

*Research*

# Vaccines and future global health needs

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Increased international support for both research into new vaccines and their deployment in developing countries has been evident over the past decade. In particular, the GAVI Alliance has had a major impact in increasing uptake of the six common infant vaccines as well as those against hepatitis B and yellow fever. It further aims to introduce pneumococcal and rotavirus vaccines in the near future and several others, including those against human papillomavirus, meningococcal disease, rubella and typhoid not long after that. In addition, there is advanced research into vaccines against malaria, HIV/AIDS and tuberculosis. By 2030, we may have about 20 vaccines that need to be used in the developing world. Finding the requisite funds to achieve this will pose a major problem. A second and urgent question is how to complete the job of global polio eradication. The new strategic plan calls for completion by 2013, but both pre-eradication and post-eradication challenges remain. Vaccines will eventually become available beyond the field of infectious diseases. Much interesting work is being done in both autoimmunity and cancer. Cutting across disease groupings, there are issues in methods of delivery and new adjuvant formulations.

**Keywords:** vaccines; global health; infectious diseases

## 1. INTRODUCTION

It is daunting for a reviewer to have the last word in a symposium where so many of the participants are the leading contributors to the future of vaccinology. Indeed, it is evident that their successes, past and yet to come, pose many challenges for the public health system of the world and for the partners in development, the nations contributing to development assistance and those in receipt of it. There will soon be an embarrassment of riches, actually a rather wonderful dilemma to face.

One of the reasons for the great success of the Global Alliance for Vaccines and Immunization (the GAVI Alliance) is the great care taken in consulting all stakeholders well ahead of its launch. There were two big international planning meetings, one at the World Bank in 1998 and one in Bellagio, Italy in 1999. As well as that, officials from the World Health Organization (WHO), UNICEF and the Rockefeller Foundation travelled extensively throughout developing and industrialized nations alike, explaining the concept of an expanded effort in global immunization. GAVI set itself three initial goals: to expand coverage of the six standard infant vaccines (diphtheria, pertussis, tetanus, poliomyelitis, measles and bacillus Calmette–Guérin (BCG)) in all countries with a gross domestic product per head of population less than US\$1000; to speed the introduction of newer vaccines; and to foster research towards vaccines of

interest chiefly to developing countries. Further goals were to improve safety in vaccine delivery by promotion of non-reusable syringes or ‘uniject’ devices and to ensure that only vaccines where the ‘cold chain’ had been adequately maintained were used. GAVI was formally launched at the World Economic Forum in Davos, Switzerland, in January 2000 where the Bill and Melinda Gates Foundation announced a magnificent initial grant of US\$750 million, which has since been doubled.

The author had the great honour to be one of the planners of the GAVI Alliance, so we should first examine its role [1]. What has the GAVI Alliance achieved? Having brought the six standard vaccines to 250 million extra children in its first decade (2000–2009), increasing diphtheria, tetanus, polio (DTP) coverage to 80 per cent, and having 233 million children immunized with three doses of hepatitis B vaccine, many of these also receiving the *Haemophilus influenzae* type b (Hib) vaccine and some the yellow fever vaccine, the programme has saved an estimated 5.4 million lives. Immediate challenges to be faced by GAVI include the following: widespread deployment of the pentavalent vaccine DTP-Hib-hepatitis B to save many injections; gradual roll-out of the new pneumococcal conjugate and rotavirus vaccines (the pneumococcal vaccine going to 19 countries in the next 2 years and the rotavirus one to a smaller number), and planning for the medium-term addition of vaccines against human papillomavirus, meningococci, rubella and typhoid. Current GAVI Alliance spending is about US\$1 billion per year. Even with the planned rise of the budget to US\$1.5 billion per year in 2015, it is clear that sources outside GAVI will be required to achieve these targets and HIV/

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AIDS, malaria and tuberculosis vaccines are not yet in the budgetary mix (box 1).

Box 1. Current and planned programme of the GAVI Alliance<sup>a</sup>.

*vaccines being offered now or soon*

- pentavalent DTP-Hib-hepatitis B
- oral poliomyelitis
- first dose measles
- BCG
- yellow fever
- pneumococcal conjugate
- rotavirus

*vaccines planned but not yet budgeted*

- human papillomavirus
- Japanese B encephalitis
- meningococcal package
- rubella
- typhoid fever

*vaccines not yet planned for*

- HIV/AIDS
- malaria
- tuberculosis
- influenza

<sup>a</sup>Some vaccines relevant only to certain countries.

