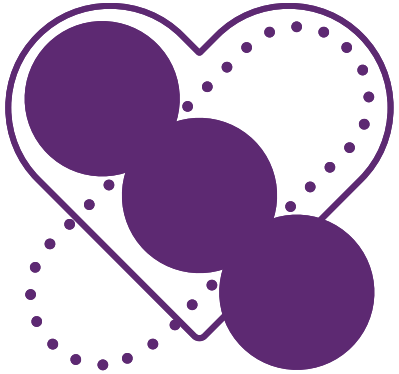

Strep A Vaccine Global Consortium

https://savac.ivi.int/

Content

- History of GAS vaccine safety
- Framework for *S. pyogenes* vaccine safety assessment
- Pathways and opportunities for vaccine safety evaluation
- Review of safety evaluation of current GAS vaccines in development
- Challenging examples from other vaccines with safety concerns
- Safety assessment guide – paving the future
- Regulatory considerations – the opportunity post-COVID

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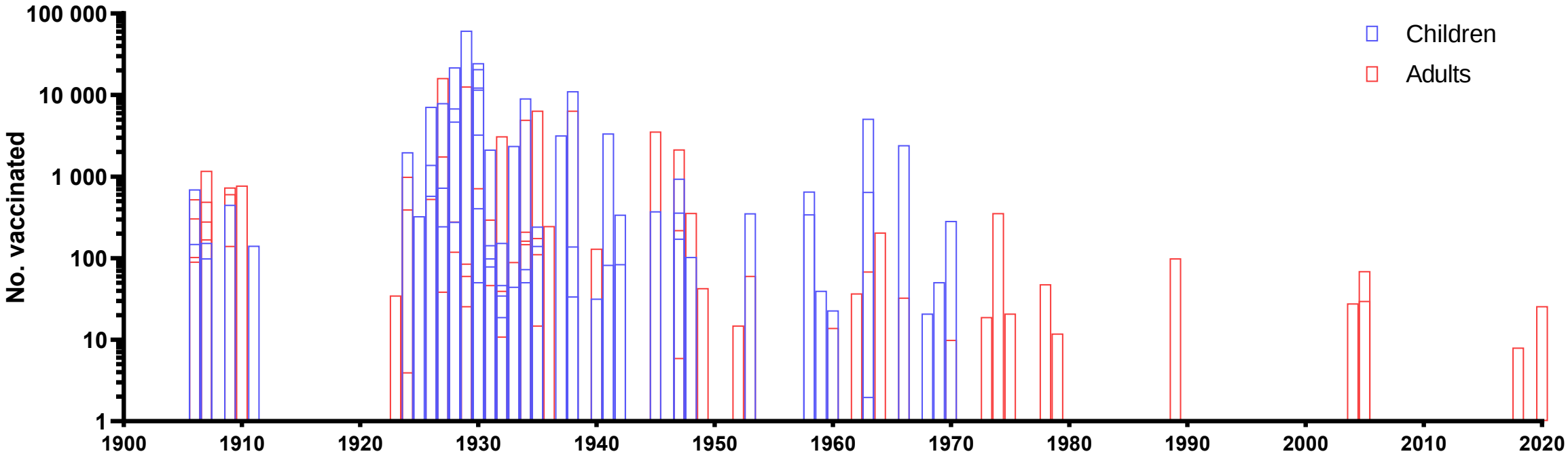
History of GAS vaccines safety

- 135 different human S. pyogenes vaccine trials between **1796 to 2019**
- Estimated **>320,000 subjects** inoculated with **investigational GAS vaccines**



Hannah Frost, Joshua Osowicki, Elise Thielemans, Andrew C. Steer. Poster at Lancefield Symposium, Stockholm 2022

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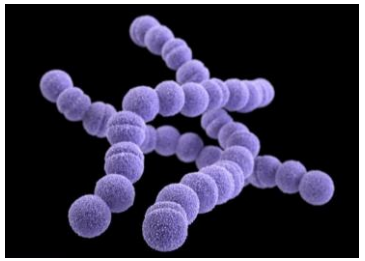
History of Vaccination against GAS in 20th century

S. pyogenes
Recognized
Scarlet Fever

1884-85

Lancefield
S. pyogenes
M types

1928-40



Heat killed GAS vaccines
Military and med students
M-protein immunity
No protection

1940-1960

B. Massell
Good Samaritan
Hospital, Boston

1965-1967

1796

1925

Section of Epidemiology and State Medicine.
President—Dr. JOHN C. MCVAIL.

Immunization against Scarlet Fever.
By S. MONCKTON COPEMAN, F.R.S., M.D., F.R.C.P.
(*Emeritus Lecturer on Public Health, Westminster Hospital Medical School.*)

1940

TYPE-SPECIFIC PROTECTION AND IMMUNITY FOLLOWING INTRANASAL INOCULATION OF MONKEYS WITH GROUP A HEMOLYTIC STREPTOCOCCI*
By ROBERT F. WATSON, M.D.,
Lieutenant Commander, Medical Corps, United States Naval Reserve,
SIDNEY ROTHBARD, M.D., AND HOMER F. SWIFT, M.D.

Children inoculated with Dick toxin (3 doses in 3 weeks)
"not given rise to any serious reaction locally or constitutionally"
Immediate AE: Scarlatiniform rash and fever
>165,000 vaccinated, from the 1920s, mostly USA

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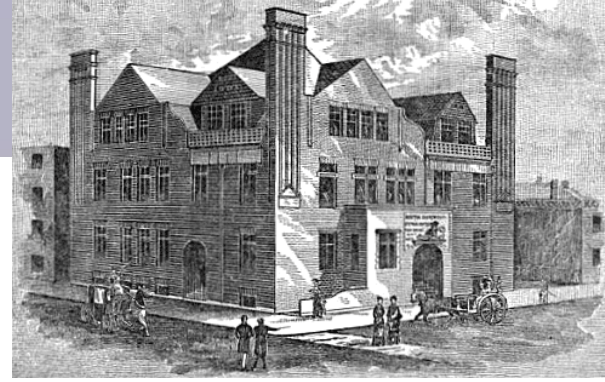
The Massell GAS type 3 M-protein vaccine study



- Conducted between 1965 and 1967 at
  House of the Good Samaritan, Children's Hospital Medical Center and the Department of Pediatrics, Harvard Medical School in **Boston**
- Hot-acid extracted **M protein of a type 3 S. pyogenes** partially purified using ribonuclease and dissolved in thiomersal
- 21 healthy siblings of randomly selected from 106 patients with rheumatic fever
- **Weekly SQ injections** of gradually increasing concentrations due to reactogenicity **(18 to 33 weeks)**
- 30 months observation - 18 episodes of *S. pyogenes* pharyngitis (none were type 3)
- **Comparison group:** Historical cohort of nonvaccinated children (all siblings of patients with rheumatic fever) observed for 15 years - 447 episodes of *S. pyogenes* pharyngitis and **5 cases of rheumatic fever (1%).**

Massell BF, Honikman LH, Amezcua J. JAMA 1969; 207: 1115-9.

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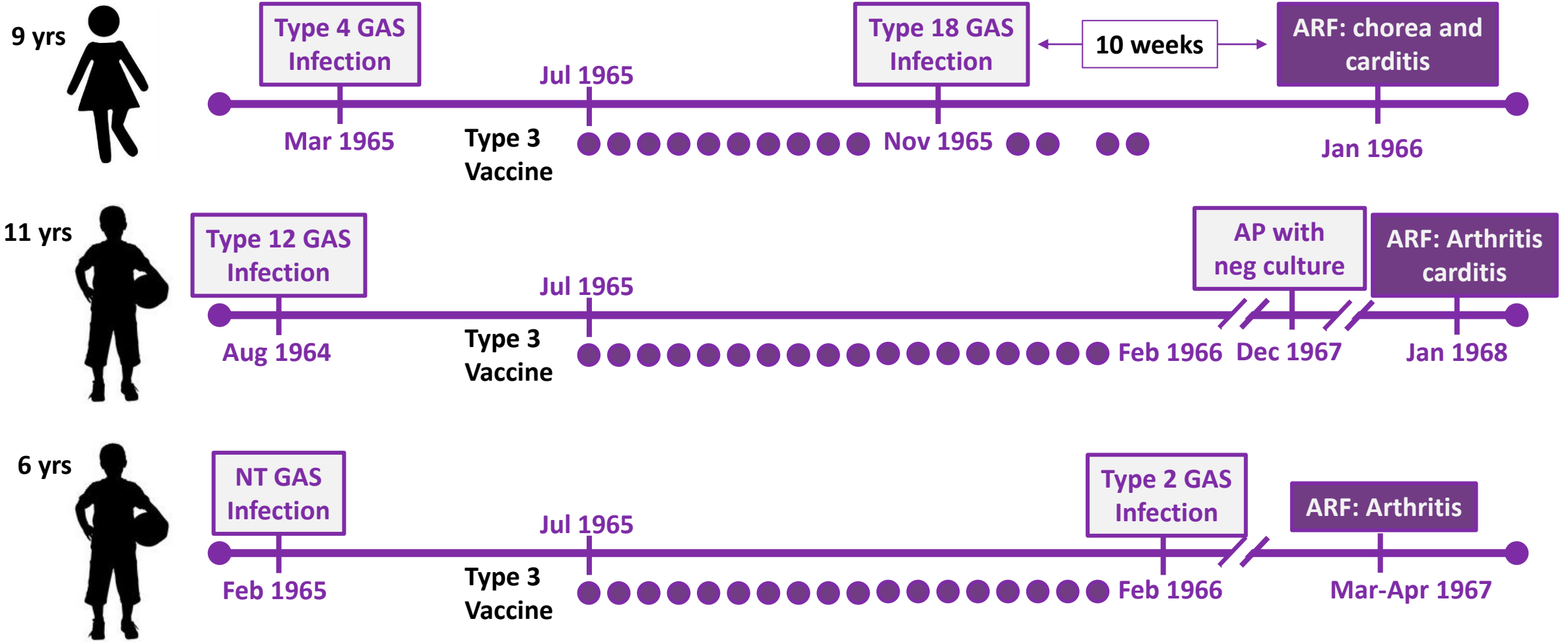
SAEs of GAS M type 3 Vaccine Study



