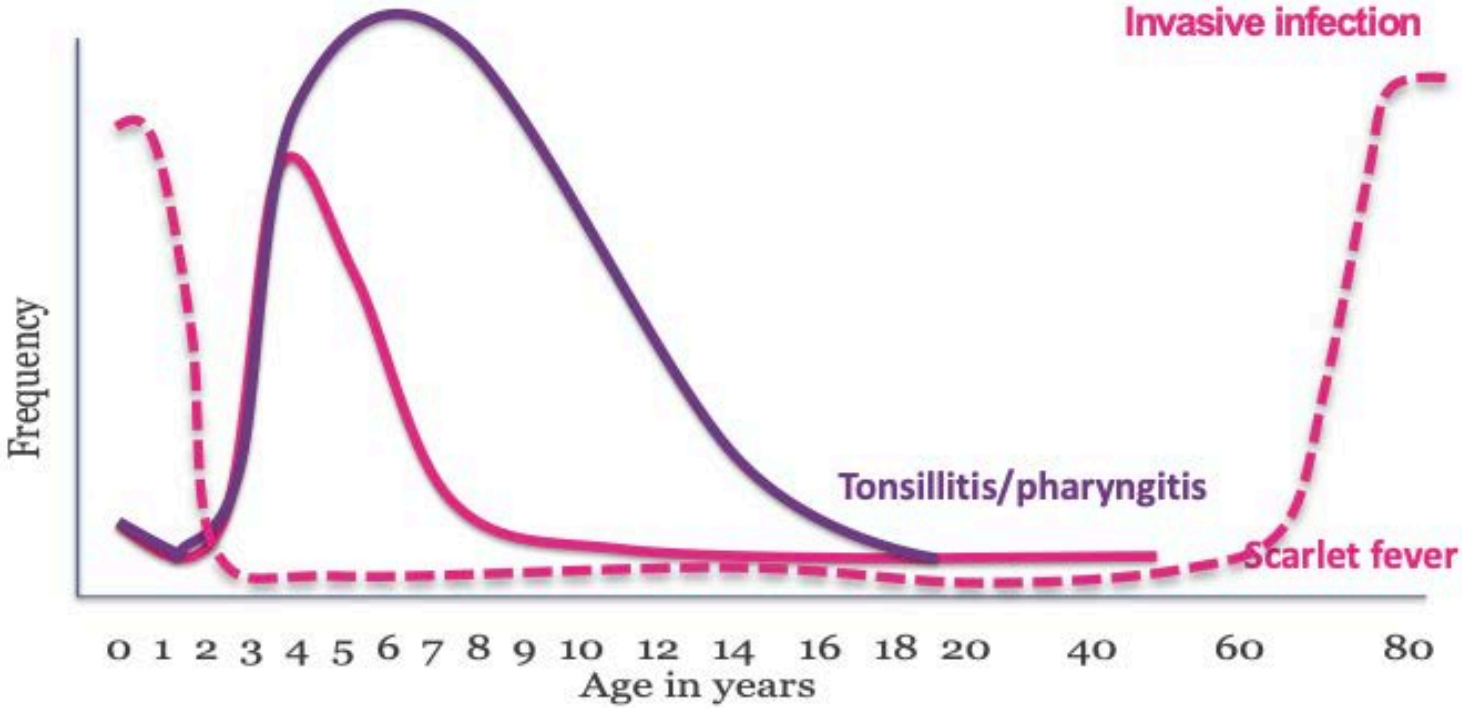
Emerging Infectious Diseases
October 2023

Increase in invasive group A streptococcal disease among Australian children coinciding with northern hemisphere surges

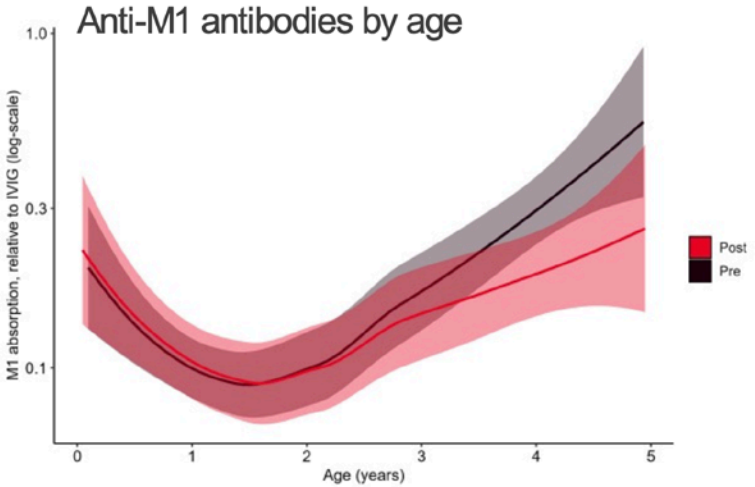
Yara-Natalie Abo,[a,b,c,d,*,o] Jane Oliver,[a,e,o] Alissa McMinn,[a] Joshua Osowicki,[a,b,d] Ciara Baker,[a] Julia E. Clark,[f] Christopher C. Blyth,[g] Joshua R. Francis,[h,i] Jeremy Carr,[j,k,l] Pierre R. Smeesters,[m,n] Nigel W. Crawford,[a,p] and Andrew C. Steer[a,b,d,p]

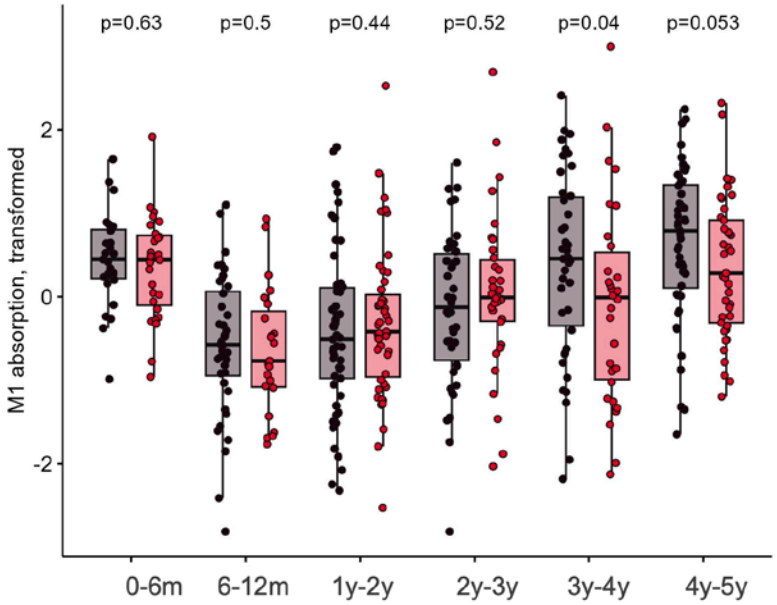
The Lancet Regional Health - Western Pacific
2023;41: 100873