The deployment of pneumococcal conjugate vaccines represents the first time that a new financing mechanism, termed AMC for Advanced Market Commitment, has been used. Through AMC, the programme pledges to purchase a certain number of doses for a given period of time, while companies supplying the vaccine agree to deliver these at a fixed price. While the 10-valent and 13-valent conjugate vaccines will cover more cases than the previous 7-valent one, a common protein vaccine would be highly desirable. The area is of central importance. Of 8.8 million children under five dying in 2008, 18 per cent died of pneumonia, many because of pneumococcus. The HIV pandemic complicates matters still further as this is a major risk factor for invasive pneumococcal disease in children.

## 2. NEW VACCINES LIKELY TO COME FORWARD IN THE NEXT 5–10 YEARS

There are two important diseases for which the existence of serogroups represents a limitation for current vaccines. They are *Neisseria meningitidis* and *Streptococcus pneumoniae*. In each case, there is advanced research in progress towards the development of a common basic protein vaccine [2]. In the case of meningococcus B, we have the problem of a carbohydrate which is too 'self-like' with sialic acid epitopes dominating. This renders the classical polysaccharide–protein conjugate vaccine approach impossible as such a vaccine could induce autoimmunity. Fortunately, using 'reverse vaccinology', that is, the identification of plausible vaccine candidate proteins by searching through the bacterial genome, Novartis has developed a trial vaccine based on several conserved proteins prepared by recombinant DNA technology as well as some outer membrane vesicles. Phase III trials of this vaccine are ongoing and a vaccine

may be ready for use by the end of 2011. Pfizer has also made progress with a protein-based vaccine.

Research towards a protein pneumococcal vaccine is not as advanced. The non-governmental organization Program for Appropriate Technology in Health (PATH) is coordinating a number of candidates which are in early clinical trial. One fairly far advanced one comes from Intercell, an Austrian biotechnology company. It consists of three separate proteins and a new adjuvant known as IC31. Another is under development by GlaxoSmithKline and is being given in conjunction with a conventional conjugate vaccine to children in The Gambia.

Another likely vaccine is a conjugate of *Salmonella typhi* Vi carbohydrate antigen (in itself a good vaccine [3]) and protein, e.g. the molecule CRM197. At least two efforts in this regard are progressing well, both within not-for-profit institutes, the International Vaccine Institute in Seoul, Korea and the Novartis Vaccine Institute for Global Health in Siena, Italy. If we can take a lead from conjugate vaccines for Hib, pneumococcus and meningococcus, these conjugate vaccines should outperform their pure carbohydrate counterparts and should work at a younger age.

## 3. INTERESTING VACCINE CANDIDATES FOR THE NEXT 5–10 YEARS BUT WITH MORE ISSUES

Great excitement attends the phase III trials of GlaxoSmithKline's malaria vaccine RTS,S. These are ongoing in 11 centres in seven countries and involve 16 000 children. Results are expected in late 2011 to early 2012. RTS,S consists of portions of the major circumsporozoite protein of *Plasmodium falciparum* together with hepatitis B surface antigen self-assembled into a virus-like particle and incorporated into a patented adjuvant formulation containing immunostimulatory oligodeoxynucleotides and monophosphoryl lipid A. The vaccine is the result of 25 years of research involving the company and the Walter Reed Army Institute of Medical Research in the USA, based on prior research by Ruth and Victor Nussenzweig at New York University. The phase II studies in infants showed an approximate 50 per cent efficacy and clear indication of reduced clinical severity [4]. The phase III study clearly represents an important milestone, yet the author believes that RTS,S will not be the definitive malaria vaccine for the world. There are several reasons for this. Efficacy and duration of action need to be higher. Given the importance of the travellers' market for commercial viability, and the inherent importance of *Plasmodium vivax* as a recurring disease, a *vivax* component would be most desirable. Further, it should be possible to combine RTS,S with one or more liver-stage antigens, so that cytotoxic T cells could reduce/eliminate infected liver cells; and one or more merozoite antigens, given that it is the blood stage of the infection that makes the patient sick. Unfortunately, merozoite antigens are mainly highly polymorphic and mutable. Merozoite surface antigens such as MSP1, MSP3 and MSP7 have been promoted as promising vaccine candidates [5], as have proteins derived from the apical organelles of the merozoite which stream on to the surface of the erythrocyte being invaded. One such, apical membrane antigen 1

(AMA1), is less variable than others, and performs well in an *Aotus* monkey model. It seems likely that several allelic variants of AMA1 will have to be provided to give broad protection.

