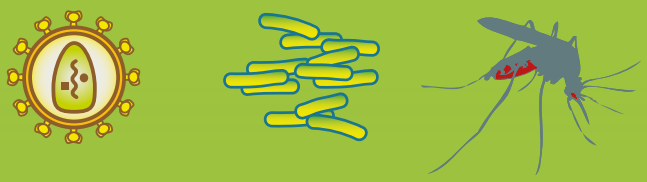
EDCTP

Seventh EDCTP Forum

The Partnership journey: New horizon for better health

PROCEEDINGS



30 June – 2 July 2014

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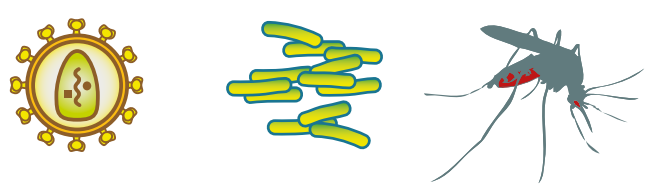

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Acronyms and abbreviations

ACT	artemisinin-based combination therapy
AE	adverse event
AL	artemether–lumefantrine
ANC	antenatal care
AQ	amodiaquine
ART	antiretroviral therapy
ARV	antiretroviral
AS	artesunate
AUC	area under the curve
AVAREF	African Vaccines Regulatory Forum
AZT	azidothymidine
BW	body weight
CDC	Centers for Disease Control and Prevention
CFU	colony-forming unit
CISM	Centro de Investigação em Saúde de Manhiça
C_{max}	maximum concentration
C_{trough}	lowest concentration of a drug just before the next dose
CNRFP	Centre national de recherche et de formation sur le Paludisme
CNS	central nervous system
CRP	C-reactive protein
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked ImmunoSpot®
ELONA	enzyme-linked oligonucleotide assay
EPTB	extrapulmonary TB
FLIP	FLICE-like inhibitory protein
FTC	emtricitabine
GI	gastrointestinal
Xpert	GeneXpert® MTB-RIF assay
HADS	Hospital Anxiety and Depression Scale
HAART	highly active antiretroviral therapy
HIVDR	HIV drug resistance
ICTRP	International Clinical Trials Registry Platform (WHO)
IFN	interferon
im	intramuscular(ly)
INH	isoniazid
IPT	intermittent preventive treatment
IPTi	IPT in infants
IPTp	IPT for pregnant women
ISHReCA	Initiative to Strengthen Health Research Capacity in Africa
ITN	insecticide-treated mosquito net
ITT	intention to treat
iv	intravenous(ly)
KEMRI	Kenya Medical Research Institute
LBW	low birth weight
LPV	lopinavir
MARC	Mapping African Research Ethics Review Capacity
MARCH	Monitoring Antiretroviral Resistance in Children
MDR	multidrug-resistant
MGIT	mycobacteria growth indicator tube
MIPPAD	Malaria in Pregnancy Preventive Alternative Drugs
MQ	mefloquine
MRC	Medical Research Council
MRTC	Malaria Research and Training Centre (Mali)
MTCT	mother-to-child transmission
NAb	neutralising antibody
NCD	non-communicable disease
NFV	nelfinavir
NID	neglected infectious disease
NoE	Network of Excellence
NRTI	nucleoside reverse transcriptase inhibitor
NTM	non-tuberculous mycobacteria
NVP	nevirapine
PACTR	Pan African Clinical Trials Registry
PanACEA	Pan African Consortium for the Evaluation of Antituberculosis Antibiotics
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	protease inhibitor
PMTCT	prevention of mother to child transmission
PPD	purified protein derivative
PRD	poverty-related disease
PRNID	poverty-related and neglected infectious diseases
PTB	pulmonary TB
PZQ	praziquantel
qPCR	quantitative polymerase chain reaction
qRT-PCR	quantitative real-time PRC
RCT	randomised controlled trial
RDT	rapid diagnostic test
RIF	rifampicin
SAE	severe adverse event
SME	small and medium enterprise
SOC	standard of care
SP	sulphadoxine–pyrimethamine
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TST	tuberculin skin test
UCAD	Université Cheikh Anta Diop (Dakar, Senegal)
VL	viral load
vs	versus
WANECAM	West African Network for Clinical Trials of Antimalarial Drugs
WANETAM Plus	West African Network of Excellence for Tuberculosis, HIV/AIDS and Malaria
WHO	World Health Organization
WWARN	Worldwide Antimalarial Resistance Network
ZDV	zidovudine

Contents

Prof. Charles Mgone's opening address at the Seventh EDCTP Forum

The Partnership journey: New horizon for better health

The partnership journey to better health is a long and hard journey that requires the full commitment of all the partners that have decided to undertake it. EDCTP started out a decade ago in 2003 when European and African countries resolved to join forces in combatting the three main diseases of poverty, namely HIV/AIDS, tuberculosis and malaria. Based on the then Article 169 (currently Art. 185) of the Treaty on the Functioning of the European Union and armed with a mission to reduce the burden of these diseases and to generally improve the health of the people living in sub-Saharan Africa, the partnership has gone from strength to strength in pursuing its objective. This is being realised through supporting clinical trials and pertinent capacity development. As we celebrate our tenth anniversary, the programme has supported 246 projects, which include 100 clinical trials. These projects involve 259 institutions in 46 countries in Africa and Europe. The programme has supported the training of 514 health research cadres including 56 Senior and Career Development Fellows, 39 Postdoctoral scientists, 177 PhDs and 229 Master's students, among others, with a retention rate of nearly 100 per cent.

The clinical trials and capacity development that have been funded by the programme are beginning to bear tangible fruits. These include results that are informing policy at national and international levels such as the WHO guidelines on the prevention of mother-to-child transmission of HIV during pregnancy and breastfeeding; rational use of drugs in the prevention of malaria during pregnancy; and treatment of severe malaria in children. Furthermore, it is encouraging to note as we travel this journey that we see African leadership emerging and being strengthened, ushering African ownership and programme sustainability. In the programme, around 70% of the projects are led by African scientists, many of them young and up-and-coming. Furthermore, the ethical and regulatory framework continues to develop with improved ethics review, national regulatory authorities, clinical trial registration and networks of excellence in conducting clinical trials.

For the second phase of EDCTP, the stakeholders have agreed to expand the programme to include all phases of clinical trials from phase I to IV, including implementation studies on the optimisation of health services. The expansion of the programme will also include working on neglected infectious diseases. Moreover, the programme will seek closer collaboration with other partners including the private sector. It will also seek stronger African commitment and involvement in decision making. It is our sincere hope that this stronger EDCTP will lead to better health.

Charles S Mgone
EDCTP Executive Director

Executive summary

Introduction

The Seventh EDCTP Forum was held in Berlin, Germany, on 30 June–2 July 2014. It was attended by 358 participants from 25 African countries and 18 other countries around the world. The theme of the Forum was **The Partnership journey: New horizon for better health**, a theme which describes both the core value underlying EDCTP strategy – *partnership* – and the *journey* EDCTP has travelled from its inception in 2003 to the present, leading, in December, to the launch of EDCTP2.

The EDCTP journey presents new horizons for better health and this is reflected among many developments, by substantial increases in funding, as announced in the opening addresses of **Plenary session I**. It is also illustrated by EDCTP's expanded agenda to include neglected infectious diseases (NIDs) under EDCTP2. The Forum agreed that since it set out on its journey, EDCTP has achieved much; however, that a great deal still remains to be done. Dr Line Matthiessen, from the European Commission, informed the Forum that when EDCTP was founded, its European member states had very different approaches to support research on HIV/AIDS, malaria and tuberculosis in Africa. Bridging these differences has been a considerable challenge. Working with different African partners has been a further challenge. Today, EDCTP offers a invaluable partnership model that puts it in a unique position to actively tackle challenges in global health by providing a platform for communication, collaboration, sharing of resources and creating synergies.

One very important aspect of partnership building is the development of research capacity. Strengthened capacity puts partners on an equal footing and enables real resource exchange and reciprocity. EDCTP plays a vital role in capacity development, through its extensive support of research projects and scientists. To date, EDCTP has funded 246 projects, 259 institutions and 100 trials, trained 514 scientists, including support of many senior fellowships. Some of the work resulting from these efforts was presented in the Forum's parallel sessions described below.

Scientific presentations

The scientific presentations dealt with research in the three main poverty-related disease (PRD) areas HIV/AIDS, tuberculosis and malaria. For each of these, a keynote address was given in **Plenary session II**, outlining recent advances in the research area. There were two main themes underlying all the scientific presentations: clinical trial findings and their implications for implementation; and strengthening of capacity of sub-Saharan African researchers and institutions. Presentations were also made on cross-cutting topics and provided an overview of research issues at the interface between two disease areas and/or research aspects. Keynote addresses on cross-cutting issues were given in **Plenary session III**. Of a total of 119 research presentations, 32 were on HIV/AIDS, 28 on tuberculosis, 30 on malaria and 29 on cross-cutting issues.

HIV/AIDS

HIV/AIDS researchers presented their findings under a range of topics such as: immunology and vaccine development; therapeutic and prevention studies (for example, HIV drug resistance in paediatric patients; a randomised controlled clinical trial (RCT) of three second-line treatment options); treatment guidelines and disease progression; comorbidities (for example, peripheral neuropathy in HIV-infected children) and coinfection (such as with hepatitis B virus).

Tuberculosis

Issues covered in tuberculosis presentations were: tuberculosis therapeutic studies; pharmacokinetics of tuberculosis drugs, and delivery of nano-encapsulated tuberculosis drugs; and clinical development of vaccines. Diagnostics studies included presentations on diagnosis of tuberculosis in HIV-prevalent settings and point of care testing of diagnostics. Drug development and drug resistance was a further topic.

Malaria

Among malaria studies were a vaccine study on controlled human malaria infections; several efficacy studies; pregnancy-associated malaria research; and drug resistance and modelling investigations in the context of artemisinin resistance. Also included were immunology studies, for instance on seasonal variations in malaria; and trialing a haemozoin detection assay to detect antimalarial resistance.

Cross-cutting

Presentations included under 'cross-cutting' covered a wide range of topics, such as research ethics and establishing a community advisory board in a sub-Saharan African country; clinical trials registries, and efforts to map African research ethics review and medicines regulatory capacity; recruitment of participants in clinical trials in African countries; and interactions of neglected infectious diseases.

Partnership

The theme of partnership was taken up throughout the Forum. It was the topic of **Plenary session IV** and a special session tasked with investigating new approaches to developing and enhancing health research partnerships. Attendees agreed that there is a need for strengthening partnerships: partnerships not only between researchers, research facilitators, funders and policymakers, and not only between the South and the North, but between the different partners and regions in the South, and also between the different partners in the North. There is further a need for facilitating partnership direction, since true partnership needs to be bidirectional. Significant progress in partnership building has already been made, as exemplified by the regional Networks of Excellence (NoEs) and their contribution to collaboration. The present Forum was another important contribution to collaboration, as it was hoped that delegates would use it as an opportunity to build new partnerships and consolidate existing ones.

One of the most important aspects of partnership is of course that all partners involved share a common goal. In the context of EDCTP and its partners, this goal is to reduce the burden of the poverty-related diseases and improve the health of people in developing countries and globally. It is important to keep in mind that beneficial scientific research as reported during the Forum can only take place through partnership.

Conclusions

Plenary session V concluded the Forum. The session included a summary of the Forum proceedings. Concluding words were then given by Dr Gianpietro van de Goor, from the Directorate General for Research and Innovation of the European Commission, who referred to the Forum as having been 'an excellent marketplace for networking and synergy'. Looking forward to EDCTP2 and beyond, he said, there was much work to be done and impressive achievements in the past should not lead to complacency. Closing the Forum, Professor Tumani Corrah of the Medical Research Council Unit in The Gambia and Chair of the EDCTP Scientific Advisory Committee, spoke of the many challenges the meeting had been presented with, challenges that could only be met through hard work and collaboration. One of these will be EDCTP meeting a new horizon for better health when it launches its second phase, EDCTP2, in Cape Town on 2 December 2014.

1 Opening addresses

The Seventh EDCTP Forum, titled **The Partnership Journey: New Horizon for Better Health**, was held in Berlin, Germany, from 30 June to 2 July 2014. The Forum was officially opened on Monday 30 June with Plenary session I.

In her welcome address, **Dr Renate Loskill** from Germany's Federal Ministry for Education and Research stressed the importance of research for better health and for the benefit of all societies. She told the audience that it has been a declared objective of the German government to contribute to the worldwide fight against diseases. The country sees its role as active partner in tackling future challenges in global health. EDCTP, with its African partnership model, holds an important position in meeting this objective. Much has already been achieved in collaboration with EDCTP over the past 11 years. Looking forward, Dr Loskill outlined new features of and research areas for EDCTP2 and said that a significant increase in funding will lead to new horizons and new opportunities.

Dr Renate Loskill at the Seventh EDCTP Forum's opening address

Vice-Chairs of the EDCTP General Assembly **Dr Detlef Böcking** and **Professor Stefano Vella** gave a brief address with the title 'Towards EDCTP2'. Dr Böcking spoke of the tremendous change that EDCTP is undergoing. It now has true African membership, having two African colleagues on its governing board, nine African members of the EDCTP Association, and several more African countries currently applying for membership. He declared that he was proud that Berlin is hosting the Seventh Forum – but added that the Forum actually belongs in Africa.

His colleague Professor Vella added that to date, EDCTP has funded 246 projects, 259 participating institutions, and 100 clinical trials. A further example of the extent of its work, commitment and impact is the 3,442 posts that have been supported on EDCTP grants, 514 scientists who have been trained, and 485 publications that have resulted from these efforts. The regional Networks of Excellence (NoEs), initiated and supported by EDCTP, have played an important part in putting together forces to do research.

With its first programme coming to an end and EDCTP about to enter its second phase, the organisation is taking huge steps forward. EDCTP2 will be building on the current programme. Besides continuing to support clinical research, EDCTP will further strengthen the enabling environment to conduct clinical research, and align and partner with governments, funders and other global initiatives on fighting poverty-related diseases (PRDs). The focus will remain on sub-Saharan Africa but the approach will be broadened to include all phases of clinical research and optimisation of health services delivery, as well as neglected infectious diseases (NIDs). There will be even stronger African participation with equal rights. With its large membership and its response to the world health crisis, EDCTP is truly becoming a global health model.

Professor Francine Ntoumi, of the Fondation Congolaise pour la Recherche Médicale, Congo, and Member of the EDCTP Association Board, talked about the evolution of EDCTP governance. She traced the development of EDCTP from its beginning phase as a European Economic Interest Group (EEIG) – a partnership, but without equal rights – to an organisation about to enter its second phase, EDCTP2, as an Association presenting new ways of thinking partnership. Among the advantages of being an Association, she said, were that this enables sovereign states of Europe and sub-Saharan Africa to be members, ensuring partnership; and it enables man-

dated institutions from these states to represent their countries. It further promotes flexibility in membership requirements and in the governance structure; and allows for EDCTP to have offices abroad, which is suited to the aims and working methods of the organisation.

Dr Line Matthiessen from the EC Directorate General of Research and Innovation presented the European Commission's perspective on EDCTP's programme. She said that when EDCTP was founded in 2003, the European member states had different traditions in and approaches to HIV/AIDS, TB and malaria research. She spoke of the challenges of bringing them together and of working with African partners.

Now, EDCTP – about to enter its second phase under Horizon 2020 – is a fine example of international collaboration. Notably, a large percentage of its projects were and are led by African researchers. There is strengthened and extended cooperation between the continents which developed in two directions: North–South and South–North. Moreover, EDCTP supported important work in capacity development. Results from EDCTP-funded clinical trials were integrated into important policy guidelines for clinical practice at WHO level. One particular success in this area regards the prevention of mother-to-child transmission of HIV/AIDS.

Dr Matthiessen told the delegates that the second EDCTP high-level meeting held in Dakar was a major milestone in EDCTP's history, as several African countries decided to join EDCTP as equal partners of European countries. This, she said, showed the value African countries attach to EDCTP. In 2014, the European Union decided to support EDCTP with a substantial increase in funding. EDCTP2, which will run until 2024, will be officially launched in Cape Town on 2 December 2014.

She closed by stressing that EDCTP's achievements and success stories notwithstanding, many areas still need to be addressed. Importantly, the benefits of research are often not accessible to the people who most need them. If poverty-related diseases are to be effectively combated, there needs to be more strategic and cost-effective implementation of health research solutions. Therefore, African governments need to be engaged to inform them better of clinical trial outcomes and possible health care opportunities.

Professor Charles Mgone, EDCTP's Executive Director, then introduced the Forum theme **The Partnership journey: New horizon for better health**. His address took a reflective approach by looking back at milestones and developments and describing what could have been done better; and what lessons have been learnt. He began by reminding the audience of EDCTP1's mission: to reduce the burden of HIV/AIDS, TB and malaria and generally to improve the health of people living in developing countries, and its objectives: to accelerate research and development of new and improved interventions through the coordination of European member states' national programmes working in partnership with sub-Saharan African countries in collaboration with like-minded organisations.

Three main areas of focus have been supporting clinical trials and studies, capacity development, as well as fostering and cementing partnerships. Regarding the third named focus, he said that the coordination between European member states was not perfect at the beginning. Many barriers had to be overcome to progress towards true partnership with sub-Saharan Africa. Planning processes weren't always smooth. Trust had to be built, and this took time.

With regard to capacity development and fostering an enabling environment to conduct clinical trials, particular areas of achievement have been support of senior fellowships, health research ethics, the launch of the African Vaccines Regulatory Forum (AVAREF), initiation and support of the regional NoEs for conducting clinical trials, and launch of the Pan African Clinical Trials Registry (PACTR).

Professor Mgone informed the meeting of the steps that have been taken in preparation for EDCTP's second phase. He was pleased to announce that EDCTP2 will include work in neglected infectious diseases (NIDs). He closed the address by stating that one area in which he wished to see improvement was greater participation of female scientists and researchers.

2 Research reports: HIV/AIDS

RECENT ADVANCES IN HIV/AIDS RESEARCH

Professor Gita Ramjee, HIV Prevention Research Unit, Medical Research Council, South Africa

Professor Gita Ramjee opened Plenary session II by giving a keynote address on recent advances in HIV/AIDS research. Quoting some global HIV statistics, she said that currently there are 35.3 million people in the world living with HIV. Every hour, 50 young women become newly infected with HIV.

During 30 years of HIV research, we have come a long way towards understanding the disease – for example, we now know that the greater viral load (VL), the greater the infectiousness. Since 2002, there has been a 40-fold increase in access to ART. Other treatment milestones have included advising circumcision as risk reduction, and use of ARVs as prevention. We have come a long way – yet much still needs to be done.

She went on to describe HIV prevention strategies, targeting unexposed, exposed, or infected individuals. Prevention options for unexposed individuals are structural and behavioural (e.g. HIV counselling and testing, circumcision, condom use and safe sex practices). For exposed persons, pre-coital and coital prevention strategies include vaccines, use of microbicides and pre-exposure ART, while post-coital measures are administration of therapeutic vaccines and post-exposure (PEP) ART. In infected individuals, on the other hand, HIV prevention aims to reduce infectivity – a prime example of which is prevention of mother-to-child transmission (PMTCT).

Professor Ramjee emphasised that across all treatment options and interventions, adherence is critical for efficacy. To address adherence, new formulations (e.g. vaginal and rectal gels) and delivery systems (e.g. long-acting injectables) are currently being trialled. Among exciting recent developments in prevention, with lowered adherence risk, are silicon rings, which are inserted for one month, and long-acting injectables with a half-life of weeks and even months.

On the subject of treatment as prevention (TasP), Professor Ramjee reminded the audience that ART has a significant impact on HIV transmission, e.g. through PMTCT of HIV not only during pregnancy and childbirth, but also during breastfeeding. Furthermore, we now know that a decrease in VL means a significant reduction in HIV transmission. The HIV VL in the infected person is a key determinant of the risk of HIV infection. A delay in ART initiation will result in greater VL and hence greater infectivity: Professor Ramjee quoted a study in which a significant reduction in HIV transmission was seen if ART was started straight away when CD4 counts were between 350 and 550. She added that TasP is associated with some individual risks (e.g. toxicity, as well as stigma) and costs to health care (e.g. overburden of resources). When combined, however, pre-exposure prophylaxis (PrEP) and TasP can provide a very powerful HIV prevention strategy. There is no doubt that ART improves the quality of life in infected individuals. However, patients need to stay on ART for life, and their full health is not restored. The goal in HIV/AIDS research is, not only to treat infected individuals, but to cure them. 'Cure' means prevention of latency, elimination of all HIV-infected cells and gradual stoppage of therapy.

Seen globally, none of the interventions on their own are sufficient to impact on the epidemic. Reducing HIV incidence will require a combined and integrated approach to both prevent and treat the disease. Professor Ramjee closed by saying that recent advances and future research will lead to safe and affordable strategies to eradicate HIV – however, this will require collaboration, effective partnerships (public/private) and a multidisciplinary approach.

Scientific presentations

The parallel sessions on HIV/AIDS research reported results obtained in 33 studies which can be grouped under the themes of:

- Immunology and vaccine development
- Therapeutic and prevention studies
- Co-morbidities
- Co-infections
- Treatment guidelines and disease progression.

HIV/AIDS immunology and vaccine development was the focus of the first three HIV/AIDS presentations [HO.01–HO.03]. Virus diversity and escape from immune responses are the two biggest challenges in both T and B cell vaccine development in HIV research. The work presented in HO.01 concerned development of a vaccine construct targeting 14 of the most conserved regions of HIV-1 which are common to most variants and affect virus fitness when mutated. The construct, HIVconserv, was inserted into three vectors, plasmid DNA, MVA and ChAdV63. The resultant vaccines were found to be immunogenic in mice and non-human primates. A phase I HIVCORE002 trial was conducted in HIV-uninfected, low-risk individuals from the UK, with promising results. Analysis showed that regions rather than epitopes elicited better immune responses. Responses were tenfold stronger compared with the Merck Sharp & Dohme Corp. (hereafter on this page: Merck) vaccine used in the STEP trial. Results further showed that vaccine-elicited CD8+ T cells can inhibit some viruses better *in vitro* than others. Findings suggested that focusing T cells early on conserved regions of HIV-1 may provide the extra edge in control of HIV-1 *in vivo*. Looking forward, the group are developing combination vaccines for prophylactic use. At present they are recruiting healthy HIV-negative volunteers in Nairobi (Kenya) for a trial to confirm vaccine immunogenicity in an African setting.

Discussion and questions Following this presentation the presenters were asked what the difference was between the Merck STEP trial and the HIV-CORE002 trial (*The current vaccine induced a T cell response tenfold stronger than the Merck vaccine. Also, different proteins were used in the vector*).

So far, HIV research has focused on T cells but, following the failure of the Merck trial, focus has recently shifted to neutralising antibodies (NAbs). The research group in HO.02 studied the evolution of NAbs in acute heterosexually acquired HIV-I subtype C infection in Botswana. Aims were to investigate the prevalence of HIV-1C NAbs in infected individuals; establish whether NAbs have a role in viral set-points; as well as establish the time of appearance of NAbs, following infection, and find out whether they can cross-neutralise other viruses. The researcher described the methods of generating infectious pseudoviruses using plasma samples from eight HIV-1C acutely infected individuals. Treatment of these individuals was started after 6 and 7 months, respectively. A decreased VL, followed by a subsequent increase, was seen in those cases with broadly NAbs. Autologous NAbs appeared around 5–8 months post-infection. Findings were that early appearance of NAbs did not seem to be protective. Potency of NAbs tended to increase with time. Two out of eight patients developed cross-reactive NAbs (one as early as 5 months).

Discussion and questions An audience member commented that consideration of dilution and titres is meaningless; did the team look at concentration of NAbs in blood? (*This will be investigated in the future.*) Other audience questions were whether all the objectives had been addressed (*Yes*), whether non-correlation with the viral set-point was due to escape (*This had not been investigated*), and what contributed to the reported decrease in VL (*This still needs to be established*).

In view of the uncertainty surrounding the functional ability and phenotype of cells to protect against HIV infection, the study described in HO.03 assessed the activity of natural killer (NK) cells by stimulating peripheral blood mononuclear cells (PBMCs) with HIV peptide pools using flow cytometry. Sampling ten discordant couples (i.e. one partner being HIV-positive and the other HIV-negative) and nine HIV-exposed but negative controls, the team investigated clade A gag, env, Reg separately and in combination and assessed the functional markers CD107a and IFN-γ, activation markers CD25 and NKG2C, and putative 'memory' CXCR6 phenotypes using flow cytometry. HIV-exposed but uninfected partners elicited higher NK functional responses with lower NK activation. HIV-exposed but uninfected subjects displayed higher NK functional response, with higher CD107a-expressing CD8+T cells and lower NK activation. There was also a trend of

higher CXCR6+ putative 'memory' NK cells in HIV-positive partners. The team concluded that exposure to HIV antigens may prime functional recall NK cell responsiveness, and this response may be important in protection.

Discussion and questions A participant question was whether cytotoxic T cells are specific to the HIV peptides in uninfected but exposed patients (*Yes*).

Among several HIV/AIDS prevention and therapeutic studies was a randomised comparison of three second-line ART regimens [HO.04]. The presenter described a multi-centre, phase III trial conducted in Dakar, Bobo-Dioulasso and Yaounde to evaluate the safety of three combinations of second-line ART at 48 weeks in 451 patients: a reference arm based on the WHO-recommended regimen of emtricitabine (FTC)/tenofovir (TDF) + lopinavir/ritonavir (LPV/r) (Arm A); didanosine + abacavir + LPV/r (Arm B); and FTC/TDF + darunavir/r (Arm C). The study population consisted of HIV-1-infected patients who had failed a standard first-line ART regimen. The study could not demonstrate non-inferiority between the three arms. The proportion of patients with VL <50 copies/mL was 65%. There was a high number of drug resistance mutations, with similar rates of mutations across all arms. The boosted protease inhibitor (PI) LPV/r second-line regimen with FTC/TDF showed satisfactory efficacy, with 80% of patients having a VL <200 copies/mL. Viral load at second-line ART initiation was found to be an important prognostic factor. The presenter emphasised the importance of early diagnosis of failure and the need for better access to VL monitoring.

Discussion and questions Questions were whether more frequent VL monitoring would be sufficient (*VL monitoring was done but is unavailable in routine care; it is supposed to be done annually but this is not happening*), and whether resistance had been due to lack of adherence and, furthermore, what the relation was to VL. (*There was a positive correlation with increase in both VL and resistance mutations. As there were no PI mutations when failing second-line therapy, whether resistance was due to lack of adherence was uncertain*).

In Uganda, the MARCH study [HO.05] investigated HIV drug resistance (HIVDR) in children and children. The study aimed to assess prevalence of primary resistance and included 369 children, 119 initiating first-line ART and 50 switching to second-line ART (46% of whom had WHO stage 3 or 4 disease). Those initiating first-line ART had <10% non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations; those exposed to PMTCT had >10% mutations. The most common NNRTI mutation was K103N. The most common NRTI mutation was M184V. Risk factors for HIVDR at baseline were breastfeeding, prior PMTCT exposure and current maternal ART. The study's conclusions were that HIVDR is underreported in children. Challenges in treating HIV-infected children include high baseline VL; limited training for health care workers in paediatric management; adherence problems; lifelong treatment; and few available regimens. These important barriers to care for children account for <35% ART coverage in most African regions. Further, extensive mutations seen at treatment switch are due to a delayed switch. The presenters expressed concern over exhausting treatment options for children and warned that the situation calls for continuous national surveillance programmes, affordable VL testing and more ART combination treatments.

Discussion and questions A member from the audience suggested investigating infection from pre-exposure in various African countries using Option B+ (*This may be a future project for EDCTP funding*).

Few data are available enabling comparison between Options B and B+.

Post-ART outcomes were studied [HO.06] in a cohort of women who discontinued maternal triple ARVs initially used to prevent MTCT during pregnancy (as per Option B). Their outcomes were compared with Option B+ outcomes (women continuing ART indefinitely). The researchers determined the maternal clinical, infant, and immunological outcomes among women who received triple ARVs from pregnancy to weaning for PMTCT in the Kisumu Breastfeeding Study (KiBS, a phase IIb one-arm trial aimed to reduce MTCT of HIV among breastfeeding women in a resource-limited setting using combination maternal ARVs from 34 weeks' gestation to 6 months postpartum). Prevalence of maternal TB, maternal and infant deaths, infant HIV

infection, and loss to follow-up between 6 and 24 months postpartum were evaluated. Infant death or HIV infection in those who discontinued triple ART was higher (10.1%) than in those who continued ART (2.4%). Changes in CD4 over the first three months differed between groups. The steepest decline in CD4 was seen among women who initiated ARV with a CD4 count <500 and discontinued it at CD4 >500. Between 3 and 18 months after discontinuing ARVs, the CD4 decline in all three groups plateaued. Rise in VL after discontinuing ARV did not differ between the groups. The presenter noted that the sample size was relatively small and the study was not population-based.

Discussion and questions Audience questions concerned the reason for the reported increase in infant mortality (*Lack of maternal adherence*) and whether the presenter would recommend Option B+ (*Yes*).

A report from western Kenya [HO.07], a secondary analysis of the KiBS (HO.06), looked at adverse foetal outcomes in HIV-1-infected women who received either NNRTI (nevirapine, NVP) or PI (nelfinavir, NFV)-based therapy for PMTCT. No significant differences between NVP and NFV were detected with regard to stillbirths, preterm delivery, low birth weight (LBW) infants, neonatal mortality at <28 days, and infant mortality at <6 months. However, more women on NFV compared with NVP had a suppressed VL. Among mothers on NVP, those with <250 CD4 counts had a higher propensity for preterm delivery compared with those with CD4 >250. Despite some study limitations, it was concluded that combivir + NVP or NFV can be used for PMTCT in resource-limited settings without increased risk of adverse foetal outcomes; however, more and larger prospective studies need to be conducted to validate these findings. The recommendation from the research team was that there is a need for a national ART pregnancy register to help monitor foetal outcomes.

Discussion and questions One attendee wanted to know whether there was a difference in HIV infection between the NVP and NFV groups (No differences were found). It was suggested that, in view of presented results, the WHO threshold of <250 CD4 may have to be revised.

Pharmacogenetics describes genetic variations in genes responsible for absorption, distribution and metabolism of drugs in, and their excretion from, the body. A study from Zimbabwe [HO.08] addressed the issue that there are variations in drug response, with respect to efficacy and safety, between different ethnicities and within different African populations. The study group investigated genetic markers with respect to adverse events (AEs) and reactions, e.g. lipodystrophy, nausea, vomiting, peripheral neuropathy, and skin hypersensitivity reactions, in TB patients and in HIV/AIDS patients on ART. Adverse events following TDF, azidothymidine (AZT), 3TC, d4T, NVP, efavirenz (EFV), LPF, rifampicin (RIF) and isoniazid (INH) treatment were seen in 83% of studied patients. Findings included the following: CYP2B6 516TT genotype and male gender were significantly associated with occurrence of EFV-induced central nervous system (CNS) disorders, and ABCB1 rs10276036TT genotype with NVP-induced skin hypersensitivity. All other single nucleotide polymorphisms (SNPs) analysed did not show any predictive value for the reported adverse reactions. The presenter concluded by stating that 20% of Zimbabwean patients have TT genotype and would require only 200 mg instead of the standard 600 mg EFV dose.

