# A Review of Malaria Vaccine Candidate RTS,S/AS02A

## This is Chapter Three of 'The Science, Economics, and Politics of Malaria Vaccine Policy', a report written in 2005 and 2006[1]

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This was extracted and made into a stand-alone file in January 2010 following a request from some malaria science colleagues to do so. This is in light of the unveiling in late 2009 by the PATH Malaria Vaccine Initiative of their new strategy for developing next-generation vaccines, that is vaccines that go beyond the RTS,S approach. A common theme running through the original report in 2006 was a concern regarding the overemphasis in much of the policy debate of the time on low efficacy vaccine goals and a scientific approach that was too narrow. Now "MVI has modified its vision to reflect a new, broader focus toward malaria vaccine development".[3] The new strategy "Raises bar, heightens the focus on achieving an 80 percent effective vaccine".[4] Given how nerve-wracking it can be at times sticking one's neck on the line on these issues, it's a relief at times to see progress in a way that one was arguing. Hopefully this file will help the debate about these issues and encourage thinking about the new strategy. The wording is as it was in the original, even though at times I was tempted to reword (and re-tone) some observations; this way the reader doesn't get an ex post rendition of my thinking with four or five more years of hindsight, but the original warts-and-all insights.

The main report from what this is derived was a submission to UK Department for International Development[5] and The Malaria Vaccine Technology Roadmap[6] and response to the Tremonti Report to G8 Finance Ministers[7]

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[1] This can be found at http://www.economics.ox.ac.uk/members/andrew.farlow/FarlowMalaria.pdf.

[2]  Further papers on vaccines, neglected diseases, and pharmaceutical R&D at: www.economics.ox.ac.uk/members/andrew.farlow. Feedback and corrections greatly appreciated: andrew.farlow@economics.ox.ac.uk. A list of thanks is to be added when those involved agree to be listed or to remain as anonymous referees, given the sensitivity of some of the feedback the author has received.

[3] http://www.malariavaccine.org/files/11_11_2009_MVI_Strategy_WhitePaper_FINAL.pdf, page 1.

[4] http://www.malariavaccine.org/files/MVIRDstrategy_PR_FINAL_2Nov09.pdf.

[5] UK Department for International Development consultation process on Advance 'Market' Commitments.

[6] www.malariavaccineroadmap.net. The draft "Malaria Vaccine Technology Roadmap" (henceforth MVTR) is available on www.malariavaccineroadmap.net/pdfs/roadmap_071905.pdf. The "Roadmap Summary Results" (henceforth RMSR) is at www.malariavaccineroadmap.net/pdfs/roadmap_results.pdf. The "Malaria Vaccine Vision Meeting Summary Results" (henceforth VMSR) is here: www.malariavaccineroadmap.net/pdfs/summary.pdf.

[7] "Advance Market Commitments for vaccines: A new tool in the fight against disease and poverty." Report to the G8 Finance Ministers by Giulio Tremonti, Minister of the Economy and Finance, Italy, London, December 2, 2005, www.dfid.gov.uk/consultations/amc-report-tremonti.pdf. Background papers to the 'Tremonti Report' at: www.dfid.gov.uk/consultations/background-papers-tremonti.pdf.

# 3. A Leading Candidate Malaria Vaccine: A Timely Case Study

This section has its origins in a small subsection that grew as the author explored a recent case study, of the candidate malaria vaccine RTS,S/AS02A, and as feedback and ideas came in from a wide range of leading figures in the vaccine and malaria science field. As it became increasingly clear that the case study had important lessons for policymakers and funders, it also became clear that it would necessitate its own chapter.[8] A variety of opinions were expressed during this process of feedback, and the author can do no more than try to report them fairly and correctly, without claiming that this is a completely balanced summary of all possible views in the 'malaria community'. Amongst those consulted, there was a spectrum from those supportive of further funding into RTS,S/AS02A right through to a sizeable minority arguing against further funding for RTS,S/AS02A. Even supporters of further funding were often candid with their critiques, and none of them expressed the more extreme position – even 'spin' – made by some politicians and in the media and, indeed, in some of the advocacy literature. Those asked, felt that a forum for more open debate would be very useful.

This section has three key purposes. The first – and a repeated refrain in feedback – is to highlight the need, whatever we conclude about RTS,S/AS02A itself, to avoid approaches that risk narrowing down the search for malaria vaccines and destroying more collaborative global efforts, but instead the need to strengthen approaches that keep many parallel and mutually supportive activities going, and to keep the 'playing field level' for all.

Second, it also becomes clear that many problems still lie ahead even for the current 'leading' malaria vaccine candidate, and we need to avoid the temptation of simplistic solutions. As one supporter for RTS,S/AS02A put it to the author:

"I am a supporter of the development of RTS.S but no zealot and I am uncertain if it will ever get used widely. However, the recent results show that it is a credible vaccine that could conceivably find a use in a combined malaria control strategy in some countries. I think that it is right to spend a modest amount on its further development through a series of phase 2b and phase 3 trials with the aim of licensure. The results of these studies will show whether it is a credible candidate for further much more extensive investment. I am sure that if deployed, RTS,S will have only a limited life to be replaced by a more effective vaccine…"

The issue is how to make sure that attention to one low-efficacy product does not distort behavior and harm the greater long-term goal. Tremonti argues that an APC would bring in only one or maybe two developers. The expectation[9] that a big chunk of the funding

[8] I am enormously grateful to malaria vaccine experts for help on this. None of them should however take any responsibility for any faults.
[9] All the time, we are thinking of investors and their expectations, and not just the ex post outcome.

made available might go on one early low-efficacy product would not leave much, if anything, to stimulate other investors. This was picked up in correspondence. The above quote continued. "…This is often the case in vaccine development – for example the Hib polysaccharide vaccines served a useful role for several years only to be replaced by much more effective Hib conjugate vaccines a few years later and there are many other examples. It would have been wrong not to develop the Hib polysaccharide vaccine even though it had only limited efficacy and many children's lives were saved by doing this." But another correspondent argued: "The difference with Hib is that alternatives to RTS,S can be conceived, i.e. they are also in clinical development, though not in industrial development. In other words, Hib polysaccharides did not cause relative harm, but a premature RTS,S might well. This harm can be estimated globally in terms of excess mortality/year; at worst it might reach several hundred thousands." In chapter 7 we will investigate the complex tradeoff between emphasizing early low specification goals and later higher specification goals, a tradeoff that has yet to be fully explored, let alone solved. Meanwhile, this is not a time for politicians to force a solution onto this tradeoff.

A third intent is to help construct a more open debate evaluating if this particular vaccine candidate – and any that follow – is adequate for major targeting of funding (of the order of billions of dollars) to 'take it all the way to market', especially in the face of financial constraints on all other parts of the malaria and health package. Given the costs and losses elsewhere, no candidate should go 'all the way' without a very good stress-testing of its value. Neither should policymakers be egged along by language indicating that even very low efficacy is perfectly fine (e.g. statements like "Even a 30 percent effective vaccine would be highly cost-effective."[10]) and that there is essentially no budget constraint to worry about. Both of these views are increasingly used by some to push for an APC-based funding scheme.

There is much more behind-the-scenes debate about this than a public debate. It would be good for this discussion to be more open in every case, and not just in the case of RTS,S/AS02A. The really big allocations, and hence possible misallocations, of resources are still some years away. Now is an opportune moment to get into the regular habit of debating these issues.

## *3.1. Introducing RTS,S/AS02A*

The Malaria Vaccine Technology Roadmap observes that "recent R&D advances have caused renewed optimism among scientists that an effective malaria vaccine is feasible." Tremonti even hints that malaria is no longer in the category of a complex scientific problem: "It is financially risky to undertake early work to develop a vaccine against complex, poorly understood diseases, such as HIV/AIDS and tuberculosis,"[11] and "fundamental scientific puzzles still bedevil efforts to design and develop vaccines against HIV/AIDS, TB and, some believe, even malaria,"[12] for the first time suggesting

[10] Berndt, et al. 2005, ibid. p19.
[11] I.e. Tremonti leaves malaria out of the list. Tremonti, G. Background Papers, 2005, p21.
[12] Tremonti, G. Background Papers, 2005, p25.

that concerns about the impact of fundamental scientific difficulties on malaria vaccine efforts is now something of a minority issue.

This pins the hope about the feasibility of a malaria vaccine on the results generated by the recent GSK Biologicals vaccine candidate RTS,S/AS02A, the leading MVI candidate. This was previously trialled on adults, and has recently been trialled in a double-blind phase IIb trial, between April 2003 and May 2004, on children in Mozambique, with 6-month results released in October 2004,[13] and in a single-blind follow-up, the results of which were released in November 2005.[14] 2022 children aged 1–4 years were recruited and 1605 (there were 391 exclusions[15]) were randomized to receive three doses of either RTS,S/AS02A candidate malaria vaccine or a control vaccination regimen. This candidate has not yet been trialled on the ultimate target group of infants (to be able to be administered as part of the standard childhood vaccine package).

Berndt et al. argued that "the promising results of the recent GSK trials suggest that developing a malaria vaccine may not be as technically difficult as many had previously thought,"[16] even though the Berndt et al. group contain not a single malaria (vaccine or otherwise) expert. Others went even further: "Malaria Vaccine to Save Millions of Lives,"[17] ran one newspaper headline. "Malaria Vaccine Battle Has Been WON" (capitalization actually in the original) headlined one internet medical site.[18] This naïvety has a long pedigree. 50 years ago we were being told that mankind had mastered malaria: "Man's Mastery of Malaria" ran a famous book title.[19]

In a similar vein, the UK Finance Minister announced days after the paper analyzing the 6 month data was released:

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[13] Alonso, P.L., Sacarlal, J., Aponte, J.J., Leach, A., Macete, E., Milman, J., Mandomando, I., Spiessens, B., Guinovart, C., Espasa, M., Bassat, Q., Aide, P., Ofori-Anyinam, O., Navia, M.M., Corachan, S., Ceuppens, M., Dubois, M.C., Demoitié, M.A., Dubovsky, F., Menéndez, C., Tornieporth, N., Ballou, W.R., Thompson, R., Cohen, J., "Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial." *The Lancet*, 2004, Vol. 364, pp. 1411-1420.
www.thelancet.com/journal/vol364/iss9443/full/llan.364.9443.primary_research.30985.1

[14] Alonso, P.L., Sacarlal, J., Aponte, J.J., Leach, A., Macete, E., Aide, P., Sigauque, B., Milman, J., Mandomando, I., Bassat, Q., Guinovart, C., Espasa, M., Corachan, S., Lievens, M., Navia, M.M., Dubois, M.C., Menendez, C., Dubovsky, F., Cohen, J., Thompson, R., Ballou, W.R., "Duration of protection with RTS,S/AS02A malaria vaccine in prevention of *Plasmodium falciparum* disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial." *The Lancet*, 2005, Vol. 366, pp. 2012-2018.

