SAVAC Safety Technical Advisory Working Group Meeting Summary

1 June 2025
Brisbane, Australia

Slides Presented to SAVAC and interested parties after the TAWG meeting

Purpose
The Safety TAWG is established to provide expert guidance on safety considerations throughout all phases of Strep A vaccine development, ensuring that safety assessments are comprehensive, standardized, and aligned with current scientific and regulatory standards.

Scope of Work
- Identify Safety Challenges: Anticipate potential safety issues in upcoming clinical trials, especially in pediatric populations and large-scale efficacy studies.
- Develop Safety Assessment Frameworks: Propose standardized approaches for safety monitoring in clinical trials and post-marketing surveillance.
- Engage with Regulatory Bodies: Collaborate with regulatory authorities to align safety evaluation strategies with regulatory expectations.

Overall Summary of discussion:
- Safety endpoints:
  - Definition
  - Criteria
  - Outline
- Recognition of immediate vaccine-induced and delayed vaccine (enhanced) events (and vaccine failure)
- Potential use of self-case-controlled series for assessment of rare AESIs
- Regulatory and policy expectations of safety
- Regulatory path and timing of need for safety data pre-licensure vs post-licensure

Main questions to the overall SAVAC group:
- What is the minimum sample size needed for efficacy and would satisfy safety requirements?
- What is the minimum duration of follow up to detect ARF in vaccinees?
- What is the perceived reliability and feasibility of detecting ARF in high RHD burden settings

Safety TAWG meeting prior to the above presentation

Present in person:
Andrew Steer
Edwin Asturias
Kimberly Davis
Josh Osowicki
Somyoung Cho
Rachel Webb
Jonathan Carapetis

Jim Ackland

Online:
Nick Andrews
Ruth Karron

Apologies:
Mimi Darko
Marco Cavaleri

Main questions:
- How do we best engage with regulatory bodies?
- What is the best way to interact with other TAWGs (Echo and X-reactive assay)?
- What is our scope of work over the next 12 months?
- What are the main AESIs anticipated to be associated with Strep A vaccines?
- How do we distinguish between lack of vaccine efficacy against Strep A infection and an AESI?
- Could vaccines delay syndromes such as ARF and RHD and could we see people getting ARF and RHD later in life? Is this an AESI?

Discussion points:
- **Safety Endpoints and Methodologies:** Edwin discussed the need to define safety endpoints, methodologies, and the importance of engaging with regulatory bodies to address safety concerns for strep A vaccines.
    - **Defining Safety Endpoints:** Edwin emphasized the need to define specific safety endpoints for strep A vaccines, including clinical trial sample size, duration of observation, and enrichment of at-risk populations.
    - **Methodologies:** We discussed the importance of developing methodologies to evaluate safety endpoints, including case definitions, surrogate laboratory, and clinical imaging (echo) endpoints.
    - **Regulatory Engagement:** Engaging with regulatory bodies was highlighted as crucial to ensure that safety evaluation strategies align with regulatory expectations and requirements.
- Important to remember that there have been no safety signals in any of the early phase Strep A vaccine trials done in the last 10 years.
- Increasing tests (echo/serology) for asymptomatic patients in Strep A vaccine trials would increase the risk of finding an unrelated and unimportant event and killing a vaccine development program
- For rare safety events it will be hard to catch them in a clinical trial setting, would need very large numbers to catch all rare safety events such as ARF
- Children will have lots of symptoms which could be ARF in early life e.g., fever without alternative diagnosis. What should be the triggers for calling something a safety event?
- As per Dengue trials, could aim to have a period of more intense monitoring (3-6 months) and then less intense monitoring for a longer period of time
- Do we understand the pathogenesis well enough to know when/if vaccine enhanced disease might happen? Will it happen with the next Strep A infection or at some point further in the future? This will help us determine follow up duration.

- We also need to describe and understand the immunological stimulus of the vaccine before we have some idea if the vaccine will induce enhanced disease
- People are susceptible to recurrent ARF for many years after an initial episode, hence the very long duration of secondary prophylaxis
- Is there such as thing as subclinical progression of RHD without ARF? Rachel and Jonathan think that ARF will be there if you look for it and enhanced surveillance is indicated in trials. This would be easiest in places with better infrastructure e.g., Australia and New Zealand
- The timing of ARF in post-pandemic NZ seems to be a bit later in life than it was pre-pandemic
- Infant acquisition if Strep A is common in the first year of life: https://www.medrxiv.org/content/10.1101/2025.02.11.25322090v1
- Important questions when designing trials and anticipating AESIs
    - What will be the triggers for safety assessments?
    - What is the duration of follow up specifically for safety reasons?
    - Should safety assessments be ad hoc (for participants with symptoms) or planned (at certain time points for all participants regardless of symptoms)?
    - Do these differ for each phase of clinical trial?
    - How do these fit in with the regulatory path?
- Differentiation between
    - Vaccine-induced disease (cardiac, renal and neurological)
    - Vaccine-enhanced disease (cardiac, renal and neurological)
- To determine if there are AESIs associated with the vaccine (which may be confused with the background rates of ARF and RHD in the population) should compare rates in vaccinees vs placebo-vaccinated, as well as rate of ARF in people before and after vaccine (self-case control study)
- Do we need to worry about infectious complications as well as post-infectious complications in vaccine trials – unlikely

Next steps:

- White paper
    - Define AESI/clinical syndromes beyond phase 1 (not just cardiac), assessment methodologies, and regulatory pathways
    - Framework across phase 2a/2b/3/4
    - Include surveillance: clinical vs non-clinical, and duration of follow-up
- Meetings for 6-9 months for ongoing discussion
- Skeleton AESI framework
- Subgroups of the TAWG could then work on different aspects of the AESI definitions
- **Phase Four Studies:** Start thinking about the design and implementation of phase four studies for post-licensure safety assessment.