Incidence of Strep A diseases by age



244 children under 5y pre-March 2020,
247 children under 5y after March 2020
(Perform and Diamonds cohorts)





Dokal, Channon-Wells et al, 2024

Prof Shiranee Sriskandan,
ESCMID Global 2024

Preparing for uncertainty: endemic paediatric viral illnesses after COVID-19 pandemic disruption

www.thelancet.com **Vol 400 November 12, 2022**

*Kevin Messacar, Rachel E Baker, Sang Woo Park, Hai Nguyen-Tran, Jessica R Cataldi, Bryan Grenfell

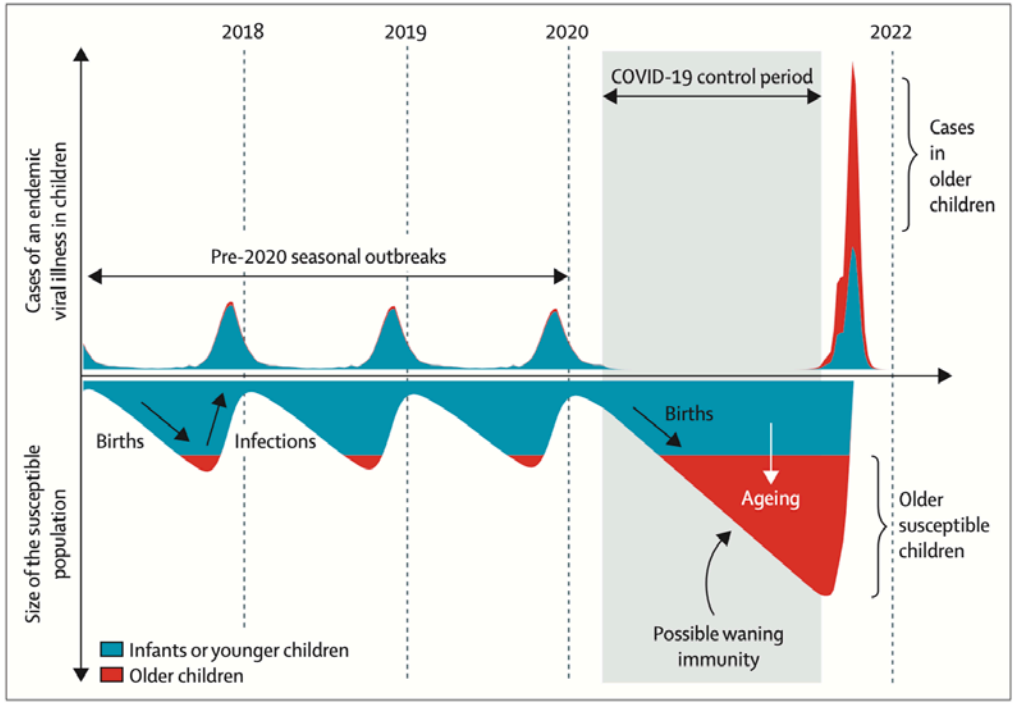
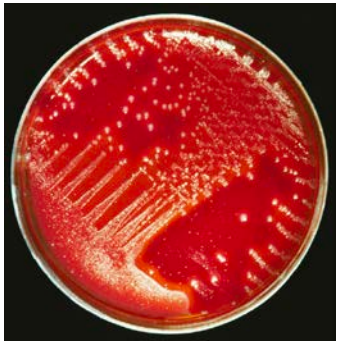
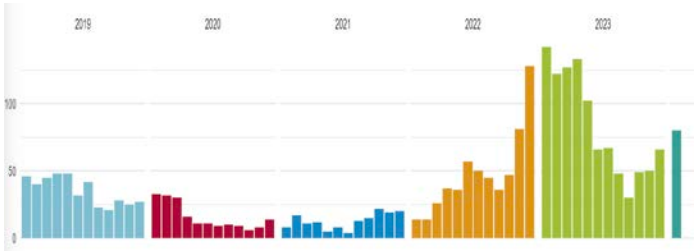


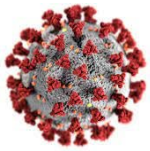
Figure: **Modelling of endemic virus circulation in children following COVID-19 pandemic disruption**

New variants

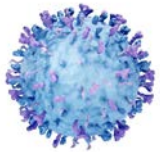


Covid-19 related reduced exposure





Covid-19



RSV

Flu

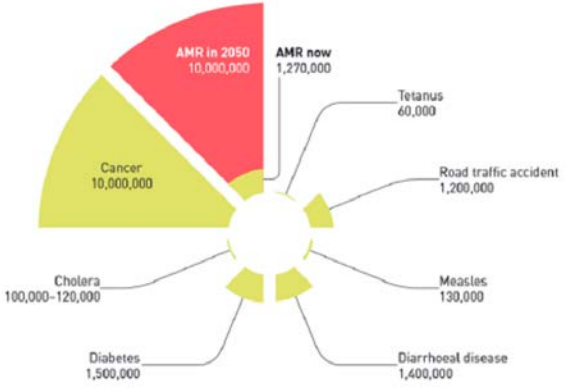
Varicela

Different Environments

3) Strep A sore throat => does not kill (much) much **BUT** Antimicrobial resistance

Sore throat = Second reason for antibiotic prescription in Europe (14% of all antibiotics)

(Recent) controversies around under and/or over-treatment of acute sore throat…



Antibiotic consumption for sore throat and the potential effect of a vaccine against group A *Streptococcus*: a systematic review and modelling study

Kate M. Miller,[a,b] Timothy C. Barnett,[a,c] Daniel Cadarette,[d] David E. Bloom,[e] Jonathan R. Carapetis,[a,f] and Jeffrey W. Cannon[a,g,*]

eBioMedicine
2023;98: 104864

Annex to Immunization Agenda 2030

Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance:

