EDCTP

European & Developing Countries
Clinical Trials Partnership

Diarrhoeal diseases

EDCTP stakeholder meeting, 5 July 2016

EDCTP

The European & Developing Countries Clinical Trials Partnership (EDCTP) is a public-public partnership of institutions mandated by European and sub-Saharan African countries, and supported by the European Union. It is dedicated to combating poverty-related diseases (PRDs).

It was created in 2003 as a European response to the global health crisis caused by the main PRDs tuberculosis, HIV/AIDS, and malaria. The mission of EDCTP is to reduce poverty in sub-Saharan Africa through improved health by funding collaborative research to enhance research capacity and accelerate the clinical development of new or improved medical interventions against PRDs.

The second 10-year programme of EDCTP (EDCTP2) was launched in December 2014 and is implemented by the EDCTP Association as part of the EU Framework Programme for Research and Innovation, Horizon 2020. EDCTP2 supports all phases of clinical trials (with a focus on phases II and III) as well as advanced testing and field validation of new diagnostic tools and health services optimisation research. These activities are integrated with and supported by capacity development for clinical trials and closely related research in sub-Saharan Africa.

In addition to HIV, TB and malaria, the scope of EDCTP2 now includes neglected infectious diseases (NIDs), diarrhoeal diseases, lower respiratory tract infections, and emerging or re-emerging infectious diseases of particular relevance for Africa, such as Ebola and yellow fever.

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List of acronyms

EDCTP	European & Developing Countries Clinical Trials Partnership
Gates Foundation	Bill & Melinda Gates Foundation
GEMS	Global Enteric Multicenter Study
MAL-ED	Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development project
NID	neglected infectious disease
PDP	product development partnership
PRD	poverty-related disease
WHO	World Health Organization

EXECUTIVE SUMMARY

The EDCTP stakeholder meeting on diarrhoeal diseases was held in Amsterdam, The Netherlands, on 5 July 2016. As diarrhoeal diseases are a new addition to the original scope of EDCTP, the stakeholder meeting on diarrhoeal diseases was organised to consult a broader range of experts in order to inform EDCTP's strategic research agenda and future work plans related to this disease area. The meeting brought together different stakeholders working in the disease area. This report presents proceedings of the meeting, along with recommendations on focus areas for activities and calls for proposals.

The objectives of the meeting were to:

- review the research landscape, including the key clinical research questions and barriers to progress in sub-Saharan Africa;
- discuss the available interventions and products in development with the major partners working in this field;
- reach out to stakeholders involved in the disease area to collaborate with in the execution of future EDCTP activities;
- identify priority areas for EDCTP in terms of disease, research and intervention priorities for both the short and the medium term.

The meeting consisted of a keynote address and two presentations on diarrhoeal diseases, each followed by a discussion. In the afternoon, the meeting divided into three focus group discussions on a particular aspect of the disease area. At the end of the discussions, the focus groups reported their recommendations back to the meeting.

Appended to the report is a list of diarrhoeal disease-related priorities identified at the meeting and subsequently compiled and categorized by EDCTP staff into four priority areas, to be put forward as recommendations, where Priority A covers areas of research or capacity of utmost importance for the short term, Priorities B and C include research priorities for the medium (Priority B) and long term (Priority C), and Priority D lists areas of research that do not need to be addressed by EDCTP.

Urgent needs identified under **Priority A** include the clinical development of vaccines for enterotoxigenic *Escherichia coli* and *Shigella*, improving laboratory capacity for diarrhoeal diseases; securing of good sites for epidemiological studies; and better drug therapies for *Cryptosporidium*. An example of a medium-term priority categorized as **Priority B** is point-of-care diagnostics for diarrhoeal pathogens.

PROCEEDINGS

Introduction

Diarrhoeal diseases are a new addition to the original scope of EDCTP. The stakeholder meeting on 5 July 2016 was organised to consult experts, in order to inform EDCTP's strategy and future work plans for this disease area. The meeting brought together different stakeholders working in the disease area, such as representatives from academic and research institutions, funding agencies, product development partnerships (PDPs) and others. The meeting on diarrhoeal diseases was attended by 28 invited participants.

