



STI Newsletter 1/2009: Vaccination – from basic research to application

Editorial

Happy New Year and all our best wishes for a successful 2009 to all our readers - it is a great pleasure to introduce our first newsletter of 2009 with some highlights from the malaria vaccine front. STI is very pleased and proud to be part of a few major steps in malaria vaccine development recently completed and ranging from the design of a virosome-based approach to the clinical trials in endemic areas. The current newsletter presents the flashes from the recent work where we were involved and indicates the way forward.

Given the formidable task of vaccine development, it is clear that no single institution can undertake the whole R&D efforts. We are happy to be able to contribute to major vaccine development platforms, mainly led by Malaria Vaccine Initiative (MVI) and supported by the Bill & Melinda Gates Foundation. These platforms bring together academic institutions, industrial partners, WHO, national research authorities, regulatory authorities and funders and allow an effective R&D process, hopefully leading to the registration of the world's most advanced malaria vaccine, RTS,S, in 2011.

The pace towards a malaria vaccine to be used for those most in need has now quickened owing to scientific achievements, the leadership of African research centers and also to the great international commitment and fine spirit of collaboration. While appreciating these developments and the momentum created for a malaria vaccine, we should not forget that successful malaria control and elimination in a specific setting will still and always require an integrated approach with early diagnosis and treatment, the use of insecticide treated nets or materials and indoor residual spraying or larval control depending on the ecological situation being the main cornerstones. A malaria vaccine will substantially strengthen the integrated approach but not replace it.

I wish you an enjoyable reading and we look forward to receiving your questions and comments.

Marcel Tanner

Table of Contents

| | |
|--|----|
| Editorial | 1 |
| Current state of the development of the malaria vaccine RTS,S | 3 |
| Development of a virosomal malaria subunit vaccine | 6 |
| Is an antimalaria vaccine directed against variable antigens of <i>P. falciparum</i> (PfEMP1) useful and feasible? | 8 |
| Malaria vaccine development – PMAL03, Phase Ib clinical trial in Bagamoyo, Tanzania | 9 |
| Simplifying pediatric immunization with fully liquid pentavalent DTP-HepB-Hib combination vaccines | 14 |
| Transmission dynamics and economics of rabies control in dogs and humans in an African city..... | 17 |
| Combined human and animal vaccination delivery services | 18 |
| Travel Medicine Vaccinations..... | 19 |
| Postmarketing vaccine safety and effectiveness | 22 |

Current state of the development of the malaria vaccine RTS,S

Prof. Marcel Tanner

Results published in the *New England Journal of Medicine* revealed that the world's most clinically advanced malaria vaccine candidate provides both infants and young children with significant protection against malaria. Two separate phase II trials reaffirmed earlier study results and support the ongoing efforts, pending regulatory approvals, to launch the phase III study of GlaxoSmithKline (GSK) Biologicals' RTS,S/AS vaccine candidate across Africa (Abdulla et al. 2008, Bejon et al. 2008). The vaccine RTS,S was invented, developed and manufactured in laboratories at GSK Biologicals' headquarters in Belgium in the late 1980s and initially tested in US volunteers as part of a collaboration with the US Walter Reed Army Institute of Research.

In infants, data show for the first time that the vaccine candidate can be administered as part of existing African national immunization programs. In children aged 5 to 17 months, the candidate RTS,S/AS01 reduced the risk of clinical episodes of malaria by 53 percent over an eight-month follow-up period and was shown to have a promising safety profile. The studies were conducted in Kenya and Tanzania and were presented as highlights at the American Society for Tropical Medicine and Hygiene (ASTMH) annual meeting in New Orleans at the day they were also published by the *New England Journal of Medicine* on 8 December 2008. The STI is very happy to have been part of these developments through its role as site partner to the Bagamoyo Research & Training Centre (BRTC) of the Ifakara Health Institute (IHI) that conducted the infant study (Abdulla et al. 2008).

Infant Study: Effective co-administration with EPI Vaccines (Abdullah et al 2008)

The infant study enrolled 340 infants under 12 months of age in Tanzania and found that RTS,S/AS02, when administered at 8, 12, and 16 weeks of age with a commonly used childhood vaccine, did not interfere with the protective immune responses to each of the vaccine components. The childhood vaccine contained antigens for Diphtheria (D), Tetanus (T), whole-cell pertussis (Pw) and *heamophilus influenzae* B (Hib). In countries where a malaria vaccine is needed most, the current immunization schedule for infants, called the WHO Expanded Program on Immunization (EPI), would provide an optimal delivery platform.

Researchers evaluated the safety and immune responses when administering the RTS,S/AS02 vaccine in conjunction with an EPI schedule. It was a randomized double-blind trial with

participants simultaneously receiving either RTS,S/AS02 and DTP w/Hib as well as oral polio vaccine; or a hepatitis B vaccine and DTP w/Hib as well as oral polio vaccine.