Discussion and questions Audience members asked whether decreasing the dose would affect side effects such as dizziness or psychiatric manifestations (*The drugs were graded with respect to seriousness of AEs, but it is difficult to quantify these CNS side effects*). A participant commented on the need to take another look at the three EFV doses, 200 mg, 400 mg, and 600 mg (*The presenter agreed that individualising medication is important*). Expert recommendations from the floor were that there is a need to balance individualism with pragmatic benefits of current population-based public health approaches – with optimised dosage for all. Another audience observation was that side effects need to be dealt with early.

A Botswanan study [HO.09] investigated HIVDR in patients failing a TDF-based first-line combination ART regimen. Botswana has an HIV prevalence of 23% among 15–49-year-olds and has a good ART programme coverage (>96%), with 200,000 individuals on ART. The drug resistance rate is <5%. A triple regimen consisting of TDF + FTC + NVP or EFV is used as first-line treat-

ment. The researchers of this study enrolled 300 patients on this regimen and followed them for 2 years. They found that the regimen is very effective and well tolerated, with a 4.85% failure rate at 24 months. Factors associated with virologic failure included female gender, NVP use, low baseline CD4+ T cell count and high baseline HIV VL. Most failures had occurred by 6 months and the most prevalent mutation in those who failed therapy was K65R (9/15). The current second-line regimen, AZT + 3TC + LPV/r, has been found to be effective against all virologic failures. The high K65R frequency may rule out use of any other NRTI than AZT in this group.

Discussion and questions A member from the audience described the finding relating to K65R as interesting but frightening, and urged that there is a need for new classes of drugs.

Presentation HO.10 described access to early infant diagnosis and care in Côte d'Ivoire, where HIV prevalence among pregnant women is 4.5%, with 70,000 infants infected. PMTCT coverage is 47%, but early infant diagnosis and ART initiation is only 10%. In 2011, national HIV care scaled up early infant HIV care by using dried blood spot (DBS) tests for all HIV-exposed infants 6 weeks-12 months old, and initiating treatment of all HIV-infected children <2 years. The study reports results of a survey on the tools for/timing of early infant diagnosis, including interviews with families. Out of 2,397 DBS tests taken in 29 health centres in Abidjan, results of only 77% of the tests were issued to the health centres and only 59% communicated to families. Among 229 diagnosed with HIV infection, only 66% were started on ART. There were 78 (34%) missed opportunities for ART initiation, due to death (45; 20%), parental refusal (24; 11%) and loss to follow-up (9; 4%). The study concluded that it is imperative to improve early identification of HIV-infected infants and promote a continuum of care for them, by: organising and strengthening linkages between PMTCT and paediatric HIV services, mobilising the community and health care staff to reduce stigma, and involving the fathers in HIV post-test counselling.

Discussion and questions Questions concerned the reason for the delay (*4 months*) of results (*Logistics of transportation*) and why so many infants died (*Some died before ART initiation*).

The EARNEST trial was next presented [HO.11], an RCT comparing three second-line treatment options for public health rollout programme settings: PI + NRTIs (according to local standard of care), PI + raltegravir (RAL), and PI monotherapy, (n=400 per arm). Primary outcome measures at week 96 were: alive with no new WHO 4 events, CD4 cell count >250, VL <10,000 c/mL and no PI resistance mutations. PI/NRTI had an excellent clinical outcome, with 90% WHO 4 event-free survival and 86% VL suppression <400 cells/mL at 96 weeks, and was found to be well tolerated and safe. PI/RAL was not superior to PI/NRTI in terms of disease control and VL suppression. Cost considerations make PI/NRTI the more viable choice of treatment in resource-limited settings. By comparison, PI monotherapy was inferior to PI/NRTI, with lower VL suppression, and increased resistance, rendering it unsuitable for public health programmes. Conclusions were that PI/NRTI merits its place as standardised regimen in second-line therapy in a public health approach with feasible monitoring.

Discussion and questions The audience wanted to know why some patients failed despite good adherence (*Drug stock-outs*), and why those on standard of care did so well (*Resistance data are not yet complete for all arms. Good results could also be due to good viral replication fitness*). A further question was whether there had been stratification into baseline resistance patterns and outcomes (*This will still be done, but it appears that there was no difference*).

HO.12 reported interim results from the Fozivudine in Africa Trials Initiative (FATI) trial which evaluated capacity of fozivudine tidoxil (FZD), a lipid-linked AZT drug, to sustain virological suppression. Three different doses (600 mg, 800 mg, and 1,200 mg) of fozivudine were compared with a standard zidovudine (ZDV) (600 mg)-based ART regimen after 24 weeks of treatment in 120 ART-naïve, non-subtype B HIV-1-infected individuals from Tanzania and Côte d'Ivoire. Despite the known association of AZT with anaemia, and the drug's toxicity profile, there were overall no safety concerns. The authors did report an 83% incidence of (clinically asymptomatic) neutropenia but mentioned that large percentages of African populations have benign ethnic neutropenia (BEN). The myelotoxicity effect of the study drugs was uncertain owing to

concomitant factors (cotrimoxazole, HIV-related myelotoxicity). The final outcome analysis is expected in late 2014.

Discussion and questions One audience question was asked whether neutropenia was episodic or sustained over time (*Sustained over time*).

Patient adherence has been a major challenge in treating HIV (and other diseases), an issue addressed in HO.13. The speaker presented baseline data analyses from a randomised trial to explore adherence failure relationships in a South African ART cohort. Altogether 230 ART-naïve individuals eligible for ART initiation were randomised to receive standard of care (SOC, or SOC + SMS reminders if they had not opened their pillbox on time). Adherence was monitored using an electronic adherence monitoring device (EAMD). Scheduled visits were at 16, 42, 48 weeks. Data were collected on factors known to affect adherence: disclosure, alcohol use (CAGE questionnaire), anxiety and depression (HADS) and life events. Compared with the general population, 32.1% of patients had indications of depression, 37.7% of anxiety and 19% of alcoholism, all of which may impact ART adherence. Final results will be available by October 2014.

Discussion and questions Audience questions concerned the number of reminders (*Where one reminder was not sufficient, another SMS was sent the following day as patients using the EAMD had agreed to this at study start*), and the basis for refusing the EAMD (*Home conditions, e.g. fear that a child may pick up the gadget and damage it. Another reason was fear of disclosure*).

Motivated by the high percentage (15%) of sub-Saharan African patients currently on (and the expected increase in patients failing) second-line ART, as well as lacking data on salvage regimens in sub-Saharan Africa, HO.14 was an Aid for AIDS (AfA) study that set out to evaluate the efficacy of third-line ART. The salvage therapy administered was darunavir/ritonavir (DRV/r), or tipranavir/r, or RAL, or etravirine, + NRTIs (different combinations). All patients had a resistance test performed showing at least one major protease inhibitor mutation. No patients needed to switch salvage drugs because of toxicity/side effects. Regimens were well tolerated but there were potential adherence challenges. One patient stopped ritonavir of their own accord because of gastrointestinal side effects. Conclusions were that third-line ART needs to be guided by genotype. The costs for third-line ART are currently high and advocacy will be required to ensure third-line drugs are available and affordable when required in resource-limited settings. The reported results justify their provision.

Discussion and questions One attendee reminded the audience of the EARNEST trial (HO.11), which reported apparent ability of recycled NRTIs to retain antiviral efficacy (*NRTIs were recycled in some patients in the AfA study. This effect will need to be studied*).

Researchers in HO.15 looked at the effects of iron supplementation in HIV-infected children in Malawi (a country with a 63% prevalence of anaemia among <5-year-olds). WHO recommendations do not provide guidelines on iron supplementation in HIV infection. Of 209 recruited 25–26-month-olds, half received multivitamin + iron supplementation and the other half received only multivitamin supplementation. Results suggested that iron supplementation improved haemoglobin and CD4 counts, and slowed HIV disease progression. However, an association with increased risk of malaria infection has been suggested. There was no association with increased risk of other common morbidities.

Discussion and questions The audience wanted to know how iron deficiency was measured (*Ferritin and CRP; hepcidin was not measured*); whether increased malaria risk would not cancel out the beneficial effect on HIV (*If we give iron supplementation we need to put in place malaria control measures as well*); and how the anaemia was affected (*The iron supplementation contained vitamin A and C, which could possibly have contributed to improvement in anaemia status*).

Access to appropriate ART formulations for children in Africa is crucial. Reporting from the CHAPAS-3 trial in Uganda and Zambia, HO.16 was an efficacy and toxicity comparison trial of d4T vs ZDV vs ABC in HIV-infected children. D4T has been used in fixed dose combinations but without previous trial data on efficacy and AEs in children. ART-naive and – experienced children were randomised between the three drug regimen arms. Data on primary endpoint (AEs >grade 2)

and secondary endpoints (efficacy, and complications of treatment) after approximately 2.5 years' follow-up were presented. High/sustained VL suppression was seen in naïve/experienced children in all three treatment arms. The study found no significant differences between arms regarding toxicity and most secondary endpoints (exceptions were ART modification due to anaemia, in the ZDV arm, despite similar event rates across all arms; and incidences of neutropenia, which are not unexpected in the treatment population). In conclusion, the children responded equally well regardless of NRTI choice.

Discussion and questions Members of the audience cautioned that the possibility of long-term differences could not be ruled out after 2.5 years. More emphasis should be placed on early enrolment of children to treatment, and less on NRTI choice.

The second presentation from the CHAPAS-3 trial [HO.17] examined cardiovascular function and structure among HIV-infected children in Uganda and Zambia. Cardiovascular disease is an important complication associated with HIV and/or ART in adults; data on HIV-infected children and adolescents are still conflicting. Cardiovascular assessments of arterial function and structure, using pulse wave velocity and carotid intima media thickness measurements were carried out on age- and site-matched HIV-infected cases and control populations. Results from preliminary measurements showed no statistically significant difference in cardiovascular assessment parameters by ARV exposure and duration. However, a significant difference in arterial thickness by HIV infection status was observed. In conclusion, findings so far show that HIV infection status, but not ART, may be implicated in development of cardiovascular complications in HIV-infected children.

Discussion and questions An audience member observed that the significant difference in aortic stiffness by infection status means that this parameter could be an early indicator of cardiovascular disease onset, and may be used in early diagnosis/identification of potential cases at baseline (*Analysis of additional parameters is still ongoing, so it may be too early to tell*).

Also reporting on CHAPAS-3 was HO.18, a study of morphological and metabolic markers/symptoms of early lipodystrophy in ART-experienced children. Lipodystrophy is a common complication of ART in adults where risk factors include regimen and length of exposure, age, gender. However, few markers exist, and data on lipodystrophy in children are insufficient. HIV-infected ART-naïve and ART-experienced children and HIV-uninfected controls were compared with regard to various morphological and metabolic lipodystrophy parameters to elucidate candidate markers. Preliminary data have shown differences in some measurements between groups, but interpretations are confounded by poor age matching across the study groups and choice of reference standards. Preliminary results show that most likely there are no differences between treatment groups; but analysis of follow-up data is still ongoing.

Discussion and questions The audience wanted to know why, rather than use WHO standards, the study used Dutch anthropometric reference data (*The WHO reference data had not provided all measurement data needed*).

A fourth CHAPAS-3 presentation [HO.19] assessed the burden of peripheral neuropathy (PN) among HIV-infected Zambian and Ugandan children on ART. Peripheral neuropathy is common in HIV-infected individuals on ART, as an AE of NRTI-based therapy, especially of d4T and INH. Data on children in an African setting are few, but there is increasing evidence from elsewhere suggesting that PN may not be uncommon in infected children. The study protocol was based on a neuropathy symptom questionnaire and a 10-point neuropathy disability score (e.g. ankle reflex, pinprick). Preliminary results show no significant association between age and PN symptoms or signs, and no statistically significant difference by HIV infection status or treatment regimen. Prevalence levels were lower than expected. Complete data analysis is awaited. (A fifth CHAPAS-3 study was presented in HO.25.)

A study from the DRC [HO.20] sought to establish the effect of ART on cognitive ability and normal life functioning of HIV-infected subjects during therapy. ART has many benefits but may come with increased neurocognitive disorders. The study looked at cognitive performance and

daily functioning parameters using CNS penetrative effective (CPE) rank, the HIV dementia scale and the scale of instrumental activities of daily living to assign neuroactivity rank by regimen and cognitive impairment diagnosis, respectively. Results suggested that some neuroactive regimens are associated with impairment in cognitive ability including risk for non-adherence to treatment.

With the improvement, over the years, of ART coverage, there has been a rise in the need for treatment modifications. Study HO.21 aimed to elucidate rates and predictors of first-line ART modifications, reasons for modifications, and factors associated with modifications in a Kenyan population. The study found the incidence of modification to be moderate, with rates being significantly higher during the early course of treatment. The main reason for modification was toxicity; other reasons included drug contraindication, treatment failure, and non-adherence. Increasing age, WHO disease stage 3/4, d4T, low CD4 counts (≤350 cells/mm^3) and baseline weight of >60 kg were identified as risk factors for combination ART (cART) modification. TDF and ACZT had lower risk of cART modification. Increasing age, baseline weight >60 kg and d4T use were associated with cART modification due to toxicity, while low baseline CD4 (≤200 cells/mm^3), WHO disease stage 3/4, d4T and TDF were associated with cART modification due to drug contraindications.

Discussion and questions Audience questions were whether drug stock-outs could have been a factor in treatment modification (*This was not considered*); and, in view of the spread of CD4 at baseline, was any CD4-dependent trend observed? (*This was not profiled*). The presenter concluded that the moderate to high rate of cART modification calls for close monitoring of patients on treatment to minimise running low on options; that association of low baseline CD4 with risk of cART modification reflects the need to adopt the new recommendations for treatment initiation at higher CD4 levels; and that continuous reports of poor tolerability and durability of d4T-based regimens indicate a need for accelerated adoption of the WHO guidelines recommending d4T phase-off.

Factors contributing to separation during partner HIV serodiscordancy among couples from Kenya were the topic of HO.22. Correlates of separation among these couples were investigated. Various reasons were given for separation; only number of years in marriage, and alcohol use were statistically significant. More targeted counselling for the most at risk categories should be encouraged.

Discussion and questions The presentation was well received, with clarifications sought on the categories 'marital issues' (*These included rape, cheating, in-law interference, disclosure*) and 'alcoholism' (*A questionnaire was administered asking for number of bottles consumed per month or periodic frequency of drinking*). It was recommended that the term 'alcoholism' should be replaced with a definition showing consumption thresholds. The presenter agreed that alcohol consumption, and not alcoholism, was associated with separation.

Two papers were presented on HIV/AIDS co-morbidities. Based on the finding that low Body Mass Index is a risk factor for high early mortality when patients start ART, the NUSTART phase III randomised clinical trial [HO.23] investigated whether nutritional support for Africans starting ART could be beneficial. Vitamins and minerals were given in a 2-stage protocol: stage 1 (weeks 1 and 2) – stabilisation: high vitamins and minerals but low calories; stage 2 (weeks 2–6) – rehabilitation: high vitamins and minerals with high calories. The intervention products were: lipid nutritional supplements without or with vitamins and minerals. Mortality was much higher than expected; so, after interim analysis by the Data and Safety Monitoring Board, recruitment was stopped at 1,815 individuals. Conclusions were that the trial intervention had no effect on the primary outcome of mortality but did benefit CD4 counts and some nutritional outcomes. The treatment of patients presenting with low electrolytes and the increased risk of high electrolytes in the LNS–VMs group (lipid nutritional supplement with vitamins and minerals) may have interfered with testing the part of the hypothesis related to low phosphate.

Discussion and questions A lively discussion followed. The audience agreed that the study raised many issues that merit further investigation. However, if individuals present late it is difficult to show impact on mortality.

Study HO.24 was performed in Abidjan, Côte d'Ivoire, and 13 health centres near Ouagadougou, Burkina Faso, and looked at 12-month virological response in children initiated on LPV ART before 2 years of age. A prospective cohort was recruited, consisting of all HIV-infected children <2 years initiated on ART twice daily with Cotrimoxazole. Parental consent and therapeutic education were provided. Children with virological success at 12 months were randomised to: either simplified ART in one daily dose (ABC–3TC–EFV) or, as a control arm, continuation of the initial ART. At 12–15 months, 72% had a VL <500 copies/mL. The correlates of 12/15-month virological failure were: no tap water; and father as the main child caregiver. The correlates of 12/15-month virological success were: mother as the main child caregiver; health support. Where VL was not available, a >10% increase in CD4 between baseline and 6 months was regarded as a good indicator of virological success. The conclusion was that improving early identification of HIV-infected children remains a health challenge in West Africa. Public health efforts should be made to identify all HIV-infected infants earlier to enable earlier access to care. Urgent mobilisation is needed in the community to facilitate a family approach to ART delivery, including both parents.

Discussion and questions Members of the audience asked: Is there an adherence challenge with LPV syrup? (*Yes, <1-year-olds are not keen on taking the syrup.*) Did you consider the socio-economic status of families as factor in virological success? (*Lack of tap water indicates low socio-economic status. However, income isn't informative.*)

Efavirenz dosing is based on weight bands, but the dosing guidelines have not been evaluated. In addition, a new 600 mg EFV tablet has been developed to improve paediatric dosing – scored once on one side and twice on the other, so that it can be broken into 200 and 300 mg doses, making it adequate for 3-year olds to adults. Reporting on the CHAPAS-3 trial, HO.25 examined whether the new, double-scored EFV tablets and WHO weight band dosing result in optimal EFV levels. Children (n=31) >3 years old in the 10–20 kg body weight (BW) range received new generic EFV tablets (with two NRTIs) at 6 weeks after initiation. Dosage at 10–14 kg BW was 200 mg; at >14–20 kg it was 300 mg. Full 24-hour pharmacokinetic (PK) profile was performed at 6 weeks, including AUC, C_{max}, C_{trough}. Final data in 29 children showed that PK variables were lower and more variable than in adults, but similar to previously reported paediatric values. The study validates WHO weight band dosing. There are ongoing studies on CNS effects and acceptability of scored tablets.

Discussion and questions Audience comments/questions were whether child and adult PK values can be compared (*The 1–4 mmol/L range is for adults. This range is also given in the literature for children. 600 mg is possibly too high a dose for adults; perhaps similar considerations apply to children*); that variation is genetic, and may be translated to treatment outcome (*Pharmacogenetics data are not yet available; also, VL, safety and adherence data are still outstanding*); and that the safety aspect needs to be considered in these young children on ART (*EFV has a well-characterised safety profile. The safety data are available, as CHAPAS is largely focused on toxicity. Results will be published*).

Despite suppressive ART, there is suboptimal CD4 recovery in treated HIV-1 subtype C patients. The aim of retrospective study HO.26 from Botswana was to search for predicative markers of immune activation and assess baseline characteristics for association with suboptimal CD4 recovery after treatment initiation. In a total of 340 records assessed, 20.1% of virologically suppressed patients (n=249) had CD4 counts <200; >66% had CD4 counts <350. Median age of patients was 33.4 years. The main discriminator was low CD4 counts at baseline. There was a definite association with soluble CD14. Analysis showed some association with use of AZT, and with elevated aspartate transaminase at baseline, and marginal association with increased age and also with IFN-γ levels. It was concluded that low baseline CD4 levels result in more suboptimal response. (Poor responders have had low CD4 counts for a long time.) Soluble CD14, as an independent predictor of morbidity and mortality, was put forward as a potential biomarker for identifying suboptimal responders.

Discussion and questions One audience question concerned whether normal CD4 counts in Africa are known, as most trials use values from the North. The few African studies conducted give an array of variables, which are too small to be used as reference ranges. However, studies have

suggested that CD4 counts are low in uninfected African populations. The recommendation was that it would be useful to pool all African datasets.

From Uganda, the meeting heard about multiple HIV-I-infection and disease progression in a cohort of female sex workers in Kampala [HO.27]. The high genetic diversity of HIV is due to rapid replication and acquisition of multiple strains. Multiple infection means infection with >1 HIV strain at once – either at initial infection (co-infection) or acquired over time (superinfection), and either within or between clades. This impacts vaccine design, as well as transmission rate. Some multiple-infected individuals have heightened immune response to HIV, but may also have ART resistance. The study, which was part of the Good Health for Women project, was conducted in 1,027 women recruited in 2008–2010 with 37% HIV prevalence. Voluntary counselling and testing was performed every three months. Samples were stored. The study analysed 285 HIV-positive women and tested first and last samples prior to ART initiation. Demographics and CD4 decline were compared between those singly (n=271) and those multiply infected (n=14). Of those with multiple infection seven had co-infection and seven superinfection (mostly clades A and D). Multiply vs singly infected women had: more sexual partners (27% vs 14%) and more recreational drug use (35% vs 21%) but similar alcohol use. CD4 counts were marginally higher in multiply infected women (528 vs 454, n.s.) who also showed a slight increase in CD4 decline (n.s.). Conclusions were that, despite small numbers affecting the power of the study, an increase in numbers of superinfected patients can be reported, with multiple infections reflecting increased risk behaviour. There is a need for increased post-test HIV counselling to reduce post-test acquisition of new strains.

Discussion and questions The meeting noted that the study had captured a comprehensive sociobehavioural dataset. Had it been possible to establish the identity of the partners? (*Partners were both locals and migrants. Plans are to also test the male clients in future research.*) One audience contribution was that a similar study has been done in West Africa, with similar rates of multiple infections.

The presentation on plasma cytokine levels in chronic asymptomatic HIV-1 subtype C infection as an indicator of disease progression in Botswana [HO.28] was cancelled.

Five presentations on HIV/AIDS co-infections [HO.29–HO.33] included a study on multipurpose prevention technology (MPT) (gels, intravaginal rings and barrier devices) in HIV and common reproductive tract infections [HO.29]. The study aim was to characterise the vaginal environment with respect to vaginal microbiota and inflammation markers, and determine prevalence of vaginal infections in prospective microbicide treatment trial candidates. Results regarding microbial content and type and their association with vaginal environment health status included: 1) Each bacterial vaginosis-associated species was associated with increased pro-inflammatory cytokines; 2) *Lactobacillus crispatus* and *L. vaginalis* were associated with decreased pro-inflammatory cytokines; 3) both *L. crispatus* and *L. vaginalis* may play an important role in the vaginal microbiota in African women. Reproductive tract infections (RTIs) are common in African women targeted for microbicide trials, and the importance of MPT for prevention of sexually transmitted infections, RTIs and pregnancy was clearly demonstrated.

Discussion and questions The audience sought clarity on quantification method of lactobacilli (*By qPCR*) and commented on the potential for introducing sampling bias by PCR (*Cultures were taken; those data will be used later to analyse mixed infections*).

The focus of a Mozambican study [HO.30] was Herpes simplex (HSV) prevalence, incidence and determinants of infection among women at high risk of HIV infection (defined as having had two or more sexual partners in the month prior to study enrolment). HSV-2 is still a substantial public health risk associated with HIV infection, as there is synergy between the two infections. Though African data are scanty, there is high prevalence in set-ups where data are available. The study analysed findings in 409 women aged 18–35. High HSV-2 incidence levels were found, corroborating findings from previous African studies.

Discussion and questions It was noted that the statistical power was limited by the small sample

size. The audience enquired whether there were plans to extend the investigation (*This will depend on availability of funds*). Another query concerned the method used for HSV testing (*Serology*). The possibility of false positives was considered. A final suggestion was that multivariate analysis should have been attempted as this may have yielded different outcomes compared with bivariate analyses. The recommendation was that a larger sample was needed for more rigorous sampling.

Hepatitis B virus (HBV) remains a global health problem, especially during HIV co-infection. This was the topic of HO.31, a study focused on molecular characterisation of circulating HBV in HIV-co-infected patients in Botswana. There are ten circulating genotypes of HBV globally, with distinct genetic characteristics and sometimes distinct geographic distribution. Data on Botswanan genotypes are not available. The study used stored samples to characterise HBV circulating in HIV co-infections in Botswana. HBV A and D were identified. Escape mutation profiles were compiled. No evidence of HBV drug resistance emergence was found. In conclusion, it was found that HBV profiles in Botswana are consistent with profiles of regional neighbours.

Discussion and questions An audience query related to the prevalence of HBV in the general Botswanan population (*These data are not available*). It was agreed that because of the anonymous nature of the sample, the patients would not directly benefit. The findings may be used to guide policy.

Another co-infection study from Botswana [HO.32] investigated toll-like receptor (TLR)4 polymorphisms and their impact on susceptibility to Kaposi's sarcoma (KS) in HIV-1 subtype C-infected patients. TLR4 is an immune gene involved in host cell pathogen immunity. The most common cancer in HIV-infected patients is KS. Predictors for KS risk are needed. The TLR4 A(896)G polymorphism has been linked to development of opportunistic infections and so could possibly also be associated with susceptibility to AIDS-related KS. However, a KS susceptibility association was not found in this study. In conclusion, despite its implication in development of opportunistic infection, TLR4 A(896)G may not be critical for development of AIDS-related KS.

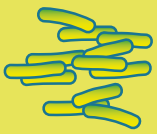
Discussion and questions One audience comment was that the low prevalence of the minor allele in the population is problematic. This study would have benefited from a larger sample, and possibly from sampling a larger fragment to detect significant differences (*The presenter agreed, but said that the work was still at a preliminary stage*).

The aim of HO.33 was to pilot a cryptococcal meningitis screening tool.

Cryptococcal meningitis pathogenesis in advanced HIV infection is still problematic. Diagnosis of HIV-associated cryptococcal meningitis is usually by invasive and unnerving clinical procedures (lumbar puncture), and not before the patient presents with signs of meningitis. In view of this, an inexpensive, less invasive assay is needed at point of care in HIV patients with CD4 <100. The study piloted a cryptococcal antigen (CrAg) screening test as possible alternative. Preliminary results are promising. The presenter concluded that such a screening tool would be important in patients with advanced HIV/AIDS infection.

Discussion and questions The audience commented on the reported discrepancy between lumbar puncture-based diagnosis and CrAg test results, and asked whether this was expected (Yes, this sometimes happens); and why the presentation had not included a comparison between intervention and control groups (*This was an interim analysis; the complete analysis will include such comparisons*). It was concluded that this work is still at a preliminary stage.

3 Research reports: Tuberculosis



RECENT ADVANCES IN TUBERCULOSIS RESEARCH

Dr Ann Ginsberg, Aeras, United States

Dr Ann Ginsberg opened her keynote address by stating that TB is the world's leading killer. This airborne disease has killed far more people compared with any other infectious disease. In 2012 alone, there were 8.6 million new cases, including an estimated 530,000 children, and 1.3 million deaths from TB. Annually, 410,000 women are killed by the disease. Tuberculosis kills one in four people infected with HIV; and 13% of TB is in HIV-positive individuals. Both multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB are of increasing concern; XDR TB has been identified in 92 countries.

Referring to the WHO goal of TB elimination by 2050, Dr Ginsberg said this goal will not be realised with present tools. Currently we are decreasing TB incidence at a rate of 2% a year. And one-third of the world population is already infected by TB bacteria.

The economic burden of TB is huge. Tuberculosis forces families and communities into the cycle of poverty. Outlining the economic impact of the disease, Dr Ginsberg told the audience that TB strikes not only at individuals and families, but also heavily impacts the business sector and governments. At individual level, it is primarily working-age adults who are affected. A study conducted in several developing countries around the world found that on average the costs to a patient equal approximately 1 year's individual income. To illustrate the cost at business level, Dr Ginsberg gave the example of the mining sector in South Africa, which loses over US$880 million annually to the disease. At government level, it has been estimated that TB costs the global economy US$1 billion per day.

It is clear that we desperately need new interventions and tools to eliminate the disease, primarily by preventing transmission, but also by blocking progression to infectious TB and by diagnosing, treating and/or sterilising active TB. In terms of current TB *diagnostics*, an estimated one in three cases per year are currently missed. Although there have been developments in diagnostics (e.g. the GeneXpert® MTB-RIF assay), there is an urgent need for rapid, accurate and affordable tests suitable for use at point of care. It is furthermore important that diagnosis should happen earlier in the disease process. Late diagnosis, as is currently too often the case, means that by the time individuals are diagnosed, they have already infected most people around them that they are going to infect. And it is also important that all drug-resistant strains can be rapidly identified.

With regard to *drug development*, she said, we need simpler and faster acting regimens, as well as ones that are compatible with ARVs. And we need paediatric formulations. Finally, effective and affordable *vaccines* against all forms of TB would be the ultimate game-changer in reaching the 2050 target, ideally both pre – and post-infection – vaccines that are suitable for children, adolescents and adults and safe for use in HIV-infected individuals. Although there have been developments in diagnostics and although new drugs (e.g. Bedaquiline, Delamanid) and vaccines (e.g. AERAS-402/Crucell Ad35.TBS) are at various phases of trialling, the lack of new drugs currently being tested in phase I and the lack of new vaccines (with BCG being the only TB vaccine available at present) is a concern.

Some key questions in our struggle with the disease remain unanswered, including:
- What are the main factors driving differences in transmission and incidence among different locales?
- What enables 90% of infected individuals to contain the infection? What, in other words, is the human protective immune response?

Dr Ginsberg concluded that if we want to eliminate this killer disease, we need to go about it by stopping transmission, neutralising latent infection and preventing reactivation, and appropriately diagnosing and treating active TB disease. The key to elimination is strong scientific research combined with development, committed leadership, advocacy and resources.

Scientific presentations

The parallel sessions on developments in TB research included 28 presentations, which were grouped into the following categories: TB therapeutic studies; TB immunology and vaccine development; diagnostics; drug development and drug resistance; TB studies.

The first of several TB dosing trials presented was a study titled 'What is the right dose of rifampicin (RIF)?' [TO.01]. Conducted in Cape Town (the 'High-RIF1', or 'HR1' study) and at two sites in Tanzania ('HR2'), this trial tested the hypothesis that the conventional RIF dose of 10 mg/kg, approved by the FDA in 1971, is too low, and that an increased dose may significantly shorten treatment duration.

