EDCTP

European & Developing Countries
Clinical Trials Partnership

Lower respiratory tract infections

EDCTP stakeholder meeting, 6 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

CRP	C-reactive protein
EDCTP	European & Developing Countries Clinical Trials Partnership
HIV	human immunodeficiency virus
LRTI	lower respiratory tract infection
NID	neglected infectious disease
PCR	polymerase chain reaction
PERCH	Pneumonia Etiology Research for Child Health study
PRD	poverty-related disease
TB	tuberculosis

EXECUTIVE SUMMARY

The EDCTP stakeholder meetings on lower respiratory tract infections (LRTIs) took place in Amsterdam, The Netherlands, on 6 July 2016. As LRTIs are a new addition to the original scope of EDCTP the stakeholder meeting was organised to consult experts in order to inform EDCTP's strategy and future work plans related to this disease area. The meeting brought together 31 different stakeholders working in the disease area, such as representatives from academic and research institutions, funding agencies, product development partnerships and others. 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 two keynote addresses and three presentations on respiratory tract infections, each followed by a discussion. In the afternoon, the meeting held a concluding discussion, during which priorities were identified and recommendations for action in the field of LRTIs were put forward.

Appended to the report is a list of LRTI-related priorities identified during 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 and long term, respectively, and Priority D lists areas of research that do not need to be addressed by EDCTP.

Urgent needs identified under **Priority A** include: portable, rapid point-of-care diagnostic tests for selection of patients for either antibiotics therapy or hospitalization; data on aetiology, severity and treatment response; and novel non-capsular antigen vaccines against pneumococcus. Some examples of medium-term needs categorized as **Priority B** are: pathogen-specific tests for detection of multiple pathogens; and data on long-term consequences of pneumonia.

PROCEEDINGS

Introduction

Lower respiratory tract infections (LRTIs) are a new addition to the original scope of EDCTP. The stakeholder meeting on 6 July 2016 was organised to consult experts in order to inform EDCTP's strategy and future work plans related to thise disease area. The meeting brought together 31 different stakeholders working in the disease area, such as representatives from academic and research institutions, funding agencies, product development partnerships and others.

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

Opening

The meeting was opened by EDCTP's Executive Director Michael Makanga, who told the gathering that this was the second stakeholder meeting in EDCTP's second programme. The first meeting, on diarrhoeal diseases, had taken place the previous day. Dr Makanga explained that under its second programme, EDCTP was expanding in scope, one new area being lower respiratory tract infections. The first step in approaching these new areas was to consult specialists in the field to get their expert opinions and thus maximise value addition and return on investment. The purpose of the stakeholder meeting was, therefore, 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 on LRTIs would make valuable recommendations that could be fed back to member states.

Outlining the 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, he said that the meeting should consider the following aspects:

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

Dr Makanga said that the high burden of disease and mortality of lower respiratory tract infections made LRTIs a health priority. He was hopeful that the meeting would identify immediate, medium- and long-term intervention priorities. He reminded participants, however, that resources were limited and that EDCTP intended to move into this new area in a guided manner.

The meeting chair, **Professor Jeremy Brown** from University College London, United Kingdom, observed that the stakeholders present were well placed to identify needs in LRTI interventions. Some of those present might have a specific interest and might want to develop partnerships with EDCTP along those lines. The day's presentations were aimed to fill in gaps on the topic but a contribution from all present was needed to get a full overview on LRTIs. Following each presentation there would be a discussion which was hoped to contribute to the outcome of the day's meeting and, ultimately, to inform policy.

Prof. Brown reminded the meeting that LRTIs could be looked at from a diagnostics perspective, with focus on the clinical syndrome, or alternatively from the pathogenic perspective, if the main goal was prevention and vaccination. With limited resources available in Africa, and with the current status of antimicrobial resistance in sub-Saharan Africa, a question of importance was whether to focus the resources on preventing infection – or instead to concentrate on more effectively diagnosing and treating existing infection.

Prof. Brown further informed the meeting that TB and influenza would not be part of the meeting's focus as they were covered by other initiatives, while TB has from EDCTP's inception been one of EDCTP's main foci.