Additionally, the study reported 65 percent reduction against first infection from malaria in those infants who received three doses of the RTS,S/AS02 vaccine and were followed over a six-month period. This study builds upon results published in October 2007 in *The Lancet*, which found a similar level of efficacy for RTS,S/AS02 when it was given in a staggered fashion with the administration of DTPw/Hib vaccine (Aponte et al. 2007).

The trial was undertaken by the BRTC of IHI led by Dr. Salim Abdulla together with a team that included researchers from the STI, the London School of Hygiene and Tropical Medicine (LSHTM), GSK Biologicals, and MVI.

Child study: 53% efficacy against clinical malaria in children (Bejon et al. 2008)

The other trial enrolled 894 children 5-17 months old in both Kenya and Tanzania within the frame of the collaboration between KEMRI-Wellcome Collaborative Research Programme (Kilifi, Kenya), the National Institute for Medical Research (Tanzania), the Joint Malaria Programme (Korogwe, Tanzania), LSHTM and other institutions in collaboration with GSK and the MVI. The study was designed to evaluate the safety and efficacy of the RTS,S/AS, combined with another GSK's proprietary Adjuvant System, coded AS01. The study was a double-blind randomized clinical trial in which children received either three doses of the RTS,S/AS01 vaccine candidate or a rabies vaccine.

It found that the RTS,S/AS01 formulation reduces clinical malaria episodes by 53 percent for up to an average of eight months. Earlier studies in Mozambique using RTS,S formulated with a different GSK Adjuvant System (AS02) demonstrated 35 percent efficacy against clinical disease for 18 months among children 1–4 years old. Researchers concluded that these study results support the use of RTS,S/AS01 for upcoming Phase 3 trials.

These studies open the way to a large scale phase-3 trial involving some 16'000 infants and small children in 11 centres in Africa. Pending approvals by national regulatory agencies and ethics committees, this multi-center phase III efficacy trial will start in early 2009. The trial will seek to confirm and evaluate with precision the vaccine's efficacy, including duration, and will continue to closely monitor safety. The clinical development of RTS,S/AS is led by the Clinical Trial Partnership Committee, a collaboration of leading African research

institutes, Northern academic partners with STI playing an important role, MVI and GSK with support from the Malaria Clinical Trial Alliance.

Key references

Abdulla S, Oberholzer R, Juma O, et al. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *N Engl J Med* 2008;359:2533-44.

Bejon P, Lusingu J, Olotu A, et al. Efficacy of RTS,S/AS01E: clinical malaria in 5 to 17 month old children. *N Engl J Med* 2008;359:

Aponte JJ, Aide P, Renom M, et al. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. *Lancet* 2007 Nov 3;370(9598):1543-51. Epub 2007 Oct 18.

e-mail: marcel.tanner@unibas.ch

Development of a virosomal malaria subunit vaccine

Prof. Gerd Pluschke

The development of a malaria vaccine represents currently one of the most important scientific challenges in global public health. One approach is the design of a subunit vaccine that incorporates several malaria protein antigens for which there is evidence of protective immunity from epidemiological data and/or experimental animal challenge models. Currently, the development of such subunit vaccines is hampered by lack of highly effective and human-compatible antigen delivery systems that are driving suitable protein antigen-specific immune responses in humans and have an appropriate safety profile. Furthermore, production of synthetic or recombinant proteins that stably mimic the native structure of the corresponding malaria antigens to induce effective humoral immune responses is a major challenge. Since no vaccine against a human parasitic disease is currently available, it is believed that novel approaches and technologies are required for the development of such vaccines.

The Molecular Immunology unit of the Swiss Tropical Institute in cooperation with Pevion Biotech Ltd. (Dr. R. Zurbriggen) and the Institute for Organic Chemistry of the University of Zürich (Prof. J. Robinson) is developing a candidate malaria vaccine based on synthetic peptides displayed on the surface of immuno-potentiating reconstituted influenza virosomes (IRIV). IRIV represent an innovative antigen delivery system derived from a mixture of natural and synthetic phospholipids and influenza surface glycoproteins. We have demonstrated that IRIV are suitable to elicit strong immune responses against peptide antigens attached to their surface via phospholipids anchors. Using an iterative antigen optimisation process, we have developed synthetic peptides mimicking the native structure of surface loops of two key *Plasmodium falciparum* vaccine candidate antigens, the circumsporozoite surface protein (CSP) of sporozoites and the apical membrane antigen 1 (AMA-1) of merozoites. Pre-clinical development and characterisation of virosomal formulations of the two peptides, designated PEV301 and PEV302, was supported by the Commission for Technology and Innovation of the Bundesamt für Berufsbildung und Technologie.

