EUROPEAN VACCINE INITIATIVE

Challenging the Current Malaria Vaccine Pipeline

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Basel

6th December 2016

Malaria Burden

Notable progresses but still major public health issue

WORLD MALARIA REPORT 2015

World Health Organization

214 million new cases

- 18% decline in 15 years
- 37 % decline in 15 years taking into account the population growth
- 75% Incidence decline in 57 on 106 transmission countries

438 000 deaths

- 48% decline in 15 years
- 60% decline in 15 years taking into account the population growth

336 000 deaths <5 years of age

88% cases in Africa

- 80% malaria cases and 78% deaths in 15 countries
- RDC and Nigeria = 35% of worldwide deaths

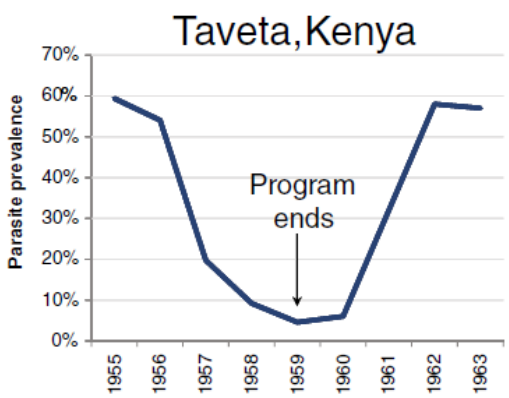
> 13.5 USD billion per year

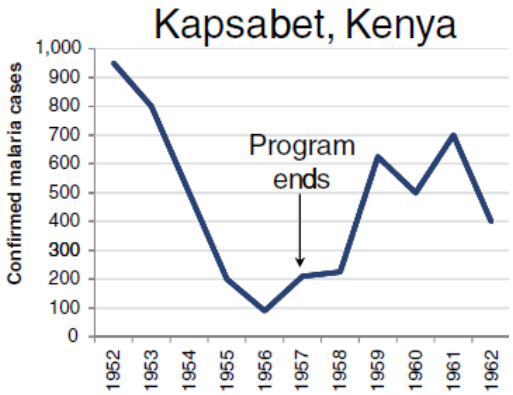
- Malaria control programmes ~ 1.5 billion per year
- Actual cost of malaria estimated ~12 billions

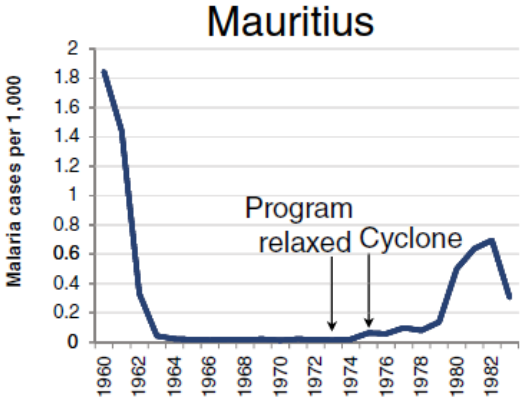
Three major challenges

- Artesimine Resistance
- Insecticide Resistance
- Financial Fragility

Malaria Resurgence, eg Africa

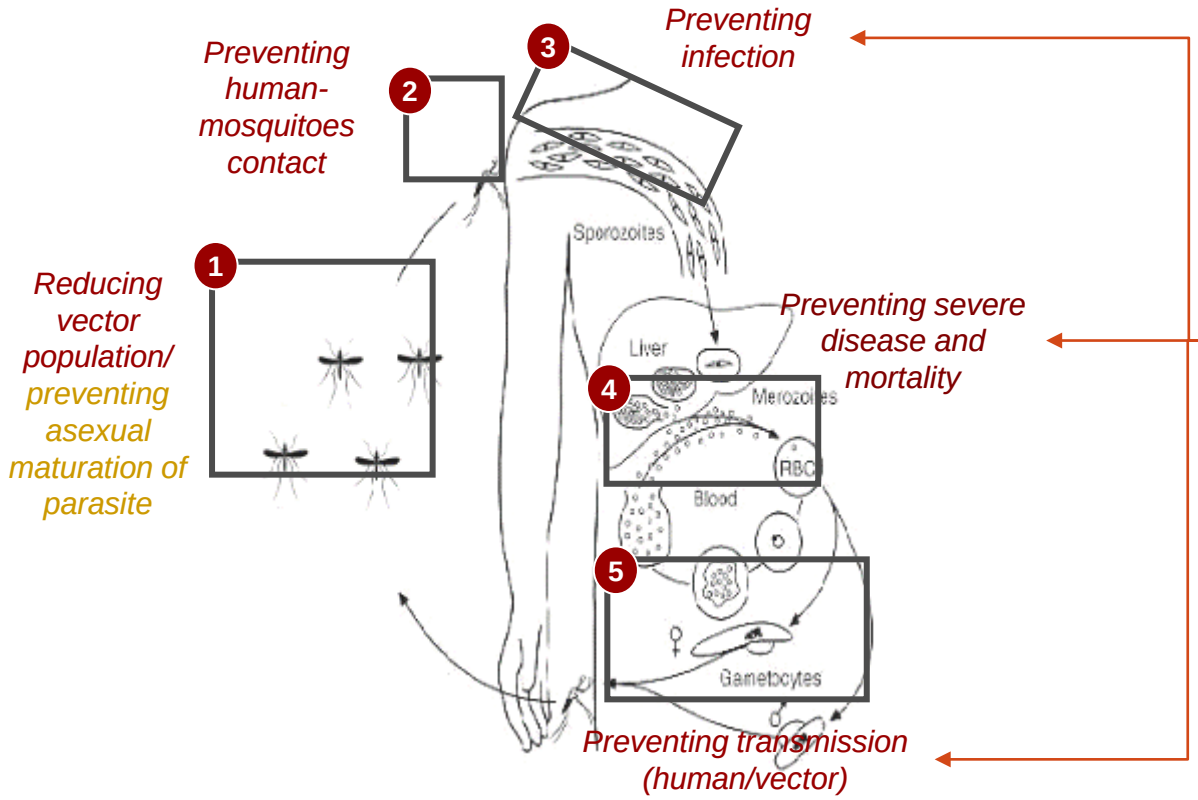






Cohen JM, Smith DL, Cotter C, et al. Malaria resurgence: a systematic review and assessment of its causes. Malaria Journal. 2012;11:122. doi:10.1186/1475-2875-11-122.