EDCTP regularly holds thematic stakeholder meetings. Previous stakeholder meetings have been on malaria, HIV, tuberculosis and other mycobacterial infections, NIDs, ethics & regulatory affairs, and capacity development.

Opening

The meeting was opened by EDCTP's Executive Director **Michael Makanga**, who gave a background to EDCTP and its programme, outlining especially its method and types of funding to support collaborative research activities in sub-Saharan Africa through calls for proposals. He told the audience that this was the first stakeholder meeting in EDCTP's second programme. Under its second programme, EDCTP was expanding its scope, two new areas being diarrhoeal and respiratory diseases. The first step in approaching these new areas was to talk to specialists in the field to establish needs and gaps and maximise value addition and return of investments. The purpose of the stakeholder's meeting was to seek advice from various stakeholders, and obtain ideas and recommendations that would contribute to shaping the programme's strategic research agenda. He was hopeful that this meeting would make valuable recommendations that could be fed back to EDCTP's member states.

Outlining the meeting objectives and expected outcomes of the meeting, he said the general objectives of the meeting were to:

- review the research landscape including key clinical research questions and barriers to progress in sub-Saharan Africa;
- discuss available interventions and products with major partners working in the field;
- reach out to stakeholders involved in the disease area to collaborate with in the execution of future EDCTP activities; and
- identify priority areas for EDCTP in terms of disease, research and intervention priorities for both the short and the medium term.

In discussing the possibilities for development of EDCTP's strategy and priorities, the meeting should consider the following aspects:

- the disease burden and need for appropriate interventions;
- gaps identified from a progressive review of the product development landscape;
- emerging opportunities for EDCTP to add best value;
- a balance between immediate, medium and long-term priorities and clinical trial phases.

Dr Makanga said that diarrhoeal diseases had been flagged with high burden of disease and high mortality, making them a health priority. He was hopeful that the meeting would identify immediate, medium and long-term intervention priorities. He reminded the meeting, however, that resources were limited and that EDCTP intended to move into this new area in a guided manner.

The chairs of the meeting were **Dr Jeffrey Mphahlele**, of the South African Medical Research Council, and **Dr Philippe Sansonetti** of Institut Pasteur, France. Dr Sansonetti informed the meeting that mortality from diarrhoeal diseases had significantly decreased in recent years due to economic development and improved education in the region. There was consequently somewhat less of a concern with mortality; disease-related morbidity, however, was a cause for concern. Repeated diarrhoeal episodes in young children could lead to malnutrition and subsequent detrimental effects on development. The most cost-effective approach to controlling diarrhoeal diseases was through vaccination.

However, he cautioned the meeting to: (a) bear in mind that initiatives over the years had suffered from a diversity of approach and strategy. In this complex landscape it was important to be as focused as possible and to simplify by pinpointing a few specific priorities; (b) consider the vaccine candidates currently available – the presentation, later, by Dr Richard Walker would inform the meeting of vaccine candidates and products in the pipeline – and (c) be mindful of the strong need across sub-Saharan Africa for capacity building in this field. Numerous successes to date included the rotavirus initiative in several sub-Saharan African countries, bringing the optimistic message that "things can be done".

Therefore, the aim of the meeting was to make a few, clear recommendations on areas that could be addressed in collaboration with other institutions, since as this was a broad field, EDCTP would want to work with others to be more effective.
Reiterating that it was not possible to address all challenges and fill all gaps, **Dr Mphahlele** reminded the meeting of EDCTP's published criteria for prioritisation and emphasised the need to identify a few specific gaps.

Keynote address

The keynote address titled 'Diarrhoeal diseases – overview of current disease burden, pathogens and diagnostics in sub-Saharan Africa' was delivered by **Dr Myron M. Levine** of the University of Maryland School of Medicine, USA. Dr Levine introduced his topic by stating that out of the 35 countries with the highest under-5 mortality, 32 were in sub-Saharan Africa. Further, that West Africa had the highest childhood mortality anywhere in the world. Pneumonia and diarrhoeal diseases were the two main causes of death in 1–59-month-olds. The main culprit for such a high prevalence of diarrhoeal diseases in developing countries was faecal contamination of water and hands. He drew on the analogy of New York City in the early 1900s, which, with crowded housing and lack of sanitation, had had similar infant mortality rates. A few decisive interventions had led to a marked decrease in diseases. This served to illustrate that a few well-placed and timely interventions could go a long way towards redressing the problem. Today, Africa was the continent with the fastest rate of urbanisation, which made the need for accelerated, specific interventions (clean water; good sanitation) more urgent.