Also present in blood are the precursors of the gametes of *P. falciparum*, the gametocytes. They, as such, do no harm to the infected person, but if strong antibodies were to be formed to the gametocytes they would not be able to develop in the mosquito in order to complete the life cycle. At the community level, this could be very important. A gametocyte vaccine could thus be considered an 'unselfish' vaccine. The most promising gametocyte antigen is Pfs 25.

An unconventional approach to a malaria vaccine has been taken by Schofield *et al.* [6]. They argue that much of the clinical symptomatology of malaria results from the release of a toxin, namely a glycosylphosphatidylinositol released when the merozoite-filled erythrocyte bursts. Accordingly, antibodies to this entity might act like antibodies against diphtheria or tetanus toxin. To this end, a synthetic saccharide has been prepared and conjugated to protein. In a mouse model of cerebral malaria, it markedly reduces mortality. Preparation is now in train for a clinical trial.

Another approach altogether is to consider live attenuated vaccines. Hoffman *et al.* have pioneered the idea of irradiated, non-replicating but metabolically active sporozoites harvested from the salivary glands of infected mosquitoes. In early experiments, these protected against challenge [7] but a recent phase I/IIa trial performed by the firm Sanaria proved disappointing. Only five of 80 volunteers were protected. The question was raised whether intravenous administration of the merozoites might raise effectiveness. The Gates Foundation is also supporting a variation of the Sanaria idea, namely the work of Kappe and co-workers on genetically engineered sporozoites which have had the genes for p36 and p52 deleted, causing developmental arrest at the liver stage of infection [8]. Immunization with such genetically attenuated parasites confers complete protection in mouse models of malaria. Early clinical studies have recently begun.

Hoffman deserves great credit for showing that it is feasible to harvest large numbers of sporozoites from infected mosquitoes and to do so on an industrial scale. Nevertheless, and in the long run, it would be much more practical to be able to grow the sporozoites in tissue culture of mosquito salivary gland cells. In the meantime, some malaria vaccine research is progressing using volunteers challenged by bites from infected mosquitoes rather than injection of isolated sporozoites.

A counterintuitive approach to live attenuated vaccines has been taken by Good and co-workers [9]. This argues that ultra-low doses of infected erythrocytes may induce T cell-based protection. It is predicated on the observation that low antigen doses favour T cell over B cell immune responses, and that T cell immunity is an important component of immunity to malaria. A small clinical trial in volunteers showed that this approach may be feasible.

It would be desirable to have a cheaper rotavirus vaccine to place beside the two licensed ones. A candidate of great interest to the author is RV3. Unfortunately, the efficacy of current rotavirus vaccines in the prevention

of severe diarrhoea in developing countries is almost 50 per cent lower than that in industrialized countries [10]. The reasons for this are not clear but could include tropical enteropathy with blunted epithelial villi in the small intestine, altered gut microbial composition and malabsorption. Further, co-infection by multiple pathogens and poor nutrition may contribute. Genetic factors cannot be excluded. For this reason, much interest attaches to so-called nursery strains of rotavirus, which are naturally attenuated and can potentially be delivered on the day of birth before the gut has had a chance to be altered by microbial or nutritional factors. RV3 is being developed by a group including the discoverer of rotavirus, Ruth Bishop, and a partnership with the Indonesian manufacturer BioFarma should guarantee a low sales price. Phase II trials of RV3 are in the late planning stages both in New Zealand and in Indonesia.

Another important cause of diarrhoea is shigellosis or bacillary dysentery. Research in this field is hampered by the existence of multiple species and strains of *Shigella* bacteria. Nevertheless, both live attenuated and subunit approaches are under active research. Protective immunity is directed at the O-somatic antigen and is narrowly type specific. In addition, cell-mediated immune mechanisms play a role in recovery and immunity. Candidate polysaccharide conjugate and live attenuated vaccines mostly focus on *Shigella flexneri 2a* and *Shigella sonnei*. Synthetic oligosaccharides that mimic the O-antigen protective epitopes are under active research. Attractive though live attenuated, orally administered vaccines undoubtedly are, the narrow margin between under-attenuation and thus excessive reactogenicity and over-attenuation leading to poor immunogenicity remains a problem. A further issue is illustrated by the live attenuated *S. flexneri 2a* strain SC602 developed at the Pasteur Institute, Paris. This proved remarkably effective in challenge studies in adult US volunteers, but disappointingly poorly immunogenic in infants in the field. A further series of interesting live attenuated strains have emerged from the Centre for Vaccine Development at the University of Maryland, USA, the most advanced of which is CVD 1208 S.

