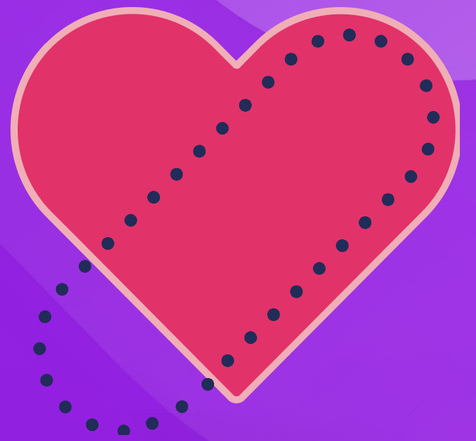
Streptococcus pyogenes vaccine development

And report from 2024 WHO meeting

Andrew Steer
Andrea Beaton



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

Outline

Disease and disease burden
Vaccine landscape
Enabler landscape
Key issues for the field
SAVAC meeting London 2024: vaccine endpoints
What’s next

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

Disease and disease burden

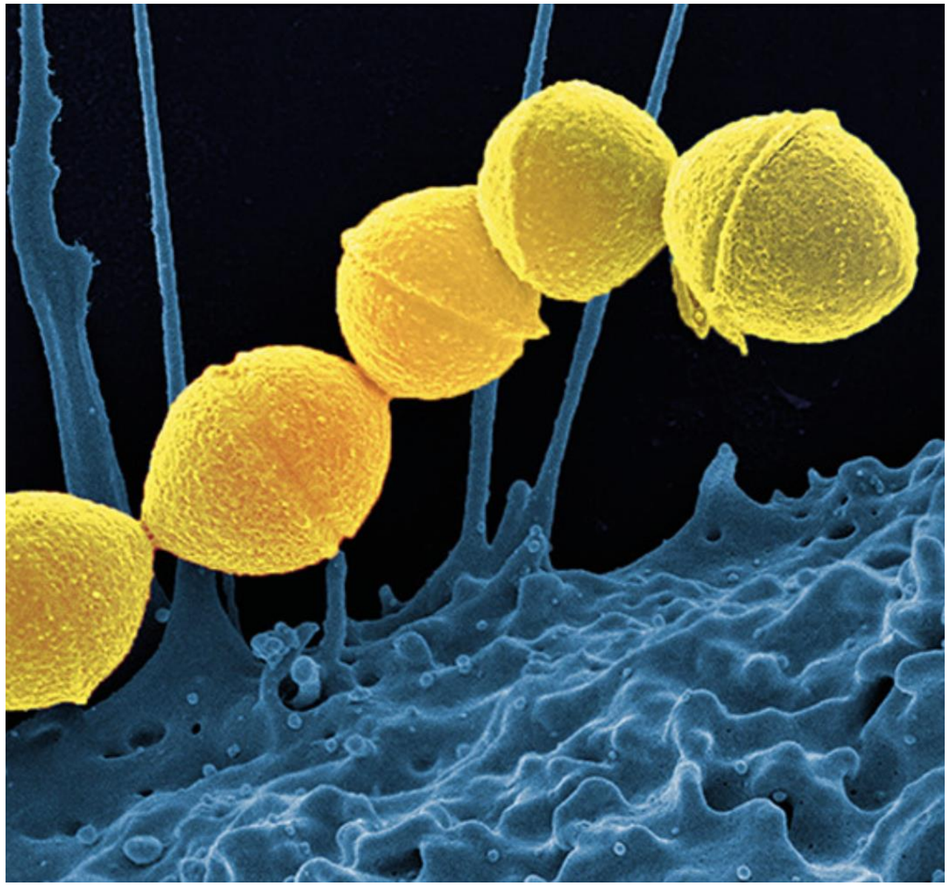
Strep A Vaccine Global Consortium
https://savac.ivi.int/

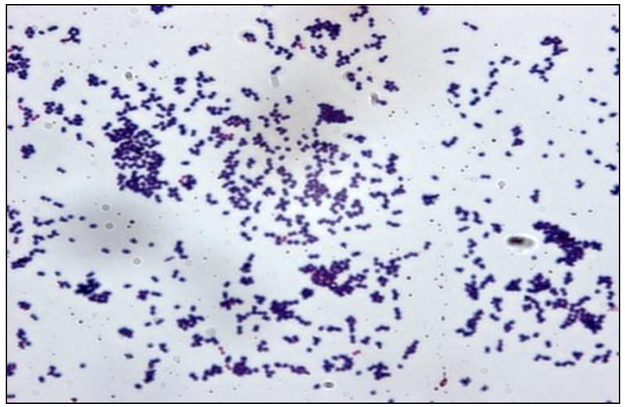
-Strep A

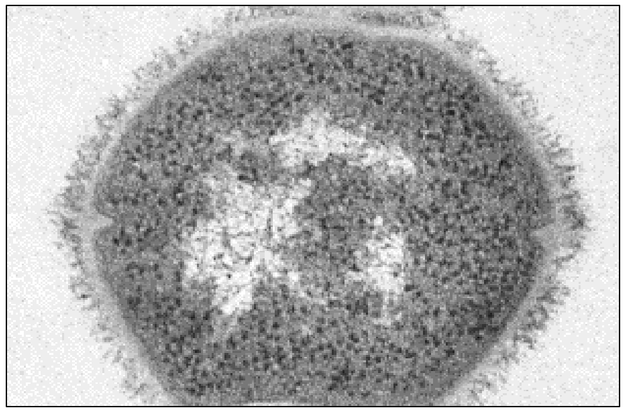
-*Streptococcus pyogenes*

-Group A Streptococcus (GAS)

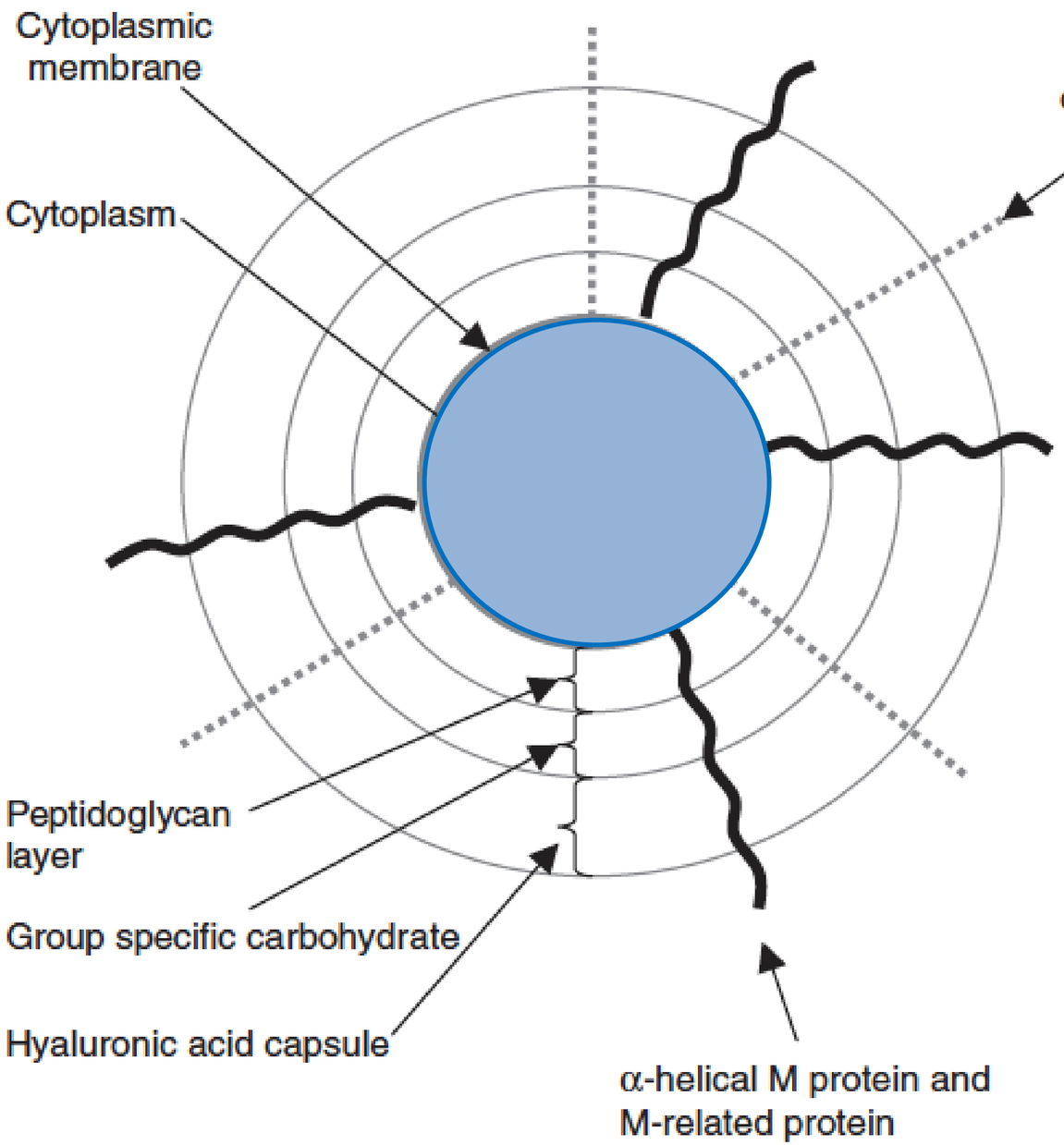
-Group A beta-hemolytic Streptococcus (GABHS)







Strep A: a complex pathogen



Other extracellular virulence factors
Streptolysin S
Streptolysin O
DNase A-D
Hyaluronidase
Streptokinase
NADase
C5a peptidase
Spe-B (Streptococcal proteinase)
Spe-A,C,G,H,J-M
SSA
SMEZ and SMEZ-2
SIC
GRAB
SOD
Mac
Sc1A and 1B
EndoS and IdeS

Steer et al JPCH 20

Malice in Chains

Courtesy: Dr Josh Osowicki

Pharyngitis

↓

Scarlet fever

Impetigo

SSTI (e.g. cellulitis)

Invasive disease

↓

Toxic shock syndrome

Acute glomerulonephritis

Acute rheumatic fever

↓

Rheumatic heart disease

Pharyngitis

↓

Scarlet fever

Superficial mucosal

Impetigo

SSTI (e.g. cellulitis)

Invasive disease

↓

Toxic shock syndrome

Acute glomerulonephritis

Acute rheumatic fever

↓

Rheumatic heart disease

Pharyngitis

↓

Scarlet fever

Impetigo

SSTI (e.g. cellulitis)

Superficial skin

Invasive disease

↓

Toxic shock syndrome

Acute glomerulonephritis

Acute rheumatic fever

↓

Rheumatic heart disease

Pharyngitis

↓

Scarlet fever

Impetigo

SSTI (e.g. cellulitis)

Invasive disease

↓

Toxic shock syndrome

Acute glomerulonephritis

Acute rheumatic fever

↓

Rheumatic heart disease

Invasive

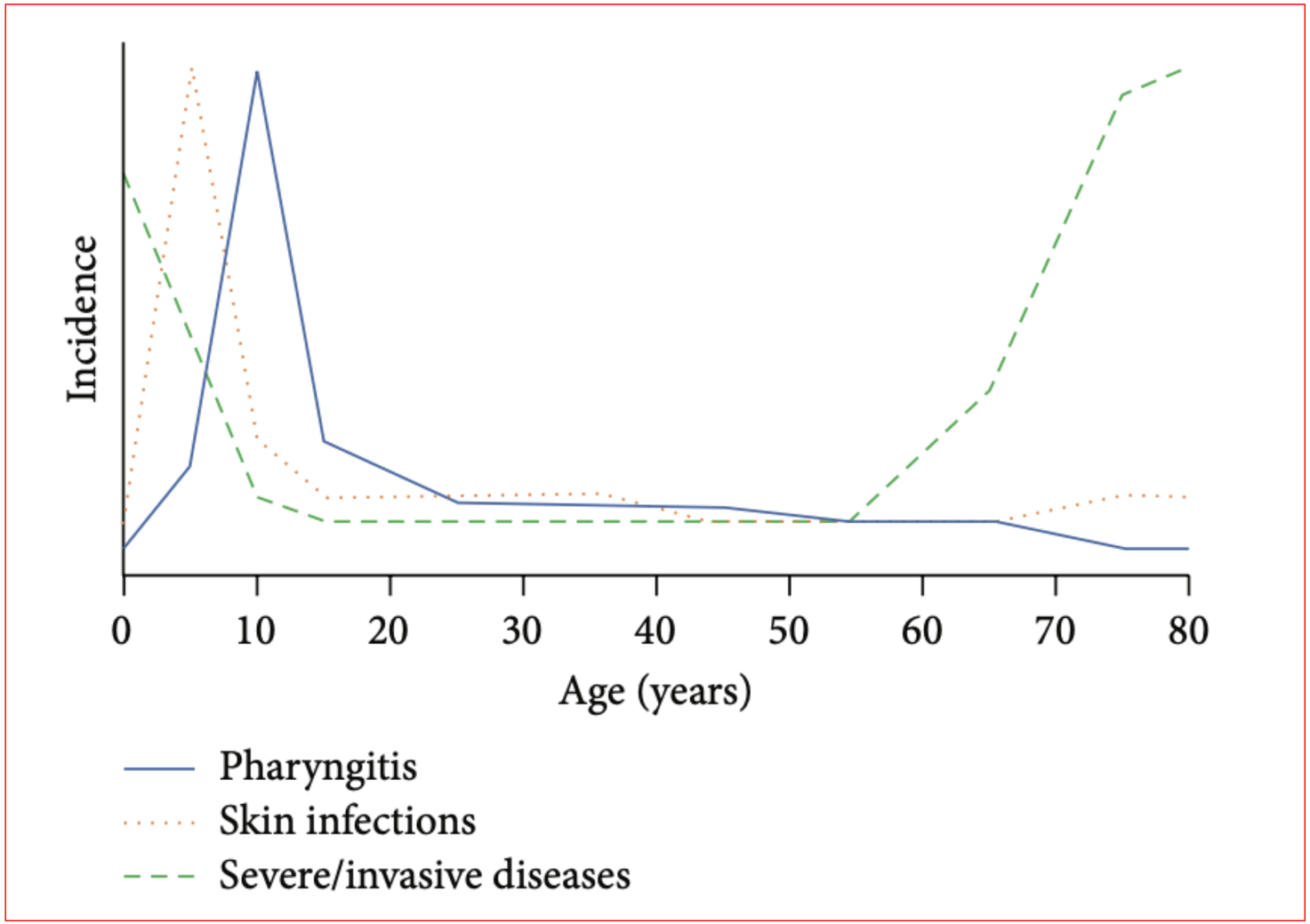
- Pharyngitis
  - Scarlet fever
- Impetigo
- SSTI (e.g. cellulitis)
- Invasive disease
  - Toxic shock syndrome
- Acute glomerulonephritis
- Acute rheumatic fever
  - Rheumatic heart disease