Next describing the clinical syndromes of diarrhoeal diseases, Dr Levine stated that even "simple" gastroenteritis could be lethal in young children and that persistent diarrhoea beyond 14 days had very high mortality and severe nutritional consequences. The findings of the Gates Foundation-supported Global Enteric Multicenter Study (GEMS) in seven African and South Asian sites illustrated that a limited number of aetiological agents may be responsible for a large fraction of moderate to severe diarrhoea; moreover, that aetiological agents differed by age group. Hence, analysis of GEMS data for under-5 diarrhoeal diseases was stratified into three age groups, 0–11, 12–23 and 24–59 months. The four main

pathogens in the two younger age strata were rotavirus, *Shigella*, Enterotoxic *E. coli* producing heat-stable toxins and *Cryptosporidium*. In 24–50-month-olds, cholera took the place of *Cryptosporidium*. The study also found much more mortality associated with diarrhoeal diseases than baseline data had led to expect, as 33% of deaths from moderate to severe diarrhoea occurred >21 days after enrolment. Furthermore, moderate to severe diarrhoea had a negative effect on nutritional status in young children, leading to stunting and short- and long-term health effects.

Dr Levine closed with two recommendations: it was a matter of high priority to (a) accelerate enterotoxigenic *E. coli* and *Shigella* vaccine development; and (b) diminish the nutritional consequences of *Cryptosporidium* infection. He also said that the GEMS study illustrated the importance of partnerships and collaborations.

Discussion and questions: One comment was that of the four main pathogens involved, was there an association with the immunological status, specifically the HIV status, of the children?
Two of the sub-Saharan African sites had high HIV prevalence. At the Kenyan site, Cryptosporidium stood out. On the other hand, the Gambian site had low HIV prevalence/exposure, and the same pathogen, Cryptosporidium, was found even in non-HIV cases. Cryptosporidium infection in the second year of life could lead to mortality or stunting with long-term health effects.
Another comment was that the prevalence of *Shigella* was underestimated. It was becoming increasingly difficult to diagnose *Shigella* from fluid culture. The question was posed whether it was time to use molecular methods in some of these environments, especially for *Shigella*?
The presenter agreed that the non-dysentery Shigella burden on stunting and mortality was high. With respect to a molecular method, he said a general test would have to be used, and the methodology might not be appropriate for all pathogens. Regarding Shigella control, the WHO were currently testing a short course of antibiotics.

A participant commented that for many pathogens, e.g. *Cryptosporidium*, the incidence was higher in the second year of life, when maternal antibodies disappeared. In the first year, enteropathogenic *E. coli* affected non-breastfed infants. It was suggested that one area to be looked into was interventions with micronutrients. Delegates also wanted to know the cause of diarrhoea among the children in the GEMS study. Was there interaction of pathogens? In animal models, several pathogens worked together to exacerbate disease.

Presentations

'Vaccines for diarrhoeal diseases: prioritisation of candidates' was the topic of a presentation by **Dr Richard Walker** from PATH, USA. Accomplishments in vaccine development over the last 10 years had been due to increased funding and, importantly, to collaboration between donors and medical institutions. The point had been reached where vaccine candidates were entering advanced clinical trials. At present, there were multiple clinical trials running concurrently – many of them coordinated efforts – and that EDCTP was taking an interest in this important area was an excellent sign.

Despite significant recent advances in diarrhoeal disease prevention, notably in rotavirus vaccination, there were, however, still no licensed vaccines for enterotoxigenic *E. coli* or *Shigella* – and they were desperately needed. Dr Walker described several vaccine candidates for enterotoxigenic *E. coli* and *Shigella* (cellular and subunit, for use in single or combination strategies) currently at various stages of development and trialling. Work was needed to develop more practical paediatric vaccine presentations for use in endemic settings. Vaccine presentation was one area where he suggested possible EDCTP involvement. Above all, his message was that these vaccines needed to be introduced onto the market as a matter of urgency.

