# A Strategic approach to understanding Strep A disease burden

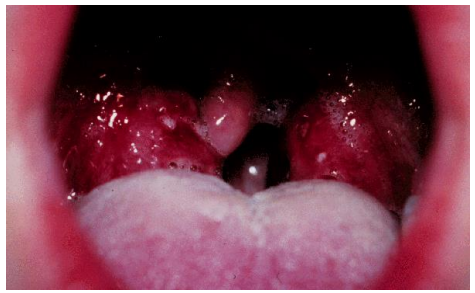
*Epidemiology / Burden of Disease Workstream*

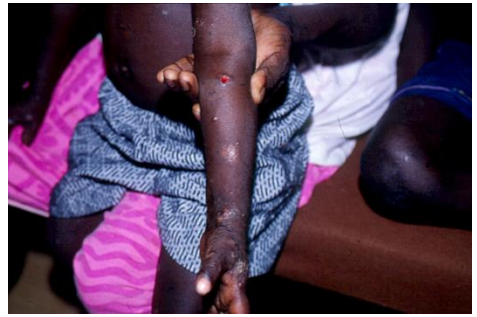
TELETHON KIDS INSTITUTE
Discover. Prevent. Cure.

# Strep A diseases

## Superficial infection

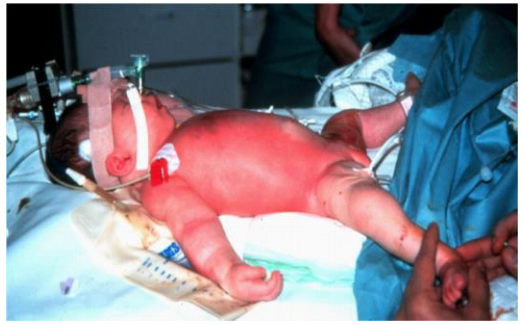
- Pharyngitis
- Pyoderma

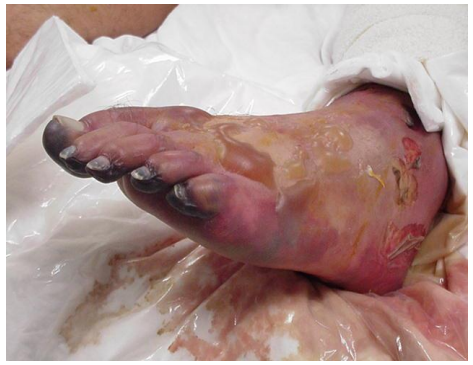




## Invasive diseases

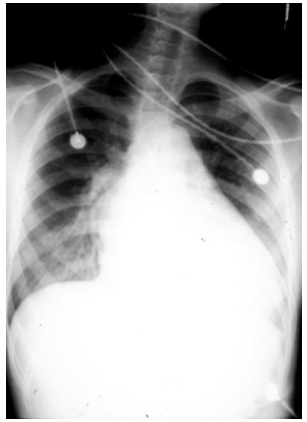
- Septicaemia
- Pneumonia, osteomyelitis…
- Necrotising fasciitis

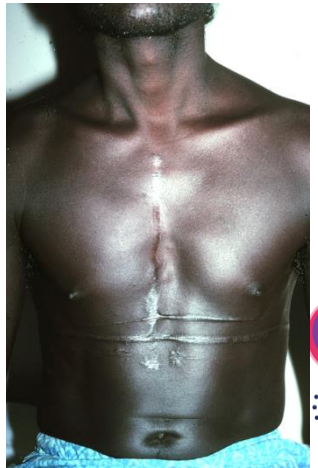




## Toxin mediated diseases

- Scarlet fever
- Streptococcal toxic shock syndrome





## Post-streptococcal autoimmune sequelae

- Acute rheumatic fever / rheumatic heart disease
- Post-streptococcal glomerulonephritis

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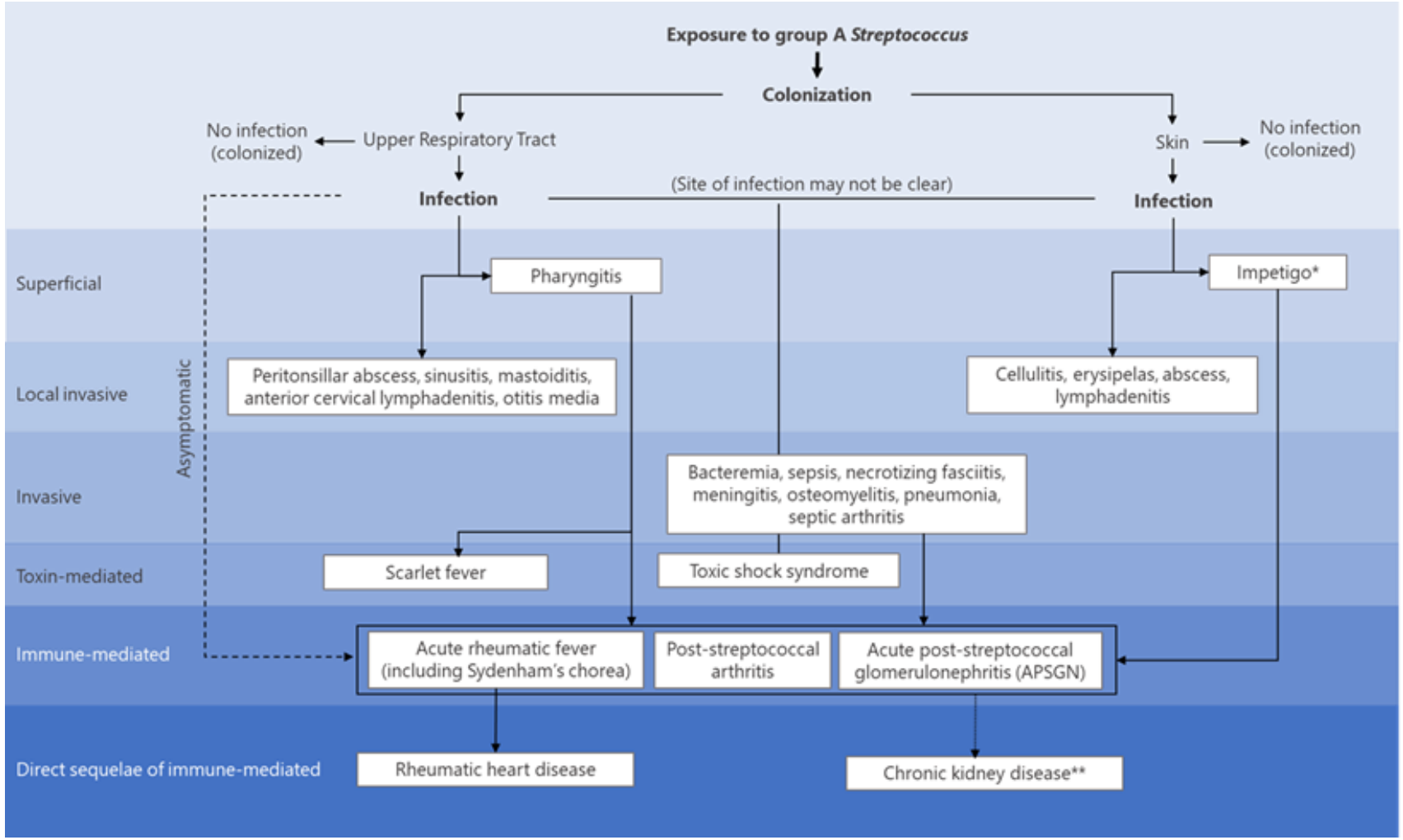
# Strep A Disease Spectrum




Adapted from Cannon et al. **An economic case for a vaccine to prevent group A *Streptococcus* skin infections**. Vaccine, 2018.



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# What do we currently know about Strep A burden of disease?

**TABLE 40.1** Summary of Estimated Global Burden of GAS Diseases

| Disease | Year of Publication | Number of Existing Cases | Number of New Cases Each Year | Number of Deaths Each Year |
|---|---|---|---|---|
| Rheumatic heart disease (RHD) | 2017<br>2005 | 33.4 million[9] | 282,000[2] | 319,000[9] |
| History of acute rheumatic fever without carditis, requiring secondary prophylaxis[2] | 2005 | 1.88 million | 188,000* | |
| RHD-related infective endocarditis[29] | 2016 | | | 14,000 |
| RHD-related stroke | 2016<br>2005 | 640,000[2] | | 134,000[29] |
| Acute post-streptococcal glomerulonephritis[2] | 2005 | § | 472,000 | 9,000 |
| Invasive group A streptococcal diseases[2] | 2005 | | 663,000 | 163,000 |
| Pyoderma[6] | 2015 | 162 million | | |
| Pharyngitis[2] | 2005 | | 616 million | |

500,000 – 600,000 deaths each year

All estimates rounded down.