In a phase I clinical trial at the University Hospital of Basel we have demonstrated the safety and immunogenicity of PEV301 and PEV302 given in two different doses alone or in combination. At appropriate antigen doses, both vaccine components elicited already after two injections long-lived peptide-specific IgG antibody responses in all volunteers immunized. IRIV seem to have both an immunopotentiating adjuvant-like activity and to act

as carrier system providing T cell help to malaria antigen specific B lymphocytes via influenza antigen-specific T cells. Correlations between high parasite binding IgG titers with positivity in PEV301 peptide specific lympho-proliferation assays indicate that malaria peptide-specific T cells can provide additional T cell help. Importantly, all volunteers had pre-existing influenza antigen specific immune responses that did not negatively affect the vaccine-induced humoral and cellular immune responses. Purified immunoglobulins from PEV302 immunized volunteers inhibited substantially sporozoite migration and invasion of hepatocytes in vitro. Combined delivery of the two IRIV-formulated peptides did not interfere with immunogenicity of either peptide, demonstrating the suitability of the IRIV system for development of multi-valent subunit vaccines. After the recent finalisation of a phase IIa clinical trial at the Centre for Clinical Vaccinology and Tropical Medicine, Oxford University (Prof. A. Hill), the safety and immunogenicity of the two components PEV301 and PEV302 is now tested in malaria-exposed Africans.

Since we assume that an effective malaria subunit vaccine has to incorporate more than two antigens, we are developing peptide mimetics of additional key *Plasmodium falciparum* vaccine candidate antigens. Within the framework of the European Malaria Vaccine Development Association, an integrated project under the Sixth Framework Programme of the European Community, pre-clinical profiling of four new components is currently being finalized. Overall goal of the project is to formulate a cost effective, multi-stage, multi-component malaria vaccine preparation that provides protection against the disease and can be employed in endemic areas most in need. The project will generally further the development of an urgently needed, versatile, human-compatible antigen delivery platform that allows stimulation of different compartments and effector functions of the adaptive immune system.

e-mail: gerd.pluschke@unibas.ch

Is an antimalaria vaccine directed against variable antigens of *P. falciparum* (PfEMP1) useful and feasible?

Prof. Hans-Peter Beck

Evidence is emerging that immunity against malaria is to a large degree due to humoral responses against variable antigens located on the surface of infected erythrocytes. *Plasmodium falciparum*, once in the red blood cell, substantially modifies the cell and, besides establishing the whole machinery for protein synthesis and transport, places a molecule into the erythrocyte membrane. This protein (PfEMP1) confers binding to endothelial cells and is considered to be the major virulence factor in malaria. However, this molecule displays significant antigenic variation, i.e. changes its antigenic property to escape elicited immune responses. Because of this, development of a vaccine based on this molecule has been considered impossible.

However, several pieces of evidence suggest otherwise. First, during pregnancy, parasites infecting the placenta commonly express one particular PfEMP1 molecule (varCSA) and thus a vaccine against pregnancy associated malaria is being developed based on this one form of PfEMP1. Secondly, a large number of PfEMP1 molecules bind to an epithelial cell protein, CD36, and recently a structural conservation of the head structure of PfEMP1 has been shown. Therefore, it seems feasible to develop a vaccine based on these structural features to block binding to CD36. Thirdly, additional evidence is emerging that parasites causing severe disease and adhering to tissues in essential organs (brain, lung, kidneys, etc.) display only a limited number of PfEMP1 molecules, and the identification of these molecules could lead to a disease blocking vaccine. Fourthly and finally, it is now possible to genetically modify parasites in such way that no PfEMP1 can be produced or no PfEMP1 will be exposed on the surface. As an experimental approach it is feasible to use these modified strains as genetically attenuated parasites (GAPs) to study immune responses elicited.

At the STI research department 'Medical Parasitology and Infection Biology' research is conducted into the last two approaches, identification of virulence associated PfEMP1 molecules and production of PfEMP1 negative mutants to be used as experimental GAPs.

e-mail: hans-peter.beck@unibas.ch

Malaria vaccine development – PMAL03, Phase Ib clinical trial in Bagamoyo, Tanzania

Dr. Hermann Garden

In the context of innovative approaches for the prevention and cure of malaria in tropical countries, the development of a potent vaccine against the *Plasmodium falciparum* parasite represents a promising but still not achieved tool. Due to the lack of cost-effective treatments in most of the sub-Saharan countries and the thread of emerging resistances, a malaria vaccine is likely to be crucial in reducing both the morbidity and the mortality of this disease. However, unlike the well-known WHO driven eradication of the smallpox virus during the 1970s and various achievements of successful vaccination against the major childhood diseases such as measles, diphtheria, pertussis, tetanus and polio effective vaccination against malaria still remains a wishful goal. Nevertheless, recent success in basic research and clinical trials shed some light into the shade and encourages the STI to further strength its commitment in the development of a viable malaria vaccine.