Immune-mediated

↓

Chronic disease

Strep A disease over the lifespan



Tsoi 2015

pharyngitis

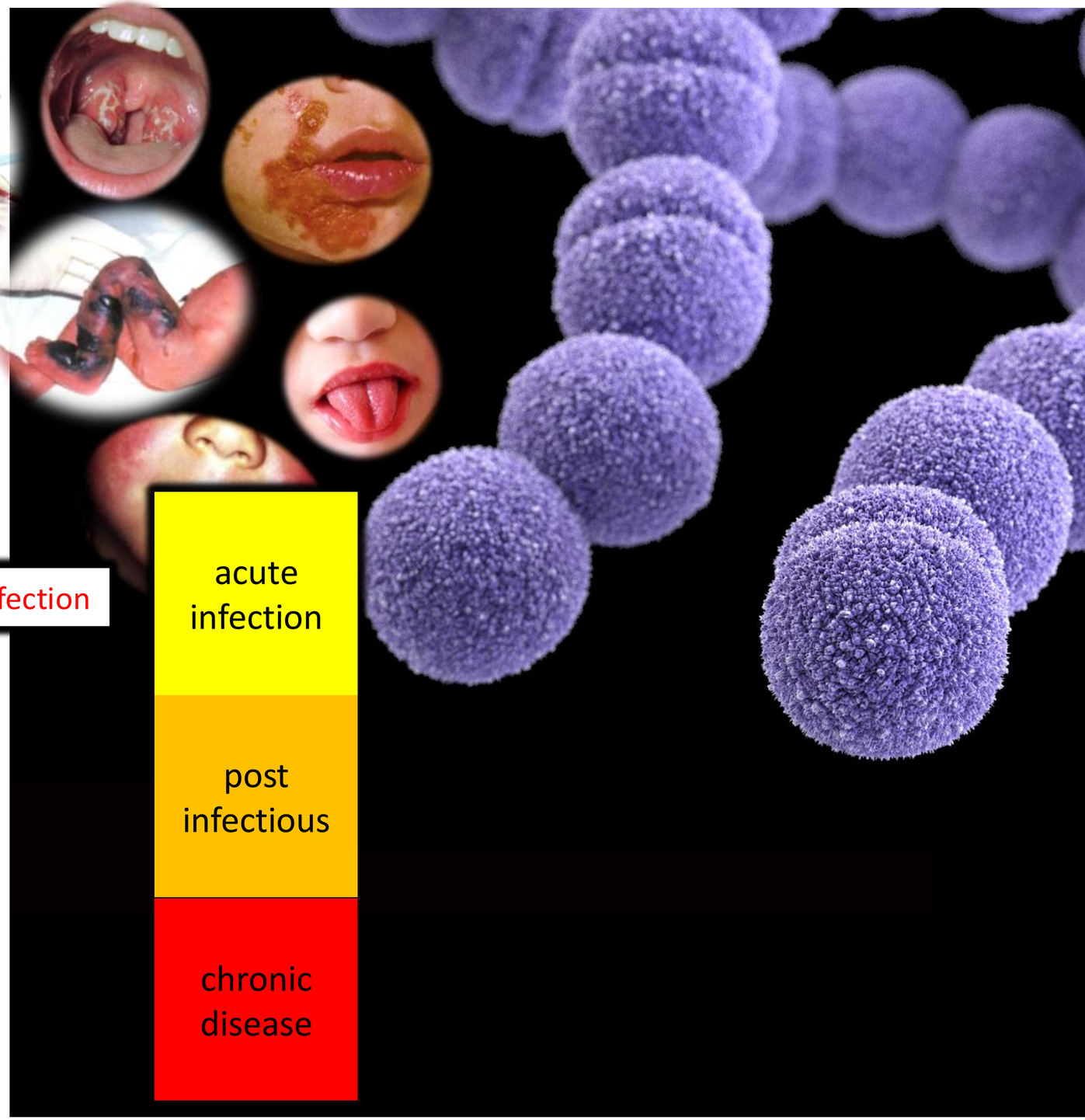
skin infection

invasive infection

acute rheumatic fever

glomerulonephritis

rheumatic heart disease



acute infection

post infectious

chronic disease

Courtesy: Dr Josh Osowicki

>600 million pharyngitis

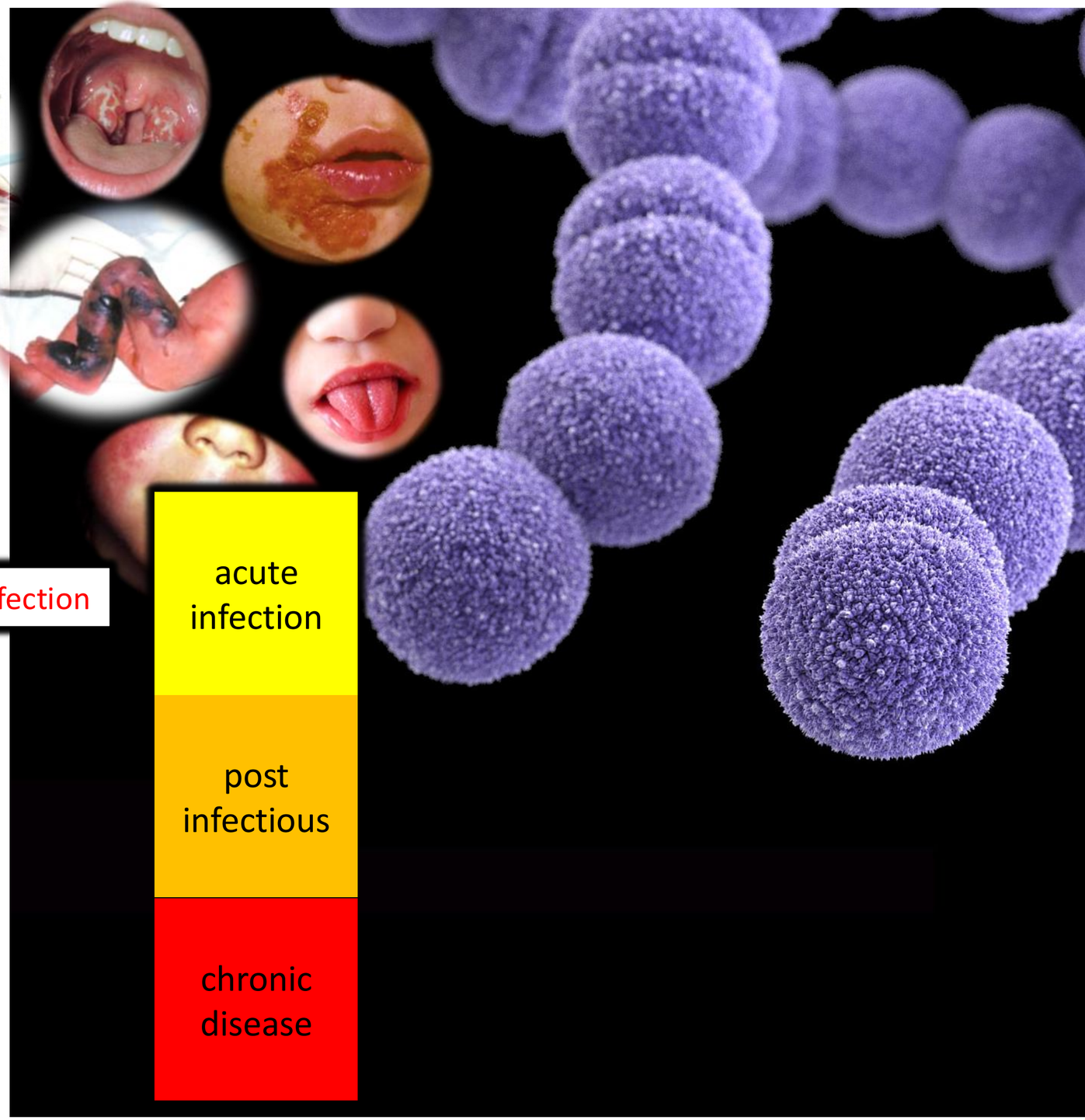
>200 million skin infection

>600k invasive infection

acute rheumatic fever

glomerulonephritis

rheumatic heart disease



acute infection

post infectious

chronic disease

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>600 million pharyngitis

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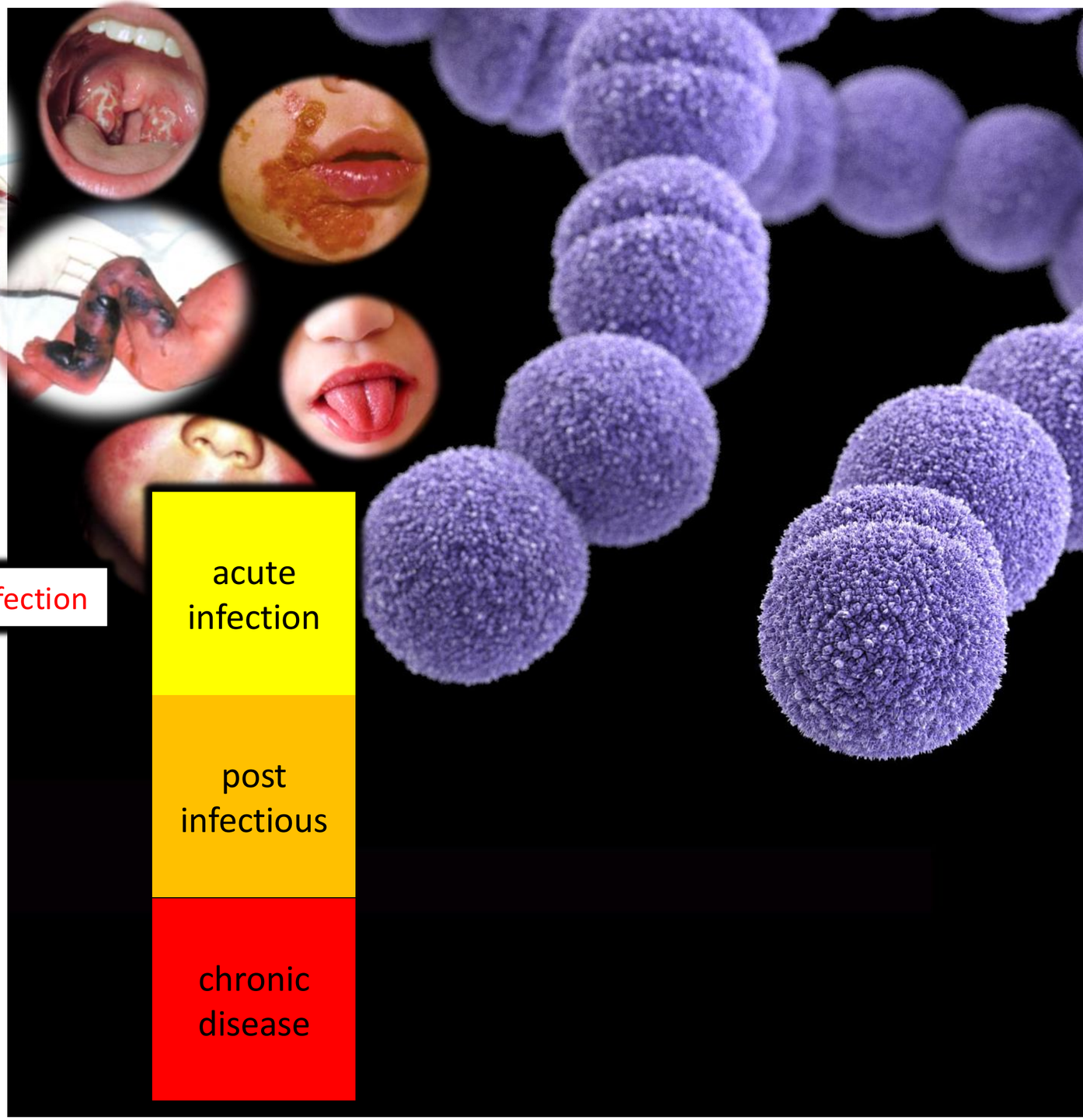
>500k acute rheumatic fever