*New RHD cases were calculated based on the proportion of incident acute rheumatic fever cases expected to develop RHD. The remainder of incident acute rheumatic fever cases are included in the "History of acute rheumatic fever without carditis" row. Therefore the total number of new acute rheumatic fever cases each year is 188,000 + 282,000 = 470,000

§No satisfactory data available to identify glomerulonephritis-induced chronic renal impairment or end-stage renal failure on the global scale.

Ω Inferred from relevant reference.

Sources: Range of WHO estimates (Lancet ID 2005), GBD RHD estimates, systematic reviews

Hand et al, Hunters Tropical Medicine and Emerging Infectious Disease, 10th edition.



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# Strep A: 5th most lethal pathogen on the planet, most neglected*

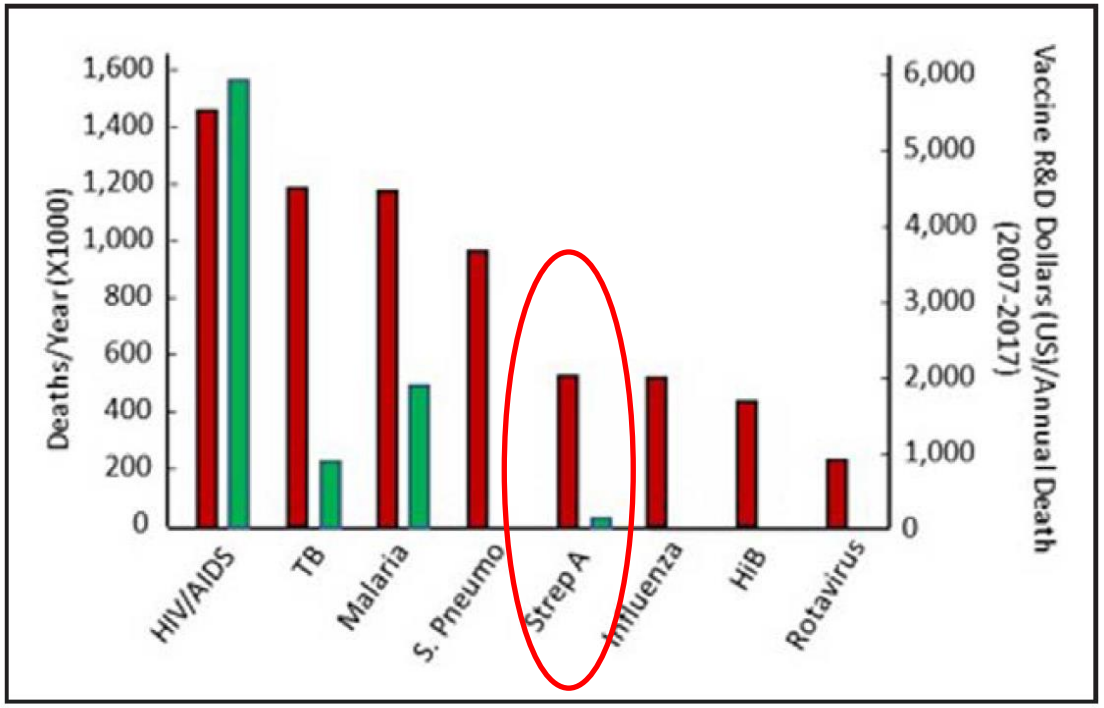
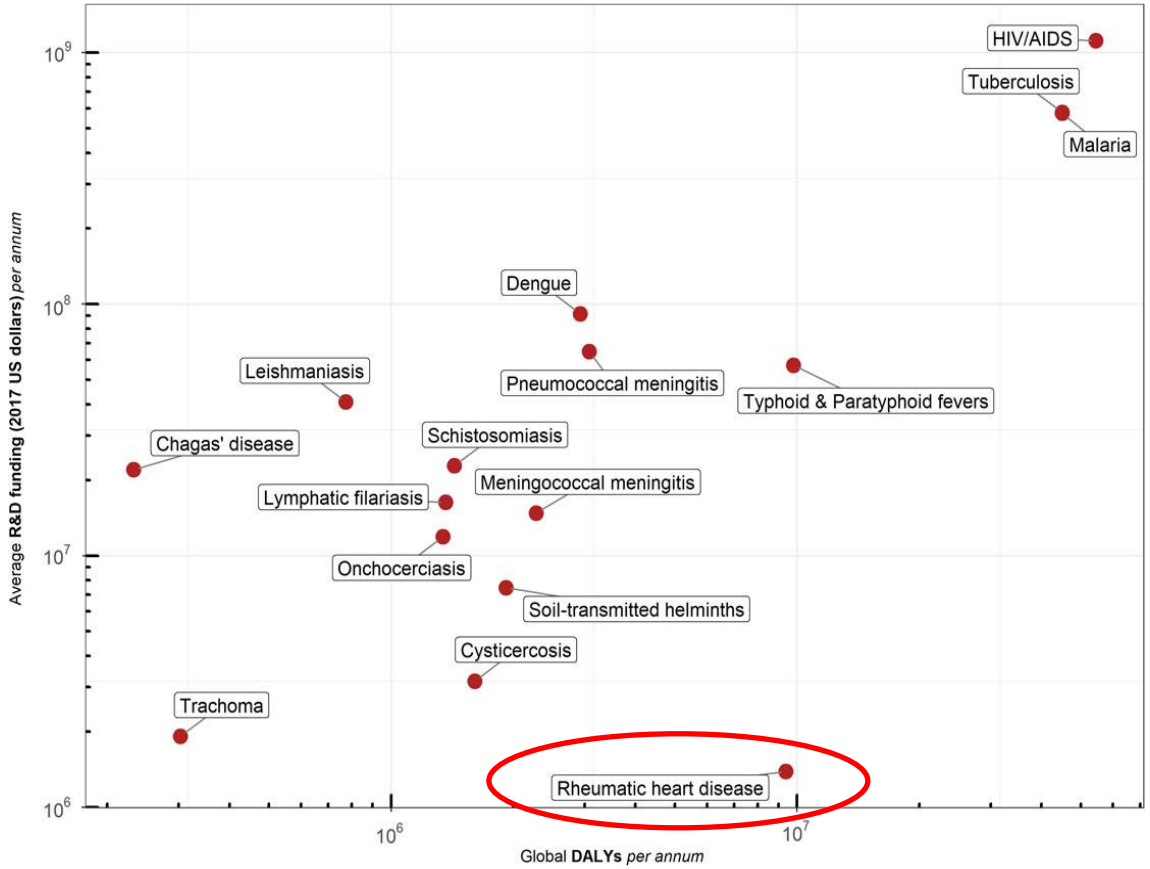



**Figure 1. Annual mortality* (2010 GBD [Global Burden of Disease][33]) attributed to the 8 leading infectious agents (red) with all-source research and development (R&D) funding for vaccine development (green) for pathogens without a vaccine (G-FINDER, 2007–2017).[34]**

*Beaton et al. Circulation 2020*




*McLeod et al. TRSTMH 2019*

* In terms of R&D spend relative to disease burden

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# Updates on Strep A Burden of Disease

**All Strep A diseases**

- **Narrative reviews by Ralph *et al.* (2013), Sanyahumbi *et al.* (2016), Hand *et al.* (2020), Craik *et al.* (2022)**

**Individual diseases**

- **Pharyngitis/sore throat**
- **Impetigo**
  - Bowen (2015), GBD (2019)
- **Cellulitis**
  - GBD (2019)
- **Invasive**
- **APSGN**
- **ARF**
- **RHD**
  - Watkins (2017), GBD (2019)



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# Strep A Sore Throat: Incidence