The HR1 study, testing 20, 25, 30, and 35 mg/kg, compared with standard 10 mg/kg, doses of RIF combined with standard INH, pyrazinamide and ethambutol (HZE) in 68 adult smear-positive TB patients, concluded that 35 mg/kg is safe and well tolerated. There was a suggestion of a dose-related increasing decline in log10 CFU/ml and an increase in time to positivity (TTP), especially at 30 and 35 mg/kg. Pharmacokinetic parameters showed nonlinear, superproportional increases in AUC and C_{max}. The HR2 study was a phase II DBRCT involving 150 patients receiving standard HZE, in combination with daily RIF 10, 15, or 30 mg/kg during the intensive phase. Grade 3 AEs were distributed equally across the three arms. One grade 5 AE was reported but was not related to the RIF dosage given. Time to culture conversion on mycobacteria growth indicator tube (MGIT) and solid medium culture (LJ medium) was essentially the same for all three arms, a somewhat disappointing result. It was preliminarily concluded that RIF 15 and 20 mg/kg/d doses combined with standard TB drugs for 2 months are safe and equally well tolerated as RIF 10 mg/kg. The difference in efficacy was modest and non-significant. Currently the results of a 40 mg/kg RIF study are being awaited.

Discussion and questions Audience suggestions were to trial increased INH or pyrazinamide dose to shorten treatment. Also discussed was the choice of site for the studies, since, as several attendees emphasised, setting can affect generalisability (*Site selection was done on the basis of site readiness, capability, and existing collaboration*).

The purpose of the RIFAQUIN trial [TO.02] was to establish non-inferiority of a short course regimen for TB treatment. Patients in this DBRCT were allocated to either standard treatment as control (Group A); or INH replaced by moxifloxacin in the intensive phase, followed by rifapentine + moxifloxacin for 4 months (Group B); or rifapentine + moxifloxacin for 4 months (Group C). Patients were followed for 18 months. A pharmacokinetics substudy was performed to determine drug–drug interactions between rifapentine and moxifloxacin when administered together. Out of 827 new smear-positive TB patients enrolled, data on 592 were available for analysis. Baseline characteristics were similar across all groups. The outcome with the control and 6-month regimen was similar, with 4.9% and 3.9% unfavourable outcomes, respectively. The outcome of the 4-month regimen was significantly inferior, with 18.2% unfavourable post-treatment outcomes (relapses). Incidence of AEs was similar across groups. No acquired rifapentine mono-resistance was found in any of the groups. It was concluded that a shorter TB regimen is needed and that the 6-month once-weekly regimen needs to be optimised.

Discussion and questions The audience asked whether the length of this study (10 years) was justified in view of the non-success of fluoroquinolones. (*Much has been learnt these past 10 years about optimising phase III trial design. Future studies will have smaller samples and more time points tested. Also, single drug substitution is problematic.*) A question concerned the 4-month regimen and whether it is possible to predict relapse before the end of treatment (*No*).

Data were presented on a study conducted in Ethiopia and Tanzania [TO.03] testing the effect of RIF co-treatment on plasma efavirenz (EFV) and treatment response in treatment-naïve HIV patients without TB and also in patients co-infected with TB and HIV, enrolled prospectively and followed for one year. Overall findings were that RIF lowers plasma EFV concentration during early therapy, but has no significant long-term effect. CYP2B6 genotype, but not RIF co-treatment, determines EFV pharmacokinetics. Further, CYP2B6*6 and high plasma EFV concentration

is associated with EFV-induced liver injury and CNS toxicity. The presenters reported a higher EFV plasma concentration and CD4 gain in Tanzanian compared with Ethiopian HIV patients. They could report no significant long-term effect of RIF on viral response. They concluded that RIF-based anti-TB therapy has no significant long-term effect on EFV plasma concentration and efficacy. These results suggest that there is no need to increase EFV during RIF co-treatment. (A recent study of a Ugandan population confirms these results. In the Ugandan patients, the plasma EFV concentration was mainly influenced by CYP2B6 genotype but not by RIF co-treatment.)

Discussion and questions There were no questions following this presentation owing to time constraints.

Challenges of development and evaluations of new TB drug regimens were presented in TO.04. The University of Munich-PanACEA presenter told the audience of several drugs currently in phase II and III clinical development. Evaluation of these used in drug combination regimens has yet to be performed. Challenges in establishing the optimal regimen include: 1) the only valid endpoint is assessment of therapy failure/relapse, which is rare (5–10%). Determination of endpoints requires 24 months' follow-up; 2) there is incomplete understanding of bacterial populations and different lesion compartments; 3) the current drug development pathway is inefficient, and guidance from regulators remains unclear, leading to the process of finding the optimal regimen taking up to 20–30 years. Novel biomarkers to measure therapeutic success are needed to shorten the drug development pathway. More research is needed to understand relapse and how poor adherence impacts the treatment: relapse appears to be caused, not by emerging resistance but by a mechanism preventing clearance of the last mycobacteria. Therefore, novel trial designs need to account for the increased risk of relapse when therapy is shortened. Also presenting preliminary results of the MAMS–TB01 four-arm trial evaluating the impact of high dose of RIF, moxifloxacin and SQ109, the team concluded that the way forward in drug development is to: 1) generate safety data for new drug combinations as soon as possible; 2) use novel markers for assessing bacterial load; and 3) focus on regimens rather than individual drugs.

Discussions and questions The audience asked whether it is possible to combine a bactericidal short treatment phase with longer term immunotherapy (*One would need to be able to assess the activity of the immune system. This is a potential pathway for the future but it would appear to have more applicability in a developed rather than a developing world setting*). Further, how do we define cure? (*If we had a toolkit that would allow a better definition of cure in a TB context this may help prevent relapse.*)

Results of a study trialling a new anti-TB drug, SQ109, on its own and in combination with RIF, in pulmonary TB (PTB) patients were reported [TO.05]. Safety and tolerability data showed 81 mild to moderate AEs (46% GI). One patient died during the 14-day follow-up due to massive haemoptysis deemed unrelated to the study drug. One patient with a pre-existing oesophageal candidiasis stopped treatment owing to epigastric pain after intake of the study drug. There was no abnormal prolongation of QT interval compared with baseline. Early bactericidal activity (EBA) on solid or liquid media (ITT analysis) results showed that SQ109 had no bactericidal effect over 14 days. Possible reasons were insufficient concentrations in extracellular lesions and short follow-up (the mouse model suggests drug activity apparent after 30 days). Conclusions were that SQ109 is a safe and well-tolerated drug. Its main side effect is nausea (most pronounced in the 300 mg dose).

Discussion and questions The discussion focused on the rationale of excluding HIV patients (*This was done to avoid complicating the protocol of the early phase II trial. Future SQ109 trials may consider including HIV patients*).

A Tanzanian study [TO.06] investigated the effect of diabetes mellitus (DM) on the pharmacokinetics of TB drugs. Patients with DM have lower plasma concentrations of certain drugs, with different absorption, distribution, metabolism and/or excretion of drugs, compared with non-diabetics. If this is true also for anti-TB drugs, this may at least partly explain the slower response to TB treatment in patients with DM, as reported in international studies. The reported study from Mawenzi Hospital and its satellite clinics was an observational pharmacokinetics study which enrolled 20 TB patients with and 20 TB patients

without DM. A multiple linear regression analysis adjusting for age, sex, dose per kg, HIV status and acetylator status found that DM remained an independent predictor of the pharmacokinetics of INH and rifampicin. However, pharmacokinetic parameters for pyrazinamide and ethambutol did not significantly differ between diabetic and non-diabetic TB patients. Recommendations were that since increasing TB drug dosage may result in increased plasma concentrations of these drugs, individualisation of the dosage and close drug monitoring are needed in diabetic TB patients. The study had several limitations, such as very small geographical area, probability of high prevalence of gastrointestinal (GI) parasites affecting absorption, and local genetic variations.

How do we improve therapeutic management of TB in a population with poor adherence? This was the question addressed in a drug delivery study from South Africa [TO.07], a country that currently has the highest incidence worldwide of TB per 100,000 population. To address persistence of TB infection and inadequate TB therapeutic management, a nanodrug was developed to enable controlled release of therapeutics and highly specific site-targeted delivery. The advantages of nanodrug delivery include reduction in dosage and dose frequency; reduced side effects; shortened treatment duration; increased patient adherence; improved drug stability; and passive or active targeting to the site of infection. For infectious diseases, a first consideration for drug targeting is to identify the receptors, used for pathogen entry, on the host cell, and follow the same mechanism of entry. Another approach is to identify surrogate markers of infection at the site where the pathogen is localised in the host tissues. If a non-toxic ligand can be identified that recognises such surrogate marker receptors, then it can be incorporated into the nanoparticle for targeting the drugs. A surrogate marker for TB is cholesterol as it accumulates at sites of active infection. The cell wall envelope of Mycobacterium species contains high molecular weight lipids called mycolic acids. In *Mycobacterium tuberculosis*, mycolic acid (MA) consists mainly of alpha-, keto- and methoxy-MA subclasses. Mycolic acid is attracted to cholesterol. It was hypothes ised that MA incorporated into nanoparticles may interact with the anti-MA antibodies present in higher concentrations at the infected areas. In this way, targeting may be achieved by an accumulation of the nanoparticles in immune complexes at the site of infection. Alternatively, MA could also serve as a ligand for cholesterol-rich areas. Another approach involves targeting via attaching nucleic acid aptamers specific for the mannose receptor (MR) which is overexpressed during activation of macrophages in presence of *M. tuberculosis* onto the surface of drug-carrying polylactate-co-glycolate (PLGA) nanoparticles.

The presenter reported studies recently undertaken to study PLGA nanoparticles, coated or not with MAs from *M. tuberculosis*, as well as aptamer-conjugated PLGA nanoparticles in infected and uninfected bone marrow-derived mouse macrophages. Preliminary results showed that coating of nanoparticles with MAs and aptamers increased the phagocytic uptake of nanoparticles. Conclusions were that the uptake of drugs by infected macrophages would be enhanced not only by the synthetic PLGA polymer carrier vehicles but also by the presence of MA or the aptamers that may facilitate opsonisation of the nanoparticles for macrophage uptake.

Discussion and questions Members of the audience asked what determined the choice of MA, since there are >80 MAs (*Three major subclasses present in* M. tuberculosis *have been investigated. Natural MAs isolated from* M. tuberculosis *were used*); and whether this was an injectable formulation (*No, oral drug delivery*).

A Kenyan study [TO.08] presented treatment outcomes in an infant TB patient population. Prevalence of TB disease in Kenyans is 299/100,000 population; paediatric TB (in infants to <15-year-olds) accounts for approximately 10% of cases, with highest incidence at 0–3 years. Diagnostics and management of paediatric TB are challenging. An early diagnosis can be difficult to establish in young children because of non-specific TB symptoms; this often leads to late diagnosis when the disease is severe, impacting outcomes. Moreover, there is poor adherence because of the long treatment duration and, in HIV–TB co-infected children, denial/stigma. In a large prospective cohort study, 2,900 children were evaluated at KEMRI/CDC sites in Kisumu, Kenya. Induced sputum, gastric aspirate, TST, chest radiograph, PCR/rapid HIV test, and Keith Edward Score were investigated in TB suspects, resulting in diagnosis of 49 (1.7%) TB cases. Of

these, 37 (75.7%) completed treatment, seven (14.3%) died, four (8.2%) dropped out, and one (2%) was transferred out. Stratified analysis showed poor outcomes for HIV-positive infants and those who delayed HAART. The presenter emphasised the need for better TB diagnostics in children, as well as for adherence counselling, effective monitoring of TB treatment outcomes and effective directly observed treatment short-course (DOTS) programmes extended to children.

Discussion and questions The questions/discussion post-presentation focused on further research to improve TB diagnostics in and TB drugs/formulations for children. It was suggested that HIV-positive children without active TB but with history of TB contact should receive INH prophylaxis.

Several presentations looked at TB immunology and vaccine development. One of these, a TB vaccine development study [TO.09], gave the background to development of H1IC, a TB vaccine antigen (Ag) in which two immune-dominant TB Ags (Ag85B and ESAT6) are fused together by recombinant technology and produced as a polyprotein. Based on the H1 vaccine, a subunit vaccine, H56IC, was developed. Results from preclinical mouse studies of H56 versus BCG suggest that H56IC is not only superior to H1 but also contains infection better after 24 weeks compared to BCG. Hence it was decided to move this vaccine forward. To date, there have been five trials involving H1, and three involving H56. H1 was developed to prevent acute TB disease as well as re-activation of existing latent TB infection, especially in adolescents and young adults in largely BCG-vaccinated populations. It was found to be safe in HIV-positive patients as well as TB patients with or without latent TB infection. After initial trialling in the Netherlands, a phase I (THYB-03) trial was conducted in Ethiopia. In a single-site Phase II study in South Africa evaluating the safety, reactogenicity and immunogenicity of H1 vaccine (THYB-04), 240 adolescents were randomised to 15 µg or 50 µg in one of two vaccination schedules (vaccine–vaccine or vaccine–placebo, 56 days apart). Preliminary results indicate similar outcome despite differences in dosage and administration, with a sustained response until day 224. Based on enzyme-linked ImmunoSpot (ELISPOT) data, it is hard to determine which dose is best owing to overlap at the end of the trial. Final ICS flow data are awaited. In Tanzania, the THYB-05 trial assessed the safety and immunogenicity of H1 in 48 HIV-infected adults with CD4 >350 without evidence of active TB. Results indicate that H1 is well tolerated, safe, and immunogenic and has durable efficacy in this population. Blood samples of the THYB-01 cohort in the Netherlands, taken after 2.5 years to test for latent immunogenicity, indicate that there is a long-term memory of the vaccine in BCG-naïve individuals. It was concluded that H1 has only short-lasting AEs and the vaccine is clearly immunogenic, even in HIV-positive patients. There will be no further clinical development of H1IC, but data from the H1 studies will support H56IC clinical development and trials.

Discussion and questions Audience questions concerned SAEs in the THYB-04 group (There were two vaccine-related SAEs in cases with high creatinine phosphokinase values) and CD8 responses (*There were no detectable CD8 responses and no high antibody levels; ongoing trials and more studies are planned to test correlates of protection*).

A progress report on a EDCTP-cofunded, phase II safety and immunogenicity trial of AERAS-402/Crucell Ad35.TBS vaccine in BCG-vaccinated, HIV-uninfected infants in Kenya, Mozambique and South Africa was given [TO.10]. The protocol has undergone several amendments, closely monitored by the Data Monitoring Committee, with nine safety data reviews carried out. The most common AEs reported were upper respiratory tract infection, diarrhoea and mild to moderate pyrexia. There were also reports of prompt injection site redness, sudden onset erythema, pain and swelling. Results showed that Ad35.TBS/AERAS-402 has an acceptable safety profile in infants. Two doses primarily induce polyfunctional CD8+ T cell responses in infants. The frequency and magnitude of CD4+ and CD8+ polyfunctional T cell responses after two doses was lower than expected and desired in infants. Among lessons learnt were that collecting and using samples from multiple sites across three countries is complex, requiring constant monitoring, complicated administration, etc. Initial regulatory issues had delayed the study start and the multiple protocol changes had complicated the study. (For example, several mothers had been unwilling to provide additional consent when an additional dose was introduced in a later version.)

It was concluded that it is important to establish criteria for adaptive trial design and data review management.

Discussion and questions One audience member argued that researchers need to prospectively plan and describe adaptive steps to be taken in certain scenarios. In vaccine development, it is normal to react to new data, i.e. have a reactive trial design. Another audience member asked whether another phase IIb trial will be conducted to evaluate efficacy (*There are plans to conduct a proper phase IIb trial, possibly in another population*). Further audience questions concerned protection from infection (Further studies are planned to address this); and what should be used as a surrogate marker for evaluation of protection by a candidate vaccine (*The question of markers was left open*).

Incidence of TB in HIV-positive adults enrolled in a TB vaccine clinical trial in Senegal was reported [TO.11]. The objective of this proof-of-concept phase IIb clinical trial was to evaluate the protective efficacy of a booster MVA85A vaccination administered to healthy, HIV-infected adults. Results from a related vaccine trial, the TB020 MVA85A infant trial in South Africa, had shown that although the MVA85A vaccine was well tolerated, it induced only modest cell-mediated immune responses and there was no efficacy demonstrated against TB and *M. tuberculosis* infection in infants. The trial protocol was revised, with safety as the primary endpoint (previously efficacy) and efficacy as the secondary endpoint (previously safety). Further, the target enrolment was scaled down from 1,400 to 650 subjects for optimum review of the safety profile. Preliminary results show that during the trial period there was a lower TB incidence rate in the population, possibly because 4/5 participants were on ART and nearly 40% of participants had received 5 months' INH preventive therapy (IPT). Previous studies have shown that IPT reduces the risk of developing active TB in a tuberculin skin test – or purified protein derivative (PPD)-positive HIV-infected individuals, and suggest that ART may reduce the risk of HIV-infected persons developing TB. A key conclusion from the presentation was that study eligibility criteria should be properly selected taking into account all factors that can affect the susceptibility of participants to TB.

Discussion and questions An attendee enquired about IPT coverage in Senegal (*IPT programmes have not yet been implemented in Senegal. There is an ongoing pilot national programme to scale up prevention*).

Presentation TO.12 sought to find out whether host markers other than IFN-γ, or new antigens other than ESAT6/CFP10, can differentiate between pulmonary TB and latent TB infection. In a South African setting, eight different host blood markers were identified following stimulation with QuantiFERON® (QFN). The presented study is an evaluation of the utility of these biomarkers in a Pan-African study, the African European Tuberculosis Consortium (AE-TBC), involving seven African sites and four European partners. The aim is to develop new, sensitive, inexpensive and field-friendly diagnostic tests for TB. The current trial evaluates several single host markers in whole blood culture assay (WBA) supernatants stimulated with ESAT/TB10.4/Tb7.7 as to their discriminating ability to differentiate between latent and active TB. Altogether, 1,384 (356 HIV-positive and 1,028 HIV-negative) participants were recruited and followed at all seven African field sites. For the purposes of this presentation, samples from 514 individuals (from all African sites) were investigated using Luminex. Participants were categorised as having definite TB, probable TB, possible TB, no TB, or uncertain diagnosis (questionable). Probable, possible and definite cases ('TB cases') were compared with non-TB cases. Owing to high overlap between TB and no-TB markers, taken singularly the markers were not viable. However, in combination they are promising, with a sensitivity of 70% and a specificity of 80%. Accuracy was increased in non-HIV-infected individuals. It is hoped to use the markers in children and in extrapulmonary TB (EPTB).

Discussion and questions An attendee asked why the study did not use bacteriology tests, i.e. the gold standard tests (*These were done on probable and possible TB cases. However, there was not much time to perform subanalyses*). Another question concerned the pre-established diagnostic definitions 'definite', 'possible', 'probable TB', etc. rather than 'TB' vs 'no TB'; clarification was also sought regarding to what extent these definitions may that have affected the analysis and findings (*This classification had been found to work in the practical*

setting and remotely. Prior to publication, analysis will be conducted to investigate any potential effect). Other questions were why a test is needed which is 80% specific and 70% sensitive when a test with 100% accuracy is already available (*In some settings, microbiological confirmations are difficult to achieve*); and whether application of systems biology approaches was intended (*The group will apply systems pathway analysis at the final stage*). Presentations TO.09-TO.12 raised much interest from the audience and a lively general Q&A discussion followed. One comment concerned the need to take into account regional variations (genetic/environmental) in the TB vaccine development stage. Another questioned the practice of doing conducting phase III vaccine trials at all. However, it was agreed that an effective vaccine will have more impact on the epidemic than drugs. (*In reality what is needed is all vaccines, new drugs and diagnostics, all at once.*) A further question was whether infant trials have been abandoned? (*Not necessarily – but this is up to other vaccine developers. With current models, adolescent and adult vaccine will be more effective on the epidemic.*) Also, it was suggested that we should conduct retrospective analysis of TB vaccine trials as part of the vaccine portfolio management. This would inform future research and enhance lessons learnt. A recommendation from one of the presenters was to continue supporting the sites where capacity was built, e.g. Ethiopia, and consider them as site options for future trials. She also stressed a need for more focus on data management and security of data and proposed that data from these sites can be used for regulatory purposes.

Five TB diagnostics studies followed, TO.13–TO.17, two of which were conducted in a childhood TB context. The first of these, TO.13, reported on the Kampala – and Tanzania-based TB CHILD project and presented evaluation of a new diagnostic test for childhood TB in high-burden countries. New diagnostics in children are urgently needed as the Xpert test is less effective in diagnosing children compared with adults: the sensitivity of Xpert in paediatric PTB is 66% compared to culture. Moreover, CD27 expression can distinguish latent from active TB in adults but not in children.

The T cell activation marker IFN-γ release assay (TAM–TB assay) examines phenotypic change in T cells. Paediatric patients were classified into five categories, viz. culture-confirmed TB, highly probable TB, probable TB, non-TB (controls), and indeterminate. Median age was 6.1 years. One-third of patients were HIV-infected, 40% of whom were on ART. Half of the patients were malnourished. The performance of the TAM–TB assay was compared with two other diagnostics, viz. culture and Xpert. The TAM–TB assay was able to provide a result within 24 hours. Its sensitivity was 83% and specificity 96%. One limitation was that the study excluded children with inconclusive outcomes. In conclusion, the TAM–TB assay offers a major advance in rapid and accurate TB diagnosis in children sputum-independently. It is the first immune-based assay that can detect active TB disease with high specificity in a TB-endemic setting. There is need for further refinement (e.g. using fresh whole blood instead of PBMCs, and regarding compatibility with CD4+ T cell count cytometer). Further evaluation in other high-burden settings and HIV-positive and malnourished children is also needed.

Discussion and questions One question was that, given the difficulties in diagnosing TB in children, should there not have been an adult comparator group? (*Yes, but because of funding restrictions this was not included.*) One attendee said that helminths can impair TB-specific responses and asked whether these had been studied (*No*). A final question was whether TAM–TB can be applied as a point-of-care test (*No*).

TO.14 presented an evaluation of the Xpert MTB/RIF assay in diagnosis of extrapulmonary TB (EPTB). Known as a rapid test for TB and rifampicin (RIF) resistance, Xpert has not yet been validated in EPTB. Patients with low CD4 counts often have EPTB. Consequently, 50–60% of the most vulnerable patients will be undetected by sputum-based Xpert testing. EPTB is paucibacillary. The group conducted several studies to examine accuracy of Xpert, in: 1) TB meningitis in a high-burden setting. Centrifuged cerebrospinal fluid (CSF) tested by Xpert had a sensitivity of 82% and specificity of 95% compared with microscopy (13% sensitivity and 100% specificity). 2) Pleural TB: sensitivity was 22.5% and specificity 98% (the test was done in smear-negative patients). 3) Tuberculosis pericarditis: a sensitivity of 63.8% and specificity of 100%. 4) Urine of HIV-negative, hospitalised smear-negative or sputum-scarce TB patients. Urine centrifugation and pelleting significantly increased the sensitivity of

Xpert compared with unprocessed urine in paired samples: 42% (95% CI: 26–58) vs 8% (0–16) (p=0.001). Concluding points were that: Xpert represents a new diagnostic standard for EPTB. It shows high sensitivity for bronchoalveolar lavage (BAL) fluid, CSF, and TB lymphadenitis. It has modest utility on urine and blood in patients with low CD4 counts. Both CSF and urine should be concentrated before testing. Poor sensitivity was seen on pleural fluid and pericardial fluid (most likely this option would not be cost-effective). Currently, limited data are available for urine, blood, and stools.

Discussion and questions Regarding testing of BAL fluid, one question was how much specimen is required (*They used as much as they could get*).

Diagnosing TB in HIV-infected patients is challenging. Undiagnosed TB is common in HIV-infected adults seeking care in HIV clinics. To illustrate one of the challenges, the presenter of TO.15 said that about 25% of TB patients do not develop symptoms. The study looked at diagnostic strategy using the Xpert MTB/RIF assay vs smear microscopy in patients presenting with very advanced HIV infection. Participants were part of a pragmatic trial integrated into routine, publicly funded HIV clinics in Tanzania. The aim was to assess a strategy for reducing mortality among HIV-infected patients presenting with CD4 <100 (later in the trial this criterion was changed to <200). Compared with smear microscopy the Xpert assay diagnosed more TB. A significant number of TB cases were diagnosed irrespective of symptoms.

Discussion and questions Members of the audience wanted to know how the sputum was collected and whether it was pooled overnight (*Spot specimens were taken*); and how the hospital where the study was done, benefitted (*Patients were started on ART immediately and staff were extensively trained*). There followed an extensive discussion regarding routine examination of sputum in patients who live in TB-endemic settings, even if they are asymptomatic. The audience agreed that more proactive screening for TB is needed, especially in HIV-infected and diabetic patients.

Also dealing with the Xpert MTB/RIF assay, TO.16 investigated its diagnostic utility to diagnose PTB in children presumed to have TB in The Gambia, a TB-endemic but low-HIV prevalence setting. Among many challenges in TB diagnosis in children are that: TB in children mimics other common diseases; chest X-ray changes are often non-specific; childhood TB is paucibacillary in nature; the TST is of limited value in resource-constrained settings and IFN-γ release assays are suboptimally sensitive to diagnose TB and latent TB infection in young children. The study investigated the diagnostic utility of the Xpert test in a community-based prospective cohort of 396 children presumed to have TB, median age 6 years. Induced sputum was collected and tested using: smear microscopy for acid-fast bacilli (AFB), liquid culture by MGIT, and Xpert. Results showed that Xpert offers more sensitive diagnostics compared with sputum smear microscopy but in the context of childhood TB, it cannot be recommended to replace culture methods (where available) and there is need for additional methods to improve TB diagnosis in children.

Discussion and questions A member of the audience commented that availability and rapidity (2 hours) of the Xpert MTB/RIF assay does not seem to impact patient management in a real-world setting and mentioned multiple operational barriers such as weaknesses and gaps in the health system chain. Furthermore, that Xpert test was not a point-of-care test, and neither cheap nor easy to use. Although the Xpert test represents an advance in TB diagnostics, the audience agreed that there is a need for a head-to-head evaluation of Xpert with new emerging TB diagnostic tools.

In an Ugandan study [TO.17], the Xpert MTB-RIF assay was used as add-on test to smear microscopy for diagnosis of PTB among HIV-infected adults. The WHO recommendation is that Xpert be used as the initial test in adults and children presumed to have HIV-associated TB; however, several low-income countries are adopting an 'add-on strategy', in which smear examination is done first and if this is negative, it is followed by Xpert. This was compared with a 'replacement strategy' in which Xpert is used as a first-line test. Findings of an economic analysis had suggested diagnostic and treatment costs for the add-on strategy were lower compared with the replacement strategy. The economic analysis had not included data on, for example, HIV-positive vs HIV-negative patients or more sensitive methods

(e.g. fluorescence microscopy). The presented study was based on a need to assess the most effective TB diagnostic strategy relevant for routine practice, using systematically collected evidence for effectiveness before implementation. The diagnostic gain of an add-on strategy was compared with a replacement strategy for diagnosis of PTB among 424 HIV-infected patients. Conclusions were that among HIV-infected TB suspects, smear microscopy prior to the Xpert assay in add-on fashion identifies only a few additional TB cases. The presenter added that, interestingly, sensitivity of the Xpert MTB–RIF assay had decreased with CD4 counts >200 compared with CD4 ≤200. The study findings support the replacement strategy, of using Xpert only, for diagnosing TB among HIV-infected patients. Where Xpert is not available on site, an add-on strategy may have benefits.

Discussion and questions A lively discussion followed, in which it was emphasised that, irrespective of availability of the Xpert MTB–RIF assay, traditional TB diagnostic testing (smear/culture) is needed for monitoring TB treatment response and therefore cannot be replaced. In the context of the replacement strategy, operational issues and weaknesses of the health system will also limit the impact of Xpert. Delegates felt that Xpert is not the answer to everything and new TB diagnostic tests should be evaluated against Xpert. Regarding the relative effectiveness and cost-effectiveness of Xpert, this was likely to differ in different populations, e.g. adults vs children and HIV-positive vs HIV-negative patients.

In response to the need for point-of-care TB diagnostics, a South African study [TO.18] is underway to investigate the potential of anti-IFNγ ssDNA aptamers to detect TB-relevant cytokines. Aptamers are synthetic nucleic acid molecules selected *in vitro* to specifically bind to: small molecules, proteins, cultured cells, and micro-organisms. They are widely used in therapeutics and diagnostics as they can bind any target with high specificity and affinity. They are small, with easy synthesis and modification, and low toxicity and immunogenicity. The study is using Systematic Evolution of Ligands by Exponential Enrichment (SELEX), an iterative process performed *in vitro* using a combinatorial library. It involves three main steps: 1) incubation of target with library; 2) separation of target-bound from unbound sequences; 3) amplification of target-bound sequences. The library comprises about 1,015 different random sequence nucleotides which have a fixed central region and two flanking primers on either side. Enzyme-linked oligonucleotide assay (ELONA) was used to determine the binding affinity between the aptamer and the target protein. Preliminary results indicate that aptamers may offer a potential tool for developing new aptasensors for TB; however, further research is needed. Diagnostic tools that could possibly benefit from this technology in TB diagnostics are colorimetric assays, electrochemical biosensor, aptasensors, fluorescence-based sensors, lateral flow assays, and ELISAs/ELONAs.

Discussion and questions A very lively discussion followed this presentation about the promise of an exciting technology as diagnostic tool for the near future. Attendees discussed the possibility of using this technology to develop a diagnostic multiplex platform.

A study dealing with TB drug development [TO.19] was presented, based on the rationale that drug-resistant TB is on the increase and that more, and more effective, TB drugs are needed. The researchers isolated 29 marine endophytic fungi (MEF) in Ghana, cultured them and tested extracts against *S. aureus*, *E. coli*, *C. albicans* and *M. smegmatis*. They also developed a simple bioassay and used it to screen a panel of organisms for antifungal and antibacterial properties. A selected number of fungal isolates were further tested and all produced antimycobacterial activity. The team reported some promising preliminary results and are in the process of setting up 20–40 L tanks to enable generation of enough material to allow product isolation in the hope of finding promising novel chemotypes.

Discussion and questions The audience asked how it is possible to tell that an isolate behaviour effect is due to growth factor extract or lack of growth factors in a particular medium (*All media are tested with standard antibiotics at very low concentrations to achieve standard growth; all extracts are subjected to the same type of culture so that the changes are intrinsic to the extracts*). Another question was whether toxicity studies have been conducted (*Toxicity studies will be conducted on the pure compound*). One attendee wanted to know if the team were part of a network of drug

developers or affiliated with a pharmaceutical company (*The University of Ghana-based group are not part of a network of drug developers but are working with a local pharmaceutical company that provides mentorship*). Participants suggested several African networks that could be joined or applied to for grants, e.g. the African Network for Drugs and Diagnostics Innovation and the Special Programme for Research and Training in Tropical Diseases.

