Considerations for use of a malaria vaccine

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Considerations for Malaria Vaccine Outline

- Review of published decision framework
- Implementation studies
- Individual considerations
- Future development of RTS,S
- Other malaria vaccines?

Country planning for health interventions under development: lessons from the malaria vaccine decision-making framework and implications for other new interventions

Alan Brooks[1,2] and Antoinette Ba-Nguz[3]*

[1]PATH Malaria Vaccine Initiative, Ferney-Voltaire, France, [2]Swiss Tropical and Public Health Institute, Basel, Switzerland and [3]PATH Malaria Vaccine Initiative, Nairobi, Kenya

Health Policy and Planning 2012;**27**:ii50–ii61

- **Policy development will be supported by**:
  - **Data** (disease burden, other malaria interventions, malaria vaccine impact, economic and financial issues, malaria vaccine efficacy, quality and safety)
  - **Implementation Decisions** (programmatic issues, socio-cultural environment)

Key Messages

- Insufficient planning is a key reason for long delays between [vaccine] development and availability
- Planning should be cautiously paced to not get ahead of, or over-promise, relative to evidence from the intervention's developmental progress

Decision-making on malaria vaccine introduction: the role of cost–effectiveness analyses

Vasee S Moorthy,[a] Raymond Hutubessy,[a] Robert D Newman[b] & Joachim Hombach[a]

Bull World Health Organ 2012;90:864–866

- Cost-effectiveness is only one criterion
- Other factors are important:
  - Implementation capacity
  - Feasibility
  - Impact on poverty and equity

Some LMICs have shared details for RTS,S decision framework

Romore *et al. Malar J (2016) 15:143*
DOI 10.1186/s12936-016-1197-6

Malaria Journal

CASE STUDY Open Access

Policy analysis for deciding on a malaria vaccine RTS,S in Tanzania

Idda Romore[1,2,3*], Ritha J. A. Njau[4], Innocent Semali[5], Aziza Mwisongo[6], Antoinette Ba Nguz[7], Hassan Mshinda[8], Marcel Tanner[1,2] and Salim Abdulla[3]

Some LMICs have shared details for RTS,S decision framework

- Example of Tanzania
  - Interviews with government officials, partners, other stakeholders
  - Decision Process Requires
    - Presentation of scientific data
    - Disseminating evidence
    - Seeking approval from Ministry of Health
  - Result
    - Clearer understanding of policy process
    - Shortening time for a malaria vaccine to become available

Considerations for Malaria Vaccine RTS,S: ongoing studies

- October 2015: WHO SAGE on immunization reviewed RTS,S Phase 3 clinical trial results
  - Recommended additional implementation projects before vaccine introduction
  - These studies will carefully assess potential for increased meningitis and cerebral malaria
  - Safety concerns deserve further investigation
    - Neuroprotective potential for rabies vaccination as an explanation for differential CNS adverse effects

Considerations for Malaria Vaccine: Multiple

- Vaccine safety
- Effectiveness and efficacy
- Cost effectiveness
- Community acceptance
- Political will
- Vaccine supply and ease of distribution
- Potential for long-term consequences:
  - Vaccine-resistant malaria
  - Rebound in malaria risk

Considerations for Malaria Vaccine Safety

- Adverse events reported with RTS,S in 5-17 month-olds
  - Pain, drowsiness, irritability, loss of appetite, and fever (36%) more frequent in vaccinees
  - Total SAEs were less frequent in RTS,S vaccinees
  - Increased risk of febrile convulsions (1 per 1000 doses)
  - Females:
    - Lower efficacy (35 versus 43%)
    - Two-fold increased mortality
  - 2 safety signals: meningitis and cerebral malaria

Considerations for Malaria Vaccine Effectiveness and Efficacy

- RTS,S efficacy (5-17 mos)
  - Against clinical malaria
    - 51% over 1 year
    - 39% for ~4 years (4-dose schedule)
  - Against severe malaria
    - 45% over 1 year
    - 32% over ~4 years (4-dose schedule)
- Measures of public health effectiveness?
  - Disease rate reduction, vaccine-preventable disease incidence (VPDI or vaccine attributable risk)