Good progress is being made on the development of a *Salmonella paratyphi A* vaccine. This pathogen is as important as *Salmonella typhi* in some parts of the world as a cause of enteric fever. Vaccine candidates include live attenuated strains and conjugate vaccines. Whether to wait for the development of a bivalent *S. typhi*-*S. paratyphi A* enteric fever vaccine or to go with a monovalent *S. typhi* conjugate vaccine as soon as it has been adequately tested is debateable. Considering the advanced stage of research, the latter course of action is favoured.

Another important group of bacteria are the group A streptococci. This is not only because of the infections themselves but also because of the immunological complications that they can cause—post-streptococcal glomerulonephritis and rheumatic fever (frequently followed by rheumatic valvular heart disease). Most of the research for a vaccine has concentrated on the M protein, which is highly diverse among strains. One 26-valent vaccine consisting of the N-terminal portion of the M protein is in phase I/II trial. At the same time, several conserved proteins are the subject of pre-clinical research.

While we have an excellent, cheap measles vaccine, there is a residual problem about infants aged four to nine months. Maternally derived antibodies wane at about four months but administration of the live, attenuated vaccine before about nine months of age results in a suboptimal response. There are at least two trials of an inhalable measles vaccine in train in the hope that these can be administered earlier than injected vaccine.

A vaccine of considerable interest for South East Asia is the dengue virus vaccine. Again, progress of research is good here and a vaccine should become available soon.

#### 4. VACCINES POSSIBLE IN THE NEXT 5–20 YEARS

The author does not wish to rehearse the possibilities for an HIV/AIDS vaccine already covered in a paper in this volume. Suffice to say that possibilities for an antibody-based vaccine, a T cell-based vaccine (or both) are very much open. A puzzling challenge is presented by recent phase III results of the Sanofi Pasteur trial which tested a heterologous prime–boost regimen consisting of priming with a canary-pox HIV vector ALVAC-HIV and a booster with a full-length recombinant gp120 envelope protein AIDSVAX B/E [11]. This RV144 trial in 16 000 Thai subjects showed a 31.2 per cent efficacy (74 sero-conversions versus 51). There was, however, no effect on viral load at the set point. This result can do no more than give modest encouragement. It will be important to evaluate the immune responses induced and to attempt to uncover correlates of protection, but the need to follow up in some way is compelling. There are many ongoing phase I and II trials using prime–boost strategies.

Similarly, tuberculosis needs mention, with at least 15 candidate vaccines in clinical trial. A vexing issue is what to do with the relatively old *Mycobacterium vaccae* vaccine [12]. It is intended as a vaccine for patients carrying latent TB but also HIV. It is given as five intradermal doses over 1 year to HIV-seropositive subjects with a BCG scar. In a trial in Dar es Salaam sponsored by the National Institutes of Health, 2013 patients were followed for a median of 3.3 years. The vaccine was well tolerated and proved 39 per cent effective in preventing definite tuberculosis.

One constant when contemplating the array of candidates for TB vaccines is the realization that clinical trials in a disease with such a long latent period will be slow and expensive. This is the logic underpinning simultaneous pursuit of various alternatives. One cannot help but be impressed with the vigour of this field of research.

#### 5. PARASITES OTHER THAN MALARIA: A NEGLECTED FIELD

Compared with malaria, other parasites have been relatively neglected as regards vaccine research. Among the protozoa the most important are leishmaniasis and trypanosomiasis. After the failure of killed whole organisms as a leishmania vaccine, the only defined second generation candidate to reach clinical trial is LEISH-111f. Additional target antigens

Table 1. Annual global medical research expenditures.

the world	US\$200 billion
USA	US\$93 billion
R&D for developing country diseases	US\$3 billion
% of developing country R&D expenditure per disease (%)	
HIV/AIDS	39
malaria	18
tuberculosis	15
protozoa, other than malaria	4.7
diarrhoeal diseases	4.5
helminths	2.3
rheumatic fever	<0.3

should be brought forward for a multi-component vaccine. In trypanosomiasis, therapeutic vaccines should be considered, e.g. in recalcitrant *Trypanosoma cruzi* infections.

As regards metazoa, the field needs to take very seriously the work of Lightowers [13] who has shown that the *Taenia solium* oncosphere antigen TSOL18 is 99.3–100% effective in protecting against cysticercosis in pigs when given as three doses with Quil A adjuvant. This shows that helminth infections can be prevented. In humans, some promising research leads exist for vaccines against hookworm, onchocerciasis and schistosomiasis, but the field is not as vibrant as it was 20 years ago. Anti-helminth vaccines would not necessarily have to cause sterilizing immunity. If they reduce parasite load, they could be adjuncts to community chemotherapy, e.g. with praziquantel, ivermectin or albendazole depending on the parasite, in programmes of integrated parasite control. It is encouraging to note that a number of drug companies are making anti-helminthic drugs available free of charge to various campaigns for the eradication of helminths. Merck is in the lead, with over 2 billion Ivermectin tablets donated for filariasis.