Keynote addresses

A keynote address on advances against LRTIs in under-fives focusing on sub-Saharan Africa was delivered by **Professor Heather Zar** from the University of Cape Town, South Africa. Reporting a significant decline in under-five mortality in the last decade, Prof. Zar said that, despite these health advances, LRTIs remained a major killer. She acknowledged that LRTIs affected both adults and children, but emphasised that with its exponential population growth, Africa was a continent of youth and that addressing childhood mortality and morbidity in Africa was therefore crucial. A group particularly vulnerable to LRTIs were HIV-exposed infants and children.

The burden of childhood pneumonia included subsequent morbidity such as reduced lung function, chronic lung disease, and chronic obstructive pulmonary disease.

LRTI aetiology may be difficult to establish, as identification of potential pathogens was usually performed on respiratory samples, making it difficult to distinguish colonising from pathogenic organisms, unless the organism was invariably pathogenic, e.g. *Mycobacterium tuberculosis* (now known to be associated with acute LRTI in areas of high TB prevalence). Further multiple organisms had increasingly been identified with improved specimen collection methods, more specimens and more sensitive detection techniques. Recent case control studies had found *B. pertussis*, *Haemophilus influenzae* and respiratory syncytial virus to be strongly associated with pneumonia; respiratory syncytial virus was the most common pathogen, for which no effective treatment currently existed. However, most children had multiple potential pathogens, including combined bacterial-viral infection. To date no biomarker was available to distinguish bacterial disease from colonisation, or bacterial from viral infection.

Regarding prevention, the pneumococcal conjugate vaccine was having a large impact with marked reductions in clinical and radiologically defined pneumonia and pneumonia complications such as empyema, especially following the 13-valent pneumococcal conjugate vaccine. Still, in some African regions, vaccination coverage was only around 50%.

Among key issues to be addressed were:

a) Epidemiology – impact of LRTIs on development of chronic lung disease, pathogen-specific associations, epidemiology in HIV-exposed children;
b) Diagnosis – point of care ultrasound for diagnosis, biomarkers to distinguish bacterial LRTI, and guide treatment;
c) Aetiology – role of bacteria in LRTIs post- pneumococcal conjugate vaccine, role of specific viruses, pathogen interactions predisposing to LRTI, and pathogens in HIV-exposed children;
d) Prevention – new strategies to prevent respiratory syncytial virus, immunisation for broader pneumococcal serotypes, impact of prevention of LRTI on chronic lung disease, strategies to prevent LRTI in HIV-exposed children, and role of micronutrients in preventing LRTI;
e) Treatment – optimal oxygen delivery systems for severe LRTI, selection of patients needing antibiotics, optimal treatment of HIV-associated LRTI (e.g. cytomegalovirus), implementation and health systems research to strengthen access to available interventions.

The key question was whether the focus should be on strengthening existing strategies or on new strategies to address the residual burden of LRTI once available interventions had been implemented?

Discussion and questions: One participant asked for the reason of the vulnerability of HIV-exposed children. *There was a combination of factors: exposure to multiple pathogens from the household; absence of breastfeeding; low immune protection via the placenta; poverty-related malnourishment; and possibly reduced lung function, increasing vulnerability to infection.*
Asked to name the top respiratory pathogens in Africa, excluding influenza, *Professor Zar said they were pneumococcus, respiratory syncytial virus and M. tuberculosis. Pertussis, though found in South African children (where the acellular vaccine was used), was relatively uncommon in the rest of sub-Saharan Africa (where the whole-cell pertussis vaccine was still used*.

Professor Markus Maeurer from Karolinska Institute, Sweden, gave a keynote address titled 'Advances against LRTIs in immunocompromised individuals'. He described the burden of respiratory tract infections in children and stated that the immune response in children was substantially different from that in adults.

Little was as yet known about LRTI aetiology in children. Common pathogens were pneumococcus, *M. tuberculosis*, *Aspergillus*, *Staphylococcus aureus*, often in combination with other pathogens, and sometimes re-emerging to become multidrug resistant, extensively drug-resistant, and totally drug-resistant forms of TB. Prof. Maeurer stressed that though inflammation played a positive role in immunity enhancement, excessive inflammation caused chronicity, which negatively affected immune response and was associated with lung damage.