At first hand, it sounds odd that after the first successful prove-of-principle experiment in mice with x-irradiated sporozoites by Dr. Ruth S. Nussenzweig (New York University, 1967) it took more than 40 years of research to achieve a 4 months lasting 60% effective vaccination against pre-erythrocytic stages of the parasite. However, even with an effectiveness of 60% the number of lives saved and the malaria symptoms significantly reduced within the most vulnerable group of young children in sub-Saharan Africa justifies our efforts in the development of a malaria vaccine. However, the development of a malaria vaccine is like a jigsaw puzzle and presents a difficult scientific challenge. Several factors account for the historic failure and may explain why at STI it necessitates a joint effort from several scientific disciplines such as parasitology, biochemistry, immunology and molecular epidemiology before one can think of the conduct of specifically designed clinical trials by the Pharmaceutical Medicine Unit.

From a research perspective, obstacles for the development a safe and effective malaria vaccine are manifold and stem from:

- Inadequate animal models
- A patchy understanding of the immune response
- A lack of safe and potent immune stimulative adjuvant

- An incomplete understanding of the functions of the thousands of proteins (and potential candidate antigens) expressed by the parasite
- A poor understanding of the relevant variable and conserved immunodominant and non-immunodominant epitopes for protection

In particular, the antigenic variability of surface proteins seems to be crucial for the parasite to evade the host's immune defense, and it's obviously a disadvantage not only for the infected individual but also for the researchers aiming to design a vaccine. At first sight, it seems to be a logical consequence that some investigators revive the idea of using attenuated Plasmodium live stages as an all-in-one vaccine and could report a high protection against malaria under laboratory conditions. Unfortunately this approach appears technically difficult to pursue and unrealistic for scale up. Thus, the focus of malaria vaccine research at STI has been focused on selected antigens (whole proteins, synthetic peptides or carbohydrates) which are presented to the immune system – the so called subunit vaccine approach. This has also been chosen for the development of the aforementioned RTS,S pre-erythrocytic stage vaccine or PEV301 and PEV302, which are candidate components for incorporation into a multivalent virosomal vaccine during a joint project between Pevion Biotech Ltd. and the STI. A bivalent vaccine candidate consisting of PEV301 and PEV302 is currently tested within the PMAL03 Phase Ib trial at the Bagamoyo Research & Training Centre (BRTC) of the Ifakara Health Institute (IHI), Tanzania.

The conduct of clinical trials in accordance to internationally accepted guidelines and ethical principles for the development of new drugs in resource limited countries demands for a thorough knowledge of the local circumstances and regulatory requirements. This holds especially true for the conduct of a malaria vaccine trial in sub-Saharan Africa. Ensuing the early laboratory research and animal testing for vaccine candidate needs to be assessed for its safety under defined conditions of clinical trials – first, in non-immune volunteers (Phase Ia trials), and then in semi-immune volunteers of malaria endemic countries (Phase Ib trials). Extended, Phase II and Phase III trials involving thousands of volunteers at various clinical sites that are followed-up, upon confirmation of the vaccine's safety and immunogenicity. However, albeit the different size and goals of the early and late phase trials, there are certain characteristics that may render challenging any stage of the malaria vaccine development.

Attention needs to be paid to the safety of the volunteers representing the focus group for the future malaria vaccine – mostly young healthy children. This has also been considered and

elaborated in the study protocol for the aforementioned PMAL03 trial carried out in Tanzania. Though the preceding Phase Ia trial did not raise any safety concerns, the malaria vaccine had been applied first in 10 healthy adult men to mitigate the risk for the 40 children vaccinated in a staggered approach thereafter. As a preliminary result of the ongoing trial, it should be pointed out that the vaccine proves to be safe and that the volunteers show a very good compliance. However, this is not always the case and can surely be attributed to the experienced study team at the BRTC.

That being said, one might ask what characterizes a successful study team, what makes a clinical trial protocol comprehensive and adequate, what constitutes an informed consent applicable to children volunteers and what are the main difficulties to carry out a vaccine trial in sub-Saharan countries. Most importantly, the study has to account for the special needs of children volunteers. Vaccine trials are complicate and comprise numerous of detailed clinical and laboratory assessments lasting over several months or even years, whereas in most cases children or infants are too young to understand the trial and to assess the possible risk versus the possible benefit. And even their parents or caretaker might not fully understand all implications of the trial when giving their consent for the child's participation. Thus, for the PMAL03 trial an adequate and understandable volunteer information had been written and translated into Swahili, the local language. Still, the investigator has to verbally provide all explanations about the trial with a thorough understanding of the person's educational background and possible concerns about a malaria vaccine trial. People might be me, for instance, concerned about the confidentiality of HIV test results and exposure to the community, giving signatures, photos taken or the blinding within a controlled trial. These topics need to be adequately explained and enough time has to be given to each participant to rethink their decision whether or not to allow their child to participate in the trial. Thus, for the PMAL03 trial, each parent or caretaker had been requested to evaluate the information presented during 2 days before taking any decision. This is of special importance to allow a family or even community based decision on the possible participation of the child.

