Schistosomiasis Vaccines: A Devils' Advocate View

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Schistosomiasis is one of the most prevalent and complex parasites of humans. For decades, scientists have been fascinated by the immunological determinants of schistosomiasis, fostering hope that a vaccine could eventually be developed[1]. As testified by recent issues of *Parasitology Today*, this quest is more alive than ever; immunological, epidemiological and biotechnological developments have led to new hopes and daring advances. Promising results in animal models have been reported with a series of antigens, although in an independent test, none of them accomplished the pre-set target level of 40% protection[2]. Many questions remain, and alternative strategies are still being explored[3–6]. Nevertheless, an international gathering of scientists accepted the move from research to vaccine development, and 'showed eagerness to learn more about immune responses to vaccine candidates through controlled human trials'[2]. At the very least, a schistosomiasis vaccine is considered 'feasible and desirable'[3]. Production under good manufacturing practice, followed by clinical trials, has been recommended for four molecules, and has already been achieved for one of them[1,2].

Humans are not experimental animals, however. Clinical trials cannot be justified by scientific eagerness alone: a vaccine candidate must be backed up by a reasonable assumption of eventual applicability, and thus, a demonstrable potential of efficacy, safety, and public health relevance. As self-designated devils' advocate[3], I will raise some scientific, ethical and social counter-arguments, which should be answered on the long and winding road to this coveted Holy Grail.

Is a Schistosomiasis Vaccine Feasible?

Developing vaccines against human parasites is a daunting challenge; the evolutionary success and very existence of parasites depends on intricate mechanisms to evade immunity. Like most viruses and bacteria, protozoa are vulnerable to (possibly artificially induced) immune reactions as individual cells, but persist as a population through antigenic variation and repressed reproduction in the human host. Helminths have taken their defence one step further and survive the host immune responses as adult individuals. Schistosomes might be considered the pinnacle of parasitic evolutionary success. After migrating through skin and tissues, they can live for decades in the bloodstream, fully exposed to all possible defence mechanisms of the human body. Without reproduction in the final host, they maintain ecologically stable populations, in spite of hazardous transmission, complicated life cycles, and formidable ecological, physiological and immunological barriers. Arguably, schistosomes have integrated the complexity of the human defences into their very nature: artificial immunization represents an awesome challenge, and antigens that solicit natural immune responses would seem unlikely vaccine candidates[3,5].

The case is not just philosophical. The belief that humans are capable of mounting a protective immune response against schistosomes and, therefore, that the development of a vaccine is feasible, is mainly based on the assumption that, in natural circumstances, after years of exposure individuals acquire effective immunity[1–4]. The most important epidemiological argument is the consistent decline of (re)infection rates in adults in endemic communities, in spite of continued water contact[4]. Studies in Burundi, Senegal and Kenya, however, have shown that such patterns are as consistent in newly exposed communities, where they cannot be explained by slowly acquired immunity[7–9]. A further argument is the variation with transmission pressure of the precise age at which resistance sets in[10]. This 'peak-shift' is compatible with epidemiological models based on acquired immunity, but has so far been validated only in two areas. Moreover, it might simply explain slight variations of the 'peak' age, but not necessarily the quantum difference between children and adults.

The biological evidence for the immunological nature of age-related resistance is based primarily on the correlation with IgE and T helper 2 (Th2)-cell responses. Although these correlations remain significant after allowing for age, they are much weaker than the correlation of resistance with age *per se*, raising questions about their interpretation. These analyses are, moreover, based on imprecise immunological, parasitological and behavioural parameters[4,11,12]. The reported association of susceptibility with genetic loci is not entirely inconsistent with age-related immunity, but is certainly no direct argument for it[13,14].

Immunity to schistosomes has been extensively studied in animal models, leading to a wide range of hypotheses on possible mechanisms and interactions[1–3]. However fascinating and promising some data might be, the relevance to humans remains questionable if only because of basic physiological differences between hosts. In natural or primate models, current vaccine candidates have, at best, resulted in a reduction of worm fecundity[1]. None of the current candidates is actually based on a plausible strategy to mimic or enhance effective mechanisms for protective immunity in humans, which are still diverse and hypothetical[1–6]. More substantial and consistent evidence, preferably from humans or relevant primate models, would seem to be a prerequisite for clinical trials.

The evidence for effective acquired immunity to schistosomes in humans is not entirely consistent with epidemiological and biological observations. If it exists, its relative contribution to resistance may be less important than, or linked to, other age-related factors such as behavioural, hormonal or physiological changes in puberty[7]. A devil's advocate might find the scientific basis for the current schistosomiasis vaccine candidates too weak to justify human trials.