Penny *et al. BMC Medicine* (2015) 13:170
DOI 10.1186/s12916-015-0408-2

BMC Medicine

RESEARCH ARTICLE Open Access

The public health impact of malaria vaccine RTS,S in malaria endemic Africa: country-specific predictions using 18 month follow-up Phase III data and simulation models

Melissa A Penny[1,2*], Katya Galactionova[1,2], Michael Tarantino[1,2], Marcel Tanner[1,2] and Thomas A Smith[1,2]

- Simulation of effectiveness using 6 model variants
- Weighted with a wide range of vaccine characteristics, health systems and transmission settings
- Country-specific data
- Predictions of public health impact in 43 countries
  - Events averted (hospitalizations, deaths, DALYS)

Penny *et al. BMC Medicine* (2015) 13:170
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Melissa A Penny[1,2*], Katya Galactionova[1,2], Michael Tarantino[1,2], Marcel Tanner[1,2] and Thomas A Smith[1,2]

Table 4 Cumulative total events averted (all ages) across 43 sub-Saharan African countries, cumulative by 5 year periods for each of the four deliveries: EPI (6–12 weeks), EPI with boosters, expanded routine (6–9 months) and expanded routine with booster

Events averted	At 5 year followup (thousands)	At 10 year followup (thousands)	At 15 year followup (thousands)
Expanded routine with booster			
Uncomplicated	79,300 (52,661-90,279)	179,372 (121,591-211,522)	250,819 (173,421-300,168)
Severe	2,060 (1,455-2,711)	3,744 (2,863-5,028)	4,839 (3,376-6,722)
Hospitalisations	982 (688-1,346)	1,786 (1,332-2,499)	2,323 (1,608-3,335)
Direct deaths	218 (137-324)	439 (305-655)	585 (385-883)
All deaths	418 (228-565)	909 (561-1122)	1333 (811-1634)
DALYs	22,409 (12,370-30,176)	48,905 (30,345-60,518)	72,513 (44,534-88,531)
Direct DALYs	12,012 (7,628-17,739)	24,429 (17,088-35,728)	33,367 (22,551-49,362)