An Action Framework

World Health Organization

4) GAS skin infections => household studies => carriage

Northern territories

The Gambia

Evaluating the role of asymptomatic throat carriage of *Streptococcus pyogenes* in impetigo transmission in remote Aboriginal communities in Northern Territory, Australia: a retrospective genomic analysis

Jake A Lacey, Adrian J Marcato, Rebecca H Chisholm, Patricia T Campbell, Cameron Zachreson, David J Price, Taylah B James, Jacqueline M Morris, Claire L Gorrie, Malcolm I McDonald, Asha C Bowen, Philip M Giffard, Deborah C Holt, Bart J Currie, Jonathan R Carapetis, Ross M Andrews, Mark R Davies, Nicholas Geard, Jodie McVernon, Steven Y C Tong

Lancet Microbe 2023; 4: e524–33

from impetigo lesions. Asymptomatic throat carriers are likely to be a source of GAS isolates that cause skin infections.

Streptococcus pyogenes carriage and infection within households in The Gambia: a longitudinal cohort study

Edwin P Armitage, Gabrielle de Crombrugghe, Alexander J Keeley, Elina Senghore, Fatoumata E Camara, Musukoi Jammeh, Amat Bittaye, Haddy Ceesay, Isatou Ceesay, Bunja Samateh, Muhammed Manneh, Beate Kampmann, Claire E Turner, Adam Kucharski, Anne Botteaux, Pierre R Smeesters, Thushan I de Silva*, Michael Marks*, on behalf of the MRCG StrepA Study Group†

Lancet Microbe 2024

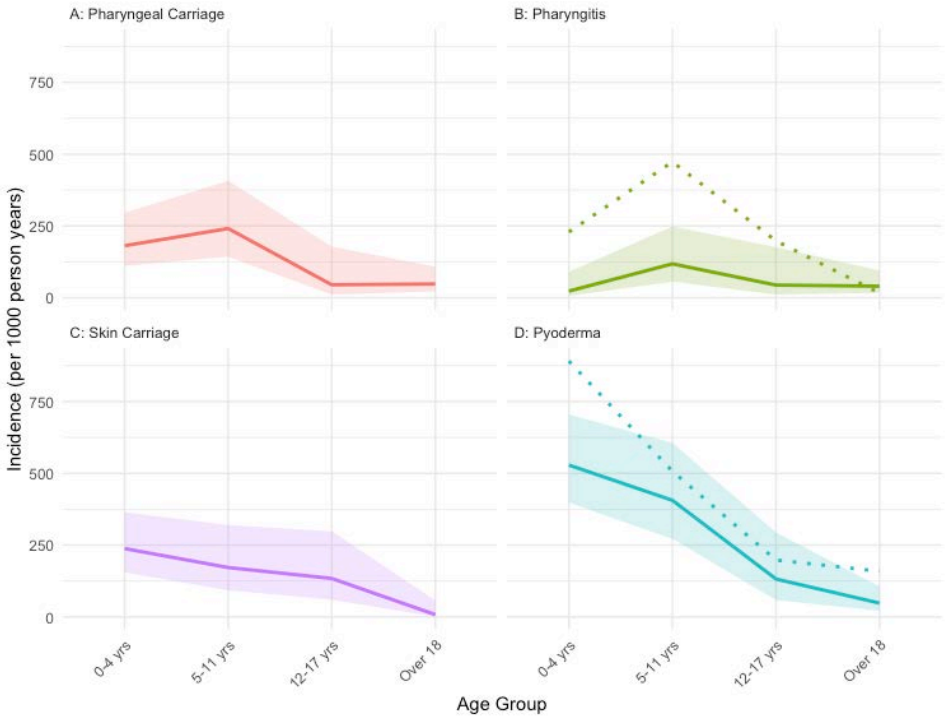
Incidence rates by age

Carriage

Infection

Pharynx

Skin



MRC Unit The Gambia

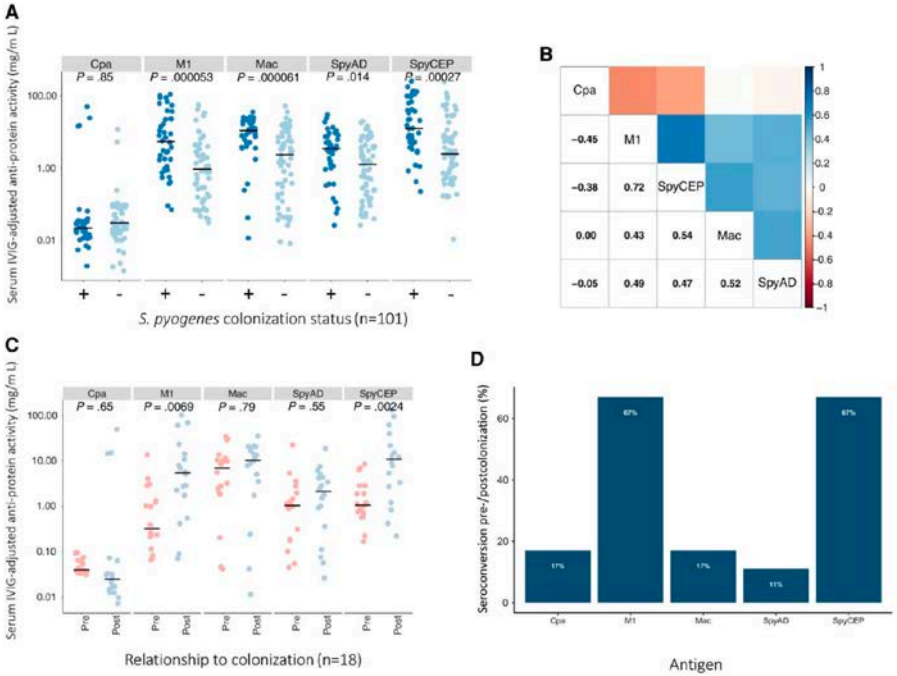
Courtesy of Edwin Armitage

The Journal of Infectious Diseases
MAJOR ARTICLE

Streptococcus pyogenes Colonization in Children Aged 24–59 Months in the Gambia: Impact of Live Attenuated Influenza Vaccine and Associated Serological Responses