[15] 156 did not meet inclusion criteria, and 235 chose not to participate. Alonso et al. 2004, Figure 2.

[16] Berndt et al. 2005, ibid. p9. Though in the same Lancet as the first Alonso study, Philippe van de Perre and Jean-Pierre Dedet, argued that there was no reason to think things will now get easier: "The road toward a safe and efficient malaria vaccine being available and usable on a large scale…will be long and chaotic." I have no idea on behalf of whom Berndt et al. believed themselves to be speaking. This author has found no malaria vaccine experts willing to take the Berndt et al. line.

[17] *The Times*, 15 October 2004.

[18] www.medicinenet.com/script/main/art.asp?articlekey=398534.

[19] Russell, P.R., *Man's Mastery of Malaria*, Oxford University Press, 1955.

*"The recent breakthrough which for the first time gives us a vaccination to prevent malaria that could be ready in three to four years time is a revolution in our time.*"
Gordon Brown, October 2004[20]

To which came the wry response:
"*Who has been briefing Mr Brown…?"*
Michel Pletschette, European Commission Directorate General for Research, 25 November 2004[21]

Brown further reported in January 2006 in the British newspaper The Guardian that: "A life-saving vaccine could soon be available for malaria to save 1 million lives each year,"[22] and that, in February 2006, he was going to push the G8 to pay for it via an APC.

As Snounou et al. observe: "Given the global and intolerable nature of the malaria burden to which the poorer half of humanity is subjected, and the influence of such trials on malaria control policy and budget allocations, the published trial outcomes merit critical appraisal."[23] So, let's give it a go.[24]

**What is it**

RTS,S consists of a recombinant polypeptide corresponding to part of the circumsporozoite protein (CSP) of *P. falciparum* fused to the S antigen of hepatitis B virus (HBsAg), in a particle that also includes the unfused S antigen. The scientists involved believe that it generates both antibody and T-cell responses to prevent infection of liver cells and that is also destroys infected cells. Over 20 years, GSK Biologicals developed this candidate vaccine in collaboration with the Walter Reed Army Institute of Research (WRAIR). In 2001, GSK Biologicals and WRAIR entered into a partnership with MVI. The reasoning for this is summarised by Heppner et al: "The recent report that RTS,S/AS02A had a significant positive impact on clinical and severe malaria in children in Mozambique strongly support our working hypothesis that a more effective RTS,S-based vaccine could be developed that would better meet the US Army military needs and perhaps also benefit global public health needs." [25]

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[20] www.hm-treasury.gov.uk./newsroom_and_speeches/press/2004/press_94_04.cfm. Contrast this with: "It could easily take a decade to develop malaria, tuberculosis, or HIV vaccines." Kremer, M., and Glennerster, R., 2004, ibid. p74.

[21] Pletschette, M., CIPIH Open Discussion Forum, 25 November 2004.

[22] The Guardian, 11 January 2005, www.guardian.co.uk/comment/story/0,3604,1683463,00.html.

[23] Snounou, G., Gruner, A.C., Muller-Graf, C.D.M., Mazier, D., Renia, L., "The Plasmodium sporozoite survives RTS,S vaccination." *Trends in Parasitology*, October 2005, Vol. 21, pp. 456-461.

[24] As an economist, this is a difficult and nerve-wracking task. The problem is that the economists and policy advocates pushing policy have not thought about this, even though the advice they proffer depends (or should depend) on a deep understanding of what is going on scientifically. The author can hardly criticize other economists and policy advocates for imposing solutions regardless of the underlying science, without at least attempting to understand it himself. Thankfully, there is an emerging literature and many helpful voices around the malaria vaccine community. Errors are all mine, and I would be extremely grateful to have mistakes and misunderstandings pointed out so that I can correct them in follow-on versions of this report.

[25] Heppner, D.G. Jr., Kester, K.E., Ockenhouse, C.F., Tornieporth, N., Ofori, O., Lyon, J.A., Stewart, V.A., Dubois, P., Lanar, D.E., et al. "Towards an RTS,S-based, multi-stage, multi-antigen vaccine against

**A little prior history**

After circumsporozoite protein (CSP) was identified as a dominant sporozoite surface antigen, experimental vaccines based on it were the first to be tested for efficacy in humans.[26] Trials of CSP vaccines have, however, proved disappointing.[27] [28] [29] [30] [31] Key to the current result therefore was over ten years of work on formulating the AS02A adjuvant to enhance an immune response in this the latest and most advanced CSP-based vaccine formulation. Indeed, in naïve volunteers, RTS,S efficacy has been found to be very strongly dependent on the adjuvant,[32] though one correspondent observed that: "There is some limited evidence that the effect of RTS,S is not due to the adjuvant. A small number of volunteers given adjuvant alone or with another antigen were not protected, and there is now some evidence for a marker of immunity in vaccinated subjects."

Given the potential for drift – when escape mutants are selected under vaccination-driven immune pressure – it may be necessary to combine immunogens by means of pre-erythrocytic or blood-stage immunogens with transmission-blocking vaccines. But also, because both humoral and cellular components of the immune system are needed for protection, the choice of immunogens and the development of potent adjuvants will also be equally critical. This explains a justifiably keen interest in an adjuvant. But one can already see that results that may be based on an adjuvant have to be placed in a much broader context.

**The Alonso Result**

In late 2004 Alonso et al. reported[33] that RTS,S combined with the adjuvant AS02A and administered in three doses over two months, achieved, at the end of the 6 months

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falciparum malaria: progress at the Walter Reed Army Institute of Research." *Vaccine*, 2005, Vol. 23, Issues 17-18, pp. 2243-2250.

[26] Nussenzweig, V., and Nussenzweig, R.S., "Rationale for the development of an engineered sporozoite malaria vaccine." *Adv. Immunol.*, 1989, Vol. 45, pp. 283–334.

[27] Ballou, W.R., Hoffman, S.L., Sherwood, J.A., Hollingdale, M.R., Neva, F.A., Hockmeyer, W.T., Gordon, D.M., Schneider, I., Wirtz, R.A., Young, J.F., et al. "Safety and efficacy of a recombinant DNA *Plasmodium falciparum* sporozoite vaccine." *The Lancet*, 1987, 1(8545), pp. 1277-81.

[28] Herrington, D.A. et al. "Safety and immunogenicity in man of a synthetic peptide malaria vaccine against *Plasmodium falciparum* sporozoites," *Nature*, 1987, Vol. 328, pp. 257–259.

[29] Guiguemde, T.R., Sturchler, D., Ouedraogo, J.B., Drabo, M., Etlinger, H., Douchet, C., Gbary, A.R., Haller, L., Kambou, S., Fernex, M., "Vaccination against malaria: initial trial with an anti-sporozoite vaccine." *Bull Soc Pathol Exot*, 1990, Vol. 8, pp. 217-227.

[30] Reber-Liske, R., Salako, L.A., Matile, H., Sowunmi, A., Sturchler, D., "A malaria vaccine field trial in Nigerian children." *Trop Geogr Med*, 1995, Vol. 47, pp. 61-63.

[31] Sherwood, J.A., Copeland, R.S., Taylor, K.A., Abok, K., Oloo, A.J., Were, J.B., Strickland, G.T., Gordon, D.M., Ballou, W.R., Bales, J.D., Wirtz, R.A., Wittes, J., Gross, M., Que, J.U., Cryz, S.J., Oster, C.N., Roberts, C.R., Sadoff, J.C., "Plasmodium falciparum circum-sporozoite vaccine immunogenicity and efficacy trial with natural challenge quantitation in an area of endemic human malaria in Kenya." *Vaccine*, 1996, Vol. 14, pp. 817-827.

[32] Stoute, J.A., et al. "A preliminary evaluation of a recombinant circumsporozoite protein vaccine against *Plasmodium falciparum* malaria. RTS,S Malaria Vaccine Evaluation Group." *N. Engl. J. Med*, 1997, Vol. 336, pp. 86-91.

[33] Alonso, et al. 2004, ibid.

surveillance period (starting two weeks after the last dose, hence measured at month 8.5), efficacy in children for the first clinical episode of 29.9% (95% CI 11.0%–44.8%; p=0.004).[34] The average age of the children at the start of the trial was 36 months with a standard deviation of 13–14 months.[35] A clinical episode was defined as a child who presented to a health facility with an axillary temperature of 37.5°C or more and presence of *P. falciparum* asexual parasitaemia greater than 2500 per μL.[36]

Few children had more than one episode of malaria, and vaccine efficacy including all clinical episodes was reported to be 27.4% (95% CI 6.2–43.8; p=0.014). At the end of the 6-month observation period (month 8.5), prevalence of *P. falciparum* infection was reported to be 37% lower in the RTS,S/AS02A group compared with the control group at 11.9% *versus* 18.9%,[37] though parasite densities were the same between RTS,S/AS02A recipients and the controls (geometric mean density 2271 *vs* 2513; p=0.699[38]). Efficacy for severe malaria was reported to be 57.7% (95% CI 16.2%–80.6%; p=0.019).[39] In cohort 2, vaccine efficacy for extending time to first infection was reported to be 45.0% (95% CI 31.4%–55.9%; p<0.0001), with 157 of 209 in the RTS,S/AS02A group and 166 of 208 in the control group having first episodes of asexual *P falciparum*. The mean density of asexual-stage parasites at time of first infection was also essentially the same (3016 vs. 3950 per μL; p = 0.354). The number of cases of severe malaria reported was reduced by 58% (95% CI 16.2% to 80.6%; p = 0.019). Vaccine efficacy against new infections was similar in the older and younger age groups (44.0% *vs* 46.5%). 15 children died during the study period. Four of those who died had malaria as a significant contributing factor and all four were in the control group, and eleven died for other reasons.