Moreover, broad vaccination programs are yet disputable and not without any doubts from a scientific and public health point of view. Possible loss of the protective immune status that has been acquired over many years in an endemic area is still a major concern, therefore representing a potential threat to the individual and to the whole community. This might occur if a continuous antigenic stimulation ceases after successful malaria vaccination and could render the vaccinees more vulnerable to malaria due to a reduced semi-immunity. Therefore,

a close and lengthy post-vaccination follow-up of each vaccinee is an indispensable requisite of a malaria vaccine trial in disease endemic areas with a high transmission rate. Effects on malaria transmission or the long-term dynamics of immunity should always be considered for such trials.

Obviously, special abilities and experiences are needed to enable the local study team a smooth and successful conduct of the trial. All PMAL03 team members at the site, the nurses, investigators, coordinators and the mobile team have to adapt their experiences gathered during clinical trials on new drugs to the special requirements of a malaria vaccine trial. By analogy to the testing of new drugs where the effect and cure is perceived within a short time frame, a vaccine might also be considered as an absolute protection – which is not the case. Understanding the fact that the protective effect of a malaria vaccine is rather gradual and ranges from an elevation of all malaria symptoms to the possible failure for an individual. Thus, especially in large vaccination programs, it is up to the community health workers (mobile teams) to inform each family as well as the village community that the positive effect of a malaria vaccine does not protect the vaccinee from the infection but aims at a reduction of malaria symptoms and a possible control of transmission.

Besides the operational and technical challenges faced during a trial in rural areas, it has already pointed out that social and community based aspects constitute further topics which need to be addressed before the launch of the trial. For the PMAL03 trial we had to take measures for:

- A consistent follow-up of the volunteers over an extended follow-up period of 2 years to capture enough efficacy endpoints and ensure the volunteers safety
- A thorough understanding of the perception of the disease within the community
- A recognition of local traditions and social norms
 - young women are often denied autonomy, their children's participation in research is therefore highly liable to be exploited
 - often it's the father to decide on the child's participation
 - the community leader has to be asked for assent; however, his decision should not override the individual's case
- A good interpersonal relationship between the staff and the volunteers

- To adequately explain why larger quantities of blood samples are needed for the assessment of the immune reaction (more than for pharmacokinetic samples in drug trials)

Basically, one has to respect the community's and the individual's concerns about the trial and has to be aware of the fact that people put their trust and high expectations in our work. This is of special importance since each volunteer will undergo through an in-depth medical assessment and possibly receive first-line treatment over a period of 2 years – which is usually not the case in rural areas. Thus, one might have to further explain why only some children are selected from a village and others are not or are even denied to participate after the preliminary health assessment.

Another challenge within the PMAL03 trial has been the implementation of the double blinded, controlled set-up. To avoid any bias from the investigator being aware about which vaccine (the malaria vaccine or the comparator vaccine) has been applied, an impartial vaccination officer had been assigned to the application and documentation of the vaccination procedure. Moreover, an adequate comparator vaccine (Inflexal[®]) had been chosen to enable a "controlled" conduct of the PMAL03 trial, which is respected as the Gold Standard in clinical development. However, unlike many drug trials there is no such Gold Standard available and for ethical reasons a vaccination of the control group with a placebo had been ruled out. Thus for the control group, a vaccine has been chosen to match the same basic virosomal structure, in addition to be functionally unrelated to the investigational vaccine but still providing some benefit. Due to the double blinded set-up, no information regarding the immunogenicity and tolerability of both vaccines, the investigational malaria vaccine or the comparator vaccine is available to date and will not be revealed before the end of the PMAL03 trial by mid 2009.

So far, we were pleased to note that that there is the high compliance by the volunteers and that no vaccine related Severe Adverse Event has been detected. Furthermore, the bridging between cultures, the implementation of a rather complicate malaria vaccine trial in a rural setting, as well as sharing the expertise have been successfully achieved within the PMAL03 trial at the BRTC of the IHI in Tanzania.

e-mail: hermann.garden@unibas.ch

Simplifying pediatric immunization with fully liquid pentavalent DTP-HepB-Hib combination vaccines

Dr. Karin Wiedenmayer

Immunization against childhood communicable diseases are among the most cost-effective **public health interventions** and is one of the most significant medical advances of our time. In recent history, it has eradicated smallpox, reduced the global incidence of polio by 99%, and dramatically decreased many other causes of illness and death. Immunization reduces the costs of treatment and of disability caused by infectious diseases. However, many obstacles remain in providing low and middle income countries with appropriate vaccines to meet global objectives of eradicating vaccine-preventable diseases. Efforts to increase coverage are hampered by weak health and immunization systems. Shortage of health staff is an important obstacle to scaling up immunization.

To meet the **Millennium Development Goal 4** (Reduce by two thirds the mortality rate among children under five by 2015), significant challenges must be overcome. There is still an important immunization coverage gap that needs to be addressed. Coverage correlates with low access in rural areas, mobility and migration, acceptance, low educational level of mothers and low socioeconomic status.

Vaccine technologies have been evolving rapidly but the benefits are unevenly spread. Formulating and testing new products is a lengthy and expensive process and the pharmaceutical industry seeks to recoup its investments by targeting rich markets. Product R&D is a first step that must be followed by developing provider and user friendly formulations and administration methods. Moreover, vaccine product profiles should also consider ease of administration, logistics and programmatic aspects. Efforts to accelerate the introduction of new vaccine products must be matched by investments to ensure their safe, efficient use.