Alexander J. Keeley,[1,2,3] Danielle Groves,[2] Edwin P. Armitage,[1,3] Elina Senghore,[3] Ya Jankey Jagne,[3] Hadijatou J. Sallah,[3] Sainabou Drammeh,[3] Adri Angyal,[2] Hailey Hornsby,[2] Gabrielle de Crombrugghe,[4,5] Pierre R. Smeesters,[4,5] Omar Rossi,[6] Martina Carducci,[6] Chikondi Peno,[7] Debby Bogaert,[7] Beate Kampmann,[1,3,8] Michael Marks,[1,9,10] Helen A. Shaw,[11] Claire R. Turner,[12] and Thushan I. de Silva[1,2,3]; on behalf of MRCG Strep A Study Group[a]

JID 2023:228



Carriage is **not** immunologically inert

nature communications

Article

https://doi.org/10.1038/s41467-024-46530-2

Inter-species gene flow drives ongoing evolution of *Streptococcus pyogenes* and *Streptococcus dysgalactiae* subsp. *equisimilis*

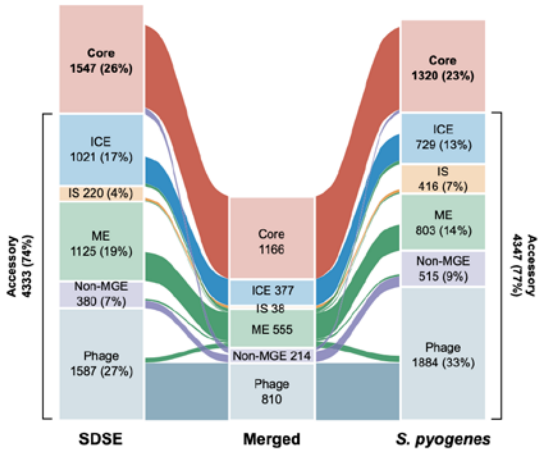
Received: 12 January 2024

Accepted: 28 February 2024

Published online: 13 March 2024

Check for updates

Ouli Xie[1,2], Jacqueline M. Morris[3], Andrew J. Hayes[3], Rebecca J. Towers[4], Magnus G. Jespersen[3], John A. Lees[5], Nouri L. Ben Zakour[6], Olga Berking[6], Sarah L. Baines[7], Glen P. Carter[7], Gerry Tonkin-Hill[8], Layla Schrieber[9], Liam McIntyre[3], Jake A. Lacey[1], Taylah B. James[3], Kadaba S. Sriprakash[10,11], Scott A. Beatson[6], Tadao Hasegawa[12], Phil Giffard[4], Andrew C. Steer[13], Michael R. Batzloff[10,14], Bernard W. Beall[15], Marcos D. Pinho[16], Mario Ramirez[16], Debra E. Bessen[17], Gordon Dougan[18], Stephen D. Bentley[18], Mark J. Walker[6,19], Bart J. Currie[4], Steven Y. C. Tong[1,20], David J. McMillan[21,22] & Mark R. Davies[3,22]



nature communications

Article

https://doi.org/10.1038/s41467-024-47816-1

Overlapping *Streptococcus pyogenes* and *Streptococcus dysgalactiae* subspecies *equisimilis* household transmission and mobile genetic element exchange

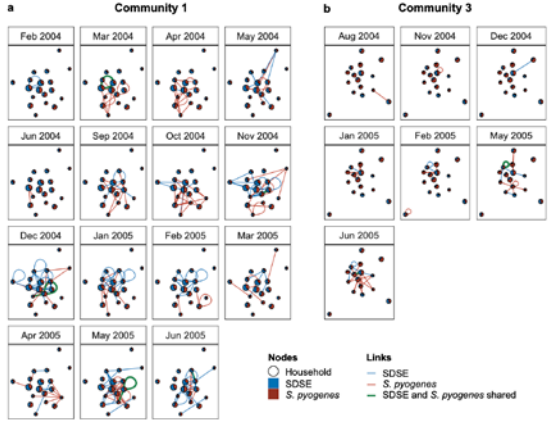
Received: 12 January 2024

Accepted: 12 April 2024

Published online: 24 April 2024

Check for updates

Ouli Xie[1,2], Cameron Zachreson[3], Gerry Tonkin-Hill[4], David J. Price[1,5], Jake A. Lacey[1,6], Jacqueline M. Morris[6], Malcolm I. McDonald[7], Asha C. Bowen[8], Philip M. Giffard[9,10], Bart J. Currie[9,11], Jonathan R. Carapetis[8], Deborah C. Holt[9], Stephen D. Bentley[12], Mark R. Davies[6,14] & Steven Y. C. Tong[1,13,14]



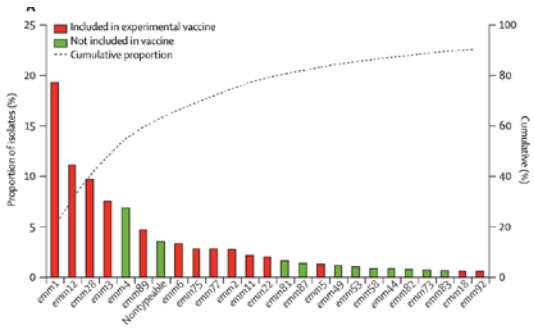
5) Strep A diversity and social determinants

Global *emm* type distribution of group A streptococci: systematic review and implications for vaccine development

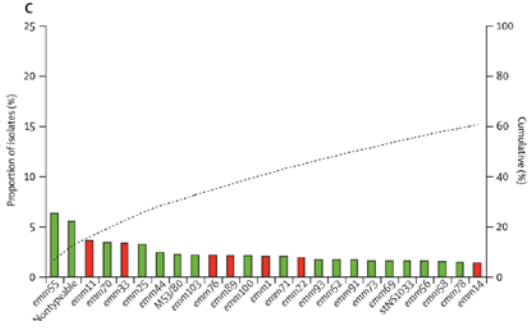
Andrew C Steer, Irwin Law, Laisiana Matatolu, Bernard W Beall, Jonathan R Carapetis

Lancet Infect Dis 2009; 9: 611–16

High-income countries



Pacific



Strain diversity differs by geographic region, with MAJOR implications for vaccine design.