In the follow-up paper in December 2005,[40] during the single-blind phase, efficacy, defined as first or only episode of fever and parasitaemia >2500/μL, was reported as 28.9% (95% CI 8.4–44.8; p=0.008). The case of first or only episode of fever and parasitaemia >0/μL was 23.3% (95% CI 2.9–39.4; p = 0.027). The adjusted efficacy including all clinical episodes was reported as 28.8% (95% CI 6.2 – 45.9; p = 0.016). Over the entire study period (months 2.5–21), efficacy was reported to be 35.3% (95% CI 21.6–46.6; p = 0.0001) and for severe malaria 48.6% (95% CI 12.3–71.0; p = 0.02). During the single-blind phase there were eight deaths; five in the RTS,S/AS02A group and three in the control group. Two of these deaths were judged to be related to malaria and both were in the RTS,S/AS02A group.

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[34] In the per-protocol analysis in cohort 1, 282 children had first clinical episodes meeting the primary case definition (123 in the RTS,S/AS02A group and 159 in the control group). This yielded a crude vaccine efficacy estimate of 26·9% (with 95% confidence interval of 7.4-42.2; p=0·009 [See Alonso et al. 2004, Figure 4]) and the adjusted estimate of 29·9% (see Alonso et al. 2004, Figure 3).
[35] See Table 1 of Alonso, et al. 2004, ibid.
[36] This case definition was established at the time of study design, before the start of the trial, based on previous background data from the site, and has been estimated to be 91% specific and 95% sensitive.
[37] p=0·0003.
[38] With p = 0.699, the two measurements are to all intents and purposes the same.
[39] Observe that this is a very wide confidence interval.
[40] Alonso, et al. 2005, ibid.

**Mortality figures**

None of these mortality numbers has any statistical significance however. One correspondent observed: "It would have been useful for the p-value for these numbers being different by chance to have been presented. I guess it would be very large." Another commented that "to assess the impact of a vaccine on child mortality would require enrollments in the range of 10,000-100,000." As Richie and Saul, put it: "In much of Africa – which has an infant mortality of about 100 in 1,000 live births – depending on the accuracy with which a cause of death can be diagnosed, group sizes of many thousands to tens of thousands would be needed to use mortality as an end point, and this is not feasible at an early stage of vaccine development. Because there are gaps in our understanding of the progression of pathology from parasitaemia to death, our choice of end point for early efficacy studies is associated with a risk of either discarding a good vaccine because if fails to give an imperfect correlate of protection in early stage testing or wasting scarce resource by taking a poor vaccine through extensive clinical testing."[41]

As with the first study, parasite densities were essentially the same at the time of the 21 month measurement in RTS,S/AS02A recipients and controls (geometric mean density 1940 vs. 1571 per μL; p = 0·575). In cohort 2, the prevalence of asexual *P. falciparum* parasitaemia was 68.8% (50 of 160) in the RTS,S/AS02A group compared with 69.4% (49 of 160) in the control group (p = 1.0), i.e. statistically, proportionately just as many in each group became infected with *P. falciparum*.

The authors of the original Lancet paper do not themselves claim a great deal explicitly. They do say things such as "Our results indicate the feasibility of development of an effective vaccine against malaria."[42] And the follow-up paper argues that RTS,S/AS02A is "a promising vaccine candidate and strongly suggests that malaria vaccines have an important role as future public-health instruments." However, the dramatic overblown statements – such as of a 50-70% effectiveness and that a "vaccine could soon be available for malaria to save 1 million lives each year" – came from a heavy dose of watering by politicians.

## *3.2. Control group given unrelated vaccine*

Several correspondents commented on the controls used. The normal scientific methodology is, if at all possible, to vary only one parameter between experiment and control. Ideally, the controls in the trials should have been immunized with HBsAg particles formulated in AS02. Instead, in both the earlier Gambia trial[43] and later Mozambique trial,[44] all control volunteers were given unrelated vaccine(s),[45] except for

[41] Richie, T.L., and Saul, A., 2002, ibid. p699.
[42] Alonso, et al. 2004, ibid. p1419.
[43] Bojang, K.A., Milligan, P.J., Pinder, M., et al. "Efficacy of RTS,S/AS02 malaria vaccine against Plasmodium falciparum infection in semi-immune adult men in The Gambia: a randomized trial." *The Lancet* 2001, Vol. 358, pp. 1927-1934
[44] Alonso, et al. 2004, ibid. and 2005 ibid.
[45] Specifically – in the case of Mozambique – because routine hepatitis B vaccination was introduced into the EPI schedule of Mozambique in July, 2001, children aged 12–24 months had already received hepatitis B immunisation. Therefore, children younger than 24 months received as control vaccines two doses of the

the older Mozambican children who received paediatric hepatitis B vaccine, and in all cases these were formulated in adjuvants *other than AS02*, and, naturally enough, they did develop titres against HBsAg. (Alonso et al. 2004, Table 2). The use of an unrelated vaccine which can benefit the population as a comparator is a standard practice, albeit with limitations. The problem is made more difficult by the complexity of choosing appropriate case definitions.

The justification for doing this would be that giving RTS,S without the malaria component of circumsporozoite – a 'dummy' vaccine having all the attributes of the test article except the specific immunogenic elements – would be unethical, since it would have an unknown, possibly detrimental effect rather than a beneficial one. But if so, some correspondents argued that the authors should have provided some evidence (even from animal models would have helped) that overall stimulation of the immune system and high titres against HBsAg are not likely to confer aspecific protection against severe complications of malaria.[46] At the very minimum, suggested several correspondents, the trial design was limited in this respect.[47] One correspondent argued that this fundamental flaw made the study "rather useless." Another, however, responded: "The trial is not useless but limited for many other reasons. Unspecific protection from these causes would always have been limited. Only a larger trial including under conditions of higher malaria transmission pressure would have been giving clearer results, also on this point."

**Specific versus nonspecific immune responses**

Snounou et al. argue that this raises the possibility that the RTS,S antigen might actually target the particles and the associated adjuvant to the liver because HBsAg possesses a hepatocyte-binding site. More precisely they observe: "The trial outcomes do not, therefore, exclude the possibility that local activation of nonspecific immune responses by this strong adjuvant could have synergized with specific responses to the CSP polypeptide to eliminate the parasite. In this case, as the liver gradually returns to its normal state after the final vaccine dose, the combined ability to inhibit PE development would diminish."[48] One correspondent argued however that no experimental data are provided for this hypothesis either.

One way to settle this issue would to administer the RTS,S–AS02 vaccine when transmission levels are low, and to start follow-up observation later, during the high transmission season.

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seven-valent pneumococcal conjugate vaccine (Prevnar Wyeth Lederle Vaccines, Madison, NJ, USA) at the first and third vaccination and one dose of *Haemophilus influenzae* type b vaccine (GSK Biologicals) at the second vaccination. For children older than 24 months, the control vaccine was the paediatric hepatitis B vaccine (GSK Biologicals).

[46] They point out that overall protection and differences in parasitaemia levels at the onset of first attack are not significant (Alonso, et al. 2004, ibid. Table 3, line 5).

[47] Bojang, K.A., et al. 2001, ibid. Patarroyo, M.E., Amador, R., Clavijo, P., et al. "A synthetic vaccine protects humans against challenge with asexual blood stages of Plasmodium falciparum malaria." Nature, 1988, Vol. 332, pp. 158-161.

[48] Snounou et al. 2005, ibid.

## *3.3. Lack of correlation with antibody titres against circumsporozoite*

In the first Alonso et al. paper, the authors report no waning of the limited efficacy against clinical disease[49] along with the waning antibodies against CS (Alonso et al. 2004, Table 2) – a decay of 75% of antibody level at 6 months – while in the same period the HBsAg antibodies even go up. In the follow-up study, antibodies against CS measured in cohort 1 continued to fall during the follow-up period. Alonso et al. observe that: "In this trial, sustained vaccine efficacy against clinical malaria was observed even though concentrations of antibody against the circumsporozoite repeat region decreased substantially from the peak levels achieved after dose 3. However, nearly two years after having received the first dose of RTS,S/AS02A, antibody concentrations remained nearly 50 times higher in the vaccine group than in controls" [50] (geometric mean titre 14.0, 95% CI 12.5–15.6, compared to controls, 0.3, 0.3–0.3). Concentrations of anti-HBsAg antibody were measured for cohort 2, and in the RTS,S/AS02A group 173 of 176 participants (98·3%, 95% CI 95·1–99·6) remained seroprotected at month 21.

Several observed that this suggests aspecific stimulation of the immune system, and the possibility that the HBsAg antibodies themselves, play a role, rather than CS. From a biological point of view several correspondents argued that it is not conceivable how CS antibodies could protect against severity of disease other than through delaying the onset of the infection and the number of liver stages resulting from one bite, allowing the immune system more time to react to the infection. In addition, if we were looking mainly at aspecific immunity, the chances for a significant benefit of direct boosting of the specific epitope-directed immunity would be low.

However, in the follow-up, Alonso et al. argue that: "These results contrast with the duration of protection seen in malaria-naïve volunteers in the USA and in Gambian adults. They also refute the notion that protection induced by RTS,S/AS02A is mediated by some undescribed, transient, non-antigen-specific mechanism. No significant difference in the prevalence of infection at month 21 was observed in cohort 2, but this cohort differed from cohort 1 in that participants experienced substantially higher malaria transmission and underwent intensive follow-up for detection and treatment of all new infections during the double-blind phase." Several have also agreed with Alonso et al. that the issue of a non-specific adjuvant effect seems a less likely explanation – especially after the most recent data was released.