There is a high rate of TB relapse in the Nigerian population. Association between leptin receptor gene (LEPR) polymorphism and TB relapse in Nigerian patients was the topic of a presentation [TO.20] focusing on host factors that predict TB relapse after successful treatment. Not many data are available on how host genetic factors contribute to TB relapse although we do know how they contribute to development and severity of TB. The prime genetic candidate is leptin. The study objective was to establish risk factors for TB relapse in a cohort from Lagos consisting of 25 TB relapse patients age-matched to 44 TB-cured (6–12 months post-treatment), HIV-negative controls. Findings were that having TB relapse is not related to continued contact with TB. In contrast to a previous study, age ≥40 years were not associated with relapse; however, the study group was perhaps too small to reach conclusive results regarding age. Persistent anaemia, decreased leptin and TNF-α level and homozygous mutant genotype of LEPR Gln223Arg polymorphism were associated with TB relapse. Key findings from this small study were that LEPR Gln223Arg polymorphisms may modulate susceptibility to relapse through impaired body weight and persistent anaemia in Nigerian patients. In addition, TB relapse is associated with low TNF levels. It is planned to expand the study to other ethnic groups (patients have thus far been from the Yoruba population). Another area for future research would be to examine how health system factors (facilities and treatment factors) may contribute to relapse.

Discussion and questions The audience suggested that the group should consider investigating strain diversity issues as Nigeria is the epicentre of several TB strains, as well as further investigating TB relapse with malaria and HIV co-infection, also examining how LEPR impacts co-infection. One attendee added that treatment adherence should be taken into account.

TO.21–TO.23 were TB immunology studies. The aim of TO.21 was to detect drug-susceptible and resistant TB strains in Cameroon, a country with a high prevalence of TB and with few effective drugs. The population is diverse and genotyping studies are very important for TB control. New strains are being discovered in Cameroon due to immigration. In addition, drug resistance is spreading. The study was conducted at the Jamot Hospital in Yaoundé, with 1,041 participants recruited. Spoligotyping was performed on positive cultures. Analysis showed no correlation between HIV status and drug resistance. There was no correlation between HIV and LAM10–CAM clade, which is associated with TB infection in Cameroon; however, the genetic diversity is complex. In total 47% katG mutations were found. Among eight RIF-resistant isolates, 2 MDR isolates were detected, both based at the rpoB531 gene. Of the strains, 98.8% were *M. tuberculosis*-resistant and 1.2% were *M. africanum*. It was concluded that RpoB may offer rapid genotypic detection for most RIF resistance. Recommendations included that the study be extended to the rest of Cameroon. In addition, further investigation of other markers is needed.

Discussion and questions The audience commented on the diversity of the spoligotypes (*This is mainly due to population migration between countries*); and the decrease in *M. africanum* in Cameroon (*Again, could be due to immigration*); and on the study's exclusion of children <15 years (*Children were excluded as they are more sensitive and not always able to cough on demand. Furthermore, for cultural reasons, it is hard to obtain parental consent for blood samples*).

TO.22 investigated the effects of a 6-week delay in BCG administration in home-delivered Ugandan infants. In Uganda, the percentage of home births is high. Home-delivered infants miss out on the vaccine at birth and only receive it at their first, 6-week post-natal visit to the clinic. The immune system in neonates is immature, making them more susceptible to infections. Blood samples were taken at 9 months and two assays performed. Results showed an association between vaccination group and income group as infants vaccinated as late as at 6 weeks are

from a lower socio-economic background. Strong CD4 and CD8 cell responses have an effect on increased vaccine take-up in infants. The results support the WHO recommendation that children should be vaccinated right after birth as a delay affects TB immunity.

Discussion and questions Questions were whether the presenter thought that exposure to non-tuberculous mycobacteria (NTM) might blunt immune response (*Recruitment had been at 9 months and had only included children with BCG scars. This excluded 40–50% of infants with weaker responses since small scars are indicative of a poor response*). It was commented that the study should have included the entire infant population.

Current TB diagnostics do not distinguish between infection (persistent or resolved) and active TB disease. Most *M. tuberculosis* infections remain asymptomatic but up to 10% will progress to active TB. This was the study rationale for TO.23 from Madagascar, a country which has 25,000 new TB cases per year. BCG is administered at birth. The study aim was to evaluate TNF-α-dependent apoptotic genes as markers for human clinical TB. The study was performed in a cohort of new TB cases and their household contacts (people cohabiting with the TB cases for ≥6 months), and community controls. The results showed that PPD-positive individuals have a higher gene expression of the FLICE-like inhibitory protein (FLIP). Active TB was associated with upregulation of TNF receptor 2 and with high monocyte and decreased lymphocyte counts. There was an association between clinical TB and expression of TNF-α-dependent apoptosis-related genes, which enabled distinguishing infection from active disease, but not identifying individuals at risk for infection. Further validation of the biomarkers is needed.

Discussion and questions The audience asked whether the data had been subjected to multiple analyses (*No, multiple analyses had been done in another study, yielding the same results*). Summing up the previous sessions, the chairs commented that from all the presentations it was obvious that there is an increase in the diversity of TB strains being observed. In addition, an ancient strain, *M. africanum*, is disappearing and an opportunity might be missed to get more information on this strain. They emphasised that samples need to be stored for future work. Also, more paediatric studies need to be done. Finally, it is important to take advantage of South–South networking so that data can be brought together.

On a different topic related to TB research, the presenter of TO.24 shared some experiences of real-time electronic vs paper-based data capturing methods in TB research conducted by the KEMRI/CDC TB research branch in western Kenya. Both data capturing methods have challenges and advantages. The presenter concluded by saying there is a need for investment in data management systems and electronic data capturing systems. Partnership is important in sharing data capturing systems.

Discussion and questions The audience shared several related experiences. It was concluded that quality assurance is a challenge in paper-based data capture. Site experience is required to combine the data capturing methods. It was suggested that this project might benefit from EDCTP support.

Another Kenyan study [TO.25] looked at prevalence of non-tuberculous mycobacteria (NTM) in HIV-infected patients. Based on modified American Thoracic Society (ATS) criteria for NTM, and using sputum sample collection for liquid culture, as well as an immunochromatographic detection method, the study diagnosed NTM in ≥7-year-old HIV-positive patients newly enrolled for ART and without history of TB in the past year. A total of 591 patients from ten HIV treatment centres were enrolled. Several NTM species were identified. One study limitation was absence of chest X-rays, making evaluation using ATS diagnostic criteria problematic. The presenter concluded that NTM is prevalent among HIV patients but its clinical significance in these patients is unclear. Recommendations were to develop a programme to deal with this emerging health problem. Further research on NTM in HIV is required, and national clinical guidelines need to be developed.

Presentation TO.26 described the experiences of conducting a study to compare post-mortem and verbal autopsy for measuring TB mortality in Kenya. Though TB is a major killer and TB control programmes are attempting to reduce mortality, the burden of TB-related mortality is not known. Where no medical records exist or where the per-

son received no medical attention it is important to establish cause of death by autopsy. Little is known about the performance of verbal autopsy compared with a gold standard of post-mortem examination. Using a cross-sectional design, this autopsy study (n=78) compared the two methods of establishing cause of death. Despite extensive efforts to sensitise the villages to the study, obtain the necessary consent, and offer incentives to family members, numerous challenges were encountered, including: breakdown of vehicles and refrigeration facilities, various misunderstandings regarding the study and processes involved, a backlog of post-mortems due to personnel shortage. The study concluded that even more extensive sensitisation is needed before study start, and that this should be done in partner collaboration. Better logistics are needed. Clinics and community leaders need to be involved. Although autopsy-based studies are difficult to conduct, the authors found this study feasible and community acceptance was generally good.

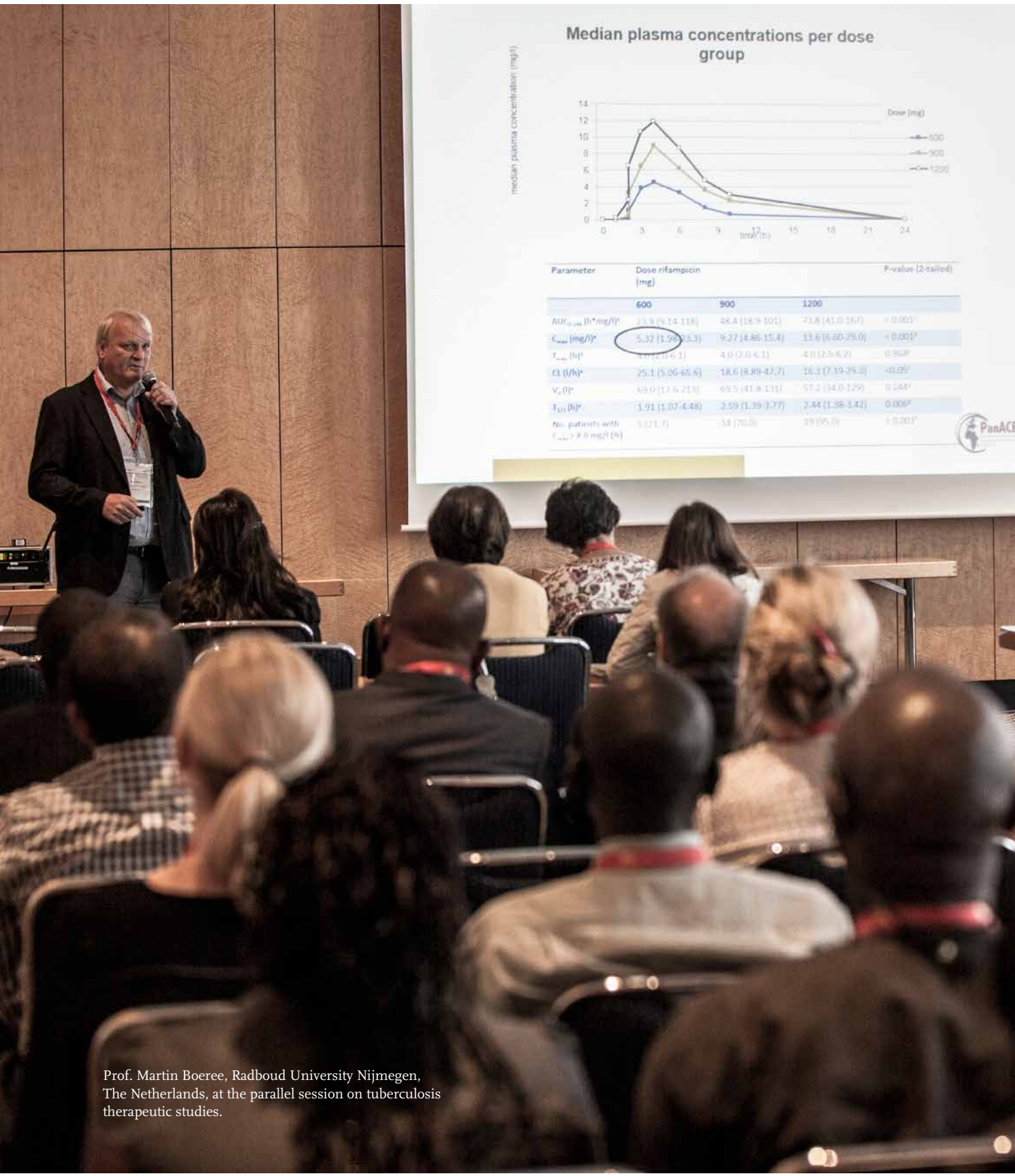
Discussion and questions The lengthy Q&A discussion that followed raised issues such as religious sensitivities (*People at places of worship had been sensitised. Initially religious leaders opposed the study but eventually accepted it*); legal requirement to perform a post-mortem (*Post-mortems have to be performed in trial subjects. This was not the case in the current samples. A larger mortality study addressing this question will follow*); and the incentives for families to participate (*The key incentive was finding out the cause of death*). One participant commented that establishing presence of TB does not necessarily mean that TB was the cause of death.

Monitoring TB patients remains a challenge, with lack of clinical staging and absence of markers of disease severity. Sputum grading and chest X-rays have been introduced in TB monitoring but these are costly, poorly interpreted and unreliable. Presentation TO.27 described a study that developed and assessed a clinical scoring system in a case–contact cohort in The Gambia. The instrument was based on an algorithm of signs (e.g. BMI <18) and symptoms (e.g. loss of appetite). It included two severity classes: 1 = score ≤9; 2 = score >9. Two patient groups were compared: those who presented for follow-up and those who did not. There was no difference between the groups at baseline and 2, 4 and 6-months' follow-up. The study found that the TB score declined sharply within 2 months of treatment and continued to decline, more gradually, until the end of treatment. The tool is planned to be validated in a larger trial.

Discussion and questions The audience wanted to know why BMI, but not height and weight, was recorded (*BMI is linked to response. It is less subjective*). Also asked was whether a separate score was applied to defaulters (*No*), and whether there was a way of monitoring treatment adherence in the study groups (*Adherence is monitored using standard parameters and drug cards given out by the national TB treatment programme. Though intended to be objective, this is fairly subjective. The study group performs active follow-up via mobile phone*).

The final presentation on TB [TO.28] dealt with sequencing of variable T cell epitopes of *M. tuberculosis* from confirmed TB cases in The Gambia. The presenter stated that BCG is an old vaccine which provides some protection against severe forms of paediatric TB but neither prevents latent TB infection nor gives reliable protection in adult PTB. A new vaccine is needed. As T cells are important in naturally acquired immune responses, a good TB vaccine should contain T cell epitopes that cover all lineages of *M. tuberculosis* and are immunogenic. The presented study set out to identify T cell epitopes and confirm immunogenicity using samples from 99 HIV-negative TB patients. Methods included DNA extraction and whole genome sequencing. Results showed seven highly variant epitopes. The highest frequency of variant sequences was found in Rv0093. Lineage-specific differences played a major role in the observed variability between the prevalent TB strains in The Gambia, *M. africanum* and *M. tuberculosis*. The study is still ongoing; however, preliminary results indicate that *M. tuberculosis* exhibits sequence diversity in 17 human T cell epitopes and that Rv0093 is highly variable.

Discussion and questions The discussion following the presentation concerned the statement that *M. tuberculosis* may have originated from Africa, as reported in a published paper. An attendee said that there are many misconceptions about TB. The disease has been with humankind for centuries. Tampering with the immune system to produce a vaccine is a worrying prospect.



Prof. Martin Boeree, Radboud University Nijmegen, The Netherlands, at the parallel session on tuberculosis therapeutic studies.

4 Research reports: Malaria

RECENT ADVANCES IN MALARIA RESEARCH

Professor Pedro Alonso, Barcelona Centre for International Health Research (CRESIB), Spain

Professor Pedro Alonso began his keynote address by stating that in 2012, an estimated 3.4 billion people were at risk of malaria. Of this number, 1.2 billion were at high risk, defined as greater than one case per 1,000 population. Of the 1.2 billion at high risk, 47% were living in Africa and 37% in South East Asia.

There are at present 97 countries with ongoing malaria transmission, and by far the largest share of this burden is borne by Africa. Thus, out of 216 million malaria episodes in 2012, 81% were in Africa. Likewise, out of 627,000 malaria deaths, 90% were in Africans living in Africa. A few countries in the world therefore carry 80% of the global malaria mortality burden. Furthermore, children are at highest risk: a total of 77% of malaria deaths globally are in under five-year-olds.

On a more positive note, between 2000 and 2012, malaria-specific mortality rates fell by 42% worldwide (by 49% in the African region, and by 48% in under five-year-olds). And of the 3.3 million deaths averted between 2001 and 2012, altogether 3 million (90%) are estimated to have been in under five-year-olds in sub-Saharan Africa.

The worldwide distribution of malaria has been shrinking since 1946 and this trend has accelerated in the last decade. Professor Alonso linked these advances directly to increases in funding. International funding for malaria research and care has increased from less than 100 million US$ per annum in the year 2000 to approximately US$2300 million per annum in 2014. However, now investment appears to have plateaued and treatment needs are not being met. For instance, only 40–60% of households that would benefit from nets have them.

There is a need to develop new drugs and new approaches, and fast. The artemisinin drug resistance in the Mekong subregion is worrying; however, an even more urgent worry is Anopheles resistance to insecticides, reported from 64 countries, with efficacy reduced to 10% in some areas. There is a call for action to maintain the effectiveness of malaria vector control.

Professor Alonso then outlined the aims of the global technical strategy, which is global acceleration of reduction, and elimination over the next decade. He said a balance is needed between technical guidelines, contextual information and advocacy.

The long-term goal is to eradicate malaria. The greatest current threat to this goal is the current financial crisis. More funding and continuous investment are urgently needed to enable us to progress from saving affected lives of infected people to interrupting transmission. Looking ahead, the malaria elimination agenda may become important in EDCTP's agenda.

Scientific presentations

In the parallel sessions on malaria, 32 presentations were planned, but presentations MO.14 and MO.25 were cancelled. The main themes of the malaria research studies were: Malaria vaccine studies; Therapeutic studies; Pregnancy-associated studies; Malaria co-infections, drug resistance and modelling; and Immunology and diagnostics.

The malaria parallel sessions opened with three vaccine studies. A phase I efficacy trial of the malaria blood stage vaccine candidate GMZ2 was presented in MO.01. This double-blind randomised controlled trial was conducted in children aged 12–60 months in Burkina Faso, Ghana, Uganda and Gabon. The candidate vaccine is a multi-component fusion protein comprising GLURP-R0 and the C-terminal part of MSP-3. The vaccine targets the blood stage of malaria infection by disrupting parasite development in the blood. Previous data show that high levels of IgG1 and/or IgG3 antibodies to GLURP and MSP-3 are associated with protection against clinical episodes of malaria in children, and that IgG antibody responses against GLURP and MSP3 promote antibody-dependent cell-mediated inhibition *in vitro*. In addition, phase Ia and Ib studies have shown that GMZ2 combined with AL(OH)2 is safe and immunogenic. The primary efficacy endpoint was number of clinical episodes of malaria during 6 months post-vaccination; secondary endpoints were anaemia, and malaria episodes at >6, 12 and 22 months post-vaccination. Malaria case detection was done during field workers' visits and via slide collection from children with fever. A modified WHO method was used for quantification of *P. falciparum*. Severe AEs were reported to the sponsor and the Data and Safety Monitoring Board. Three doses were given at 1-month intervals in a total of 1,849 children enrolled. Half of the children received GMZ2/alum; the other half received rabies vaccine as control. Preliminary results show that 1,100 malaria episodes were recorded 6 months after the last injection. Antibody response of 1,601 paired samples was captured. Statistical analysis will be performed before the end of September 2014. The presenter mentioned that data were captured electronically. Owing to data management issues, it was decided to re-enter data at a site in Tübingen, Germany, using a different validated database. This process was started in June 2014.

Discussion and questions The ensuing discussion revolved around use of OpenClinica and the lesson to be learnt from the presented experience. Another issue discussed was the impact of site diversity on the result (*The antigens GLURP and MSP-3 are conserved and diversity will not affect the result. Also, the sites are similar in terms of malaria endemicity*).

MO.02 was titled 'Speeding up the development of malaria vaccine: the example of P27A bridging phase Ia and Ib.' The presented ongoing trial focuses on a novel blood stage vaccine candidate and is a multi-centre (Lausanne, Switzerland/Bagamoyo, Tanzania) phase Ia/Ib trial in healthy, non-malaria-exposed European and malaria-exposed African adults aged 18–45. The investigational product is P27A (10 µg and 50 µg) combined with adjuvants Alhydrogel® 0.85 mg or GLA–SE 2.5 µg and 5 µg administered im. The control product is rabies vaccine (Verorab®). The primary objective is to evaluate the safety of P27A, with Alhydrogel or GLA–SE as adjuvant, in healthy European adults not previously exposed to *P. falciparum* and in healthy African adults previously exposed to the parasite. The secondary objective is to assess the immunogenicity response to the vaccine antigen. The study rationale, design and method were described. As the trial is ongoing, with phase Ib planned for mid-July 2014, no results were reported.

Discussion and questions Questions included: Why are females excluded from the Bagamoyo trial? (*For practical reasons, women should not become pregnant once enrolled into the trial and it is 'very difficult to guarantee this in Tanzania'. Also, participants have to stay at the trial centre for a week, which would be logistically difficult if there were women among the participants.*) Was any immunogenicity seen in Lausanne, and if so, how would this affect the Tanzanian study? (*The Lausanne study is ongoing. The Bagamoyo trial will start soon. The two studies will continue in parallel, i.e. the Bagamoyo vaccinations will not wait for the results from Lausanne.*)

To facilitate development of capacity for phase I studies in Africa, controlled human malaria infection (CHMI) has been used for the dual purpose

of product evaluation and capacity building. MO.03 reported on an initiative to set up seven CHMI centres in seven African countries and use them as a CHMI studies platform as well as a platform to support Phase I and bio-equivalence studies, to conduct whole sporozoite vaccine studies, and promote networking between the centres. The sites are MRTC (Mali), CNRFP (Burkina Faso), Kintampo HRC (Ghana), Lambarene (Gabon), KEMRI Nairobi (Kenya), Bagamoyo (Tanzania) and CISM Manhiça (Mozambique), working in collaboration with five European research partners. Two studies have been completed, a challenge study in Bagamoyo using iv administration and one in Nairobi with im administration of a higher dose. Results from Bagamoyo showed a 92% infection rate and no SAEs. In Nairobi, all subjects were infected. One individual had subpatent parasitaemia by microscopy. Significant correlation between parasite multiplication rate and anti-schizont antibody was observed. No SAE was noted during the 90-day follow-up. Moreover, some collaborative capacity-building is ongoing, e.g. microscopy training and proficiency testing as well as harmonising the clinical evaluation procedures. Some studies are planned in Gabon, involving an iv challenge study in 30 adults for malaria exposure with and without sickle cell disease.

Discussion and questions Concerns expressed by the meeting were related to issues or difficulties regarding importation of live sporozoites (*There were no issues with importation. There is an agreement that unused sporozoites will be sent back to the manufacturer*); and the acceptability of sporozoite injection in any country (*So far, there have been no acceptability concerns*).

Malaria therapeutics studies included a report on a phase II dose optimisation study and a phase III follow-up trial of a simplified artesunate regimen for severe malaria in children [MO.04]. The goal of this project was optimisation of parenteral artesunate treatment in children with severe malaria in Africa, with a simplified administration scheme. The phase II dose optimisation study (Study I) showed that a simplified once daily iv artesunate regimen over 3 days is equivalent to the conventional 5-day iv regimen. It showed non-inferiority of the 3-day, once daily dosing regimen, compared to conventional treatment, in African children hospitalised for severe malaria. The follow-up study (Study II) tested a simplified regimen by im vs iv route for optimisation of artesunate. In a randomised, open-label, three-arm, follow-up trial, a five-dose regimen of im artesunate was compared with a simplified three-dose iv and a three-dose im regimen in 1,047 African children with severe *P. falciparum* malaria receiving a total dose of 12 mg/kg artesunate. The primary endpoint was the proportion of children who cleared at least 99% of their admission parasitaemia at 24 hours. Efficacy analysis revealed very good cure rate and excellent parasite clearance rate in all three cohorts. Good tolerability and similar artesunate clearance rates were seen with all three administration schemes.

Discussion and questions It was concluded that these studies indicate good efficacy of im administration and support the aim to establish a simplified treatment of severe malaria. Questions raised concerned the potential danger of the simplified treatment promoting development of artesunate resistance (*In a number of patients, delayed haemolysis occurred. This observation has led to much discussion and is being further investigated by the team*). Also, there were questions about the underlying mechanism: whether it was antibody-related or a side effect of artesunate. There were only 16 deaths, which raised the audience question whether future severe malaria treatment studies should continue considering mortality endpoints.

MO.05 is a phase IIIb/IV comparative, randomised, multi-centre, open-label, parallel 3-arm clinical study aiming to assess the safety and efficacy of repeated administration of pyronaridine-artesunate (Pyramax®), dihydroartemisinin–piperaquine (DHAP) or artemether–lumefantrine (AL), or artesunate–amodiaquine (ASAQ) over a 2-year period in children (weighing ≥20 kg) and adults with acute uncomplicated Plasmodium spp. malaria infection. The presentation focused on the safety data gathered so far from the WANECAM longitudinal trial in Mali, Burkina Faso and Guinea. A sub-study to test non-inferiority between initial and repeat Pyramax dosing in terms of the hepatotoxicity event rate was performed to generate data for the expansion of the current Pyramax® label. To date, a total of 4,722 patients have been recruited in the three countries. Among these, 219 patients were included in the Pyramax sub-study and received

more than one Pyramax treatment; 54 received more than two Pyramax treatments. No increase in incidence, severity of liver function test results or AEs were observed. Pyramax seems, based on these preliminary data, to be well tolerated on a repeat dosing regimen and to date, no increase in frequency of AEs has been reported.

A trial from Bobo-Dioulasso, Burkina Faso [MO.06], tested efficacy of DHAP in the treatment of uncomplicated *P. falciparum* malaria in African patients and associations between treatment responses and day 7 plasma piperaquine concentration in children. This single-arm, open-label trial enrolled 379 participants who received one daily dose of DHAP (40 mg/320 mg) for 3 days and were followed up for 42 days. Day 7 plasma concentrations of piperaquine were measured in a subset of children aged 2–10 years. The primary endpoint was the risk of recurrent malaria, both adjusted and unadjusted. A capillary sample was collected from 226 children and venous blood from 198 children. The cumulative unadjusted treatment failure rate was 31.25% in children <2 years old and 16.04% in those 2–5 years of age. The risk was lower in the 5–10-year age group (9.38%) and null in children >10 years old. After genotyping, only three cases were recrudescent. Piperaquine day 7 concentrations were significantly lower in patients with recurrent malaria during the 42 days of follow-up. In conclusion, DHAP was highly effective for uncomplicated malaria treatment, had a good safety profile and was associated with rapid fever and parasite clearance within 48 hours.

Discussion and questions No questions followed this presentation.

Resistance of *P. falciparum* to antimalarials necessitates new approaches to malaria control and there is a need for more epidemiological data. The purpose of the study presented in MO.07 was to prospectively assess the clinical and parasitological responses to artesunate (AS) + amodiaquine (AQ) used in treatment of uncomplicated *P. falciparum* malaria in the village of Mafèrinyah, in the Republic of Guinea. A clinical efficacy study using the combination of AS and AQ was performed in a cohort of 223 subjects aged 3 months to 45 years. Patients with uncomplicated malaria were treated orally for 3 consecutive days at recommended doses and were followed for 28 days. The results of this study show that artemisinin-based combination therapy (ACT) of AS+AQ (vs monotherapy) is clinically effective (PCR-corrected cure rate of 97%) in the treatment of uncomplicated malaria in Mafèrinyah. Although cases of anaemia were observed during follow-up, side effects were rare and were dominated by low blood sugar, dizziness and physical weakness.

To reduce *P. falciparum* malaria transmission, interventions in asymptomatic carriers should also be effective against gametocytes. This was the rationale behind MO.08, a 12-month, cluster-randomised (9-intervention, 9-control) study from Burkina Faso on the impact of community screening and treatment of asymptomatic carriers of *P. falciparum* with AL vs no treatment of asymptomatic and gametocyte carriage, detected by rapid diagnostic test (RDT) during community screening campaigns (CSCs 1–3). While CSCs 1–3 took place before the rainy season, CSC 4 took place after it, marking the end of the study. Symptomatic malaria episodes were treated with AL in both arms of the study. In this community setting study, there were significant reductions in prevalence of asymptomatic carriers and gametocyte carriers compared with the control arm at CSC 2 and CSC 3, relative to CSC 1 ($p<0.0001$). However, asymptomatic and gametocyte carriage prevalence in the intervention arm rose thereafter, to reach levels similar to the control arm at CSC 4. The use of qRT-PCR can lead to higher levels of asymptomatic carrier detection and can thus impact disease transmission. No significant difference was seen in the incidence of SMRC5000 in children <5 years during the study period. The study shows that the systematic screening and treatment of asymptomatic carriers at community level can reduce gametocyte carriage in a population. However, in this setting, the impact of the intervention was not sustained.

Discussion and questions There were audience questions about whether the team assessed multiplicity of infections, and the meeting sought an explanation for the similar proportions, between treatment arms, of gametocyte and parasite carriage at the end of the study. There was also uncertainty regarding any recommendation for practice from these observations.

Tying in with MO.08, the last presentation [MO.09] in the malaria therapeutic studies ses-

sion focused on asymptomatic carriers of *P. falciparum* acting as parasite reservoirs and being at risk of developing anaemia. This study compared the effect of systematic treatment of asymptomatic carriers of *P. falciparum* with AL vs no treatment on Hb levels and anaemia status. In a 12-month, single-centre, controlled, parallel, cluster-randomised study, inhabitants of 18 villages in Burkina Faso were randomised (1:1) to intervention and control arms. They participated in four CSCs (CSC 1–4). While CSCs 1–3 included treatment of asymptomatic carriers in the intervention arm, conducted 1 month before the rainy season, CSC 4 was conducted after the rainy season and marked the end of the study (as in MO.08). Results suggested that systematic screening and treatment of asymptomatic carriers at community level can reduce prevalence of anaemia in children in the short term. However, the impact of the intervention was not sustained in the subsequent transmission season. A statistically significant, but not clinically meaningful, change in Hb level from day 1 to day 28 of CSC 1 was observed. However, as the baseline Hb level of the asymptomatic carriers was in the normal range, a large increase in Hb level cannot be expected. A significant increase in Hb levels, of 0.5, 1, 1.5 and 2 g/dL, was seen in the intervention vs control arm after 28 days. Haemoglobin levels in the community (all subjects) increased over 12 months, with no significant difference in mean levels or distribution between the intervention and control arms. The conclusion was that systematic screening and AL treatment of children who are asymptomatic carriers of *P. falciparum* can reduce the prevalence of anaemia in the short term. Although the difference between the arms was not sustained at 12 months, the number of subjects with anaemia was still reduced in both groups.

Discussion and questions This presentation elicited heated discussion on the role of preventive antimalarial treatment in anaemia prevention.

A project created to integrate phase I and II trialling of viral vectored malaria vaccine candidates with capacity building and networking in East and West African countries was presented [MO.10]. The Malaria Vectored Vaccines Consortium (MVVC) is a partnership between four African (KEMRI Kenya, CNRFP Burkina Faso, MRC The Gambia, UCAD Senegal) and four European partners (the Jenner Institute at the University of Oxford, the European Vaccine Initiative, Vienna School of Clinical Research, and Okairos). The overall objective of the project was to develop a safe, non-reactogenic, effective and affordable malaria vaccine. The piloted vaccine candidate ChAd63/MVA ME-TRAP showed significant efficacy in UK vaccinees following sporozoite challenge. Phase Ib clinical trials of the vaccine in healthy Kenyan and Gambian male adults, and Gambian children (2–6 years) and infants showed that the vaccine was well tolerated, with mild AEs, and there were high T cell responses. Three phase IIb clinical trials are ongoing in Burkina Faso, Kenya and Senegal.

Regarding capacity building, considerable progress has been made in the development of clinical trial capabilities, infrastructure and human resources that will sustain the trial sites even after the project has ended. Capacity building has included training at MSc, PhD and postdoctoral level as well as training courses in good clinical practice, standard operating procedure development, data and financial management, immunological assays and study write-up. Networking successes have included collaboration and presentations at international meetings.