Complex biology of parasite is a challenge for controlling the disease



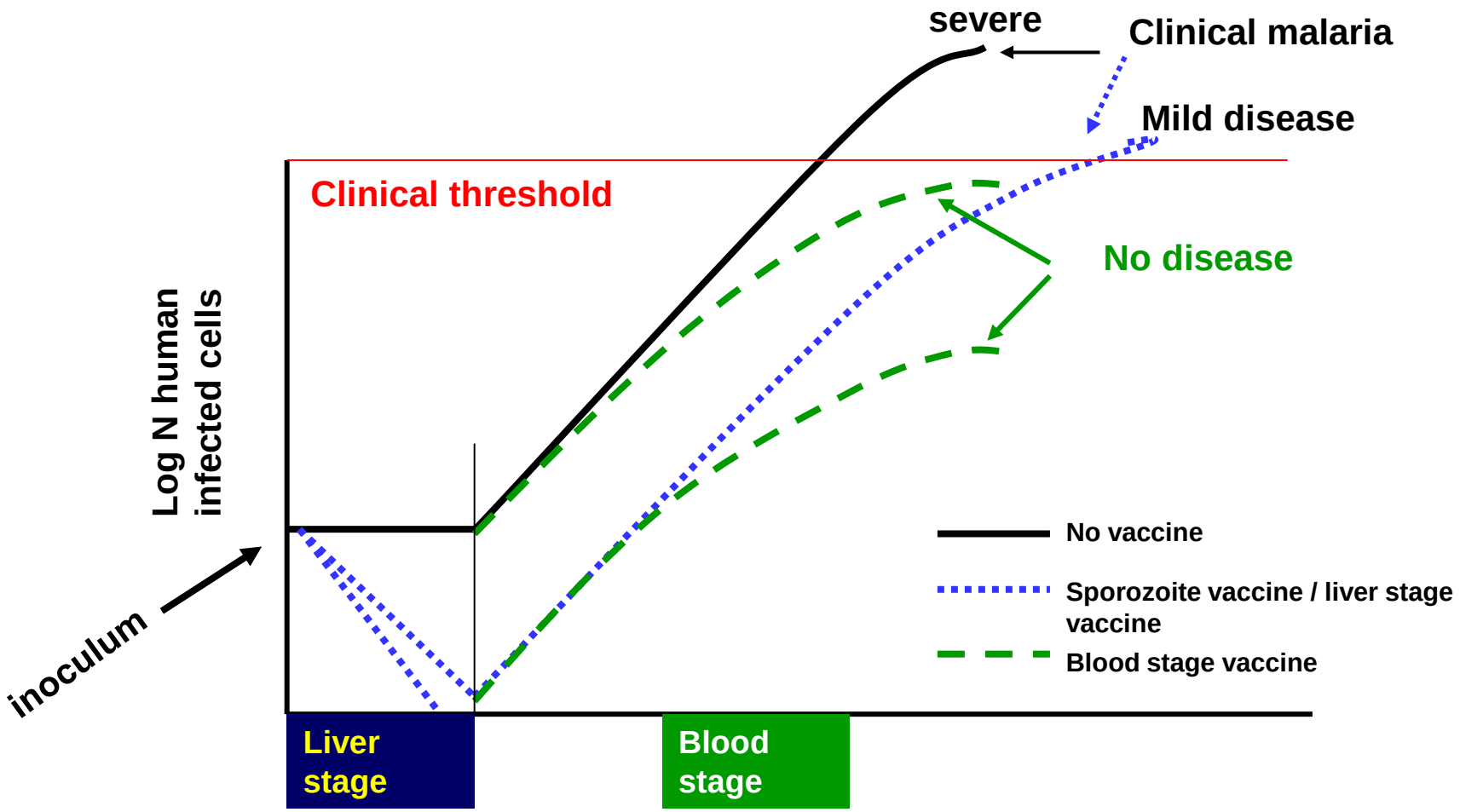
Vaccine targets

Three major challenges

- Identification of antigens
- Induction of protective immunity
- Prevention of immune escape

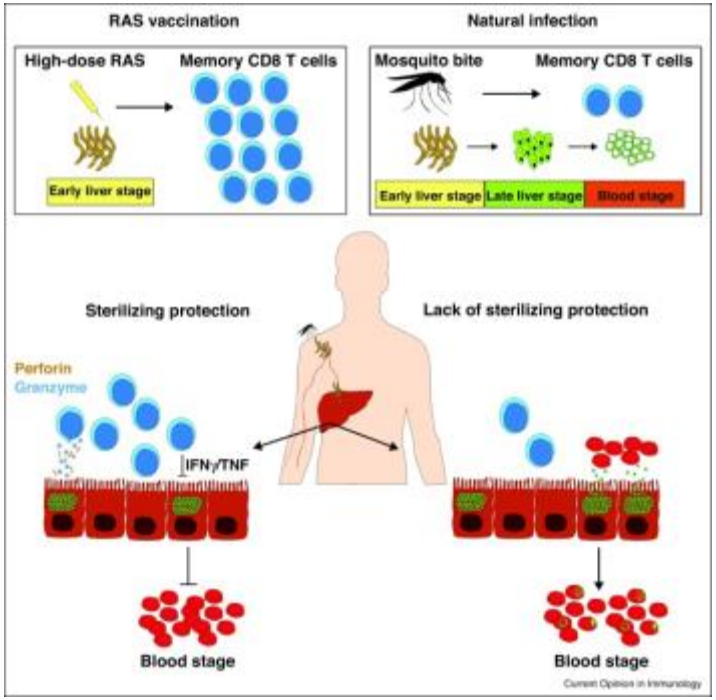
Source: Image from Jones and Hoffman (1994)