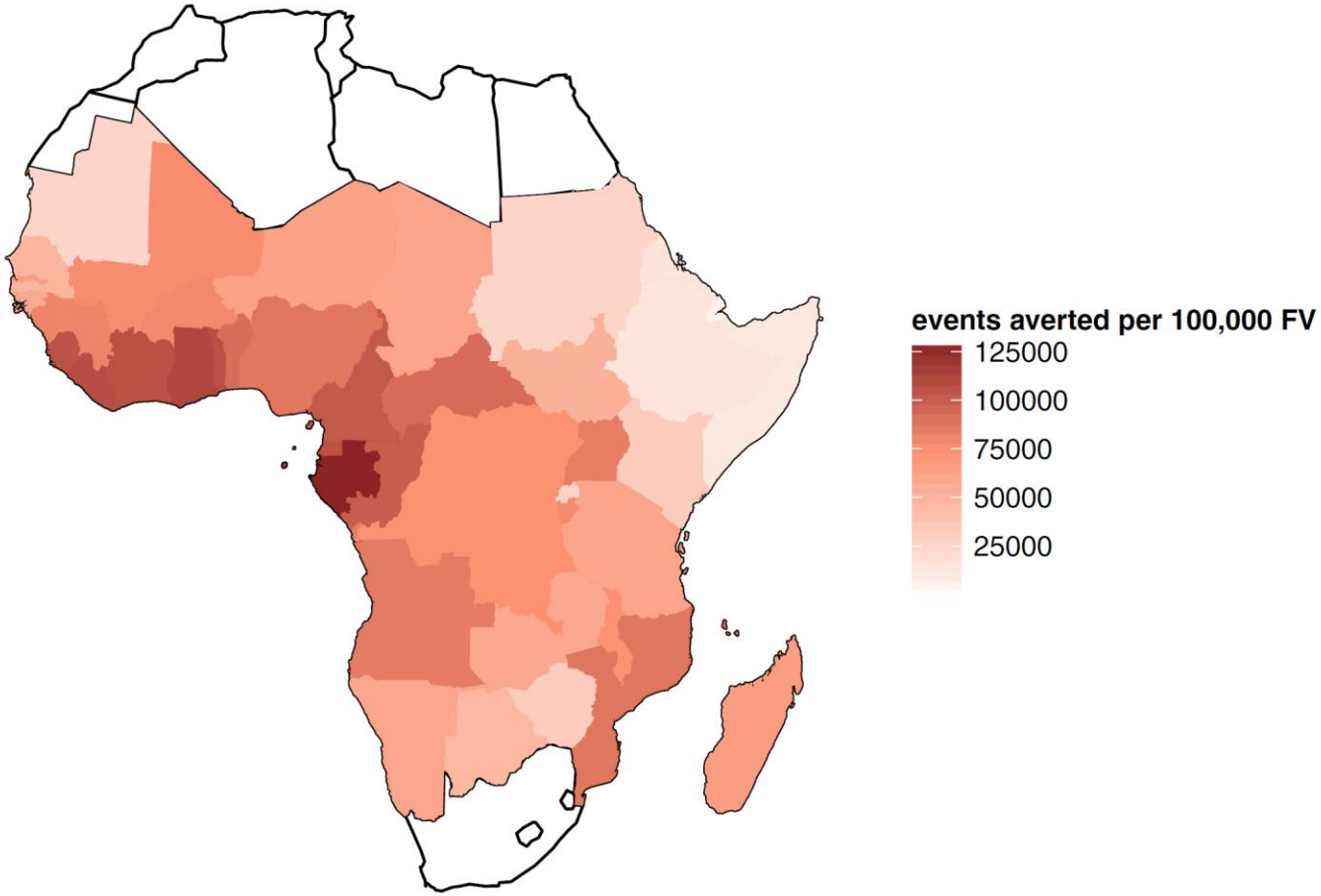


Fig. 10 Mean predicted total uncomplicated and severe events averted per 100,000 fully vaccinated after 10 years by country for extended routine (6–9 month) immunisation schedule. Cumulative total uncomplicated and severe events averted per 100,000 fully vaccinated by country, cumulative at 10 years post introduction immunising via extended routine immunisation schedule of 6–9 months (vaccination coverage is at 75 % of DTP3 levels of country immunisation)

Considerations for Malaria Vaccine Model Effectiveness (continued)

- In summary, over 10 years RTS,S would avert (per 100,000):
  - 100-580 deaths
  - 45,000 to 90,000 clinical events
- Effectiveness similar to Hib and pneumococcal vaccines

www.thelancet.com Vol 387 January 23, 2016

Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models

Melissa A Penny, Robert Verity*, Caitlin A Bever*, Christophe Sauboin*, Katya Galactionova, Stefan Flasche, Michael T White, Edward A Wenger, Nicolas Van de Velde, Peter Pemberton-Ross, Jamie T Griffin, Thomas A Smith, Philip A Eckhoff, Farzana Muhib, Mark Jit, Azra C Ghani*

- Four doses will avert 116,480 cases and 484 deaths per 100,000 vaccinated
- Little impact where prevalence is below 3%
- Median incremental cost-effectiveness ratio compared to current interventions:
  - $25 per case averted
  - $87 per DALY averted

Considerations for Malaria Vaccine Community Acceptance of RTS,S

- Reactogenicity anticipated (fever)
- CNS safety signal with unknown etiology?
- Will use of a malaria vaccine change attitudes and practice with regard to other antimalarial interventions (bednet use, treatment seeking behavior)?

Considerations for Malaria Vaccine Political Will

- Global-level advocacy can help, and must begin early
- There is strong political will to combat malaria illness and death
- Any new intervention takes time to be understood and accepted
- Political commitment follows acceptance of a given intervention