Discussion and questions An audience query was whether there is collaboration between the MVVC and other networks in the region engaged in similar activities of capacity building (*MVVC members from the West African region are also members of WANETAM and WANECAM. Further, MVVC workshops, e.g. on ethics, standard operating procedure, good clinical practice, are open to other members of the scientific community*).

Adenovirus serotypes vector-based vaccines have been shown to be immunogenic in several clinical trials. However, natural immune responses to these vectors may block the desired responses against the vaccine antigen, thus raising concerns about the efficacy of this vaccine delivery method. A study [MO.11] aimed to determine the prevalence rate and quantify the level of neutralising antibodies to chimpanzee adenovirus serotype ChAd63 in a population living in a hyperendemic, seasonal and stable malaria transmission area and likely to benefit from a viral vectored-based malaria vaccine was presented. This cross-sectional serological study, conducted at Banfora, Burkina Faso, during a high malaria

transmission season, involved two participant age groups: 6 months to 3 years (group A) and 10–45 years (group B). A total of 399 blood samples were collected and assayed for ChAd63 specific neutralising antibody titres using the secreted alkaline phosphatase quantitative assay at the University of Oxford, UK. Results showed that 56.7% of the study participants were positive for malaria parasites, the most predominant being *P. falciparum* (52.9%). Regarding neutralising antibodies, the lowest titre recorded was 17 while the highest was 2,144 (range: 17–930 in children and 17–214 in adults). Children had significantly lower geometrical mean titre neutralising antibodies compared to adults (41.2 vs 153.1). The presenter informed the audience that chimpanzees have since disappeared from the community and the high titre of neutralising antibodies in adults may not be against serotype 63 from chimpanzees. It was concluded that the low prevalence of high titre neutralising antibodies to ChAd63 in children was very encouraging as this population of children are those who will benefit from the malaria vaccine delivered by a vector.

Discussion and questions Among audience questions were why chimpanzees had disappeared from the community (*Human behaviours, e.g. hunting for food, and environmental changes may have caused their extinction from the site*); and whether the high titres of antibodies in adults may not have been due to natural adenoviruses in humans cross-reacting in the assay (*This may be the case and there may be ChAd63 serotypes that are still circulating at the study site. Nevertheless, it has been shown that the presence of high titre antibodies against this vector does not affect the immunogenicity of the vaccine it is designed to deliver*).

A phase I/IIb DBRCT to test the efficacy, safety and immunogenicity of heterologous prime-boost (d0-d56) immunisation with candidate malaria vaccines ChAd63 ME-TRAP and MVA ME-TRAP was conducted in 5–17-month-old Burkinabe infants and children (n=730) living in a malaria-endemic area. The presenter [MO.12] described ChAd63 ME-TRAP/MVA ME-TRAP heterologous prime-boost immunisation as a highly promising candidate malaria vaccination strategy which has shown durable partial efficacy in malaria challenge in a previous study from the UK. This trial was the first phase IIb trial of this malaria vaccine candidate in children living in an endemic area. Solicited/unsolicited AEs were recorded from the day of first immunisation until one month post-boost; SAEs were recorded throughout the study duration. Malaria cases were documented by passive case surveillance methods. Conclusions were that the results will help define the potential role of these viral vectors as a vaccine in malarial control in Africa.

Discussion and questions Audience questions related to the level of insecticide-treated net (ITN) coverage in the study area (*80%; the government has been distributing nets strategically to the community each year*); whether efficacy was evaluated per arm (*Further statistical analyses will include evaluation of efficacy by arm*); and how effects of confounding factors such as ITN use and intermittent preventive treatment in infants (IPTi) were controlled for (*The study was designed to take these factors into account in the efficacy evaluation*).

Also testing ChAd63-MVA ME-TRAP efficacy was a study from Kenya and Senegal [MO.13]. The primary objective was to assess the immunogenicity and efficacy of a heterologous prime-boost vaccine strategy with ChAd63 ME-TRAP and MVA ME-TRAP in healthy Kenyan and Senegalese adults. Secondary and tertiary objectives included assessing the safety and reactogenicity of this vaccination approach; assessing its impact on natural immunity (cellular and humoral) on time to re-infection; and evaluating the efficacy of pooled datasets through a meta-analysis combining the Kenyan and Senegalese trial results. No safety concerns were reported after either priming or boosting, except for mild pain at the site of injection in the Senegal study. The vaccine was found to be immunogenic at both study sites. However, geometric antibody titres were higher in Kenyan compared with Senegalese participants. Also, Kenyan participants had significantly higher ELISPOT-derived spot-forming units (SFUs) (mean 1,700 cells/million cells) compared with Senegalese participants (1,000 cells/million cells). Comparison of SFUs during the follow-up period continued to be higher in the Kenyan participants. It was concluded that the vaccine is safe and immunogenic, with demonstrated efficacy of 66% (any parasite density) and 80% (10 parasites per field). The protection observed was lower in Senegalese compared with Kenyan participants.

Discussion and questions The audience wanted to know whether number of SFUs correlated to protection (*There was a good positive correlation between SFU and protection. However, this was not recorded in the Senegalese population, probably because of the reduced immunogenicity evidenced by the low mean SFU obtained. The difference in immunogenicity was probably due to the difference in malaria endemicity, being higher in Kenya. The number of infective bites per year at the Kenyan study site Kilifi is about 22/year compared to ca. 5/year at the Senegalese site in Dakar region*).

MO.14, titled, 'Maternal immunisation protects mice pups against malaria', was cancelled.

The rationale for three studies [MO.15–MO.17] focusing on mefloquine (MQ) as malaria intermittent preventive treatment (IPT) in pregnancy (IPTp) was that pregnant women are extremely vulnerable to malaria. Malaria control strategies for them include: ITNs, IPT with sulphadoxine–pyrimethamine (SP), and prompt and effective case management. However, increasing resistance to SP in many malaria-endemic areas necessitates development and evaluation of alternative drugs for IPTp. Mefloquine is particularly attractive for this purpose because of its long half-life, ability to be administered as single dose, and acceptable profile. Moreover, addition of MQ-IPTp to cotrimoxazole (CTX) prophylaxis in HIV-infected pregnant women (who are especially vulnerable to malaria) was hypothesised to be more efficacious than CTX alone in prevention of malaria, while SP is not recommended in pregnant women receiving daily CTX. There was therefore the need to evaluate drugs to be used as IPTp in HIV-infected women receiving CTX.

MO.15 was a three-arm trial conducted in Benin, Gabon, Mozambique, and Tanzania to compare a two-dose MQ with a two-dose SP regimen and to compare tolerability of two different MQ regimens. There were no differences in efficacy between the treatment groups and no differences in efficacy, frequency of AEs or adverse pregnancy outcomes, and drug tolerability between the MQ full dose and the MQ split-dose groups. Conclusions were that MQ had a better prophylactic antimalarial effect than SP and that it is a safe drug in terms of adverse pregnancy outcomes. However, MQ 15 mg/kg had worse tolerability than SP. Splitting the MQ dose did not seem to confer benefits in terms of drug tolerability. The overall conclusion was that MQ at the dose used in this study is not an alternative to SP for IPTp. The implementation of the current WHO policy in high to moderate malaria transmission areas should be strengthened, with SP-IPTp administration at each scheduled ANC visit from the second trimester of pregnancy.

Reporting from Kenya, Tanzania and Mozambique, MO.16 evaluated the efficacy of IPTp with MQ in HIV-infected women on CTX. Mefloquine was administered in three doses and compared with a three-dose placebo control. Findings included reduced rate of maternal parasitaemia at delivery, placental infection and hospital admissions in the arm receiving IPT with MQ. There were no differences in frequency of adverse pregnancy outcome. No maternal SAEs related to medication were reported; however, there was higher frequency of vomiting and dizziness, as well as higher HIV VL at delivery and higher rates of MTCT of HIV. It was concluded that the increased MTCT of HIV calls for the need of specifically designed studies to fully understand the effects of antimalarial and ARV co-administration. These results may also have implications regarding the antimalarial drug combinations containing MQ currently recommended for malaria treatment.

Discussion and questions An animated discussion followed, regarding the higher VL and increased MTCT associated with MQ treatment (*The presenter highlighted that increased resistance to ART has been observed in Mozambique, which could explain the findings. The study participants all received nevirapine, ZDV and lamivudine*). One attendee advised that there may have been some pharmacokinetic interactions to explain this and that pharmacokinetic data should always be collected in such studies to be able to provide explanations relating to drug concentrations and interactions.

Presentation MO.17 on the MIPPAD (Malaria in Pregnancy Preventive Alternative Drugs) study was the third study in the MQ-IPTp series, comparing the pharmacokinetics of full-dose with split-dose MQ-IPTp, and assessing MQ concentrations at delivery in maternal and cord blood. Findings demonstrated a complex concentration-time profile of MQ, with double peaks during the

absorption phase. No significant differences were seen between the full and the split-dose regimens. In the population pharmacokinetics analysis there was evidence for a modest increase in bioavailability (16%) in the split-dose group although this difference is most likely of limited clinical significance. It was concluded that split-dose administration is therefore not required to reach adequate exposure from a pharmacokinetics perspective. Concentrations of MQ at birth in maternal blood were measurable at around 50–100 nmol/L in maternal and cord blood. There was rapid transplacental distribution of MQ. The authors proposed more frequent dosing at ANC visits.

Although SP-IPTp is a convenient and widely deployed intervention, there are challenges such as increased resistance to SP, and low coverage of IPT. Alternative options include drugs such as MQ, azithromycin/chloroquine and alternative strategies for managing malaria in pregnancy, such as intermittent screening and treatment. Study MO.18 sought to answer the question whether screening using RDT at scheduled antenatal clinic visits, and treating only those who are parasitaemic with AL, a strategy termed 'intermittent screening and treatment (IST)', is as safe and as effective as SP-IPTp in protecting against LBW, maternal anaemia and malaria infection of the placenta among pregnant women using a long-lasting insecticidal net and living in an area of low SP resistance. Results from this study demonstrated that in areas of low SP resistance, IST was as effective as SP-IPTp in prevention of LBW, maternal anaemia and placental malaria. Mean birth weight was slightly lower in IST. However, IST was associated with fewer minor side effects. In conclusion, IST appears to be a feasible strategy in routine ANC; however, data on cost effectiveness and acceptability are required.

The next two papers [MO.19–MO.20] were systematic reviews on IPTp. MO.19 compared two vs three or more doses of SP, and associated risk of LBW. This review influenced WHO's Updated SP-IPTp policy in April 2013, which recommends SP-IPT at each scheduled ANC visit until delivery, at least one month apart, to start as early as possible in the second trimester. According to WHO policy, the last dose can be administered up to delivery without safety concerns. The rationale for giving three or more doses of SP-IPTp is that it may protect women during the last 4–10 weeks, and improves the coverage of two-dose IPTp. It is already used in HIV-negative women in several countries and has been recommended for HIV-positive women not on CTX. The review included seven trials, with 6,281 pregnancies altogether. Implications from this review are that three or more doses of SP-IPT are a highly cost-effective way to reduce risk of placental malaria and LBW, and that they could enhance ANC attendance. Adding extra doses of SP significantly reduces the risk of severe maternal anaemia among HIV-negative, pregnant women. The presentation closed with the recommendation that countries switch to the new WHO regimen. To help countries make the switch, it was said that implementation research is needed, possibly a project for EDCTP2.

MO.20 was a systematic review and meta-analysis intended to define the relationship between population-level prevalence of molecular markers of SP resistance and IPTp effectiveness. This review included 26 observational studies and 17 surveys, eight of which were EDCTP-funded. Resistance to SP is conferred by mutations in the dhps gene. One of these, the dhps540E mutation, has been found mainly in East and southern Africa and to a lesser extent in West Africa. Another, dhps581G, is very important in determining resistance. Super resistance to SP occurs when there is >10% dhps581G prevalence, and there is no beneficial effect from SP if the additional mutation in Pfdhps581G is present at prevalence >1%. The review shows how effectiveness of SP-IPTp decreases with increasing resistance: in West Africa, with PfdhpsA437G and in East and southern Africa, with Pfdhps540E and A581G. However, it appears that even in areas with >95% prevalence of PfdhpsA540E, SP-IPTp is associated with 8% lower risk of LBW with each dose of SP.

In March 2012, WHO issued a policy recommendation for implementation of seasonal malaria chemoprophylaxis (SMC) in children under five years old. Delivery of SMC through community case management (CCM) schemes has potential advantages including economies of scope. With all CCM schemes, there is a focal person in the community who has been trained in administering antimalarial treatment, with breakthrough cases being diagnosed and treated promptly, providing monitoring information about SMC effectiveness. The authors of MO.21 sought to answer several questions regarding SMC and

whether it can be effectively combined with CCM, namely: What is the impact of SMC where there is ready access to prompt malaria treatment in the community?; Can SMC can be offered to a wider age range; and, Is delivery of SMC feasible and well tolerated over a longer period? Findings showed remarkable effectiveness against malaria, with substantial benefits in older children. No impact was seen on drug-resistance molecular markers. Advantages of delivering SMC through CCM include promoting appropriate drug use, prompt treatment of breakthrough cases with an ACT, and providing surveillance data for monitoring SMC effectiveness.

Several clinical trials have been conducted during the last two decades on the efficacy of fosmidomycin as an antimalarial agent but its clinical development has been very slow. The aim of MO.22 was to assess the role of fosmidomycin as an alternative, non-artemisinin combination for treating uncomplicated *P. falciparum* malaria. A systematic review and meta-analysis of published phase I and II paediatric formulation trials was performed. The authors searched for studies that had evaluated fosmidomycin (administered alone or in combination with clindamycin or artesunate) in the treatment of participants with uncomplicated *P. falciparum* malaria and reported the day-28 cure rate. Six studies were analysed, five from Gabon and one from Mozambique. The overall cure rate at day 28 was 85% (CI: 70–100%). Heterogeneity was observed as the Mozambican trial had an extremely low cure rate (46%). The differences in results between Gabon and Mozambique were largely attributed to the younger age of study participants (<3 years in Mozambique vs 1–14 years in Gabon) and the drug formulation (water-soluble granules in Mozambique vs capsules in Gabon). It was concluded that at the current level of available data, registration of fosmidomycin as an antimalarial drug is premature. Additional studies are needed to answer questions of appropriate formulation that will ensure bioavailability across different genetic pools in Africa.

Discussion and questions The meeting wanted to know whether relevant *in vitro* data exist (*Published data on* in vitro *efficacy of the drug exist; however, the current study looked at clinical trials specifically*).

A study from Bobo-Dioulasso, Burkina Faso looked at the *in vivo* activity of artesunate on *P. falciparum* forms in *Anopheles coluzzii* mosquitoes [MO.23]. The main objective was to assess *in vivo* the effect of artesunate on gametocyte fertilisation and development to oocyst in the mosquito. Blood was collected from mono-infected children with ≥56 gametocytes/µl of blood and a membrane feeding assay performed using artesunate at various doses. Mosquitoes 3–4 days old were fed on blood mixed with different doses of artesunate through pre-warmed membrane feeders, dissected on day 7 post-feeding, and examined for oocysts. The transmission blocking activity of the drug was evaluated by determining prevalence and density of oocysts. Results showed that at the doses of artesunate examined, 1.5–5 ppm, the prevalence of oocysts per mosquito ranged from 44% to 83% while the densities were 1.25–21.91 oocysts per mosquito. In the control group, oocyst prevalence was 52–74% and oocyst density 2.35–29.7 per mosquito. The results showed that artesunate, which is well known for its gametocidal properties, did not block sporogonic development at the doses tested. However, there was a correlation between oocyst density and gametocytaemia.

Discussion and questions Audience questions were whether no simpler methods exist for testing multiple drug effects on transmission (*There are two standardised methods: membrane feeding technique and direct human feeding experiments*); and whether it was artesunate itself or its metabolite that had the gametocidal effect (*Artesunate, once consumed, is metabolised to dihydroartemisinin, which kills gametocytes*). Referring to the complex feeding experiments, one participant asked whether *in vivo* studies in which artesunate is administered and gametocyte numbers counted would not be preferable to and more reliable than using membrane feeding experiments (*It was agreed that there is a need for additional studies to test this*).

Moving on to the topic of malaria co-infections, MO.24 investigated co-endemicity of malaria and schistosomiasis and detailed steps taken to evaluate the efficacy of MQ IPTp against *S. haematobium* infection in pregnant, HIV-negative women in Gabon. Although praziquantel (PZQ), the recommended drug, is considered safe, in practice there are no screening programmes and no treatment offered during pregnancy. This

study evaluated MQ as an alternative candidate drug against malaria in pregnancy. Mefloquine is highly active against *S. japonicum* in rodent models and has significant clinical activity against *S. haematobium*. Women were included at <28 weeks' gestation and outcome was assessed 10 weeks post-screening. Out of 902 women screened, 79 were schistosomiasis patients. Of these, 65 were randomised to either MQ (n=48) or SP (n=17). Baseline characteristics were the same between the two arms. Urinary egg excretion was lower in the MQ-IPTp compared with the SP arm. Six weeks after the second IPTp administration, nearly 50% of women were cured of *S. haematobium* infection. Mefloquine may have a longer prophylactic effect (due to longer half-life) compared with PZQ, preventing early re-infection during pregnancy. Study limitations include small sample size and that birth outcome and genital pathology were not assessed. It was concluded that MQ-IPTp is a preventive tool against malaria and schistosomiasis in pregnancy.

Discussion and questions This presentation raised much audience interest. It was pointed out that MQ is not yet recommended for IPTp. Other issues raised by the audience were why the women who were randomised to receive IPTp with SP were not treated for their Schistosoma infection immediately, as opposed to after the study. Most thought that it is unethical to diagnose an infection in a participant and leave it untreated (*This had been discussed in detail with the ethics committee. Because the infection was asymptomatic and not usually screened or treated in pregnancy it had been decided that it was ethical not to treat. Another team member added that in pregnancy, PZQ is not indicated; therefore they could not treat*). Other discussion points revolved around the use of monotherapy rather than combination therapy for IPTp (*Currently, guidelines deal with combination therapy for treatment only; not for prevention*). A final issue raised was the lack of CNS assessment in the study (*The team followed the women and conducted assessment in the context of the MIPPAD study*).

Presentation MO.25, on the effect of ART on malaria parasitaemia and clinical episodes among HIV-infected adults in rural Uganda, was cancelled.

The aim of MO.26 was to investigate the optimal sampling design for reliable estimates of parasite clearance rate. Frequent counts are needed to define the clearance rate; as yet, there is uncertainty regarding the sampling frequency required to ensure reliable estimates. Data on 4,652 patients from 13 studies in Cambodia, Thailand, Vietnam, Mali, Tanzania and Kenya from 2001–2011 were pooled. Patients were treated with artesunate alone or as combination treatment. The WWARN parasite clearance estimator was used to standardise estimates of parasite half-life. The relationship between estimated half-life and different sampling schemes was calculated. A simulation study was performed based on parasite count data generated for half-life and investigated sampling schemes. For the effect of sampling schemes on half-life estimation, the best scheme was sampling at 0, 6, 12, and 24, 36 and 48 hours; for the simulated data, the best performing scheme was <6 counts up to 48 hours. Among recommendations were that including measurement at 6 hours is important, especially in regions with unknown *P. falciparum* susceptibility. If measured parasitaemia at 2 days exceeds 1,000/µL, sampling at least once a day should be continued. Measurement at 72 hours might be considered to assess drug efficacy.

Discussion and questions The audience discussion focused on the applicability of the parasite clearance models/curves that seemed to differ in different geographical areas: e.g. an audience member said that Africans in general had faster clearance times than Asians. Additionally, the audience asked whether the slower clearance curves were indications of drug failure and, if so, whether they could be used for evaluation and monitoring of drug resistance (*Yes, as long as transmission and immunity remain constant*).

A modelling study from Bougoula-Hameau in south-eastern Mali [MO.27] analysed repetitive malaria episodes with continuous and discontinuous risk interval models. The aim was to identify the best models for recurrent episode data. The 780 subjects enrolled yielded a total of 1,649 malaria episodes. Discontinuous and continuous interval models gave similar RR estimates and p-values in all models. Incidence rates were higher in the discontinuous compared with continuous risk interval models. The authors concluded that discontinuous interval models are more appropriate from an epidemiological point of view as they take into account the time when a

subject is not at risk of a disease in a given period of time. Modified Cox models (Anderson-Gill, Prentice-Williams-Peterson) and frailty models provided significant covariate effects, compared with the GEE Poisson model.

Discussion and questions The meeting asked why a washout period of 14 (instead of 28) days between infections was used (*This was based on previously published studies*). There followed a discussion on the need to make a model for each malaria drug based on drugs' different half-lives, which would affect the time when a person would not be at risk (*The model used in MO.27 was based on AL, which is the mainstay of antimalarial treatment in Mali*).

Three presentations [MO.28–MO.30] were made by a Burkinabé team. The study presented in MO.28 aimed to estimate the malaria-attributable fraction of fever, according to transmission season, at a malaria vaccine trial site in Burkina Faso; determine the prevalence of fever and its relation to malaria parasitaemia; and establish a pyrogenic threshold for malaria disease in a vaccine trial site area. Malaria transmission in four villages in Saponé Health District is markedly seasonal. Two community-based cross-sectional surveys were conducted during the malaria high and low transmission seasons involving 555 children <5 years living in the study area for ≥3 months. Surveys included clinical examination of study participants and blood sampling for parasitaemia diagnosis. The malaria-attributable fraction of fever, sensitivity, and specificity of alternative parasite thresholds for the malaria case definition were calculated according to previously described methods. Fever was more prevalent during the high transmission season (11.6%) than the low season (9.1%). The malaria-attributable fraction of fever presented the same trend, with 59.6% during the high season and 17.2% during the low season. The alternative parasite thresholds for the malaria case definition that achieved optimal sensitivity and specificity (70–80%) were 2,780 parasites/µl during the low season and 2,930 parasites/µl during the high season. It was concluded that the relationship between fever and parasitaemia depends on season. Cut-off levels of parasitaemia should be used during the two seasons to define malaria cases in this area.

Discussion and questions Questions raised concerned the specificity of malaria fever: development of fever is associated with many conditions, not only parasitaemia. Did the team take other pyrogenic factors into account? (*The team were aware of this; data relevant to this question had been collected but had not been included in this presentation*.) The meeting concluded that fever is more likely to be due to malaria during the wet season than during the dry season.

MO.29 was a study on seasonal variation and clinical protection of antibodies against a panel of malaria antigens in under five-year-olds in Burkina Faso. The presenter told the meeting that the mechanism behind acquisition of non-sterile immunity to malaria in people living in different malaria transmission settings is still unknown. Antibodies play an important role, but still remain to be identified. The objectives of the study were to assess total IgG response against three *P. falciparum* pre-erythrocytic (LSA, CSP, MR48a) and five erythrocytic (MR198, LR179A, LR181, AS155.4 and 1574) antigens during the malaria transmission seasons; and to explore the relationship between immune response and clinical protection against malaria across different malaria transmission seasons. The study in 529 children included two cross-sectional surveys (at the beginning and the peak of malaria transmission, respectively) and biweekly active malaria case detection for one year. During each cross-sectional survey, thick and thin films were prepared for malaria diagnosis. Plasma from venous blood was used for immunological measurements. Results showed a strong seasonal variation in antibody levels, with higher levels during the high compared with the low malaria transmission season for the majority of antigens assessed. Only antibody response to AS155.4 was associated with protection against clinical malaria. Future investigations are needed to study the assessed antigens, mainly AS155.4, and to determine the type of protection conferred by this antigen.

Discussion and questions Audience questions concerned the method for calculating antibody titres (*Using ADAMSEL*); and the relevance of measuring antibody against pre-erythrocytic antigen (*This was done based on epidemiological studies. It is difficult to find a good biomarker of protection and the team used what was available*).

Finally, in MO.30, the Burkinabe researchers sought to find out why there is a differential response to malaria infection, i.e. why some children tend to develop severe malaria when exposed to infection while others do not. A cross-sectional survey was conducted in children less than five years old presenting with severe malaria. The control group consisted of children of the same age group with asymptomatic malaria parasitaemia. Blood samples collected were analysed by flow cytometry to determine lymphocyte count and regulatory T cells (Tregs) by intracellular staining. Results showed that mean absolute lymphocyte counts were higher in the control group compared with the severe malaria group. However, the proportion of Tregs in the severe and control group was similar. When compared with malaria parasite-negative individuals, however, those with severe malaria had a higher proportion of Tregs. Additionally, severe malaria cases presented with higher proportion of IL-10-producing T cells compared with those who were asymptomatic. The results suggest that Tregs may contribute to modulation of the severity of malaria infection in children.

A study on reduced antibody responses against *P. falciparum* vaccine candidate antigens in the presence of *Trichuris trichiura* was presented in MO.31. The background to the study was that in malaria-endemic areas where helminth infections are prevalent, co-infection may occur and it has been suggested that malaria–helminth co-morbidity may influence the immune response to vaccines owing to the immune modulatory effect. The study therefore was aimed at assessing the influence of helminth infection on immune responses induced by the malaria vaccine GMZ2 in Gabonese children during a phase Ib clinical trial.

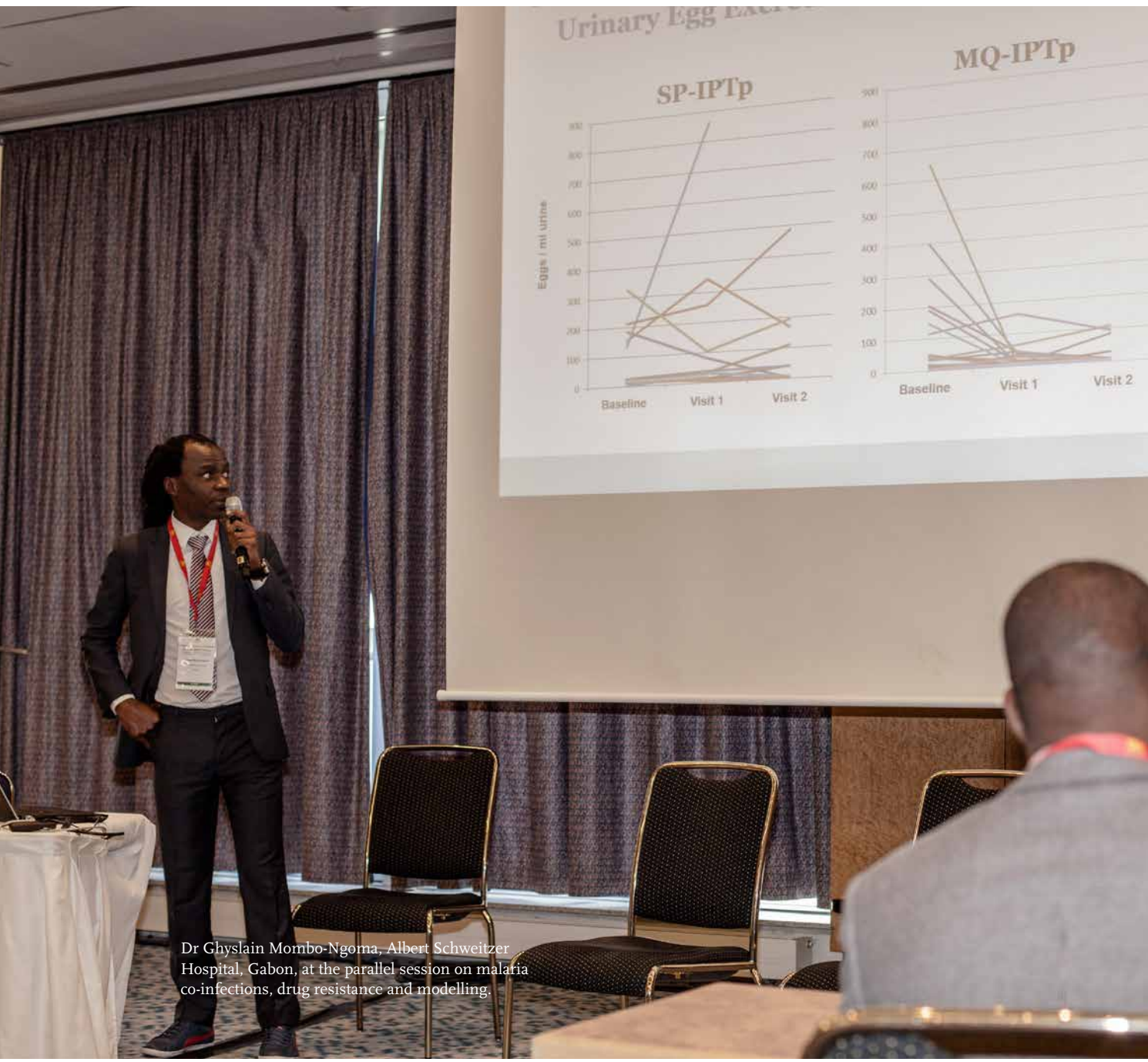
Twenty Gabonese children of pre-school age were vaccinated with GMZ2, a blood stage vaccine candidate, at two different concentrations. Another ten children received rabies vaccine as control. Blood samples were collected for measurement of antibodies to GMZ2 and GLURP by ELISA, memory B cell numbers by ELISPOT, and helminths using Kato-Katz technique. Results demonstrated that antibody responses to GMZ2 and GLURP were higher in *T. trichiuria*-uninfected children compared with positive cases. Levels were similar for the other helminths detected (hookworm and *Ascaris lumbricoides*). Memory B cell responses tended to be higher in *T. trichiura*-negative children although the difference was not significant. In conclusion, significantly lower GMZ2 and GLURP-Abs concentrations were recorded in *T. trichiura*-infected children. This observation needs to be confirmed in a prospective study. Meanwhile it is not clear how *T. trichiura* modulates antibody production against vaccine antigens. Planned phase IIb multicentre trials should provide further insight on the effects of helminth and other parasites on vaccine efficacy.

Discussion and questions A question following the presentation was whether egg density was measured and compared with immune responses (*No, these were preliminary data and the study is ongoing. This issue will be investigated in the future including B and T cell responses in infected compared with non-infected persons*).

The final malaria presentation [MO.32] introduced the meeting to a novel *ex vivo* assay for detection of antimalarial drug resistance. Monitoring antimalarial drug resistance is an important part of malaria control and eradication. Existing methods are cumbersome, unautomated and time-consuming. The presenter described attempts to measure resistance to antimalarials by detecting and measuring haemozoin (Hz), a crystal formed in the cytoplasm of cells infected mostly by schizonts. Haemozoin has the potential of depolarising light and this property can be exploited to measure its concentration. The current study assessed the performance of the novel Hz detection assay using blood samples from Gabonese malaria patients. Blood samples were incubated with chloroquine, artesunate and artemisinin. The percentage of Hz-containing erythrocytes, detected by flow cytometry, was used as maturation indicator, determined at 24 and 48 hours. Parasite maturation and antimalarial drug effects could be detected after 24 hours' incubation. IC50 concentrations of >200 nM, 1–31 nM and 2–118 nM were obtained for chloroquine, artesunate and artemisinin, respectively. These preliminary results demonstrate that chloroquine resistance still exists in Gabon. However, IC50s obtained for artemisinin and artesunate were higher than previously reported, which may be attributed to the higher parasitaemias used in the Hz assay. In conclusion, the results suggest that the Hz assay can determine the sensitivity/resist-

ance pattern of parasites in clinical isolates after 24 hours of incubation.