Expected effects of sub-unit vaccines



D'après Kumar *et al* 2002 in Chemical Immunology

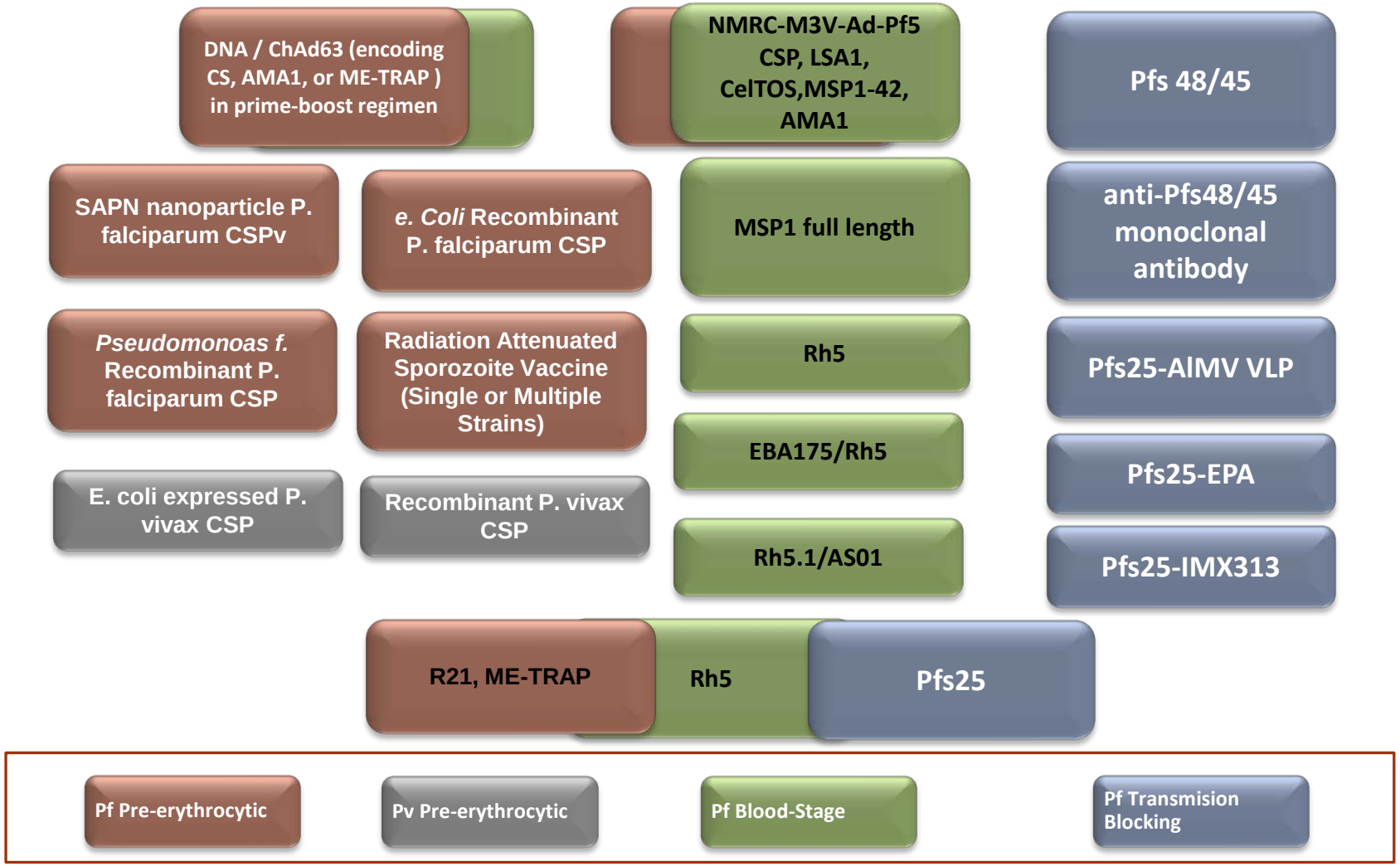
Regulatory issues in immunity



Natalija Van Braeckel-Budimir, Samarchith P Kurup, John T Harty
Regulatory issues in immunity to liver and blood-stage malaria. Current Opinion in Immunology, Volume 42, 2016, 91–97

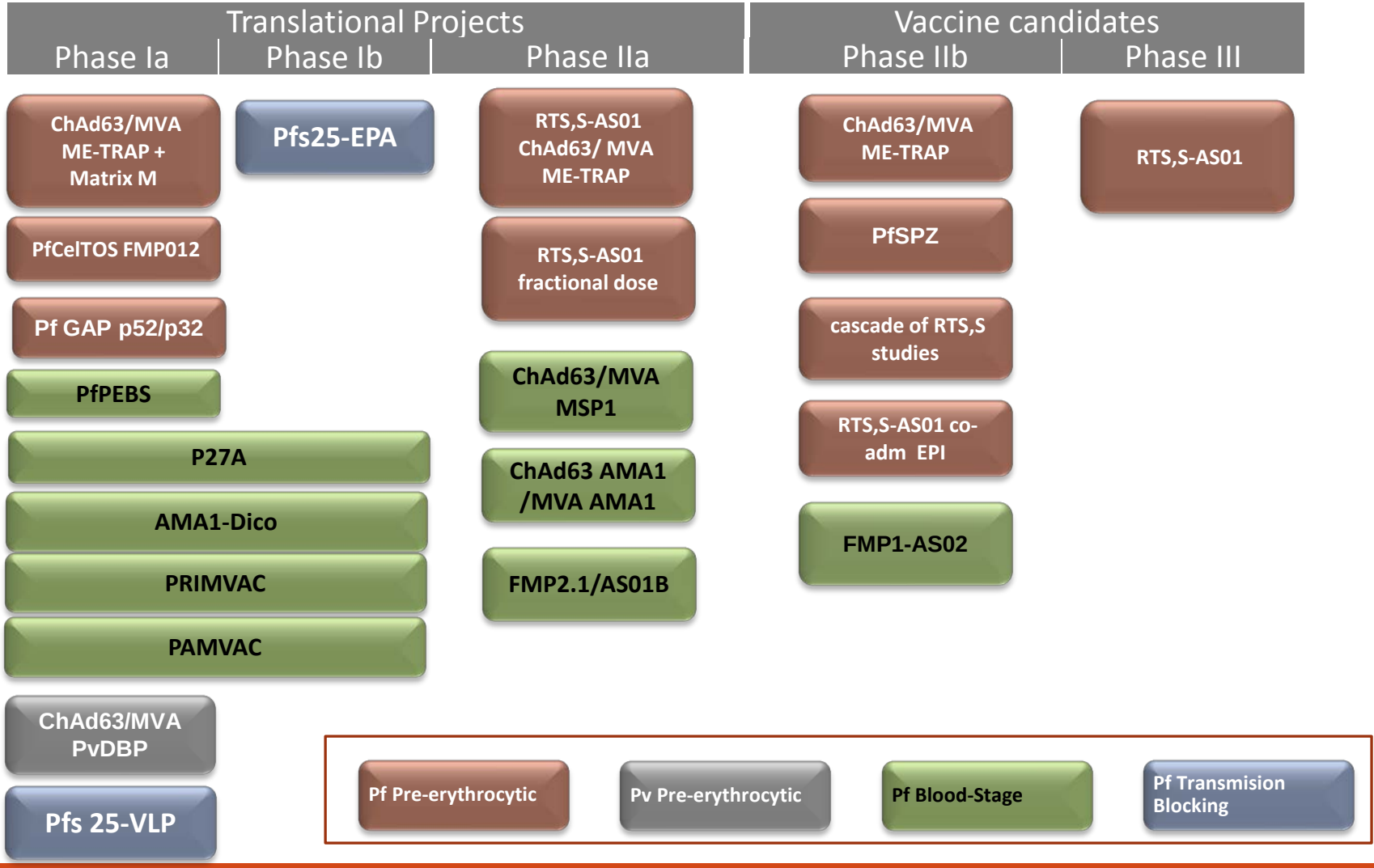
Active Global Malaria Vaccine pipeline

Pre-clinical (GMP) WHO rainbow table 2016



Active Global Malaria Vaccine pipeline

Clinical - WHO+ clinical trial.gov



Global Malaria Vaccine Pipeline
Keyword : tenacity

Oxford
ChAD63/MVA
Recombinant + Adj
All stages

Sanaria
Attenuated Sporozoites

GSK
RTS,S + others
AS0 class of adjuvants

And a myriad of others ….

Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial, RTS,S Clinical Trials Partnership, *Lancet* 2015; 386: 31–45

36 – 48 months median follow-up

3 doses		
Vaccinees Age	**6-12 weeks**	**5-17 months**
Clinical Malaria	28% [23 - 33]	18% [12 - 24]
Severe Malaria	1% [-23 - 21]	10% [-18 - 32]
Booster dose at M20		
Clinical Malaria	36% [32 - 41]	26% [20 - 32]
Severe Malaria	17% [-9 - 38]	32% [14 - 47]

Greenwood *et al. Lancet* 2015

RTS,S efficacity

Efficacy against severe malaria in 5-17 month olds	
Vaccination to M 20:	**36%** [15, 51%]
M21 to M48 with booster:	**-10%** [-67, 27%]
Month 21 to M48 without booster:	**-52%** [-123, -4%]
Efficacy against severe malaria in 6-12 week olds	
Month 21 to M48vwithout booster :	**11%** [-35, 42%]

Clinical malaria averted cases:

5-17 months:

1774 cases/1000 children (95% CI 1387–2186) vaccinated with 4 doses

6-12 weeks:

983 cases/1000 children (95% CI 592 to 1337) vaccinated with 4 doses

Greenwood *et al. Lancet* 2015

WHO PDVAC report 2016
WHO recommendation for RTS,S October 2015

SAGE and the Malaria Policy Advisory Committee (MPAC)

pilot implementation studies

- 4-dose schedule of the RTS,S/AS01 vaccine
  - in 3–5 distinct epidemiological settings in sub-Saharan Africa, at sub-national level, covering moderate-to-high transmission settings,
  - with three doses administered to children between 5 and 9 months of age, followed by a dose 15–18 months later. The intent of these pilot studies is to assess:
- • the feasibility of providing all four doses of RTS,S
- • the impact of RTS,S on child mortality;
- • whether there are any safety issues, particularly evidence of any causal relationships between RTS,S administration and either meningitis or cerebral malaria (both signalledin the phase III trials),
- • whether introduction of the vaccine impacts posively or negatively on existing country immunization programs and on the use of currently recommended malaria control measures.

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

RTS,S Malaria Vaccine and Increased Mortality in Girls

Sabra L. Klein,[a] Frank Shann,[b] William J. Moss,[c] Christine S. Benn,[d] Peter Aaby[e]

TABLE 1 RTS,S malaria vaccine and mortality by sex

Sex and age of group	No. of deaths overall [no. of deaths due to malaria]/no. of persons in group (%)				RTS,S recipient/control risk ratio (95% CI)
	R3R[a]	R3C[b]	R3R and R3C groups combined	C3C[c]	
Males					
5–17 mo	26 [4]/1,509 (1.7)	19 [9]/1,472 (1.3)	45 [13]/2,981 (1.5)	29 [8]/1,471 (2.0)	0.77 (0.48–1.22)
6–12 wk	24 [3]/1,116 (2.2)	26 [8]/1,118 (2.3)	50 [11]/2,234 (2.2)	26 [3]/1,079 (2.4)	0.93 (0.58–1.48)
Total			95 [24]/5,215 (1.8)	55 [11]/2,550 (2.2)	0.84 (0.61–1.17)
Females					
5–17 mo	35 [9]/1,467 (2.4)	32 [8]/1,500 (2.1)	67 [17]/2,967 (2.3)	17 [4]/1,503 (1.1)	2.00 (1.18–3.39)
6–12 wk	27 [5]/1,064 (2.5)	29 [4]/1,060 (2.7)	56 [9]/2,124 (2.6)	16 [3]/1,100 (1.5)	1.81 (1.04–3.14)
Total			123 [26]/5,091 (2.4)	33 [7]/2,603 (1.3)	1.91 (1.30–2.79)

P=0,0006

[a] R3R, 3× RTS,S plus booster RTS,S.
[b] R3C, 3× RTS,S plus comparator vaccine.
[c] C3C, controls (comparator vaccines).

American Journal of Epidemiology
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Vol. 138, No. 9
Printed in U.S.A.

Divergent Mortality for Male and Female Recipients of Low-Titer and High-Titer Measles Vaccines in Rural Senegal

Peter Aaby,[1, 2] Badara Samb,[1] Francois Simondon,[1] Kim Knudsen,[2, 3]
Awa Marie Coll Seck,[4] John Bennett,[5] and Hilton Whittle[6]

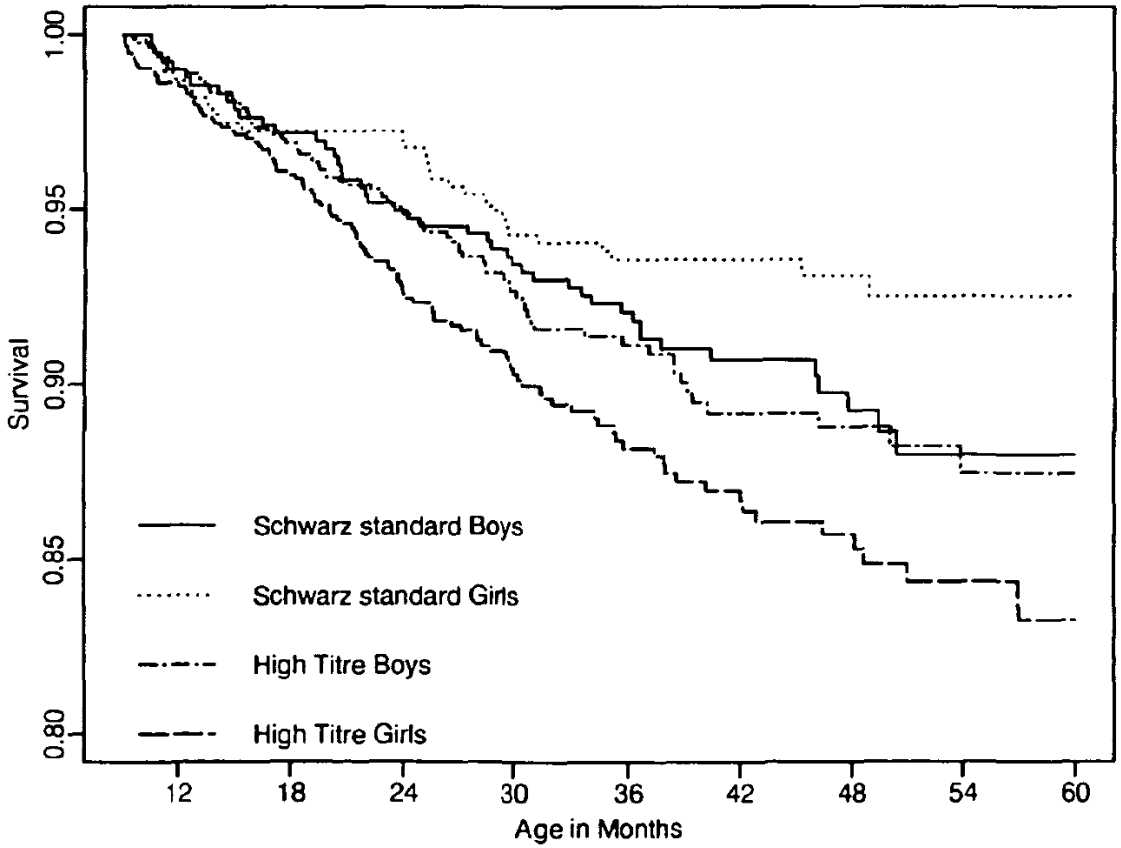


FIGURE 2. Survival curves from 9 months of age by sex for recipients of the Schwarz standard and high-titer measles vaccines. Children were born between February 1987 and April 1990 in Niakhar, Senegal.