However, Alonso et al. observe that there is no correlation with antibody titres against CS: "In RTS,S/AS02A recipients, we failed to detect an association between level of CS antibody and risk of malaria."[51] They also concede that the analysis was potentially constrained by the high titres achieved by nearly all vaccine recipients and the possibility that a relatively low threshold protective level of immunity might exist potentially constrained the analysis. But then the authors suggest that even the lowest titres were

[49] Alonso et al. 2004, ibid. p1419: "Waning efficacy over the 6-month observation period was not noted for the primary endpoint when analysed by different methods."
[50] Alonso, et al. 2005, ibid. p2015.
[51] Alonso, et al. 2004, ibid. p1418.

enough, and that – just maybe – non-measured cellular mechanisms were involved. One correspondent argued that "the scientific method would be that the most simple and elegant explanation should be followed until falsified by further experiment, and the correct hypothesis should be that CS antibodies are not involved in the marginal protective efficacy being picked up".

In the follow-up paper, Alonso et al. are a bit more specific, arguing that: "The immunological mechanisms that underlie the observed protective efficacy of this vaccine against clinical malaria are probably complex. The RTS,S/AS02A vaccine was developed to induce both humoral and cellular immune responses against circumsporozoite protein, since preclinical data indicated that both were required for protection against infection...The very low levels of naturally occurring anticircumsporozoite antibodies in the control group confirms the poorly immunogenic nature of native circumsporozoite protein, even with substantial *P. falciparum* exposure. In this trial we did not measure cellular immune responses, but their potential role in protection is well supported by data derived from surrogate animal models as well as from a few clinical vaccine trials. We suggest that the observed vaccine efficacy results from an interplay between cellular and humoral immune responses induced by the vaccine. Both of these mechanisms might be amenable to natural boosting, and could contribute to sustaining vaccine efficacy. Future trials with this vaccine may offer the opportunity to evaluate and better understand the respective roles of these multiple factors in mediating sustained protection against malaria disease."

One correspondent, otherwise supportive of Alonso et al., observed nevertheless that "this [claim by Alonso et al.] is as good a guess as any, but we simply don't have the data to be dogmatic." While, another equally senior figure argued that since sustained vaccine efficacy against clinical malaria was observed even though concentrations of antibody against the circumsporozoite repeat region decreased substantially from the peak levels, and all the evidence pointing to the fact that the antibodies being measured are not the protective mechanism, this: "Indicates clearly that the trial design was deficient – They should have measured cellular as well as humoral responses. Also there should have been an adjuvant control." Another correspondent responded "Absolutely" to this comment and argued that the "Alonso explanation is useless. There are no recognized correlates of protection what so ever. The way to develop them goes via experimental clinical trials, explanatory trials, or hyper-empirical trials."[52]

Alonso et al. observe in the follow-up paper: "Although the efficacy estimate for severe malaria was higher than that for clinical malaria, this difference still could be due to chance. However, other methods of malaria control, such as insecticide treated nets, that could involve reduction in the infecting dose of sporozoites, have also yielded higher estimates of efficacy for the more severe forms of the disease than for the mild forms. This exciting possibility needs to be further explored in the case of this vaccine." One correspondent observed: "This calls for trials evaluating a vaccine in the context of other ongoing interventions. However, since trials are limited in number for various reasons,

[52] The same correspondent who made the observation above starting "The trial is not useless…"

one would need to decide first when a vaccine achieved enough as a single intervention to be evaluated in such a way. Clearly RTS,S is not yet sufficiently developed for this."

## *3.4. Parasite density figures*

At the six month period geometric mean parasite density for RTS,S/AS02A was measured as 2271, and at the 21 month period as 1940. For the control, the corresponding figures are 2513 and 1571. In other words, density in the RTS,S/AS02A cohort started a few hundred lower than the control but ended up several hundred higher than the control, and the control group density fell by 1000, while RTS,S/AS02A fell only by about 300. This contrasts with the observation that "At month 21, prevalence of *P. falciparum* infection was 29% lower in the RTS,S/AS02A group than in the control (p=0·017),"[53] since 'infection' refers to something else. In a much bigger study (such that these figures had statistical meaning), this would suggest that the RTS,S/ASO2A group are suffering less, but that they are carrying more parasite load at the end.

One correspondent argued that from a co-evolutionary perspective this would generally be interpreted as bad news for the greater human population. Another pointed out that drug resistance is more likely to develop when parasite numbers in an individual are high, affecting how one interprets a combined package of measures involving a vaccine that does this alongside malaria drugs. However, another argued we did not have the luxury of ruling out use of vaccines *even if* this was the case – that we simply cannot wait until we have all the science in place. Nor, it was further argued, do we have the benefit of science to rule out that this co-evolutionary and resistance thinking may not be a significant effect anyway; it was pointed out that such worries in the case of insecticide-treated mosquito nets had delayed their mass roll out even though the worry had proven unfounded.

**Measurements of parasitaemia are imprecise anyway**

However, estimates of parasitaemia are subject to wide variation. They are, as one correspondent put it "notoriously imprecise". The mature dividing form of the organism sequestrates in the deep tissues, with only the young, so called ring forms seen on blood smears. This means that one should not really read too much into the parasite density figures for the two cohorts: "To all intense and purposes, they are the same." On reading this, one correspondent went a bit further: "They are indeed the same." But this creates another problem. Given that the parasite densities between RTS,S/ASO2A recipients and controls are in effect the same, how does one read in to the efficacy figures when generated on a definition such as: "fever and parasitaemia > 2500/ μL"?

**No statistical difference in geometric mean parasite densities**

Another correspondent observed: "At the first press conference in connection with the first publication in Lancet, the lack of statistical significant difference in geometric mean parasite density was commented on. The authors simply stated that the primary end point for efficacy is delay or absence of clinical malaria [defined as "first or only episode of fever and parasitaemia >2500/μL"], and that the study was not designed to test density

[53] Alonso et al. 2004, ibid. p1418.

differences. The reported decline in parasite density in the two groups is compatible with age related increase in exposure and gradual increase in the ability to control parasite multiplication [The average age at month 8.5 of the trial was 44.5 months, and at 21 months was 56 months]. It is indeed disturbing that the density decreases more in the control group. It could be loosely interpreted that the control group was more capable of controlling asexual parasitaemia, which causes the disease, than the immunized group (because of the immunization), but this would require specialist statistical analysis. I think this deserves real discussion. The dogma is that children in endemic areas can first control death, then disease and finally parasites. I fully agree with [the] worries that the mean densities are fairly similar, and what is then the judgment call?"

However, another correspondent, themselves arguing that the difference are not statistically significant, observed that "It's irrational to 'be disturbed' by differences that are not statistically significant at any reasonable value of alpha. One can only conclude that belief is not based on observation in such cases," and that "I don't know of any statistical analytic approach to address this question. It can only be addressed by increasing the power of the analysis by increasing the number of observations. This will happen as additional trials are performed."

One correspondent, after a life-long career in malaria observed: "Truly, the differences in the two arms of the study before and after vaccination are totally unremarkable...i.e., they in no way signal an effect of any kind," and that, spelling it out for the educated layman: "To put it in more precise terms, I would be very surprised that if the 95% confidence intervals [of the parasitaemia] values were available (and they could be calculated from the information that is available) they did not overlap extensively both in the case of the two 8.5 month data points and in the case of the two 21 month data points. Roughly interpreted, this could be taken to indicate that there is less than 1 chance in 20 that there is a difference in the true mean parasite densities in the two arms at either time. In fact, I'd expect the confidence intervals for all four data points to overlap, although I would be less surprised if the 8.5 and 21 month intervals did not (i.e., if the mean values were statistically different). Of course if the values were different at 8.5 vs. 21 months, this could be attributed to seasonal difference in transmission, etc. and isn't relevant to the questions being addressed. To further illustrate the point, the published P value for a difference between the 8.5 month data points is 0.699 and for a difference between the 21 month data points, 0.575. These values are estimates of the probabilities that the observed difference occurred by chance. Any P value > 0.05 is usually taken as the point at which observed differences are not indicative of true mean differences in the populations under study. None of this is to say that there are no differences...only that the evidence does not suggest that there is. A statistician would probably not think I have expressed this exactly correctly, but would agree with the overall conclusion!"

## *3.5. Case definition*

Clinical malaria was defined in the Alonso et al. study according to the first definition, of "fever and parasitaemia > 2500/μL." Fever and parasitaemia below this level could be due to one of a variety of bugs, not just malaria parasites. As one correspondent put it:

"Lots of kids are walking around with malaria parasites and no clinical symptoms. Hence the need for debate." While another noted: "There is no agreed marker of vaccine protection in malaria; Alonso is using a surrogate of his own after having used another one (fever) in earlier studies. Since the results are interesting and important but far from overwhelming, it is not a surprise that the surrogate marker used here, i.e. parasite density, is also not giving very clear information. All the measurements are probably true but all the data correlations discussed cannot change anything in the modesty of the results…Since there are no agreed correlates of protection, I wonder how a regulatory agency can give the label malaria vaccine to the RTT,S product even if it is the most advanced prototype." Another correspondent observed that "An alternative would have been to have set up a complex of parameters and compare the values via spectral statistical analysis".

**The inherent difficulties of case definition**

And yet another observed that: "The problem of case definition is a very difficult one. In the context of this discussion it may be worth noting that fever is arguably a marker for illness; i.e. most people with fever don't feel good. On the other hand, parasite density is a marker for the etiology of that illness. If the vaccine protects from fever (i.e. illness) it is providing benefit. But since a malaria vaccine won't prevent all fevers, in order to have maximum specificity (essential to detect vaccine efficacy) the fevers not due to malaria must be removed from the tally. In practice, the cutoff density is chosen to maximize specificity."

Obviously one of the hurdles to avoid is that of data mining. One form of data mining happens when lots of equations/regressions are run on a set/series of data. Each result on its own generates a 95% confidence interval. However, these confidence intervals only make sense if the choice of equation/regression to run is truly random. If after a range of equations/regressions are run, the data handler chooses the one most supportive of their result, the 95% confidence interval it generates means nothing.[54] The story is similar if a range of measures and markers are tried and then one is chosen from the set. We presume, for example, that when Alonso et al. say "We also determined VE [vaccine efficacy] for other case definitions and for episodes of severe malaria,"[55] that they reported all the findings,[56] and the chosen surrogate marker was also truly random.