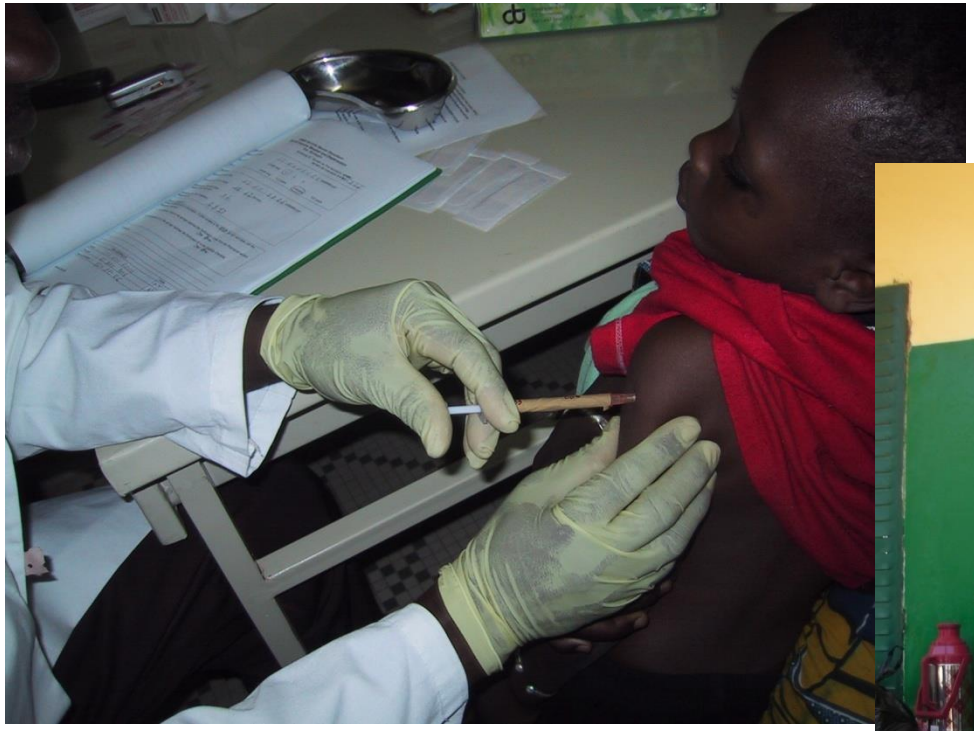
Considerations for Malaria Vaccine Vaccine Supply and Distribution

- Global supply will meet demand?
  - Manufacturer must plan well in advance
  - Countries must decide well in advance
  - Who makes the first move?
- Distribution: transport and storage
- Training: local health personnel

Considerations for Malaria Vaccine Potential Consequences

- Vaccine-resistant malaria
  - Will this happen if RTS,S is implemented?
  - Models do not currently account for this possibility

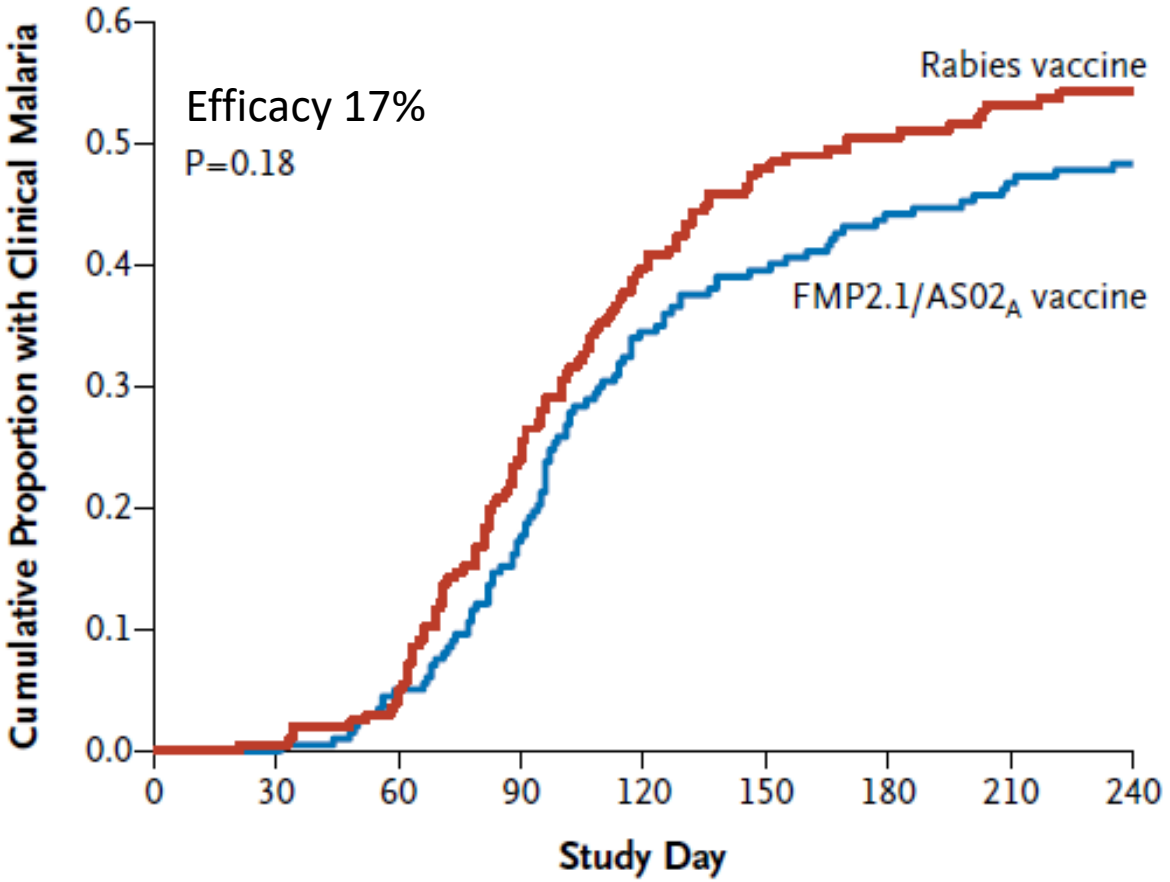
Pediatric malaria vaccine trials in Mali