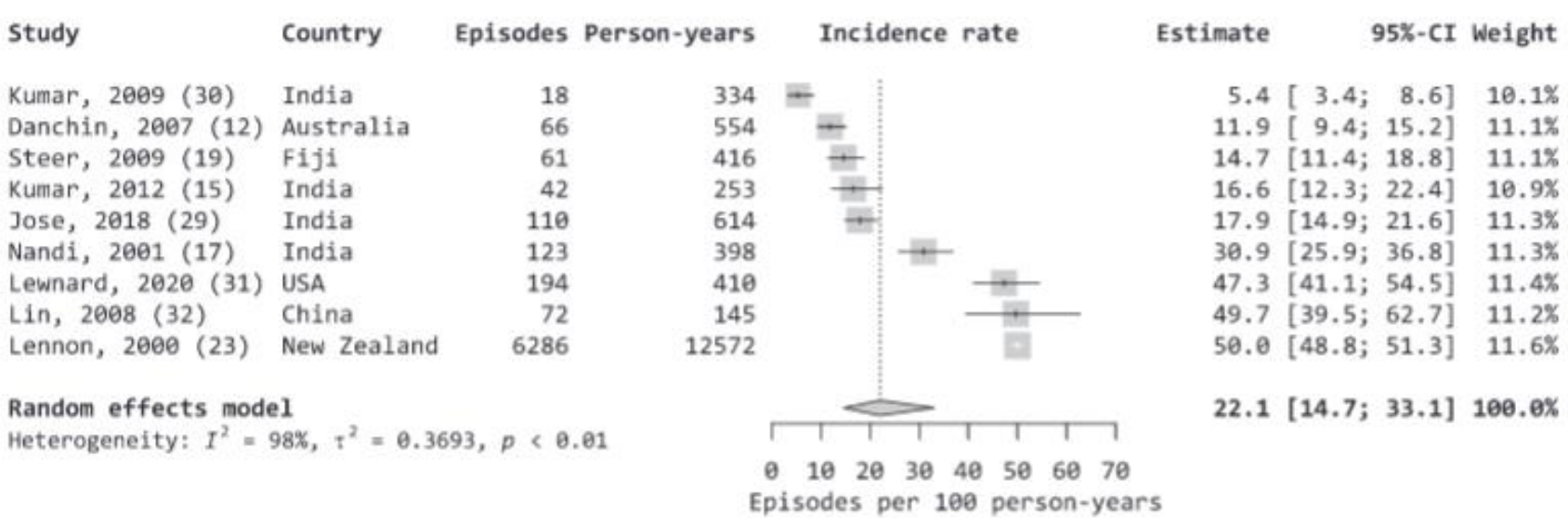


**Figure 4.** Pooled incidence rate of Strep A sore throat for children.Random effects model, heterogeneity: I2 = 98%, $p < 0.01$.

Miller KM, et al. The global burden of sore throat and group A Streptococcus pharyngitis: A systematic review and meta-analysis. eClinicalMedicine 2022; 48: 101458.



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# Sore Throat: Heterogeneity in Study Methodology

| Study variable | Choices used |
|---|---|
| Length of follow-up and seasonality | Ranged from 6 months (for the meta-analysis) to ?5 years |
| Case identification | Parents, children, teachers |
| Case confirmation (sore throat) | Self-diagnosed, parent-diagnosed, specialist-diagnosed |
| Freq. of case identification | Daily, periodically during the week, bi-weekly, monthly, irregular, upon self-identified symptoms |
| Freq. of microbiological testing | Each case, periodic (cases presenting on day of week, fortnight, month) |
| Setting | Household, schools, medical centre |
| | |



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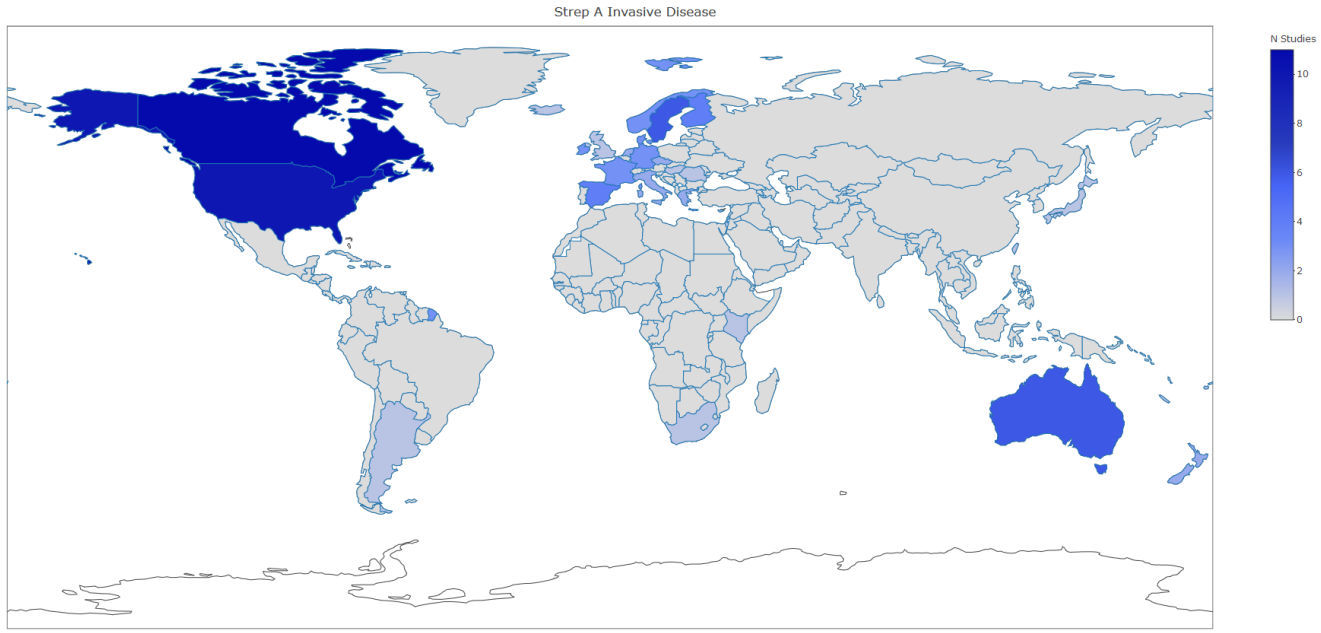
# Invasive Infection: Incidence

**Invasive disease** (any sterile site) - 81 studies from 29 countries




Cannon, et al. The global epidemiology of invasive infection by group A *Streptococcus:* A systematic review and meta-analysis. Manuscript in preparation.



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# Conclusions and limitations

- **Updated picture of the global burden for Strep A**
  - Pharyngitis
  - Impetigo
  - Cellulitis
  - Invasive infection
  - RHD

- **Methodological heterogeneity in Strep A sore throat surveillance**

- **Limited data from LMICs for the incidence and mortality due to invasive infection**



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# Epidemiology / Burden of Disease Objectives

- ***Epidemiology & Burden of Disease* 1 of 5 workstreams**
- **Goal** = Provide updated estimates of Global Strep A Disease Burden
- Objectives:

1. Develop consensus disease case definitions and disease surveillance protocols
2. Identify, maximise and collate existing global data sources
3. Raise awareness of Strep A burden of disease globally
4. Identify key stakeholders and regions/jurisdictions who will comprise the Global Burden of Disease Working Group (BoDWG)
5. Develop new funding proposals to assist future burden of disease work

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# Epidemiology Workstream Activities

- **Complements work of the Full Value Vaccine Assessment**
- **Establish Burden of Disease Working Group**
  - Guide and advise on all ongoing work of the workstream
- **Develop standardized case definitions & surveillance protocols**
- **Formation of a Systematic Data Purpose Matrix**
  - Guiding principles for burden of disease data
- **Identification of priority projects to fill knowledge gaps**
  - Initial progress on key projects



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# Burden of Disease Working Group

- **Established in 2020**
- **Membership considerations:**
  - Broad range of expertise
  - Gender balance
  - Geographical representativeness
- **Coordination from Telethon Kids Institute, Perth, Western Australia**
- **Regular online meetings**
- **Volunteer involvement of all members**