A further correspondent observed: "You would think that the definitions would be objective enough so there would be few occasions where a judgment call would be needed. But these things happen with some frequency in clinical trials. There could have been plain mistakes or there could have been borderline parasite counts which changed the category on final analysis." Another observed: "There will inevitably be cases that will be classified in one category or the other when in fact the density figures are so close to the cut off that a repeat reading could easily go the other way. The saving grace is that

[54] For three meanings of data mining, see Hendry, D.F., *Dynamic Econometrics: Advanced Tests in Econometrics*. Oxford University Press, 1995, pp. 544-555.
[55] Alonso et al. 2005, ibid. p2012.
[56] To this untrained eye, it seems that they do report all.

in a study with adequate numbers of subjects the "noise" will on the average be the same in different study arms and such borderline cases will cancel each other out."

All hospital admissions were independently reviewed by two groups of clinicians, with discrepancies resolved in a consensus meeting before the database of the single-blind phase was locked.[57] It would be interesting to have more details about the numbers of borderline cases. One might imagine that with parasitaemia the same, the results might be more than usually sensitive to the details of how cases were allocated. We know, for example, that the candidate vaccine was 15 times more likely to cause injection-site swelling of more than 20mm (swelling after 224 doses for the candidate vaccine, or 7.7%, versus swelling after just 14 doses, 0.5% of the control). Do otherwise trivial signs become more significant when half of the definition of the end point is effectively non-operative?

**End points based on elevated temperature?**

Another correspondent (head of another vaccine initiative) puzzled: "I'm getting more and more puzzled when I study the results of the RTS,S vaccine trials. Efficacy is determined by recording clinical cases (over time/the observation period) and clinical cases are defined based on parasite density and elevated temperature. There is no difference in geometric mean parasite density. The difference between the RTS,S and control groups is thus the number of cases with elevated temperature!! Strange." Thus, an endpoint based, for example, on "time to first clinical episode of symptomatic *P. falciparum* malaria" becomes, on average, "time to first presentation of a child to a health facility with an axillary temperature of 37.5°C, with a decision made by clinicians as to which of the many possibilities, including malaria, is inflicting the child".[58]

**Analysis suggesting that measured efficacy heavily dependent on case definition**

Recent analysis demonstrates how reported efficacies from vaccine trials may depend heavily on the clinical case definition used. The dependence is particularly striking for diseases such as malaria, in which no single case definition is appropriate. Rogers, et al.[59] used logistic regression modeling of the relationship between parasitaemia and fever in data sets from Ghanaian children. They determine the fraction of fevers attributable to malaria and model how the choice of a threshold parasitaemia in the clinical case definition affected the measured efficacy of malaria vaccines. They found that calculated clinical attack rates in their data sets varied 10-fold as a function of the threshold parasitaemia. Most striking of all, measured vaccine efficacies in reducing clinical malaria depended heavily on the threshold parasitaemia, varying between 20% and 80% as the threshold varied between 1 and 5000 parasites/μL: "We suggest that clinical case

[57] Alonso et al. 2005, ibid. p2013.

[58] It wasn't clear to this author how the specific roles of the location of health facilities in cohorts 1 and 2, and the passive case-detection in one and the mix of passive and active in the other were dealt with. But this may be more an indication of this author's ignorance. Adjusted vaccine efficacy included adjustment for distance to health centre.

[59] Rogers,W.O., Atuguba, F., Oduro, A.R., Hodgson, A., Koram, K.A., "Clinical Case Definitions and Malaria Vaccine Efficacy" The Journal of Infectious Diseases, electronically published 27 December 2005, Vol. 193, pp. 467-473, www.journals.uchicago.edu/JID/journal/issues/v193n3/35118/35118.html.

definitions of malaria that incorporate a threshold parasitaemia are arbitrary and do not yield stable estimates of vaccine trial end points."

However, Rogers et al. also observe that their models are not directly applicable to a preerythrocytic-stage vaccine such as RTS,S. Although, they say, it is possible that there was a differential effect of the RTS,S vaccine on severe disease, compared with that on mild disease, "the different efficacies for mild and severe malaria may result from differences in the sensitivity and specificity of case definitions for mild and severe malaria. Validation of the models presented here will depend on analysis of the results of large-scale field trials of blood-stage vaccines."

One general conclusion reached elsewhere in this report, is that if there had not been such a need just recently to make one study so salient and even to have it hyped by politicians and in the media, perhaps normal scientific debate about its limitations, and the evidence still needed to make a conclusion, would have been encouraged in the public eye, and critical observations would have treated as no more than normal scientific skepticism, rather than as a challenge to what politicians are wanting to do?

## *3.6. Duration of response*

At first there was some concern about the length of duration of response achieved. Smith and Milligan,[60] before the 21 month data were made available, pointed out that the evidence of a protective effect against malaria infection in the earlier trial in adults in The Gambia lasted for only 2–3 months, and that the new data were compatible both with sustained protection over 6 months, but also with there being little protection against clinical malaria or malaria infection for more than 3 months after vaccination. Referring to Alonso et al. 2004, Figure 4, they noted that among those who had not developed clinical disease by 3 months after vaccination, the risk of an episode of malaria in the next 3 months was similar (about 7%–8%) whether in the vaccinated or unvaccinated groups. The risk of acquiring infection by 6 months among those not infected at 3 months was also similar in both groups (about 65%). Also during the 6-month period, the numbers of children infected were similar (157 and 166, respectively). Additionally, they argued that there was little evidence of protection against clinical episodes of malaria other than the first; indeed, after a first episode, the rate of subsequent episodes was slightly higher in the vaccinated group than in the unvaccinated group. This can be calculated from Alonso et al. 2004, Table 3: In the vaccinated group there were 30 episodes in 19.4 person years at risk, PYAR, generating a rate of 1.5 per year. In the unvaccinated group there were 31 episodes in 27.2 PYAR, generating a rate of 1.1 per year.[61] [62]

[60] Smith, P., Milligan, P., "Malaria vaccine: 3 or 6 months' protection?" *The Lancet*, 2005, Vol. 365, pp. 472-473.

[61] Smith and Milligan also pointed out that though the prevalence of parasitaemia at month 8.5 months was lower in the vaccinated group than in the unvaccinated group in both the cohort followed up for clinical episodes and the cohort followed up for incidence of infection is consistent with a lasting protective effect of the vaccine, this is not strong evidence of such an effect because the prevalence of parasitaemia would have been affected by the early effect of the vaccine and also by drug treatments, which would have occurred later in the malaria vaccine group than in the controls.

Smith and Milligan were at pains to point out that: "These observations are not intended to detract from the importance of the finding of the overall protection conferred by the vaccine during the follow-up period, including against severe malaria, but they do emphasize the importance of the continued follow-up of the trial population to examine longer term protection, as is planned by Alonso and colleagues."

In the Alonso et al. follow-up, the authors however observe that "By contrast [to Smith and Milligan], the results of this extended follow-up show that vaccine efficacy did not wane and that protection against clinical malaria lasts for at least 18 months after vaccination with RTS,S/AS02A. These findings are further reinforced by the significant difference between RTS,S/AS02A-vaccinated people and controls in the prevalence of infection seen in this same cohort at the last cross-sectional survey towards the end of the high transmission season. These results contrast with the duration of protection seen in malaria-naïve volunteers in the USA and in Gambian adults. They also refute the notion that protection induced by RTS,S/AS02A is mediated by some undescribed, transient, non-antigen-specific mechanism. No significant difference in the prevalence of infection at month 21 was observed in cohort 2, but this cohort differed from cohort 1 in that participants experienced substantially higher malaria transmission and underwent intensive follow-up for detection and treatment of all new infections during the double-blind phase."

One well-respected correspondent, considered neutral perhaps, observed "The new results are convincing that protection is sustained for many months and, as this has happened in the face of declining antibody levels, it is possible that protection may continue for longer. These new results need detailed scientific scrutiny during the coming months, and some flaws may emerge, but on the face of it they look to be convincing."

## *3.7. Protective efficacy that is not strain specific*

In another study (before the recent Mozambique phase IIb trial) Alloueche et al.[63] explored whether RTS,S/AS02 has a protective effect only against parasites with a CSP sequence similar to that of NF54.[64] Samples of parasites from breakthrough infections in control and vaccine groups from a trial in semi-immune Gambian adults were genotyped at two polymorphic regions of the CSP gene encoding T cell epitopes (csp-th2r and csp-

[62] Vaccines against pre-erythrocytic stages are designed to prevent blood infection and so the true measure of vaccine efficacy is the induction of sterile immunity, based in the Gambian and Mozambican trials on the time to first parasitaemia as detected by microscopy. However, Snounou et al. (2005, ibid.) also pointed out that by the end of the 6 month observation period, the cumulative numbers of control and vaccinated volunteers who developed a parasitaemia did not differ significantly (72% versus 66%, respectively, after four months in the Gambia, and 93% versus 83%, respectively, after six months in Mozambique).

[63] Alloueche, A., Milligan, P., Conway, D.J., Pinder, M., Bojang, K., Doherty, T., Tornieporth, N., Cohen, J., Greenwood, B.M,, "Protective efficacy of the RTS,S/AS02 Plasmodium falciparum malaria vaccine is not strain specific." *Am J Trop Med Hyg*, 2003, Vol. 68, No. 1, pp. 97-101.

[64] Remember that the RTS,S/AS02 is a recombinant protein malaria vaccine that contains a large portion of the C-terminal of the circumsporozoite protein (CSP) sequence of the NF54 isolate of *P. falciparum* fused to the hepatitis B virus surface antigen.

th3r) to determine if the RTS,S/AS02 *Plasmodium falciparum* malaria vaccine conferred a strain-specific effect. They found that the overall distribution of CSP allelic variants was similar in infections occurring in both the vaccine and the control groups, although the vaccine had a marked effect on the incidence of infection. Indeed, the mean number of genotypes per infection in the RTS,S/AS02 group was not reduced compared with the controls. As Alloueche et al. observe "This study demonstrates that RTS,S/AS02 protected Gambian semi-immune adults against *P. falciparum* infections in a non-allele-specific manner." In their own words (for the more scientifically minded amongst the readers):

"If RTS,S/AS02 had an allele-specific effect, a reduction in the prevalence of the *csp-th2r*03* and *csp-th3r-03* alleles should have been observed. Given the prevalence of the *csp-th3*03* allele (35%) and the sample size in each group, the study had 99% power to detect a two-fold allele-specific effect of RTS,S/AS02. Since the prevalence of the vaccine type at *th2r* (*csp-thr2*03*) was 16%, the study had 60% power to detect a two-fold effect at that locus. Thus, the statistical power was very high for *th3r* and reasonably high for *th2r*, so the lack of an allele-specific effect is well supported."