- AMA1 malaria vaccine developed by U.S. Army and GlaxoSmithKline
  - Monovalent recombinant protein + $AS02_A$ Adjuvant System
- Safe and immunogenic in U.S. adults and in Malian children and adults

Vaccine efficacy against first episode of clinical malaria

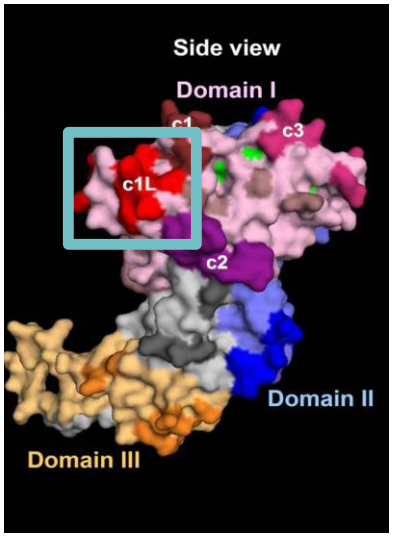
A



No. at Risk									
FMP2.1/AS02$_A$ vaccine	199	198	188	163	129	119	108	103	100
Rabies vaccine	201	198	188	149	118	101	94	89	86

N ENGL J MED 365;11 NEJM.ORG SEPTEMBER 15, 2011

Vaccine efficacy against first episode of clinical malaria with AMA1 c1L identical to the vaccine strain 3D7



No. at Risk									
FMP2.1/AS02$_A$ vaccine	199	198	196	192	189	188	184	184	184
Rabies vaccine	201	199	195	188	177	173	169	165	163

N ENGL J MED 365;11 NEJM.ORG SEPTEMBER 15, 2011

The NEW ENGLAND JOURNAL of MEDICINE

Genetic Diversity and Protective Efficacy of the RTS,S/AS01 Malaria Vaccine

CONCLUSIONS

These results suggest that among children 5 to 17 months of age, the RTS,S vaccine has greater activity against malaria parasites with the matched circumsporozoite protein allele than against mismatched malaria. The overall vaccine efficacy in this age category will depend on the proportion of matched alleles in the local parasite population; in this trial, less than 10% of parasites had matched alleles. (Funded by the National Institutes of Health and others.)

N ENGL J MED 373;21 NEJM.ORG NOVEMBER 19, 2015

Considerations for Malaria Vaccine Potential Consequences

- Rebound in malaria risk in Kilifi, Kenya
  - 7-year efficacy in 3-dose vaccinees aged 5-17 months showed no efficacy after 4 years
  - During years 5-7 of follow-up, negative rebound in vaccine efficacy was demonstrated
  - 3 other sites are also evaluating for rebound in both 3 and 4 dose groups

Conclusion

- RTS,S remains in development
- Desire to increase safety, immunogenicity and efficacy:
  - Dose regimen optimization
  - Adjuvant reformulation
  - Transmission-blocking and/or other antigen additions
  - Delivery enhancement
  - Regular boosting
- Research integral to implementation