>500k glomerulonephritis

>40 million rheumatic heart disease



acute infection

post infectious

chronic disease

Courtesy: Dr Josh Osowicki

>600 million pharyngitis

>200 million skin infection

>600k invasive infection

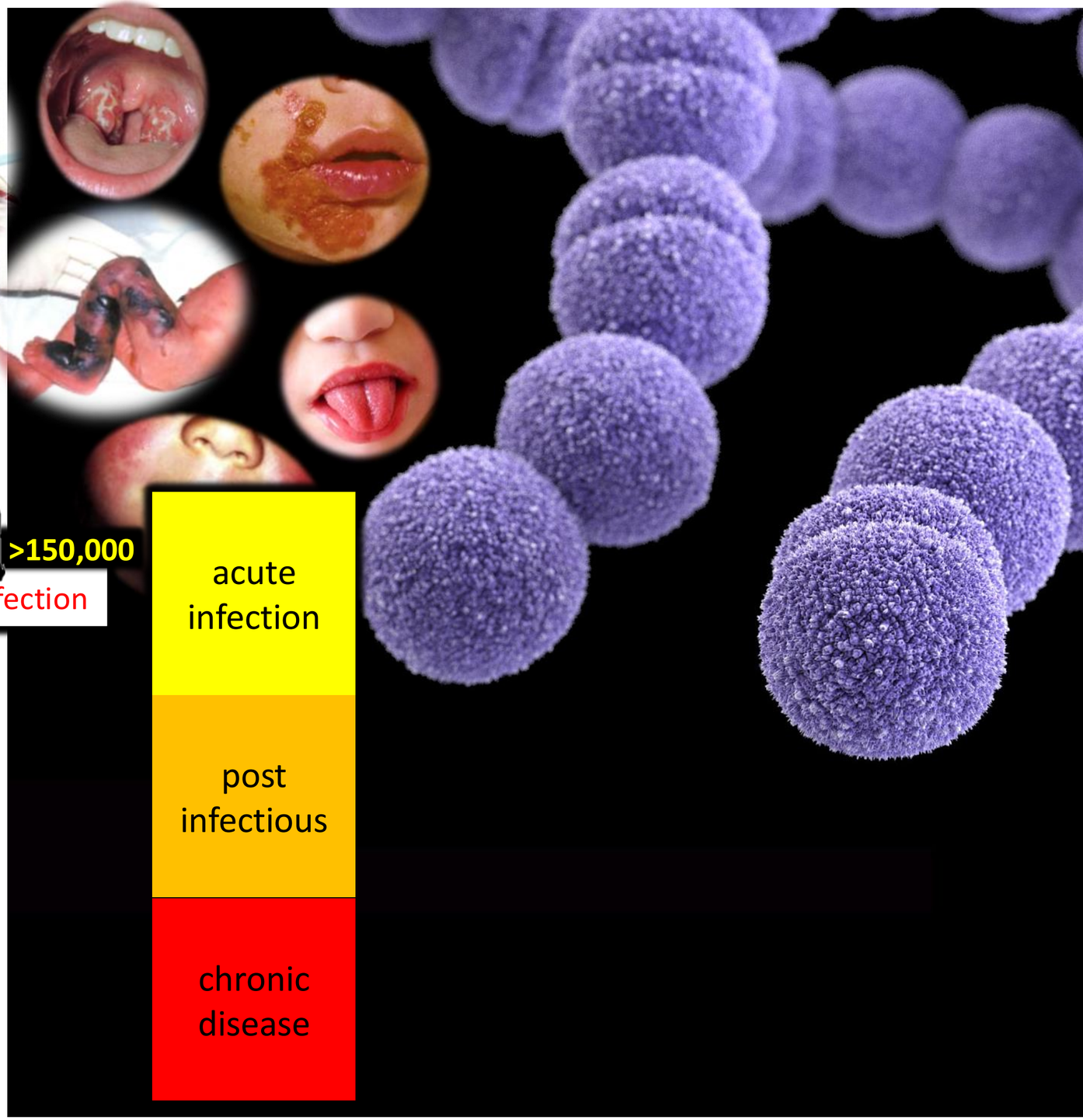
>150,000

>500k acute rheumatic fever

>500k glomerulonephritis

>300,000

>40 million rheumatic heart disease

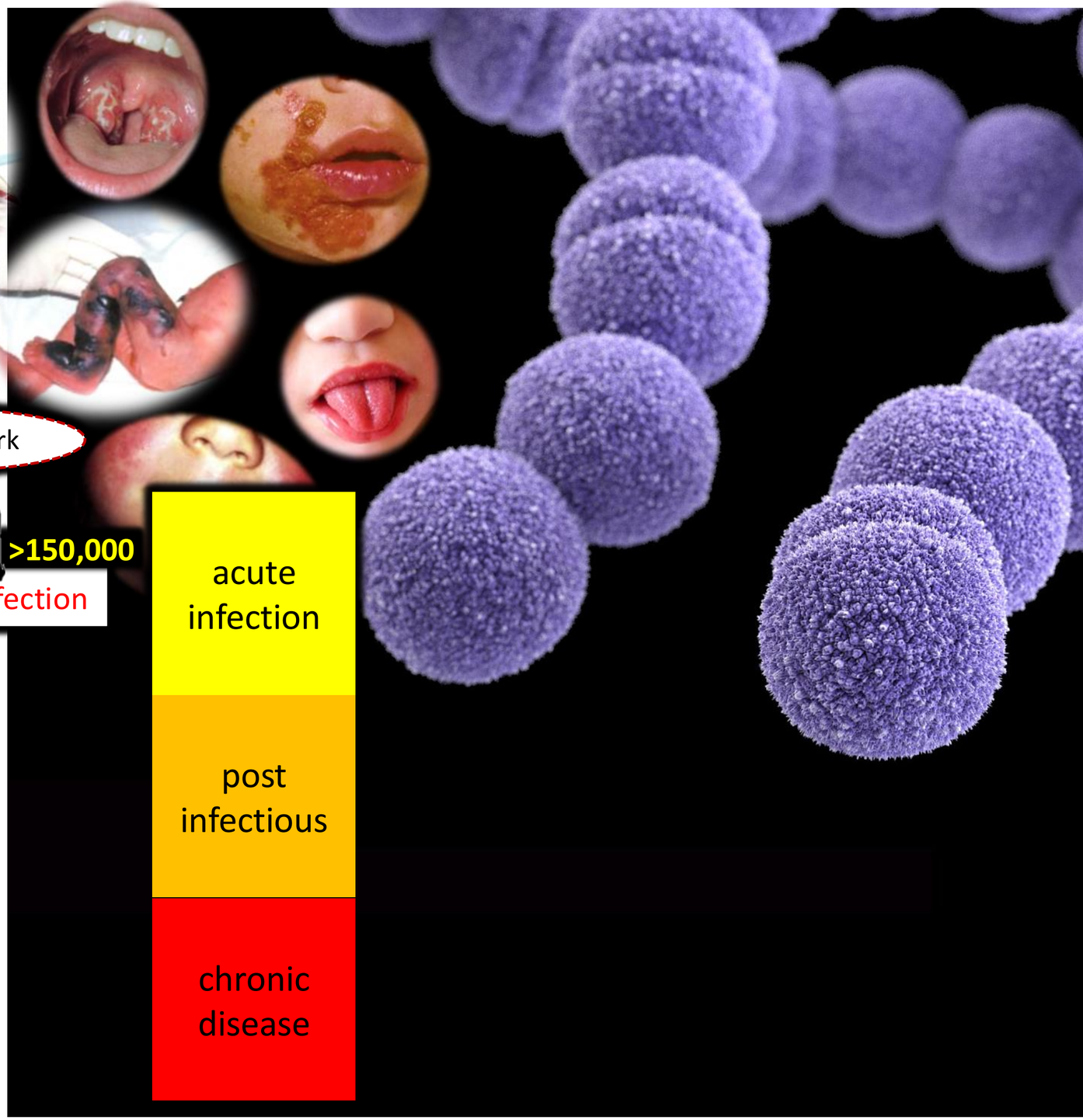


acute infection

post infectious

chronic disease

Courtesy: Dr Josh Osowicki



AMR

antibiotic misuse

healthcare $$$

missing work

>600 million pharyngitis

>200 million skin infection

>600k invasive infection

RIP >150,000

>500k acute rheumatic fever

>500k glomerulonephritis

>40 million rheumatic heart disease

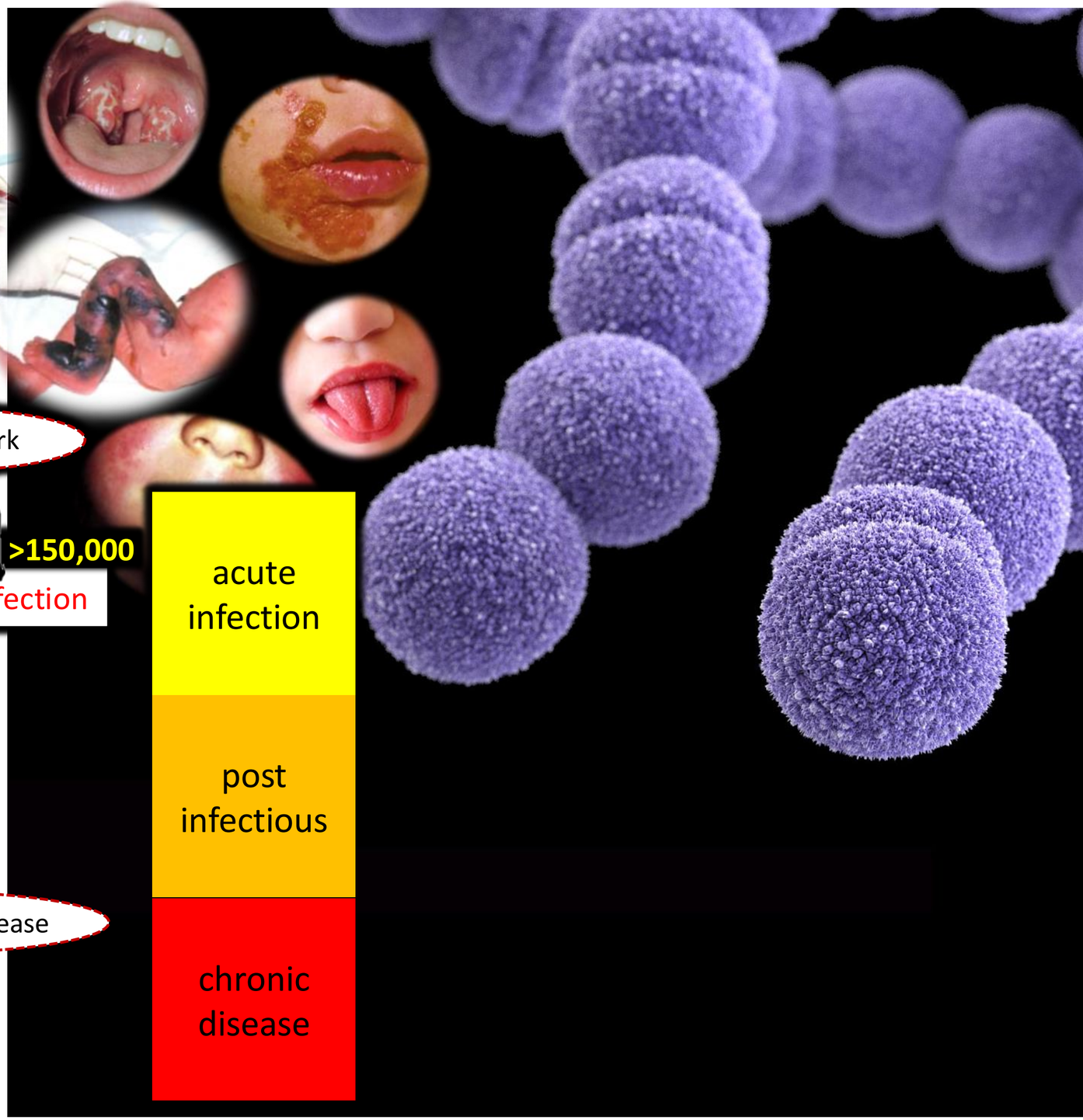
RIP >300,000

acute infection

post infectious

chronic disease

Courtesy: Dr Josh Osowicki



AMR

antibiotic misuse

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>200 million skin infection

>600k invasive infection

RIP >150,000

>500k acute rheumatic fever

>500k glomerulonephritis

>40 million rheumatic heart disease

RIP >300,000

chronic kidney disease

heart failure

stroke

acute infection

post infectious

chronic disease

Courtesy: Dr Josh Osowicki

Rheumatic heart disease

Infectious disease

Immune-mediated disease

Chronic non-communicable disease

1
Strep A Infection(s)

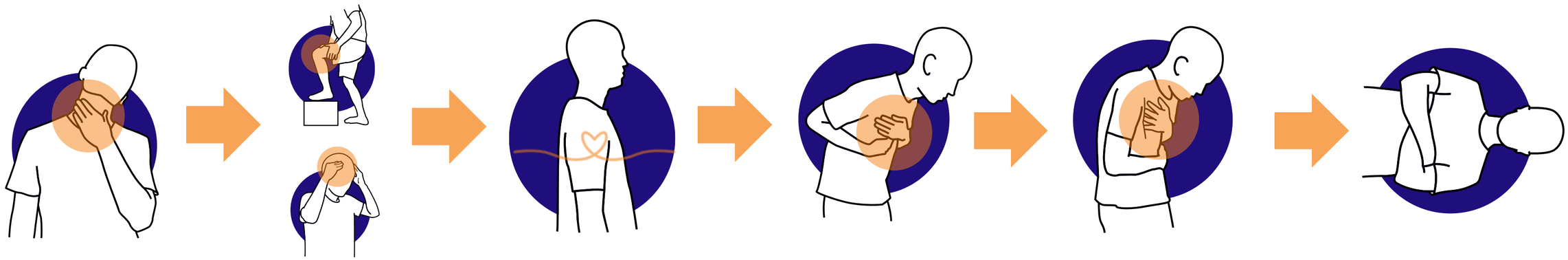
2
Rheumatic Fever

3
Early RHD

4
Advanced-Stage RHD

5
End-Stage RHD

6
Death



HPV infection → CIN 2/3 → Cervical cancer

HPV DNA, VIN

Asymptomatic*

CIN 2/3

HPV infection → Cervical cancer

HPV DNA, VIN

Asymptomatic*

Strep A infection → Advanced RHD

ARF, latent RHD

Symptomatic*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 24, 2017 VOL. 377 NO. 8

Global, Regional, and National Burden of Rheumatic Heart Disease, 1990–2015

1 Strep A Infection(s)

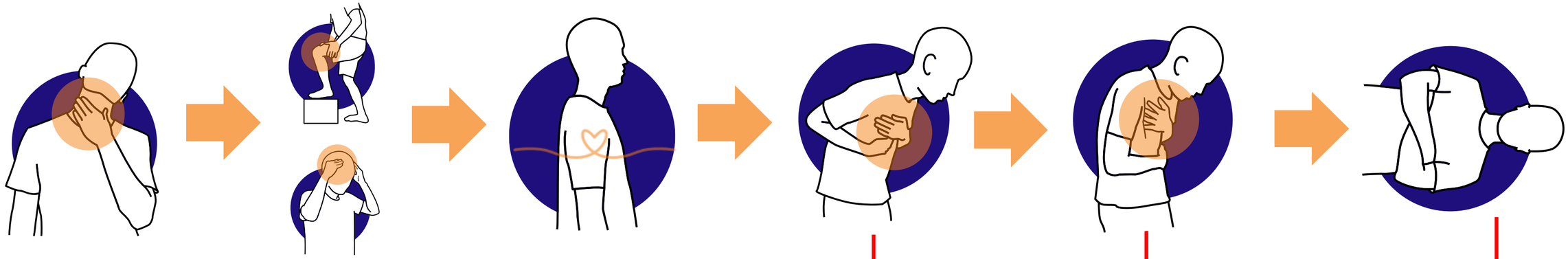
2 Rheumatic Fever

3 Early RHD

4 Advanced-Stage RHD

5 End-Stage RHD

6 Death



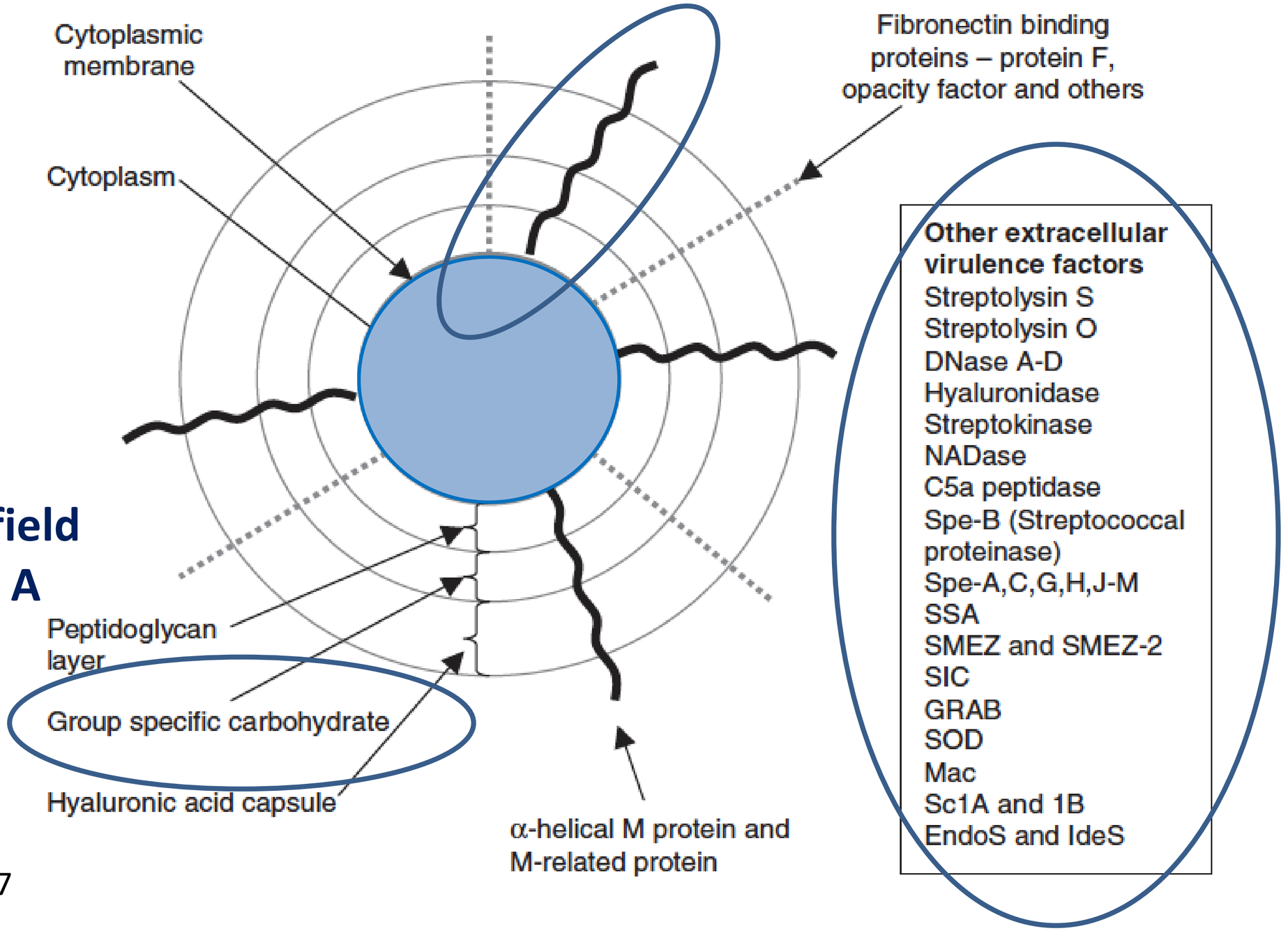
>40 million patients

>300,000 deaths p.a.

Vaccine landscape

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

M-typing (~260 M-types)



Lancefield Group A

Steer JPCH 2007

npj | vaccines

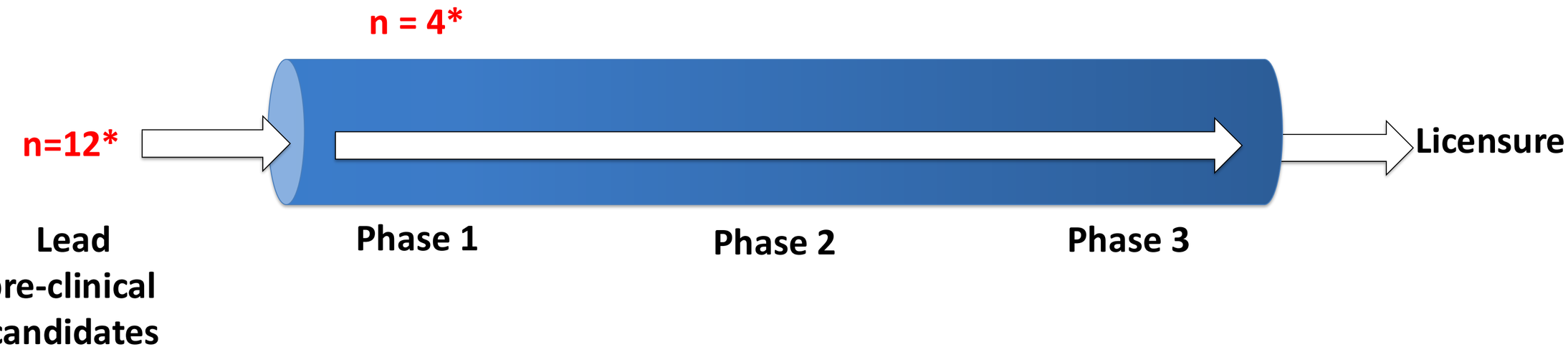
www.nature.com/npjvaccines

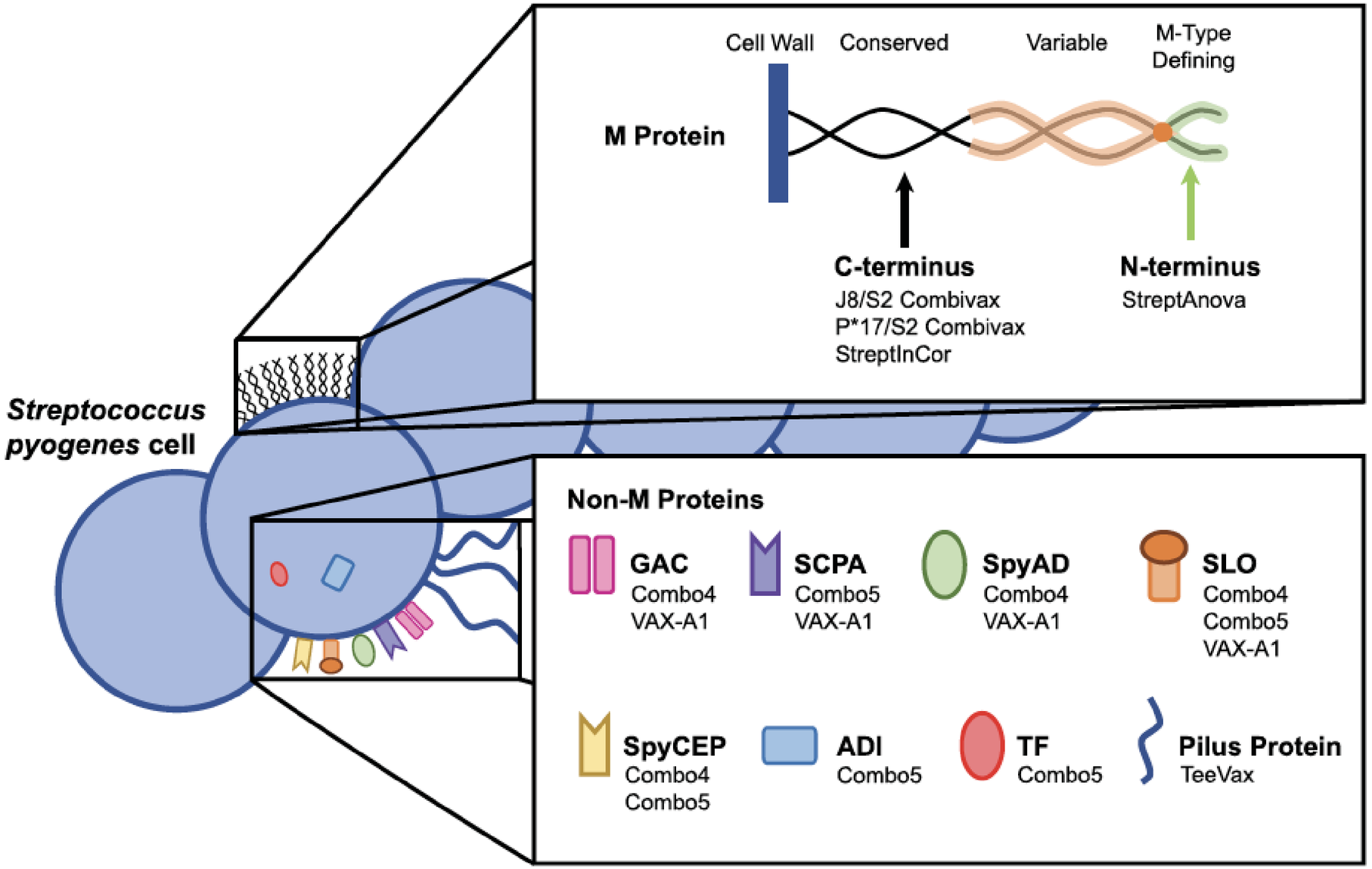
REVIEW ARTICLE OPEN

February 2023

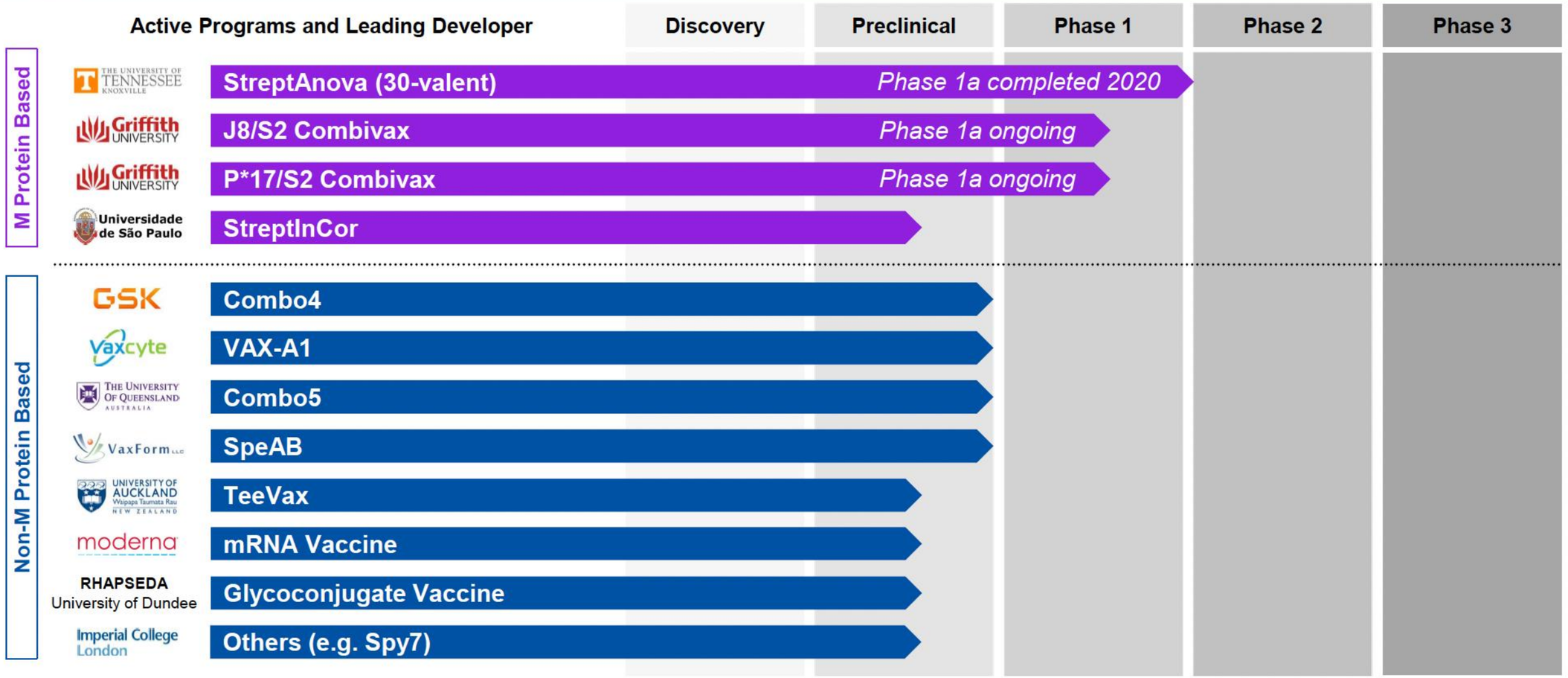
The *Streptococcus pyogenes* vaccine landscape

Donald R. Walkinshaw[1]✉, Meghan E. E. Wright[1], Anne E. Mullin[1], Jean-Louis Excler[2], Jerome H. Kim[2,3,4] and Andrew C. Steer[3,5,6]