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# Membership

| Name | Institution | Country |
|---|---|---|
| Jonathan Carapetis (Co-Chair) | Telethon Kids Institute | **Australia** |
| Chris Van Beneden (Co-Chair) | Centers for Disease Control | **USA** |
| Hannah Moore | Telethon Kids Institute | **Australia** |
| Jeff Cannon | Telethon Kids Institute | **Australia** |
| Asha Bowen | Perth Children's Hospital / Telethon Kids Institute | **Australia** |
| David Kaslow | PATH | **USA** |
| Thomas Cherian | MMGH Consulting | **Switzerland** |
| Theresa Lamagni | UK Health Security Agency | **UK** |
| Mark Engel | University of Cape Town | **South Africa** |
| Anna Seale | London School of Hygiene & Tropical Medicine | **UK** |
| Gagandeep Kang | Christian Medical College | **India** |
| David Watkins | University of Washington | **USA** |
| Sam Kariuki | Kenya Medical Research Institute | **Kenya** |

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# Surveillance protocols

- **Two sets of protocols initially developed in 2008 (WHO/NIAID)**
  - Acute diseases (pharyngitis, impetigo and invasive infections)
  - Autoimmune sequelae (ARF, RHD and acute post-streptococcal glomerulonephritis)

- **Revise into stand-alone protocols (and published manuscripts)**
  - Pharyngitis - *include scarlet fever not previously included*
  - Impetigo
  - Cellulitis – *new clinical condition*
  - Invasive group A strep infections
  - Acute rheumatic fever
  - Rheumatic heart disease
  - Acute post-streptococcal glomerulonephritis



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# Surveillance protocol update

## Journal Supplement: *Open Forum Infectious Diseases*

- "Standardized case definitions and best practice surveillance protocols for clinical manifestations of group A *Streptococcus* infections"
- Guest Editors: Hannah Moore and Kate Miller

## Timeline for completion of individual chapters

| | Initial submission | Decision notification | Final Outcome |
|---|---|---|---|
| Introduction article | Submitted | Received | Accepted |
| Pharyngitis | Submitted | Received | Accepted |
| Impetigo | Submitted | Received | Accepted |
| Cellulitis | Submitted | Received | Accepted |
| Invasive Diseases | Submitted | Received | Accepted |
| Rheumatic Heart Disease | Submitted | Received | Accepted |
| Acute Rheumatic Fever | Submitted | Received | Accepted |
| Acute post-strep glomerulonephritis | Submitted | Under review | Pending review |



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# Identified Expert Sub-committee Members

**Pharyngitis**

- Katherine Fleming-Dutra (*USA*)
- Stan Shulman (*USA*)
- Bob Tanz (*USA*)
- Alma Fulurija (*Australia*)

**Impetigo**

- Roderick Hay (*UK*)
- Michael Marks (*UK*)
- Lucia Romani (*Australia*)

**Cellulitis**

- Laurens Manning (*Australia*)
- Roderick Hay (*UK*)
- Lucia Romani *(Australia)*
- Michael Marks (*UK*)

**Invasive Disease**

- Katherine Fleming-Dutra (*USA*)
- Tom Parks *(UK)*
- Richard Adegbola (*Nigeria*)

**Acute Rheumatic Fever**

- Andrea Beaton (*USA*)
- Judy Katzenellenbogen (*Australia*)
- Tom Parks (*UK*)

**Rheumatic Heart Disease**

- Andrea Beaton (*USA*)
- Judy Katzenellenbogen (*Australia*)
- Tom Parks *(UK)*
- Katherine Fleming-Dutra (*USA*)

**Acute Post-Streptococcal Glomerulonephritis**

- Bernardo Rodrigues-Iturbe (*Venezuela*)
- Malcolm McDonald (*Australia*)
- William Wong (*New Zealand*)
- James Wetmore (*USA*)

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# Structure of Protocols

## ➢ Common structure across all chapters

**Sections updated:**

- ➢ Disease characteristics
- ➢ Objectives
- ➢ Standardisation of case definitions and case classifications
- ➢ Specimen collection and detection of Strep A (include contemporary diagnostic methods (e.g. Nucleic Acid Amplification Tests))
- ➢ Expanded data sources for disease surveillance
- ➢ Minimal requirements for surveillance and guidance for enhanced surveillance
- ➢ Special considerations for surveillance for each disease manifestation (e.g., ICD codes, measure of disease burden, sample size, frequency of screening)
- ➢ Minimum data requirements and data collection and case report forms (list of recommended and optional variables for inclusion in case report forms)



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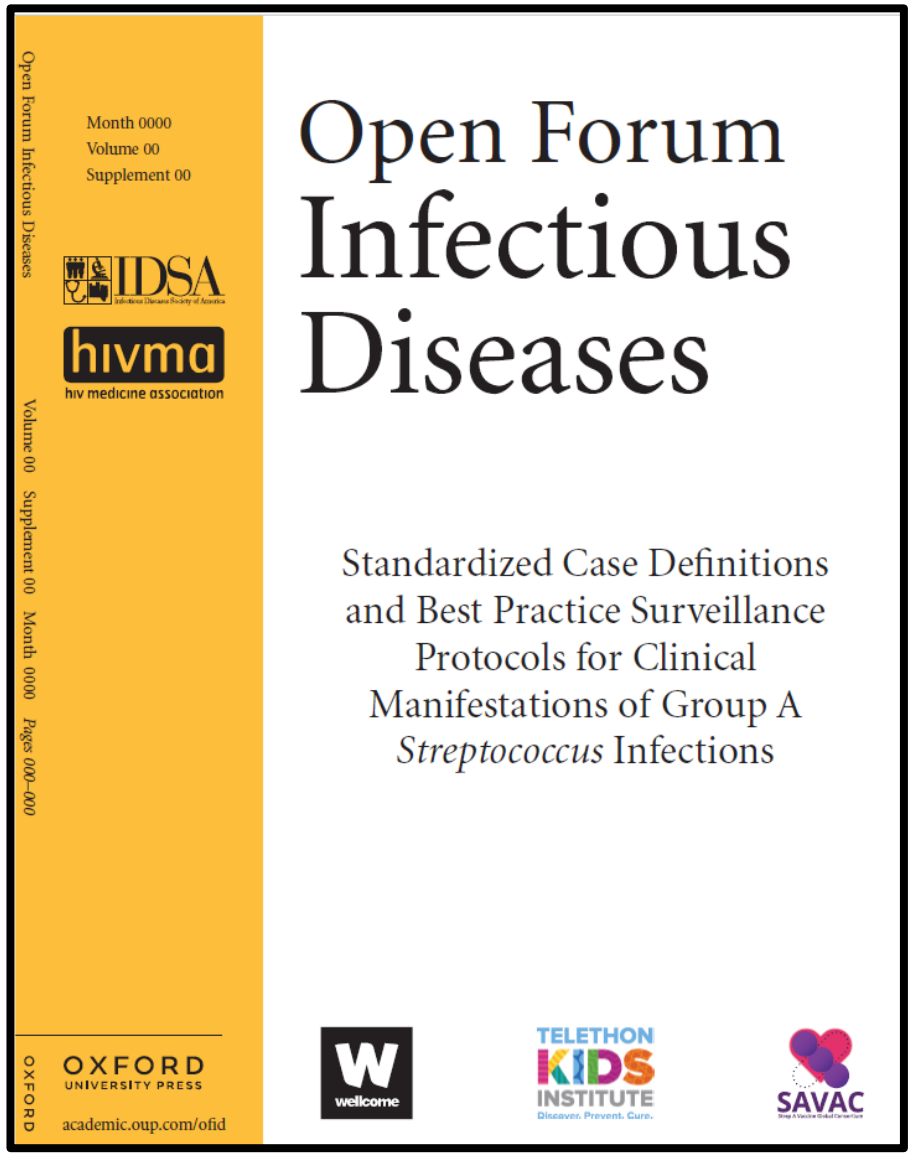
# Case definitions

| Clinical condition | Case definitions | Case classifications |
|---|---|---|
| **Pharyngitis** | Pharyngitis (non-specific), Strep A pharyngitis, scarlet fever, Strep A throat carriage, serologically confirmed Strep A pharyngitis, asymptomatic but immunologically significant Strep A pharyngitis, persistent asymptomatic throat carriage of Strep A following pharyngitis, asymptomatic acquisition and carriage of Strep A in the throat without an immune response. | • Suspect, probable, confirmed |
| **Impetigo** | Clinical bullous impetigo, clinical non-bullous impetigo, Strep A impetigo | • Incidence/prevalent case<br>• Active/inactive lesions |
| **Cellulitis** | Clinical cellulitis, Strep A cellulitis | • Initial, recurrent |
| **Invasive Strep A** | Invasive Strep A infection, STSS, necrotizing fasciitis, invasive Strep A peripartum infection | • Probable case, confirmed |
| **ARF** | Acute Rheumatic Fever | • Initial, recurrent |
| **RHD** | Clinical RHD (for both those with and without a history of ARF), Latent RHD, Suspected RHD | • Definite, borderline |
| **APSGN** | Clinical APSGN, Subclinical APSGN | • Confirmed, probable |