This suggests the RTS,S/AS02 vaccine candidate should be tested in transmission settings where the NF54 strain is not the predominant type.

Alloueche et al. then explore another possibility, that RTS,S/AS02 reduced the genetic complexity of infection. They assessed this by investigating typing of unrelated polymorphic loci. Differences in multiplicity were found between villages, suggesting local variations in the level of transmission, and these correlated with parasite density. As they put it: "Although the vaccine reduced the incidence of infection, it did not reduce the multiplicity per infection compared with the controls. A liver stage vaccine would be expected to induce a reduction or no change in the number of genotypes depending on whether it was strain-specific, but this was not observed in this study," and yet overall vaccine efficacy was still maintained at 34% at the end of the follow up-period in the samples they used.

## *3.8. Worries about the statistics and the nature of what is happening*

Some correspondents argued that Alonso et al. used "clever statistics" to hide the fact that they were studying an essentially marginal effect. Vaccine efficacy in extending time to first infection was determined in cohort 2. The argument made by these critics is that having found a slight but statistically significant decrease in the numbers of children experiencing at least one clinical episode of malaria in the 6 month study period after the last dose in the first study – 323 children had first episodes of asexual *P. falciparum* parasitaemia, of which 157 were in the RTS,S/AS02A group and 166 were in the control group – they manage to achieve with parasitaemia related parameters an estimated vaccine efficacy for extending time to first infection of 45%.[65]

[65] 95% CI 31.4-55.9; p<0·0001; Alonso et al. 2004 ibid. Figure 4 and Table 3.

At the same time, like others critical of the results, they also point out that there is little indication that significant reductions in parasite densities occurred in the RTS,S-vaccinated children. Indeed, there is no difference between the groups in geometric mean parasitaemia when looking at first episodes of malaria. Nor did the incidence of first episodes associated with hyperparasitaemia (>100,000 parasites/μL) differ between the two groups: "This suggests that a mere numerical reduction in the inoculum (i.e. a delay in the prepatent period) is unlikely to account for a reduction in peak parasitaemia and, possibly, severe disease incidence. This seems to indicate that the onset of malaria in vaccinated children is somewhat delayed and the severity might be slightly reduced, which is an interesting enough finding in its own right, but, this is nowhere near what the press and political coverage would indicate."

Another correspondent observed that if, the average number of infective bites per child in the study period was around 15[66] and the CS titres, maybe helped by the alerted immune system per se and other factors induced by an also 'liver specific antigen' from HepB in the vaccinated group, have reduced the number of sporozoites that made it to the liver intact by, say, 50%, this alone would be capable of explaining all the observations made. This would not even require an additional role for overall immune stimulation and aspecific or HBsAg related effects during the blood stage infection.

On this correspondent's rather glum interpretation, the vaccine targets the massively produced smokescreen antigen on the sporozoite (that has fooled the immune system for millennia) and it helps to keep the number of liver stages below threshold. The recipient is denied, say, half of the little bit of liver stage based protective immunity during the period of elevated immune system response and CS antibodies killing half of the sporozoites during transition to the liver. Then, it helps to delay the onset of clinical problems, hence treatment and death of the patient, so that the parasite gets even more time to make gametocytes and spread to the next host.[67] That is, after all, its evolutionary goal. Indeed, unlike *P. vivax*, *P. falciparum* has only recently adapted to humans and, unlike *P. vivax,* still has to find a way to deal with the problem of mortality. On this correspondent's interpretation, the vaccine helps to overcome this problem for the parasite. The issue then is what are the consequences for individuals and for the greater population. From a commercial point of view, observed this correspondent, vaccines that are marginally protective in this way might be part of a solution (involving revaccination and drugs) for tourists and soldiers, but it was less clear they would be suitable for the purposes intended here. This was also the concern of a leading medical ethicist.[68]

One other concern was the way that dramatic-sounding figures can be driven out of very small actual numbers. For example, vaccine efficacy in extended time to first infection of 45% was determined in cohort 2 (95% CI 31.4-55.9; p<0001, Figure 4 and Table 3 of

[66] As suggested by Alonso et al. 2004, ibid. p1412.
[67] Indeed, we have long had evidence that the burden of morbidity could simply be shifted. A unique set of experiments dating back to the Second World War showed that a reduction in the number of inoculated *P. falciparum* sporozoites by at least 90% simply led to a two- to three-day increase in the prepatent period, with no alteration in the course of the primary infection. Fairley, N.H., "Sidelights on malaria in man obtained by subinoculation experiments." *Trans. R. Soc. Trop. Med. Hyg.* 1947, Vol. 40, pp. 621-676.
[68] I would give the person away without their consent if I said more than this, and this would be unfair.

Alonso et al. 2004). This came from 157 children in the RTS,S/ASO2 group and 166 in the control group with first episodes of asexual *P. falciparum* parasitaemia.

## *3.9. Problems in generalizing results to all potential users and infants*

The study excluded children who were malnourished, had a history of allergic disease, had a packed-cell volume less than 25%, exhibited clinically significant acute or chronic disease, such as HIV that we know may lead to poor immunogenicity and reduce vaccine effectiveness,[69] or displayed abnormal haematological or biochemical characteristics. The results are therefore not immediately generalizable to populations having such features. This is normal for a phase 2 study. These sorts of issues will be addressed in phase 3 and especially in the phase 4. The concern here however is with the way some of these important caveats are missing from the political and media coverage of these issues.

It would be useful, nevertheless, to see the population from which the sample was drawn before these exclusions were made. If Alonso et al. hardly had to do anything to the original population to get the sample, then this would be interesting to know in its own right. And it would be further useful to compare the actual sample used with typical populations where this potential vaccine would be used. Though ignoring these features is reasonable at such an early stage of vaccine development, some correspondents felt that more information on this would be helpful to decision makers – and for media and political coverage – even at this stage. One correspondent observed that it would be very valuable to know "who were excluded. For what reasons?" Another observed "I'm sure the data exists. We should ask Pedro [Alonso]."

**Efficacy did not significantly change with decreasing age**

There is one generalization that is hinted at. In the first paper, Alonso et al. observe that: "No interaction was recorded between age and vaccine efficacy, suggesting that efficacy did not change with increasing age." [70] Further exploratory analysis was done in the first paper on subgroups which suggested that vaccine efficacy might be higher in the youngest children. In the follow-up paper, however, Alonso et al. report (twice) that: "We noted no evidence of an interaction between age at first dose and VE, suggesting that efficacy did not significantly change with increasing age,"[71] and there was no subgroup analysis. The quotes in the second paper, and the lack of subgroup analysis, suggest there was lack of *significance* in any analysis Alonso et al. tried to do to find any age-related effect.

These quotes could, of course, be read the other way too – that efficacy did not significantly change with decreasing age, i.e. that efficacy rates were similar for 1 year

[69] One correspondent wondered about haematological examination included CD4 counts instead of HIV testing.
[70] Alonso et al. 2004, ibid. p 1418.
[71] Alonso et al. 2005, ibid. p 2015, and again on 9 2016

olds and 4 year olds (referring to age at the start of the trial).[72] Alonso et al. seem to be hinting that the effect will not be much higher for infants – unless there is some discontinuity at, say 6–12 months. We know that if the Alonso et al. figures are sound there *has* to be some discontinuity somewhere higher up the age range, given that there is constant rate of efficacy up to 4 years, but that, eventually, this drops dramatically: "Results from previous trials of RTS,S/AS02A in malaria-naïve volunteers or hyperimmune Gambian adults suggested that protection against infection induced by this vaccine might be short-lived."[73]

This is not inconsistent with a story of some sort of boosting effect to the acquisition of natural immunity (and hence with the loss of efficacy at a higher age). The Alonso et al. data suggest a linear stretch with age – then at some point a collapse; though there is no story yet to explain this. Similarly, if there is no statistically significant change in efficacy with age, this also raises issues when it comes to visualizing boosting efficacy for those of the youngest age, since this would seem to imply an ability to shift the schedule for *all* ages, when we already know that efficacy has to collapse at some age, such that the shifting of the schedule for all ages would seem to create ever-increasing conflict with the need for efficacy to collapse at some age. Having efficacy rise as children get younger would have been a very useful finding. One correspondent observed that this reiterates also that the acquired immunity developed by children as they get bitten is not the same as that conferred by the vaccine, and that this backs up the previous observation that the antibodies directed to this vaccine and to those of the naturally acquired sporozoites with CS on their surface, are not the same.

Several correspondents were very struck by the revelation that there is no statistically significant age-related difference in efficacy. But another correspondent observed "What will happen from here on out is anybodies guess. Mine is that the differences observed will persist. This is because IMO the best explanation for the persistence is that the vaccine has given the kids a jump start on developing naturally acquired immunity." Alonso et al. indeed argue that "First, the vaccine was much more immunogenic in this study population than it was in adults, and sustained immune responses might have resulted in persistent protective efficacy. Second, the high level of sporozoite exposure that happened during this trial could have resulted in natural boosting of protective immune responses not revealed by antibody measurements."[74]

**Another problem in generalizing the result**

Snow et al[75] find that the risk of death after a clinical attack of *P. falciparum* is much higher in Africa than in South East Asia and the western Pacific. They argue that the incidence of severe, life-threatening complications of *P. falciparum* malaria in Africa is at least tenfold that in similar malaria endemic areas in India and Vanuatu. Why this is so

[72] At the same time: "For both circumsporozoite and HBsAg, immunogenicity of the vaccine was greater in children younger than 24 months of age." Alonso, et al. 2004, ibid. p1416.
[73] Alonso et al. 2005, ibid. p2016.
[74] Alonso et al. 2004, ibid. p 1419.
[75] Snow, R.W., Guerra, C.A., Noor, A.M., Myint, H.Y., and Simon I. Hay, S.I., "The global distribution of clinical episodes of Plasmodium falciparum malaria." *Nature*, 2005, No. 434, pp. 214-217, www.nature.com/nature/journal/v434/n7030/full/nature03342.html.

is not clear, but Snow et al. suggest that it might include better access to prompt treatment and some cross-*Plasmodium* species protection against severe disease outcomes.