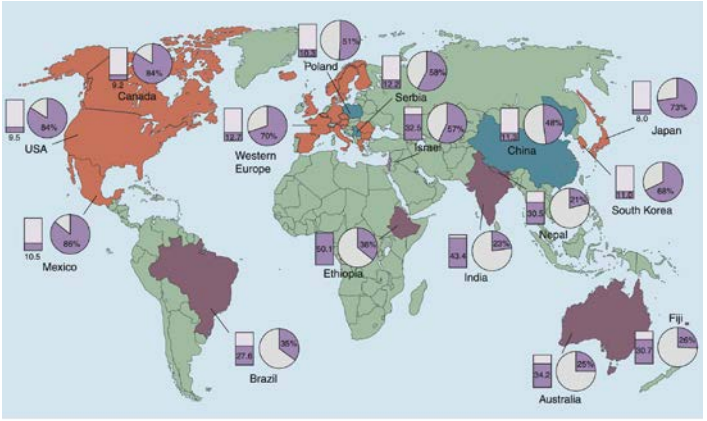
EXPERT REVIEWS

Differences among group A streptococcus epidemiological landscapes: consequences for M protein-based vaccines?

Expert Rev. Vaccines 8(12), 1705–1720 (2009)

Pierre R Smeesters, David J McMillan†, Kadaba S Sriprakash and Melina M Georgousakis

Group A streptococcus (GAS) is a bacterial pathogen responsible for a wide array of disease pathologies in humans. GAS surface M protein plays multiple key roles in pathogenesis, and serves as a target for typing and vaccine development. In this review, we have compiled GAS epidemiological studies from several countries around the world to highlight the consequences on the theoretical efficacy of two different M protein-based vaccine strategies.



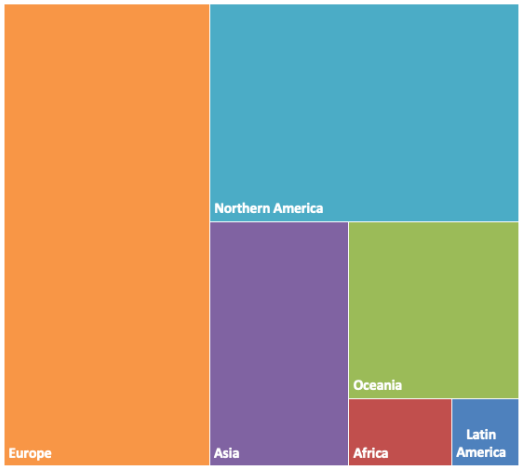
Global *Streptococcus pyogenes* strain diversity, disease associations, and implications for vaccine development: a systematic review

Pierre R Smeesters, Gabrielle de Crombrugghe, Shu Ki Tsoi, Céline Leclercq, Ciara Baker, Joshua Osowicki, Caroline Verhoeven, Anne Botteaux, Andrew C Steer

Lancet Microbe 2024; 5: e181–93

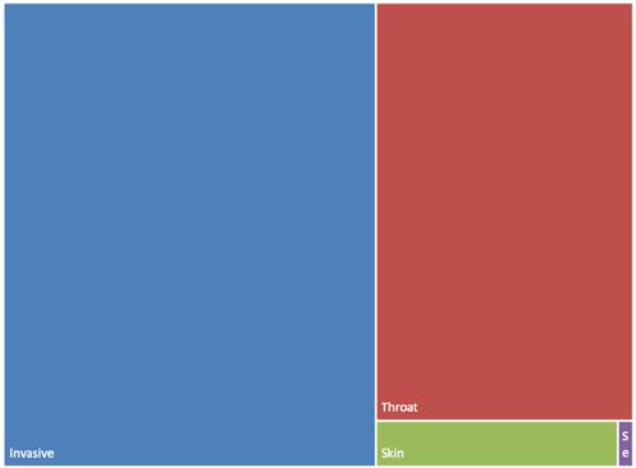
Isolates by geography

(N = 74 488)



Isolates by clinical site

(N = 60 813)

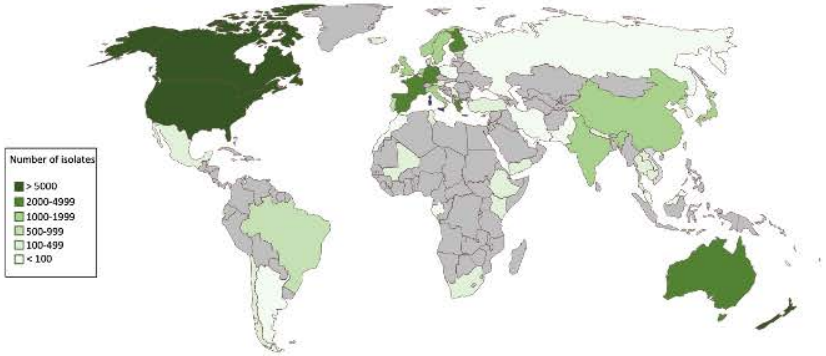


~75,000 isolates from 55 countries

- Nearly twice as many isolates (from 2009)
- 18 (48·6%) more countries
- More data from countries in Africa and South America.

Number of studies

Number of isolates



- Strep A studies still needed in Africa and Middle East
- Focus on Skin and iGAS needed in low-income countries
- Focus on carriage needed in high-income countries

Not just geography (or climate)…

Tartof *et al. BMC Infectious Diseases* 2010, **10**:327
http://www.biomedcentral.com/1471-2334/10/327