High titer measles vaccine

Table 5. Underlying cause of confirmed death by vaccine group and sex.

	Schwarz						Edmonston-Zagreb			
	Standard (controls)		Medium		High		Medium		High	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Diarrhea	1	0	2	1	2	2	2	2	0	6
Malnutrition	0	2	3	2	3	3	2	2	1	4
Sepsis/meningitis	0	0	0	0	0	2	0	1	0	0
Accident	1	0	0	0	0	0	1	0	0	0
Measles	0	1	0	0	0	1	0	0	0	0
Other specified	0	0	2	0	0	0	1	0	0	1
Undetermined	2	0	3	0	0	0	0	0	0	1
No verbal autopsy available	4	3	1	3	1	2	3	4	7	4
Total	8	6	11	6	6	10	9	9	8	16

Biological explanation? Sex and gender based differences in immune response

1. In outcome of vaccination some evidence of sex differences:
   - higher antibody response in females than males : BCG, influenza, yellow fever, rubella, measles, mumps, hep A and B, herpes simplex 2, rabies, smallpox and dengue (up to x2 in females)
   - Higher cell-mediated immunity in adult females : measles, herpes simplex 1, influenza
   - Females more frequent and severe adverse reactions
2. Sex-based differences in immunity and sexual hormones
   Oestrogen / testosterone influences immunocompetence

Sexist diseases., Garenne M(1), Lafon M. Perspect Biol Med. 1998 Winter;41(2):176-89.

In light of these findings, it is striking to note that Th-1 response-healing diseases or Th-2 response-exacerbating diseases (measles, whooping cough, tuberculosis) belong to first and second groups (evidence of excess female mortality), whereas diseases regarded as Th-1 response-exacerbating disease or Th-2 protective (cerebral malaria, schistosomiasis) belong to the third group (systematic excess male mortality). This suggests that females tend to be more susceptible to Th-2 response-exacerbating diseases, and males to Th-1 response-exacerbating diseases.

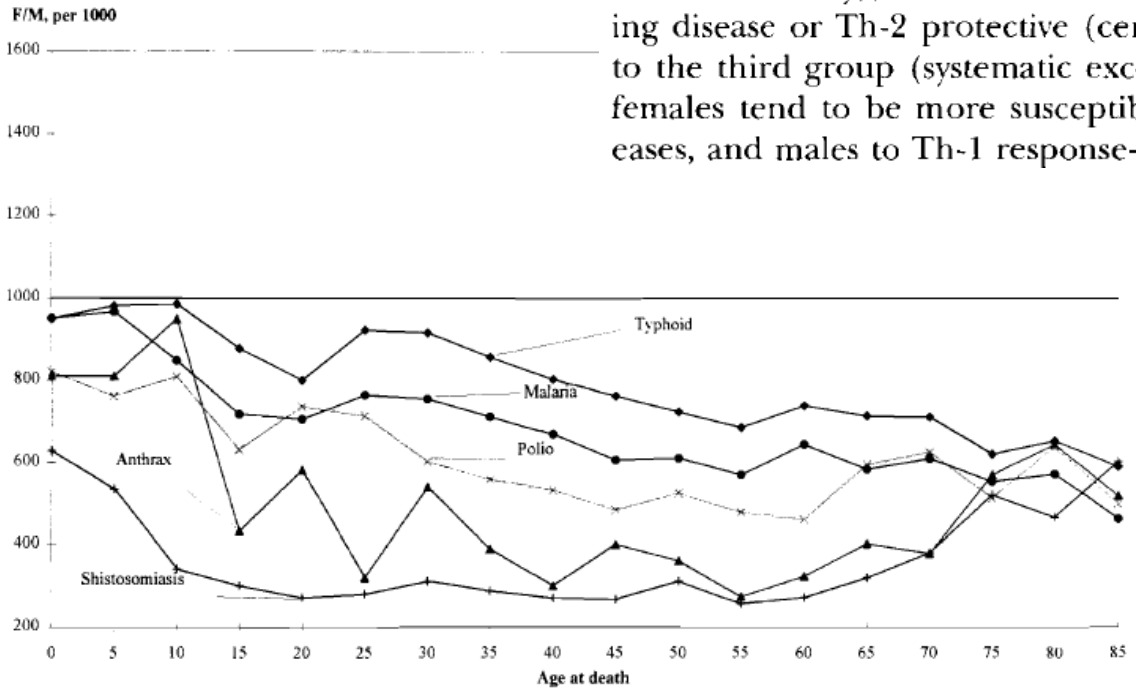


Fig. 3.—Gender differences in mortality by age: Third group of diseases, with systematic excess male mortality (selected diseases).

Sex Differences in Parasite Infections: Patterns and Processes

MARLENE ZUK* and KURT A. McKEAN

Department of Biology, University of California, Riverside, CA 92521, U.S.A.

International Journal for Parasitology, Vol. 26, No. 10, pp. 1009–1024, 1996

"This is really a rather esoteric topic." Anonymous parasitologist, July 1995.

Pediatr Infect Dis J, 1993;12:462–5
0891-3668/93/$03.00/0

Vol. 12, No. 6
Printed in U.S.A.