Alonso et al. point out that there was "intense follow-up and early management of disease"[76] during the trial, unlike what would be typical in field use. Indeed, this was given as one reason – along with the fact that the average age of recipients was 3 years at commencement of the trial[77] – for why the incidence of anaemia was low in both cohorts.[78] One correspondent pointed out that in this context there is an additional sociological/health systems problem potentially offsetting a low efficacy malaria vaccine in resource-poor settings and under conditions much less ideal than those of a vaccine trial, and that may lead to slower access to treatment, slower response of parents, and more deaths. As the correspondent observed, telling (low literate and illiterate and innumerate) mothers in some of the poorest areas of the world that their child is now vaccinated against malaria along with a range of other diseases (with the various different percentages for malaria enumerated) will have a negative effect on their alertness for malaria over the following months. Key to treating severe malaria and preventing the death of a child from malaria is diagnosis and access to treatment within 48 hours. As this correspondent pointed out, how do you tell the mother of a child vaccinated against malaria that she still needed to bring her child for treatment at first signs of symptoms?

**Anaemia**

Similarly, by the time the average age of the recipient is in the target range for EPI (and not the current average age of 3 years at first dose) the trial will be back into "the high-risk window when anaemia is a frequent complication of *P. falciparum* infection,"[79] with this aggravating the result. Again, this has yet to be faced. Alonso et al. comment that the rates of anaemia during the study were much lower than expected. Indeed, this "surprised" them.[80] They observe that at 21 months none of the 649 children in the RTS,S/AS02A group and only two of the 663 in the control group had anaemia ($p = 0.5$).[81] This is very low, and also partly related to the average age of the children being 3 years at commencement of the trial, and hence approaching five years towards the end of the trial, with many therefore out of the high-risk window for anaemia.

This limited the ability of the trial to detect significant vaccine efficacy for that endpoint: "Intense prompting of mothers or guardians to take their children to health facilities early in the disease process might have ensured prompt treatment of malaria cases and reduced the incidence of anaemia." Similarly, a switch in Mozambique in November 2002 to a more effective first-line treatment for malaria meant that "children who received these

[76] Alonso et al. 2005, ibid. p2021.
[77] Alonso et al. 2005, ibid. p2021 "This low rate of anaemia is probably the result of intense follow-up and early management of disease and the fact that as children get older, they leave the high-risk window when anaemia is a frequent complication of *P. falciparum* infection."
[78] This would also have affected the definition of severe malaria, which was a composite of measures including severe malaria anaemia. At 8.5 months the prevalence of anaemia was 0.29% (2/692) in the control group versus 0.44% (3/688) in the vaccine group (p=0.686).
[79] Alonso et al. 2005, ibid. p2016.
[80] Alonso et al. 2004, ibid. p1419.
[81] Alonso et al. 2005, ibid, p2016

drugs had more rapid clearance of parasites, less recrudescence, and therefore shorter duration of infections than did children who did not receive these new drugs. Each of these interventions could have had an effect on the recorded incidence of anaemia."[82]

**GSK**

One correspondent explained: "It is certainly true that a malaria vaccine trial has two objectives at least: First, to provide high quality data supporting licensure and, second, to provide experimental data of reliable quality. In contrast to other vaccines where clinical trials are conducted to deliver data related to specific laboratory values showing the build-up of an immune response, this is elusive for a malaria vaccine as no agreed parameters on biological correlates of protection from the disease exist: The parasite biology, and the immune response to it since the disease features are too complex. This explains why the GSK trials have so many supporters, as they help to advance the scientific debate and provide data on which others can capitalize. However, GSK has taken a step further. They believe that there is no alternative to their product and that trials have to continue with more and more younger aged children so as to cover the most vulnerable part of them (the group where mortality from malaria is highest). However, there are increasing challenges regarding the understanding of the immune response in very young children including RTS,S in a mixture of EPI vaccines.[83]"

## *3.10. Keeping the malaria vaccine playing field open and level*

Why are these issues and counter-issues important? And why must we cross-examine things in this way? Mainly because the parasite is very 'clever'. Just over half (948) of the proteins detected in proteome analysis[84] of *Plasmodium* have been found in one stage only, suggesting that stage-specific specialization is substantial. However, many of these stage-specific proteins are found to belong to protein families whose expression is *strategy-specific*, reflecting both conserved mechanisms of parasite development between different stages and subtle molecular adaptations dictated by specific parasite-host interactions. The evolutionary goal of the parasite is, after all, not to make as many parasites as possible in one particular host and risk killing the host.

Instead, by injecting only very few sporozoites per bite, the number of liver stages can be kept low, since these are mainly responsible for triggering pre-erythrocytic immunity. Even for appropriately activated T-cells, few parasites are difficult to find in the enormous liver. So, by keeping the numbers of liver stages lower, time to onset of first parasitaemia and the moment of reaching clinically relevant levels of parasites in the blood can be delayed too, and the course of infection and the onset of severe

[82] Alonso et al. 2004, ibid, p1419.
[83] The correspondent continued, observing that some of these issues are presently addressed by regulatory authorities.
[84] Hall, N., Karras, M., Raine, J.D., Carlton, J.M., Kooij, T.W.A., Berriman, M., Florens, L., Janssen, C.S., Pain, A., Christophides, G.K., James, K., Rutherford, K., Harris, B., Harris, D., Churcher, C., Quail, M.A., Ormond, D., Doggett, J., Trueman, H.E., Mendoza, J., Bidwell, S.L., Rajandream, M-A, Carucci, D.J., Yates, III, J.R., Kafatos, F.C., Janse, C.J., Barrell, B., Turner, C.M.R., Waters, A.P., Sinden, R.E.,
"A Comprehensive Survey of the *Plasmodium* Life Cycle by Genomic, Transcriptomic, and Proteomic Analyses." *Science*, 2005, Vol. 307, Issue 5706, pp. 82-86.

complications can be delayed. The immune system gets more time to react. Natural premunity to malaria is a delicate balance between the parasite and the immune system where small changes can disturb the balance and lead to clinical manifestations in previously premune people, and an overall, aspecific stimulation of the immune system can significantly alter the course of a single malarial infection.

In a new layer of parasite-human interaction, the risk is that some advocates and politicians may respond in just the way the parasite (if it had a 'strategy' and a PR exercise) would want them to, by issuing astonishing statements such as that this result may "suggest that developing a malaria vaccine may not be as technically difficult as many had previously thought,"[85] that "fundamental scientific puzzles do not still bedevil efforts to design and develop malaria vaccines,"[86] that "a life-saving vaccine could soon be available for malaria,"[87] and, even, that we have "a vaccination to prevent malaria that could be ready in three to four years time,"[88] and then lobbying hard for funding structures pitched towards these early outcomes.

**No evidence things have got easier, even as the high efficacy goal is pushed off**

This author finds no evidence for the Berndt et al. claim that the Alonso et al. trials have radically altered the time-frame to a highly efficacious malaria vaccine, or reduced the cost of reaching that vaccine. Indeed, the Malaria Vaccine Vision Statement goal was that "By 2015, we will have significantly reduced death and illness in young children in sub-Saharan Africa due to the successful development and introduction of an affordable malaria vaccine." During the Roadmap process, and even as the Alonso results were being reported, the ultimate high efficacy goal was pushed off till 2025.

As Van de Perre and J-P Dedet observe in their accompanying article to the original Alonso et al. paper: "In any case, the road toward a safe and efficient malaria vaccine being available and useable on a large scale, or even incorporated into an expanded programme of immunization, will be long and chaotic. Thus, for many decades ahead, the expansion of preventive and therapeutic strategies, including those new ones with an evident added value (e.g. insecticide-impregnated bed nets and treatment with artemisinin-containing regimens) should remain an utmost priority to stop the malaria hecatomb. In parallel, new drug developments are also needed to face the worldwide extension of resistance by *Plasmodium* spp. More than ever, infants, young children, and pregnant women, who are heavily affected by the direct and indirect consequences of malaria in endemic areas, deserve worldwide scientific, political, and financial commitment. Such commitment is a question of equity, of human rights, and of disease exposure for half the inhabitants of our planet."[89]

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[85] Berndt et al. 2005, ibid.
[86] A corruption of a quote made in the Tremonti, G. Background Papers (p25) that suggests that fundamental scientific problems are no longer an issue in the case of malaria.
[87] Gordon Brown, The Guardian, 11 January 2005, www.guardian.co.uk/comment/story/0,3604,1683463,00.html.
[88] Gordon Brown, www.hm-treasury.gov.uk./newsroom_and_speeches/press/2004/press_94_04.cfm.
[89] Van de Perre, P., Dedet, J.P., "Vaccine efficacy: winning a battle (not war) against malaria." *The Lancet*, 2004, Vol. 364, pp. 1380-1383.

**The dangers of policy distortions**

One former malaria biology and vaccine expert[90] when asked to react to the current situation and after reading the paper on the Mozambique study very carefully, described the eagerness with which policymakers and politicians so desperately need something – anything – that they "look where the light is, not where they lost their keys," and that maybe "public pressure on malaria vaccine research is driving researchers into a desperate mode where they cannot afford the same scientific rigor that they would have if as few people died from malaria as from more lucrative diseases." One correspondent responded to this observation with his/her own observation that: "It is more a problem that the increased attention to malaria has attracted more policy-hacks, overeager to appropriate themselves with a substantial chunk of the policy debate."

Past vaccine failures suggest extreme caution in over-hyping one particular vaccine candidate over all others, and in supporting apparently simplistic solutions to the problem. We saw this excess optimism before with respect to previous candidate malaria vaccines, such as SPf66 that after much attention proved ineffective in infants in Africa. These had plenty of hype, just no chance of the sort of large new financial payments now being floated for RTS,S/AS02A.