# Dissemination Plan

- **Publication:** OFID supplement (expected Sept 2022)
- **Websites:** One page fact sheets + link to full manuscripts.
- **Twitter:** IDSA, OFID, CID, JID + organizations and individual accounts of those on the BoD WG and Expert sub-committee.
- **Conference presentations:** Relevant upcoming conferences (e.g., symposium at ASTMH, Workshop on the Eradication of RHD (Nov 22), International Conference on Emerging Diseases (Aug 2022)
- **Newsletter article:** associations, committees, organisations, councils, working groups



# Burden of Disease (BoD) data

- BoD= Broad range of outcomes covering entire spectrum of morbidities, sequalae, health-related costs

**"What data are needed?"** to advance vaccine development & implementation

*versus*

**"Where are the current gaps in knowledge?"** from systematic reviews (through FVVA workstreams)

*versus*

**"What data exist that can be leveraged?"** to fill these gaps

What is the purpose of these data and how can these data be used to achieve the SAVAC mission?

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# Formation of a systematic “Data purpose matrix”

- **Four different vaccine evaluation objectives**
  - Advocacy
  - Regulatory Oversight and Licensure
  - Policy Evaluation and Post-Licensure
  - Post-licensure Financing
- **Key elements/requirements of burden of disease data across each objective**
  - Timing on the vaccine pipeline
  - Key stakeholder and audience
  - Overall purpose of the data & key requirements
  - How might these differ for different Strep A disease endpoints
    - Acute Diseases
    - Immune-mediated Sequelae

**Goal = Use matrix to prioritise future data activities and identify research priority areas**

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# Guiding principles for burden of disease data

| | Vaccine Development and Evaluation Objective | | | |
|---|---|---|---|---|
| | **ADVOCACY** | **REGULATORY / LICENSURE** | **POLICY & POST-LICENSURE EVALUATION** | **FINANCING** |
| **Timeline** | | | | |
| **Stakeholders** | ▪Public/private funders & donors<br>▪Advocacy groups<br>▪Manufacturers/Developers<br>▪Wider community/society | ▪National government/Regulators<br>▪WHO vaccine pre-qualification<br>▪Manufacturers/Developers<br>▪Funders & donors | ▪Global, regional, national policy makers<br>▪Public sector immunisation programs<br>▪In-country "champions" | ▪GAVI funding Vaccine Investment Strategy (VIS)<br>▪National government bodies<br>▪Industry/Manufacturers |
| **Data Purpose** | | | | |
| **Requires** | Full disease spectrum<br>Specific & non-specific disease endpoints | Age-specific incidence of endpoints guided by WHO PPC | Vaccine preventable disease burden (population-based where feasible)<br>Specific & non-specific disease endpoints | Vaccination cost to prevent disease<br>Cost of illness<br>Impact on quality of life (QALYs, DALYs) |

# Guiding principles for burden of disease data

| | Vaccine Development and Evaluation Objective | | | |
|---|---|---|---|---|
| | **ADVOCACY** | **REGULATORY / LICENSURE** | **POLICY & POST-LICENSURE EVALUATION** | **FINANCING** |
| **Timeline** | All stages | | | |
| **Stakeholders** | ▪Public/private funders & donors<br>▪Advocacy groups<br>▪Manufacturers/Developers<br>▪Wider community/society | ▪National government/Regulators<br>▪WHO vaccine pre-qualification<br>▪Manufacturers/Developers<br>▪Funders & donors | ▪Global, regional, national policy makers<br>▪Public sector immunisation programs<br>▪In-country "champions" | ▪GAVI funding Vaccine Investment Strategy (VIS)<br>▪National government bodies<br>▪Industry/Manufacturers |
| **Data Purpose** | Quantify **overall preventable disease burden comparable across countries/regions**<br>Data most likely to influence decisions<br>Contextualise in relation to global/ regional/national development goals | | | |
| **Requires** | Full disease spectrum<br>Specific & non-specific disease endpoints | Age-specific incidence of endpoints guided by WHO PPC | Vaccine preventable disease burden (population-based where feasible)<br>Specific & non-specific disease endpoints | Vaccination cost to prevent disease<br>Cost of illness<br>Impact on quality of life (QALYs, DALYs) |

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| | Vaccine Development and Evaluation Objective | | | |
|---|---|---|---|---|
| | **ADVOCACY** | **REGULATORY / LICENSURE** | **POLICY & POST-LICENSURE EVALUATION** | **FINANCING** |
| **Timeline** | All stages | Pre-licensure/Licensure | | |
| **Stakeholders** | ▪Public/private funders & donors<br>▪Advocacy groups<br>▪Manufacturers/Developers<br>▪Wider community/society | ▪National government/Regulators<br>▪WHO vaccine pre-qualification<br>▪Manufacturers/Developers<br>▪Funders & donors | ▪Global, regional, national policy makers<br>▪Public sector immunisation programs<br>▪In-country "champions" | ▪GAVI funding Vaccine Investment Strategy (VIS)<br>▪National government bodies<br>▪Industry/Manufacturers |
| **Data Purpose** | Quantify **overall preventable disease burden comparable across countries/regions**<br>Data most likely to influence decisions<br>Contextualise in relation to global/ regional/national development goals | Provide foundation needed to design/plan clinical trials to **measure vaccine efficacy** & safety | | |
| **Requires** | Full disease spectrum<br>Specific & non-specific disease endpoints | Age-specific incidence of endpoints guided by WHO PPC | Vaccine preventable disease burden (population-based where feasible)<br>Specific & non-specific disease endpoints | Vaccination cost to prevent disease<br>Cost of illness<br>Impact on quality of life (QALYs, DALYs) |

# Guiding principles for burden of disease data

| | Vaccine Development and Evaluation Objective | | | |
|---|---|---|---|---|
| | **ADVOCACY** | **REGULATORY / LICENSURE** | **POLICY & POST-LICENSURE EVALUATION** | **FINANCING** |
| **Timeline** | All stages | Pre-licensure/Licensure | Post-licensure<br>(early analyses good) | |
| **Stakeholders** | ▪Public/private funders & donors<br>▪Advocacy groups<br>▪Manufacturers/Developers<br>▪Wider community/society | ▪National government/Regulators<br>▪WHO vaccine pre-qualification<br>▪Manufacturers/Developers<br>▪Funders & donors | ▪Global, regional, national policy makers<br>▪Public sector immunisation programs<br>▪In-country "champions" | ▪GAVI funding Vaccine Investment Strategy (VIS)<br>▪National government bodies<br>▪Industry/Manufacturers |
| **Data Purpose** | Quantify **overall preventable disease burden comparable across countries/regions**<br>Data most likely to influence decisions<br>Contextualise in relation to global/ regional/national development goals | Provide foundation needed to design/plan clinical trials to **measure vaccine efficacy** & safety | **Measure effectiveness post-licensure**<br>Predict potential impact pre-licensure<br>Provide evidence to form reco mmendations | |
| **Requires** | Full disease spectrum<br>Specific & non-specific disease endpoints | Age-specific incidence of endpoints guided by WHO PPC | Vaccine preventable disease burden (population-based where feasible)<br>Specific & non-specific disease endpoints | Vaccination cost to prevent disease<br>Cost of illness<br>Impact on quality of life (QALYs, DALYs) |