Increased mortality after high titer measles vaccines: too much of a good thing

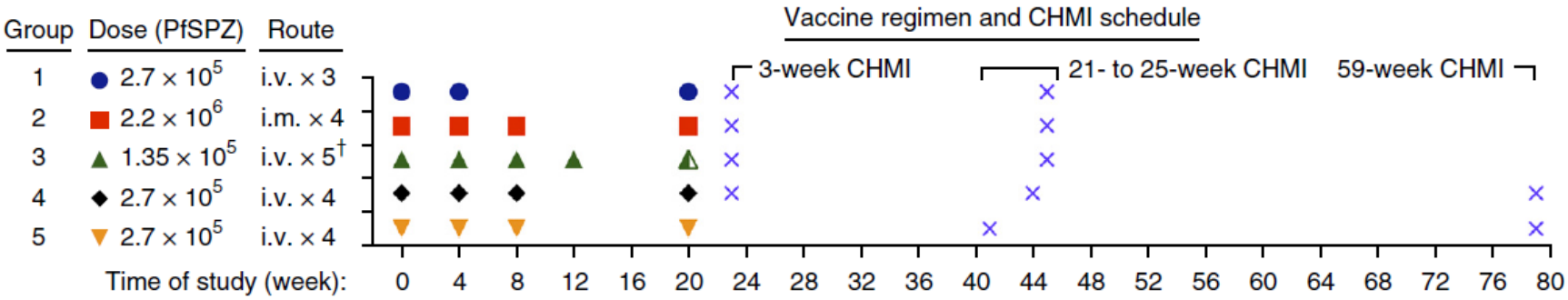
NEAL A. HALSEY, MD

In retrospect I and other investigators were too easily convinced of the safety of high titer vaccines based on low rates of adverse events in the few weeks after vaccination. At the time we had no reason to expect sex-specific delayed mortality after further attenuated vaccines. We are attempting to minimize the impact of the high titer vaccines in the surviving children by providing nutritional supplementation and improved access to medical care. Hopefully the adverse events and the unfortunate reduced survival in the vaccine recipients will not be in vain. The increased understanding of measles pathogenesis may help to identify improved means to prevent measles and the long term complications from this disease.

Efficacy of PfSPZ in CHMI

SANARIA

a



g

	Vaccination		3-week CHMI			21- to 25-week CHMI					59-week CHMI			
Group	Dose	No. of inj.	No. of subjects	Parasite free	First VE	No. of subjects	Parasite free	First VE	Subgroup VE	Cumulative VE	No. of subjects	Parasite free	Subgroup VE	Cumulative VE
1	2.7×10^5	3	9	3	24%	3	2		67%	16%				
2	2.2×10^6	4	8	3	29%	3	0		0%	0%				
3	1.35×10^5	5†	12	8	62%	7	4		57%	35%				
	Naive		8	1		6	0							
4	2.7×10^5	4	9	7	73%	4	3		75%	55%	1	1	> 100%	55%
5	2.7×10^5	4				11	6	55%		55%	4	4		
	Naive		6	1		6	0				6	1		

PfSPZ challenges

- heterologous (cross-strain) protection?
- high numbers of parasites (large scale and consistent GMP production challenge)
- intravenous route of delivery
- liquid nitrogen cold chain

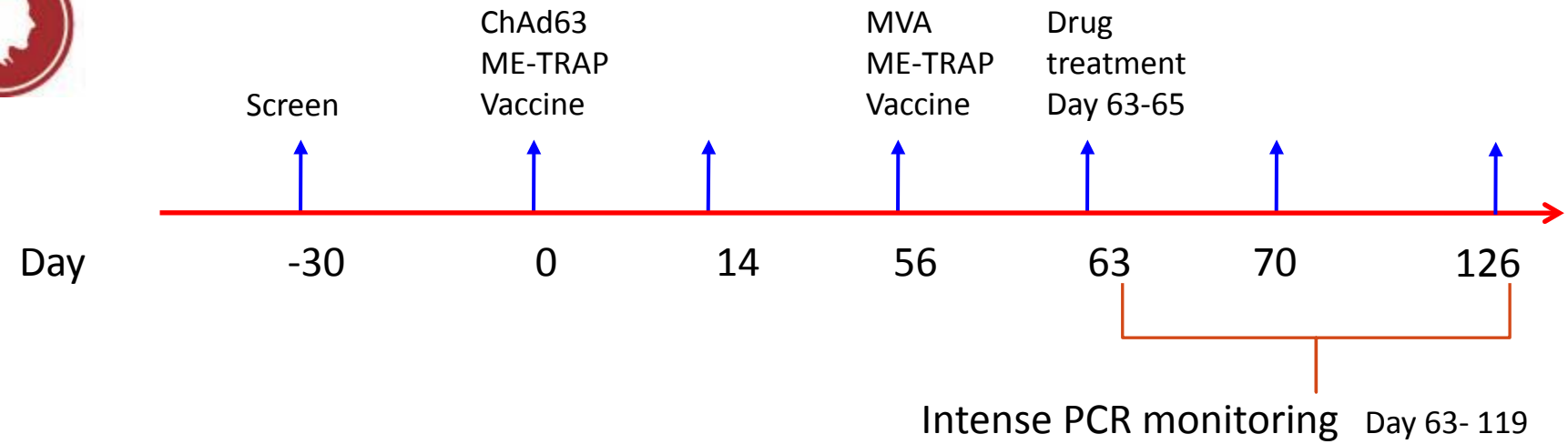
Oxford approaches

- From poxvirus to adenovirus platforms
- Heterologous Prime-boost
- Multistage approaches

Another example of tenacity….
> 20 years of research.
>50 clinical trials,
> 20 since 2010 …

Eg: A Four-Stage Vaccine against *P. falciparum*

- Sporozoite Stage: R21in AS01 or matrix M
- Liver Stage: ME-TRAP in vectors
- Blood Stage: PfRH5 in vectors
- Mosquito Stage: Pfs25-IMX313 in vectors



Vaccine efficacy by Cox regression

N,number of participants; *n*,number of end points identified. Efficacy figures are estimated from Cox regression, where efficacy = (1 – HR) × 100%.

	ME-TRAP		Control		Unadjusted efficacy		Adjusted efficacy	
	N	*n*	*N*	*n*	Efficacy (95% CI)	*P*	Efficacy (95% CI)	*P*
Any PCR positivity	61	11	60	28	67% (33–83%)	0.002	66% (31–83%)	0.003
>10 parasites/ml	61	4	60	19	82% (46–94%)	0.002	81% (42–94%)	0.03
New genotype	61	5	60	14	67% (7–88%)	0.035	65% (2–87%)	0.046

Ogwang C, Kimani D, Edwards NJ, et al. Prime-boost vaccination with chimpanzee adenovirus and modified vaccinia Ankara encoding TRAP provides partial protection against *Plasmodium falciparum* infection in Kenyan adults. *Science translational medicine*. 2015;

One century of research on malaria vaccine and what?