Discussion and questions: Questions and comments following the presentation related to conjugate vaccines. One participant said that not all ages responded equally. The opinion was that we did not need new candidates when we already had so many. In developing vaccines, there should be more concern about optimisation of candidates. Another comment related to the seasonality of pathogens. Were vaccines developed for epidemics or sporadic incidence?

- *Vaccines were protective against endemic diseases. The idea had been to immunise children very early but a booster would be available. Outbreaks had not really been considered.*

One question was about optimising packaging and presentation of vaccines. Had the acceptability of different types of presentation been field-tested? Was vaccines delivery part of PATH's job?

- *The response was that EDCTP might consider playing a role in delivery and presentation. Practicality of use was important. PATH had only begun looking at that.*

A final comment in this section pertained to the compatibility of vaccines and an interaction between the discussed vaccines and rotavirus.

The final presentation was on 'Implementation research: optimising vaccine effectiveness'. Beginning on a positive note, presenter **Dr George Armah** of Noguchi Memorial Institute for Medical Research, Ghana, reported significant successes since 2000 in reducing mortality from rotavirus, especially in Asia. Two vaccines, ROTARIX® (GSK) and RotaTeq® (Merck), were recommended for use by WHO after having been trialled in South Africa and Malawi (Rotarix) and Mali, Ghana, Kenya, Bangladesh and Vietnam (RotaTeq). Children 6–18 months old were at greatest risk of rotavirus infection.

Presenting findings from a Ghanaian post-vaccination immunogenicity trial, Dr Armah reported a decline in efficacy in the second compared with the first year of life. The study had shown a significant difference in microbiota between infants with and without rotavirus immune response, and suggested that diminished vaccine effectiveness in children in developing countries may be microbiota-related. Microbiomes affect immunity to enteropathogens and immune response to vaccines; modulating the intestinal microbiota may therefore improve rotavirus vaccine immunogenicity. The question arising was whether additional doses of rotavirus vaccine might improve immune response to vaccination? Findings of the trial suggested that three doses including a delayed dose had improved effectiveness in a high-disease burden population where the current two-dose schedule provided only moderate protection.

In conclusion, Dr Armah listed several factors for consideration:

- multiple pathogens were associated with severe childhood diarrhoea in West Africa; >33% were co-infections, most commonly involving rotavirus, adenoviruses, enteroagregative *E. coli*, enteropathogenic *E. coli* and *Shigella*;
- co-infections may impact the efficacy of rotavirus vaccination;
- chronic exposure to enteropathogens may lead to paediatric environmental enteropathy (PEE), which may cause malnutrition and stunting, oral vaccine failure, and impaired cognitive development
- a wide diversity in rotavirus strain types has been seen in African countries, which could adversely affect vaccine efficacy and presents several challenges and recommendations, including:
  - the financial sustainability of immunisation programmes;
  - the need for data, including longitudinal data, on incidence of Shigellosis, and current levels and trends in diarrhoea incidence and mortality;
  - the suggestion to expand the African Rotavirus Surveillance Network to investigate other pathogens using existing trial sites;
  - the need to evaluate different control strategies and make projections;
  - the need to consider timing, safety and immune response of a booster dose co-administered with other vaccinations;
  - the need to develop new molecular tools to address new evolving strains.

Discussion and questions: One participant commended the Ghanaian study for exploring age specificity, but remarked on the difficulty in developing age-specific delivery. Another commented on the efficacy of the rotavirus vaccine falling off in the second year of life, adding that the vaccine was obtaining better results in "first world" and transitional countries.
The meeting responded that in another decade the same rotavirus vaccines would behave differently. Immunisation coverage gave indirect protection in more developed countries. The rotavirus vaccination had only been started recently, so it was still early for a full evaluation. The recommendation was to look for trends, including assessment of vaccine effectiveness in countries transitioning, and investigate safety issues in giving a third dose.