Discussion and questions A question was asked regarding non-synchronisation of the parasites before culture to optimise the assay (*Laboratory isolates were synchronised but this was not done for field isolates. Sorbitol treatment was used for these*). The audience was interested to hear that the chloroquine resistance rate is still high in Gabon as the drug was abandoned a while ago (*The current first-line malaria treatment in Gabon is artesunate/amodiaquine and the Pfcrt 76 allele may still be propagated by amodiaquine*).



Dr Ghyslain Mombo-Ngoma, Albert Schweitzer Hospital, Gabon, at the parallel session on malaria co-infections, drug resistance and modelling.


Africa needs an AIDS vaccine
KENYA NEEDS AN AIDS VACCINE
AFRICA NEEDS AN AIDS VACCINE

5 Capacity development, networking and other cross-cutting issues

Summarised in this chapter are three presentations made in Plenary session III: 'Recent advances in neglected infectious diseases (NIDs), health services optimisation research and an update on Horizon 2020'. Also included is a special session on the EDCTP Africa mapping project reporting on health research on poverty-related diseases and NIDs in sub-Saharan Africa. Finally, the chapter reports cross-cutting presentations made in the parallel sessions, including presentations on NIDs and their interactions with HIV, TB and malaria.

RECENT ADVANCES IN NEGLECTED INFECTIOUS DISEASES

Professor John Gyapong, University of Ghana, Ghana

Plenary session III began with a presentation on NIDs by **Professor John Gyapong**. What all the NIDs have in common, he said, is that they are associated with poverty. Also, they thrive in the tropics. They impair the lives of a billion people worldwide, with the health of millions being threatened.

Eighteen diseases defined as NIDs in Africa will be included under EDCTP2's programme, namely: dengue, rabies, leishmaniasis, cysticercosis/taeniasis, dracunculiasis, echinococcosis, lymphatic filariasis, onchocerciasis, schistosomiasis, soil-borne helminthiasis, human African trypanosomiasis, food-borne trematodiases, Buruli ulcer, leprosy, trachoma, yaws, diarrhoeal diseases, and respiratory infections. (That the list included respiratory infections and diarrhoeal diseases created considerable audience interest during the discussion that followed Professor Gyapong's presentation.)

Professor Gyapong told the audience of a recent increase in interest in NIDs. We now have a better understanding, he said, of the epidemiology of NIDs. What is also new in the field of NIDs is improved diagnostics and mapping strategies, better drugs and improved delivery mechanisms. These have already led to a significant decline in the annual number of new dracunculiasis cases worldwide. Drawing on the example of dracunculiasis, Professor Gyapong said that already 197 countries and territories are certified free of the disease, with nine countries still needing to be certified, four of which (Chad, Ethiopia, Mali and South Sudan) are endemic regions. In Chad, an unusually large number of dogs infected with *D. medinensis* presents a threat of potential infection to humans. In some regions, political unrest can result in inability of health workers to implement interventions, and displaced populations may spread the disease.

Among programme implementation challenges are low doctor–patient ratios; the fact that the NIDs have not been integrated into government health budgets; not enough clinical trials; and lacking infrastructure (e.g. poor roads and lack of transport), preventing impoverished rural communities from being reached.

In summary, Professor Gyapong said that there is a need for investment in the tools to fight these diseases. Global health workers must make the case for development of new drugs even if the field of NIDs is relatively 'small' and even if drug development may not bring large financial profits. An important recent development has been the formulation by WHO of a comprehensive resolution on accelerating work on NDIs to overcome their global impact. Also, importantly, NIDs will be included under EDCTP2's programme.

RECENT ADVANCES IN HEALTH OPTIMISATION RESEARCH

Professor Shabbar Jaffar of the London School of Hygiene & Tropical Medicine, United Kingdom

Professor Shabbar Jaffar, in his presentation on health services optimisation research, discussed how access to, and use of, new interventions can be increased. Using the example of HIV/AIDS,

Professor Jaffar described huge advances made in our understanding of and fight against the disease. For instance, with ARTs, the life expectancy of patients has risen significantly. There are major challenges in getting the medication to the patients, however. Patients infected with HIV need to spend a large portion of their monthly earnings on transport to the clinic. Moreover, 30% of eligible patients who present to the clinic do not start ART, and a further 20% are lost to care during the first year. Another problem is how to deliver treatment in the context of shortage of doctors. Professor Jaffar gave an example from Malawi, of 1–2 doctors per 240,000 population.

The evidence from comparative studies on how to deliver ART in Africa is very weak. One possibility for optimising care, he proposed, is through task shifting and community care using lay persons. To summarise, he said that we need innovative models of HIV care. And we need better HIV prevention. We need point-of-care tests. However, advances in our understanding of the disease, and using ART as prevention are making a huge contribution to our fight against HIV/AIDS.

He went on to discuss health services optimisation in TB and malaria care, concluding that there are many commonalities between the three diseases – and that what we learn from one can be applied to the other two.

Professor Jaffar concluded by warning that another epidemic is upon us, namely, cardiovascular diseases, diabetes and other non-communicable diseases (NCDs). These diseases are rapidly increasing and affecting both younger and poor people in Africa. They will, he said, present a far greater challenge than has HIV/AIDS.

Horizon 2020

Dr Line Matthiessen of the Directorate General for Research and Innovation, European Commission, concluded Plenary session III by introducing Horizon 2020, the new EU research and innovation (R&I) programme. She said that at a time of recession and austerity, R&I was the only activity of the EU that so far had not suffered from budget cuts. Horizon 2020 has a total budget of € 79 billion for 7 years (2014–2020) and € 7.5 billion has been allocated to health R&I, including € 683 million to EDCTP2. A major aim is to achieve global health research collaboration, in cooperation with public and private European as well as other international funders. To that end, the European Commission signed a Memorandum of Understanding with the Bill & Melinda Gates Foundation in 2013, and is going to sign one with the Calouste Gulbenkian Foundation for strategic cooperation on global health R&I.

One of Horizon 2020's features is that it is an integrated programme coupling research to innovation. It is challenge-based and has a strong focus on involving small and medium-sized enterprises (SMEs). Its three priorities are excellence in science, industrial leadership, and societal challenges. Regarding health research specifically, she pointed out that the EU is the world's third largest funder of research on poverty-related and neglected infectious diseases. Health research continues to be one of its main points of focus. More information about how to apply for research funding, and about Horizon 2020 generally, is available at http://ec.europa.eu/programmes/horizon2020.

The EDCTP Africa mapping project: current state of health research on poverty-related and neglected infectious diseases in sub-Saharan Africa

A special session reporting on the EDCTP Africa mapping project was held on Tuesday 2 July. As background, the audience were informed that the overall objective of the project was to conduct a landscape analysis on research and research funding in 46 sub-Saharan African countries in order to inform strategy for EDCTP's second phase and, further, maximise South-South and North-South collaborations. The mapping, conducted with EC funding, had been commissioned to gain a better understanding of the focus of research in sub-Saharan Africa.

Specific objectives were to investigate:
- The landscape, and the funding landscape, of health research on PRDs in sub-Saharan Africa, as presented in the literature
- Gaps in health research and funding for health research
- Clinical research capacity across sub-Saharan Africa.

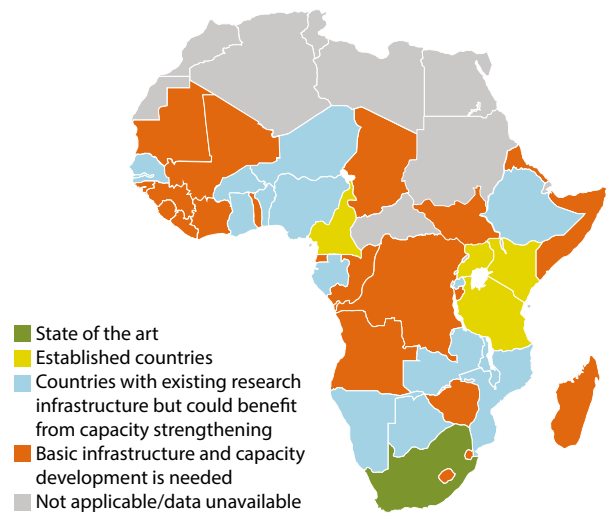
The project methodology included a review of relevant literature (conducted by RAND Europe), and field work consisting of in-depth interviews (conducted by BAIRD's CMC) with 303 key stakeholders, including research institutions, policymakers and multi-lateral agency staff, in 46 sub-Saharan African countries using a semi-structured questionnaire.

The aim of the special session on the Africa mapping project was to obtain audience feedback on the issues involved. The audience were invited to identify areas that have been overlooked by the project, and suggest what should be done differently if EDCTP were to do this research again.

Findings of the literature review, regarding 1) the disease focus for both health research and funding of R&D and 2) the geographical focus of health research in sub-Saharan Africa, were that by far most of health research, as well as funding for R&D, focuses on HIV/AIDS, followed by malaria and TB. The geographical focus of sub-Saharan African R&D efforts is South Africa, followed by Kenya, Uganda, Tanzania and Malawi.

Issues focused on during the face-to-face interviews were: 1) priority diseases; 2) knowledge of policies to fight PRDs; 3) national programmes and 4) government funding for clinical research; 5) awareness of government policies to support clinical research; and 6) barriers to development of clinical research capacity.

Among the main findings were the following:
- Most countries have published government policies in place for control of and research on HIV/AIDS, malaria and TB. High levels of awareness of such policies were displayed by respondents from South Africa, Kenya, Tanzania, Uganda and Ghana, compared with low levels of awareness in Angola and Eritrea
- Awareness of existence of published government policy to support clinical research was seen in respondents from Burkina Faso, Gabon, Kenya, Senegal, South Africa, Uganda and Zambia, as compared with little or no awareness in respondents from Chad and Sierra Leone
- Regarding annual government spending on research, the great majority of funding is provided by donors. With the exception of South Africa and Equatorial Guinea, nearly all funding was from donors; furthermore, few respondents had knowledge of government funding for research
- The main barriers, by rank, to clinical research that were identified by respondents were: lack of 1) funding; 2) policy understanding; 3) human resources; and 4) infrastructure
- Countries were categorised by research capacity, South Africa being rated as having best capacity, with other countries at the other end of the scale, such as the DRC, often lacking basic infrastructure and needing capacity strengthening.



Discussion and questions A lively discussion followed the presentation. Some of the comments and questions are given below.

The audience wanted to know on what criteria the cohorts had been selected for interviewing. One audience member argued that selecting, e.g., researchers would inevitably result in them giving their own research area as the priority area. A certain sampling method would result in showing, not the real research priorities but, rather, what the international community has been supporting for the last 10 years. (*The presenters agreed that most funding has gone into HIV/AIDS, TB and malaria research; however, a substantial number of respondents had named NCDs as an emerging threat, an area that currently receives no funding. It was concluded that the question of priorities should also be asked to health care and service workers.*)

A further comment was that many countries do not have a health research plan. In some cases, it is difficult to find out what the health research priorities are. In such cases, what should funders do to support countries to find out the health research priorities? (*This is a challenge for funders, researchers and policymakers alike. Indeed, one of the aims of the project is to locate national research priority documents.*)

One delegate commented that the entire focus was on funders prescribing research priorities. However, end use priorities seem to have been disregarded. The audience agreed that funders should engage with governments and communities to ensure that research is taken up in policy and health planning at a national level. The audience also wanted to know why operational research and other areas had not been included in the mapping project. (*The presenter responded that the remit of the project was clinical research, but that some questions on operational research had in fact been posed.*)

Finally, it was noted that the language of interviews can impact results. (*The presenter answered that some interviews had been conducted in languages other than English, e.g. in French in the DRC.*)

Among the recommendations arising from the project and the special session were: that there is a need to improve understanding of issues such as 1) training needs and ways to meet them, and 2) how outside research funding affects nascent systems; and that among opportunities to be explored are 1) public–private collaboration, as well as 2) building research into existing initiatives. The final mapping report and recommendations for future work will be published on EDCTP's website.

Cross-cutting oral presentations

Topics discussed in the oral presentations on cross-cutting included: Policy, ethics and good practice; Planning, implementation and impact evaluation of clinical trials; Registering clinical trials; Capacity building including training and networking; as well as Interactions of neglected infectious diseases (NIDs) with HIV, TB and malaria.

The first presentation updated the meeting on the Pan African Clinical Trials Registry (PACTR) [CO.01]. The presenter informed the audience that as yet, >50% of clinical trials worldwide do not report their results. Outlining the reasons why trial registration is important, she said that information about planned, ongoing and completed trials and their findings needs to become part of the public record. Only then can it influence thinking of researchers, clinicians and those who write guidelines, as well as the patients themselves. Moreover, a trial registry help to ensure that ethical obligations to trial participants are met. An international network of clinical trial registries can offer a single point of access and the unambiguous identification of trials globally. PACTR is a partner registry of the WHO International Clinical Trials Registry Platform (ICTRP). As a networking resource, it provides users with contact details of those involved in research and of funders in a particular research area. It provides a regional, up-to-date overview of research in Africa. One of its features, GIS mapping of the locations of all African trial sites, facilitates the understanding of regional research patterns. It can help scientists identify research gaps for future studies. Initially only registering HIV/AIDS, TB and malaria trials, PACTR has since 2009 expanded to all trials. Currently, 215 single-centre trials in 25 countries and 98 multi-centre trials with 264 trial sites in 29 African and some overseas countries are registered with PACTR. There is collaboration with a number of organisations in Africa, e.g. COHRED and AVAREF. Future plans include creation of a discussion forum, and partnership with other, national or regional registries.

The ethical review process is a cornerstone of international guidelines on research with human participants. CO.02 was a presentation on the Mapping African Research Ethics Review Capacity (MARC) project, which identifies and maps existing African research ethics capacity. To date, the project has identified 169 Research Ethics Committees (RECs) across 37 African countries. The presenter discussed some capacity issues faced by these research ethics committees, mainly concerning infrastructure, organisational budgets and member remuneration. Other information from the research ethics committees concerned the training level of members, as well as membership terms, time to obtain ethics clear-

ance, and administrative support. The MARC project has formed a number of partnerships, e.g. with a similar project in Latin America, and has taken up contact with organisations such as the West African Health Organisation (WAHO), the South African Research Ethics Initiative (SARETI) and the South African Research Ethics Network (SAREN). The presenter concluded by saying that MARC is a valuable tool to all key stakeholders, especially in view of the current increase in the scope, complexity and magnitude of health research in Africa.

Institutions around the world that handle large volumes of research frequently rely on effective information management systems to facilitate their strategic and operational activities. In Africa, the majority of research ethics committees rely on complex paper-based systems to manage their research ethics review process, from submission of protocols, to project registration, to conducting reviews and communication with researchers and reviewers. Results from the MARC project show that it can take up to 12 months to get a study through the review process. With the Research for Health and Innovation organiser Ethics (RHInnoEthics) tool, presented in CO.03, this process is shortened.

RHInnoEthics is a cloud-based ethics review tool developed to improve the quality of the ethics review and to be used an administrative tool. Backup of data is stored on Cloud rather than on a single computer. The data are owned and controlled by the user, with the system keeping a complete record of any changes made to data. The dashboard of performance is selected by the administrator of the research ethics committee. This leads to increased accountability. Information in MARC can be linked with RHInnoEthics, enabling research ethics committees to build a set of global reviewers as the tool facilitates communication between members and researchers. The cycle of review is managed digitally. RHInnoEthics has been piloted in Nigeria, Senegal, Swaziland, Mozambique and Malawi and its mass roll-out is currently being investigated. Through this, it is hoped to harmonise ethics review processes in Africa and improve the capacity of African research ethics committees. Using the MARC social network ETHICall, research ethics committees will be able to connect with other research ethics committees and create a closed discussion group and share information with and pose questions to the global community. Further, EthiXPERT allows the user to keep up to date with research ethics developments worldwide, as well as having the latest guidelines available on a cloud.

Discussion and questions A comment following CO.02 was that Cameroon had not been listed among the 37 African countries with research ethics committees, but does in fact have a research ethics committee (*No information for Cameroon had been received*). One delegate asked if it is known whether all disciplines are presented in research ethics committees (*This has been looked into, but was not included in the presentation*). Another member of the audience suggested that medicine regulatory authorities should also be investigated. (*This process has started in 26 countries.*) Attendees praised MARC for being dynamic and showing capacity in Africa. Suggestions were that MARC can be used by other research ethics committees for benchmarking their standard operating procedures and that there should be a link between MARC and PACTR. This will make it possible for research ethics committees to establish whether studies have been registered.

Presentation CO.04, on the impact of clinical trials on the quality of health care services in Nanoro and Dafra districts in Burkina Faso, was cancelled.

Cross-cutting studies included several presentations on planning, implementation and impact evaluation of clinical trials [CO.05–CO.08]. An observational study from The Gambia [CO.05] looked at factors influencing the recruitment of participants for clinical trials in Africa and sought to highlight factors that can delay implementation of clinical trials, impacting their duration, cost and validity. Five factors identified as key to recruitment are 1) the environment, 2) the social organisation, 3) available channels of communication, 4) literacy and 5) the socio-cultural background of the population. Among strategies that can enhance recruitment and participation in clinical trials, are: regular visits, e.g. to recruitment centres, phone calls, meetings, presentations and workshops; adequate staffing; and support from community leaders. Strategies that are less effective are: advertising via the media; incentives for recruitment; presentations at

national and international meetings; and newsletters. It was concluded that recruitment strategies should take into account the environment and social context, availability of resources, availability of communication channels, literacy levels and socio–cultural background. Tailoring the recruitment strategy plan to each context is important.

Discussion and questions This presentation sparked lively discussion. Questions included whether the study considered using community advisory boards as a recruitment strategy (*Yes. Two types of community groups are used: groups comprising elders and traditional community leaders, and groups comprising women. Each group addresses different community members of different importance for the clinical trial and its objectives.*); whether the study had compared the strategies of clinical trials that recruited participants quickly vs those that recruited slowly (*Yes. However, it is difficult to make clear comparisons as clinical trial sites operate in different socio–cultural contexts. As an example, during the month of Ramadan, some sites may struggle to recruit participants because people are not attending the clinic.*); and whether general rules of thumb in recruitment have a part to play in all contexts (*Yes, but the context still needs to be understood in terms of different ways to engage community members. This is necessary before you can begin to implement activities such as community workshops, community open days, site visits, etc.*).

A pragmatic and innovative strategy to improve quality of clinical trials in five East African countries was presented in CO.06. The East Africa Consortium for Clinical Research (EACCR)-initiated and EDCTP-funded Reciprocal Monitoring Scheme, implemented in partnership with the University of Oxford, aims to find a cheaper and practical approach to trial quality management and build African capacity by training monitors in different countries. Among its successes and projects are: two recent monitoring workshops, training 60 monitors; 24 clinical trial sites in East African countries that have signed up for monitoring; 11 new monitors, mentored by 11 experienced regional monitors; 16 clinical trial sites monitored by those newly trained. The programme has been demonstrated to have a positive impact as it shows potential to expand networks and generate additional funding. Among challenges faced are communication breakdowns between sites in different countries and limited funding for further training and implementation activities. The overall finding was that the Reciprocal Monitoring Scheme offers cheaper monitoring of clinical trials and provides checks and balances to make sure monitors adhere to good conduct standards. However, the programme still needs to be certified, and standardisation of monitoring practices is currently not in place. In conclusion, the Reciprocal Monitoring Scheme has much potential as a programme for monitoring quality clinical trials. In addition, it offers the opportunity to build capacity for clinical trial monitoring in resource-limited settings and exchange knowledge and best practice across sites and countries. Plans for future activities are to evaluate sustainability; provide certification for Reciprocal Monitoring Scheme monitors; and compare traditional monitoring vs the Reciprocal Monitoring Scheme by conducting a cost analysis.

Discussion and questions This presentation aroused much interest. Audience questions included whether the programme has well-defined criteria for selecting and training monitors (*Yes. These include that the person must have good clinical practice and good clinical laboratory practice training as well as ≥5 years' experience in clinical research*), and whether the laboratory monitors have experience in laboratory upgrade (*This component will be included in the future*).

The impact of international research collaboration on institutional and individual research capacity is underresearched, mainly due to lack of context-sensitive tools. A project tasked with developing indicators and instruments for monitoring and evaluating health research capacity strengthening (HRCS) activities was presented in CO.07. The project aimed, firstly, to evaluate capacity of groups conducting trials and, secondly, to identify indicators to measure the capacities of research institutions. The research was conducted in three steps: 1) a literature review of existing frameworks for evaluation of HRCS was performed; 2) tools for evaluation of HRCS activities at the individual and the organisational level were reviewed and developed; and 3) the evaluation instrument was tested in a pilot. A framework was developed to analyse the goal, structure and needs of institutions, the work process, and the outcomes and impact of their activities. Factors evaluated were: 1) capacity to manage the research

institution (as demonstrated by e.g. financial sustainability); 2) synergy between the institution and other organisations (resulting in joint projects); and 3) capacity to apply and share research results (leading to public/private/NGO collaboration). The developed instrument was tested on the Fozivudine in Africa Trials Initiative (FATI), with visits made to the FATI sites in Ghana and Tanzania. Using interviews and questionnaires, self-perceived research skills and job satisfaction were assessed and needs identified. Conclusions were that research skills are enhanced if needs are identified. Needs assessment at an individual level is key as it helps identify gaps and thus build capacity from the bottom up. At the same time, an organisation's mission, vision, culture and tradition must be communicated to the research team early. Career pathways and career development programmes for research capacity development must be communicated. A key lesson learnt was that before a project commences it must involve all stakeholders (preferably using face-to-face meetings), provide supportive documentation, and define capacity needs and indicators and outcomes.

Discussion and questions The audience wanted to know whether the project had obtained ethics approval (*It was approved by the ethics committee at all FATI participating sites*). A general audience question was: Do you have a formula to avoid 'brain drain'? The argument was that institutions in the North may build capacity, but at the same time they pick up the bright stars from institutions in the South, thereby hindering development (*This triggered animated discussion*).

Implementation challenges in a regional phase III WANECAM study in children and adults with acute uncomplicated malaria were presented in CO.08. This research was unique because it was an investigator-initiated study funded by an African institution, Bamako University. Some of the challenges highlighted in implementing the WANECAM study were that: the number of participants had far exceeded the study design, with effects on costs. Setting up a clinical laboratory and biochemistry validation were likewise challenging. Initially, local capacity to maintain laboratory equipment was lacking. Furthermore, a database had to be developed from scratch; the study data management team created an in-house MS Access database. Lessons learned from the study were: when purchasing lab equipment, studies should select equipment that can be serviced locally and for which reagents are easily available. Regarding data management, it is important that a study should invest in data management software, that staff be trained in data management and that a clear process for data entry, transmission and validation is established before a trial begins. Consideration should furthermore be given to the geographical location of sites and the challenges of accessing and transmitting data between the trial sites.

Discussion and questions Several audience questions were asked, one of which sought to obtain clarity on whether the study was a placebo-controlled superiority trial (*A superiority trial concerned with safety of repeated dosing*).

Four papers [CO.09–CO.12] were presented on interactions between neglected infectious diseases (NIDs) and HIV, TB and malaria. CO.09 investigated HIV and *Schistosoma mansoni* co-infections among adults in fishing communities along Lake Victoria, Uganda. As background information, the meeting was informed that worldwide, 700 million people in 74 countries suffer from *S. mansoni*. Also, that there is a high prevalence of HIV (29%) and *S. mansoni* (55.8%) in the study area. The study hypothesis was that the interaction between the pathogens may lead to an increase in susceptibility to infection and disease progression. Baseline data were taken from a clinical trial investigating HIV VL in HIV-positive individuals from the study area, who were co-infected with *S. mansoni* and treated with PZQ at different doses. The main finding was that in the study population of HIV-infected individuals, men, fishermen and younger individuals were at higher risk of *S. mansoni*.

Discussion and questions A question from the audience concerned sample size calculation which may not have been suitable for the analysis. The audience also noted that the hypothesis had not been tested and that this limited the discussion.

A group from Gabon delivered a paper titled 'Detangling immune interactions between schistosomiasis and malaria in co-infected individuals' [CO.10]. Analyses were reported from a cross-sectional study in school-aged children,

performed to determine how plasmodial- and schistosome-specific immune responses are affected during co-infection with helminths and malaria. Baseline data of study participants were given and the immunological assays used were described. Four groups were created, consisting of individuals: 1) with malaria only; 2) with schistosomiasis only; 3) with malaria and schistosomiasis co-infection; and 4) negative for both. Methods included staining and analysis on benchtop analyser FACSCanto™; *in vitro* stimulation with infected red blood cells (iRBCs) and uninfected red blood cells (uRBCs); whole blood stimulation with toll-like receptor (TLR) ligands (LPS, PAM3, CPG, CL097), *S. haematobium* egg antigens, LPS and SEB; and Luminex® assays (LUMC). Main findings were that: malaria-only infected individuals responded to iRBCs; while co-infection with Schistosoma reduced response to iRBCs. There was evidence of a polarisation towards type 2 and regulatory immune responses during *S. haematobium* infection, for both adaptive and innate immunity. However, no clear impact of *S. haematobium* infection on concurrent *P. falciparum*-specific immune responses was demonstrated in this population.

Discussion and questions Members of the audience made a comment regarding the B-regulatory panel and advised to investigate the functional immune responses.

Diagnostic tests are urgently needed for detection, in non-expert settings, of asymptomatic mycobacterial infection or prediction of progression to clinical disease. This was the rationale behind CO.11, a field evaluation of an up-converting phosphor-lateral flow assay (UCP-LFA) for detection of cellular and humoral immunity against mycobacteria. The presentation opened with background information on leprosy, which is highly endemic in the tropics. Although rapid diagnostics and treatment have improved the leprosy survival rate, there frequently are delays in leprosy diagnosis. The evaluation showed good correlation between the UCP-LFA and ELISA. The author concluded that the UCP-LFA allows simultaneous detection of cellular and humoral immunity.

The fourth study in this series was titled 'Effect of concurrent gastrointestinal nematode infections on antimalarial total IgG in school-aged children in Mfou, Cameroon' [CO.12]. Main findings were that: co-infection was associated with low intensity of infection with gastrointestinal nematodes; and malaria-intestinal helminth co-infection is prevalent in Mfou, with a predominance of *P. falciparum/Ascaris lumbricoides* co-infection. The children were high producers of antimalarial total IgG. No significant correlation was reported between IgG level and parasite load or density. Co-infection did not significantly affect the amount of produced IgG in children. Mixed co-infection resulted in high levels of IgG.

Several presentations on ethics and good practices followed, including, in the first instance, CO.13, a paper on 'Research ethics in Africa: a resource for research ethics committees'. The aim of the presented project was to develop a research ethics resource for African research ethics committees to assist in strengthening research ethics capacity in Africa. This project was developed as a result of the need, raised by South African students, for research ethics training programmes, but addresses this need in the broader African context. The project culminated in a book titled *Research Ethics in Africa – a Resource for Research Ethics Committees* by main authors Lyn Horn and Mariana Kruger. Among the wide range of topics discussed in the book are issues crucial to the African as well as general research context, such as issues surrounding vulnerability, especially in research involving vulnerable populations such as children; research and auxiliary care in settings with limited health care services; training in research ethics; evaluation of clinical trials; and tools for use by research ethics committees (e.g. for monitoring research). The book is available in e-format free of charge from the websites of Stellenbosch University, EDCTP, Fogarty International Center (FIC), South African Research Ethics Initiative (SARETI) and MARC.

A project whose aim was to simplify standard operating procedures was presented by the Ethics Review and Consultancy Committee (ERCC) of the Cameroon Bioethics Initiative (CAMBIN) [CO.14]. The presenter began by stating that the high disease burden in Africa and the HIV/AIDS pandemic have brought about an explosion in research. This has increased the workload of research ethics committees, whose work has become increasingly important, with the ever-expanding nature and complexity of research on humans. Standard operating procedures are

crucially important for the work and functioning of these committees. Most committee standard operating procedures are long and detailed, and often complex. This is undesirable, especially in the African context, where ethics committee members are often unpaid volunteers within a predominantly oral (as opposed to a literate) culture who, moreover, can afford very little time to dedicate to review work. Based on the need to develop simpler standard operating procedures that can address this situation, this EDCTP-funded project involved designing a tool for the CAMBIN ERCC that would be brief, clear and simple, so as to make standard operating procedures more user-appropriate in their specific context. The result of this work is a 7-page standard operating procedure written in easy-to-understand language. The document has seven subheadings and 18 glossary items including terms like 'conflict of interest' and 'expedited review'. The abridged, user-friendly standard operating procedure contains all the information that is essential for a smooth functioning of a research ethics committee. The presenter proposed that the standard operating procedure be used as a model and template for similar research ethics committees.

The aim of study CO.15 was to do a capacity needs assessment of ethics review committees and independent review committees of East, Central and Southern African (ECSA) member states and document the status of institutional review boards in these countries to identify opportunities for supporting institutional review boards through a regional body. Assessment of capacity needs was done in the following areas: the review process; time taken for the review process; and capacity of the institutional review boards as well as of the ministries of health regarding coordination and regulation of ethics research in the region. Furthermore, the study sought to identify and document best practice in coordination and regulation of ethics research, and assess human resource and financial needs in the conduct of ethical research in the region. To this end, the team developed a 9-page questionnaire. This was administered to institutional review boards in ECSA's ten member states. Results showed that there was gender parity but diverse professional backgrounds among members of institutional review boards. There was also a wide range in the volume of work handled: while one board at the top end of the scale reviewed 900 proposals per year, another processed fewer than five. Some institutional review boards still store paper documentation while others rely on electronic storage. Major gaps identified were lack of self-improvement, e.g. through continuing education for members. The results also showed gaps and needs, such as the need for ethics training in researchers submitting protocols for review. Templates for submission of documents need to be developed. The follow-up of reviews needs to be investigated and a policy put in place for the expedited review of protocols. It was envisaged that this tool will be able to assist in harmonising ethics approval processes through guiding policies and strategies, useful especially for multi-country studies.

Discussion and questions It was suggested that the details on institutional review boards identified through this project but not identified by the MARC project should be forwarded to MARC. Another comment concerned the quality of the review process when 900 protocols are reviewed per year, with only monthly meetings scheduled. The conclusion was that institutional review boards should have regular meetings, receive training and have standard operating procedures in place for the review process.