PLOS | ONE

Identification of Novel Pre-Erythrocytic Malaria Antigen Candidates for Combination Vaccines with Circumsporozoite Protein

Cate Speake[1☯¤], Alexander Pichugin[2☯], Tejram Sahu[3], Vlad Malkov[1], Robert Morrison[3], Ying Pei[1], Laure Juompan[2], Neta Milman[1], Stasya Zarling[2], Charles Anderson[3], Sharon Wong-Madden[3], Jason Wendler[1], Andrew Ishizuka[1], Zachary W. MacMillen[1], Valentino Garcia[1], Stefan H. I. Kappe[1], Urszula Krzych[2‡], Patrick E. Duffy[3‡*]

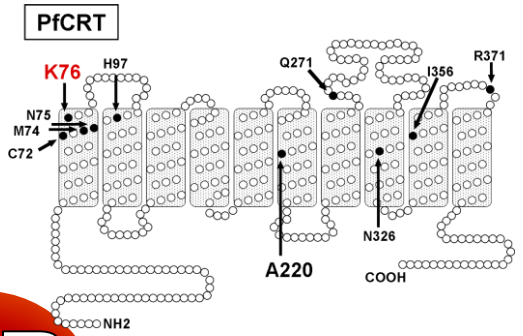
Other candidate malaria vaccines

- Live, attenuated whole organism vaccines
  - Sanaria® PfSPZ Vaccine received U.S. FDA fast track designation in September 2016
    - Designed to expedite review of drugs to treat serious conditions and fill unmet medical need
  - PfSPZ Vaccine is currently in Phase 2 testing in several countries in sub-Saharan Africa

Thank you!

Extra Slides

Drug resistant falciparum malaria



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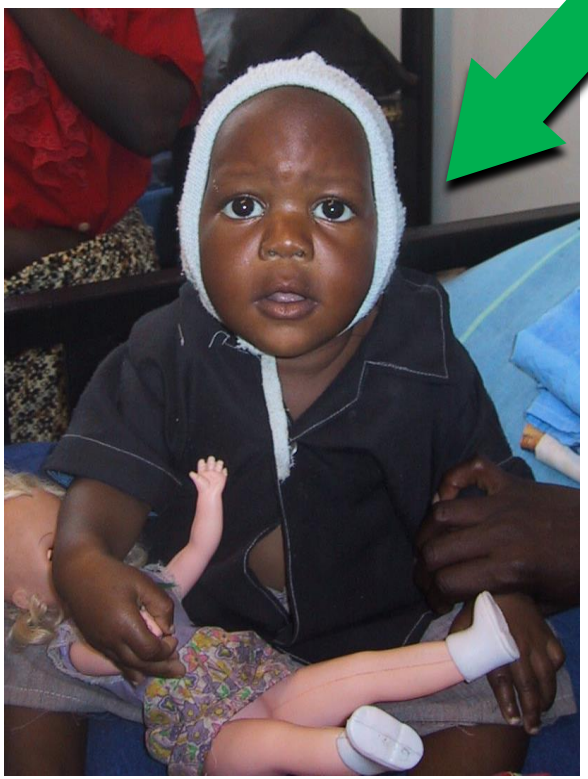