Several issues emerging from the evidence were summarised by **Dr Makanga** as in need of attention, including the issue of co-infection; the diversity in strains and need to prioritise pathogens; and the microbiota issue. Furthermore, a delayed dose / age-specific dose should be looked at and optimised. Also emerging from the evidence was the need for capacity development, which might be of interest for EDCTP. Dr Makanga said he was hoping that the afternoon's focus group discussion would consolidate ideas for EDCTP involvement.

Focus group discussions and recommendations

The afternoon's session was devoted to focus group discussion. The meeting was divided into three focus groups, each assigned with a topic. Groups discussed:
1. Opportunities for testing products
2. Gaps in the pipeline for all clinical trial phases and implementation research
3. Capacity development priorities.

During a final discussion session, the focus groups reported their recommendations back to the meeting. The aim of the session was for the groups, and the meeting at large, to come up with recommendations to be passed on to the EDCTP Scientific Advisory Committee for discussion and approval.

1. Opportunities for testing products

Focus group 1 identified *Shigella* and enterotoxigenic *E. coli* as clear priorities. Recommendations were to:
- conduct earlier phase (≤II) trials in (adult) African populations where the need for enterotoxigenic *E. coli* and *Shigella* vaccines is greater than in other parts of the world;
- perform comparative studies in multiple (epidemiologically well defined) sub-Saharan African sites using standardised assays (diagnostics including serotyping);
- give emphasis to development of combination vaccines (At present, some of the cellular combination vaccines for enterotoxigenic *E. coli* and *Shigella* were nearest to enter advanced field trials compared with subunit candidates.).

Other areas discussed were:
- Cryptosporidium (focus on drugs and diagnostics; vaccines not being considered at the moment);
- Rotavirus (vaccines were not a priority at the moment; currently in phase IV).

Further recommendations concerned diagnostics, specifically the need for:
- Point-of-care diagnostic tests
- Sensitive assays for use in clinical trials
- Severity score definitions for enterotoxigenic *E. coli* and *Shigella*.

2. Gaps in the pipeline for all clinical trial phases and implementation research

Focus group 2 identified five priority disease areas, which were, in descending order of importance:

- Rotavirus
- *Shigella*
- enterotoxigenic *E. coli*
- *Cryptosporidium*
- Cholera.

The group suggested several priority topics:

- All diseases:
  - Point-of-care diagnostics
  - Delivery and presentation
  - Use of probiotics as an intervention.
- *Cryptosporidium*:
  - Clinical trial designs for evaluation of treatment (e.g. nitazoxanide) contributing to reduction of stunting.
- *Shigella*/enterotoxigenic *E. coli*:
  - Clinical trials accelerating development of promising phase II/III vaccine candidates (single or in combination) in the pipeline.
- Cholera:
  - Clinical trials on adaptation of existing vaccines traditionally developed for travellers; further developing single-dose practical formulations for phase II/III clinical trials for epidemic situations in rural settings.
- Other:
  - Phase I/II clinical trials to accelerate evaluation of any invasive non-typhoidal salmonella vaccines in sub-Saharan Africa.

3. Capacity development priorities

Group 3's recommendations concerned six areas for capacity development:

- Surveillance systems: establish/build on existing surveillance networks (with increased focus on bacterial and protozoan diarrhoeal diseases);
- Epidemiological data: meet needs for solid data collection (mortality, strain, serotype, and resistance data) across sub-Saharan Africa;
- Laboratory capacity: build on existing laboratories in existing EDCTP or rotavirus networks or establish new laboratories with capacities for diagnosing diarrhoeal diseases;
- Training: use trainer-of-trainer models to facilitate training on diarrhoeal diseases across sub-Saharan Africa (epidemiology and diagnostics);
- Collaboration across the region: enhance inter-project collaboration between Anglophone, Francophone and Lusophone-speaking African countries;
- Cross-cutting issues: meet support needs beyond medical and technological interventions to include hygiene, education, nutrition and behavioural change trials and sanitation.