AR baseline 0.9-1.1% vs 11.1% in 18 siblings vaccinated

Massell BF et al. JAMA 1969; 207: 1115-1119

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Vaccine Safety Evaluation Pathway

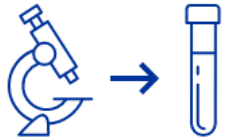
Vaccines development phases

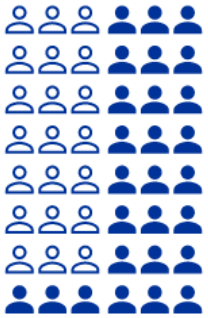
Safety monitoring

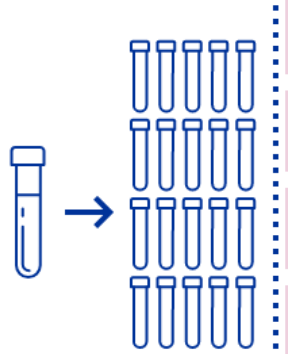
Vaccine in use

Quality | Toxicity | **EudraVigilance** - European database of suspected adverse reactions to medicines

Extended clinical trials (phase IV)







- Medical literature
- Post-marketing safety monitoring
- Safety studies
- Reports from patients and healthcare professionals

Pharmaceutical quality	Non-clinical	Clinical trials	Evaluation & decision	Manufacturing	**Post-marketing safety monitoring**

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Framework to Anticipate/Investigate Vaccine Safety

- **Clues from Natural History of GAS infections/complications**
  - Background rates of GAS infection complications
  - Biomarkers for disease severity and sequelae
- **Clues from GAS Vaccine Preclinical Studies**
- **Most recent GAS phase I studies**
- **Use of vaccine safety methods and causality assessment framework for GAS safety assessment during phase II and III studies**
- **Regulatory Considerations**

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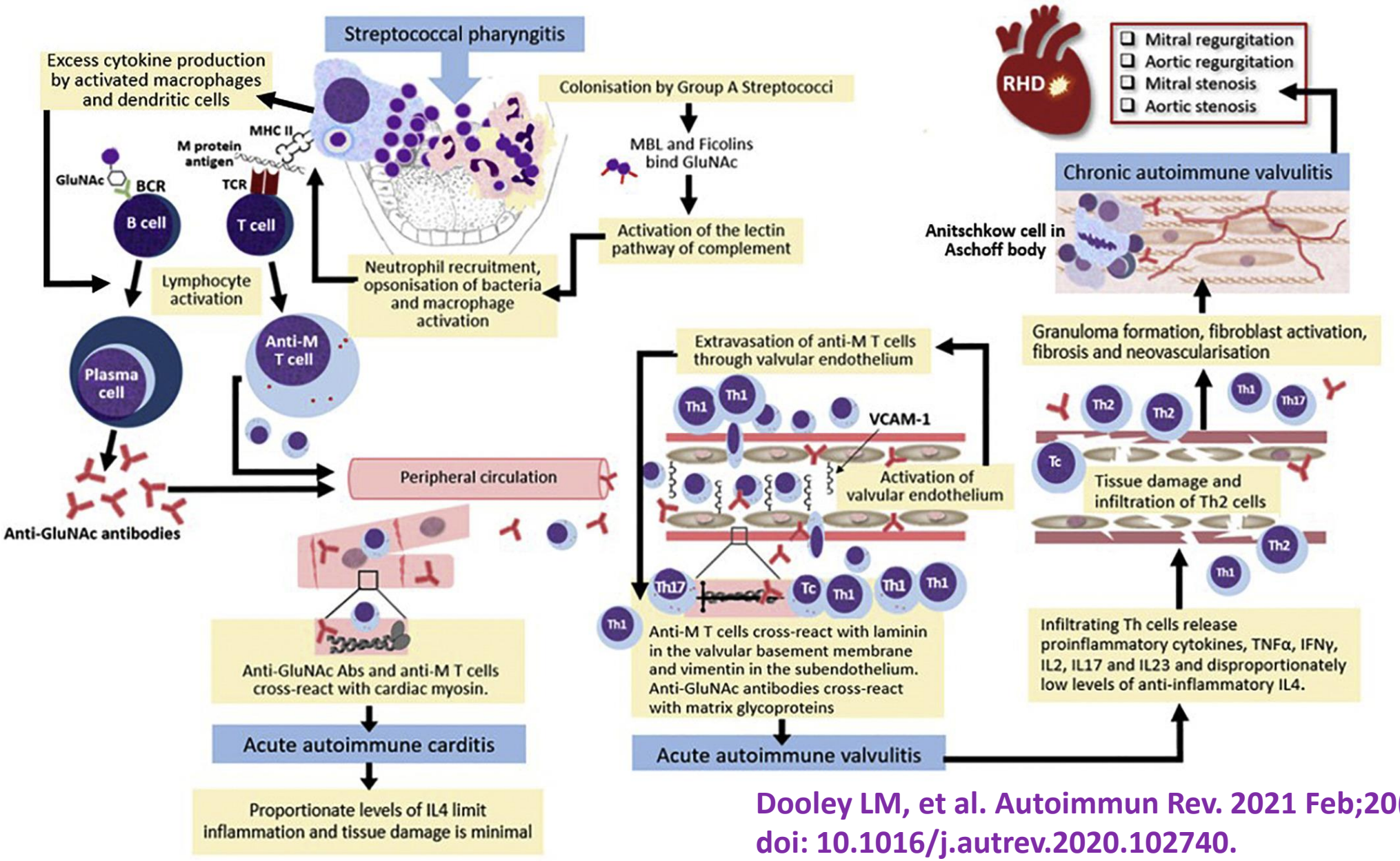
Immuno-pathogenesis of ARF and RHD



Dooley LM, et al. Autoimmun Rev. 2021 Feb;20(2):102740.
doi: 10.1016/j.autrev.2020.102740.

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Measuring background rates and endpoints of interest

Methods to estimate incidence and prevalence		Advantages and disadvantages of estimation methods
Continuous and active surveillance of the community for cases of ARF	Acute rheumatic fever ↓ Subclinical definite rheumatic heart disease ↓ Clinical RHD and sequelae	Ideal metric of ARF incidence; estimation is resource-intensive and not feasible in low-income countries
Echocardiographic screening of children (5–14 years) using standardised criteria		Pragmatic surrogate for ARF incidence and time-trends; easily measured, repeatable, and less costly
Community surveys, hospital-based registries, administrative databases, and vital registration systems		Poor surrogate for ARF incidence, but can mirror long-term trends in ARF incidence*