Cell Wall
Conserved
Variable
M-Type Defining
M Protein
C-terminus
J8/S2 Combivax
P*17/S2 Combivax
StreptInCor
N-terminus
StreptAnova
Streptococcus pyogenes cell
Non-M Proteins
GAC
Combo4
VAX-A1
SCPA
Combo5
VAX-A1
SpyAD
Combo4
VAX-A1
SLO
Combo4
Combo5
VAX-A1
SpyCEP
Combo4
Combo5
ADI
Combo5
TF
Combo5
Pilus Protein
TeeVax

Current Strep A Vaccine Pipeline[1]



1. Strep A vaccine pipeline as of December 20, 2023

Walkinshaw et al., The Streptococcus pyogenes vaccine landscape, npj Vaccines, 2023

Castro and Dorfmueller, Update on the development of Group A Streptococcus vaccines, npj Vaccines, 2023

The Australian Strep A Vaccine Initiative (ASAVI)

Shift HEALTH SAVAC

Development enablers

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

Enablers: 1

SAVAC

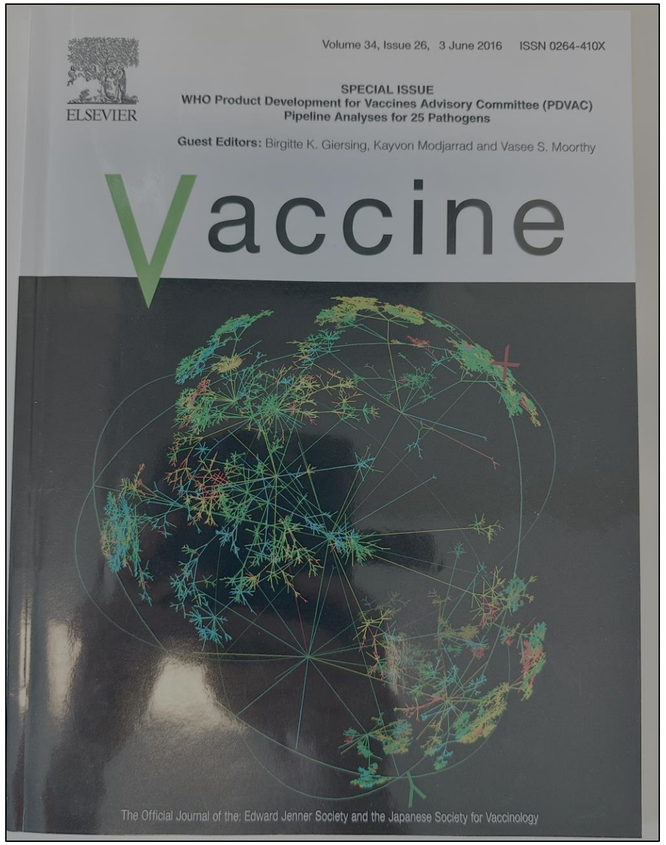
Strep A Vaccine Global Consortium

IVI

murdoch children's research institute

The Path to SAVAC: Strep A Vaccine Global Consortium

The First Step: PDVAC meetings from 2015 onwards



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Status of research and development of vaccines for *Streptococcus pyogenes*

Andrew C. Steer[a,b,*], Jonathan R. Carapetis[c], James B. Dale[d], John D. Fraser[e], Michael F. Good[f], Luiza Guilherme[g], Nicole J. Moreland[h], E. Kim Mulholland[i,j], Florian Schodel[k], Pierre R. Smeesters[a,b,l]

The Path to SAVAC: Strep A Vaccine Global Consortium

The Next Steps…

World Health Organization

INTERNATIONAL VACCINE INSTITUTE

WHO/IVI Global Stakeholder Consultation
on Group A Streptococcal Vaccine Development
12-13th December, 2016, Sheraton Seoul Palace Gangnam Hotel, Seoul, Korea
Supported by: Shinil Corporation, CANVAS, RHD Action, MCRI

Conference report

WHO/IVI global stakeholder consultation on group A *Streptococcus* vaccine development: Report from a meeting held on 12–13 December 2016

Joshua Osowicki [a,*], Johan Vekemans [b], David C. Kaslow [c], Martin H. Friede [b], Jerome H. Kim [d], Andrew C. Steer [a]

→ **Develop Preferred Product Characteristics**

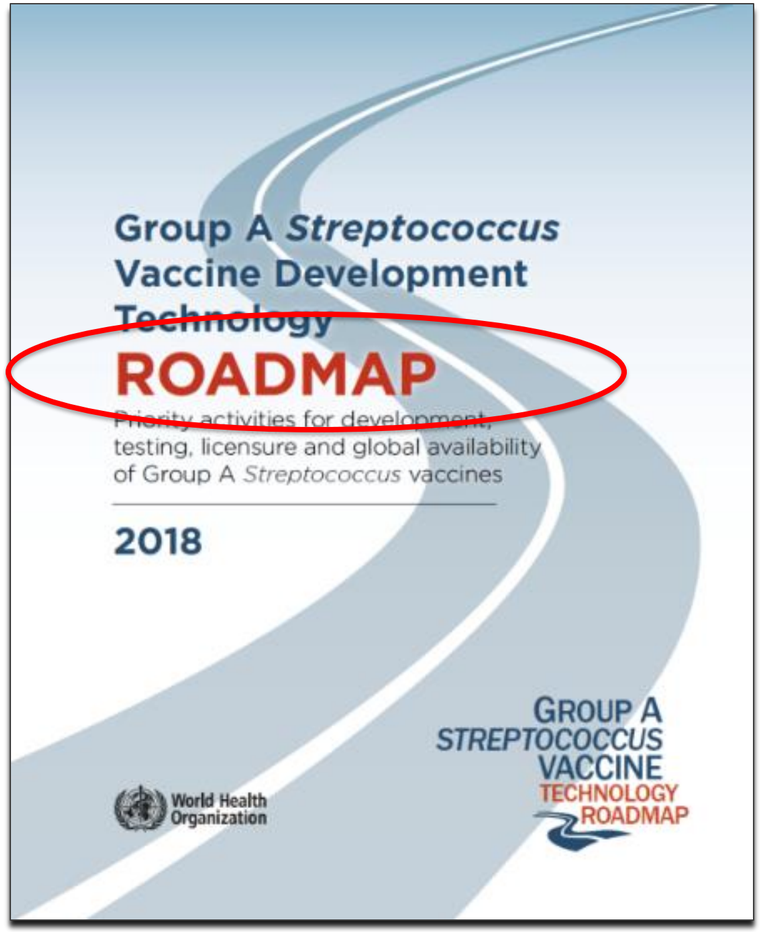
→ **Develop a Roadmap for Vaccine Development**

→ **Develop a value proposition for GAS vaccines**

→ **Formation of a Global Strep A Vaccine Consortium**

The Path to SAVAC: Strep A Vaccine Global Consortium

The Next Steps…



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

SAVAC 1.0
Strep A Vaccine Global Consortium

Funded by the Wellcome Trust 2019

The mission of SAVAC is to ensure that safe, effective and affordable Strep A vaccines are available and implemented to decrease the burden of Strep A disease in the most in need.

WHO

FVVA

Burden of disease

Immune correlates

Vaccine safety

Global engagement

SAVAC 2.0

Officially launched November 2023

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

SAVAC
Strep A Vaccine Global Consortium

wellcome

LEDUCQ

Open Philanthropy

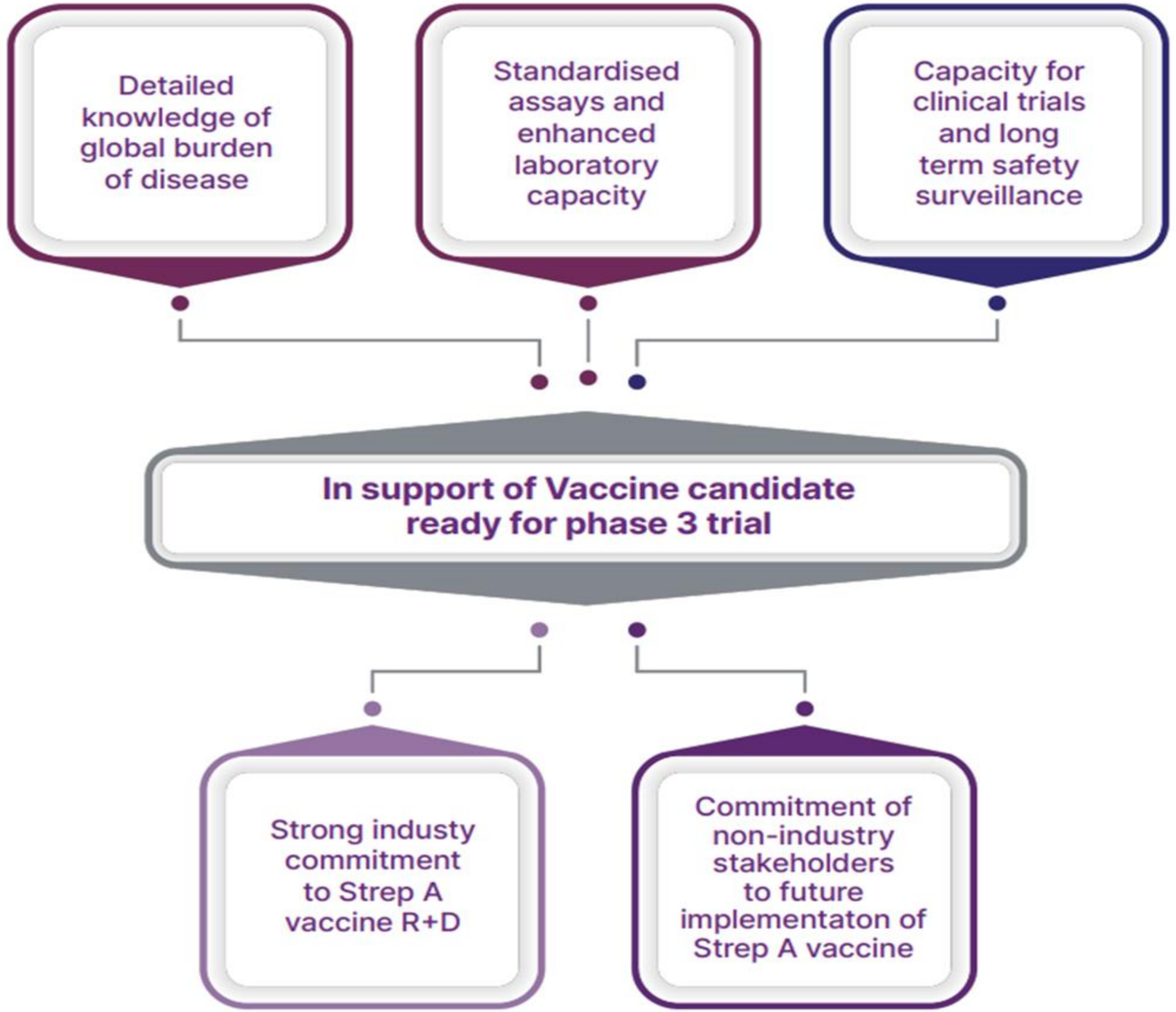
Funders

SAVAC 2.0

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

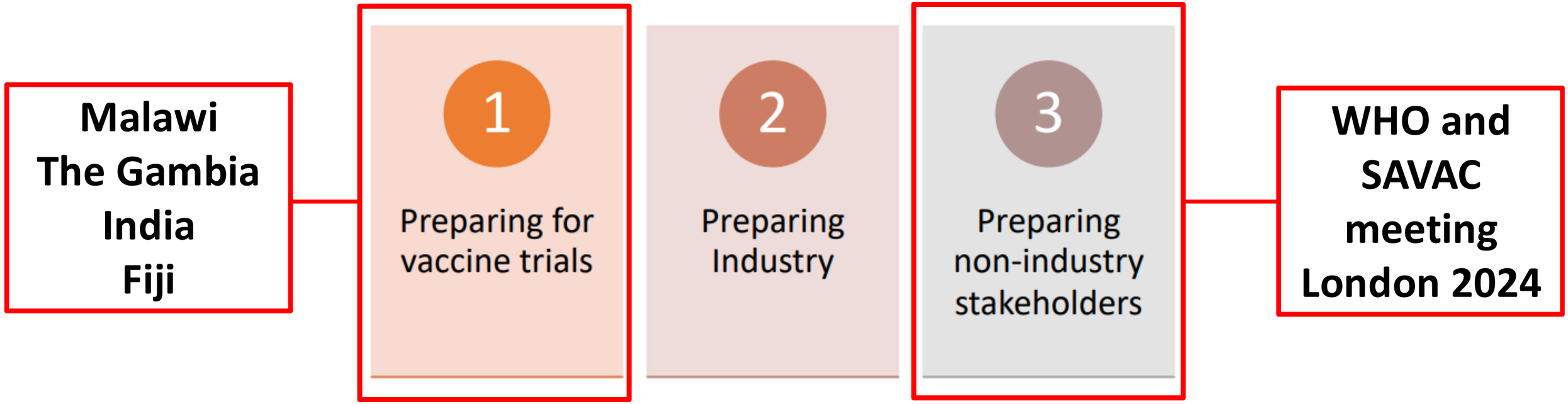
SAVAC 2.0
Strep A Vaccine Global Consortium

SAVAC is the key global technical advisory group for vaccine development for *S. pyogenes*.



SAVAC 2.0
Strep A Vaccine Global Consortium

Paving a path for development of a Strep A vaccine through three cross-disciplinary workstreams

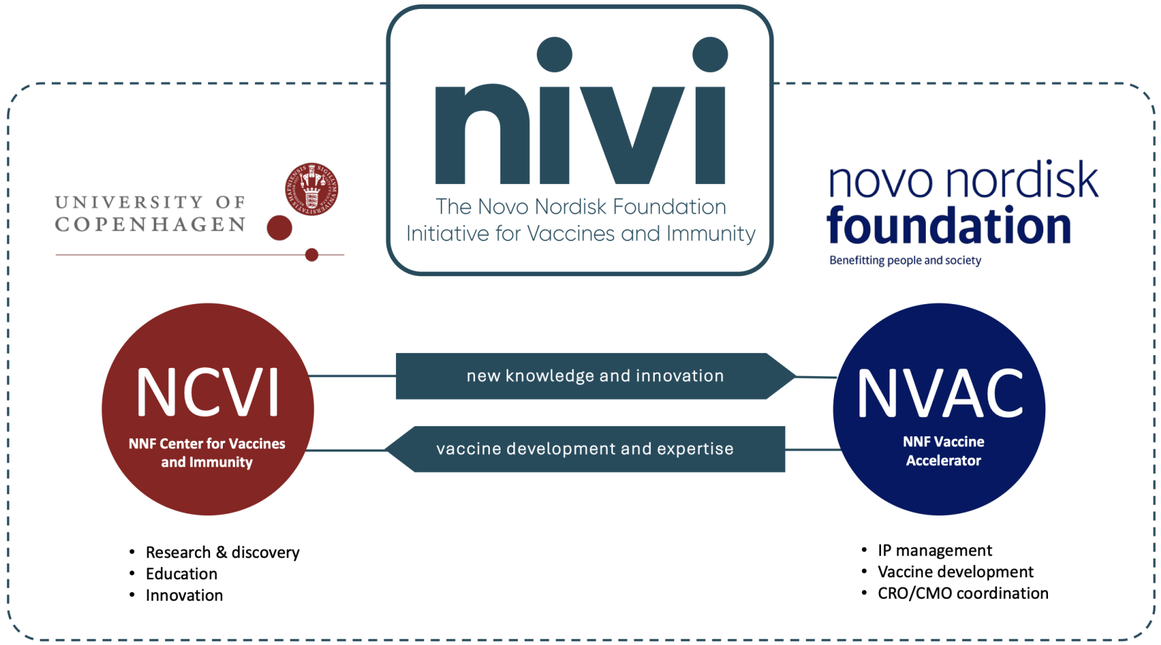


Enablers: 2 and 3

ASAVI
The Australian Strep A Vaccine Initiative

The KIDS RESEARCH INSTITUTE AUSTRALIA

murdoch children's research institute



Key issues for the field

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

Pharyngitis

Scarlet fever

Impetigo

Invasive disease

Toxic shock syndrome

Acute glomerulonephritis

Acute rheumatic fever

Rheumatic heart disease

- Pharyngitis
  - Scarlet fever
- Impetigo
- Invasive disease
  - Toxic shock syndrome
- Acute glomerulonephritis
- Acute rheumatic fever
  - Rheumatic heart disease

Endpoints for clinical trials

Vaccine design: peptide, protein, mRNA, glycoconjugate, others

Immune Correlates of protection

Vaccine safety

Role of echocardiography

Cross-reactive immunity testing

Mucosal vs parenteral delivery

Optimal antigen selection

- Pharyngitis
  - Scarlet fever
- Impetigo
- Invasive disease
  - Toxic shock syndrome
- Acute glomerulonephritis
- Acute rheumatic fever
  - Rheumatic heart disease

Symptomatic vs asymptomatic pharyngitis

Vaccine dosing timing/ schedule

Strain coverage (next slide)

Role of human challenge model (human only pathogen

Vaccine design: peptide, protein, mRNA, glycoconjugate, others

Optimal antigen selection

Vaccine dosing timing/ schedule

Strain coverage (next slide)

GLOBAL HEALTH

What pivotal clinical study evidence is needed for a vaccine with a recommendation to prevent rheumatic heart disease through an indication for prevention of X among individuals aged X-Y years?

ocardiography

Cross-reactive immunity testing

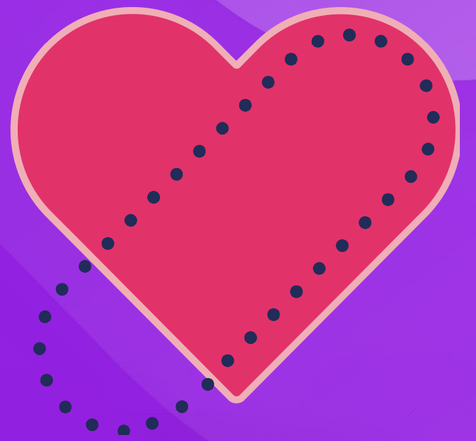
Mucosal vs parenteral delivery

Endpoints for clinical trials

Symptomatic vs asymptomatic pharyngitis

SAVAC meeting London 2024:

Endpoints to advance vaccine clinical development



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

Joint Meeting of SAVAC and WHO
Streptococcus pyogenes vaccines: an expert review of evidence needs to guide policy

September 30, 2024
Wellcome Trust, London

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

SAVAC
Strep A Vaccine Global Consortium

wellcome

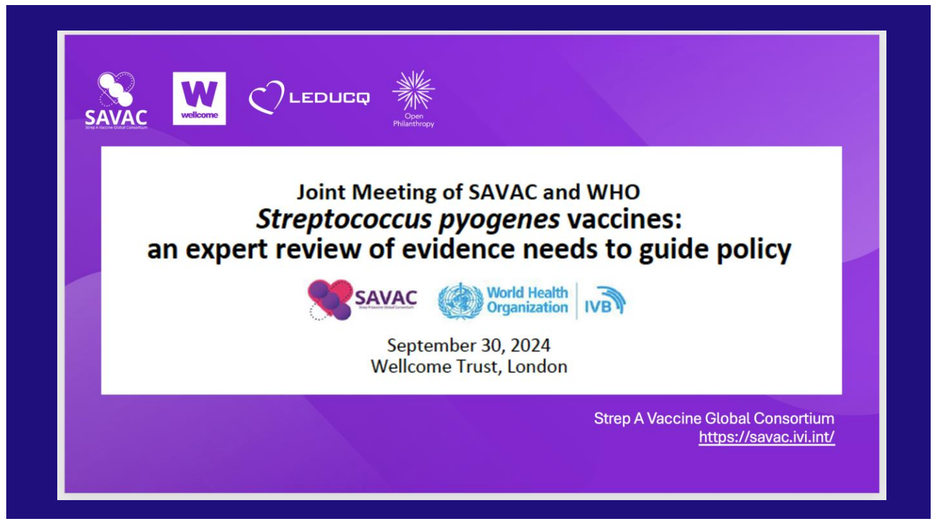
LEDUCQ

Open Philanthropy

Joint Meeting of SAVAC and WHO

***Streptococcus pyogenes* vaccines: an expert review of evidence needs to guide policy**

A Global Objective
The Joint SAVAC and WHO Meeting



What pivotal study evidence is needed for a vaccine with a recommendation to prevent **rheumatic heart disease** through an indication for prevention of _____ among individuals ___ to ___ years of age?