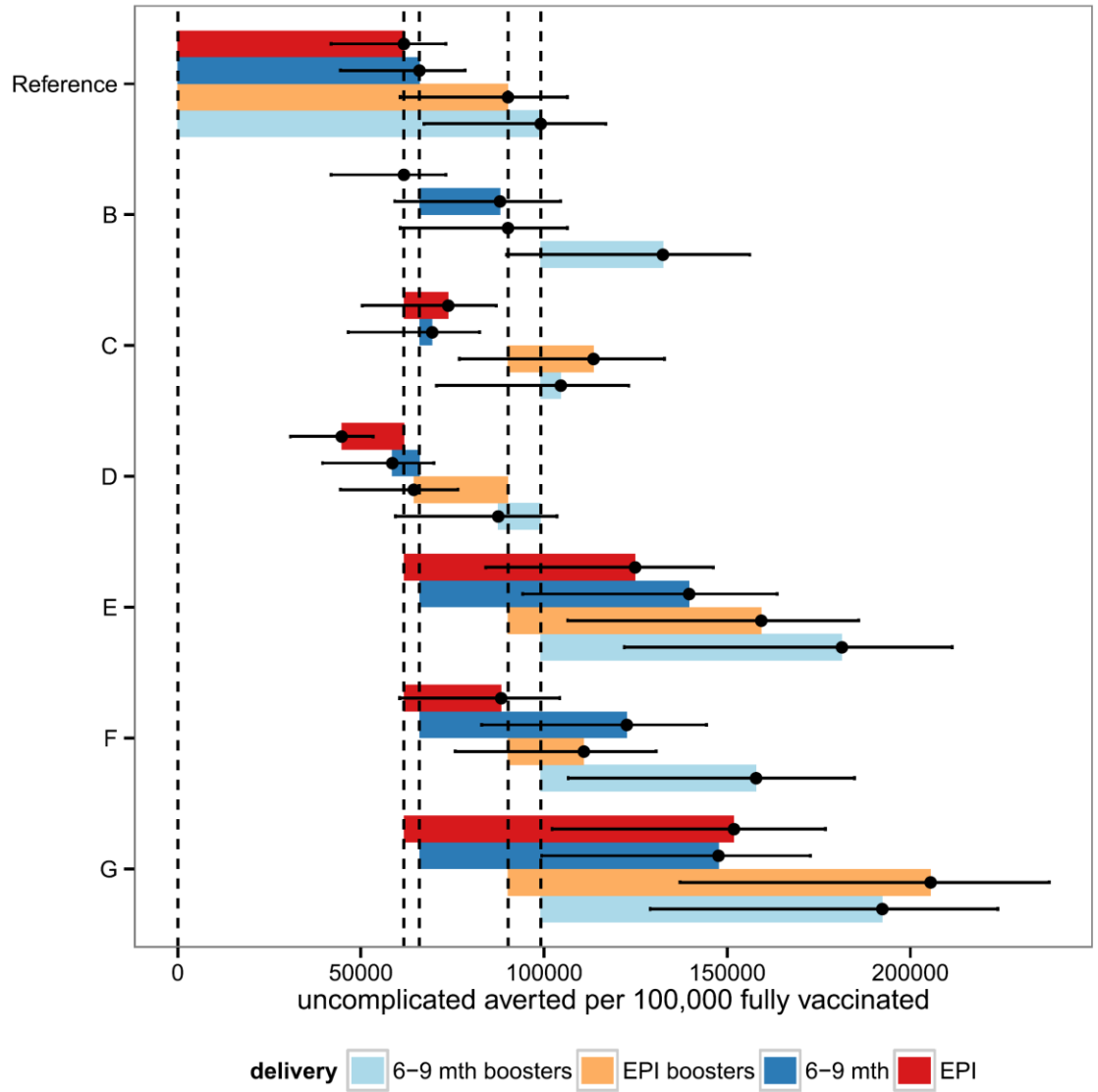

Fig. 5 Predicted cumulative uncomplicated cases averted per 100,000 fully vaccinated over 10 years for sub-Saharan Africa for each of the four vaccine implementations: EPI, EPI with boosters, extended routine and extended routine with boosters. Predictions of the overall number of uncomplicated cases averted per 100,000 fully vaccinated over ten years, for vaccine and coverage sensitivities B-G (see Table 3), for EPI (red), EPI with boosters (orange), extended routine (dark blue), and extended routine with booster (light blue). Points correspond to the means of the predictions based on weighted averages over all simulations of the vaccine profile. Vertical lines correspond to the means of the predictions for the reference vaccine profile for each of the four vaccination schedules. Error bars represent the minima and maxima of the predictions based on replication of the simulations with 6 different model variants each with 5 random number seeds