The need to engage local policymakers in clinical trials to accelerate policy formulation in sub-Saharan Africa was a recurrent theme of the Forum (as also discussed in Plenary session IV). This need was the topic of presentation CO.16. The background to the presentation was that substantial investment is going into clinical trials, strengthening capacity. However, critical gaps in the link between research and policy making prevent the knowledge gained from trials from being quickly utilised for the benefit of people in affected communities. The presented work summarised views of senior African scientists regarding barriers to the uptake of research evidence into policy and solutions. The consensus was that this gap needs to be corrected by building confidence and trust to make all stakeholders appreciate the links between research and policy making.

Discussion and questions A lively discussion ensued. Some of the points highlighted were: generally, inadequate interaction with policymakers is a major impediment to building confidence and acceptance of research results for policy

formulation. For research evidence to impact policy, it is imperative that researchers proactively engage with policymakers and other stakeholders from an early stage of the research planning and throughout the research project development process. This could be facilitated by a developed system for research and knowledge management. The audience concluded that African countries need to strengthen their capacities for coordinated research and policy making processes and systems. Researchers need training in communications skills to engage with various stakeholders in the policy making process. And sponsors should actively encourage researchers to engage with policymakers.

An RCT comparing training methodologies in the Botswana ethics training initiative was the subject of CO.17. The aim was to assess the effectiveness of different ethics training methods. The study population consisted of institutional review boards from various institutions and organisations in Botswana. Altogether 71 individuals participated, 35 in the intervention arm and 36 in the control arm. The intervention arm received an online training module including case studies. The control arm received the online module only. The results showed that completion of the case-based intervention improved respondents' test scores. Those who completed all six cases scored roughly 10% better than those who failed to complete this task as well as those in the control arm. Results suggested that intensive case study work may improve ethical issue identification, although there was limited ability to assess this outcome due to a high drop-out rate. Although the training was very time-consuming for the facilitators, the participants felt that the training was an excellent skill-building exercise. It is planned to offer the course to be taught at the University of Botswana as part of undergraduate and postgraduate training in research ethics reviews.

Discussion and questions The response to an audience question concerning the availability of this training outside Botswana was that Botswana is willing to share this training concept.

CO.18 looked at ethical implications in clinical genetic and genomic research for the emerging countries. Rapid advances in genetic research during the past two decades have challenged scientists, health care professionals, ethicists, policymakers and consumers to reflect on new developments. Being constantly updated on scientific advances and their implications is important for all stakeholders involved in making informed decisions about the ways in which genetic research and information will affect the lives of current and future generations. The potential benefits and risks associated with genetics and genomics research are different from those associated with other types of health research, e.g. clinical trials involving human subjects. After mentioning some issues and complexities peculiar to genetics research and listing fields concerned with application of genetics research insights (e.g. pharmacogenetics and toxicogenomics) the presenter discussed some methods of handling genomic research samples, e.g. using sample personalised identifier; anonymised samples; reversibly de-linked samples (linking code kept) and irreversibly de-linked samples (linking code destroyed). Issues surrounding genetic research results concern the source of samples; samples collected prospectively without informed consent; archived samples (with potential exploitation issues); intellectual property rights – especially where collaborators are involved – and patent issues regarding gene sequence, and leading to ethics issues regarding ownership and how the data will be used.

Discussion and questions The floor agreed that when a researcher obtains informed consent to collect samples, the project for which the samples will be used should be clearly stated in order to reduce the exploitation of stored samples.

What happens with one product, in one trial, in one region, affects all biomedical HIV/TB prevention stakeholders: trial participants, research teams, funders, sponsors, community stakeholders, and product developers. Good participatory practice plays an important role in the conduct of clinical trials, as it furthers stakeholder understanding, as well as transparency and accountability. This was the rationale behind developing guidelines for good participatory practice, as outlined in CO.19. Originally developed for biomedical HIV prevention trials, the guidelines have been extended to include TB drug trials, have been translated into many languages and are being implemented in many regions internationally after demonstrating success in a South African HIV RCT setting. They aim to provide

trial funders, sponsors and implementers with systematic guidance on how to effectively engage with stakeholders in the design, conduct and outcome of biomedical trials. Besides facilitating the training of the research team and institutional review board members, adherence to the guidelines can give insight into community perceptions and increase community understanding of, and trust in, drug trials. Among ultimate benefits are that fewer trials will be closed and that communities can be involved as 'watchdogs' over the research.

Discussion and questions An audience question was whether the guidelines were a checklist to be used by researchers and whether they were sufficient as a tool (*They should not just be considered a checklist; GPP is a process that can enhance research and stakeholder participation*).

All drugs need to be monitored for their entire market life. Early detection of adverse drug reactions can lead to alerts that protect patients from harm. The most common method for discovering previously unknown safety issues post-marketing is through spontaneous reports. CO.20, a paediatric pharmacovigilance study, examined the feasibility and usefulness of data mining algorithms for signal detection in phase IIb clinical trial safety data from Africa. In the study, data mining algorithms were used to detect rare AE signals in pooled safety data from an EDCTP-funded clinical study carried out in 2007–2009 at twelve African sites evaluating efficacy and safety of artemisinin-based combination therapies (AEs) in paediatric patients, and reporting AEs and SAEs. The presenter described pharmacovigilance data mining methods based on contingency table-structured databases. The study concluded that regulatory authorities can use safety data reported in late phase clinical studies for key pharmacovigilance activities like signal generation and can employ data mining algorithms for signal detection in spontaneous reports. Today's zero tolerance drug safety environment calls for new strategies to proactively identify and expeditiously manage emerging safety risks. The approach described in the study could be a first step in identifying signals and generating hypotheses that may guide larger pharmacovigilance activities.

Four papers [CO.21–CO.24] dealt with training and networking. CO.21 presented experiences of an e-learning programme aimed to strengthen the capacity of African scientists in South Africa. The programme, a collaborative effort between the Health Science e-Training (HSet) Foundation and the MRC South Africa HIV Prevention Research Unit, was developed to provide training through web-based teaching and workshops to capacitate African post-graduate scientists and enhance self-directed learning in a cost-effective manner. Curriculum content was customised to issues pertinent to Africa. The workshops sought to engage students to think in innovative ways, e.g. to produce an effective HIV vaccine. Student evaluations of the programme indicated high satisfaction with the pre-workshop material and workshop (70%) and face-to-face activities (80%). Large parts of the materials are currently being used in South Africa for teaching purposes. The presenter concluded that there is scope for more such capacity-building efforts for post-graduate students committed to HIV research and vaccine discovery.

Discussion and questions The audience were curious to know whether there were any drop-outs from the programme (*No, students were informed that they needed to do 80% of the work prior to attending the face-to-face sessions and all students fulfilled this requirement*).

Health research institutions in Africa lack coordination and suffer from inadequate research infrastructure and inconsistent and limited funding. To address these challenges, regional NoEs have been set up with support from EDCTP and other organisations. Three of these bodies reported on their activities and area of expertise and specialisation: EACCR, the West African Network of Excellence for Tuberculosis, HIV/AIDS and Malaria (WANETAM Plus), and the Pan African Centre of Excellence (PACE). EACCR [CO.22] works to coordinate malaria research and programmes in Uganda, Tanzania, Kenya, Ethiopia and Sudan. Its primary purpose is to strengthen capacity among EACCR regional partners and improve South-South and North-South collaboration, facilitate acceleration of malaria drug development, and provide development support to junior trial sites in the region. Because of the junior sites' lack of experience in and infrastructure for running successful clinical research, it has developed a tool to assess the needs of these sites (which are, firstly, infrastructure needs and, secondly, training needs). Much of EACCR's work has been devoted to addressing these needs, through

infrastructural upgrades conducted at junior trial sites as well as through short training courses, a scholarship scheme, and a reciprocal monitoring scheme, the aim of which is to develop a pool of competent monitors in the East African region.

WANETAM Plus [CO.23], a sister organisation to WANETAM, consists of 18 research groups from 12 institutions and 7 countries in West Africa that work in HIV, malaria and TB, with a focus on capacity building. Similarly to EACCR, WANETAM Plus provides specific training courses to leverage skills within the network and also offers home-grown training courses aiming to build greater South-South collaboration. Objectives are to consolidate ongoing scientific training, as well as support services such as lab management. Achievements to date include good clinical practice/good clinical laboratory practice training, as well as training in a range of specialised topics, e.g. fluorescence microscopy for TB studies. Courses in English for second language speakers have also been provided. Post-training, members can share their ideas, problems and solutions online on the WANETAM website. This enhances collaboration between network partners, including collaboration on calls for grants. Future plans include exploring joint collaborations between regional networks.

The activities of PACE [CO.24] focus on research and training on PRDs. The aim of PACE is to develop a nanomedicine-based drug delivery platform in PRD treatment. Secondary aims are to develop infrastructure and a critical mass of African scientists. In South Africa, the major PRD is TB. PACE has developed a drug with an extended half-life and with slow release, reducing the frequency of administering/taking the drug from 5 to 10 days. The significant impact that nanomedicine has in providing solutions to Africa's health problems is the decrease in unit cost for treating diseases such as TB. The achievements of PACE thus far include securing of funds to develop laboratories to carry out this work; a regional workshop on PRDs to discuss the possibilities of nanomedicine; and a follow-up workshop for students from African countries.

Discussion and questions Presentations CO.22–CO.24 sparked much audience interest. The WANETAM Plus presenter was asked whether they had considered linking up with universities to deliver the training courses via their existing database (*This has been discussed among members and may be explored in the future*); and whether there are specific criteria that WANETAM Plus uses for new membership applications (*Membership criteria will depend on the value that a new member can bring to the group. A key consideration will be how the new member can financially support some of the initiatives of the consortium*). The PACE delegate was asked how infectious diseases are compounded by NCDs and how these affect drug absorption (*Nanomedicine can improve absorption by, e.g., coating the pill with a lipid-based product that allows for easier absorption in the small intestine*) and whether researchers had considered how spacing the treatment regime might affect adherence (*The presenter was hopeful that people would prefer this method to taking a daily dose*). Another question was whether the PACE training programme offers continued mentoring and support to its students after they have returned to their home institutions (*Institutions sign a partnership cooperative agreement with PACE. There are plans to mentor students after they have left, e.g. through co-supervisory roles on MSc and PhD projects*).

There is a need to leverage limited resources and eliminate redundancies and duplication in the review of clinical trials applications. This was the background to CO.25: 'Establishment of an integrated clinical trials register in Kenya: a hub for knowledge sharing and exchange across two institutions'. The project brought together two government institutions, KEMRI and the Pharmacy and Poisons Board (PPB), under the Kenyan Ministry of Health to establish and implement a centralised clinical trials registry and an integrated national pharmacovigilance electronic AE reporting system. It was felt, and has since been confirmed, that the implementation of a clinical trials registry with inbuilt functions for reporting of AEs from health facilities across the country and for submitting and reviewing clinical trials applications would go a long way towards strengthening clinical research in the country. The presenter told the audience that the two institutions benefit from shared information on clinical trials in Kenya since the database captures information from all Kenyan-based institutions conducting trials. The Ministry of Health and other government agencies receive periodic reports generated through this platform. It is

hoped that this clinical trials registry will serve as a model for other organisations and countries to ensure that regulatory structures and processes for the approval and oversight of clinical research are synergised.

Presentation CO.26 focused on practical challenges faced by institutional review board and research ethics committee members in developing countries. The presenter opened by saying that the establishment of research ethics committees in Africa is a fairly new development. He proceeded to present a case study to illustrate the challenges faced in cases where there are unclear or no national or institutional guidelines to guide the operations of a research ethics committee. It is, he stressed, crucial to train institutional officers in research ethics committee management. They further need to strategically position themselves in the organisation so as to maintain their independence. Importantly, research ethics training on its own does not automatically translate into proper research ethics committee administration. Among many challenges, a lack of guidelines, training and support, as well as institutional and personal conflicts of interest were mentioned. Ethics committees need to operate independently despite financial dependence. A key message from the presentation was that corporate governance becomes important and clear guidelines are imperative in establishing and sustaining research ethics committees that protect the rights, safety and wellbeing of research participants.

Another presentation related to ethics, CO.27, described a Nigerian project aimed to build capacity through training in reviewing research protocols. The project was motivated by the realisation that most ethics committees in Nigeria lack expertise to review protocols. The project also sought to provide infrastructural support to selected ethics committees as well as to provide a platform for networking, collaboration and discussion on contemporary ethical issues through electronic media. Enrolled ethics committees were trained in the use of Pro-IRB, an electronic institutional review board management software application intended to improve the efficiency and effectiveness of institutional review boards. Three ethics review committees in Nigeria received institution-based training. Post-training operational competence was evaluated. Results showed a significant improvement in both knowledge levels of the ethics committee members and operational capacity of the ethics committees. Improvements were particularly noted in: provision of constructive feedback; turnaround time; the working environment; and efficiency in protocol submission and communication between ethics committee staff and the researchers. Despite notable improvements, it was noted that the ethics committees are still functioning below their optimum capacity owing to challenges in monitoring approved research. This may be attributable to lack of financial and human resources for embarking on the monitoring activities. Conclusions were that while this EDCTP project has provided a basis for the operations of the ethics committees, there is need for political commitment to sustain the operations of ethics review committees.

Community participation in health research and especially in clinical trials is important. CO.28 investigated the challenges of establishing and running a community advisory board (CAB) in Botswana. Such boards serve to identify and protect the interests of the community they represent. They interface between the researcher and the participating community and individual trial participant to ensure that the research is conducted in an ethical manner and that the entire community benefits from access to information about a particular clinical trial. One of the prime functions of CABs is to discuss the critical issues they/the community have identified concerning the proposed/ongoing research with the affected communities and responsible researchers, and to keep the community abreast of the research activities taking place and inform them of the importance of receiving research results and information about the disease condition being studied. The Botswanan CAB studied in CO.28 has a wide membership representing diverse interests, age groups and positions within the community. The study interviewed 30 randomly selected community and CAB members. Results showed that the interviewees clearly understood the role of a CAB. Among main challenges in establishing a CAB were: lack of financial resources, establishing criteria for selection of members, and differences in educational levels and understanding of the research process. Lack of scientific understanding can make it difficult for CABs to protect the interests and rights of the communities they serve. More training in science and research ethics is

needed for CAB members. The presenter also proposed using incentives to ensure commitment of CAB members, and conducting CAB business in the language best understood by them.

A Gambian study set out to establish whether the international guidelines for informed consent procedures are suitable for low-literacy research settings [CO.29]. A meta-analysis of existing literature had revealed that: there is poor comprehension of basic scientific research concepts; no clear definition of comprehension; and limited evidence of assessment of comprehension of the informed consent process. The presenting research team conducted a project to develop and psychometrically evaluate a multimedia-informed consent tool for assessment of informed consent among low-literacy research participants in The Gambia. The tool, a 34-item questionnaire on the key elements of informed consent, was translated into three major Gambian languages, Mandinka, Wolof and Fula, validated, and administered to 250 participants enrolled in two clinical trials in urban and rural areas. The primary outcome was the questionnaire's reliability and validity. Experienced native speakers were deployed to translate and produce an audio recording of the questionnaire. Delivery through a digitised format ensured that the questions were consistently presented to all participants. The presenter concluded that this novel approach of developing and delivering questionnaires permits rapid measurement of informed consent comprehension in remote rural as well as urban research settings. It overcomes the many obstacles of producing multiple written translations and questionnaire administration to a low-literacy population.

Owing to the resource disparity between high- and low-income countries there is often the tendency to a 'top-down' relationship in North-South collaborations, to the disadvantage of all partners but especially of the resource-poor countries. The study described in CO.30 was motivated by the need of organisations in Africa to select just the 'right' partners for overseas collaboration in research, and achieve the type of partnership that fosters trust and true collaboration. Findings were gathered in an Initiative to Strengthen Health Research Capacity in Africa (ISHReCA) manifesto to guide researchers as they engage in health research partnerships. The presenter added that most African countries have made significant strides in developing and sustaining equitable partnerships in research, through efforts such as government commitments to meet the Abuja 2001 declaration target of committing ≥15% of the national budget to health; and increased funding of MSc and PhD programmes. Competitive health research grants aimed at strengthening the capacity of staff to implement health research have also been introduced in some countries. However, much more remains to be done, especially in ensuring that the rights, safety and wellbeing of research participants are protected.

Ms Elizabeth Pienaar, Medical Research Council, South Africa, at the parallel session on cross-cutting issues.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6 Health research partnerships

This chapter features health research partnerships with EDCTP partner organisations. These were presented in Plenary session IV and in a special session titled EDCTP and CAAST-Net Plus: building bridges.

Plenary session on partnership

Plenary session IV took place on Wednesday 2 July and brought together EDCTP partners in a panel discussion. It differed from the other sessions inasmuch as rather than report on achievements it looked at aims for the future, and how to achieve them. The Chairs opening the session spoke of partnership as being key to success. The role of EDCTP was to facilitate partnership between different parties, the researchers, research facilitators and policymakers. The goal of the panel discussion was to discuss ways of creating synergy between different organisations.

The session was split into two panels, representing public/private funding agencies and other global health organisations with different levels of collaboration with EDCTP. The seven panellists were invited to speak in two sets of speakers, stating their organisation's core function; describing how their organisation can contribute to the mission of EDCTP; and outlining areas for potential collaboration with EDCTP. Following this, discussion was opened to the floor.

The session had two main objectives: 1) to inform EDCTP stakeholders on the current activities and core functions of the represented organisations; and 2) to identify potential areas of collaboration with EDCTP. Chair Dr Ole Olesen, EDCTP Director of North-North Cooperation, said it was hoped that this session would trigger discussion and thought processes on synergy.

The organisations represented were:

The Research Council of Norway

The aims of its Norad-funded Programme for Global Health and Vaccination Research (GLOBVAC) are to support health research and achieve health equity for poor people in low- and lower middle-income countries. Programme priorities are communicable diseases; reproductive, neonatal, child and youth health; diarrhoea and respiratory illnesses; NIDs; and health policy and implementation research. The Research Council of Norway offers funds and grants for research through its Young Scientist grants, PhD fellowships, support for events and other programmes. Regarding areas of potential collaboration with EDCTP, panellist Wenche Dageid said that EDCTP and GLOBVAC have overlapping research interests and capacity building aims and that further avenues for collaboration should be explored.

The Department of Science and Technology (DST), South Africa

The DST was represented by Glaudina Loots, who spoke of her organisation's capacity for clinical research. She said that the DST is looking for possibilities to collaborate with more institutions from the rest of Africa, e.g. on TB research. To provide sustainability, the DST is aiming to provide training to all centres, both inside South Africa and beyond the country's borders. Already, it is providing training in grant writing and data management across Africa.

The Bill & Melinda Gates Foundation

The Bill & Melinda Gates Foundation is a global product development network that optimises and aligns strengths of partners to discover, develop and deliver affordable and appropriate products. The goal of the Foundation's health programme is to help develop tools to fight diseases – from diagnostics, to treatment vaccines, and vector control – especially in lower-income countries. The Foundation is already collaborating with

EDCTP on several PanACEA studies on TB as well as on malaria studies and HIV vaccine trials. Representative Samia Saad listed some areas for potential collaboration with EDCTP and other partners, including: HIV/AIDS, malaria, TB, NIDs, diarrhoeal diseases, respiratory diseases, and regulatory capacity building and cross-cutting surveillance.

The Wellcome Trust

The Wellcome Trust is a health research funder with goals to strengthen the evidence base for improving health in low- and middle-income countries. The Wellcome Trust provides funding to clinical trials and to researchers applying for fellowships. Val Snewin spoke of the Trust's recent policy decision to expand its funding activities by increasing funding directly to African institutions. Areas for collaboration with EDCTP are research, training, and support of the research environment.

Lion's Head Global Partners

Christopher Egerton-Warburton of the Lion's Head Global Partners (LHGP) group referred to his organisation as an investor providing advisory, financial structuring and capital raising services. LHGP provides companies and scientists with capital while projects are ongoing, such as HIV vaccine, TB diagnostic, and drug development projects.

Institut Pasteur

The Institut Pasteur has its own research and training institutes across the world, several of which are located in TB – and malaria-endemic regions: Senegal, Cameroon, Cote d'Ivoire, Niger, Bangul and Madagascar. Although it does not fund non-Institut Pasteur research activities, it is strongly involved in international partnerships and consortia working in the areas of HIV, TB, malaria, as well as NIDs. It is involved in partnerships, in collaboration with EDCTP, with organisations such as CANTAM, WANETAM and TESA. Panellist Nadia Khelef spoke of the benefits of, and her organisation's commitment to, developing new partnerships, linking institutions with common research interests.

German Foundation for World Population (Deutsche Stiftung Weltbevölkerung, DSW)

This largely self-funding organisation promotes global health development by identifying funders and research needs, especially in PRNIDs, and promoting dialogue on and awareness raising of health issues, health research and capacity development. Goals are to strengthen stakeholders' and decision makers' support for investments in global health R&D, and provide support for creating and maintaining enabling policy environments. Regarding areas of potential collaboration with EDCTP, DSW representative Katharina Scheffler said the DSW aims to increase political decision makers' awareness of EDCTP and its activities.

Discussion and questions One of the comments made to the panel in the interactive discussion session was that funding is often too short, normally not exceeding three years. This means that funding often ends in the middle of a programme, resulting in no continuity and little sustainability. One of the Chairs commented that this is why funding of capacity development is so important, since with strengthened capacity, a project can continue even after funder withdrawal. One audience suggestion was to obtain greater government involvement so as to ensure continuity. Governments should be encouraged to co-fund research projects. If governments were involved in a project from the outset, they could both take over funding when outside funders withdraw, and negotiate for other funders to take over the project. It was added that funders need longer-term visions, ensuring that engagement is at a higher level. They need to be less project-focused and more institution-focused. Most importantly, they need to talk to each other and work in better synergy so as to harmonise funding.

One delegate made a comment concerning the lack of, and difficulty in procuring, funding for basic science in Africa. There is a need to train basic scientists who can develop products. Africans should be testing drugs created in Africa, not only drugs created in the North. The delegate was told that several organisations such as the Pasteur Institute do engage in basic science training. Moreover, basic science projects are funded under Horizon 2020. Additionally, regarding drug development funding, LHGP provides capital to companies while drug development is on-

going. However, it was agreed that basic science research in Africa needs to be supported, and partnerships need to be developed to this end. Delegates should be using this Forum to start building collaboration with European partners.

A comment that elicited a vivid audience response concerned the absence of reference laboratories. It was argued that, e.g. for TB trials, we need strong reference laboratories, as currently there are only three in Africa. There needs to be sustained support and funding for reference capacities.

In conclusion, the Chair summarised the main points, saying that for the identified sustainable infrastructure needs to be met, governments need to be involved in helping find long-term solutions of sustainability. There are models of early involvement of African governments that can be used as examples. Since funding institutions have regulations on the duration of funding, it is important that funders should talk to each other and consider different ways of collaborating with each other and with EDCTP to benefit the research on a sustainable basis. The session was concluded with the recommendation that delegates should use this Forum to start building collaboration with each other and with European partners.

EDCTP and CAAST-Net Plus: Building bridges – opportunities and challenges for greater involvement of the private sector in health research cooperation

A recurrent theme, the need for strengthening collaboration between the main health research actors, including the private and the public sector, during the second EDCTP phase and beyond, was also highlighted in the EDCTP and CAAST-Net Plus special session that took place on 2 July. Objectives of this session were to: 1) identify concrete possibilities for closer collaboration between pharmaceutical companies, small and medium enterprises (SMEs), product development partnerships, EDCTP, and other funders; 2) identify opportunities for and barriers to greater involvement of the private sector, particularly pharmaceutical companies and SMEs, in European and African health research cooperation; 3) discuss the role of the private sector in the fight against PRNIDs; 4) discuss future collaboration with and participation of SMEs in collaborative research projects; and 5) highlight opportunities for public entities in Europe and sub-Saharan Africa to partner with pharmaceutical companies and SMEs.

The session's co-Chair Mr Mmboneni Muofhe, Deputy Director-General International Cooperation and Resources of the Department of Science and Technology, South Africa, opened the session by introducing CAAST-NET Plus, a network of 25 partners based in Europe and Africa. Co-chair Dr Ole Olesen, EDCTP Director of North-North Cooperation, summarised the session's two main aims, which were to secure support for clinical trials in Africa and create an enabling environment for these trials in partnership with both public and private actors.

The session took the form of a panel discussion, the panellists being Dr François Bompart, of the European Federation of Pharmaceutical Industries and Associations (EFPIA); Dr Lluís Ballell-Pages from GSK Tres Cantos; Dr Claudia Schacht, of Fit for Health 2.0; Dr Jude Aidam, of the West African Health Organisation (WAHO); Professor John Mugabe of the University of Pretoria, South Africa; Ms Jennifer Dent, of BIO Ventures for Global Health; Dr Philippe Leissner, of bioMérieux; and Mr Gift Mphefu, from MedTechEngineers.

Panellists were asked to address the following question: *What are the key challenges for involvement of pharmaceutical companies or SMEs in transnational health research cooperation, particularly in sub-Saharan Africa, and how could these challenges be overcome?* They identified the following key challenges to involvement: 1) a need to invest in centres of excellence and find good, skilled research partners; 2) a lack of human resources (e.g. local pre-clinical and clinical expertise); quality epidemiological data; standards and regulatory requirements; and a need for quality and reliable expertise in health research biostatistics and bioinformatics to facilitate interpretation and implementation of key findings generated in applied research; 3) a lack of health systems for ensuring the existence of a market and the uptake of products; 4) the need to build a culture of transnational/regional research; and 5) the need for greater integration, cooperation and experience sharing between organisations. Enlarging on this challenge, it was argued that to enable

the implementation of projects with involvement from industrial and academic partners, there is a need for open communication from the beginning of a project. There is ineffective communication of the needs of the research community to the industry. This overall lack of communication is due, in part, to language barriers. Finally, 6) it was argued that the disease areas that EDCTP is involved in, with the exception of HIV/AIDS, do not offer high returns on investment, which acts as a disincentive for industry involvement. The notion that there will be no commercial gains is linked firstly to the perception that the science coming out of the research community does not warrant the investment of the industry, and secondly to the small market size, with competition from larger markets such as India or China.

Discussion and questions Enlarging on the panellists' comments regarding human resource needs, one delegate told the audience that in the pharmaceutical SME sector, the challenge is not so much funding, but finding scientists to conduct the clinical trials. A major limiting factor in the biotech industry is low science capacity. Therefore, an issue to address is how the various initiatives can support building the critical mass of scientists needed to perform the research. One way of supporting scientists in the field was to address logistical and other practical challenges, such as laboratory equipment breaking down. The audience agreed that research proposals must be formulated so as to include the practicalities of research. A role for EDCTP would be, not only to support researchers, but to ensure the capacity of technicians and service providers.

Another challenge was identifying the right partners to work with. An initiative that may be of interest in this regard is ISHReCA, which can be useful in searching for suitable research partners. The audience argued that a multi-disciplinary approach was needed to properly understand the issues at hand and develop a strong business case. There is a need for SMEs to address the multi-disciplinary space of health research.

On the topic of incentives for industry involvement, the audience proposed that there was a need to find ways in which the public sector in African countries could encourage the private sector to engage more in clinical research. In many African countries, health is currently considered a social sector issue. Health funding is often linked to funding for e.g. youth. If African governments could be persuaded to regard health research as a core economic activity, this would help raise awareness and attract greater industry involvement. Furthermore, governments should be encouraged to expedite the process of getting compounds registered and research activities approved in order to attract private sector involvement.

Moreover, Africa consists of a diverse set of countries, and a more regional approach is needed to encourage industry involvement. Guidance issues need to be addressed at regional level, so that SMEs can enter into research collaborations with a holistic understanding of what is involved. In the context of market and product development, it is likewise important to develop guidance documents at regional level. The recent example of WAHO working with the West African Monetary Union and the national regulatory agencies of 15 countries to develop shared regional governance mechanisms might serve as a model for overcoming barriers to regional collaboration. Regarding regulatory assurance, one delegate asked whether there is an accreditation and quality assurance system that could be used at regional level to ensure the quality of research partners (*WAHO has already been looking into this, including developing standard training for health care personnel at all levels in the region*).

In conclusion Summarising the session, the Chairs reminded the audience of the issue of regulation, which had been raised by several panel and audience members. Further, governments have the responsibility to develop a market that is conducive to private sector engagement, notwithstanding the importance of regional differences. In addition, sharing information and knowledge is critical. To achieve sustainability it is important to ensure funding for capacity building. Finally, although some diseases might not offer commercial gain, it is important to consider health as part of the economic sector. A powerful argument is that of the impact of health on society and the economy.

7 Final plenary session

Plenary session V was held on Wednesday 2 July. A brief summary and a few closing remarks were given by Chairs **Dr Michael Makanga** and **Professor Tumani Corrah**. Prof. Corrah commented that throughout the Forum, he had not heard the word 'difficulties' spoken. Instead, the word 'challenges' had been used again and again – a very promising sign. Dr Makanga, EDCTP Director of South-South Cooperation and Head of the Africa Office, thanked the audience for their contributions and added that he hoped all present had made new contacts to kick-start or strengthen networking and exchange ideas to be translated into future research action.

The Forum proceedings and recommendations arising from the Forum were briefly summarised by chief rapporteur **Karin Fischer-Buder**. One recommendation for future strategy consideration was based on the finding that, across all disease areas, there is a scarcity of high-quality local reference values. Where they exist, they are from very small studies and not systematically collected. This was a major gap that EDCTP may consider breaching systematically using its existing platforms, such as the regional NoEs. A further recommendation related to funding for non-communicable diseases (NCDs). These are currently outside the scope of EDCTP funding. As a recommendation at this stage, EDCTP may consider liaising with funders for NCDs to explore synergy with these areas in its current scope.

Closing remarks were heard from Professor Charles Mgone, who said he had never attended a Forum where presentations were consistently of such high standard. The experience had been enjoyable, he said. Moreover, most presentations had come from young, confident and competent African presenters. The presence and skills of these young people was an illustration of capacity development taking place, and it made him look forward to having many leaders at EDCTP in the future. Professor Mgone told the audience that the high number of delegates and attendees at the Forum demonstrated the commitment and level of engagement in global health.

Dr Gianpietro Van de Goor, from the DG for Research and Innovation of the European Commission, spoke of the significance of this Forum taking place in Berlin. Berlin had not long previously been a city divided by a wall – a wall that had split up even families: until the cry to 'Tear down this wall' had gone up and brought it down. Developing the analogy of a wall, Dr Van de Goor said, walls can make us feel comfortable and safe. But at the same time, they divide us and prevent us from working together and combining forces. The Seventh EDCTP Forum had torn down walls. It had been an excellent marketplace for networking and synergy.

New and ambitious projects and joint actions were being planned. However, it should be noted that the health of people in Africa will not be improved by good intentions. We need to stand up to fight for health and remove the walls that are preventing this. Dr Van de Goor reminded the audience that across the globe around 400 children die every thirty minutes mostly due to infectious diseases combined with malnutrition, and half of them in Africa – a fact that calls for more effective health solutions. However, how to find and implement solutions in times of austerity? He spoke of the EU strategy to support global health research in the face of recession.