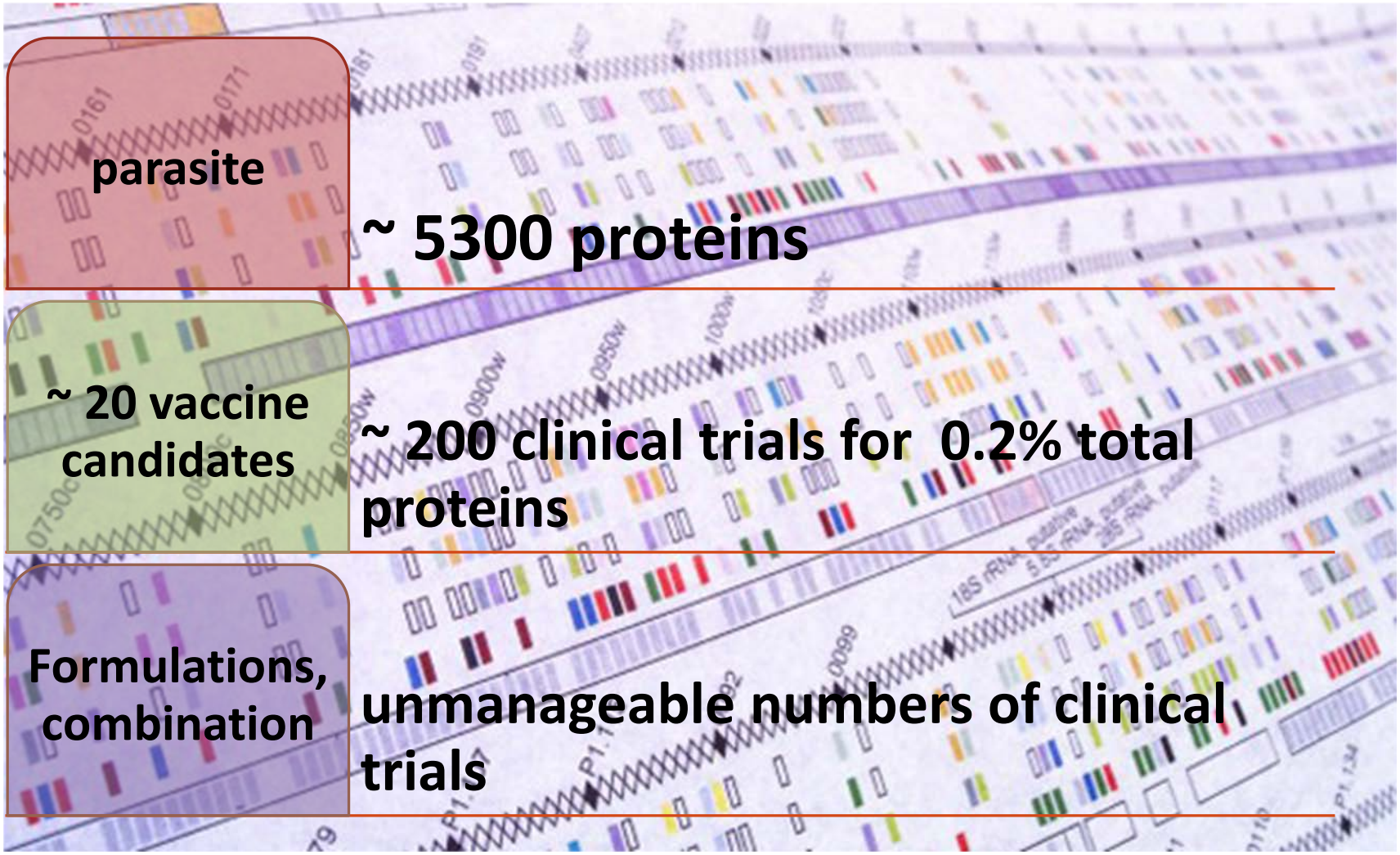
Edmond & Etienne Sergent

Les Comptes Rendu de l'Academie des Sciences

151: 407-409, 1910

Sur l'immunité dans le paludisme des oiseaux. Conservation in vitro des sporozoites de Plasmodium relictum. Immunité relative obtenue par inoculation de ces sporozoites

Malaria vaccine development

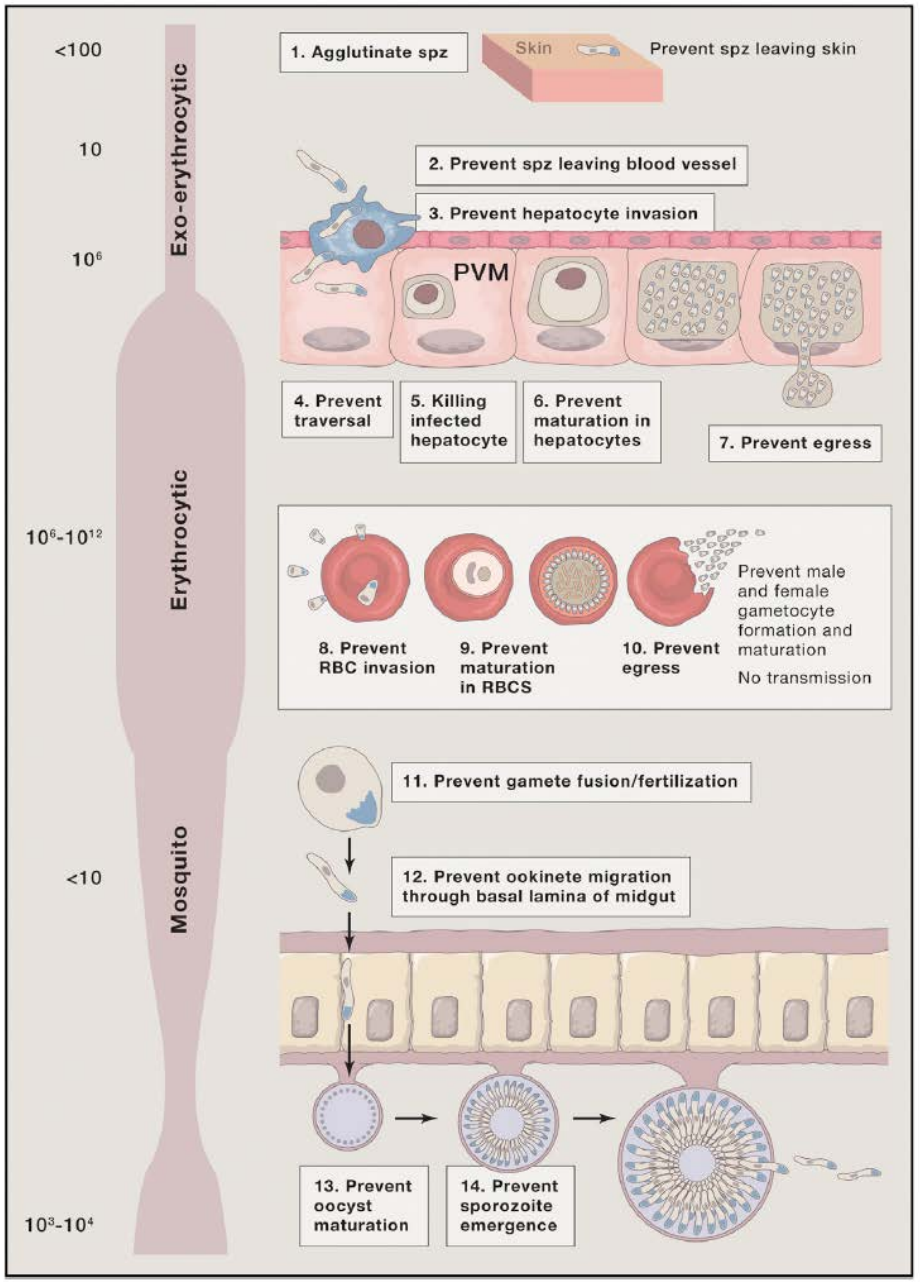


Need to revisit the portfolio

1. Start by discovery
   - Connect data to screen antigens
     D. Huw Davies, Patrick Duffy, Jean-Luc Bodmer, Philip L. Felgner, Denise L. Doolan . Large screen approaches to identify novel malaria vaccine candidates *Vaccine*, Volume 33, Issue 52, Pages 7496-7505,
   - Improved antigenicity (structural biology)
   - Development of functional assays
2. Direct comparative platforms