Is Schistosomiasis Vaccine Effectiveness Measurable?

The safety and efficacy of any vaccine must be scientifically established before the vaccine can be applied. More than for any other known vaccine, the methodological and ethical challenges for schistosomiasis are considerable[4]. For one thing, chemotherapy is – or should be – becoming widely available in most endemic areas, where a vaccine would also be applied[15]. Both at the individual and community level, the impact of vaccination will be supplementary to the effect of chemotherapy. Chemotherapy stongly reduces egg counts; the

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difference between vaccinees and placebo patients will have to be based on the follow-up of re-infection, which is often slow and unpredictable. At any follow-up, positive individuals must be given chemotherapy, complicating further vaccine evaluation. Furthermore, egg counts and antigen detection, the available outcome measures of vaccination, cannot distinguish anti-fecundity from protective effects[16,17].

At the community level, it is already difficult to show the differential impact of various treatment strategies or of additional tools[12]. Therefore, the impact of the partial protection expected from current vaccine candidates will not be easy to demonstrate. The effect on morbidity will be particularly hard to show, as it is even more profoundly and lastingly affected by chemotherapy than are egg counts[18,19].

Establishing safety is perhaps a still greater challenge. Schistosomiasis is largely the consequence of chronic, complex immunopathological interactions[20]. The pathways are only partially known; the possible effects that artificial immunization might have on them are unpredictable and could be far-reaching. Exposing (previously) infected individuals, particularly in field situations, carries a risk of unpredictable disease exacerbation. Neither experiments in animal models, nor safety trials in uninfected humans are of much relevance for this purpose. A long and careful safety-assessment period should be undertaken before going into large-scale application. Moreover, the assessments should not be limited to the usual healthy adult males, because susceptibility to infection and disease in schistosomiasis varies greatly with age and gender.

An unedited safety aspect of partial immunization is the likely confusion with the popular perception of vaccines being fully protective. A false sense of security may lead to persistent, even increased water contact. At worst, the sociological impact of such a vaccine can even lead to more intense infections and pathology. Anti-fecundity effects would further compound this problem: vaccinees might accumulate large, sterile worm loads that cannot be diagnosed microscopically, but can still cause systemic, immunopathological and ectopic pathology, or lead to unpredictable rebounds of egg production. Such a reduction of diagnostic possibilities raises serious medical and ethical concerns.

To meet the requirements of scientific measurability and applicability, a vaccine will have to provide a very high level of protection against incoming infections, and an obvious lack of immunopathological consequences. None of the current candidates has a demonstrable, even likely potential in this respect, and so cannot be justified in human trials.

Is a Schistosomiasis Vaccine Desirable?

The attractiveness of vaccines as a tool in public health stems mainly from the successes of the campaigns against viral and bacterial infections in children, the vaccines providing individuals and communities with almost absolute and lifelong protection. Scientists should also be aware, however, that vaccination is not by definition a valuable public health intervention. The benefits of a vaccination programme must be very substantial to justify the high costs and strains on the health services; even then, the long-term impact on community health is not always straightforward[21,22].

Vaccination against schistosomiasis is a different public health concept than child immunization programmes. Most of the morbidity, intestinal and urinary disease, can easily be diagnosed and treated at the primary health care level[15,23]. Severe and irreversible disease occurs in only a small proportion of people, mostly adults, and can largely be prevented or controlled by chemotherapy[15,23,24]. Available evidence warrants no real concern for widespread praziquantel resistance and alternative drugs are available[25,26]. Even for a safe and effective schistosomiasis vaccine, the public health rationale might thus be rather doubtful. In addition, scientists should realise that, by redirecting scarce resources from other priorities – such as strengthening existing health services – the eventual impact on local health care of internationally advocated control programmes can be negative.

A schistosomiasis vaccine might also harm development in a broader sense. The occurrence of schistosomiasis invariably reflects a lack of safe water, sanitation, education and accessible health care. A vaccine can further reduce the already weak commitment to the basic human needs as the best and most durable prevention against schistosomiasis – and many other diseases.

Conclusion

As is argued elsewhere, the quest for a schistosomiasis vaccine is a noble cause and a fascinating scientific project[1–4]. However, the scientific and public health concepts to be applied differ fundamentally from those of other vaccines. The potential feasibility, measurability and applicability of current candidates are simply not sufficient to justify human trials at this stage.