Following presentation of each group's recommendations, the meeting queried whether the focus groups' recommendations covered areas that were already funded by other groups. A few final recommendations were added to those already listed:

- There is a need for immunomonitoring trials (These should be a natural component of the research, but there had been funding limitations. It would be more realistic to build immunology into vaccine trials.);

- Treatment with and resistance to existing drugs should be given attention (These are part of EDCTP's programme: investigating new drugs and improving existing drugs.);
- There is a need for universally recognised and accepted standards for assays. (Globally recognised, e.g. WHO, standards will inform decisions where multiple vaccines are available.).

In closing

The stakeholder meeting was concluded by **Michael Makanga**, who described the discussions as very constructive, providing EDCTP with extremely useful recommendations. The list was long: where to go from here?

As a first step, recommendations would be presented to the Scientific Advisory Committee for discussion and refinement. Furthermore, priorities would be categorised into immediate, medium and long-term (Appendix 1). These priorities and recommendations would be used to update our strategic research agenda and annual workplans. These recommendations would also be shared with member states. There would also be a call upon different funding institutions and agencies to look into partnerships and potential joint calls where there is shared interest.

Dr Makanga closed the meeting by thanking all participants, the Chairs, the speakers, the Secretariat and the organisers for a day of fruitful discussion. **Prof. Sansonetti** expressed his thanks and the hope that the recommendations from the meeting be put into action.

Appendix 1 - Priorities

Diarrhoeal diseases — Priorities for research and research capacity development

The following is a list of research and research capacity development priorities in diarrhoeal diseases that were identified at the stakeholder meeting, to be put forward as recommendations to EDCTP's Scientific Advisory Committee.

Priority indication

Priority A: Areas of research or capacity that provide information of utmost importance for the short term.
Priority B: Areas of research or research capacity for the medium term.
Priority C: Areas of research for the long term.
Priority D: Areas of research that do not have to be addressed by EDCTP.

	Topic	Description	Priority
1.	**Pathogens**	Diarrhoeal diseases are caused by a wide variety of pathogens, a number of which were identified in recent studies as important causes of diarrhoeal diseases in sub-Saharan Africa: • Rotavirus • *Shigella* • Enterotoxigenic *E. coli* (heat-stable and/or heat-labile toxins) • *Crypotosporidium* • Norovirus. Other pathogens of more local interest (but possibly of great importance in such settings) include adenovirus, cholera and others.	n/a
2.	**Disease profile**	Diarrhoeal diseases may cause different clinical symptoms including mild to severe diarrhoea, dysentery, fever, dehydration and others. Chronic infections may lead to malnutrition and effects on cognitive and physical development. Despite a decrease in mortality rates from diarrhoeal diseases, the incidence of infection in children remains high. There is a need for standardised clinical severity scores for some diseases such as *Shigella* and ETEC.	n/a
3.	**Epidemiology**	Although the GEMS and MAL-ED studies have been instrumental in understanding burden of diarrhoeal pathogens in selected sites in sub-Saharan Africa, in many places surveillance data on burden of diarrhoeal diseases and pathogens involved are not available and so any clinical trial will need robust collection of baseline data to assess burden.	Priority A/B; but best addressed as part of clinical trials/ studies

	Topic	Description	Priority
4.	**Pathogenesis/ host response**	Oral vaccine effectiveness of diarrhoeal diseases may be influenced by host genetic strain susceptibility, histo-blood group antigens, the gut microbiome (possibly resulting from chronic/ repeated diarrhoeal episodes) and co-infections. Additional research to better understand these factors is warranted.	Priority A/B
5.	**Immune response**	Detailed immunological studies may not be essential to discover new vaccines; still immunology is essential to improve vaccine performances. Key issues are: • Improving immunogenicity of parenteral vaccines in infants and improving the development of good mucosal responses upon parenteral immunization. • Immunology is also essential to define/optimize immuno-monitoring assays and correlates of protection (i.e. B cell memory); this will be difficult with oral vaccines, feasible for parenteral vaccines.	Priority A/B
6.	**Diagnosis and tracking**	Point-of-care diagnostics were identified as a need for key diarrhoeal pathogens. However, few point-of-care devices are currently in development and the burden of diarrhoeal pathogens in asymptomatic individuals makes this a challenge. There has been recent progress in molecular techniques (e.g. multiplexing, quantification). There is a need for robust field tests based upon these techniques. Another identified need is the development of sensitive and standardized diagnostic methods to be used in clinical trials and transfer of this knowledge to sub-Saharan African laboratories. This is best addressed as part of a clinical trial.	Priority B Priority A
7.	**Treatment**	Zinc and antibiotics are standard treatments. Besides the issue of antimicrobial resistance (not unique to diarrhoeal diseases) there is a need for better drug therapies for *Cryptosporidium*. The only licensed drug available is nitrozoxanide and a clinical trial to look at the effect of this drug on child development (stunting) was suggested. Research into better drugs for *Cryptosporidium* is needed, but there are few candidates in the pipeline at the moment (all pre-clinical).	Priority A/B