Key Questions that were asked and answered at the meeting

Question 1

Is the evidence of prevention of S. *pyogenes* pharyngitis by a vaccine sufficient for a **recommendation to prevent advanced RHD**?

Key Questions that were asked and answered at the meeting

Question 1

Is the evidence of prevention of S. *pyogenes* pharyngitis by a vaccine sufficient for a **recommendation to prevent advanced RHD**?

Question 2

Would prevention of an earlier (than advanced RHD) recognized disease stage (ARF or Early RHD) be sufficient for a **recommendation to prevent advanced RHD?**

Key Questions that were asked and answered at the meeting

Question 1

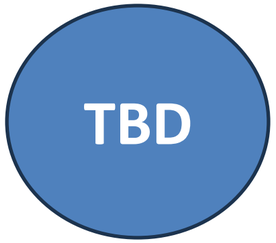
Is the evidence of prevention of S. *pyogenes* pharyngitis by a vaccine sufficient for a **recommendation to prevent advanced RHD**?

Question 2

Would prevention of an earlier (than advanced RHD) recognized disease stage (ARF or Early RHD) be sufficient for a **recommendation to prevent advanced RHD?**

Question 3

What is the **best strategy** for a pivotal study to reach a vaccine recommendation to prevent advanced RHD?



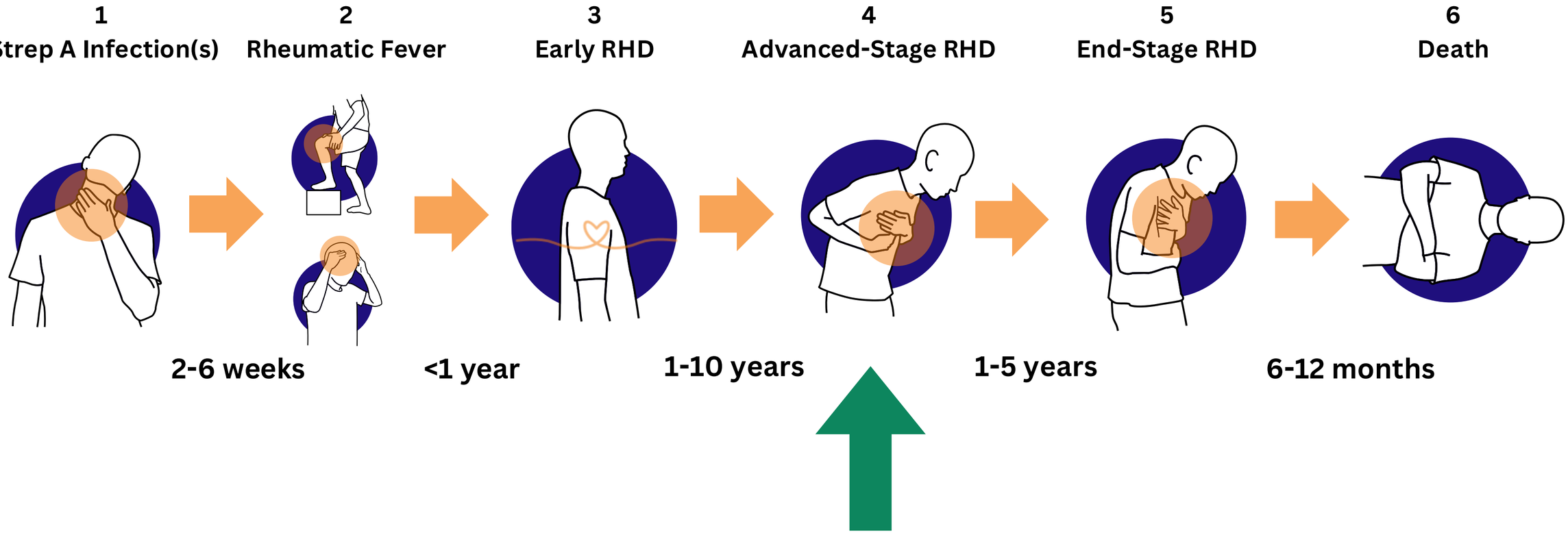
A CONSIDERATION OF INTERMEDIATE ENDPOINTS