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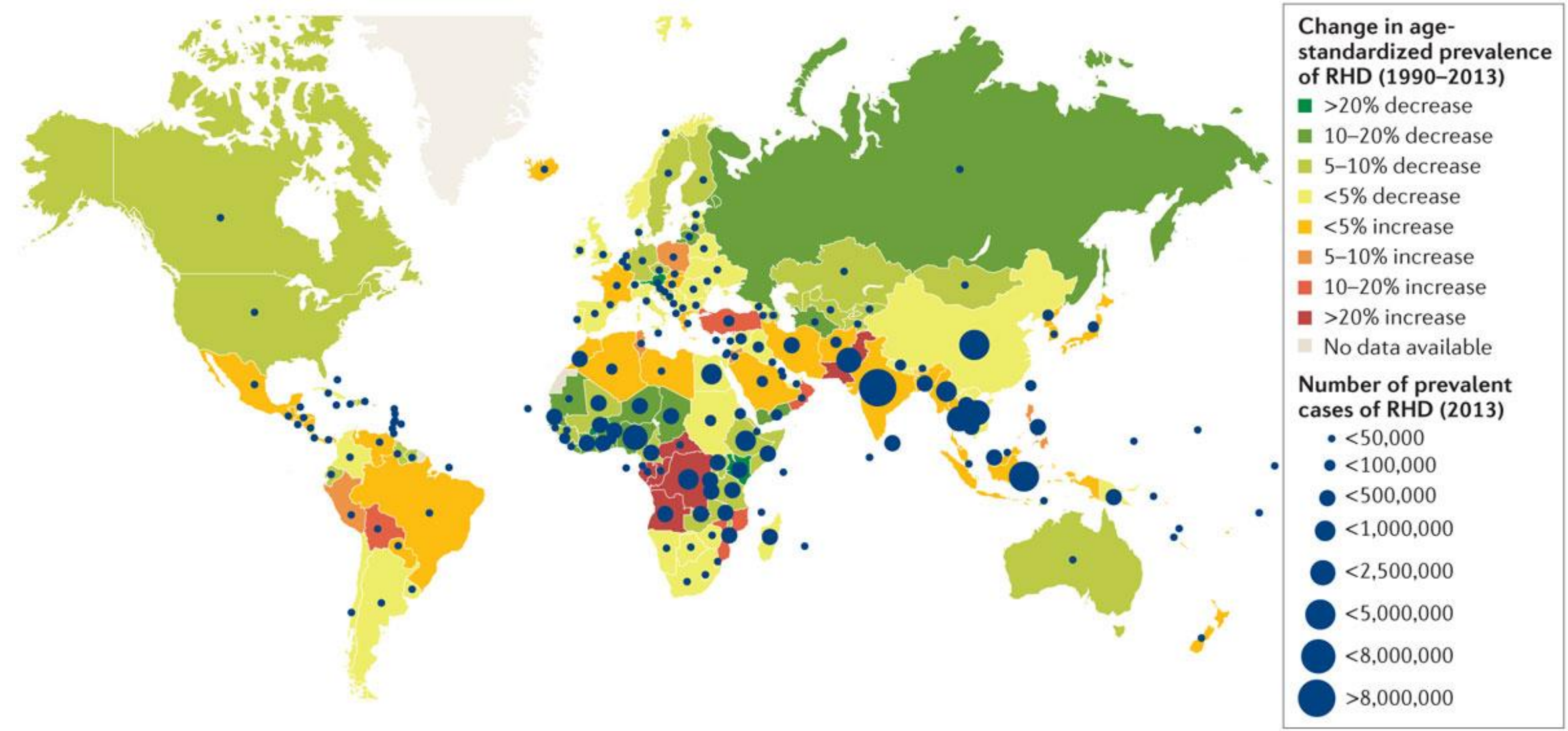
Burden of RHD as background rates for Safety



Nature Reviews | Disease Primers

Vaccine studies likely to concentrate in countries with high incidence/prevalence

If ARF/RHD is an efficacy and safety endpoint, background rates are critical

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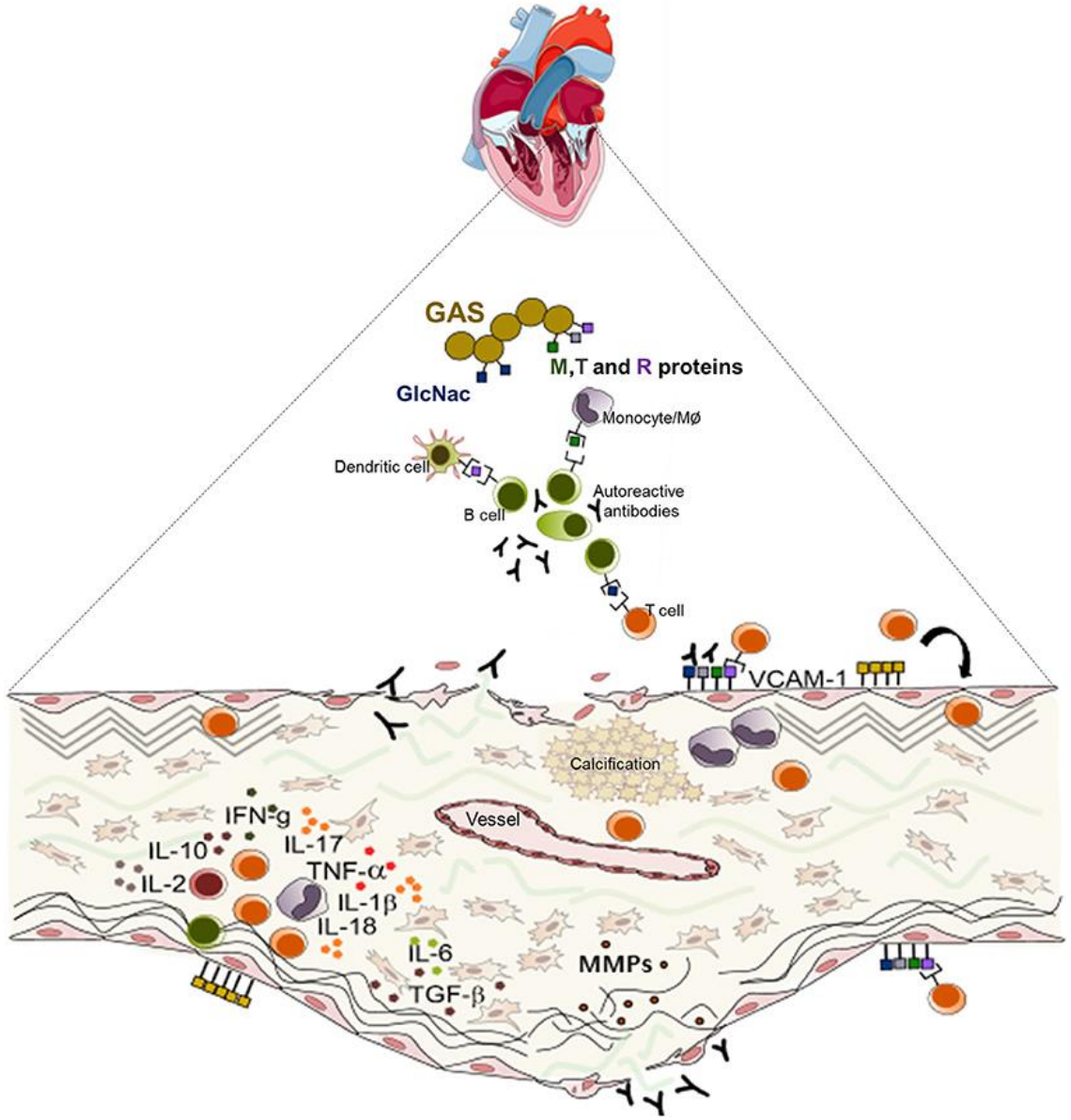
ARF Pathogenesis and biomarkers for GAS safety



Process or Marker	Causality component	Immune/non-immune surrogate
Autoimmune reaction **B-cells** **T-cells**	Biological plausibility Molecular Koch's postulates	TLR2 (−308A, −238 G), FCN2 (G/G/A), MASP2 (371D, 377V , 439R), MBL (A, O) MIF (-173CC) , FCγ RIIa (393A)
GAS carbohydrate epitope N-acetyl-β- d -glu cosamine (GlcNAc)	Biological plausibility Molecular Koch's postulates	
Upregulation of VCAM-1	Biological plausibility Molecular Koch's postulates	
Cardiac myosin Ag	Challenge/rechallenge Dose responses	T-cell reactivity
Susceptibility to ARF or o ther autoimmune phenomena		HLA class II genes (s everal HLA-DR and DQ alleles)

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Limitations of biomarkers for GAS Vaccine Safety

- No well-defined immune markers that could act as a surrogate for risk of ARF development.
- Significant gaps in knowledge of mechanistic correlates of ARF/RHD development and biomarker identification
- Natural infection studies are warranted, as well as application of innovative immune-profiling technologies before and during trials
- Development of biologic time windows for sequelae of GAS infection may inform vaccine safety assessment
- **Jones criteria with echo will be essential for vaccine safety evaluation**

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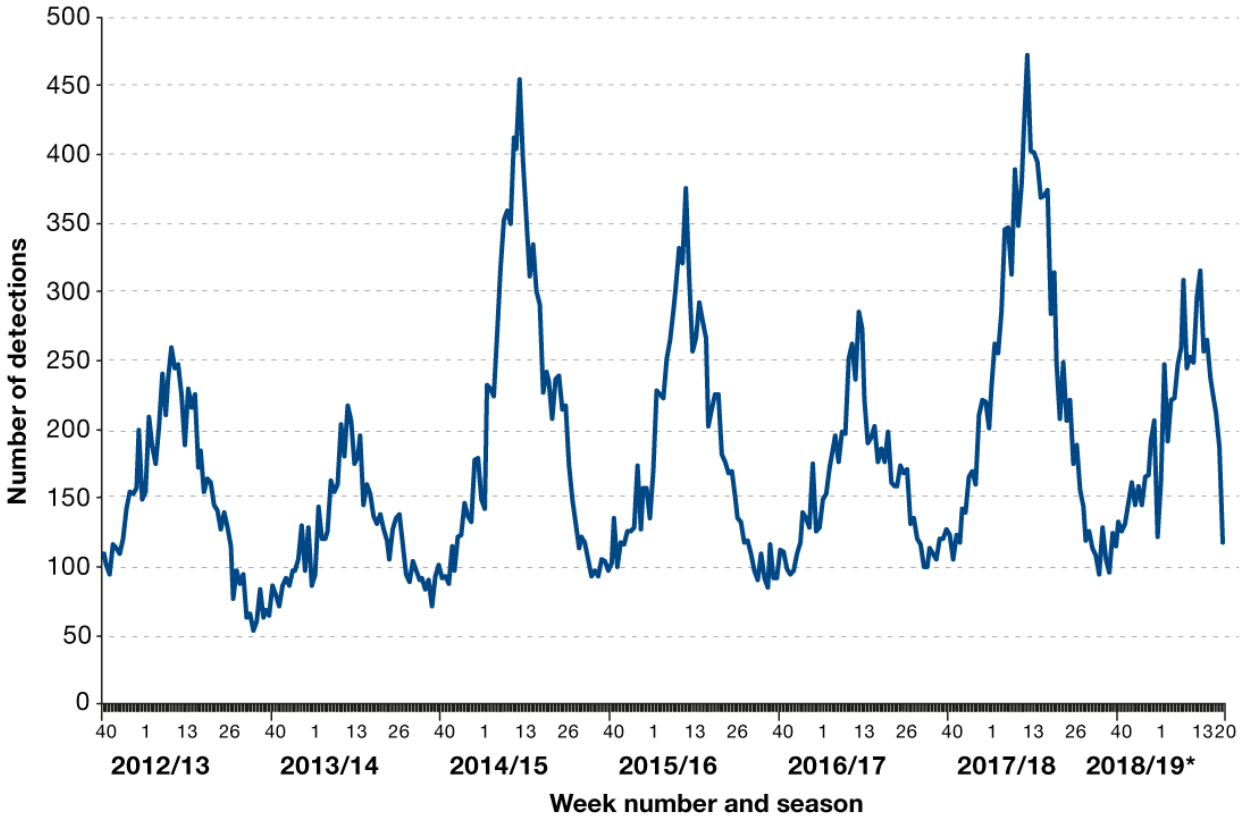
GAS seasonality should be considered in trials