# Guiding principles for burden of disease data

| | Vaccine Development and Evaluation Objective | | | |
|---|---|---|---|---|
| | **ADVOCACY** | **REGULATORY / LICENSURE** | **POLICY & POST-LICENSURE EVALUATION** | **FINANCING** |
| **Timeline** | All stages | Pre-licensure/Licensure | Post-licensure (early analyses good) | Post-licensure (pre-evidence needed for 5yr VIS) |
| **Stakeholders** | ▪Public/private funders & donors<br>▪Advocacy groups<br>▪Manufacturers/Developers<br>▪Wider community/society | ▪National government/Regulators<br>▪WHO vaccine pre-qualification<br>▪Manufacturers/Developers<br>▪Funders & donors | ▪Global, regional, national policy makers<br>▪Public sector immunisation programs<br>▪In-country "champions" | ▪GAVI funding Vaccine Investment Strategy (VIS)<br>▪National government bodies<br>▪Industry/Manufacturers |
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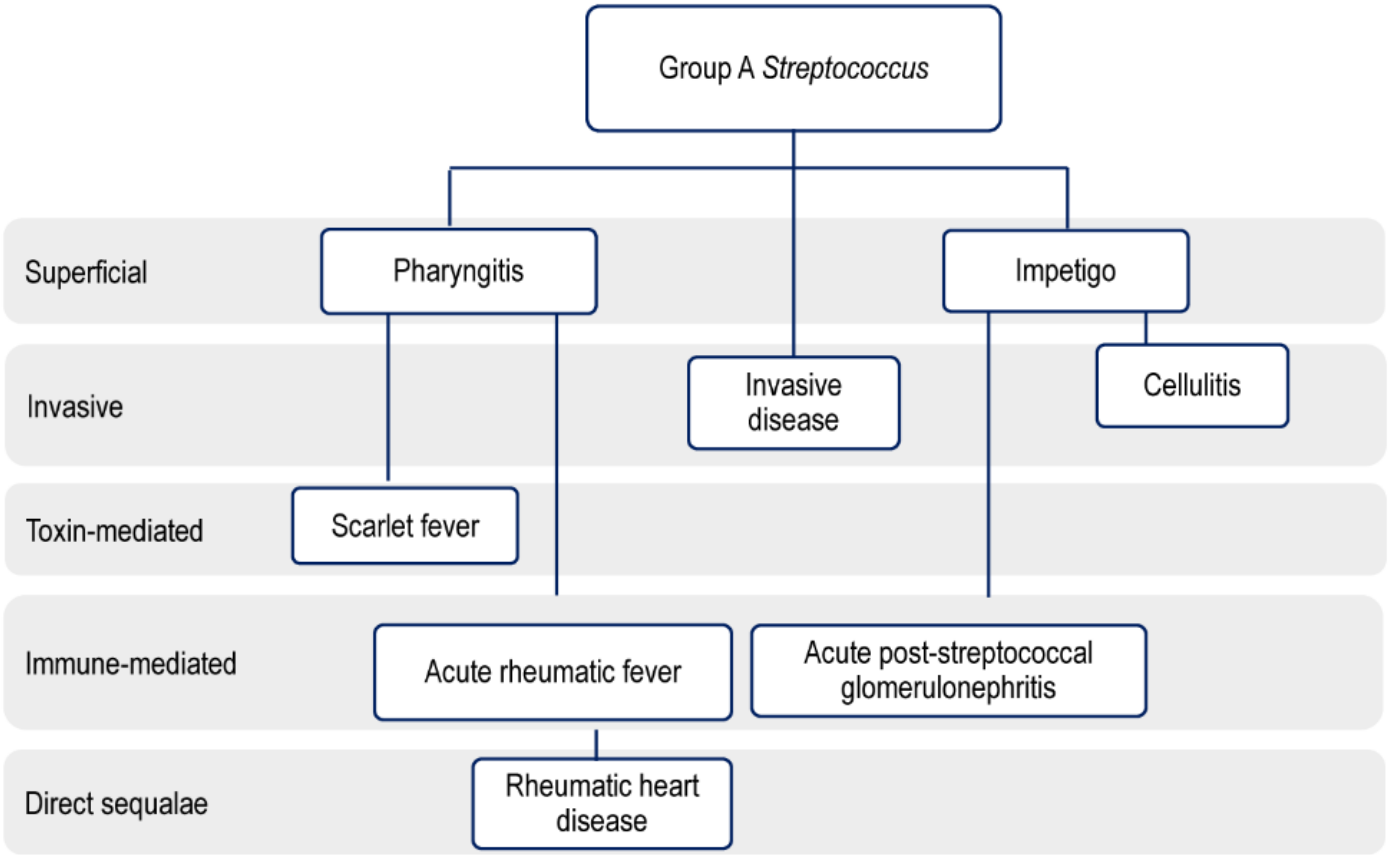
| **Requires** | Full disease spectrum<br>Specific & non-specific disease endpoints | Age-specific incidence of endpoints guided by WHO PPC | Vaccine preventable disease burden (population-based where feasible)<br>Specific & non-specific disease endpoints | Vaccination cost to prevent disease<br>Cost of illness<br>Impact on quality of life (QALYs, DALYs) |

# What Strep A clinical endpoints to focus on?

- **Clinical spectrum of Strep A is broad**
  - Lack of a single focused disease entity likely contributes to the lack of consensus on the global public health importance
  - Consensus reached by BoDWG on what endpoints to focus on

- **5x Acute Diseases**
- **3x Immune-mediated Sequalae**



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# Priorities for burden of disease data for **acute** diseases

*Clinical indications specifically targeted in the WHO PPC of a Strep A Vaccine

| | ADVOCACY | REGULATORY / LICENSURE | POLICY EVALUATION / POST-LICENSURE | FINANCING |
|---|---|---|---|---|
| **Pharyngitis* (children)** | Passive & Active surveillance measuring incidence / prevalence<br>Strain (*emm* type) distribution<br>Vaccine acceptance<br>Markers of immune response: carriage *vs* infection | Prospective active surveillance, lab-confirmed clinical endpoints<br>Establish infrastructure/data mechanism for Phase II/III clinical trials<br>Markers of immune response: carriage *vs* infection | Prospective & Retrospective age-specific or age-standardised incidence<br>Trends in antibiotic use/AMR | Cost of illness from all levels (primary care)<br>Level/cost of antibiotic use<br>Trends in AMR |
| **Impetigo* (children)** | Passive & Active surveillance measuring incidence / prevalence<br>Vaccine acceptance<br>**LMIC:** syndromic surveillance data | Prospective active surveillance with laboratory-confirmed clinical endpoints | Prospective & Retrospective age-specific or age-standardised incidence rates | Cost of illness from all levels |
| **Cellulitis** | Passive & Active surveillance measuring incidence / prevalence (and disease outcomes) | Not critical<br>**HIC:** Consider Phase III trials in targeted populations (e.g. elderly) | Prospective & Retrospective age-specific or age-standardised incidence<br>(focus on adults) | Cost of illness from all levels<br>**HIC:** loss of productivity |
| **Invasive Strep A** | Passive & Active surveillance measuring incidence / outcomes<br>Include mortality<br>Strain (*emm* type) important<br>**HIC:** High-risk populations | Not critical but plan for post-licensure evaluation | Prospective & Retrospective age-specific incidence data<br>Lab-confirmed where possible<br>**HIC:** Assess key foci separately | Cost of illness (hospitalisation/death)<br>Cost of sequalae/DALYs |
| **Scarlet Fever** | Passive & Active surveillance measuring incidence | Not critical | Prospective & Retrospective age-specific or age-standardised incidence | Cost of illness (primary care)<br>Level/cost of antibiotic use<br>Trends in AMR |

# Priorities for burden of disease data for **immune-mediated sequelae**

| | ADVOCACY | REGULATORY / LICENSURE | POLICY EVALUATION / POST-LICENSURE | FINANCING |
|---|---|---|---|---|
| **Acute Rheumatic Fever (ARF)** | Passive & Active surveillance measuring incidence and changes over time | Not critical but plan for post-licensure evaluation<br>Determination of pathway for evaluating impact on severe outcomes from early acute infection | Age-specific incidence and changes over time<br>**LMIC:** data on socio-economic indicators | Cost of illness (hospitalisations/treatment) |
| **Rheumatic Heart Disease (RHD)** | Prevalence in certain at-risk groups<br>**LMIC:** severity of RHD | Not critical but plan for post-licensure evaluation<br>Determination of pathway for evaluating impact on severe outcomes from early acute infection | Age-specific prevalence and changes over time<br>Need to understand progression from acute infection<br>**LMIC:** data on socio-economic indicators | Cost of illness (hospitalisations/death and treatment) |
| **Acute post-streptococcal glomerulonephritis** | Not a critical driver | Not required | Age-specific incidence and changes over time | Cost of illness (hospitalisations/treatment)<br>Potential impact on chronic renal disease |

Moore et al, *Clin Infect Dis* (2022)