	Topic	Description	Priority
8.	**Prevention**	Vaccine candidates for enterotoxigenic *E. coli* and *Shigella* were discussed. A number of these candidates have undergone or soon will be undergoing Phase I/II testing in the North, but are only beginning to be tested in endemic settings. Once these (cellular) candidates are ready they should move into Phase II/III field trials in sub-Saharan Africa. Although a combination vaccine would be preferred, it is likely that individual components will be evaluated independently for part of their development.	Priority A,B,C (depending on when they are ready to move to endemic settings)
		The need to support a cholera epidemic vaccine for rural communities was also briefly discussed.	Priority B/C
		Support to vaccine candidates in clinical trials I/II for invasive non-typhoidal salmonella was also briefly discussed.	Priority B/C
		Rotavirus was considered less of a priority and existing vaccines are adequate at the moment. However, vaccine effectiveness needs continued monitoring to assure that vaccines cover strain diversity seen in sub-Saharan Africa.	Priority D
		Trials into improving effectiveness of existing rotavirus vaccines are warranted, such as research into benefit of an additional third booster dose or immunisation schedule.	Priority D
		Research into paediatric formulations of oral liquid vaccine candidates is warranted; this is best performed alongside clinical trials.	Priority B
		There is a need for standardized clinical severity scores for vaccine trials for enterotoxigenic *E. coli* and *Shigella*. This is best performed alongside clinical trials.	Priority A/B
		Maternal immunization to prevent infant episodes was mentioned but there are no candidates yet in the pipeline.	Priority D
9.	**Cultural aspects**	Not discussed and there seem to be few cultural issues associated with diarrhoeal diseases.	Priority D
10.	**Behavioural aspects**	Not discussed, yet most diarrhoeal diseases are related to sanitation and hygiene practices, so improvements in these conditions and practices remain key to prevention of these diseases.	Priority D

	Topic	Description	Priority
11.	**Implementation & evaluation of control measures**	Discussion was mainly around implementation and evaluation of rotavirus vaccine campaigns; however, these appear to be well monitored already.	Priority D
		Other areas that may be addressed under these evaluation criteria include community programmes to reduce child morbidity and mortality through the integrated community case management programme where diarrhoeal diseases are treated with zinc.	Priority D
12.	**Critical infrastructure needs**	Laboratory capacity for diarrhoeal diseases was identified as a major need; either through strengthening existing (reference) facilities or through creating new reference laboratories.	Priority A
		Improved sentinel/surveillance networks for diarrhoeal diseases within and across regions are warranted.	Priority D
		It is important to secure good sites for epidemiological studies as phase III trials will need these data to gain significance. This has to be done alongside the clinical trials themselves. Much capacity building and/or maintenance will be necessary.	Priority A
		In addition, the need for training of laboratory personnel in diagnostics and medical staff in prevention and treatment of diarrhoeal diseases was identified. Training can be done through a train-the-trainer model following cascade training (but this falls under health system strengthening activities as part of vaccine or surveillance programmes).	Priority D

Appendix 2 - Participants

Name	Institution	Country
Eleni Aklillu	Karolinska Institutet	Sweden
George Armah	Noguchi Memorial Institute for Medical Research	Ghana
Christian Burri	Swiss Tropical and Public Health Institute	Switzerland
Megan Carey	Bill & Melinda Gates Foundation	United States
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Haroon Saloojee	University of the Witwatersrand	South Africa
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