Lab confirmed GAS infections

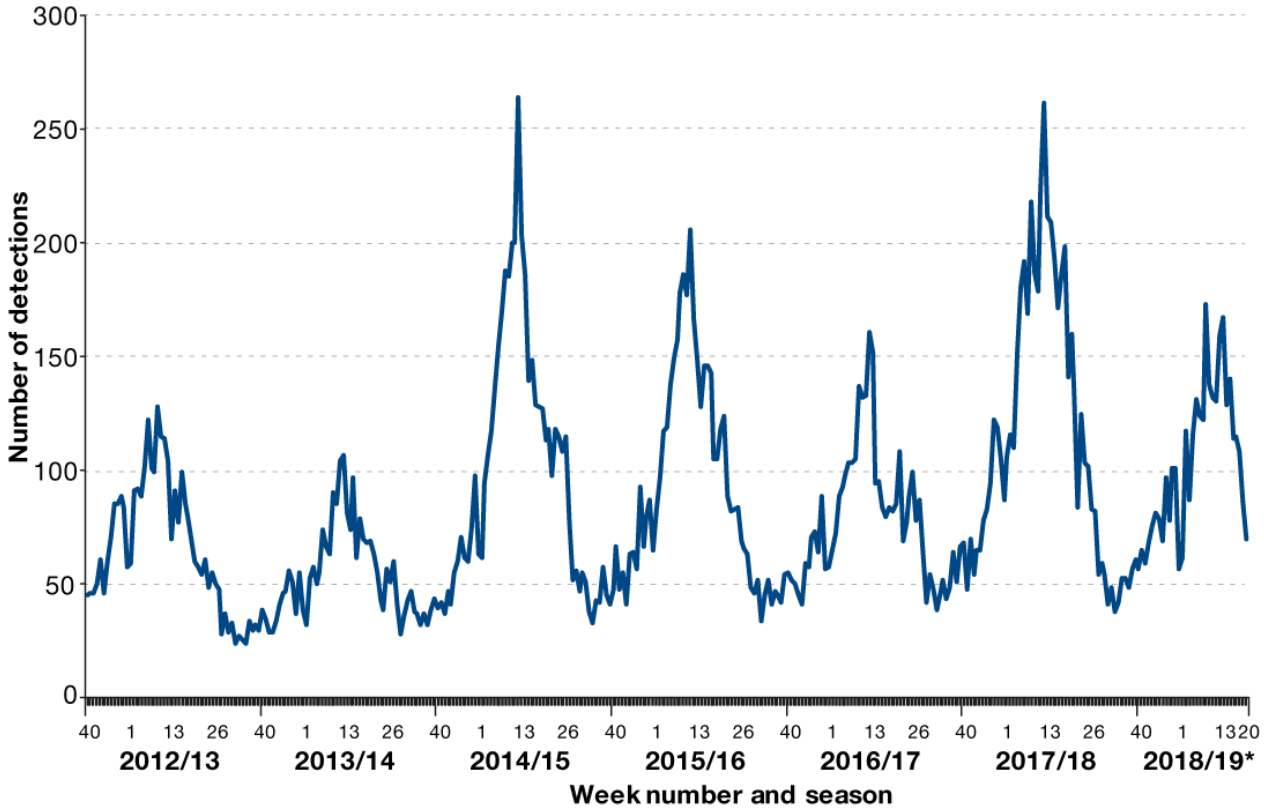
Figure 1: Number of laboratory diagnoses of Group A Strep by week and season, from 2012/13 to 2018/19 week 20



*Numbers will change retrospectively in later weeks as more data is received

Lab confirmed Scarlet Fever

Figure 2: Number of laboratory diagnoses of Scarlet fever† by week and season, from 2012/13 to 2018/19 week 20



*Numbers will change retrospectively in later weeks as more data is received
†Laboratory confirmed reports of GAS from upper respiratory samples are used as a proxy for scarlet fever

Health Protection Scotland

https://www.hps.scot.nhs.uk/a-to-z-of-topics/streptococcal-infections/group-a-streptococcal-infections/

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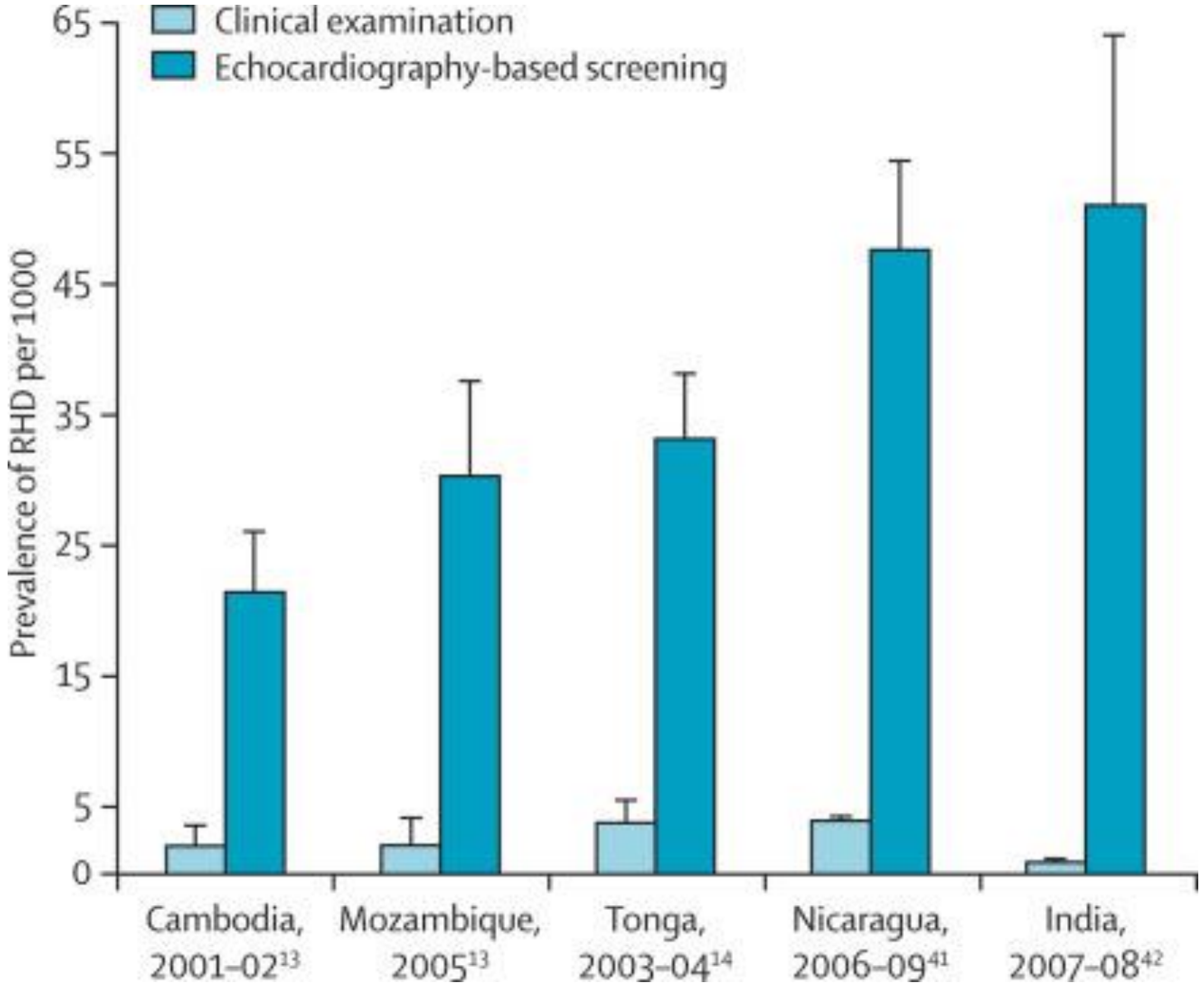
Echocardiography vs. clinical ascertainment of RHD

- RHD Case detection rate when using **echo- cardiography-based screening is 10x greater** than that achieved by careful clinical examination alone.
- Simple on-site 5-10 minute protocol per child to screen for valvular lesions with a referral for confirmation. needed
- Issues remaining
  - Absence of **gold-standard** echo criteria for subclinical RHD
  - Optimum management strategy for patients with clinically silent and mild valvular abnormalities.