Technological improvements such as fully liquid combination vaccines in a single injection have been developed to rationalize vaccine delivery and to simplify supply and administration of vaccines. The availability of new vaccines and easy-to use technologies will strengthen vaccination delivery systems, alleviate immunization workload and hence contribute to increasing health service performance. A fully liquid DTP-HepB-Hib vaccine offers advantages and including it in national immunization programs might prove to be a cost-effective use of resources.

Rationalising **vaccination delivery**, for example by combining vaccines, can enable the introduction of new vaccines into immunization programs without necessitating additional visits to the healthcare provider. Furthermore, simplification of vaccine delivery reduces the potential for handling errors, facilitates training and enables vaccination programs to reach children in remote areas.

Analyses of the costs and **cost-effectiveness** of vaccines are important because of the need to determine the level of resources required for improving immunization programs and to optimise the allocation of scarce public and external resources available for immunization.

The Swiss Tropical Institute carried out a **time-motion study** in Calcutta, **India** to understand implications of a single vial fully liquid pentavalent DTP-HepB-Hib vaccine given as one injection in terms of resource requirements, efficiency and impact on vaccination programs. Study results indicated:

- Statistically significant time savings for vaccine preparation and total vaccine consultation for the single vial combination vaccine of about 50% and 20% as compared to multiple vial combination vaccines.
- At current vaccine load, working time savings at the Institute of Child Health, Calcutta are estimated to be about 20 working days per year. Extrapolated to India, delivery time savings could be over 100,000 working days per year.

In addition, the STI conducted an **economic assessment** to highlight potential financial and economic implications of introducing a fully liquid DTP-HepB-Hib vaccine into the national immunization program of **South Africa**. Results indicated that

- the total potential financial savings of replacing the currently used DTP-Hib plus HepB vaccines with a fully liquid DTP-HepB-Hib vaccine, would be around US\$ 2.5 million per year.
- Financial savings hide more important economic benefits of a fully liquid vaccine such as the reduction of over 7000 health staff working days yearly.

A DTP-HepB-Hib fully liquid vaccine provides substantial financial and economic benefits in all aspects including storage and distribution, vaccine delivery and waste management. However, the most important advantage is related to economic benefits due to simplified vaccine delivery reducing delivery time, given the country's shortage of health workers.

Wiedenmayer K et al (2008) Simplifying paediatric immunization with a fully liquid DTP-HepB-Hib combination vaccine: evidence from a time-motion study in India.
Submitted to *Vaccine*

Tediosi F et al (2008) Exploring the potential financial and economic implications of a fully liquid DTP-HepB-Hib vaccine: an assessment for South Africa. *Report STI*

GAVI Alliance

www.gavialliance.org

www.gavialliance.org/resources/Fact_Sheet_New_Technologies_en.pdf

www.gavialliance.org/resources/GAVI_Alliance_Strategy_2007_2010_.pdf

GIVS, Global Immunization Vision and Strategy 2006-2015

www.who.int/immunization/givs/en/index.html

www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf

e-mail: karin.wiedenmayer@unibas.ch

Transmission dynamics and economics of rabies control in dogs and humans in an African city

Dr. Jakob Zinsstag

Despite the odds of working in Chad, the project on rabies control of the Human and Animal Health unit worked very well and showed, after a first study by another group in Tanzania (Lembo et al. 2006), that the new direct immuno-histochemical test (dRIT, Biotinyl coupled anti-rabies antibody, streptavidin-peroxidase detection system) of CDC has the same performance as the Immunofluorescence gold standard. The main advantage is that it does not need a fluorescence microscope and thus has a tremendous potential to be extensively used in peripheral field laboratories throughout Africa and Asia. Human rabies in developing countries can be prevented through interventions directed at dogs. To address potential cost-savings for the public health sector, cost-benefit and cost-effectiveness of interventions aimed at animal host reservoirs should be assessed. Existing deterministic models of rabies transmission between dogs were extended to include dog to human rabies transmission and fitted to routine weekly rabid dog and exposed human cases reported in N'Djaména (Chad). Estimated transmission rates were used to compute the basic reproductive ratio, R_0 , which was very close to 1, indicating low level endemic stability of rabies transmission. We simulated the effects of two interventions, mass dog vaccination and the culling of a percentage of the dog population. A single parenteral dog rabies mass vaccination campaign reaching an immune protection of at least 70% of the susceptible dogs appears to be sufficient to interrupt transmission of dog rabies for at least six years. Human post-exposure prophylaxis (PET) alone has no effect to reduce future human exposure. Combining human PET with a parenteral dog vaccination campaign becomes more cost effective than PET alone beyond a time horizon of 6-7 years. Owner valuation of dog vaccination cost indicates that dog mass vaccination must be free to the owners to reach a sufficiently high coverage to interrupt transmission.