#### 6. GLOBAL HEALTH R&D PRIORITIES NEED TO BE RESET

The work of the George Institute in Sydney known as the G-FINDER study has revealed that the total spending on research and development for diseases of the developing countries totals US\$3 billion per year which is approximately 1.5 per cent of the approximately US\$200 billion which the world (chiefly governments and industry) spends on health and medical research. This is actually much less than the oft-quoted '90/10' formula claiming 90 per cent spending on the diseases of 10 per cent of the people. Moreover, the lion's share of this US\$3 billion goes to just three diseases: HIV/AIDS (39%), malaria (18%) and tuberculosis (15%). In other words, acute respiratory diseases, diarrhoeal diseases and parasites other than malaria are being seriously short-changed (table 1).

#### 7. IMPLICATIONS OF VACCINE R&D ON IMMUNIZATION BUDGETS

If we take an optimistic look at 2030, there could be some 20 important vaccines available. The present annual birth cohort is 130 million and we shall assume that it

stabilizes. We shall guess mature market vaccine costs at US\$3 per dose, recognizing that some will cost much less and others, e.g. 'prime–boost' regimens, much more. We shall also assume three doses per immunized child and an estimated global coverage of 80 per cent. For the purposes of this exercise, we shall ignore the very much higher prices which will be charged in industrialized countries. In that case, the cost of all vaccines would be US\$19 billion. We may then ask what is the present world position as regards funding flows for developing country vaccines—both R&D and delivery programmes? The GAVI Alliance spends US\$1 billion; polio eradication is running at about US\$800 million per year; R&D towards an HIV/AIDS vaccine is at about US\$800 million, so we can surmise that the grand total might be US\$3–3.5 billion per year. The total of official development assistance globally is presently US\$120 billion. If global gross national income increases by 3 per cent per annum, and if (a very big if!) the donor nations raise their contributions to official development assistance (ODA) to 0.7 per cent of gross national income, global ODA by 2030 would be US\$320 billion. It is unreasonable to demand that US\$19 billion, or 6 per cent of the total, go to just one purpose, i.e. vaccines. The conclusion is obvious. Much of the money for vaccination will need to be found from within the developing countries themselves. This vindicates the present GAVI policy of seeking increasing co-payments.

## 8. THE GLOBAL POLIOMYELITIS ERADICATION INITIATIVE

The global polio eradication initiative is among the highest priorities for both the WHO and for UNICEF. It is also high on the list for Gates' benefactions, and Rotary International's commitment is well known. The new strategic plan calls for eradication by 2013, but funding continues to be a problem. Current running costs are about US\$800 million per annum and the total expenditure between 1988 and 2009 has been over US\$8 billion. Fortunately, affected country contributions are starting to be significant—now accounting for about 20 per cent of costs (table 2).

Support for polio eradication is by no means universal. There is indeed a dilemma in spending billions of dollars on a campaign of surveillance and mass immunization when the actual present public health threat is minuscule in comparison with many other infections. Critics point to children in North India where 10 or more doses of Sabin vaccine have (for whatever reason) failed to give protection, and to the difficulty and expense of switching to injectable (Salk-type) polio vaccine in such areas. Questions of efficacy of the cold chain have also been raised and the adequacy of surveillance in countries like Afghanistan is an issue. On the other hand, there is a big past investment to protect, and eventually a 'polio dividend' to be obtained when, in due course of time, routine immunization can be halted. In this regard, it is worth noting the remarks of the new Executive Director of UNICEF, Anthony Lake, who said recently: 'It is apparent where polio is making its final stand—in the most forgotten places among the most forgotten people. We must all dedicate ourselves to writing this final chapter

Table 2. Number of confirmed poliomyelitis cases to 14 December.

	2009	2010
endemic countries		
India	672	41
Nigeria	388	13
Pakistan	84	134
Afghanistan	31	23
Horn of Africa		
Sudan	45	0
Kenya	18	0
Uganda	82	2
selected re-infected countries		
Tajikistan	0	458
Angola	29	30
the world	1503	874

and closing the book on polio forever. For every child'. The author subscribes to this view.