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

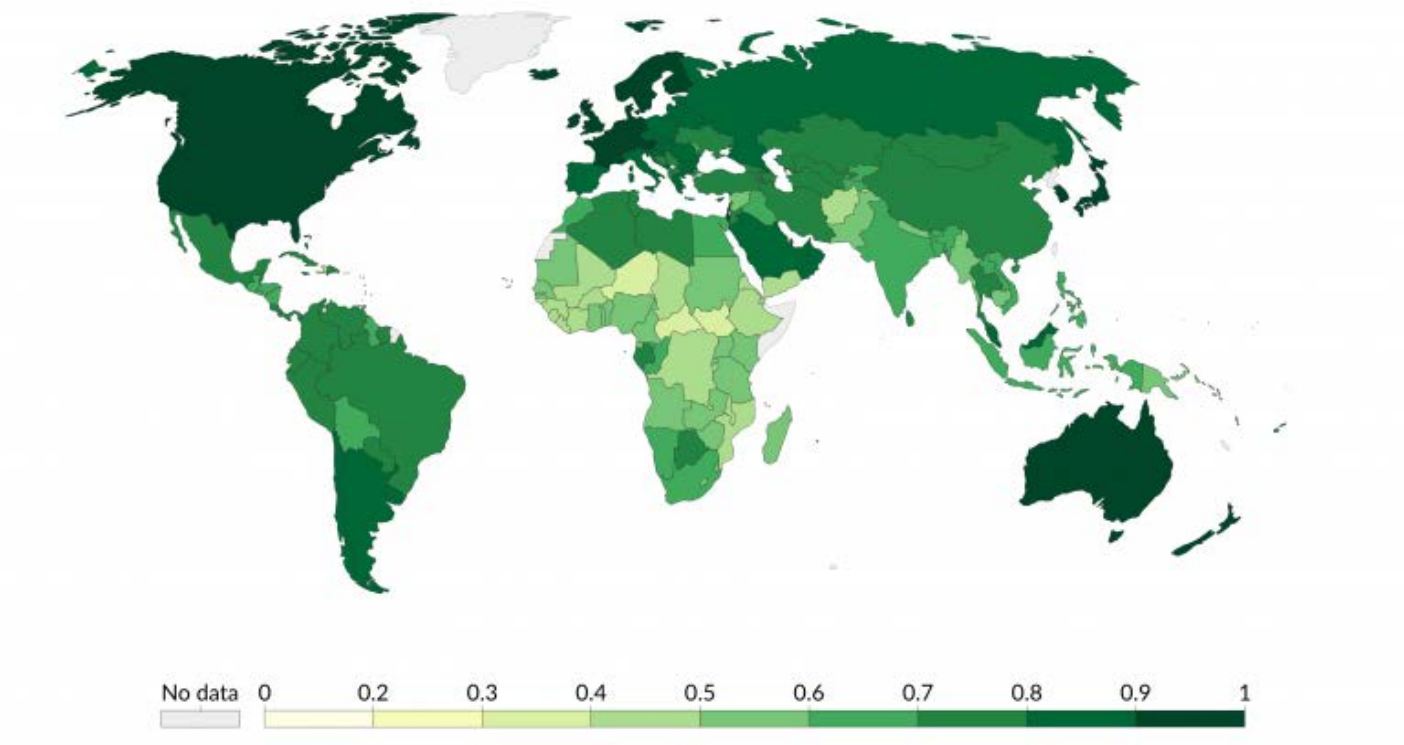
Factors associated with Group A *Streptococcus emm* type diversification in a large urban setting in Brazil: a cross-sectional study

Sara Y Tartof[1], Joice N Reis[2], Aurelio N Andrade[3], Regina T Ramos[4], Mitermayer G Reis[5], Lee W Riley[6*]

Brazilian study in Salvador

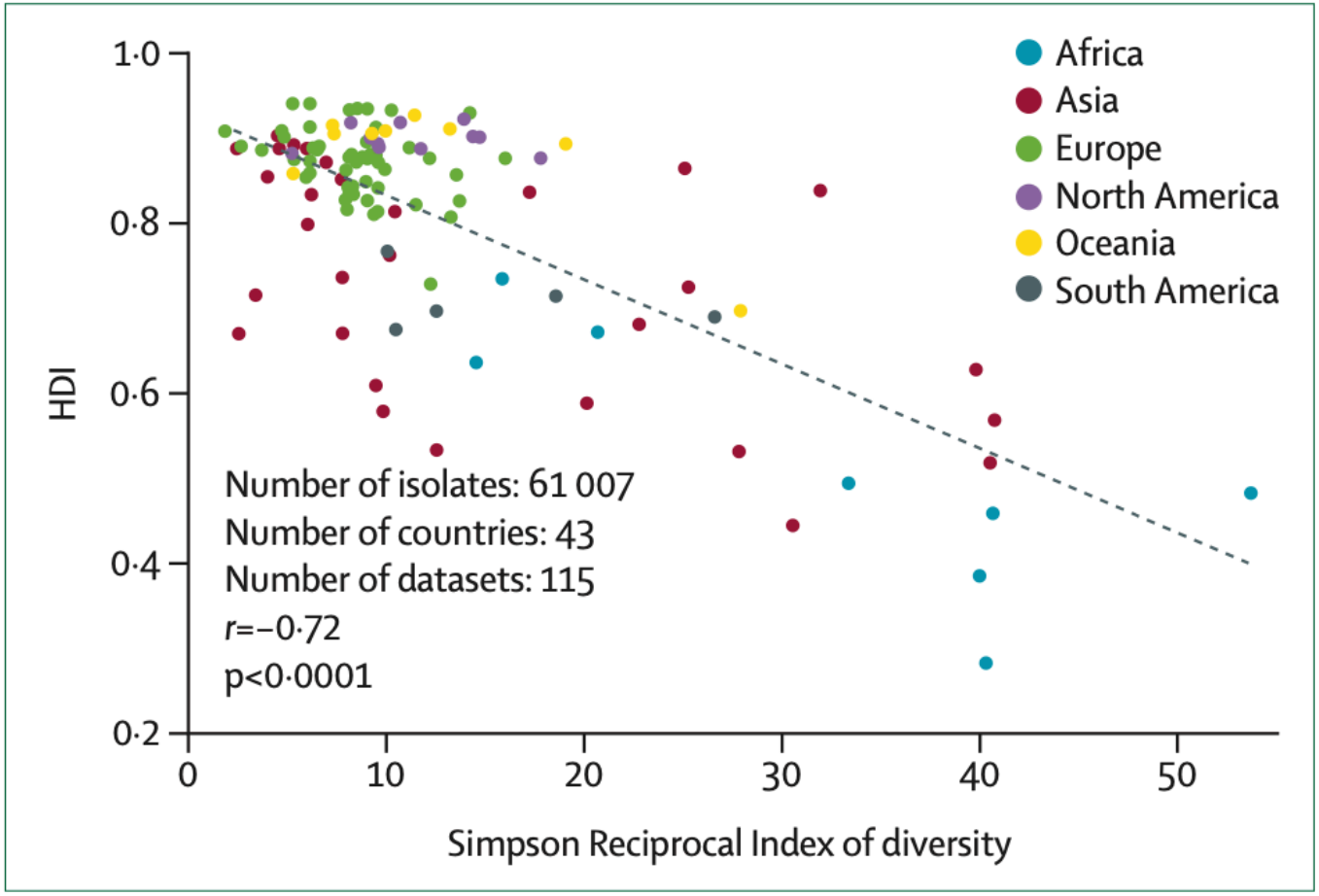
High *emm*-type diversity at the bottom of the hill, in a slum