Marijon E et al. *Lancet* 2012; 379: 953–64

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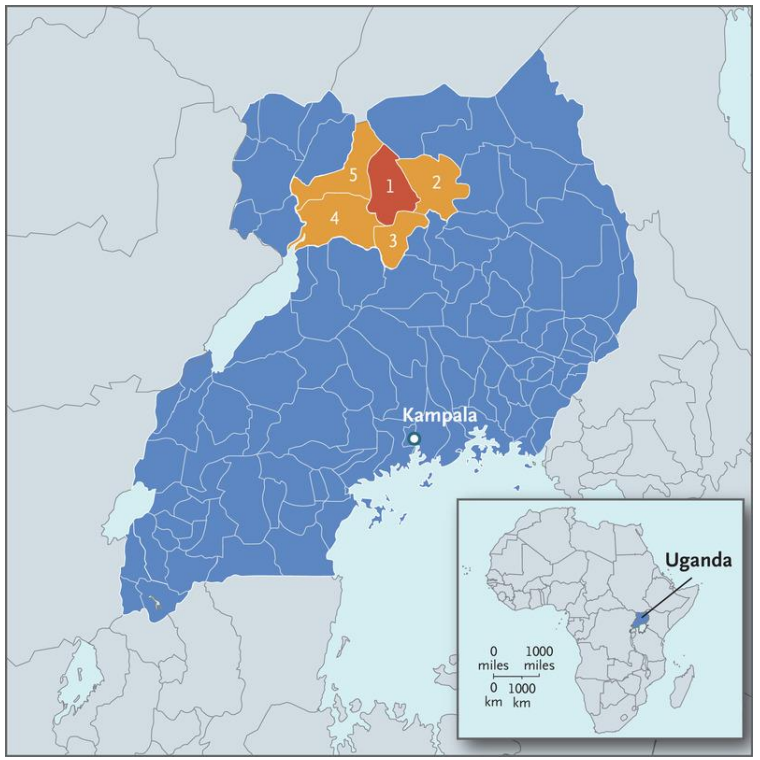
Echo diagnosis of RHD in schools: a moving target

- 102,200 children 5-17 years of age in Uganda screened
- **3,327 (3.3%) positive screening echocardiogram**
- **916 with latent RHD randomized and followed up**



Variable	PNC Prophylaxis (n=409)	Control Group (n=409)
RHD category		
Borderline	328 (80.2%)	339 (82.9%)
Definite	81 (19.8%)	70 (17.1%)
Sore throat past 4 wks	78 (19.1%)	67 (16.4%)
Skin infection past 4 wks	26 (6.4%)	26 (6.4%)

Progression or Regression of Latent RHD at 2 years			**Risk Ratio (95%CI)**	***p-value***
Progression – No. (%)	3 (0.8%)	33 (8.2%)	0.09 [0.03-0.29)]	<0.001
Regression – No. (%)	**195 (48.9%)**	**191 (47.8%)**	**1.03 [0.89-1.19]**	

Beaton A, et al. N Engl J Med 2022; 386:230-240

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S. pyogenes (GAS) vaccines in development (5 trials, 195 subjects)

Trial	Product	Dose Regimen	Control	Population	N	Design	Regulatory Agency
Hexavalent Phase I [75]	Hexavalent Prototype; N-terminal peptides M1,3,5,6,19 & 24	Successive cohorts received: • 50 µg IM; on days 0, 28 and 56 (N=8) • 100 µg IM; on days 0, 28 and 112 (N=10) • 200 µg IM; on days 0, 28 and 112 (N=10)	None	Healthy adults, 18 – 50 years	29	Open-label, dose-escalation	**US FDA**
Adult Phase I [76]	StreptAvax 26-valent N-terminal M peptides	400 µg IM on days 0, 28 and 120	None	Healthy adults, 18 – 50 years	30	Open-label	**Health Canada**
Adult Phase II [77]	StreptAvax 26-valent	400 µg IM on days 0, 28 and 180*	Hepatitis A vaccine	Healthy adults, 18 – 50 years	90	Randomized double-blind, comparator-controlled (70 StreptAvax, 20 comparator)	**Health Canada**
Adult Phase I [56]	StreptAnova 30-valent, N-terminal M peptides	600 µg IM on days 0, 28 and 180	Selected licensed vaccines	Healthy adults, 18 – 50 years	36	Randomized double-blind, comparator-controlled (23 StreptAnova, 13 comparator)	**Health Canada**
Adult Phase I [78]	MJ8VAX (J8-DT) C-terminal 29 aa M peptide	50 µg IM on days 0	Saline	Healthy adults, 20 – 44 years	10	Randomized double-blind, placebo-controlled (8 MJ8VAX, 2 placebo)	**QIMR Human Research Ethics Committee**

Comparison of Safety Assessment in recent GAS vaccine trials

Safety Evaluation	Hexavalent Prototype Multivalent M [75]	26-valent (Phase I) Multivalent M [76]	26-valent (Phase II) Multivalent M [77]	30-valent (Phase I) Multivalent M [56]	J8-DT Conserved C-terminal M peptide C conjugate [78]
Reactogenicity Diary	7-days	14-days	14-days	14-days	7-days
Cardiac and Neuro clinical examination	0.5, 6 & 12 months No Neuro	7 and 14 days after each dose	7 and 14 days after each dose	7 and 14 days after each dose	0.5, 6 , 9 & 12 m No Neuro
Echocardiogram & ECG screening	14 days after each dose, & 6 & 12 m	Baseline and 1 month after 3rd dose	Baseline and 1 month after 3rd dose	Baseline and 1 month after 3rd dose	Baseline, 1, 3 and 12 months
Routine clinical labs + troponin-I, C3, CRP	Baseline screen	Baseline screen	Baseline screen	Baseline screen and when clinically indicated	Baseline screen and 1, 6 , 9 & 12 months
Human tissue cross-reactive antibodies by IFA	14 days after each dose, & 5 and 12 m	1 month after doses 2 and 3	1 month after doses 2 and 3	14 days after each dose	Serum stored screen & day 350 for future assays
Long term AE follow-up	12 months	12 months	12 months	12 months	12 months

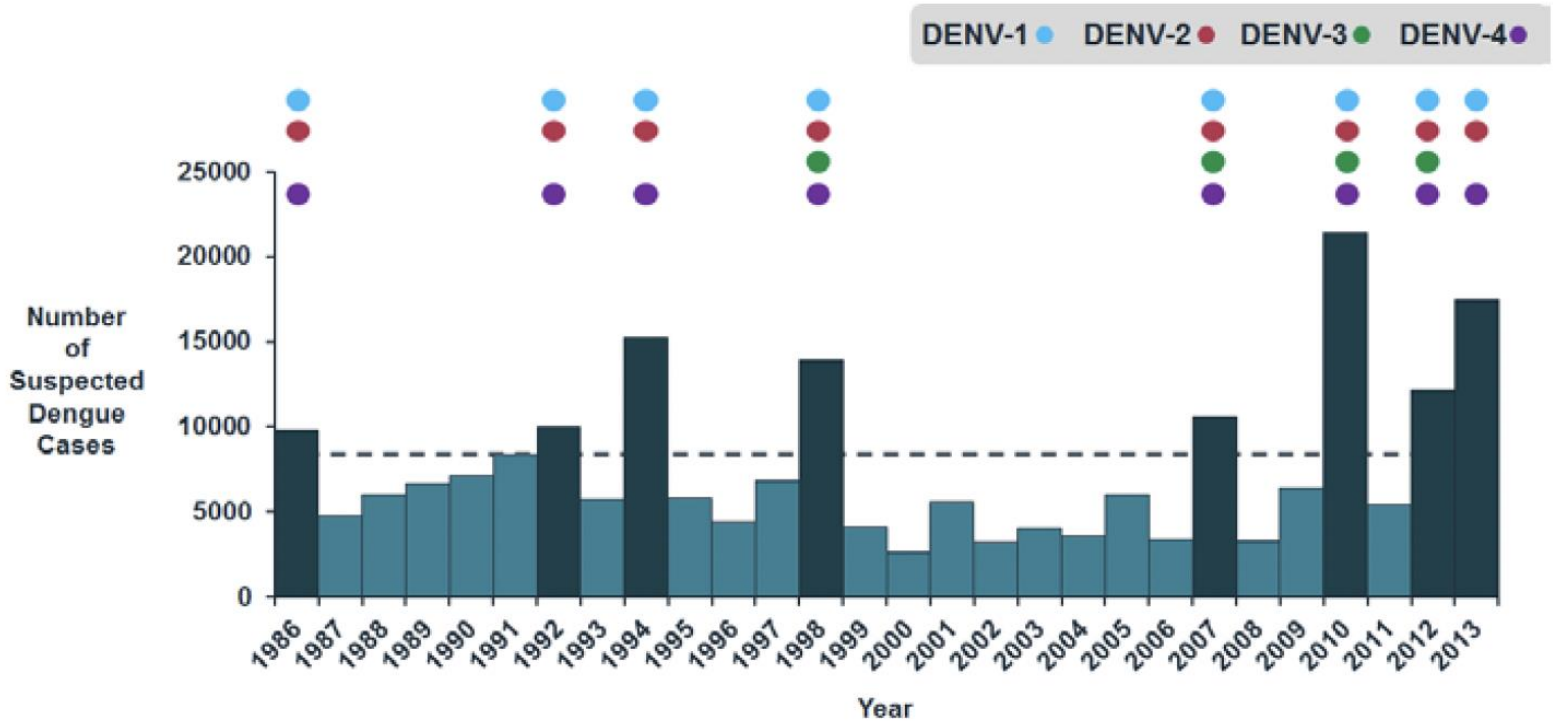
Outcomes of recent 4 phase I and 1 phase II GAS vaccine trials