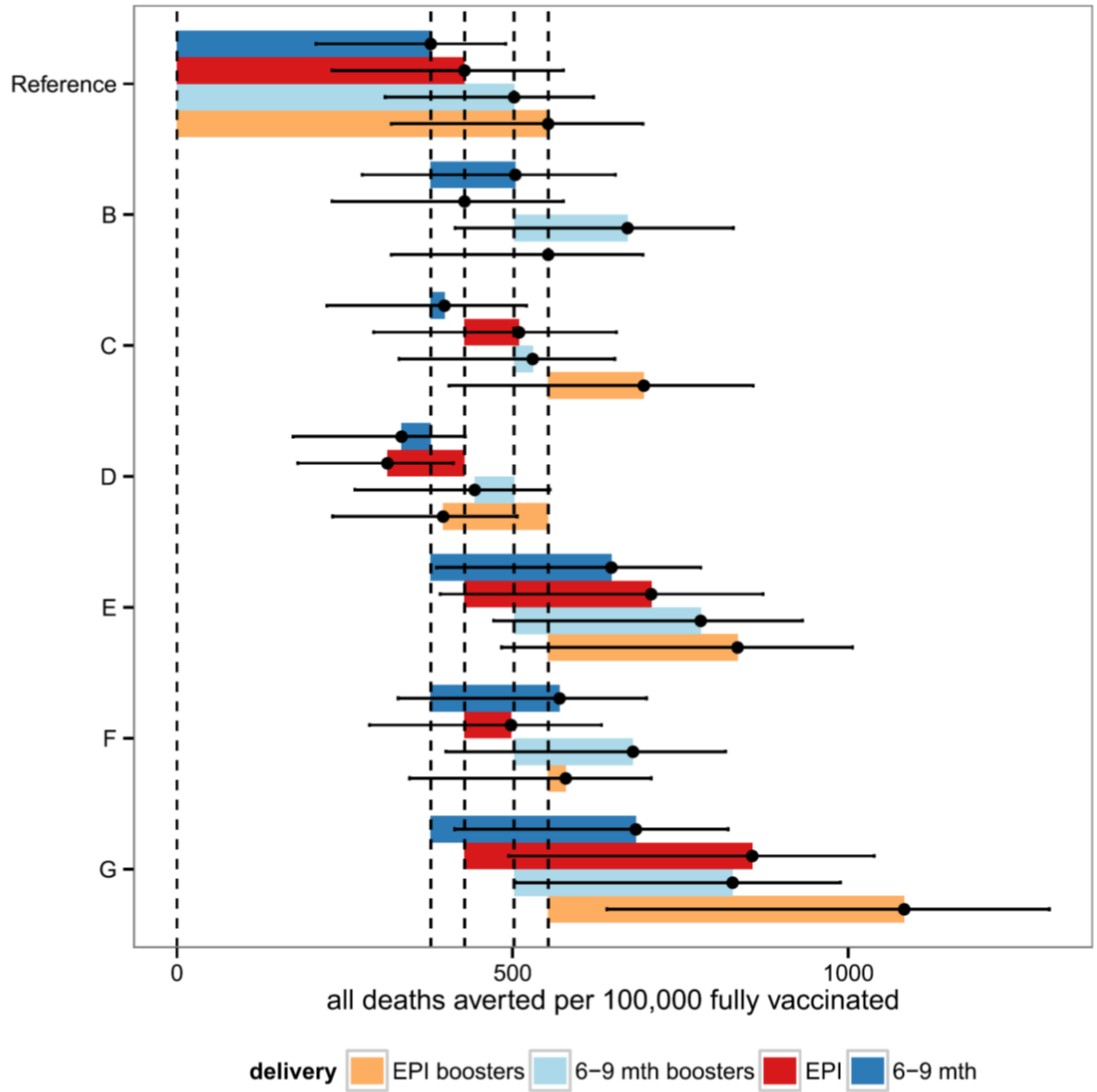

Fig. 6 Predicted cumulative all deaths averted per 100,000 fully vaccinated over 10 years for sub-Saharan Africa for each of the four vaccine implementations: EPI, EPI with boosters, extended routine and extended routine with boosters. Predictions of the overall number of all cause deaths averted per 100,000 fully vaccinated over ten years, for vaccine and coverage sensitivities B-G (see Table 3), for EPI (red), EPI with boosters (orange), extended routine (dark blue), and extended routine with booster (light blue). Points correspond to the means of the predictions based on weighted averages over all simulations of the vaccine profile. Vertical lines correspond to the means of the predictions for the reference vaccine profile for each of the four vaccination schedules. Error bars represent the minima and maxima of the predictions based on replication of the simulations with 6 different model variants each with 5 random number seeds