Vaccine targetable processes within the malaria life cycle – bottlenecks approach

Malaria: Biology and Disease, Cowman, Alan F. et al. Cell , Volume 167 , Issue 3 , 610 - 624



Conclusion

1. Consider safety seriously for all vaccine approaches

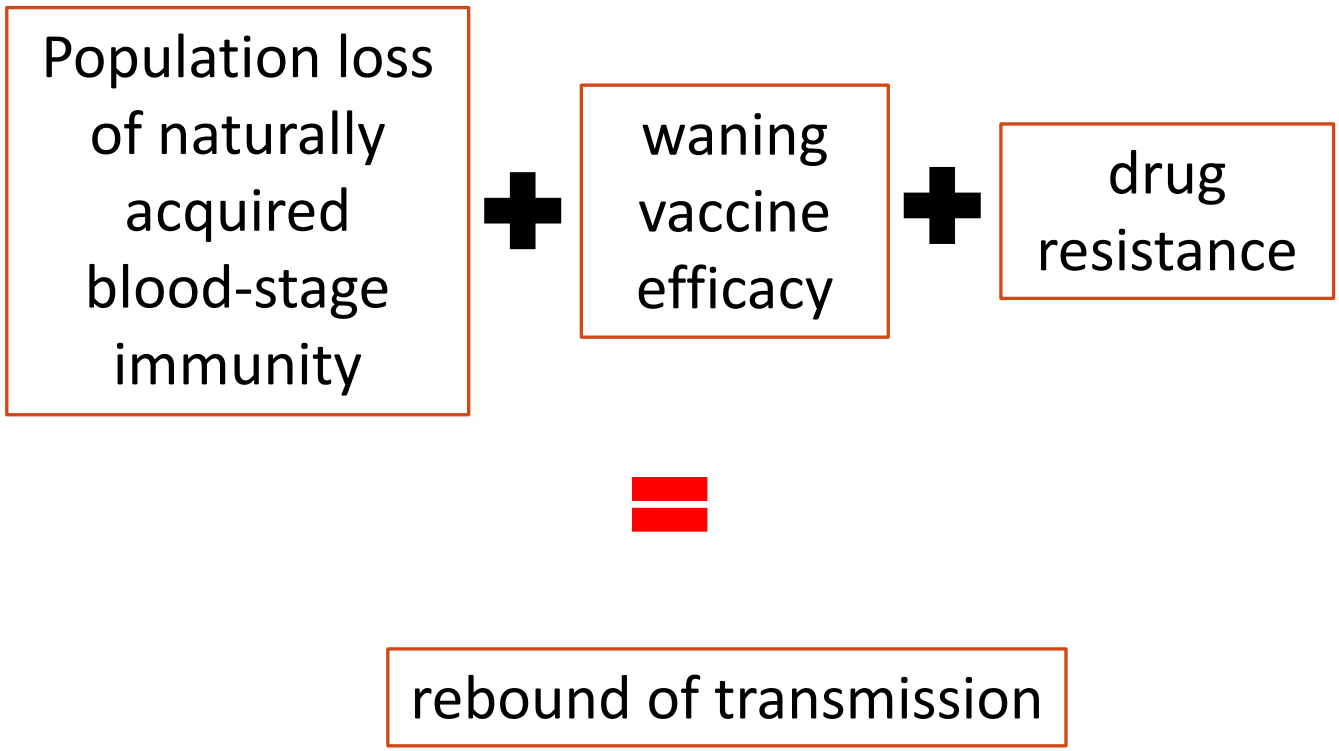
2. Consider collaborative work “big data” + omics+ structural biology to identify new antigens

3. Develop platforms for direct comparison across competitive institutional groups

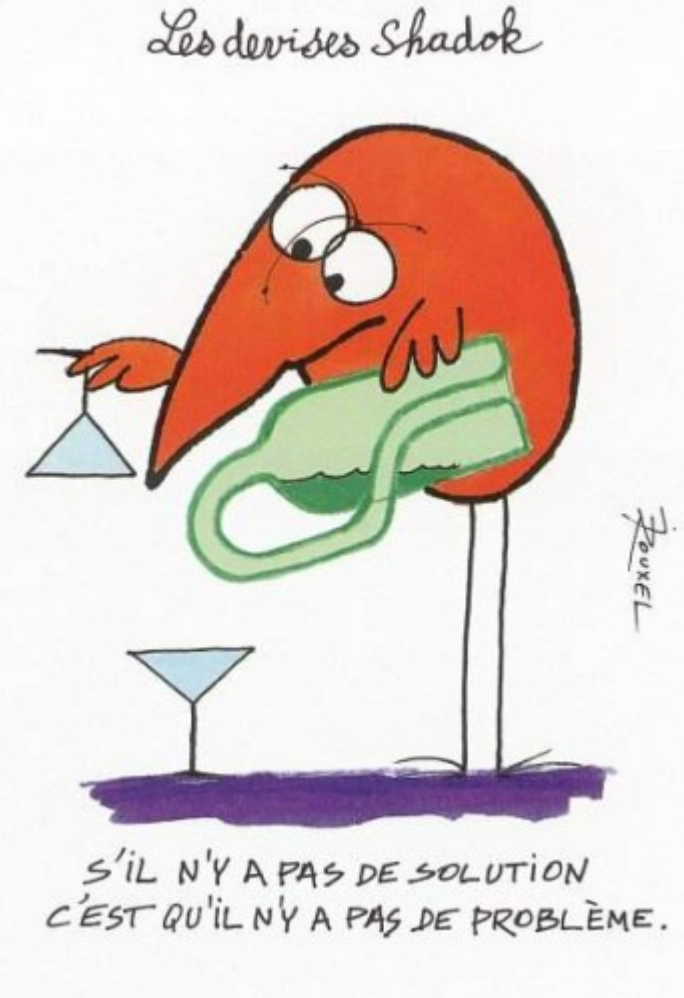
GOAL:

vaccine based on conserved antigens, inducing lifelong sterile protection in infants with few doses

Chef Recipe !


Population loss of naturally acquired blood-stage immunity
waning vaccine efficacy
drug resistance
rebound of transmission

Has the malaria vaccine scientific community adopts the Shadok slogans?



1. If there is no solution, there is no problem

2. When you continuously try, you finally succeed Thus, more you fail more you have chance to succeed

3. Why make it simple when you can make complicated

Contribute to make a better world
free of diseases of poverty