A recent study of Duintjer Tebbens *et al.* [14] has attempted to quantify the economic benefits of global polio eradication. It comes to the conclusion that the incremental net benefits (1988 net present value in 2008 dollars) is US\$40–50 billion. In addition, as many polio campaigns also give oral vitamin A with the polio drops, saving many lives, a further net benefit of US\$17–90 billion can be inferred. The study used the period 1988–2035.

Among the four countries in which polio transmission has never ceased, Nigeria and India are doing well with, respectively, a 97 and 94 per cent reduction in confirmed cases between 2009 and 2010—Pakistan and Afghanistan are not doing as well. Giving two doses of oral polio vaccine two weeks apart around the index case works well in re-infected countries. For example, the Horn of Africa is now virtually polio free after 71 cases in 2009. However, the 2010 outbreak in Tajikistan is a harsh reminder that under-immunized populations are vulnerable to re-infection until polio is eradicated globally. Prior to 2010, Tajikistan's last indigenous case was in 1997. In 2010, a wild poliovirus type 1 originating in India caused 458 cases, clustered in the west of the country. Fortunately, the epidemic may be over as the last case was in July 2010. High population immunity is the only protection against such outbreaks. Moreover, re-infection can be quite stubborn. Angola had 29 cases in 2009 (to 14th December) and 30 in 2010 (to 14th December).

Episodes of diarrhoea may limit the efficacy of Sabin vaccine. Perhaps zinc supplementation should be routine in areas such as Bihar and Uttar Pradesh in India to combat diarrhoea and hence enhance vaccine effectiveness.

If polio has been eradicated by 2013, post-eradication challenges will remain. These include containment of laboratory stocks of wild poliovirus. Two hundred and fifteen facilities currently hold the virus. This should be reduced to a handful of tightly regulated facilities post-eradication. Consideration should also be given to a global round of injectable polio vaccine after the cessation of oral polio vaccine administration to limit the possibility

that persisting oral polio vaccine could infect children and revert to virulence. Routine immunization should only cease when vaccine strains are no longer circulating.

## 9. VACCINES AND CHRONIC DISEASES

One of the more intriguing developments in modern medicine, by no means fully understood, is that patients with a variety of chronic diseases not usually thought of as infectious in nature, display signs of inflammation such as a raised erythrocyte sedimentation rate or raised serum levels of acute phase proteins. Indeed, a somewhat worrying trend is the widespread 'off label' use of intravenous  $\gamma$  globulin in such inflammatory conditions. In the long term, this raises the issue of whether vaccines of the future will include some outside the field of classical infectious diseases. This area is covered by Bachmann and Jennings [15] elsewhere in this volume. It is perhaps merely a semantic point, but should administration of antigens with the purpose of suppressing rather than stimulating immune responses be classified as vaccines? These could perhaps be considered as 'negative vaccines'. Desensitization in allergy is one and immune approaches to autoimmunity another example of this approach. At the risk of exceeding the scope of the present paper, and of entering a highly speculative area, I shall briefly present two studies from the Walter and Eliza Hall Institute of Medical Research which illustrate the potential power of the negative vaccine approach. In particular, the diabetes study makes the point that, while autoimmunity usually involves a multiplicity of antigens, raising suppressor cells against just one antigen can have surprising effects.

### (a) *Autoimmune diseases: insulin-dependent diabetes*

Insulin-dependent diabetes is an autoimmune disease in which the insulin-secreting  $\beta$  cells of the islets of Langerhans are progressively destroyed. The closely related disorder of NOD diabetes in non-obese diabetic mice can be prevented by mucosal administration of islet autoantigens, most notably pro-insulin, insulin or glutamic acid decarboxylase (GAD). In the human, first degree blood relatives of known diabetics are at increased risk of diabetes. Prior to complete loss of insulin production, a pre-diabetic state can be identified characterized by autoantibodies to insulin, GAD and other islet cell antigens and by marked reduction of the first phase insulin response to intravenous glucose. In Melbourne, Australia, with adjunct efforts in New Zealand and Germany, a major double-blind trial is underway to test whether intranasal insulin can delay or prevent the onset of diabetes [16]. Two hundred and sixty-four relatives aged 4–30 are involved. Subjects receive 1.6 or 16 mg insulin or placebo intranasally daily for 7 days, then weekly for a year. The relatives must have autoantibodies to at least two islet antigens and, furthermore, have a first phase insulin release of more than the 10th percentile to ensure that some  $\beta$  cells have remained undestroyed. Results of the trial will be available in 2012.