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# Matrix considerations

- **High-income countries (HIC) vs low-middle income countries (LMIC)**
  - *HIC*: Strep A-specific data; trends in antibiotic use; impact on AMR
  - *LMIC*: Syndromic surveillance with lab-confirmation from high-performing sites; data on socioeconomic indicators
  - Dichotomy is not always appropriate

- **Matrix is large and complex, *BUT***
  - Strep A has a large clinical spectrum
  - Data requirements differ according to the 4 vaccine objectives

Presenting
Wed 3pm
"Novel Vaccine
Concepts"

- **Adaptable and flexible framework**
  - Update as Strep A vaccine candidates progress through trials
  - Could be used for other pathogens on the vaccine development horizon

Moore et al, *Clin Infect Dis* (2022)

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# Identifying priority projects

**Collate information from:**

- Burden of Disease Working Group Meeting Discussions
- Data Purpose Matrix
- Current work under SAVAC FVVA workstream – systematic reviews, Shift Health Landscape Report for Business Case



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# Utility of the matrix to identify priority areas for research

| | ADVOCACY | REGULATORY / LICENSURE | POLICY EVALUATION / POST-LICENSURE | FINANCING |
|---|---|---|---|---|
| **Pharyngitis (children)** | | Prospective active surveillance, lab-confirmed clinical endpoints<br>Establish infrastructure for Phase II/III clinical trials<br>Markers of immune response: carriage *vs* infection | Trends in antibiotic use/AMR | |
| **Impetigo (children)** | | Prospective active surveillance with laboratory-confirmed clinical endpoints | | |
| **Cellulitis** | | | | |
| **Invasive Strep A** | | | | |
| **Scarlet Fever** | | | | |
| **ARF** | | | | |
| **RHD** | | | | |
| **APSGN** | | | | |

- Sentinel surveillance sites needed for **pharyngitis (and impetigo)**, focusing on school aged-children
  - Clinical endpoint in WHO PPC
  - Critical value of surveillance protocols and importance of dissemination strategy
  - Important to establish in LMIC as well as HIC
- Role of asymptomatic infection vs carriage
- Level of antibiotic use and AMR likely to be key driver for cost and therefore critical to include into economic models

# Utility of the matrix to identify priority areas for research

| | ADVOCACY | REGULATORY / LICENSURE | POLICY EVALUATION / POST-LICENSURE | FINANCING |
|---|---|---|---|---|
| **Pharyngitis (children)** | | | | |
| **Impetigo (children)** | | | | |
| **Cellulitis** | | | | |
| **Invasive Strep A** | Passive & Active surveillance<br>measuring incidence / outcomes<br>Include mortality<br>Strain (*emm* type) important<br>**HIC:** High-risk populations | | Prospective & Retrospective<br>age-specific incidence data<br>Lab-confirmed where possible<br>**HIC:** Assess key foci separately | Cost of illness (esp. hospitalisation/death)<br>Cost of sequalae/DALYs |
| **Scarlet Fever** | | | | |
| **ARF** | | | | |
| **RHD** | | | | |
| **APSGN** | | | | |

- Gap in incidence of **invasive disease**
- Dearth of age-specific incidence rates, especially in LMIC
- Need to include burden assessment of puerperal sepsis
- Could leverage existing surveillance networks

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# Utility of the matrix to identify priority areas for research

| | ADVOCACY | REGULATORY / LICENSURE | POLICY EVALUATION / POST-LICENSURE | FINANCING |
|---|---|---|---|---|
| **Pharyngitis (children)** | | | | |
| **Impetigo (children)** | | | | |
| **Cellulitis** | Passive & Active surveillance measuring incidence / prevalence (and disease outcomes) | Not critical<br>**HIC:** Consider Phase III trials in targeted populations | Prospective & Retrospective age-specific or age-standardised incidence<br>(focus on adults) | Cost of illness from all levels<br>**HIC:** loss of productivity |
| **Invasive Strep A** | | | | |
| **Scarlet Fever** | | | | |
| **ARF** | | | | |
| **RHD** | | | | |
| **APSGN** | | | | |

- Incidence of **cellulitis**, especially in adults
  - ??Adult vaccine in HIC
- In Aus/NZ: Major contributor to Strep A burden, cost and value of a vaccine
- Some data should be Strep A specific – asses attributable fraction of Strep A to cellulitis
- Important for HIC; perhaps not a priority for LMIC?

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# Utility of the matrix to identify priority areas for research

| | ADVOCACY | REGULATORY / LICENSURE | POLICY EVALUATION / POST-LICENSURE | FINANCING |
|---|---|---|---|---|
| **Pharyngitis (children)** | Incidence / prevalence<br>Strain (*emm* type) distribution<br>Vaccine acceptance<br>Markers of immune response: carriage *vs* infection | | | |
| **Impetigo (children)** | Incidence / prevalence<br>Vaccine acceptance | | | |
| **Cellulitis** | Incidence / prevalence<br>(and disease outcomes) | | | |
| **Invasive Strep A** | Incidence / outcomes (include mortality<br>Strain (*emm* type) important<br>**HIC:** High-risk populations | | | |
| **Scarlet Fever** | Incidence | | | |
| **ARF** | Incidence and changes over time | | | |
| **RHD** | Prevalence in certain<br>at-risk groups<br>**LMIC:** severity of RHD | | | |
| **APSGN** | Not a critical driver | | | |

- Burden of disease data broadly needed to raise profile of Strep A Vaccine development
- Important for both HIC and LMIC
- Country-level BoD data important across all Strep A endpoints
- Contextualise in relation to global, regional and national public health goals

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# Consolidated Priority Projects

| Top Disease Burden priority projects |
| --- |
| 1. Establish sentinel surveillance sites for pharyngitis (and impetigo) |
| 2. Data to describe incidence of invasive Strep A disease in LMIC |
| 3. Assessing the attributable fraction of Strep A to cellulitis in different settings |
| 4. Strep A Global Burden of Disease estimate through Global Burden of Disease project (IHME) |
| 5. Multi-country epidemiological record linkage studies |
| **Important, but not solely disease burden** |
| 6. Understanding country, regional and international decision-making for vaccines |
| **Other priority disease burden projects of interest** |
| 7. Measure maternal / puerperal sepsis (incl record linkage studies) |
| 8. Quantify antibiotic use for pharyngitis |
| 9. New diagnostic methods |
| 10. Explore incidence and burden of ARF through modelling |



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# Progress to date

## Project 2: Collate data to describe incidence of invasive Strep A

- **Exploring data from surveillance programs in Africa *with Andrea Haselbeck, Florian Marks (IVI)***
  - Typhoid Fever Surveillance in Africa Program (TSAP): 2010-2014
  - Severe Typhoid Surveillance in Africa Program (SETA): 2015-2019
  - Blood culture-based fever surveillance across 10 countries from Sub-Saharan Africa
  - Collate aggregated data on positive cultures for Strep A
  - Population denominators adjust for health seeking behaviour
  - Ethics/Agreements completed and signed, data transferred, analysis ongoing
  - Few cases of invasive Strep A but proof-of-concept to obtain existing data to enumerate age-specific invasive Strep A incidence from existing networks

**Next steps:** Contact/Identify other existing bacterial surveillance networks

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# Progress to date

## Project 2: Collate data to describe incidence of invasive Strep A

- **Exploring contemporary data from surveillance systems and research networks**
  - MD Student (University of Western Australia / Telethon Kids Institute
  - Aims:
    - Identify and catalogue surveillance networks and systems that record data on invasive Strep A disease across LMIC and HIC
    - Develop concept dictionary/metadata: case definitions, years of available data, data items captured through surveillance
  - Scope of the project (due to time constraints) is to identify data, not collate/analyse data

**Next steps:** Leverage networks from the Burden of Disease Working Group

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# Progress to date

## Project 5: Multi-country epidemiological record linkage studies

- **Develop standardised research protocols to conduct a multi-country collaborative study**
  - Aims:
    - Describe epidemiology of Strep A diseases; age-specific incidence rates of acute Strep A clinical endpoints
    - Where possible, estimate pathogen-specific burden using lab data (+ve blood cultures; molecular detection)
    - Describe incidence of Strep A endpoints by characteristics of interest (socioeconomic status, ethnicity)
  - Administrative data to focus on: hospital admissions (ICD-coded), emergency department, death records, demographic data
  - Identify collaborators/centres/countries with available data

**Next steps:** Contact record linkage networks and collaborators, build up research protocol

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# Next Steps – with what we have available