Literature:

Dürr S, Naïssengar S, Mindekem R, Diguimbye C, Niezgodá M, Kuzmin I, Rupprecht CE, Zinsstag J. Rabies diagnosis for developing countries PLoS Negl Trop Dis. 2008 Mar 26;2(3):e206.

Salome Dürr, Martin I. Meltzer, Rolande Mindekem, and Jakob Zinsstag (2008) Owner Valuation of Rabies Vaccination of Dogs, Chad. EID Volume 14, Number 10–October 2008

e-mail: jakob.zinsstag@unibas.ch

Combined human and animal vaccination delivery services

Dr. Esther Schelling

Public health and veterinary vaccination services often fail to achieve sufficient coverages in Africa's remote rural settings due to financial, logistical and service delivery constraints. In 2000, the prevalence of fully immunized nomadic pastoralist children and women in Chadian Chari-Baguirmi and Kanem was zero. In the same nomadic camps, however, the livestock was compulsorily vaccinated by circulating veterinary teams. During a stakeholder workshop in 1999, the Chadian Ministries of Health and of Livestock Production (hosting the veterinary services), together with the pastoralist communities, recommended the testing of the feasibility of joint human and livestock vaccination campaigns to make best use of visits by professionals in nomadic communities. Since 2000, a project of the Swiss Tropical Institute supported the implementation of several joint campaigns and played a facilitating role in harmonising the timing of activities of the public health and veterinary services. The joint campaigns were organized in consultation with the local health and veterinary personnel, and made use of existing personnel and infrastructure (cold chain and transportation means). Sharing of transport logistics and equipment between the public health and veterinary sectors reduced total costs. In addition, joint human and animal health service delivery is adapted to and highly valued by hard-to-reach pastoralists. In the intervention zones, for the first time approx. 10% of mobile pastoralist children (0 – 11 months) were fully immunized annually. A key statement repeatedly made by parents was, 'Measles and whooping-cough have disappeared among pastoralists, although it remains at the market-sites we visit. And when we attend markets, we no longer contaminate our camps with these diseases'. By optimizing the use of limited logistical and human resources, public health and veterinary services both become more effective, especially at the district level.

Bechir M, Schelling E, Wyss K, Daugla DM, Daoud S, Tanner M et al. 2004; Approche novatrice des vaccinations en santé publique et en médecine vétérinaire chez les pasteurs nomades au Tchad: expériences et coûts. *Médecine Tropicale*, 64[5]:497-502.

Schelling E, Bechir M, Ahmed MA, Wyss K, Randolph TF, Zinsstag J. 2007; Human and animal vaccination delivery to remote nomadic families, Chad. *Emerging Infectious Diseases*, 13[3]:373-379.

Text Foto: Polio vaccination of a nomadic child in Chad. At the same time, the camp's livestock is vaccinated by veterinarians

e-mail: esther.schelling@unibas.ch

Travel Medicine Vaccinations

Prof. Christoph Hatz

Some 10'000 clients visit the Travel Clinic of the Swiss Tropical Institute every year for pre-travel advice. The counselling is based on the growing body of evidence-based data and on long-term experience of the five physicians working at the Institute. The recommendations are also based on the consensus of the Expert Committee for Travel Medicine, a group consisting of representatives of the leading travel clinics in Switzerland (Genève, Lausanne, Bern, Basel and Zürich), the Swiss International Airlines, experts from Germany, Austria, France and England, and the Swiss Federal Office of Public Health. The latter publishes updated lists of recommended vaccinations and malaria prevention in their bulletin at least three times a year.

Routinely recommended vaccinations for all travellers include shots against tetanus and diphtheria. The consultation of the mostly adult clients provides further a chance to offer missing vaccinations of the regular schedule of the Swiss recommendations such as vaccinations against hepatitis B, measles, mumps, rubella, varicella, pneumococcal and meningococcal disease and human papilloma virus. Hepatitis A vaccine is recommended for all travellers visiting countries with poor hygiene standards. The vaccination which likely prevents most infectious episodes is the one against influenza. There are vaccines available for the Northern and the Southern hemisphere which are given before the respective transmission periods in the winter months of the North (from October to January) and the South (from April to July).

The recommendations for special vaccinations are tailored to the individual needs of the clients. Travel itinerary, travel style and duration are among the criteria to assess potential exposure to pathogens against which vaccinations exist.

Travellers visiting areas where tick-borne encephalitis is prevalent are informed about the respective risks, especially when outdoor activities are envisaged.

Yellow fever vaccinations is mandatory for entering some African and Latin American countries. Other countries with elevated risk, but without compulsory vaccination are included in the recommendations according to the continuously updated epidemiological situation of the disease in endemic areas. Poliomyelitis booster vaccinations are given to travellers going to areas where the disease is still widely spread or where it has been re-emerging. All vaccinations documents are screened for a complete basic vaccination against this disease that

is now virtually unknown in Switzerland, but could be reintroduced if the herd immunity is neglected.