### (b) *Gluten intolerance: coeliac disease*

Coeliac disease is a genetic condition in which the gut reacts violently to antigens in grain. Recently, a

comprehensive map has been obtained of all the T cell epitopes in gluten which stimulated the T cells from individuals recently fed cereal [17]. Surprisingly, T cells specific for just three peptides accounted for most gluten-specific T cells. This limited diversity offers the hope that it may be possible to devise peptide-based therapeutics as a 'negative vaccine' in this disease. The idea is that repeated administration of dominant epitopes switches off disease-causing T cells and induces clinical tolerance. Pre-clinical proof of concept has been obtained in a transgenic mouse model. Success in the clinic would mean that patients could avoid the difficult lifestyle change of a gluten-free diet and avoid the extensive intestinal damage of this disease. A phase II clinical study is in the planning stage. The final dream would be oral dosing in infancy, i.e. pre-gluten exposure thus preventing the disease in at-risk infants.

Among many other diseases in which the 'negative vaccine' approach could be helpful are rheumatoid arthritis and multiple sclerosis, although results so far have been disappointing. Still more speculative are atherosclerosis for which it is postulated that antibodies including those to oxidized low density lipoproteins, heat shock protein and  $\beta$ -2 glycoprotein 1 contribute to the disease, and Alzheimer's disease, for which the aim would be the prevention of  $\beta$  amyloid plaques.

### (c) *Cancer*

Despite the enormous amount of work that has been done on anti-cancer vaccines, the practical yield has been disappointing. I refer to vaccines designed to combat established cancer, and not, of course, to the brilliant success of vaccines against viruses which cause cancer, such as the human papilloma virus or hepatitis B. Quite a few anti-cancer vaccines have 'looked good' in phase II trials only to fail at phase III. Two exceptions are the patient-specific anti-idiotypic vaccine in B cell lymphoma, which offers a modest prolongation of remission, and Dendreon's Provenge, a vaccine against advanced prostate cancer approved by the FDA in April 2010. Therefore, there is currently a deal of interest in quite a different approach to cancer vaccines, namely to seek to inhibit regulatory pathways which down-modulate the body's own immune response to tumour-associated antigens. For example, blockers of CTLA-4 look promising in advanced melanoma [18].

A final reflection on cancer immunology is that, in the long run, a better target for vaccine-induced immunity may be minimal residual disease rather than extensive metastatic deposits. In that case, cancer immunotherapy or anti-cancer monoclonal antibodies could be compared with adjuvant chemotherapy, namely a treatment modality designed to improve the outlook in situations where the prognosis is already quite good. Lifting the 5 year survival rate in breast or colon cancer staged at 50 per cent, to say 75 per cent would save many more lives than adding a few months of life to end-stage metastatic disease. Adjuvant chemotherapy and adjuvant immunotherapy ought to be at least additive, if not synergistic.

### (d) *Adjunct issues*

There are a number of important disease non-specific issues that vaccine science will have to address. The

number of needle-pricks that infants and young children face is already a worry, and as new vaccines come on stream this number will increase. One answer to this challenge is more extensive combinations of vaccines. Already, a hexavalent vaccine consisting of diphtheria, tetanus, acellular pertussis, *H. influenzae type B*, injectable poliomyelitis and hepatitis B is in widespread use. We do not know how far we can go with combinations. In this case, there is a slight but significant lowering in the response to Hib polysaccharide. Another popular combination is live, attenuated measles-mumps-rubella-varicella. There is a small price to pay here. This vaccine carries twice the (still very low) risk of febrile convulsions when compared with separate MMR and varicella. Doubtless experimentation with new combinations will continue.

Needle-free delivery systems must be explored further. Up till now, work on transdermal delivery has been disappointing. Vaccination practice is understandably conservative. New delivery modalities will probably be reserved for new vaccines. Certainly mucosal approaches deserve much more research. An intranasal influenza vaccine works very well and research is well advanced on an inhalable measles vaccine capable of immunizing infants younger than nine months of age as mentioned above. This would be very useful, as in some developing countries, measles mortality between four months (when maternally derived antibodies wane) and nine months is significant. Mucosal approaches will go hand in hand with new mucosal adjuvants.

Indeed, the field of adjuvants as a whole is set to explode. Many new adjuvants target evolutionarily ancient receptors capable of recognizing pathogen-associated molecular patterns. Best studied are the toll-like receptors (TLRs) but there are other elements of the innate immune system, such as NOD-like receptors, RIG-I-like receptors and c-type lectin receptors, worthy of attention. Defining the molecular signals which pathogens impart to these constituents of the immune system will be very important. Clearly, these interactions promote adherence to accessory cells (dendritic cells and macrophages), followed by engulfment and/or specialized processing and presentation of antigens. Up to now, research has focused on empirically determining which adjuvant components are needed to induce particular adaptive immune effector responses. A more systematic (systems immunology) approach to the relevant signalling cascades and how they interact with one another could yield a rich harvest.