Clinical Trial	Population	N	Phase I	Phase II	Phase III
Hexavalent M-protein [75]	Healthy adults 18 – 50 years	29	Mild local reactions: • 6/29 subjects (29%) ≤7 days post dose 1 • 12/28 (43%) ≤ 28 days post 2 or 3 dose • 1 moderate reaction: neutropenia and borderline low C3 (not vaccine related) • **No Echocardiography**		
StreptAvax 26-valent [76] [77]	Healthy adults 18 – 50 years	30 & 90	• Headache (40%–53%) • Tiredness (17%–23%) • Sore joints 3%–7% • Muscle aches in 13%–17% • **Echo and ECG normal**	• Most AEs were local, mild and self-limited. • Systemic AEs uncommon & similar to Havrix™ control	
StreptAnova 30-valent [56]	Healthy adults 18 – 50 years	36	• Muscle aches post dose 2 statistically significant (44.0% vs. 0.0%) • Drowsiness (38.5% • No SAEs • Local AEs mild (1 subject g3 redness) • **Echo and ECG normal**		
MJ8VAX (J8-DT) C-terminal 29 AA M peptide [78]	RCT Healthy adults 20 – 44 years	10	• 13 AEs: 2 associated to vaccine: 1 with headache and 1 with abdominal pain • No changes in anti-streptococcal Ab • **Echo and ECG normal**		

GAS infection and its similarities to other VPD (Dengue)

- Caused by different serotypes
- Seasonal and inter-year variability
- Variability of incidence among populations
- Cross protection may be important but also a risk for more severe disease expression

Figure A: Dengue is endemic in Puerto Rico with periodic epidemics (1986-2013)



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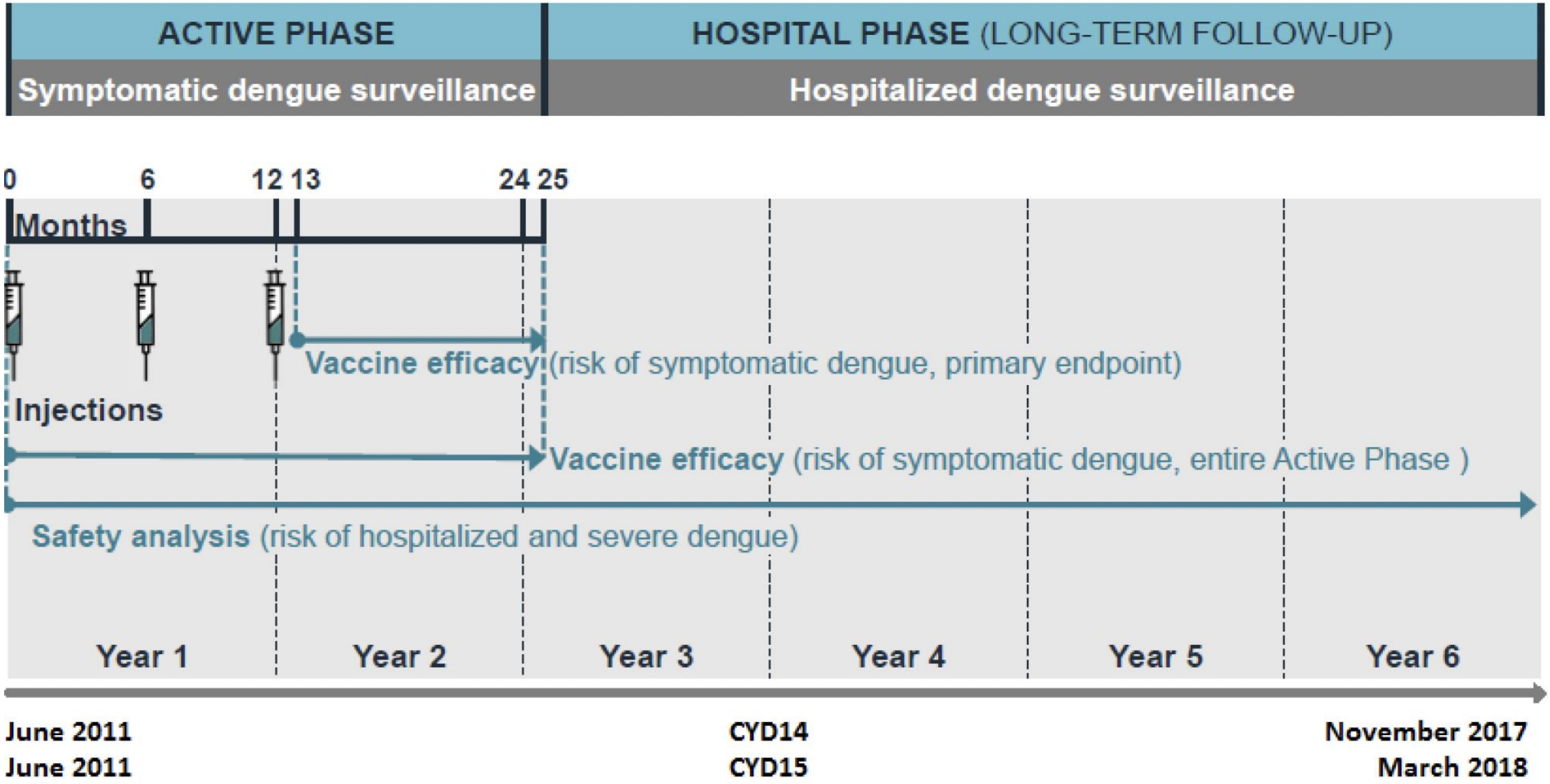
Dengue vaccines study design to accommodate Safety



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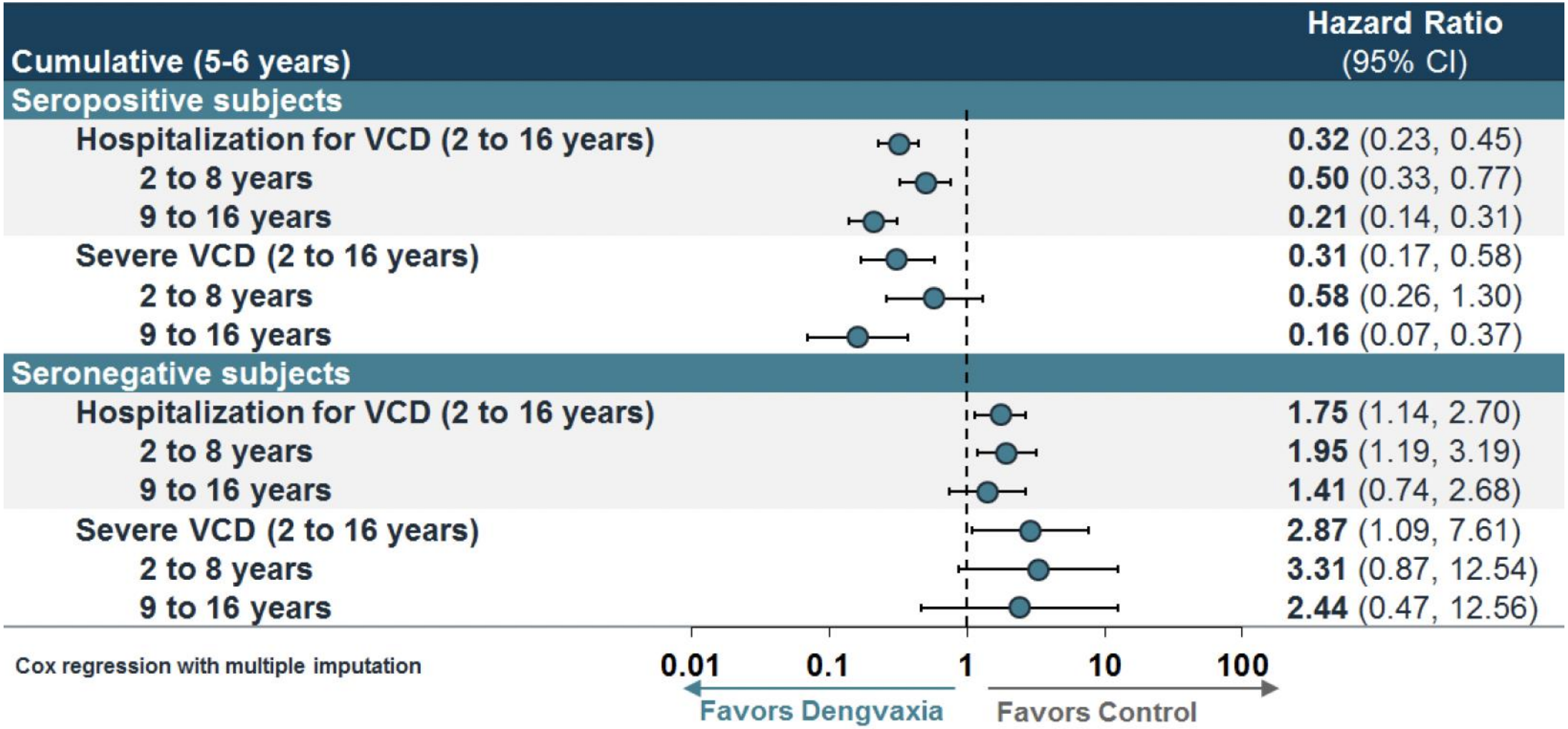
Risk of hospitalization from dengue according to serostatus and age