Low *emm*-type diversity at the top, in a neighboring high-income suburb



HDI

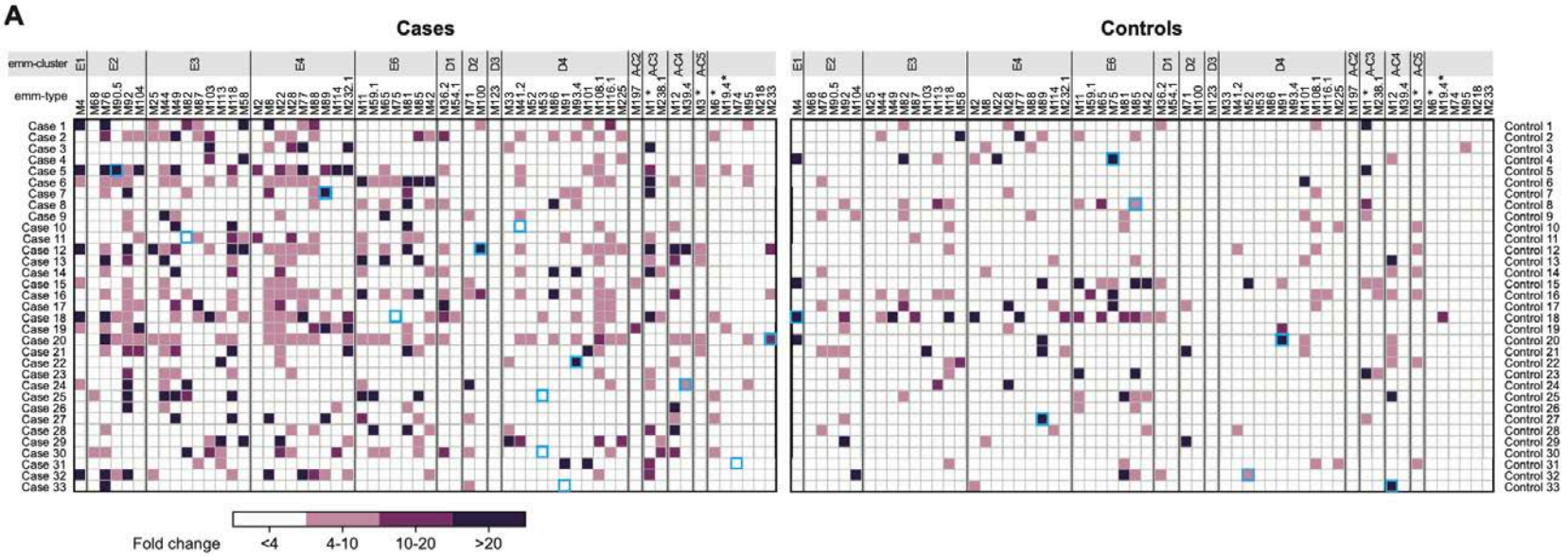
Human Development Index


1·0
0·8
0·6
0·4
0·2
HDI
0
10
20
30
40
50
Simpson Reciprocal Index of diversity
Africa
Asia
Europe
North America
Oceania
South America
Number of isolates: 61 007
Number of countries: 43
Number of datasets: 115
r=–0·72
p<0·0001

Serological Profiling of Group A *Streptococcus* Infections in Acute Rheumatic Fever

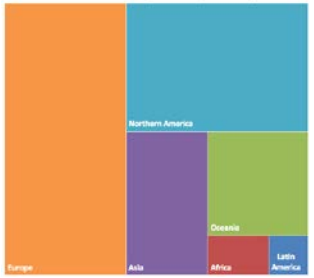
Natalie Lorenz,[1,2] Timothy K.C. Ho,[1] Reuben McGregor,[1,2] Mark R. Davies,[3] Deborah A. Williamson,[3] Jason K. Gurney,[4] Pierre R. Smeesters,[5] Michael G. Baker,[2,4] and Nicole J. Moreland[1,2]

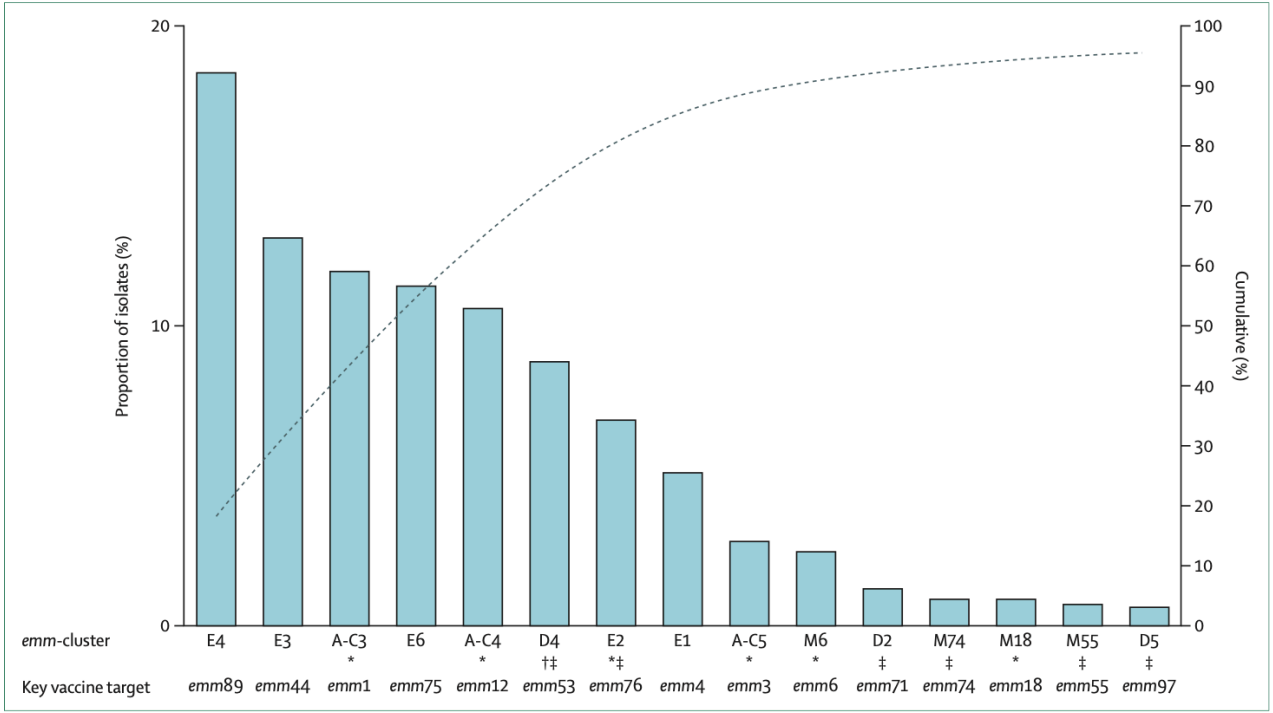
Clinical Infectious Diseases® 2021;73(12):2322–5