Vaccinations against typhoid fever are cautiously recommended as the risk for the average traveller is low and as the protection level is below 70%. The risk of contracting the disease is highest in South Asian countries or in other endemic countries if travellers are expected to live under very poor hygienic conditions. A new and excellent cholera vaccine is recommended for humanitarian workers under highly difficult hygienic conditions. This vaccine also provides partial protection against coli bacteria, but the calculated rate of protecting against some 10% of those pathogens does not merit the broad use of this vaccine against *Escherichia coli* infections for cost-effectiveness reasons.

The quadrivalent polysaccharide vaccination against meningococci types A, C, W135 and Y, the most prevalent pathogens found in the meningitis belt of West and Central Africa, is compulsory for visitors of the Hadj. Because of the dramatic course of the disease, the vaccination is also highly recommended for travellers and long-term residents in endemic areas during the transmission periods although very few imported infections are reported in industrialised countries.

Rabies is another rare disease among travellers. No imported case has been recorded in Switzerland over the past 50 years, but some dramatic cases have been reported from France and Germany. Nevertheless, several hundred Swiss travellers are vaccinated every year after a potential rabies exposure after a bite in enzootic countries, requiring passive and active vaccinations in low economy countries with reduced access to those vaccines. Persons embarking for trips to remote enzootic areas and long-term travellers should therefore be offered this vaccine in order to avoid dangerous and frightful experiences and to save the few critical vaccines available in poor countries for their own population. Children, trekkers and persons travelling on two wheels are at a particular risk to be bitten by dogs which are responsible for more than 90% of human rabies worldwide.

The risk of Japanese encephalitis is considered to be very low for travellers, i.e. at 1-2 cases worldwide every year. However, the individual risk can be high as rare cases staying only few days in endemic areas document.

Vaccinations against tuberculosis are not recommended except for newborns before travelling with their parents to high risk settings. As the presently available vaccination is providing

virtually no protection against any form of the disease in children and in adults, the potential adverse effects are rendering the BCG vaccine useless or even dangerous in those groups.

Effective vaccinations against tuberculosis, dengue fever, hepatitis C and malaria are only a few among many that would be highly welcome to protect our resident as well as the travelling clients.

Special emphasis is given to counselling immigrant persons and their families as they are at higher risk to contract infectious diseases when they return to their countries of origin, visiting friends and relatives in high risk areas.

e-mail: christoph.hatz@unibas.ch

Postmarketing vaccine safety and effectiveness

Tippi Mak, MD

Vaccines provide one of the most effective health interventions, with a profound impact on reducing morbidity and mortality. When considering just 4 vaccines, WHO estimates that worldwide, 2.5 million deaths from diphtheria, tetanus, pertussis and measles are averted each year.¹ Most vaccines administered routinely in populations are scheduled for infants and young children. In many countries with well-established immunisation programs, the incidence of vaccine-preventable diseases has sharply fallen and public attention has shifted towards issues of vaccine safety. Furthermore, over the next decade, several new vaccines will reach the market and be considered for national immunisation programs.

In collaboration with several institutions, the Swiss Tropical Institute participates in global reviews on the postmarketing evidence for safety and effectiveness of vaccines in targeted subpopulations. The aim is to contribute knowledge towards best immunisation policy and practice.

Phase I-III clinical trials capture and report more common vaccine-related adverse events. Pre-licensing studies, however, are not powered to detect rare adverse events, nor can they adequately represent certain subpopulations for whom vaccination may pose a higher benefit or risk. Continuous postmarketing, population-based surveillance thus plays a crucial role in identifying any rare, serious vaccine-related adverse events and unexpected effects in vaccinated subgroups.

In general, there is a higher expectation for safety of primary prevention measures such as vaccination, because they target healthy recipients. The vaccine is expected to provide substantial health benefits that are proven and safe; any serious risks from the intervention are expected to be known and rare. Other important areas of immunisation safety include vaccine quality, safe technique for administration, and safe disposal of vaccine-related products.

Most of our current understanding of vaccine-related adverse events remains largely from data from industrialised countries. In 2004, only 68% of countries identified a national system to report vaccine-related adverse events.¹ There is a need to improve global postmarketing surveillance of vaccine safety, and to consider safety monitoring a fundamental component of all immunisation programs.

Reference

1. WHO (2005). Global status of immunization safety: report based on the WHO/UNICEF Joint Reporting Form, 2004 update. Weekly epidemiological record 80: 361-8.

Resources

WHO Immunization Safety

http://www.who.int/immunization_safety/en

e-mail: tippi.mak@unibas.ch

Impressum of the STI Newsletter

Dr. Joachim Pelikan
Knowledge Management, eLearning & Communication
Swiss Tropical Institute
Socinstrasse 57

CH - 4051 Basel
Switzerland

joachim.pelikan@unibas.ch

Tel. +41 61 284 81 55
Fax: +41 61 284 81 06
www.sti.ch