- **Dissemination of the surveillance protocols**

- **Formalise Burden of Disease Working Group into a "Scientific Advisory Group"**
  - Offer honorariums for service/commitment (requires funding)

- **Progress where possible 2 priority projects**
  - Seek funding to progress efficiently
  - Identify collaborators and possible funding avenues



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# Next Steps – realizing the potential

- **Make the most of the work to date and the passion and expertise of those involved**
  - Develop protocols for each priority project
  - Make sure they are funded and supported
  - Coordinate, communicate, advocate, update
  - Learn from other VPDs as well as set an example using the data purpose matrix



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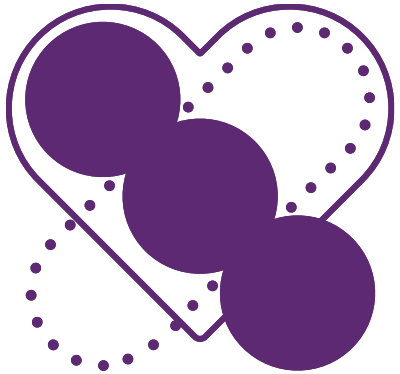
# Acknowledgements

**Strep A Vaccine Global Consortium**
**https://savac.ivi.int/**



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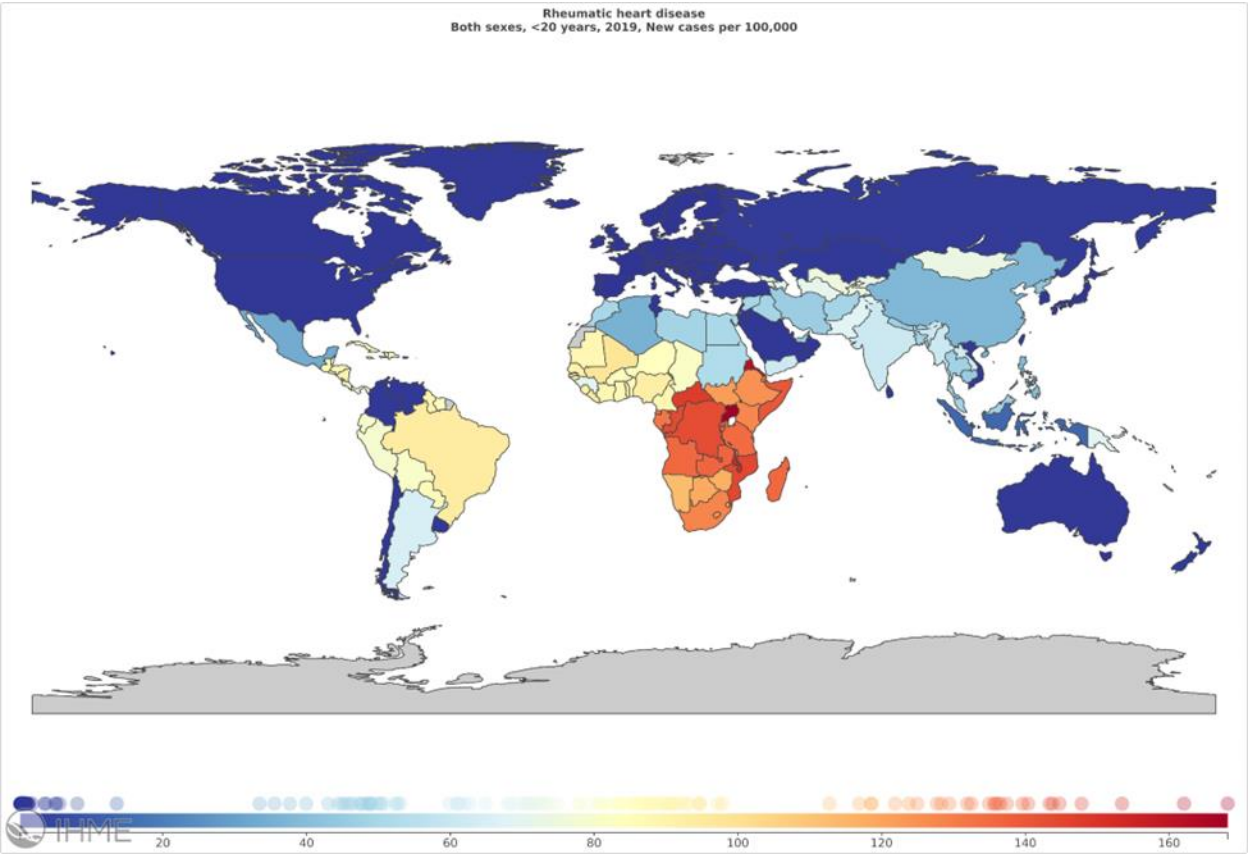
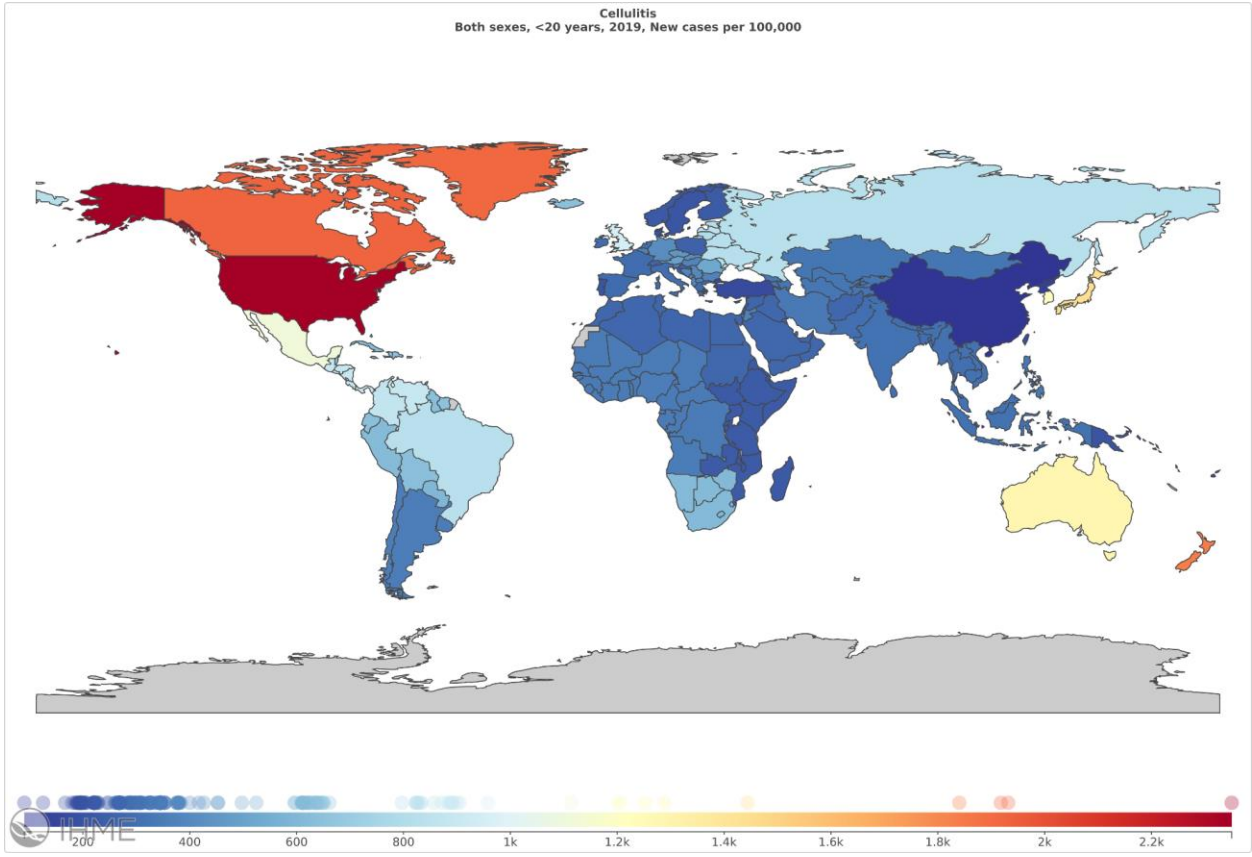
# RHD, Cellulitis, and Impetigo (GBD, 2019)

Incidence of RHD among people <20-years-old




Incidence of cellulitis among people <20-years-old



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