An important role for vaccination was to prevent damage and shorten the time frame of treatment. Prof. Maeurer also stressed that much more emphasis should be placed on treating the entire patient, taking factors like exposure history and nutrition into account. He argued that the issue of bacterial infections could not be tackled just with drugs alone.

In closing, he put forward some recommendations for countering the global burden of LRTIs, including:

- develop biomarkers
- use adjunct host-directed therapies to shorten treatment duration and reduce lung damage
- repurpose drugs
- build capacity.

Discussion and questions: An audience question related to inflammatory markers in blood – and whether other markers were available to check lung damage. (*Markers of immune cells in exhaled air.*)

The meeting agreed that the association between acute LRTIs and subsequent chronic respiratory disease needed further study.

Participants also commented that pathogens such as group B streptococcus (for which a number of vaccines are currently being developed), *Staph. aureus* (described as a major pathogen in neonates up to 1 year of age), respiratory syncytial virus, *Bordetella pertussis*, and *H. influenzae* non-type B needed to be further assessed. Pathogens could be targeted through immunisation of the pregnant mother. Hospital-acquired pneumonia in neonates was an emerging problem, which raised the need for worldwide data collection. Pathogens generally were undermeasured and data collection should take account of geographic differences. The general consensus was that more epidemiological data were needed.

Moreover, participants suggested that there was a need to take a "broader human biology approach". Often the entire focus was on fighting one pathogen, when the aim should be to achieve a mix of immune responses. Work needed to be done on building a healthy microbiome; emphasis on environmental/non-infective components of life might be useful.

The decrease in mortality brought about by medical interventions had, however, been encouraging. (It was noted that reduction in poverty had played a key role in bringing down mortality rates.) Since this suggested that the current approach was working, surely the efforts should be focused in that direction? Interventions that had been proved effective should be strengthened. However, there was simultaneously a need to move beyond focusing on mortality – and expand the work to include morbidity and long-term illness.

Presentations

In his presentation on 'Advances in rapid diagnostics for LRTIs at points of care', **Dr Yakhya Dieye** of the University Cheikh Anta Diop of Dakar, Senegal, spoke about the importance of developing rapid detection techniques without cell culture in view of (a) the emergence of new lethal viruses with epidemic/pandemic potential; and (b) antimicrobial resistance. Rapid diagnostics at point of care were needed to discriminate between different types of respiratory pathogens, accurately identify the aetiological agent, and detect antibiotic resistance.

Two approaches to rapid LRTI diagnostics were currently available: (a) pathogen identification (mainly using PCR (polymerase chain reaction); and (b) measurement of host biological parameters, e.g. C-reactive-protein level (CRP). The PCR multiplex technique allows simultaneous detection of multiple viral and bacterial organisms. PCR was available in many platforms, e.g. Seegene (up to 16 viruses including influenza A subtypes, and seven bacteria), Alere BinaxNOW (influenza, pneumonia, respiratory syncytial virus), TB LAM (*M. tuberculosis*). The 4-minute CRP finger prick blood test had the potential to distinguish between viral and bacterial infections. (*One participant reminded the meeting of the successes of GeneXpert in diagnosing TB in children.*)

Among technologies under development for rapid LRTI diagnostics were:

- next generation frequencing-based tests
- transcriptomics
- metabolomics-based tests (using gas chromatography-mass spectrometry)
- electricity-free nucleic acid amplification (RT-LAMP).

Despite their availability, rapid point-of-care diagnostics were not being used in sub-Saharan Africa. The reasons for this included: small point-of-care centres with limited resources, high costs of molecular tests, and lack of trained personnel to interpret results. In rural areas, there was reliance on traditional medicine.

Looking forward, Dr Dieye said that the main criteria for future technologies in rapid diagnostics in sub-Saharan Africa were: ease of use, cost-effectiveness, and electricity-free and cold chain-free applications. Gaps in capacity were foremost in training of staff.

In closing, he said that there were gaps in the knowledge of lung microbiota and also in the knowledge of traditional medicine, which might offer some solutions.