These considerations should not stop anybody from pursuing or funding research on the immunology or control of schistosomiasis; on the contrary, they may help to generate fruitful debate, and possibly reorient future work. When human trials are being considered, however, these devil's advocate questions are no longer academic and should be effectively answered.

References

1 Capron, A. (1998) Schistosomiasis: Forty years' war on the worm. *Parasitol. Today* 14, 379–384
2 Bergquist, N.R. and Colley D.G. (1998) Schistosomiasis vaccines: research and development. *Parasitol. Today* 14, 99–104
3 Wilson, R.A. and Coulson, P.S. (1998) Why don't we have a schistosomiasis vaccine? *Parasitol. Today* 14, 97–99
4 Hagan, P. *et al.* (1998) Schistosome immunology: more questions than answers. *Parasitol. Today* 14, 407–412
5 Doenhoff, M.J. (1998). A vaccine for schistosomiasis: alternative approaches. *Parasitol. Today* 14, 105–109
6 Mountford, A.P. and Harrop, R. (1998) Vaccination against schistosomiasis: the case for lung-stage antigens. *Parasitol. Today* 14, 109–114
7 Gryseels, B. (1994) Human resistance to *Schistosoma* infections: age or experience. *Parasitol. Today* 10, 380–384
8 Stelma F.F. *et al.* (1993) Epidemiology of *Schistosoma mansoni* infection in a recently exposed community in northern Senegal. *Am. J. Trop. Med. Hyg.* 49, 701–706
9 Ouma, J.H. *et al.* (1998) The development of schistosomiasis mansoni in an immunologically naive immigrant population in Masongaleni, Kenya. *Parasitology* 117, 123–132
10 Woolhouse, M.E.J. (1998) Patterns in parasite epidemiology: the peak shift. *Parasitol. Today* 14, 428–434
11 Gryseels, B. and Polderman, A.M. (1992) Acquired immunity in schistosomiasis. *Parasitol. Today* 8, 271–272
12 Gryseels, B. (1996) Uncertainties in the epidemiology and control of schistosomiasis. *Am. J. Trop. Med. Hyg.* 55, 103–108
13 Abel, L. *et al.* (1991) Evidence for the segregation of a major gene in human susceptibility/resistance to infection by *Schistosoma mansoni*. *Am. J. Hum. Genet.* 48, 959–970
14 Muller-Myshok, B. *et al.* (1997) Further evidence suggesting the presence of a locus on human chromosome 5q31-q33, influencing the intensity of infection with *Schistosoma mansoni*. *Am. J. Hum. Genet.* 61, 452–454
15 World Health Organization (1999) Report of the WHO Informal Consultation on Schistosomiasis control. Geneva WHO/CDS/CPC/SIP/99.2
16 Gryseels, B. and De Vlas, S.J. (1996) Worm burdens in schistosome infections. *Parasitol. Today* 12, 115–119
17 Van Lieshout, L. *et al.* (1995) Analysis of worm burden variation in human *Schistosoma mansoni* infections by determination of serum levels of circulating anodic antigen and circulating cathodic antigen. *J. Infect. Dis.* 172, 1336–1342

18 Wagatsuma, Y. *et al.* (1999) Resolution and resurgence of *Schistosoma haematobium*-induced pathology after community-based chemotherapy in Ghana, as detected by ultrasound. *J. Infect. Dis.* 179, 1515–1522
19 Frenzel, K. *et al.* (1999) Evidence for a long term effect of a single dose of praziquantel on *Schistosoma mansoni*-induced hepatosplenic lesions in northern Uganda. *Am. J. Trop. Med. Hyg.* 60, 927–931
20 Brunet, L.R. *et al.* (1998) Cytokine interaction and immune responses during *Schistosoma mansoni* infection. *Parasitol. Today* 14, 422–427
21 King, M. (1990) Health is a sustainable state. *Lancet* 336, 664–667
22 Jefferson, T. *et al.* (1998) Evidence-based vaccinology: the work of the Cochrane Vaccines Field. *J. Epidemiol. Community Health* 52, 207–208
23 World Health Organization (1992) The control of Schistosomiasis. *WHO Technical Series* 830
24 Gryseels, B. (1989) The relevance of schistosomiasis for public health. *Trop. Med. Parasitol.* 40, 134–142
25 Cioli, D. (1998) Chemotherapy of schistosomiasis: an update. *Parasitol. Today* 14, 418–421
26 Geerts, S. and Gryseels, B. Drug Resistance in Helminths of Humans: Current situation and lessons from Livestock. *Clin. Microbiol. Rev.* (in press)