A number of impressive achievements had already been made. However, he cautioned that this should not lead to complacency. There remained much more to be done. He encouraged all those present to participate in finding solutions and putting them into action, in collaboration with EDCTP.

Concluding remarks were provided by **Dr Joachim Klein** of the German Ministry for Education and Research. Referring to the Seventh EDCTP Forum as a high-quality scientific conference, he said it was particularly impressive that so many young researchers had come to present their results. But health research is about more than fighting diseases; it also is about fighting for societal development. The step to include ethics in EDCTP's programme was an important step

in this direction; and plans to include NIDs were equally important. He further commended recent developments to provide a new, stronger role for EDCTP's African partners. He closed by stating that the German government endorses the approach of and plans for EDCTP2.

In closing the Forum, Professor Corrah spoke of the challenges the meeting had discussed. He said if there was a magic wand, we would have vaccines for all diseases – and an efficacious, cheap drug for malaria. TB, HIV and malaria would in fact be eradicated. And so on. There was no 'magic wand', however. Only hard work and collaboration would get us there. One step in that direction was EDCTP launching its second phase in December 2014.

Appendix 1 Forum programme

Sunday 29 June 2014	Monday 30 June 2014
	REGISTRATION | 08:00–09:00 FOYER, CONFERENCE CENTRE
	PLENARY SESSION I | 09:00–10:30 Forum prologue | HALL I B-C
	COFFEE AND TEA BREAK HALL II | 10:30–11:00
	MARKETPLACE VIEWS HALL II | 10:30–11:00
SATELLITE MEETING | 09:00–17:00 Sustainable investment in research for health | SALON 3–4	**PLENARY SESSION II** | 11:00–12:30 Recent advances in HIV/AIDS, tuberculosis and malaria (keynote addresses) | HALL I B-C
	LUNCH HALL II | 12:30–13:30
	MARKETPLACE VIEWS HALL II | 12:30–13:30
	PLENARY SESSION III | 13:30–15:30 Recent advances in neglected infectious diseases, health services optimisation research (keynote addresses) and update on Horizon 2020 | HALL I B-C
	COFFEE AND TEA BREAK HALL II | 15:30–16:00
	MARKETPLACE VIEWS HALL II | 15:30–16:00
REGISTRATION | 16:00–18:00 FOYER, CONFERENCE CENTRE	**PARALLEL SESSIONS** | 16:00–17:00 • HIV/AIDS immunology and vaccine development | HALL I B-C • Tuberculosis therapeutic studies | SALON 2 • Malaria vaccines studies | HALL I A • Cross-cutting: policy, ethics, regulatory and trials registration activities | SALON 3–4
	MARKETPLACE VIEWS HALL II | 17:00–18:00
	SPECIAL SESSION | 17:00–18:30 EDCTP2 Fellowship Schemes | SALON 2
	SATELLITE MEETING | 17:00–18:30 Combatting neglected tropical diseases: the case of visceral leishmaniasis in Africa | SALON 7
	CONFERENCE DINNER | 19:00–20:30

Tuesday 1 July 2014	Wednesday 2 July 2014
REGISTRATION | 08:00–09:00 FOYER, CONFERENCE CENTRE	**REGISTRATION** | 08:00–09:00 FOYER, CONFERENCE CENTRE
SPECIAL SESSION | 08:00–08:50 EDCTP Fellowship Alumni | SALON 2	**PARALLEL SESSIONS** | 08:00–09:30 • EDCTP and CAAST-Net Plus: Building bridges | HALL I B-C • EDCTP Africa mapping project: current state of health research on poverty-related and neglected infectious diseases in sub-Saharan Africa | HALL I A
SATELLITE MEETING | 08:00–08:50 Discussion to explore ways to support clinical trials for malaria and neglected tropical diseases | SALON 3–4 *(by invitation only)*	
PARALLEL SESSIONS | 09:00–11:00 • HIV/AIDS therapeutic and prevention studies | HALL I B-C • Tuberculosis therapeutic studies | SALON 2 • Malaria therapeutic studies | HALL I A • Cross-cutting: planning, implementation and impact evaluation of clinical trials | SALON 3–4	**PARALLEL SESSIONS** | 09:40–11:00 • HIV/AIDS treatment guidelines and disease progression | HALL I B-C • Tuberculosis immunology | SALON 2 • Malaria coinfections, drug resistance and modelling | HALL I A • Cross-cutting: training and networking activities | SALON 3–4
COFFEE AND TEA BREAK HALL II | 11:00–11:30	**COFFEE AND TEA BREAK** HALL II | 11:00–11:30
MARKETPLACE VIEWS HALL II | 11:00–11:30	**MARKETPLACE VIEWS** HALL II | 11:00–11:30
PARALLEL SESSIONS | 11:30–13:00 • HIV/AIDS therapeutic studies | HALL I B-C • Tuberculosis immunology and vaccine development | SALON 2 • Malaria vaccine studies | HALL I A • Cross-cutting: interaction of neglected infectious diseases with HIV, tuberculosis and malaria | SALON 3–4	**PLENARY SESSION IV** | 11:30–13:00 EDCTP Partners' session | HALL I B-C
LUNCH HALL II | 13:00–14:00	**LUNCH** HALL II | 13:00–14:00
MARKETPLACE VIEWS HALL II | 13:00–14:00	**MARKETPLACE VIEWS** HALL II | 13:00–14:00
PARALLEL SESSIONS | 14:00–16:00 • HIV/AIDS comorbidities | HALL I B-C • Tuberculosis studies on diagnostics | SALON 2 • Pregnancy associated malaria studies | HALL I A • Cross-cutting: ethics and good practices | SALON 3–4	**PARALLEL SESSIONS** | 14:00–15:30 • HIV/AIDS coinfections | HALL I B-C • Tuberculosis | SALON 2 • Malaria immunology and diagnostics | HALL I A • Cross-cutting | SALON 3–4
COFFEE AND TEA BREAK HALL II | 16:00–16:30	**COFFEE AND TEA BREAK** HALL II | 15:30–16:00
MARKETPLACE VIEWS HALL II | 16:00–16:30	**MARKETPLACE VIEWS** HALL II | 15:30–16:00
PARALLEL SESSIONS | 16:30–17:10 • HIV/AIDS comorbidities | HALL I B-C • Tuberculosis drug development and drug resistance | SALON 2 • Pregnancy associated malaria studies | HALL I A • Cross-cutting: ethics and good practices | SALON 3–4	**PLENARY SESSION V** | 16:00–17:30 Summary and closing remarks | HALL I B-C
MARKETPLACE VIEWS HALL II | 17:10–18:00	**Thursday 3 July 2014**
SATELLITE MEETING | 17:30–19:00 Global TB Vaccine Partnership | SALON 3–4	**EDCTP STAKEHOLDER MEETING ON CAPACITY DEVELOPMENT** | 09:00–17:00 *(by invitation only)* HALL I A
SATELLITE MEETING | 17:30–20:30 ESSENCE on Health Research initiative, members' dinner meeting | SALON 2 *(by invitation only)*	

Appendix 2 Forum presentations

HIV/AIDS

HO.01 **Tomáš Hanke**, University of Oxford, United Kingdom: Targeting HIV-1 by vaccines at conserved regions

HO.02 **Keabetswe Bedi**, University of Botswana/BHP, Botswana: Evolution of neutralising antibodies in acute heterosexually acquired HIV-1 subtype C infection in Botswana

HO.03 **Moustapha Mbow**, CHU Le Dantec, Senegal: Natural killer cells of HIV-1-exposed but uninfected subjects exhibit recall responsiveness to HIV-1 peptides

HO.04 **Laura Ciaffi**, University of Montpellier 1 (IRD 233), France: Randomised comparison of three second line ART regimens in Africa: the 2Lady/ANRS/EDCTP study

HO.05 **Cissy Kityo**, JCRC, Uganda: HIV drug resistance in paediatric patients initiating antiretroviral therapy in Uganda: a multicentre observational study

HO.06 **Frank Angira**, KEMRI-CDC, Kenya: Post-antiretroviral outcomes in a cohort of women who discontinued maternal triple-antiretrovirals initially used to prevent mother-to-child transmission of HIV during pregnancy

HO.07 **Richard Lando**, KEMRI-CDC, Kenya: Adverse foetal outcomes in HIV-1 infected women who received either NNRTI or PI-based therapy for prevention of mother-to-child transmission of HIV in Western Kenya

HO.08 **Collen Masimirembwa**, AiBST, Zimbabwe: Evaluation of genetic variants of drug metabolising enzymes and drug transporters as possible biomarkers for adverse drug reactions in an HIV/AIDS cohort

HO.09 **Simani Gaseitsiwe**, BHP, Botswana: High K65R levels in HIV-1 subtype C-infected patients failing a tenofovir-based first-line combination antiretroviral therapy regimen in Botswana

HO.10 **Divine Avit Edi**, PAC-CI, Site ANRS, projet Monod, Côte d'Ivoire: Access to early infant diagnosis and antiretroviral therapy: barriers and challenges in Abidjan, Côte d'Ivoire in 2011–2013

HO.11 **Nicholas Paton**, National University of Singapore, Singapore: A pragmatic randomised controlled strategy trial of three second-line treatment options for use in public health rollout programme settings: the EARNEST trial

HO.12 **Nogbou Frédéric Ello**, CHUT, Côte d'Ivoire: The Fozivudine in Africa Trials Initiative: first results from the FATI-1 phase II trial conducted in Mbeya, Tanzania and Abidjan, Côte d'Ivoire

HO.13 **Catherine Orrell**, University of Cape Town, South Africa: A randomised trial to explore adherence-failure relationships in a South African antiretroviral cohort: baseline data analysis

HO.14 **Graeme Meintjes**, University of Cape Town, South Africa: Efficacy of third line ART in Africa: outcomes on ART salvage regimens in the Southern African private sector

HO.15 **Kamija Phiri**, University of Malawi: Benefits and risks of iron supplementation in HIV-infected Malawian children: results of a double-blind, randomised controlled trial

HO.16 **Veronica Mulenga**, University Teaching Hospital, Zambia: CHAPAS-3: A randomised trial comparing two-year toxicity and efficacy of stavudine vs zidovudine vs abacavir as NNRTI-based fixed dose combination antiretroviral drug regimens for starting or substituting from stavudine-based antiretroviral therapy in 478 HIV-infected children in Uganda and Zambia

HO.17 **Grace Mirembe**, JCRC Kampala, Uganda: Cardiovascular structure and function in HIV-infected children in Zambia and Uganda: CHAPAS-3 trial

HO.18 **Victor Musiime**, JCRC Kampala, Uganda: Anthropometric measurements and lipid profiles to detect early lipodystrophy in antiretroviral therapy experienced HIV-infected children in the CHAPAS-3 trial

HO.19 **Chishala Chabala**, UTH, Zambia: Assessment of peripheral neuropathy among HIV-infected children on fixed-dose antiretroviral therapy in Zambia and Uganda: the CHAPAS-3 randomised clinical trial

HO.20 **Guy Bumoko**, University of Kinshasa, Democratic Republic of Congo: Cognition abilities and daily life functioning of HIV-infected subjects under antiretroviral therapy

HO.21 **Seth Inzaule**, KEMRI, Kenya: Incidence and predictors of first-line antiretroviral regimen modification in western Kenya

HO.22 **Ismail Mbowo**, Moi University, Kenya: Correlates of separation among HIV-serodiscordant couples enrolled in partners PrEP study site clinic in Eldoret western Kenya

HO.23 **Suzanne Filteau**, LSHTM, United Kingdom: Nutritional intervention to reduce early mortality in HIV-infected African adults starting antiretroviral therapy

HO.24 **Valériane Leroy**, University of Bordeaux Segalen, France: Twelve-month virological response in children initiated on lopinavir containing antiretroviral therapy before 2 years of age in Abidjan, Côte d'Ivoire and Ouagadougou, Burkina Faso

HO.25 **Vincent Tukei**, BIPAI, Uganda: Using WHO 2010 dosing guidelines, efavirenz levels remain slightly lower and highly variable in Ugandan and Zambian children weighing 10–20kg

HO.26 **Gaone Retshabile**, BHP, Botswana: Sub-optimal CD4 T cell recovery in HIV-1 subtype C patients on antiretroviral therapy: a search for predictive biomarkers and baseline characteristics

HO.27 **Deogratius Ssemwanga**, MRC-UVRI AIDS, Uganda: HIV-1 multiple infection and disease progression in a cohort of female sex workers in Uganda

HO.28 **Thato Iketleng**, BHP, Botswana: Plasma cytokine levels in chronic asymptomatic HIV-1 subtype C infection as an indicator of disease progression in Botswana: a retrospective case control study

HO.29 **Mary Mwaura**, ICHR, Kenya: The need for multipurpose prevention technologies targeting HIV and common reproductive tract infections: data from the Microbicide Safety Biomarkers study

HO.30 **Ivete Meque**, UCM, Mozambique: Prevalence, incidence and determinants of Herpes simplex virus type 2 infection among HIV-seronegative

women at high risk of HIV infection: a prospective study in Beira, Mozambique

HO.31 **Motswedi Anderson**, BHP, Botswana: Molecular characterisation of hepatitis B virus in HIV-coinfected patients in Botswana

HO.32 **Lerato Magosi**, BHP, Botswana: Toll-like receptor 4 polymorphisms in Botswana and impact on susceptibility to Kaposi's sarcoma in HIV-1 subtype C-infected patients

HO.33 **Bernard Ngowi**, NIMR, Tanzania: Screening for cryptococcal meningitis in patients with advanced HIV infection: the role of serum cryptococcal antigen test

Tuberculosis

TO.01 **Martin Boeree**, Radboud University Nijmegen, The Netherlands: What is the 'right' dose of rifampin?

TO.02 **Amina Jindani**, St. George's, University of London, United Kingdom: High dose rifapentine with a quinolone for treatment of pulmonary tuberculosis: the RIFAQUIN trial

TO.03 **Eleni Aklillu**, KI, Sweden: Optimisation of TB-HIV co-treatment in sub-Saharan Africa: no need to increase efavirenz dose during concomitant rifampicin-based antituberculosis therapy in HIV patients

TO.04 **Michael Hoelscher**, University of Munich (LMU), Germany: Challenges of and perspectives on development and evaluations of new tuberculosis drug regimens

TO.05 **Norbert Heinrich**, University of Munich (LMU), Germany: Results for SQ109, a new antituberculosis drug candidate, from a fourteen-day early bactericidal activity study

TO.06 **Charles Mtabho**, KCRI, Tanzania: The effect of diabetes mellitus on the pharmacokinetics of tuberculosis drugs in Tanzanian patients

TO.07 **Yolandy Lemmer**, CSIR, South Africa: Providing an address for delivery of nanoencapsulated tuberculosis drugs

TO.08 **Prisca Rabuogi**, KEMRI/CDC, Kenya: Evaluation of tuberculosis treatment outcomes in an infant tuberculosis incidence study in western Kenya

TO.09 **Ingrid Kromann**, SSI, Denmark: Clinical development of tuberculosis subunit vaccine H1IC

TO.10 **Michele Tameris**, SATVI, South Africa: Phase II safety and immunogenicity study of Aeras-402 in BCG-vaccinated, HIV-uninfected infants

TO.11 **Birahim P. Ndiaye**, Laboratoire de Bactériologie et Virologie, Senegal: Incidence of tuberculosis among a cohort of HIV-positive adults enrolled in a TB vaccine clinical trial in Senegal

TO.12 **Novel N. Chegou**, Stellenbosch University, South Africa: Utility of *Mycobacterium tuberculosis*-specific host cytokine signatures in whole blood culture supernatants in the diagnosis of tuberculosis disease

TO.13 **Klaus Reither**, Swiss TPH, Switzerland: Evaluation of new and emerging diagnostics for childhood tuberculosis in high-burden countries: update from the TB CHILD project

TO.14 **Grant Theron**, University of Cape Town, South Africa: Xpert MTB/RIF assay for the diagnosis of tuberculosis using non-sputum samples in a HIV-prevalent setting

TO.15 **Sokoine Kivuyo**, NIMR Muhimbili, Tanzania: Diagnosing tuberculosis in advanced HIV infection in Africa: the role of the Xpert MTB/RIF assay

TO.16 **Abigail Ayorinde**, MRC, The Gambia: Contribution of the Xpert MTB/RIF assay to the diagnosis of pulmonary tuberculosis in a West African childhood TB clinic

TO.17 **Willy Ssengooba**, Makerere University, Uganda: Comparative effectiveness of Xpert MTB/RIF assay when used as add-on test to smear microscopy for diagnosis of pulmonary tuberculosis among HIV-infected Ugandan adults

TO.18 **Boitumelo Fanampe**, University of Cape Town, South Africa: Development of an aptamer to a Th1 cytokine

TO.19 **Patrick Kobina** Arthur, University of Ghana: Analysis of anti-mycobacterial compounds produced by marine endophytic fungi

TO.20 **Bamidele Iwalokun**, NIMR, Nigeria: Association between leptin receptor gene (Leprgln233arg) polymorphism and tuberculosis relapse in Nigerian patients

TO.21 **Veronique Penlap Beng**, University of Yaounde 1, Cameroon: Insight of the genetic variability of *Mycobacterium tuberculosis* complex and drug resistance in Yaounde, Cameroon

TO.22 **Fredrick Lutwama**, Makerere University, Uganda: Distinct T cell responses when Bacillus Calmette Guerin is delayed from birth to six weeks of age in Ugandan infants

TO.23 **Niaina Rakotosamimanana**, Institut Pasteur de Madagascar: Peripheral blood TNF-α-dependent apoptotic genes expression and white blood cell count to characterise the tuberculosis clinical status of individuals in a high-burden setting

TO.24 **John Hongo**, KEMRI-CDC Kenya: Experiences in using real-time electronic and paper-based data capturing methods among studies conducted by the tuberculosis research branch, KEMRI-CDC programme in western Kenya

TO.25 **Barbara Burmen**, KEMRI-CDC Kenya: Prevalence of non-tuberculous mycobacteria in HIV-infected patients, Nyanza province, Kenya

TO.26 **Peter Onyango**, KEMRI-CDC Kenya: Experiences in implementing a study comparing post-mortem and verbal autopsy for measuring tuberculosis mortality in Kenya

TO.27 **Toyin Togun**, MRC, The Gambia: Assessing responses to tuberculosis treatment using a simple clinical scoring system: data from the tuberculosis case-contact cohort in The Gambia

TO.28 **Tutty Isatou Faal-Jawara**, MRC, The Gambia: Sequencing of variable T cell epitopes of *Mycobacterium tuberculosis* from confirmed tuberculosis cases in The Gambia

Malaria

MO.01 **Michael Theisen**, SSI, Denmark and Benjamin Mordmüller, ITM Tübingen, Germany: Phase IIb efficacy trial of the malaria blood stage vaccine candidate GMZ2

MO.02 **Seif Shekalaqhe**, IHI, Tanzania: Speeding up the development of malaria vaccines: the example of P27A, bridging phase Ia and Ib

MO.03 **Bernhards Ogutu**, KEMRI-Walter Reed, Kenya: Controlled human malaria infections and irradiated whole sporozoite vaccine evaluation in Africa

MO.04 **Peter G. Kremsner**, ITM Tübingen, Germany: A simplified artesunate regimen for severe malaria in children

MO.05 **Abdoulaye Djimdé**, MRTC, University of Bamako, Mali: Safety of artesunate-pyronaridine in the repetitive treatment of uncomplicated malaria in sub-Saharan Africa

MO.06 **Issaka Zongo**, IRSS, Burkina Faso: Efficacy of dihydroartemisinin-piperaquine in the treatment of uncomplicated *P. falciparum* malaria in African patients and day 7 plasma piperaquine concentration

MO.07 **Sidikiba Sidibe**, CNFRSR, Guinea: Therapeutic efficacy of artesunate-amodiaquine combination in the treatment of uncomplicated malaria at Mafèrinyah, Republic of Guinea

MO.08 **Alfred B. Tiono**, CNRFP, Burkina Faso: Impact of community screening and treatment of asymptomatic carriers of *Plasmodium falciparum* with artemether-lumefantrine on asymptomatic and gametocyte carriage: a 12-month, cluster-randomised study

MO.09 **Alfred B. Tiono**, CNRFP, Burkina Faso: Treatment of asymptomatic carriers of *Plasmodium falciparum* with artemether–lumefantrine: impact on the prevalence of anaemia

MO.10 **Nicola K. Viebig**, EVI, Germany: The Malaria Vectored Vaccines Consortium (MVVC): integrating capacity building and networking in the design and conduct of clinical trials in East and West Africa

MO.11 **Nébié Issa Ouédraogo**, CNRFP, Burkina Faso: Assessing chimpanzee adenovirus serotype ChAd63 neutralising antibodies prior to the implementation of a candidate malaria vaccine regimen based on viral vectors

MO.12 **Alfred B. Tiono**, CNRFP, Burkina Faso: Safety and immunogenicity of heterologous prime-boost immunisation with candidate vaccines ChAd63 ME-TRAP and MVA ME-TRAP in healthy Burkinabè children aged 5–17 months

MO.13 **Victorine Mensah**, University Cheikh Anta Diop, Senegal: Efficacy study of ChAd63-MVA ME-TRAP prime-boost vaccination against *Plasmodium falciparum* infection in healthy adults in Senegal

MO.14 **Thomas Egwang**, Med Biotech Laboratories, Uganda: Maternal immunisation protects mice pups against malaria

MO.15 **Raquel González**, CRESIB, Spain: Efficacy and safety of mefloquine as malaria intermittent preventive treatment in pregnancy: results from a multicentre randomised clinical trial

MO.16 **Raquel González**, CRESIB, Spain: Efficacy and safety of mefloquine as malaria intermittent preventive treatment in pregnancy in HIV-infected women receiving daily cotrimoxazole prophylaxis

MO.17 **Michael Ramharter**, CERMEL, Gabon: Rich and population pharmacokinetics of mefloquine intermittent preventive treatment against malaria in pregnant women in Gabon

MO.18 **Feiko ter Kuile**, LSTM, United Kingdom and KEMRI, Kisumu, Kenya: Impact of sulphadoxine-pyrimethamine resistance on the effectiveness of Intermittent Preventive Therapy for malaria in pregnancy (IPTp) in Africa: A systematic review and meta-analysis

MO.19 **Harry Tagbor**, LSHTM, United Kingdom: A trial of intermittent screening and treatment as an alternative to intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria in pregnancy

MO.20 **Kassoum Kayentao**, MRTC, University of Bamako, Mali: Intermittent preventive therapy for malaria in pregnancy using 2 vs 3 more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: a systematic review

MO.21 **Jean Louis Ndiaye**, University Cheikh Anta Diop, Senegal: Effectiveness of seasonal malaria chemoprevention combined with community case management for malaria in southern Senegal: a cluster-randomised trial

MO.22 **José Francisco Fernandes**, Albert Schweitzer Hospital, Lambaréné, Gabon: Fosmidomycin as an antimalarial drug: review of clinical trials

MO.23 **Rakiswendé Serge Yerbanga**, IRSS-DRO, Burkina Faso: Artesunate *in vivo* activity on *Plasmodium falciparum* forms in the mosquito *Anopheles coluzzii*

MO.24 **Ghyslain Mombo-Ngoma**, CERMEL, Gabon: Efficacy of mefloquine intermittent preventive treatment in pregnancy against *Schistosoma haematobium* infection in Gabon: a randomised controlled clinical trial

MO.25 **Peter Kimbowa**, Save A Life Foundation, Uganda: Effect of antiretroviral therapy on malaria parasitaemia and clinical episodes among HIV-infected adults in rural Uganda, 2009: a prospective population-based cohort study

MO.26 **Philippe Guerin**, WWARN: Investigation of sampling designs for accurate estimation of parasite clearance in the context of artemisinin resistance

MO.27 **Issaka Sagara**, MRTC, University of Bamako, Mali: Modelling recurrent events: comparison of statistical models with continuous and discontinuous risk intervals on repeated malaria episodes data

MO.28 **Alphonse Ouédraogo**, CNRFP, Burkina Faso: Pyrogenic threshold for malaria disease definition in an endemic area of Burkina Faso

MO.29 **Amidou Diarra**, CNRFP, Burkina Faso: Seasonal variation and clinical protection of antibodies against a panel of malaria antigens in children under five years of age in Burkina Faso

MO.30 **Guillaume S. Sanou**, CNRFP, Burkina Faso: Assessing regulatory T cells in children with severe malaria in Burkina Faso

MO.31 **Larissa Aurore Tobol Bouyoukou Hounkpatin**, CERMEL, Gabon: Reduced

antibody responses against *Plasmodium falciparum* vaccine candidate antigens in the presence of *Trichuris trichiura*

MO.32 **Maria Rebelo**, CERMEL, Gabon: Haemozoin detection assay: a novel ex vivo assay to detect antimalarial drug resistance

Cross-cutting

CO.01 **Elizabeth Pienaar**, MRC, South Africa: The Pan African Clinical Trials Registry (PACTR) five years later: where are we now?

CO.02 **Boitumelo Mokagtla-Moipolai**, COHRED, Botswana: Mapping African research ethics review and medicines regulatory capacity: the MARC project

CO.03 **Carel IJsselmuiden**, COHRED, Switzerland: The 'Research for Health and Innovation Organiser (RHINNO)' for ethics review

CO.04 **Maxime K. Drabo**, IRSS/Centre Muraz, Burkina Faso: Impact of clinical trials on the quality of health care services in Burkina Faso: perception of community and health staff in Nanoro and Dafra districts

CO.05 **Elisabeth Stantley-Batchilly**, MRC, The Gambia: Factors influencing the recruitment of participants for randomised clinical trials in Africa: an observational study in The Gambia

CO.06 **Elizabeth Ayuo**, KEMRI-CDC, Kenya: A pragmatic and innovative strategy to improve quality of clinical trials in East Africa: update from the reciprocal monitoring scheme

CO.07 **Daniel Bauer**, University of Munich (LMU), Germany: Monitoring and evaluation of health research capacity development activities: development of tools and instruments using the example of the Fozivudine in Africa Trials Initiative

CO.08 **Ghiorghis Belai**, Family Health International, Kenya: Implementation challenges of the WANECAM study: a monitor's perspective

CO.09 **Josephine Wanyenze**, MRC-UVRI, Uganda: HIV and *Schistosoma mansoni* coinfections among adults in fishing communities along Lake Victoria, Uganda

CO.10 **Marguerite Massinga** Loembé, CERMEL, Gabon: Detangling immune interactions between schistosomiasis and malaria in coinfected individuals

CO.11 **Annemieke Geluk**, LUMC, The Netherlands: Field evaluation of an up-converting phosphor-lateral flow assay for detection of cellular and humoral immunity against mycobacteria

CO.12 **Clovis Seumen**, University of Yaounde I, Cameroon: Effect of concurrent gastrointestinal nematode infections on antimalarial total IgG in school-age children in Mfou

CO.13 **Lyn Horn and Mariana Kruger**, Stellenbosch University, South Africa: Research Ethics in Africa: a resource for Research Ethics Committees

CO.14 **Godfrey B. Tangwa**, CAMBIN, Cameroon: Small is beautiful: demystifying and simplifying SOPs: the model of the Ethics Review and Consultancy Committee of the Cameroon Bioethics Initiative

CO.15 **Martin Matu**, ECSA-HC, Tanzania: Status of research ethics bodies in East, Central and Southern Africa Health Community region

CO.16 **Modest Mulenga**, TDRC Ndola, Zambia: Engaging policy makers in clinical trials to accelerate policy formulation in sub-Saharan Africa

CO.17 **Mary Kasule**, University of Botswana, Botswana: Building research capacity in Botswana: a randomised trial comparing training methodologies in the Botswana ethics training initiative

CO.18 **Charles N. Fokunang**, University of Bamenda, Cameroon: Ethical implications in clinical genetic and genomic research for the emerging countries

CO.19 **Kevin Fisher**, AVAC, United States of America: Global implementation of good participatory practice guidelines for biomedical HIV prevention and tuberculosis research: charting progress and setting milestones

CO.20 **Dan Kajungu**, Catholic University of Leuven, Belgium/Uganda: Paediatric pharmacovigilance: data mining algorithms for signal detection in phase IIIb clinical trials safety datasets from seven African countries

CO.21 **Photini Kiepiela**, MRC (HPRU), South Africa: Experiences in using e-learning to improve the capacity of African scientists in South Africa

CO.22 **Peninah Menza**, DNDi, Kenya: EACCR: coordination of the malaria node activities

CO.23 **Dembo Kanteh**, MRC, The Gambia: Towards strengthening the West African network of excellence for tuberculosis, HIV/AIDS and malaria: WANETAM Plus

CO.24 **Hulda Swai**, CSIR, South Africa: The Pan-African Centre of Excellence in Nanomedicine: research and training on poverty-related diseases

CO.25 **Christine Wasunna**, KEMRI, Kenya: Establishment of a centralised clinical trials register in Kenya: a model for knowledge sharing and exchange across two institutions

CO.26 **Joseph Gaie**, University of Botswana: Opportunities and challenges: sharing experiences of IRB/REC members in a developing country

CO.27 **Kolawole Oyedeji**, NIMR, Nigeria: Capacity building and evaluation of post training operational capacities of three ethics review committees in Nigeria: best practice

CO.28 **Galekgatlhe Bailey Balekang**, Health Research Division, Ministry of Health, Botswana: Challenges of establishing and running Community Advisory Boards in Botswana

CO.29 **Muhammed Afolabi**, MRC, The Gambia: Digitised audio questionnaire for assessment of informed consent comprehension in a low literacy African research population: development and psychometric evaluation

CO.30 **Palmer Netongo**, ISHReCA, Cameroon: Towards an ISHReCA manifesto to guide researchers as they engage in health research partnerships

Colophon

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European & Developing Countries
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Photo acknowledgement

Page 10: Laboratory staff at the KAVI-Kenyatta National Hospital inNairobi, Kenya, part of the HIV-CORE004 project (led by Prof. Tomáš Hanke)
Page 22: Medical staff and volunteer at the Kibong'oto National TB Hospital in Tanzania, part of the PanACEA-MAMS project (led by Prof. Martin Boeree, Prof. Michael Hoelscher and Prof. Stephen Gillespie)
Page 36: Researcher at the Regional Hospital of Banfora, Burkina Faso, part of the WANECAM project (led by Prof. Abdoulaye Djimdé)
Page 50: Residents of the Kangemi Community in Kenya receive information about AIDS vaccine research
Page 66: Prof. Graeme Meintjes and the PredART project team meet at the Ubuntu Clinic in Khayelitsha, South Africa
Page 71: Participants at the plenary session on Monday 30 June 2014
Page 73: Participants at the exhibition area

The Partnership journey: New horizon for better health