Discussion and questions: A participant asked about the primary purpose of point-of-care diagnostics: to assess disease burden, obtain aetiological information, or inform therapy? Was diagnosis done to alter management in order to improve outcome or screening/identification? *The primary purpose was to identify the cause of a clinical syndrome, in order to guide both prevention and treatment. A participant commented on the role of diagnostics in assessing whether vaccination has been useful.*
The meeting was reminded that as EDCTP funding is product-focused and that the point of this meeting was to come up with recommendations for future EDCTP calls for proposals. In rapid diagnostics, this would translate into trials to establish efficacy of diagnostic tests.
One participant asked whether focus should be on single tests for single pathogens or, alternatively, on a panel of tests? *Criteria had to be realisable in, and applicable to, Africa.*

The next presentation was titled 'Capacity for diagnosing and treating LRTIs in sub-Saharan Africa: experience from the field' by **Dr Syed Zaman** from MRC Unit The Gambia. He pointed out that accurate diagnosis of acute LRTI was complex as patients with other medical conditions, e.g. malaria, may present with the same signs and symptoms as acute LRTI and that co-morbid conditions (e.g. malnutrition) could also modify the signs and symptoms. More importantly, clinical diagnostic criteria lacked specificity and existing routine microbiological diagnosis had poor sensitivity.

The capacity for diagnosis of acute LRTI in most sub-Saharan African countries was less than adequate, with suboptimal care and health facilities. In this setting, many primary caregivers were unable to recognise the critical signs of severe acute LRTI requiring urgent medical attention. Many health facilities lacked competent staff and high-quality diagnostic laboratories. However, a few sub-Saharan African centres had the capacity to diagnose LRTIs, and were performing acute LRTI-related studies, e.g. the PERCH project conducted at five centres, i.e. in The Gambia, Mali, South Africa, Zambia and Kenya.

Given the overall poor infrastructure and technical support, criteria for developing new LRTI diagnostic tests must include: ease of performance; no reliance on sophisticated equipment; and a high level of specificity.

Concluding, Dr Zaman reiterated that many sub-Saharan African centres lacked basic equipment and facilities required for treating acute LRTI, such as pulse oximeters, regular oxygen supply, electricity, and cold storage facilities. There was limited access to good quality medicines and there was often no standard pricing for medicines. Some major barriers to increasing the capacity for diagnosing and treating LRTIs were limited access to health services; brain drain among medical staff; and lack of medical technology.

The last speaker of the day, **Dr Eric Wobudeya** from Makerere University, Uganda, spoke about 'Health services optimisation research: from clinical research to implementation'. He said much effort was invested in the initial phase (research) but that not much thought went into implementation. There were gaps, therefore, between the different stakeholders. Developers of drugs and equipment should evaluate

the applicability of these drugs and this equipment in the environment where they were intended to be used. There was a need for health services research to inform the targeting of resources. There was further a need for cost-effectiveness studies to inform decision making.

Another problem was the long time lag from product licensure to implementation. Testing different delivery methods and improving the efficiency of implementation would give the public faster and easier access to research products. One barrier to easy access was that research scientists, implementers and policy makers worked in isolation. Communication between the different parties needed to be improved. Another was lack of funding, infrastructure and human resources. Steps needed to be taken to strengthen health support for implementation and to strengthen governmental advisory health research institutions; to make public funding available for implementation research; and to standardise approaches to implementation research conduct and reporting (e.g. to policy makers, health care workers and the community).

A lively **discussion** followed, which included a question from the floor as to who took responsibility for funding, communication, training, etc. since most funders funded technology development. *In Uganda, the Ministry of Health provides some limited funding; some funding was provided by EDCTP in the past. Who provides funding differs, however, between different countries.* One participant suggested that government officials be involved at local level to facilitate planning and implementation. EDCTP should be called upon to fund this area of capacity building. It was suggested that large-scale trials should include a communications and implementation component.

Discussion and final recommendations

The final discussion of the stakeholder meeting aimed to produce recommendations that could be fed back to the Scientific Advisory Committee and EDCTP's member states. What had emerged from discussions throughout the day was that more data were needed, which would then inform intervention planning. There was a lack of data for development of products, e.g. in pneumonia treatment, as well as surveillance and aetiology data. There was also consensus regarding the need for better communication, especially with governmental agencies and health policy makers.

Needs and priorities were highlighted under four key words: pathogens, interventions, capacity strengthening, and health services implementation.

The main **pathogens** in LRTIs, stratified according to age group, were:

- neonates – group B streptococcus, respiratory syncytial virus, and pneumococcus
- children – respiratory syncytial virus, pneumococcus, *H. influenzae*; possibly cytomegalovirus
- adults – pneumococcus.