Companies are exploring combinations of adjuvant principles such as two or more TLR agonists, virus-like particle formation and emulsification. Apart from alum, there are now four licensed adjuvants: MF59 (Novartis), AS03 and AS04 (GlaxoSmithKline), and liposomes (Crucell). Quite a few other adjuvants are in advanced clinical trial. An interesting candidate is IC31 from the Austrian firm Intercell. It consists of the antimicrobial peptide KLK mixed with the immunostimulatory oligodeoxynucleotide ODN1a, simply mixed with the antigen (no conjugation required). It is safe and well tolerated in humans, forms a depot for at least two months and stimulates both T and B cells.

#### (e) *Anti-vaccine activists*

In contrast with most pharmaceutical products, which seek to cure illness when it occurs, vaccines are given to healthy individuals, especially to infants and children, deemed to be especially vulnerable. Therefore, it is entirely appropriate that vaccine safety is a prime concern. Fortunately, history has shown vaccines which have been through the appropriate clinical trial procedure have been extraordinarily safe. Minor adverse events, such as local redness and swelling, mild fever or local lymph node soreness are relatively common. More serious complications, such as febrile convulsions, are rare but not excessively so. Fatalities are genuinely vanishingly rare. Nevertheless, a minority of the public harbour the misconception that vaccines are dangerous, either somehow compromising the proper immune development of the child, or causing some serious problem like encephalopathy or autism. Any such claim must be taken quite seriously, must be subjected to rigorous research, and, when the relevant evidence is in, must be politely but firmly refuted. Anti-vaccine activists tend to have forgotten what real epidemics are like. In a way, immunization has become the victim of its own success. In industrialized countries, wards full of people in respirators with bulbar palsy from polio, or children rushed to emergency departments with bacterial meningitis, have become things of the past. It is only when complacency allows vaccine coverage to fall below a certain threshold that new disease outbreaks occur, and then mothers frequently change their minds!

While the author has found that sweet reason is one weapon against anti-vaccine activists, simply presenting honest adverse event statistics over and over again and contrasting these with the frequency of malvolent complications from diseases like measles and whooping cough, alone is not enough. Extensive educational effort is needed to overcome inertia on the one hand and outright opposition on the other hand. In Australia, one stratagem that has worked quite well is to give general practitioners extra financial incentives to achieve adequate vaccine coverage for their patients. Nevertheless, there will be some zealots who will never be convinced.

A few years ago, Australia conducted a nationwide, school-based measles vaccine 'catch up' campaign. It provided a good opportunity to catalogue adverse events (serious ones extremely rare) and to gauge community attitudes to vaccination. It turned out that only 8 per cent of parents failed to avail themselves of the chance to immunize their child. Interestingly, of these only a quarter, or 2 per cent of the global total, had an intellectual reason for declining. The other three-quarters refused owing to trivial reasons (losing the form, going on vacation, forgetting, etc.). As it happens, herd immunity could easily look after that residual two per cent. But well-targeted publicity campaigns on the benefits of vaccines and the overwhelmingly positive risk/benefit equation continue to be worthwhile.

## 10. CONCLUSIONS

If we compare the global public health scene now to the situation 15 years ago, it is apparent that there

has been a radical change. The world has been alerted to the fact that all those preventable deaths in developing countries are not just a humanitarian disgrace but a barrier to economic development and a more peaceful world. As a result, under five mortality is coming down (13 million deaths in 1990, estimated 8 million in 2010), and at least some of the Millennium Development Goals are nearly within reach. Immunization programmes have made a major contribution to this change, but a great deal more remains to be done. The situation with the 'big three', HIV/AIDS, malaria and tuberculosis, is still uncertain and the peer group represented at this Symposium has a significant role to play here. The vaccinology community is poised at the interface between science and politics—one way or another it must be active in both fields. This is not a time to be hiding our light under a bushel. Actually, we would be wise to heed the words of the Secretary-General of the United Nations, Ban Ki-moon, when, at the Millennium Development Goals Summit in October 2010, he said: 'In the past, we have seen that when the spotlights are switched off, world attention quickly moves to other issues. With only 5 years left, we cannot let that happen. Between now and 2015, we must make sure that promises made are promises kept. The consequences of doing otherwise are profound: death, illness and despair, needless suffering, lost opportunities for millions upon millions of people. The MDGs . . . (are) based on global solidarity . . . linked fates in an interconnected world'.

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