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Proposed Safety Monitoring Phase IIb and III studies

Safety Monitoring Category	Variables	Frequency
Common Safety	• Clinical exam and V/S • Immediate Local and Systemic Reactions • Daily local and systemic reactogenicity • Unsolicited adverse events • SAE and SUSAR • Adverse events of special interest • Routine laboratories	D#1,7,14 post each dose 60 minutes Daily up to 7 days Daily up to 28 days Duration of study Duration of study D#1,7,14 post each dose
Strep A-specific assessments	• Non-specific inflammation parameters: CRP, C 3, C4 • GAS culture monitoring • anti-DNase or anti-streptolysin O (ASO) • anti-tissue responses (heart, kidney, myelin)	Baseline, D14 and every 3 months Baseline and every 3 months?
Cardiac function assessment	• Need for ECG • Need for Echocardiogram? (nested, only MAE?)	Baseline and end of FU Baseline, q12 months and illness

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Standardization of Safety Outcome measures for GAS vaccines

Given the scarcity of solid data to recommend tools for measuring safety/efficacy outcomes, probably important to convene expert groups in:

1) **Echocardiography**
   - Pre-trial validity of criteria and age/illness standards
   - Optimal times for measurement (baseline? Post-dose? Illness?)
   - Instrument standardization and interpretation guide
2) **Screening assays for Cross-Reactive Proteins (ELISA-based)**
   - Possible CR antigens:
     - » Identical amino acid sequences in different proteins
     - » Similar protein structures shared among different proteins
     - » Diverse molecules such as DNA, carbohydrates and proteins
   - Pre-defined **normal ranges across pre-and post-immune sample differences**

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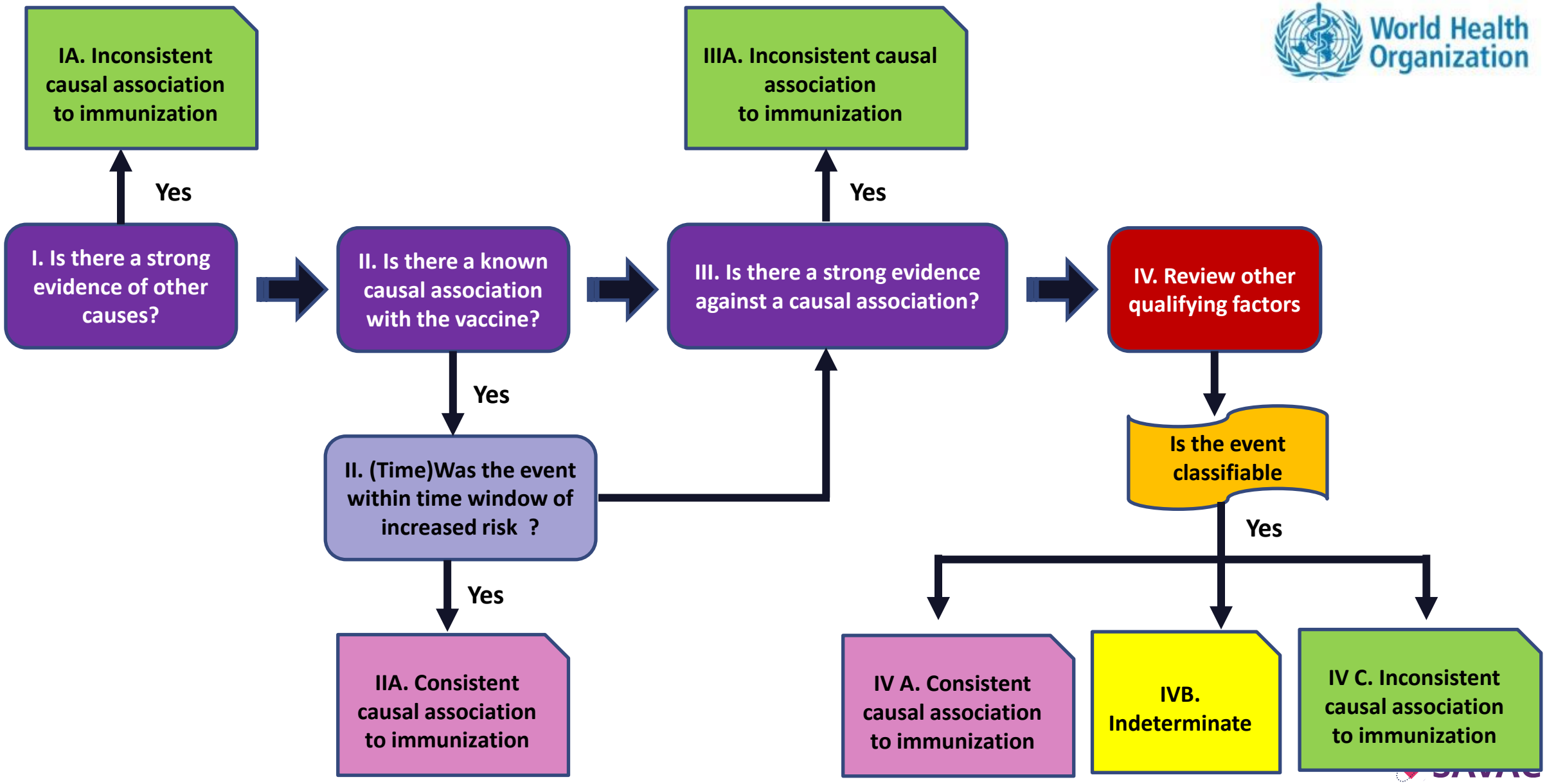
Use of WHO CAP to evaluate AEFI for GAS Vaccine



Safety parameters required for Causality Assessment

Requirement	Parameter	Sources
Background rates of possible safety signals	• Incidence/prevalence of ARF/RHD • Incidence/prevalence of proteinuria and CKD • Others	Retrospective studies Prospective surveillance
Case Definitions	• ARF and RHD • Severity and certainty case definitions for possible AEFI signals	Consensus guidelines Brighton Collaboration development
Safety Assessment Methods	• Self controlled case series methods • Immuno-profiling of cases and controls • Minimum incidence rates	Multiple sources Experience with other vaccine clinical trials
Guidelines for Causality Assessment of SUSAR, AESI	• Adaptation of WHO AEFI causality assessment guideline • Development of alternative causes guide to investigate AESI cases • Laboratory parameters and agreed assays	

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Size of safety database to support licensure (FDA)

- Expectations for the size of the safety database* are typically discussed at end of **phase 2 or earlier.**
- Factors considered include:
  - Characteristics of the vaccine
  - Review of early-phase safety data
  - Any safety signals or theoretical safety issues
  - Target population (children)
  - Seriousness of disease targeted for prevention
- **For preventive vaccines, the size of the safety database is typically on the order of several thousand population**