IN THE CONTEXT OF STREP A VACCINE TRIALS

RRCUganda.org

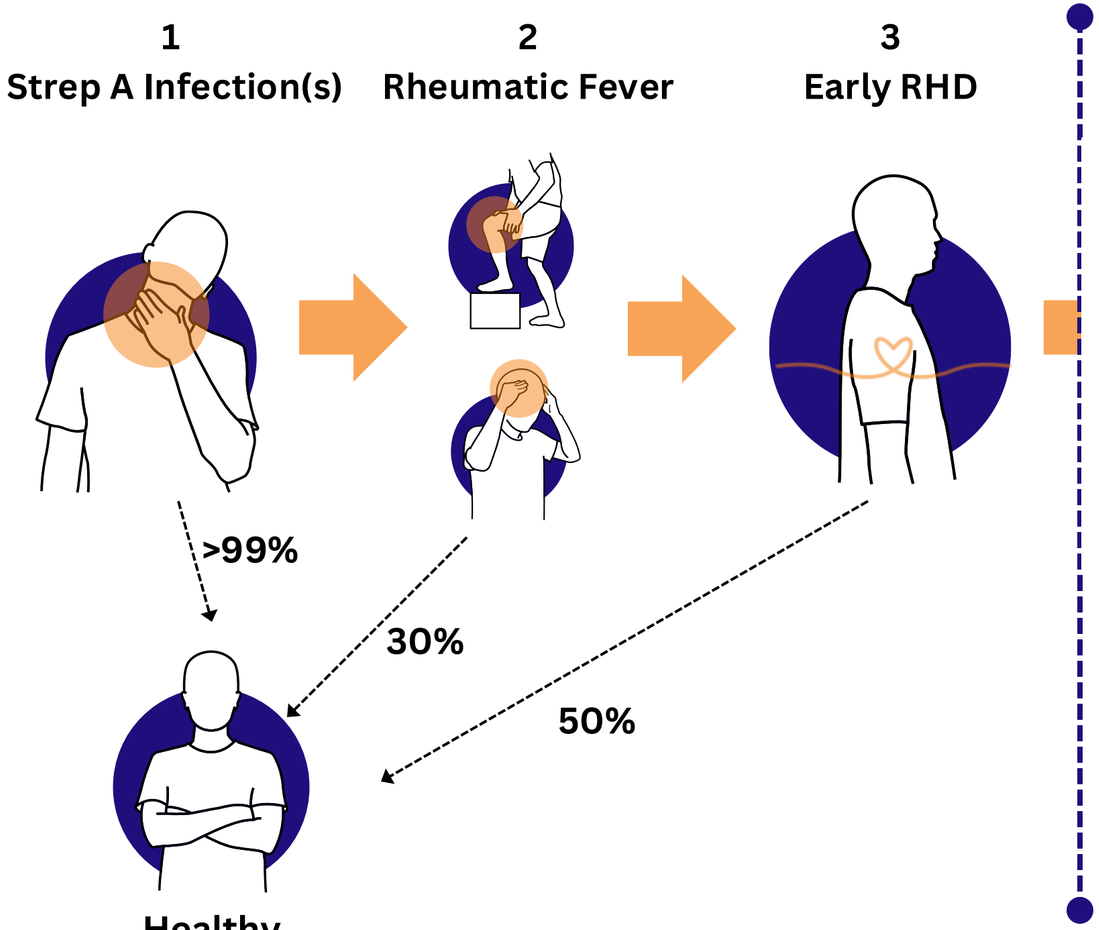
A Strep A Vaccine for LIMCs

Globally, we need to prevent Advanced-Stage RHD



Early in the disease

Outcomes are heterogeneous



Many children will end up healthy, even without intervention

A Strep A Vaccine for LIMCs

Advanced-stage RHD

Is rapidly progressive with high mortality

1 Strep A Infection(s)

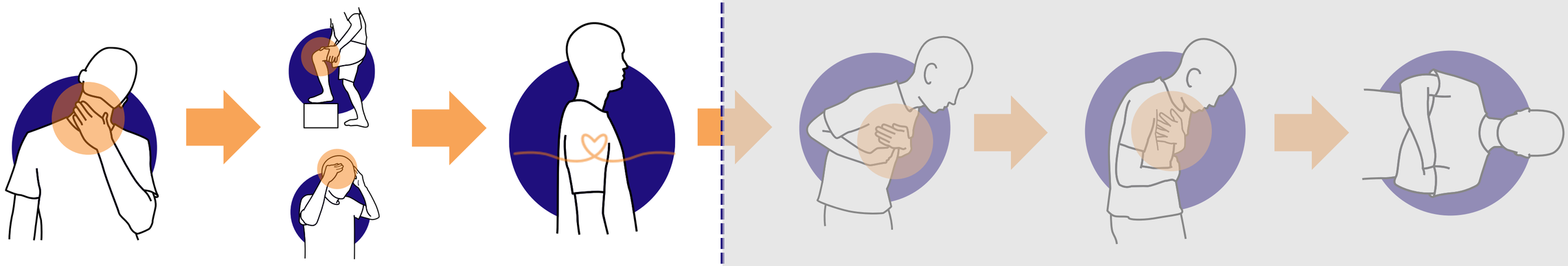
2 Rheumatic Fever

3 Early RHD

4 Advanced-Stage RHD

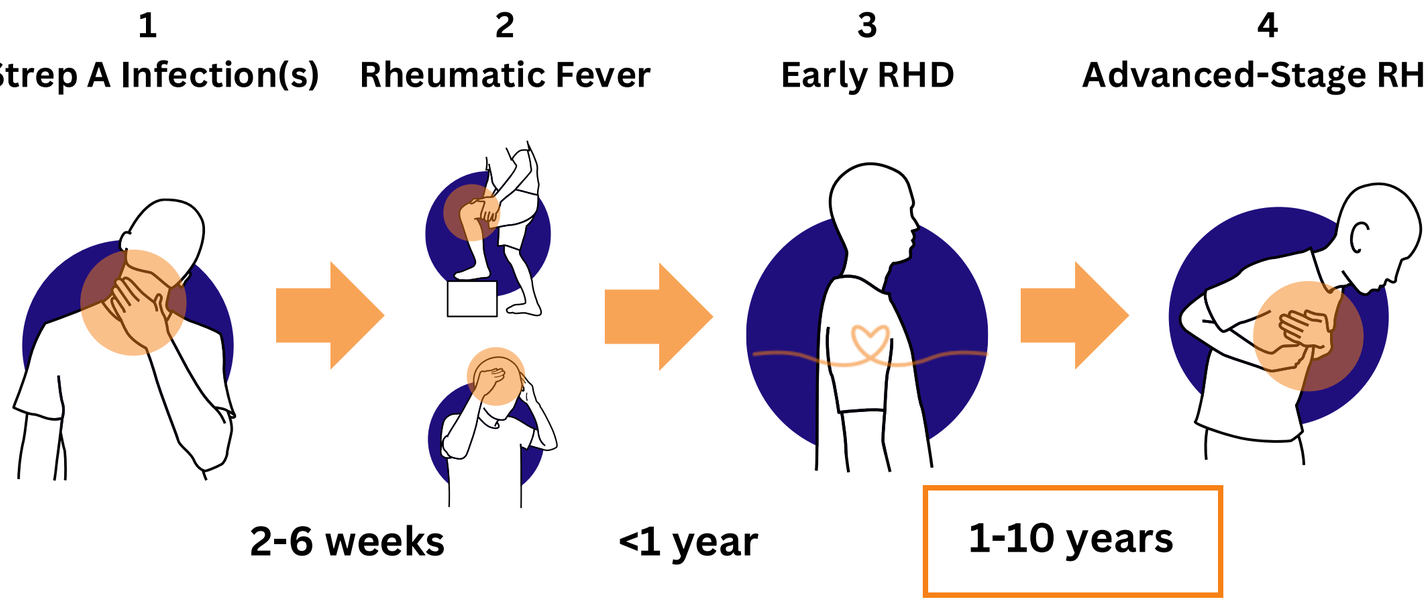
5 End-Stage RHD

6 Death



Point of Irreversibility

Advanced-stage RHD



Time to advanced-stage RHD makes it an impractical for Strep A vaccine trials

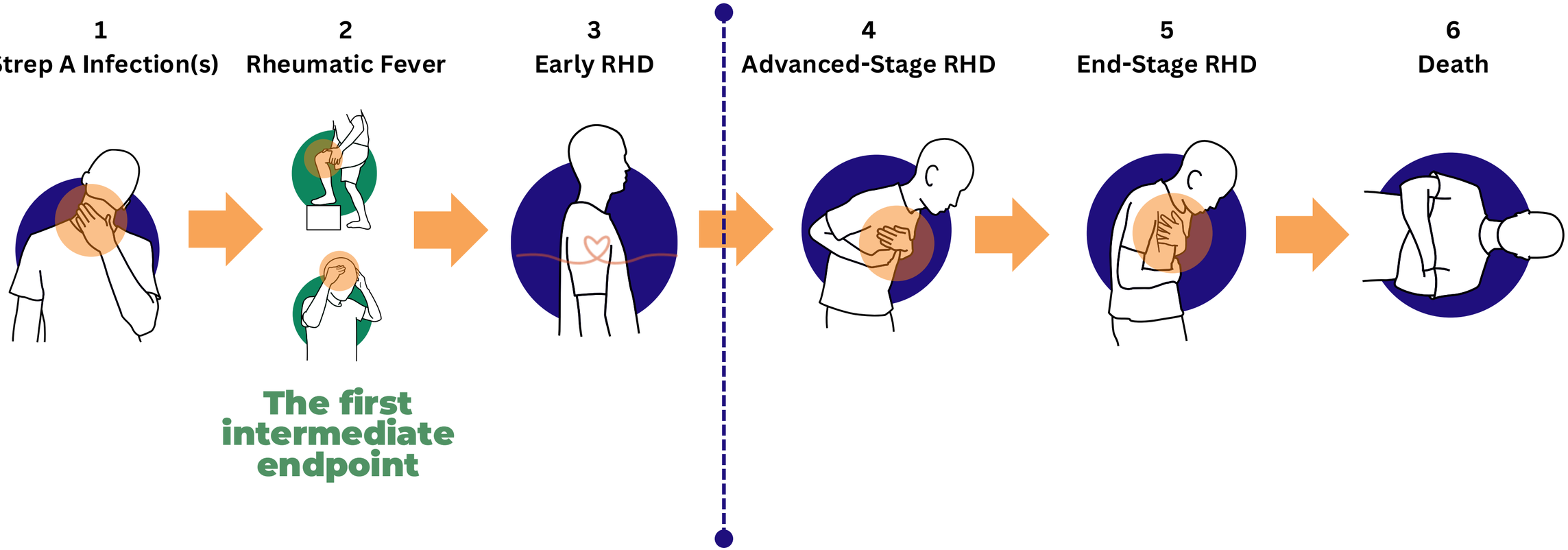
INTERMEDIATE MARKERS BEFORE ADVANCED RHD DEVELOPS

A Strep A Vaccine for LIMCs

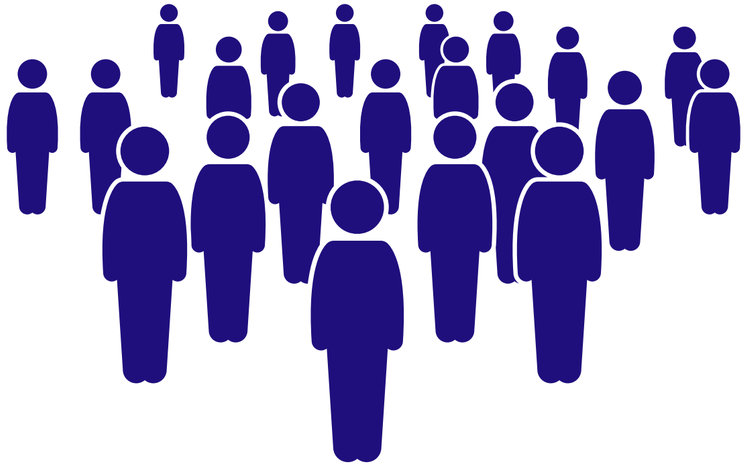
Acute Rheumatic Fever

The first intermediate endpoint

Actue rheumatic fever is the immune over-reaction to Strep A



ARF is Hard to Find



Superficial Strep Infections

Acute Rheumatic Fever

Rheumatic Heart Disease

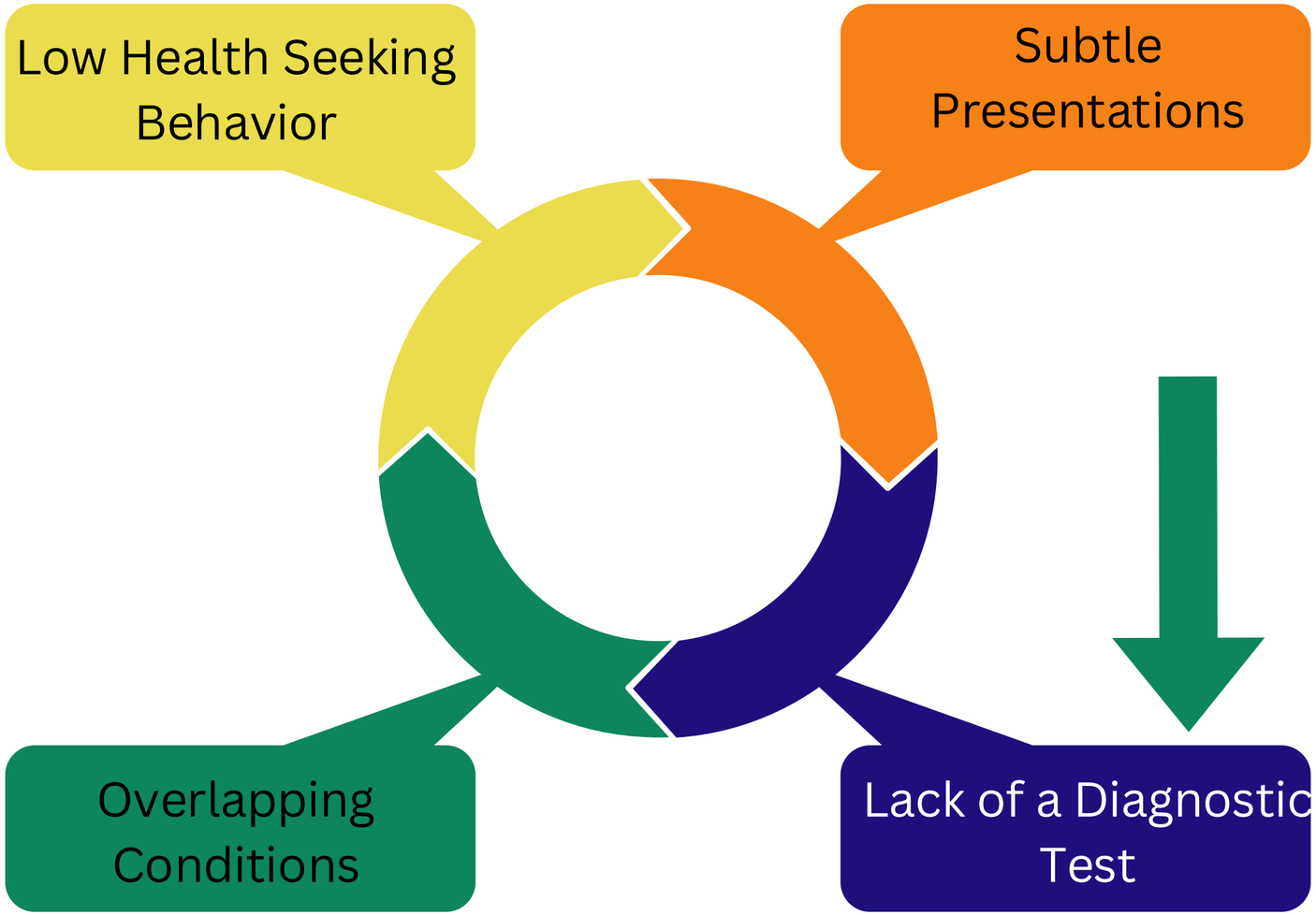
While many present with superficial Strep A infections and many present with RHD, diagnosis with ARF is uncommon

Prospective Epidemiological Surveillance only Captures a Fraction

Uganda data + Fijian data suggest for every case found; 1-2 are missed

Prospective epidemiological surveys only capture a fraction of RF, could potentially do better in a closed cohort design.

Why is ARF Under-diagnosed?

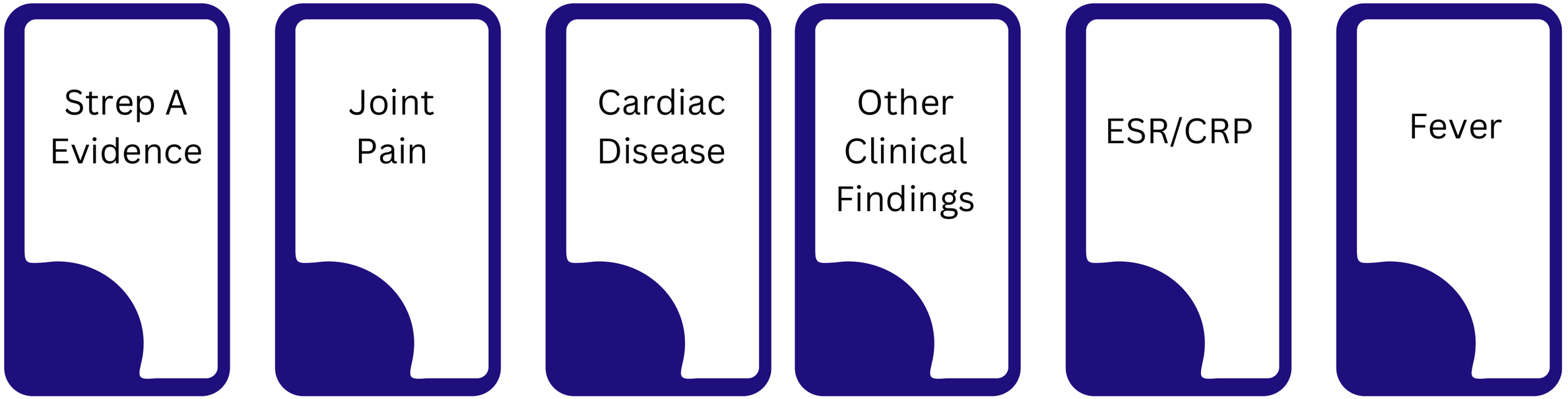


A Strep A Vaccine for LIMCs

Very likely a combination of factors . .

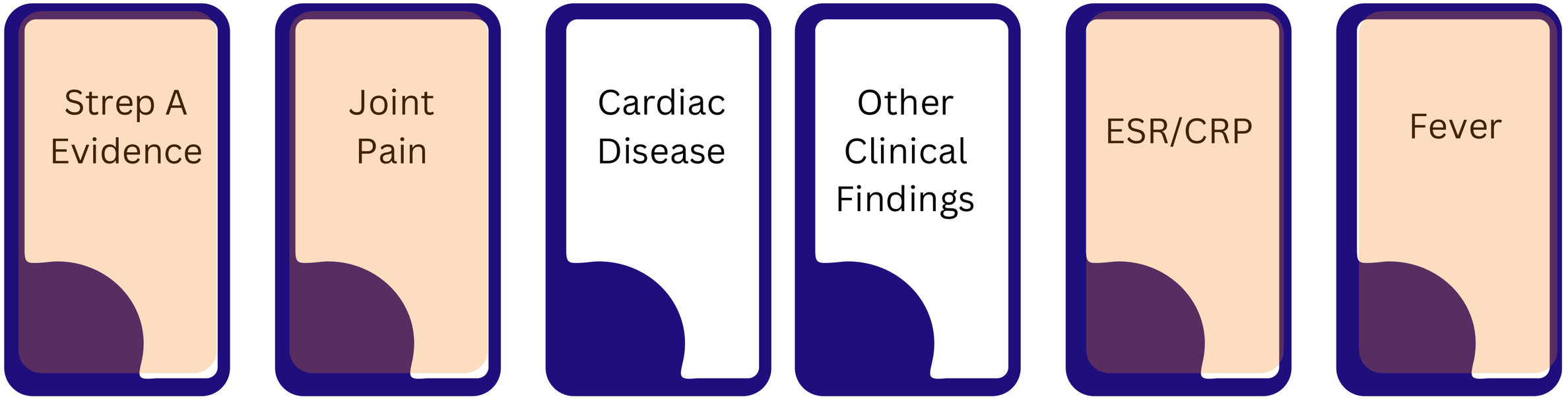
But, lack of a diagnostic test is a HUGE challenge

The Jones Criteria
(Last Revision 2015, Gewitz et. al.)



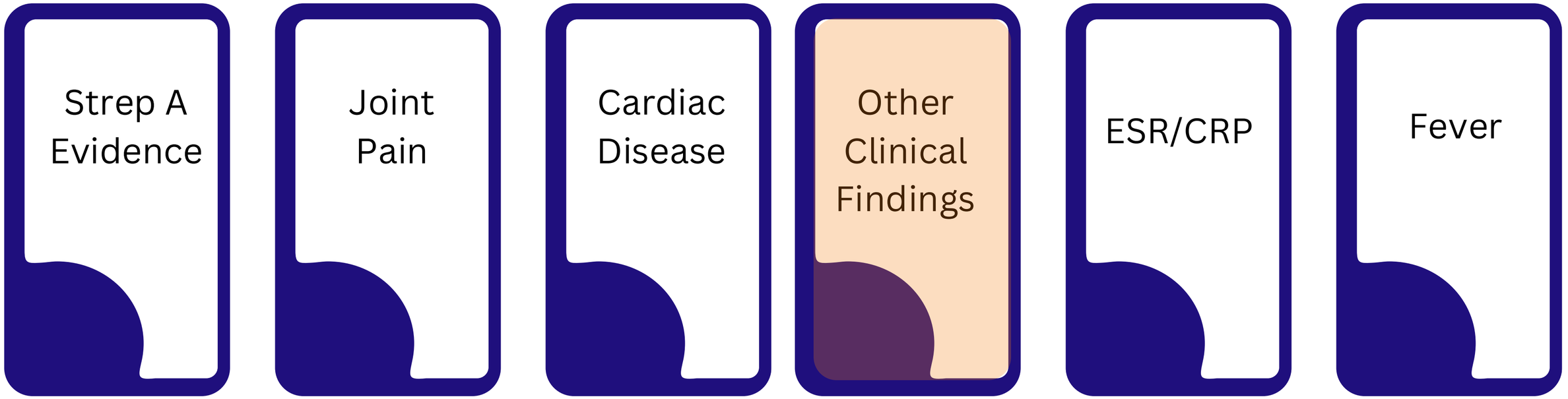
Clinical Decision Tool + Diagnosis of Exclusion

The Jones Criteria
(Last Revision 2015, Gewitz et. al.)



Most Components are Non-specific (orange)

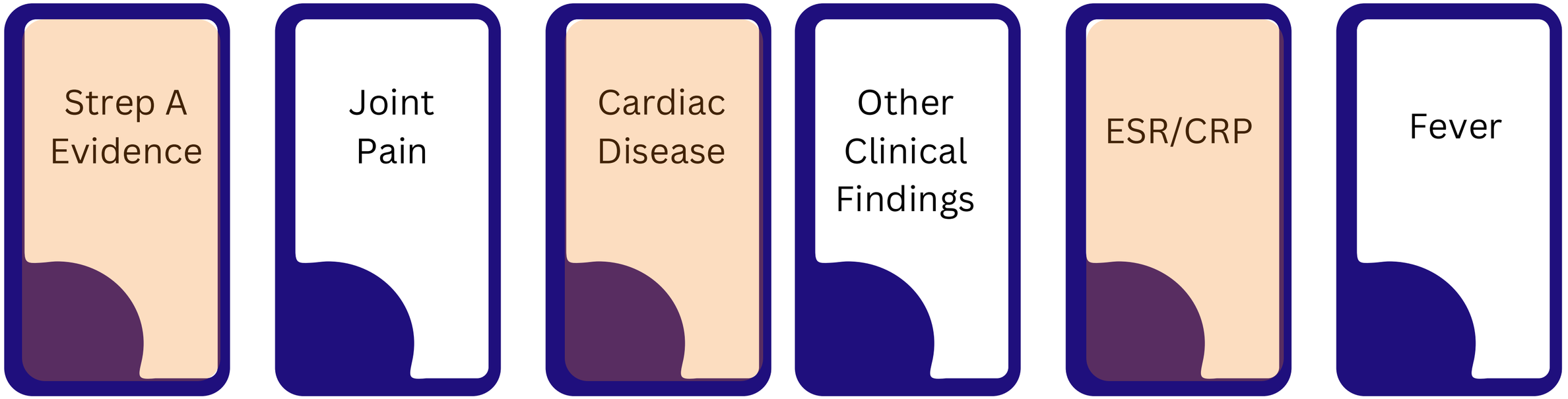
The Jones Criteria
(Last Revision 2015, Gewitz et. al.)



A few are highly specific but rare

(Major criteria: Subcutaneous nodules + Erythema marginatum <2%)

The Jones Criteria
(Last Revision 2015, Gewitz et. al.)

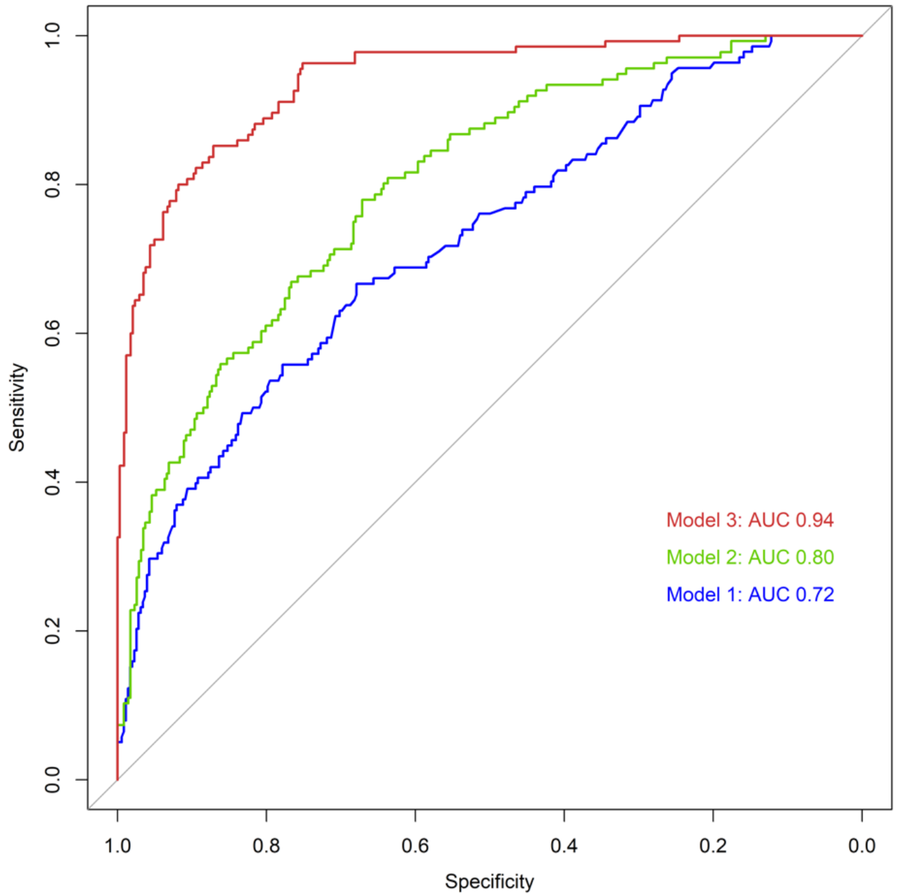


And many critical criteria cannot be routinely assessed in LIMCs

(including need to rule out overlapping conditions)