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Bednets, Size and Culture on the Web

Malaria Discussion Group

Bednets and history

Torben Vestergaard (Disease Control Textiles, Kolding, Denmark) was keen to know why people in Africa are reluctant to buy bednets, when formerly they were in common use. Is it just the cost? They were usually imported from Europe and costs have risen and incomes in Africa have fallen. Import duties of 60–100% are prohibitive. Furthermore, in India, it is illegal to import them ready-made, and 85% duty is charged on importing raw materials to make them. But are there other factors? He had heard that, in Zambia, improved sanitation and drainage combined with the use of DDT had changed peoples' habits, and that now the mosquito is taking its revenge. Christian Lengeler (Swiss Tropical Institute, Basel) thought that Europeans in Africa in the late 19th and early 20th century had reduced their mortality considerably by using bednets, but unfortunately 'history has not often mentioned the fate of non-Europeans (especially in rural areas)'. Jo Lines (London School of Hygiene & Tropical Medicine, UK), from his experience there in the early 1980s, believed that, in Tanzania, poverty is the answer, because of the state of its economy. So, economists and historians: 'is it true that the average African household has been poorer in the 1980s and 1990s than in the 1960s and early 1970s, when many African countries were becoming independent?' Reza Alemi (Zahedan University, Iran) said that in Iran 25–30 years ago 'everybody slept under bednets, now, nobody does'. Then no insecticides or repellents were available, but following industrialization 'spraying gardens and houses became popular, the decrease in mosquito population led to decreased use of bednets, until they were abandoned all together'. However, Marina Chua (Philippine General Hospital) said bednets are still commonly used in the Philippines. Made of nylon, without insecticide impregnation, they are 'quite affordable for even the lowest income family' and it is the rich who use them less, mainly because they have screens on windows and doorways.

Newspapers again

Colin Sutherland (London School of Hygiene & Tropical Medicine, UK), without comment, posted an extract from *The Observer* of Sunday, 17 October 1999: 'Every 20 seconds a child somewhere in the world dies of malaria. Scientists are racing to find a vaccine as deadlier strains threaten even Europe. Every six months, Dr Stephen Hoffman, a captain in the US navy, enters an insectary swarming with irradiated mosquitoes and allows himself to be bitten repeatedly on the arm. A few days later he repeats the torture until he is sure he has received more than 1000 bites. Then, and only then, is it safe for him to travel to the front zone of the navy's war against malaria – countries such as Kenya and Ghana where *Plasmodium falciparum*, the deadliest form of the disease, is rampant'. Some desultory discussion followed, mainly wondering if the mosquitoes were infected (not clear!) and if Steve was boosting his immunity to mosquito saliva. Rob Anderson (Simon Fraser University, Canada) presumed the mosquitoes carried sporozoites of a chloroquine-sensitive strain of *P. falciparum* and hoped immunity was induced to resistant strains too.

How many gametocytes can fit into one red blood cell?

Roger Jovani (Universitat de Barcelona, Spain) wanted papers on multiple infections of erythrocytes by *P. falciparum* gametocytes, and even subjective impressions. He received more of the latter than the former, and not all *P. falciparum* gametocytes either! Chimanuka Bantuzeko (Vrije Universiteit, Brussels, Belgium), working with *P. chabaudi,* believed that multiply infected red blood cells (RBCs) generally lyse even before schizonts develop, but Lisa Ranford-Cartwright (University of Edinburgh, UK) sometimes sees RBCs containing two gametocytes of *P. falciparum* in cultures, though never more. They appear to survive up to stage V and express normal gametocyte antigens by IFA. Mark Wiser (Tulane University, New Orleans, LA, USA) agreed about *P. chabaudi,* suggesting that perhaps the RBCs can accommodate only a limited amount of parasite growth or that the spleen efficiently removes multiply infected cells – or both. Jack Williams (Walter Reed Army Institute of Research, USA) thought a single RBC capable of supporting two gametocytes but more destroyed the cell: 'Occasionally there will be three young gametocytes ... but we only see stage IVs in doubly infected cells'. He quoted J.B. Jensen, Observations on gametocytogenesis in *Plasmodium falciparum* from continuous cultures. *J. Protozool.* 26, 129–132, 1979, which shows two stage IV gametocytes in one RBC.

Shenyi He (Kobe University, Japan) then did some counts on cultures of *P. falciparum* (K1): 20% of infected cells contained more than one parasite, sometimes five ring forms in one cell, and sometimes even a ring, a trophozoite and a

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