Worldwide “**population adapted**” vaccine priorities

Europe and North America together contributing 68·2%





Structural Heart 7 (2023) 100219

Articles and Issues Available at ScienceDirect

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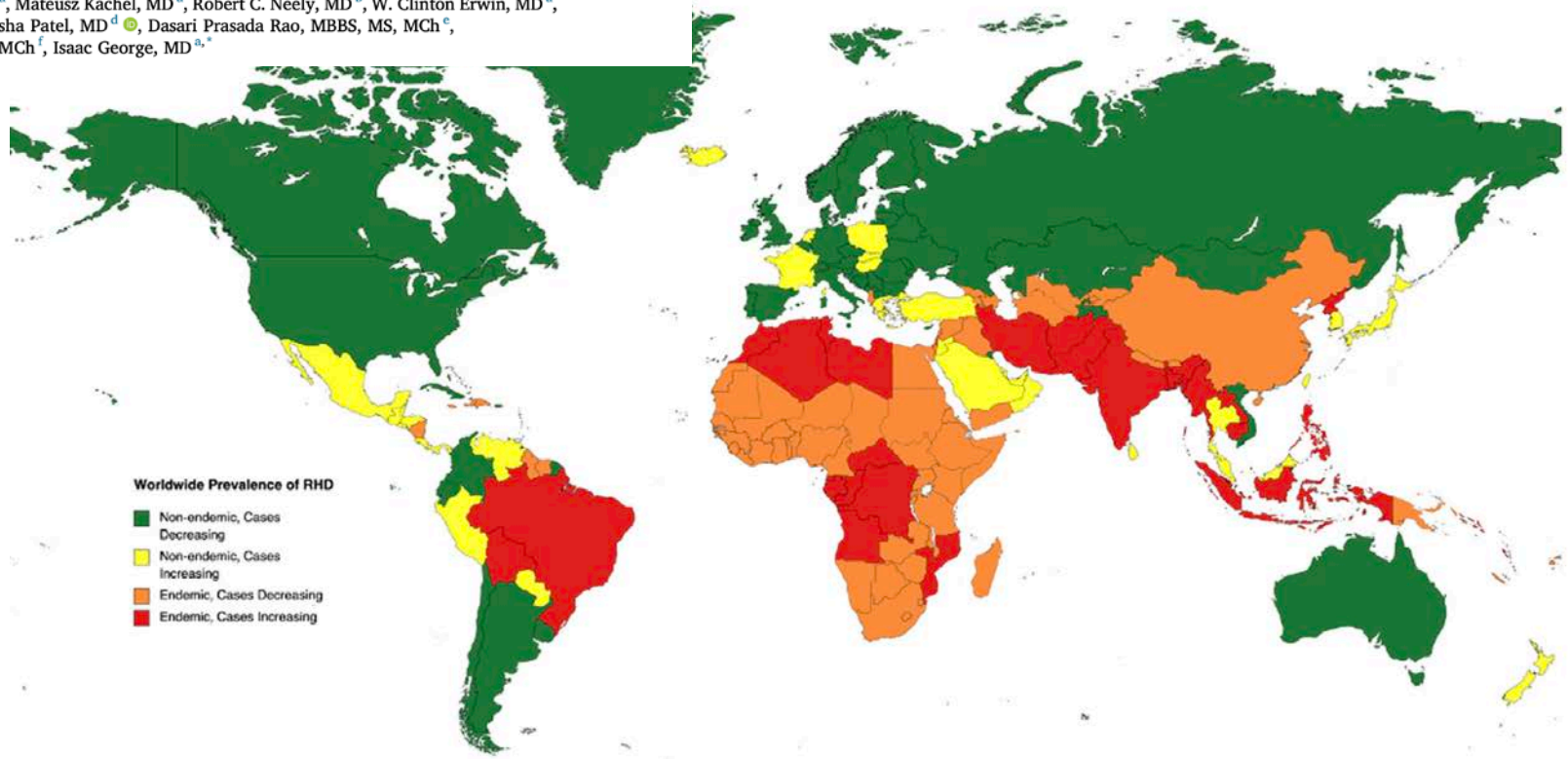
journal homepage: www.structuralheartjournal.org

Review Article

Rheumatic Heart Disease in the Developing World

Michael T. Simpson, MD [a], Mateusz Kachel, MD [a], Robert C. Neely, MD [b], W. Clinton Erwin, MD [a], Aleena Yasin, MD [c], Amisha Patel, MD [d], Dasari Prasada Rao, MBBS, MS, MCh [e], Kaushal Pandey, MBBS, MCh [f], Isaac George, MD [a,*]



Conclusions

- **Strep A is associated with a highly significant disease burden:**
  Morbidity, Mortality, AMR,…
- **Increase in iGAS peaked in winter 22-23 and is most likely multifactorial**
- **Human social determinants are an epidemiological marker of *emm*-type diversity**
- **Importance of taking those social factors more seriously into account in future epidemiological studies**
- **Importance of keeping a helicopter view when dealing with specific research, or public health, questions**

Conclusions (2)

To prevent RHD and iGAS, we need…

- A vaccine with high strain coverage globally
- Social justice

The needle and/or the guillotine (or gentler methods)…

European Plotkin Institute for Vaccinology

Botteaux Anne

Deneubourg Geoffrey
Schiavolin Lionel
Lakhloufi Dalila
Delforge Valérie
Botquin Gwenaelle
Widomski Cyprien
Laho Delphine
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