As a result

The ability to diagnose ARF in LIMCs is limited



Community Health Center

Model 1

Sensitivity= 66%

Specificity= 68%

District hospital

Model 2

Sensitivity=77%

Specificity=67%

National referral hospital

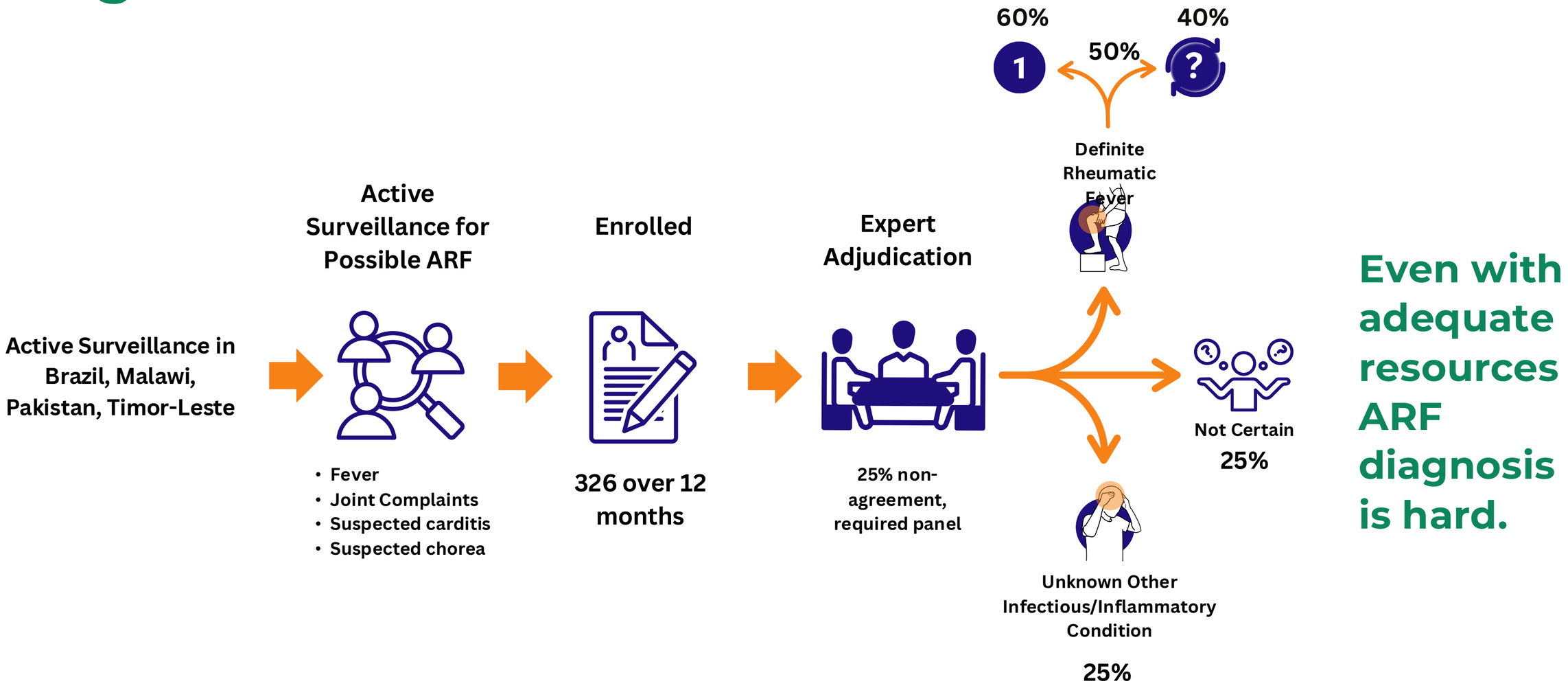
Model 3

Sensitivity= 84%

Specificity= 87%

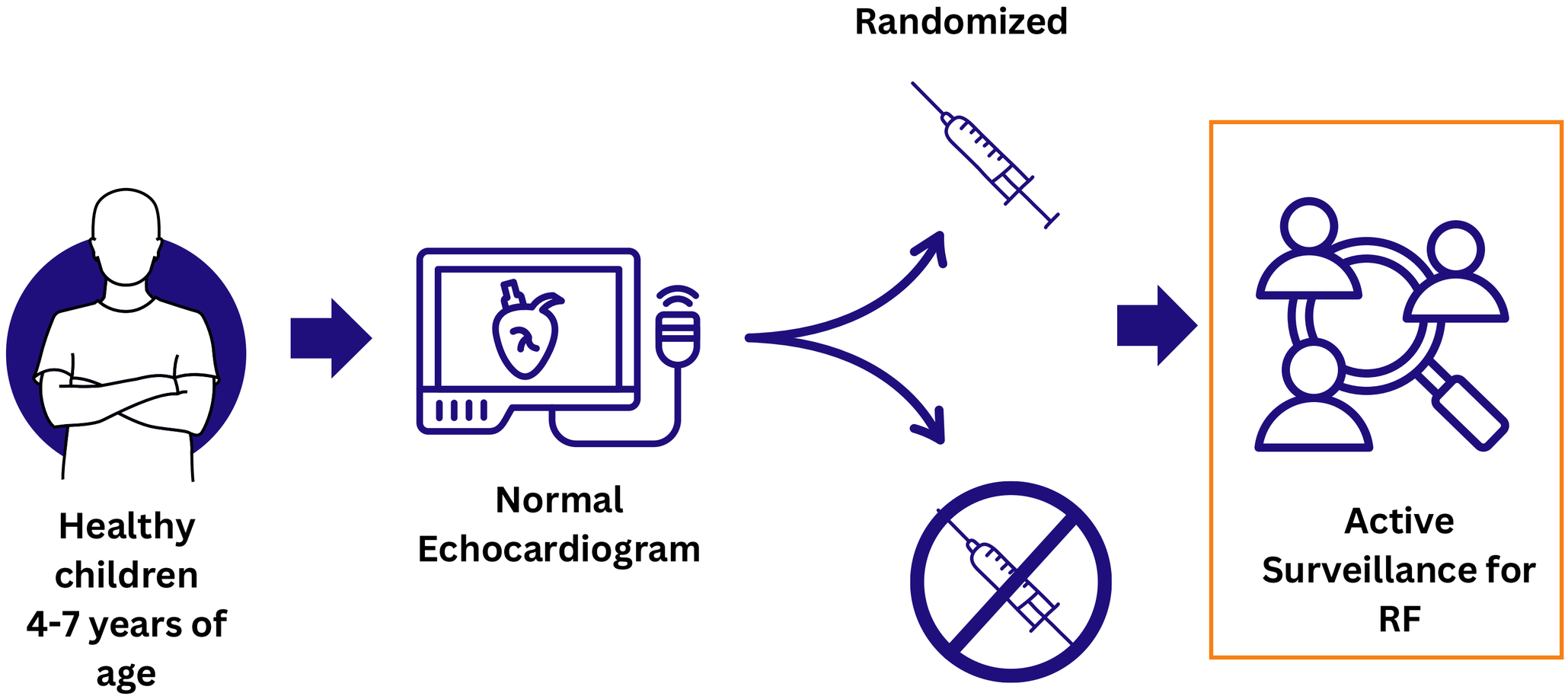
A Strep A Vaccine for LIMCs

Even when all resources availible
Diagnosis of ARF is still hard



Even with adequate resources ARF diagnosis is hard.

Other considerations for an efficacy trial look like with ARF prevention as your primary endpoint?



Large sample sizes will be required in most RHD endemic settings

If you target 50% reduction in RF incidence (HR=0.5)							
Country	RF incidence		1 Year	2 Years	3 Years	4 Years	5 Years
Indigenous Australia	245 per 100,000	0.00245	35918	17959	11973	8980	7184
NZ Pacific	81 per 100,000	0.00081	108642	54321	36214	27160	21728
NZ Maori	25 per 100,000	0.00025	352000	176000	117333	88000	70400
Uganda (Lira)	25 per 100,000	0.00025	352000	176000	117333	88000	70400
Fiji	15.2 per 100,000	0.00015	578947	289474	192982	144737	115789
Uganda (Mbarara)	13 per 100,000	0.00013	676923	338462	225641	169231	135385

You need 66 events

Sample size for a 2-year trial 17,959-338,462

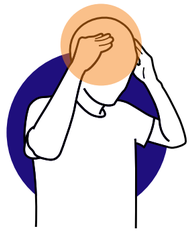
Large sample sizes will be required in most RHD endemic settings

If you target 80% reduction in RF incidence (HR=0.2)							
Country	RF incidence		1 Year	2 Years	3 Years	4 Years	5 Years
Indigenous Australia	245 per 100,000	0.00245	6531	3265	2177	1633	1306
NZ Pacific	81 per 100,000	0.00081	19753	9877	6584	4938	3951
NZ Maori	25 per 100,000	0.00025	64000	32000	21333	16000	12800
Uganda (Lira)	25 per 100,000	0.00025	64000	32000	21333	16000	12800
Fiji	15.2 per 100,000	0.00015	64000	32000	21333	16000	12800
Uganda (Mbarara)	13 per 100,000	0.00013	123077	61538	41026	30769	24615

You need 12 events
Sample size for a 2-year trial 3,265-61,538

Key Conclusions

Rheumatic Fever



The first intermediate endpoint

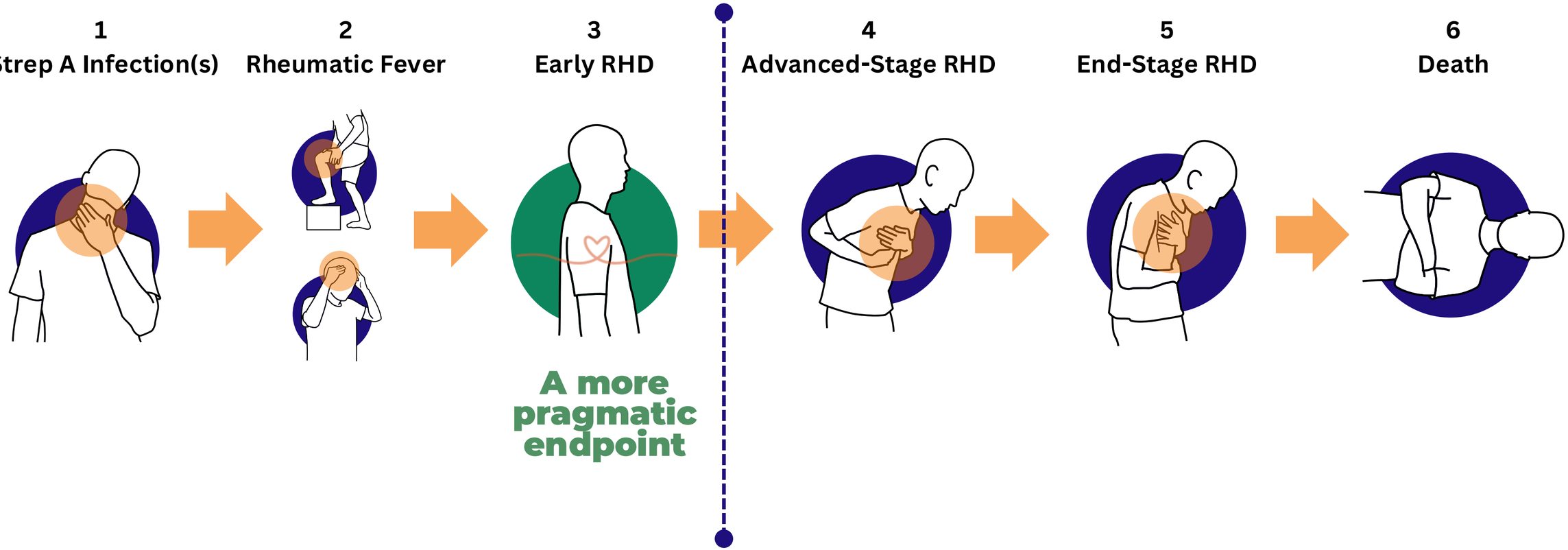
1. ARF diagnosis is a huge challenge in LMICs leading to ARF not being a practical intermediate Strep A vaccine endpoint in these settings

2. A Strep A vaccine with ARF as the intermediate endpoint ***MIGHT*** be possible in Australia and New Zealand – but formative work is needed to understand regulatory, cost, and logistical feasibility

Early Rheumatic Heart Disease

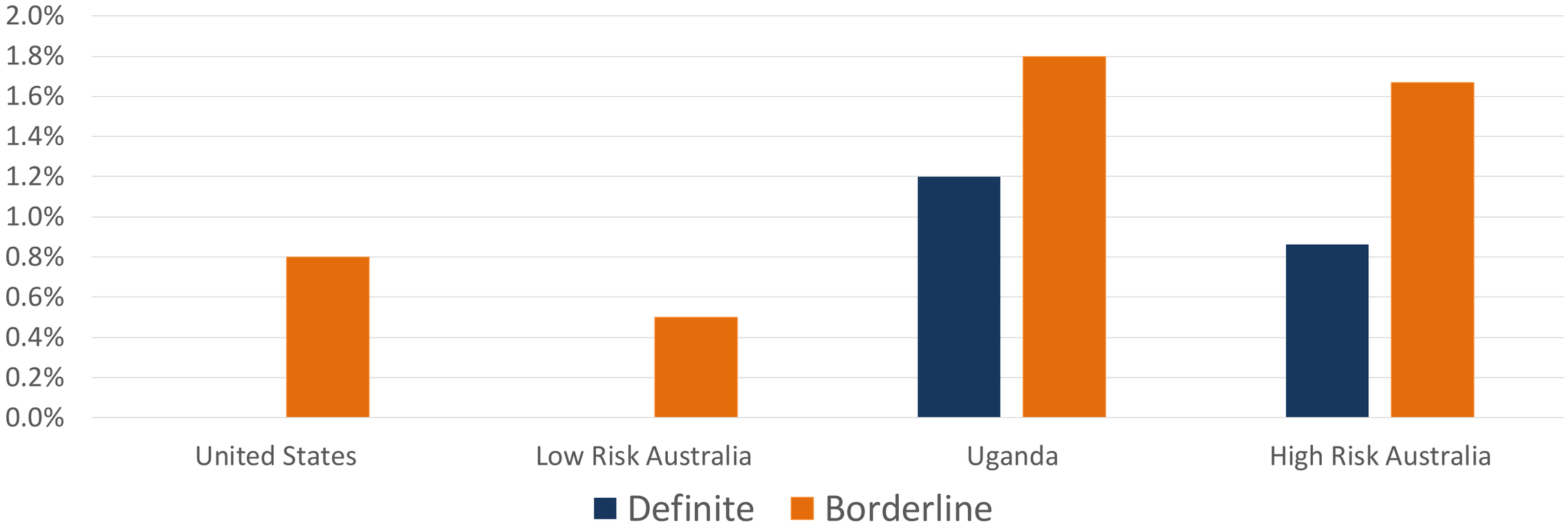
A practical intermediate endpoint

Early RHD is slient on clinical exam, but able to be found by echocardiography



Early RHD has become recognized as a Intermediate endpoint

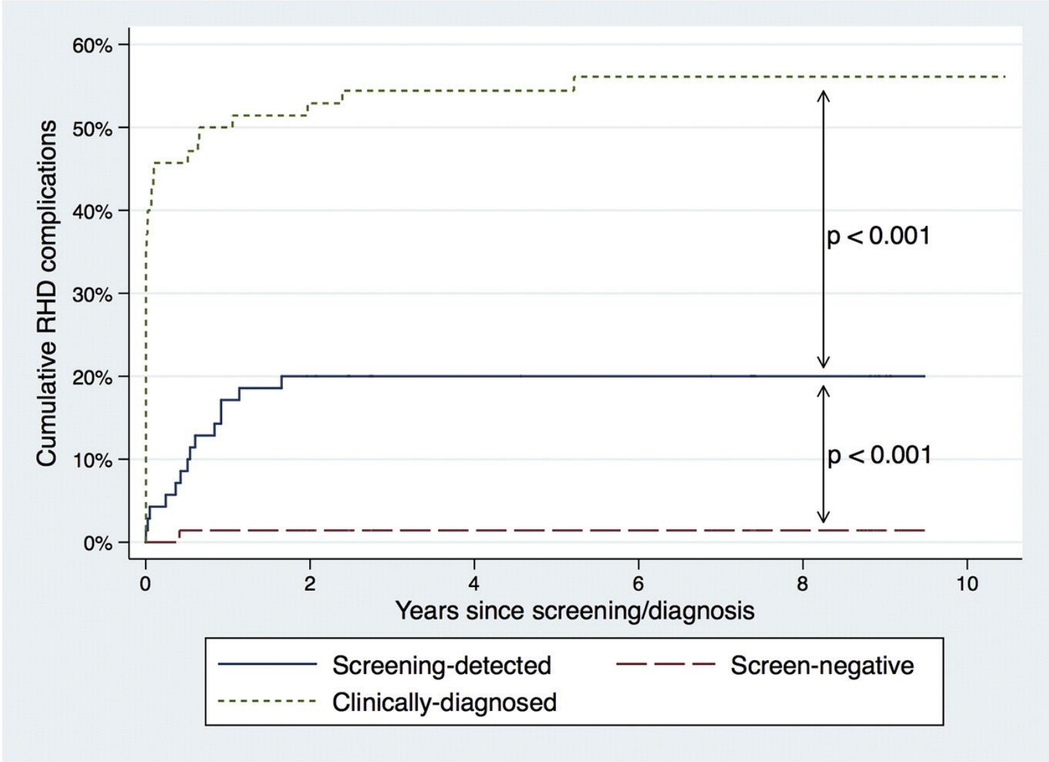
Roberts (2014), Clark (2015)



Early RHD is specific to RHD-endemic environments

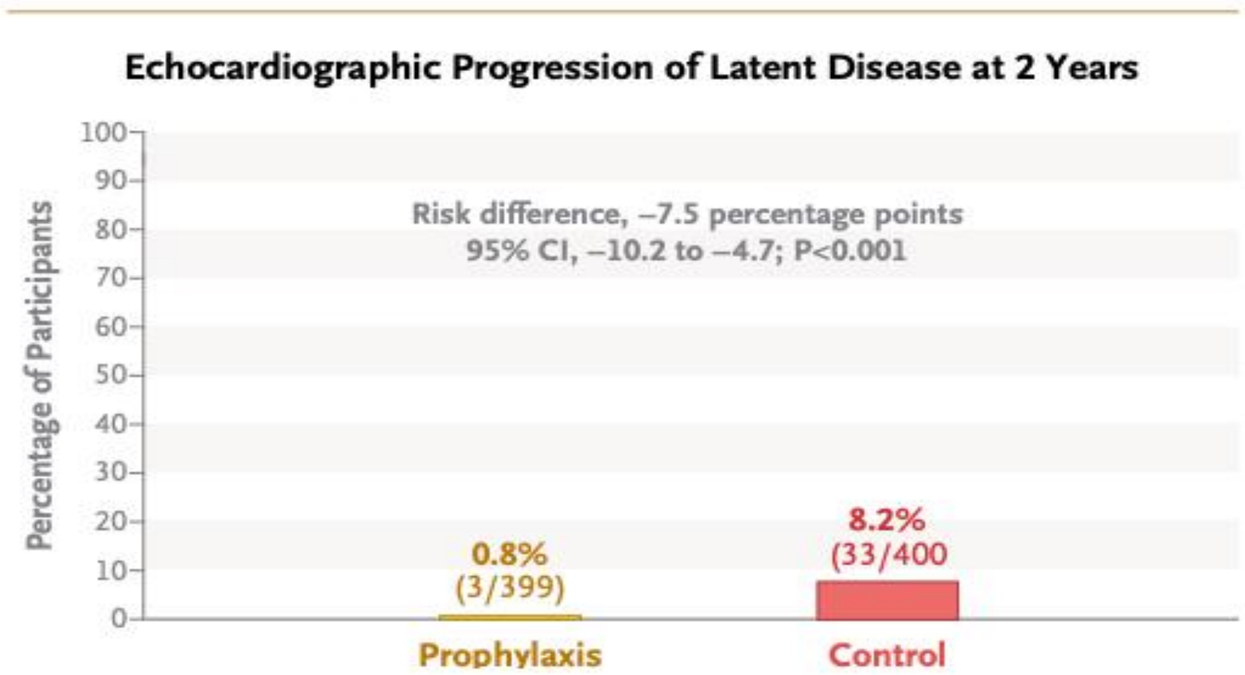
Early RHD has become recognized as a Intermediate endpoint

Engelman (2017)