We also run the danger of repeating the mistakes that led to rotavirus vaccines still being unavailable in poor countries today: Glass et al. put it thus: "As the world waited for the rhesus vaccine to become a successful global product, other vaccine manufacturers were reticent to push vigorously ahead, knowing that they would arrive late to the market. They anticipated difficulty in testing their new vaccines when a licensed product was already universally recommended…The lesson from the withdrawals of the first two rotavirus vaccines is that we should never count on developing one candidate vaccine alone. If multiple candidate vaccines had been tested simultaneously, at least some of these might have survived the development process and be licensed and used today."[91] The whole Glass et al. article is worth reading and reflecting on for the case of malaria, since it suggests that there were complete other histories for rotavirus vaccines that were missed because of poor policy at the time.

**A long way to go still…**

When Alonso et al. observe that "Our results indicate the feasibility of development of an effective vaccine against malaria,"[92] this statement relates, as one correspondent put it "only to the experimental validity, and not to the validity of their trials as part of a clinical-industrial development process…The exercise to find more long-term protected children is huge and better data than those provided by Alonso lately would require a

[90] Personal correspondence.
[91] Glass, R.I., Bresee, J.S., Parashar, U.D., Jiang, B., Gentsch, J., "The future of rotavirus vaccines: a major setback leads to new opportunities." *The Lancet,* 2004, Vol. 363, pp. 1547-1550. One correspondent observed that "Actually, this is what happened in effect, only that companies were not loquacious about it and it took some time for them to bring their products, put on the back-burner, forward again to the front-burner."
[92] Alonso et al. 2004, p1419.

larger trial population and consequently a much more expensive trial outlay."[93] The bottom line is that a great deal more Phase 2 investigations will be needed for RTS,S/AS02A both on its own and in combination with other antigens and with alternative or additional adjuvants. It will be a long time before a Phase 3 will be justified, and then, as one correspondent put it "mega-Phase 4 studies" will be needed to assess its impact in the real world of malaria in Sub Saharan Africa.

**So, do not distort incentives**

And all the time it will be critical to keep the malaria vaccine playing field balanced with multiple parallel activities, should this particular candidate not pan out. One correspondent observed that "GSK has asked repeatedly for more support from various agencies, including the EC, but was always discouraged by the fact that funding was conditioned on giving up the usual company monopoly rights on the design and results of the projects. Most public research funding in the world will always require a certain tranche of funding from the company itself".[94]

**Why there is so little public debate?**

There is much more critical debate behind the scenes about RTS,S/AS02A than is sometimes let on. For various reasons there seems a natural tendency for scientists to be reticent: They often draw (or seek to draw) from the same limited funding streams; there is a natural tendency not to want to be too public with criticisms of the work of colleagues; and this is science, so sometimes the unexpected happens, and risk-aversion and concern for reputation may lead those involved to be guarded about comments that may come back to haunt them later. From a psychological perspective, no individual is particularly keen to pour too much doubt on something that may turn out to 'prove' them wrong (including if sponsors destroy better outcomes that nobody gets to see), but which does nothing to improve *their* chances of success.

This author is not a malaria vaccine scientist, and does not have a reputation in the field to sustain. Independence makes raising uncomfortable issues a little easier (but not painless). And an economist (at least this one) tends to view these issues probabilistically: Maximizing the probabilities of a good solution is the goal, and small probability unexpectedly positive outcomes should not become overweighed in policy thinking. Neither should we judge ex post with the benefit of hindsight those decisions that had no such benefit ex ante. Nor should we worry ourselves that we will be judged this way, should it thus paralyze a proper critical assessment ex ante.

[93] The same correspondent described the Alsono et al. claim that RTS,S/AS02A is "a promising vaccine candidate and strongly suggests that malaria vaccines have an important role as future public-health instruments," as "all rather wishy-washy."

[94] The next line is "MVI is only in the role of a cash provider for GSK and serves as a transactor to Gates," which, though only someone's personal opinion and fair to report, sounds a bit harsh in the body of the text.

## *3.11. A few closing thoughts*

When the GSK announcement was first made, it triggered a flurry of commentary from malaria experts. At the risk of taking their remarks out of context, the response to the Lancet study, in a letter to Chancellor Gordon Brown, by Professors Bob Snow and Nick White of Oxford University, stood out (these are extracts from that letter, the reader should really read the whole letter[95] to see the more positive remarks too):

*"This was associated with vigorous and eye-catching publicity, notably the banner headline in The Times the preceding day claiming "New malaria vaccine will save millions of children".*

*But we have had false dawns with malaria vaccines before — and it would be prudent to be cautious. Under normal circumstances, this report would herald a concerted effort to confirm or refute the findings in different populations in different parts of Africa with studies large enough to measure the impact on mortality from malaria; one study is certainly not enough to be sure of anything. But instead, you announced a week ago that the British taxpayers would pre-buy 300 million doses of vaccine for sub-Saharan Africa, costing probably £3 billion (US$5.75 billion).*

*… We are seriously concerned, therefore, that while millions of people suffer every year, you are proposing to allocate precious funds to a future uncertainty. This good intention is misguided. We fear you have been advised poorly…*

*The sad truth is that, despite having now developed…effective tools (with substantial support from donors such as the UK government), the international community has failed in its promise to make them accessible to people most in need. Furthermore, partnerships such as the World Health Organization, Roll Back Malaria, and the Global Fund against HIV, tuberculosis, and malaria — also supported generously by the UK government — have missed opportunities to go to scale with comparatively cheap, life-saving interventions…*

*Why, then, has the UK government decided to invest in an intervention that is more expensive and less effective than bednets and effective drugs? One argument might be that the bill does not have to be paid today. And when it does, it will probably be paid to a British multinational pharmaceutical company.*

*We have truly effective measles and tetanus vaccines (they are much more effective than the current malaria vaccine), and we have had them for decades. But these vaccines still do not reach all those who need them. Together measles and tetanus kill over a million children each year (World Health Reports 2003, 2004). Similarly, although we have a pneumococcal vaccine, it does not reach anyone because it is so expensive that no developing country government can afford it.*

[95] Full copy at: www.scidev.net/gateways/index.cfm?fuseaction=printarticle&rgwid=2&item=Opinions&itemid=341&language=1. Snow, R., is Professor of tropical public health at the Kenyan Medical Research Institute in Nairobi and the University of Oxford. White, N., is Professor of tropical medicine at Mahidol University, Bangkok, Thailand, and the University of Oxford.

*The prospect of a new vaccine against a killer disease has a seductive 'high-tech', 'feel-good' allure that is appealing to donors who seek neat solutions in modern technology.*

*Yes, prevention is better than cure. But this works both ways. If we provide insecticide-treated bednets and make effective drugs available, this will also reduce the incidence of malaria, and we will achieve better effects than with a weakly effective vaccine — and importantly we will spend less money."*

*We need to raise sufficient funds from the rich world to support scale up and deployment of what we know works best, and we must do it now*."

**The take-home result from RTS,S**

There have now been many well-conducted efficacy trials of various formulations of RTS,S. As Snounou et al. observe: "In the vast majority of the trials, including those in naïve volunteers, the important take-home result is not necessarily that some individuals have been protected from infection but, instead, that the induced sterile immunity failed to be sustained for a sufficient length of time in an important proportion of the recipients. In its present form, the RTS,S vaccine might prove useful for transient visitors to endemic areas, such as tourists or military personnel. However, to fulfill its humanitarian goal, the ultimate aim of vaccination against PE stages is to confer protection against malaria infections through immunization regimens that are equally suitable for deployment in infants, as part of the expanded programme for immunization, and older residents of endemic areas. Considering that proven affordable measures to alleviate suffering, such as insecticide-treated bed nets and combination therapies, are available, one important issue that the malaria community should address is when to abandon onerous development programmes that fall short of these goals."[96]

One correspondent observed: "A lot more studies need to be done (and are actually inscribed into the GSK product development plan). The final aim is to integrate the vaccine into routine childhood immunization at a very low age and there are no data available as yet if this is possible. More and more studies will be needed in lower age groups. Pedro Alonso is tenacious and paves the way for these studies by developing a trial methodology for them. However, there are still so few trials that no valid conclusion can be drawn on specific correlates let alone the values of immunizing with a one antigen construct alone when there is already evidence that the molecular immune response profile is highly variable from transmission site to transmission site."

Another correspondent, heading another vaccine PPP, observed that "GSK deserve credit for their persistence, and MVI for their ability to invest altruistic funds. I'm convinced that [the correspondent's vaccine PPP] would have been unable to convince [its] financial donors to allocate large amounts of money for a RTS,S vaccine, until it had been proved, beyond doubt, that it could confer malaria specific clinical protection in the target population – infants. Other vaccines have failed when tested for efficacy in infants. The current GSK/MVI clinical development strategy is to conduct several inter-linked efficacy and dose-finding studies in infant populations under various transmission

[96] Snounou et al. 2005, ibid.

intensities. This can be seen as a moderate to high risk approach, but if successful, will considerably shorten the length of time it will take to register the vaccine. Meanwhile, GSK/WRAIR/MVI are looking for additional antigens such as MSP1 and AMA1 etc. to incorporate into the RTS,S vaccine. This is a commercially feasible/acceptable strategy. If the RTS,S, on its own, fails in infants (but failure by whose definition?), I'm afraid we will have a backlash of donor skepticism and fatigue."[97]

Another correspondent argued: "We should not be rejoicing about reaching the famous 30% range that was reached by earlier 'promising vaccines' that were tested before (partly overlapping study designers) and from which we never heard again after lots of fuss. This time the fuss may lead to an even greater distortion in the already skewed malaria funding and policy world. I wished this whole discussion went on in an open forum rather than just between selected groups. Brown won't listen to scientists ('just jealous they did not find this glorious vaccine') but would listen to a public outcry."

Another correspondent blamed the current policy environment on policy consultants: "So why all this hype? It appears that the policy consultants have discovered a new market opportunity for themselves. It is the same as the one created by sectarian cults. They create a big artificial debate on an issue where the science is inconclusive and trap profile-hungry politicians. On the other hand, GSK has also some responsibility in this."

From an ex ante scientific perspective, without the benefit of hindsight, the best scientific strategy is to keep multiple parallel leads open, and not to risk distorting funding and destroying this. As one correspondent put it much more capably than this author, the task of funders is to "hope for the best, but plan for the worst." This is the core argument and purpose of this chapter.

[97] An engineer colleague explained to the author the collapse of interest in cold fusion research following early extremely over-hyped results that proved impossible to replicate.