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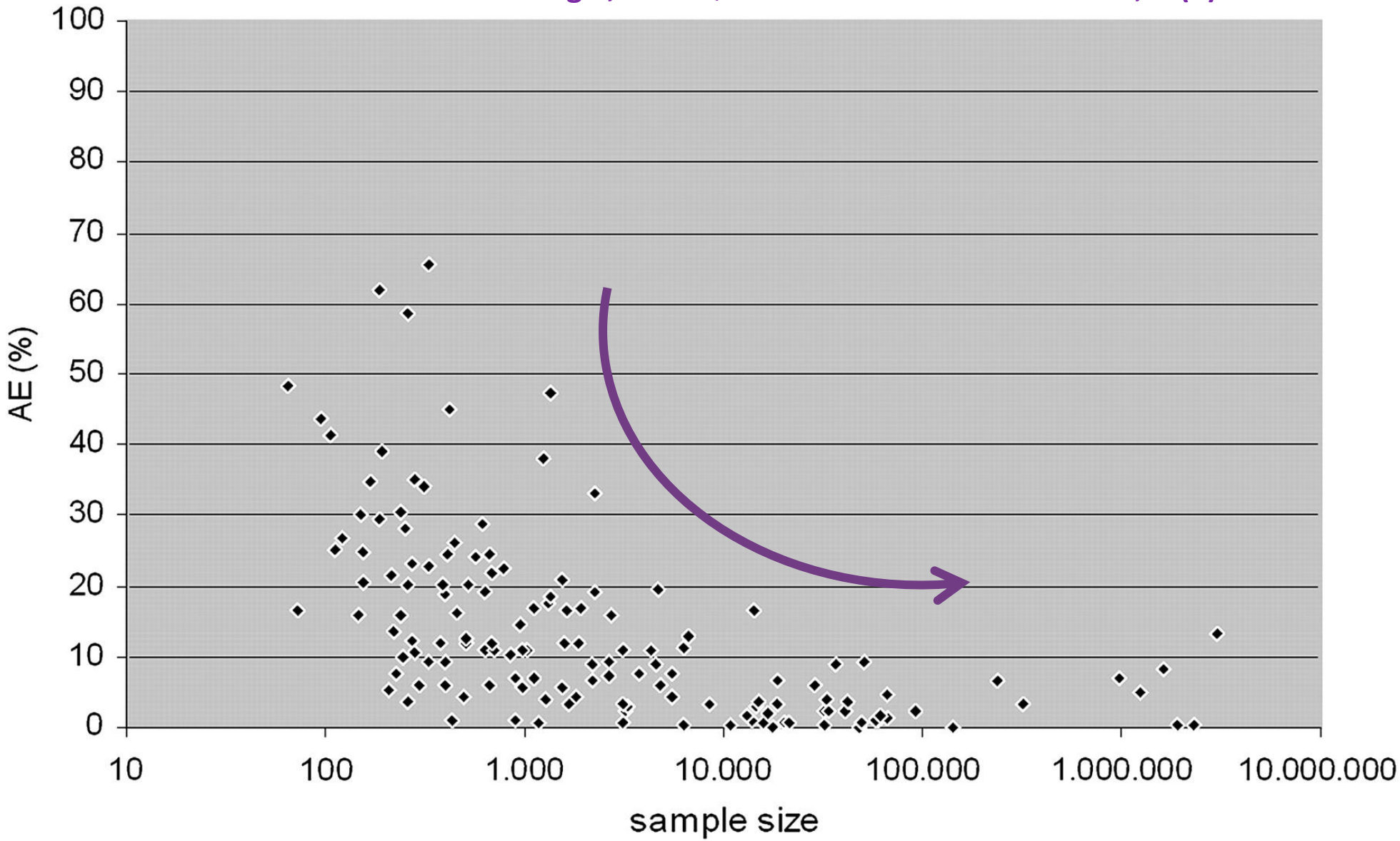
Rare AEFIs will require larger samples sizes

Lessing C, et al Qual Saf Health Care. 2010 Dec;19(6):e24. doi: 10.1136/qshc.2008.031435



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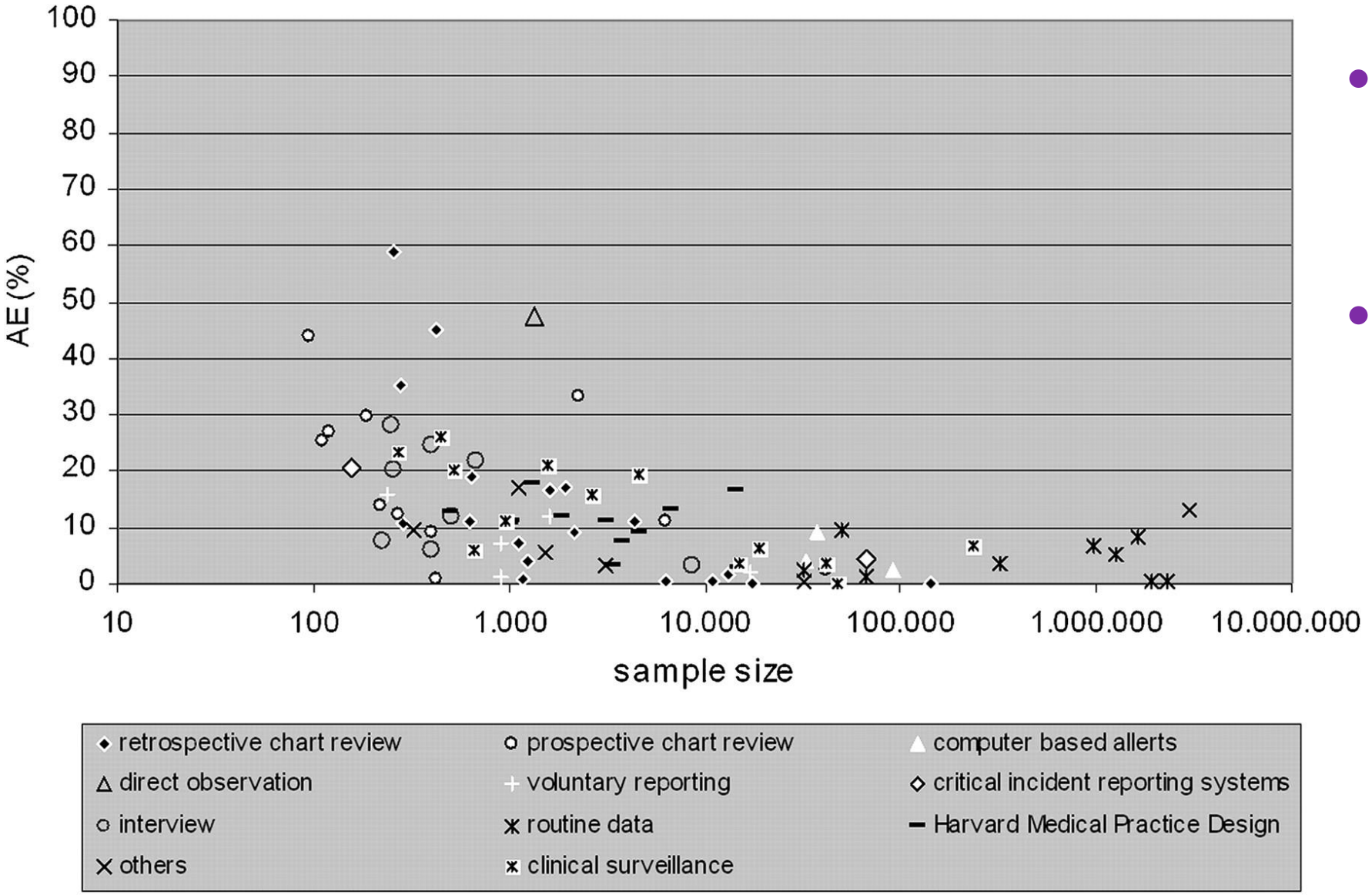
Safety endpoints for GAS vaccines will need good baseline immunization registries and EMR systems



- Smaller studies rely on chart review and comprehensive data source documents
- Large studies require **reliable administrative data**

Lessing C, et al Qual Saf Health Care. 2010 Dec;19(6):e24. doi: 10.1136/qshc.2008.031435

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The Rotavirus Vaccine Phase III studies (Safety concern)

- **Objective:** **Safety of Rotavirus vaccine** with respect to definite intussusception (IS) within 31 days (Day 0 to Day 30) after each HRV vaccine dose in all subjects **(N = 60,000).**
- **Upper limit 95%CI of Risk Difference was below 6/10,000,**

Large scale cohort (n=68,000) for:

- Evaluation of Safety Endpoint
- Efficacy of vaccine against hospitalization and ED visits

Clinical efficacy cohort (n=5,600)

- Efficacy against RVGE
- Efficacy against RVGE office visits

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Complexity of New Vaccines Present Challenges to NRAs

- New technologies used in product development
- Quality and process validation concepts
- Evaluation of non-clinical and clinical data for novel vaccines
- **Testing capacity**, e.g., assay development and evaluation
- **Risk benefit assessment** as part of product evaluation
- Review of risk management plans
- **Specific pharmacovigilance commitments and phase IV studies**
- Assessment of potential Public Health Impact particularly for vaccines for which efficacy may be lower than generally observed

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Regulatory Considerations for GAS Vaccine Safety

- **Adverse of special interest (AESI) based on:**
  - Product-specific mechanism of action
  - Platform and vaccine composition
  - Preclinical data and the cumulative clinical safety experience: should include all severe GAS-related disease manifestations
- **Detect all new-onset GAS infections that can result in ARF/RHD**
- Antibiotic treatment regimen of new-onset GAS infections should be standardized in vaccine trials
- **Need for long term follow up of GAS vaccine study participants** (post-marketing to include identified and potential risks)

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Conclusions on GAS Vaccine Safety Guidance

- New complex vaccines with **partial protection and concerns for immune-related adverse events** pose a challenge for developers and regulators, but:
  - Technological advances now could provide solutions
  - Definition of public health outcomes of interest and background of AESI
- New development phases (IIb and III) for GAS vaccine need consensus in the next 2 years on:
  - Validity and usability of echocardiography and cross-reactive test for ARF
  - Framework of vaccine safety assessment including duration of follow up
- Safety of GAS vaccines should **not be a barrier** to development: other vaccines are overcoming similar obstacles (RV, dengue, Zika, COVID-19)

SAVAC

Acknowledgements

- **Wellcome Trust**
- **SAVAC Executive Committee**
- **Initiative for Vaccine Research, World Health Organization (WHO IVR).**
- **SAVAC Safety Working Group**

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James Dale	University of Tennessee Health Science Center, Memphis TN, USA
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Alma Fulurija	Telethon Kids Institute, Perth, Australia
Raj Long	Consultant, Seattle WA, USA
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Thank you

Gracias

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