Children with early RHD show progression to advanced-stage RHD

Early RHD has become recognized as a Intermediate endpoint

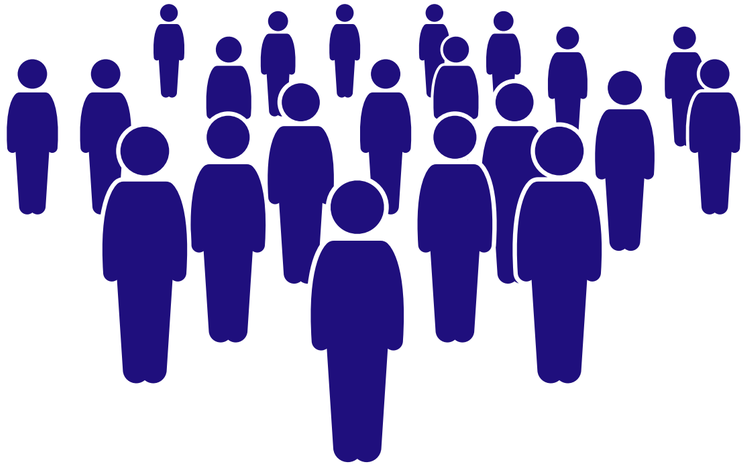


GOAL
GwokO Adunu pa Lutino
PROTECT THE HEART OF A CHILD

Prophylaxis protects children with early RHD from progression

Early RHD is easy to find

A Strep A Vaccine for LIMCs



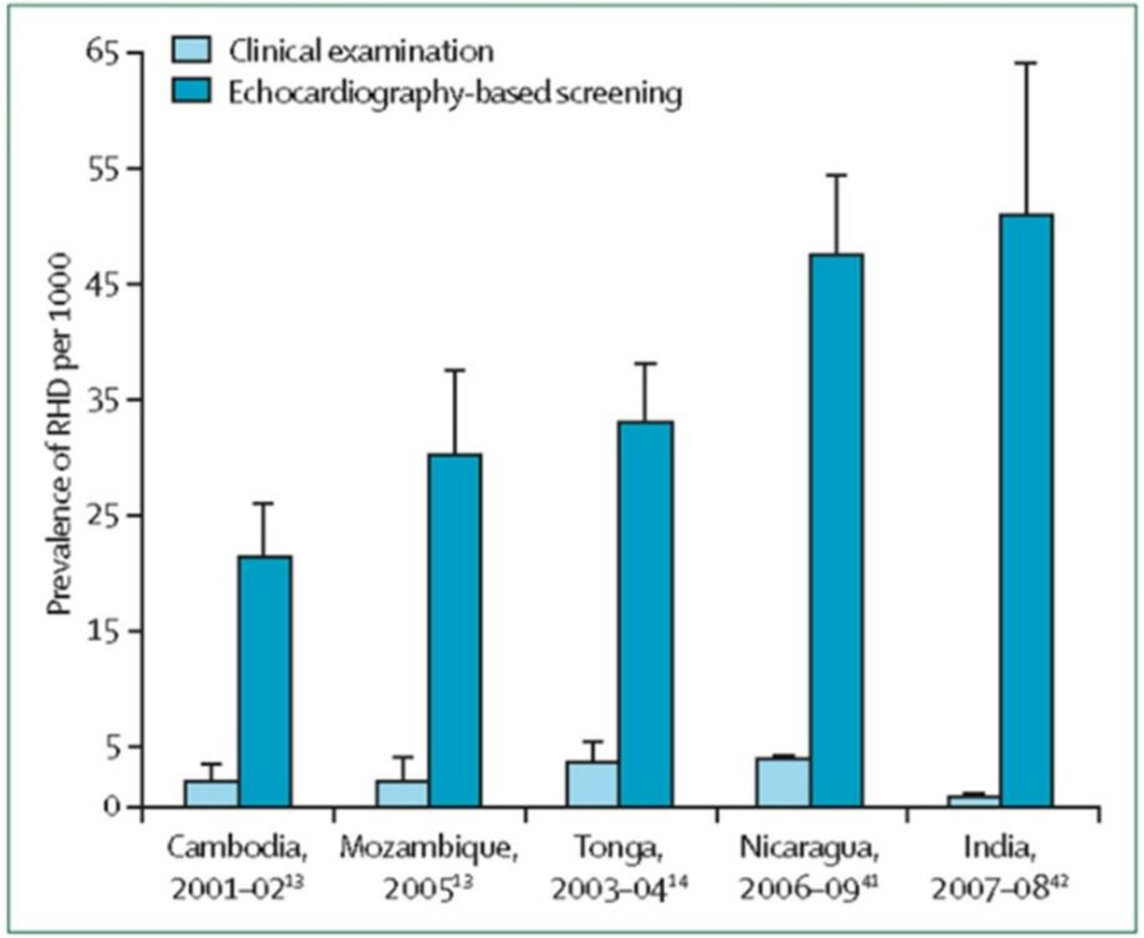
Superficial Strep Infections

Acute Rheumatic Fever

Rheumatic Heart Disease

Echo screening is

Is the most sensitive approach to diagnosis



- Screening with auscultation is no longer recommended
- Echo screening on 6 continents, finding 1-2% in most high-risk populations
- 1/3 advanced + 2/3 early-stage RHD

Echo screening for early-RHD

Is practical, feasible, and efficient in LMICs


Two-step screening protocols
Screen --> Diagnose
95% sensitive + specific


School + community settings with high uptake
99% consent to screening

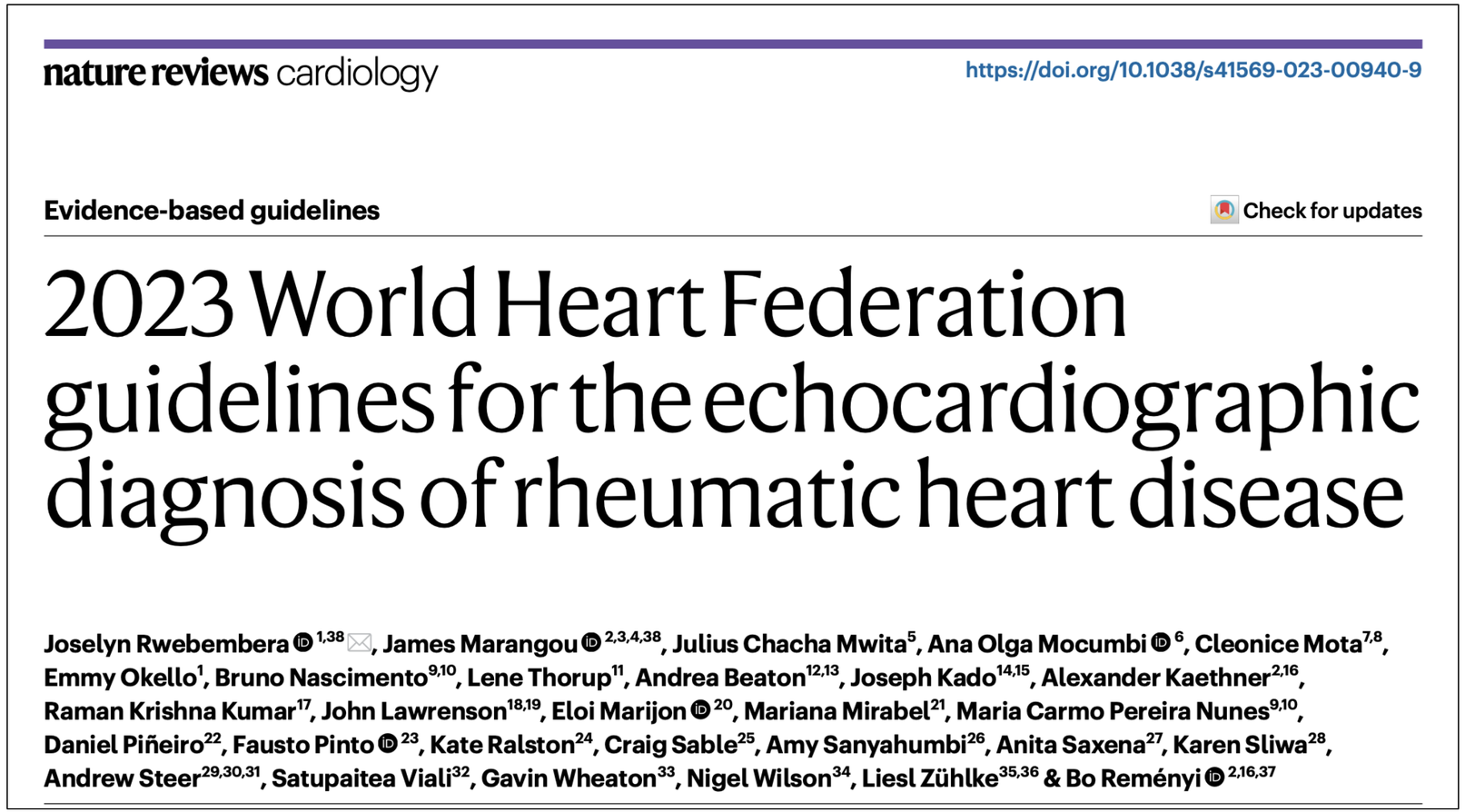

New trainees - rapid training
4 weeks
96% for image aquisition


Cloud-based echo reading
Image transfer from low-bandwidths, 100%

- **In Uganda, across 2 clinical trials, >300,000 children screened**
- **Now at a rate of >2500/day with a team of 5 nurses**
- **Cost of screening is $1-2 per child in this setting**

Standardized evidence-based Guidelines exist

- Revised in 2023 to improve reproducibility
- Provided disease stages (A-D)
- Screening recommended in the 2024 WHO Guidelines in high-risk settings



nature reviews cardiology

https://doi.org/10.1038/s41569-023-00940-9

Evidence-based guidelines

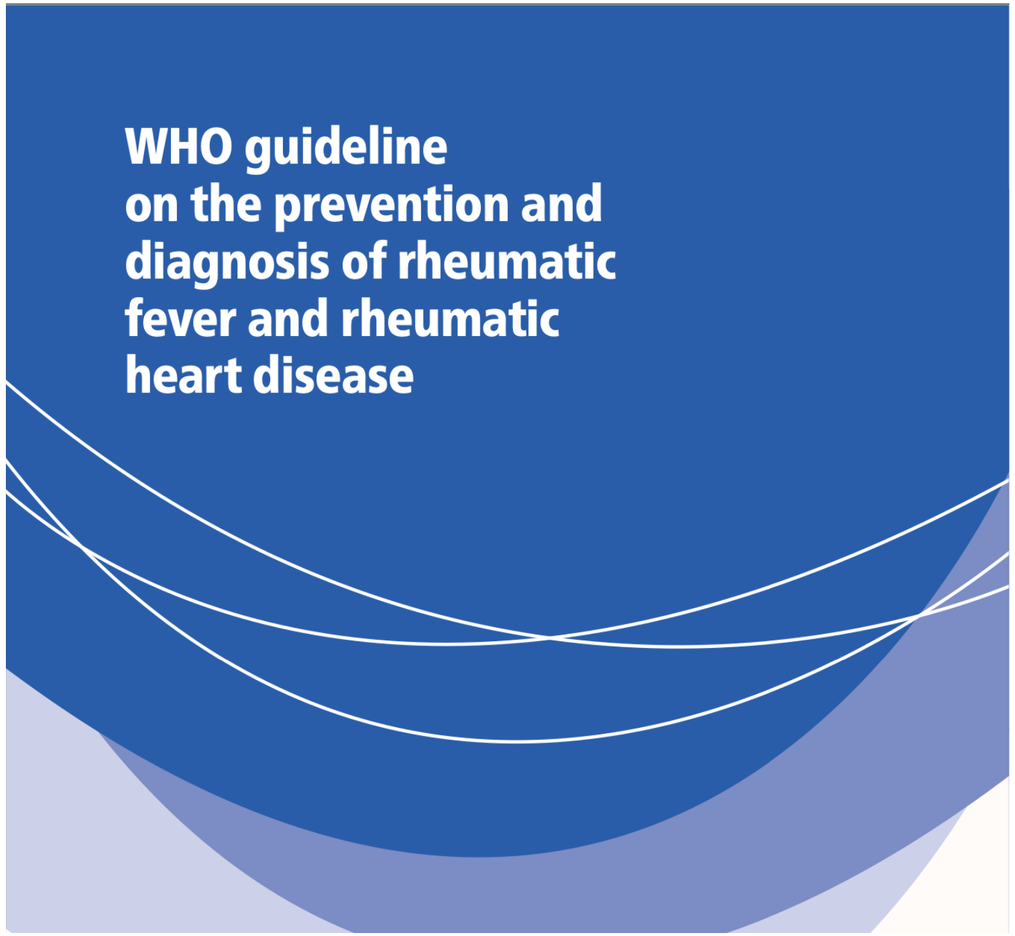
Check for updates

2023 World Heart Federation guidelines for the echocardiographic diagnosis of rheumatic heart disease

Joselyn Rwebembera[1,38], James Marangou[2,3,4,38], Julius Chacha Mwita[5], Ana Olga Mocumbi[6], Cleonice Mota[7,8], Emmy Okello[1], Bruno Nascimento[9,10], Lene Thorup[11], Andrea Beaton[12,13], Joseph Kado[14,15], Alexander Kaethner[2,16], Raman Krishna Kumar[17], John Lawrenson[18,19], Eloi Marijon[20], Mariana Mirabel[21], Maria Carmo Pereira Nunes[9,10], Daniel Piñeiro[22], Fausto Pinto[23], Kate Ralston[24], Craig Sable[25], Amy Sanyahumbi[26], Anita Saxena[27], Karen Sliwa[28], Andrew Steer[29,30,31], Satupaitea Viali[32], Gavin Wheaton[33], Nigel Wilson[34], Liesl Zühlke[35,36] & Bo Reményi[2,16,37]

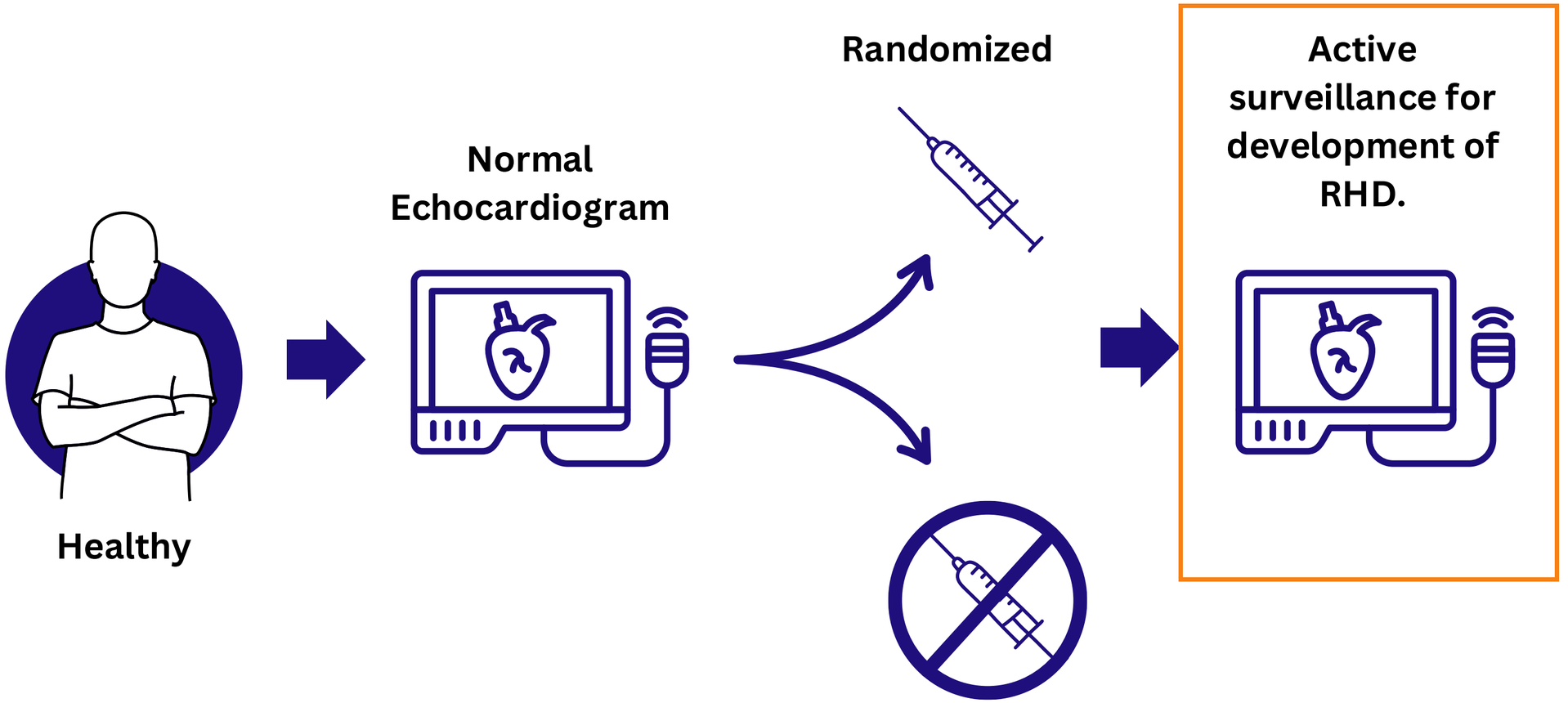
Screening for Early-Stage RHD

Now recommended in RHD-endemic areas



- Published in 2024
- For the first time provide a formal recommendation for screening echocardiography to diagnose early-stage RHD

Other considerations for an efficacy trial look like with RHD prevention as your primary endpoint?



Sample sizes are lower and achievable

A Strep A Vaccine for LIMCs

If you target 50% reduction in RHD incidence (HR=0.2)						
Assumed RHD prevalence at end of 5 years (no intervention)	Annual Incidence	1 Year	2 Years	3 Years	4 Years	5 Years
0.50%	0.0010	88000	44000	29333	22000	17600
1.00%	0.0020	44000	22000	14667	11000	8800
1.50%	0.0030	29333	14667	9778	7333	5867
2.00%	0.0040	22000	11000	7333	5500	4400

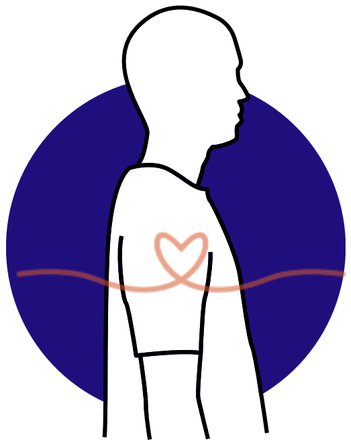
In Uganda - Sample size decreases from 338,462 to 14,667

If you target 80% reduction in RHD incidence (HR=0.2)						
Assumed RHD prevalence at end of 5 years (no intervention)	Annual Incidence	1 Year	2 Years	3 Years	4 Years	5 Years
0.50%	0.0010	16000	8000	5333	4000	3200
1.00%	0.0020	8000	4000	2667	2000	1600
1.50%	0.0030	5333	2667	1778	1333	1067
2.00%	0.0040	4000	2000	1333	1000	800

In Uganda - Sample size decreases from 61,538 to 2667

Key Conclusions

Early-Stage Rheumatic Heart DIsease



A pragmatic and recognized clinical intermediate

1. Early RHD is the most pragmatic intermediate endpoint for advanced-stage RHD in LMICs
2. Early RHD is simple to diagnose, highly sensitive and replicable test
3. Established pathways to local capacity building in LIMCs
4. Low cost per child screened

THANK YOU

What’s next

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

SAVAC 2.0
Strep A Vaccine Global Consortium

Paving a path for development of a Strep A vaccine through three cross-disciplinary workstreams

1. Early RHD as a recognized clinical intermediate

-London meeting report in draft

-Other technical papers in draft

-Position statement being developed by cardiology experts

-Role of PDVAC in endorsement and convening around this topic

2. Roadmap and PPC

-Roadmap will be revised in 2025

-PPC will be revised in 2025 - question to PDVAC on how to deal with two use cases:

- HIC: pharyngitis
- LMIC: rheumatic heart disease

Final comment

PDVAC has been critical in advancing efforts for Strep A vaccine development

We request PDVACs ongoing involvement and support

SAVAC
Strep A Vaccine Global Consortium

wellcome

LEDUCQ

Open Philanthropy

murdoch children's research institute

RRCU
RHD RESEARCH COLLABORATIVE IN UGANDA

Thank you

GAS section - Questions to PDVAC

1 - Does PDVAC have specific recommendations on pursuing a parallel pathway to policy for a GAS vaccine to be indicated against:
- pharyngitis in low-RHD burden settings (e.g. HIC)
- RHD in RHD-endemic settings (e.g. LMIC+HIC marginalized communities)

2 - Does PDVAC have specific feedback on using **early RHD** as **intermediate clinical endpoint for RHD** in pivotal clinical studies to be conducted in RHD endemic settings ?

3. Does PDVAC agree to update the existing PPC to include two use case scenarios (prevention of pharyngitis and RHD) once consensus has been reached on the intermediate clinical endpoint?