Other pathogens that were discussed but generally thought to be of lower priority included non-typable *H. influenzae*, *B. pertussis*, and AMR/Gram-negative bacteria. A need for new technology to establish aetiology of multiple pathogens and for diagnostics (including non-PCR methods) was identified.

Intervention priorities were identified in three areas: vaccines, diagnostics, and other.

Vaccine-related recommendations included a childhood vaccine for respiratory syncytial virus, improved adult vaccination against *S. pneumoniae*, and consideration of maternal immunisation against respiratory syncytial virus and, potentially, streptococci (Group B streptococcus and possibly *S. pneumococcus*). These were areas suggested for potential EDCTP involvement in partnership.

In diagnostics, identified needs were: point-of-care rapid diagnostic tests (among others, a cheap point-of-care diagnostic tool for bacterial pneumonia was needed), e.g. portable ultrasound for easy interpretation by personnel with minimal training, pulse oximetry, pathogen-specific tests and host response-specific tests. Tests needed to be simple, cheap, and easy to administer, preferably requiring no external power source and minimal training. Two additional recommendations were to consider biobanking of samples for future investigation, and investigate the extent and range of LRTIs caused by antimicrobial-resistant organisms.

Under other interventions, maternal targeting (vaccines) was flagged as important, as were assessment and prevention of the potential long-term lung effects of LRTIs. A comparative respiratory syncytial virus trial in several African sites was suggested, to determine best practices for long-term outcomes. As companies were not interested in financing long-term trials, this might perhaps be a role for EDCTP. A participant further mentioned the lack of data on the effect of maternal smoking on child pneumonia. It was suggested that EDCTP might consider an intervention and evaluation regarding maternal smoking stoppage (plus or minus vitamin C) as part of a larger trial.

Priorities for capacity strengthening covered: training, laboratory capacity, and data.

- Training was to ensure oxygen and better ventilation strategies for severe LRTI (it was suggested to look for ways to store oxygen so as to circumvent the power problem); better management, e.g. identifying appropriate patients for antibiotic administration and monitoring; optimal treatment of HIV-associated LRTIs.
- Laboratory capacity concerned the need to train local scientists.
- Data needs concerned long-term effects of LRTIs on lung health, and the epidemiology, aetiology and outcomes of adult LRTIs. Other suggested areas of need included data on antimicrobial-resistant infection in hospital patients, and detailed assessment of the actual causes of mortality in patients presenting with LRTIs.

Recommendations were to integrate issues of **health services implementation** into clinical trial designs. It was crucial that LRTIs are prioritised within health systems. To allow for planning and implementation, country-specific data were needed, as were cost-effectiveness data. Capacity building in this area was identified as important. Finally, there was the need for communication across bureaucratic barriers – and researcher awareness of this need. It was suggested that EDCTP might be involved in engagement of policy makers in this area, to influence governmental health policies.

In closing

Closing remarks were made by **Dr Michael Makanga**, who thanked the meeting participants for their recommendations. Both these and the criteria for prioritisation would be taken into account. However, there were too many to implement them all. He said that, as LRTIs were a new area for EDCTP, the aim was to move into this area cautiously and step-wise. The first step had been to talk to partners and collect expert views. The recommendations would be published in a report, to be shared with EDCTP member countries. The next step was for the Scientific Advisory Committee to review the recommendations and identify immediate goals. The report would also inform strategic planning for the 2017 work plan and more long-term planning. In closing, he referred the participants to EDCTP's calls for proposals for 2016.

Appendix 1 - Priorities

LRTIs – priorities for research and research capacity development

The following is a list of research and research capacity development priorities in the LRTI disease area 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**	Pathogens of importance in sub-Saharan Africa Neonates: Group B streptococcus, respiratory syncytial virus, pneumococcus; Children: respiratory syncytial virus, pneumococcus, (cytomegalovirus also highlighted); Adults: pneumococcus.	Priority A
2.	**Disease profile**	Risk factors and outcomes of pneumonia (lack of data on adult pneumonia was highlighted).	Priority A
3.	**Epidemiology**	Aetiology, severity and treatment responses.	Priority A
		Causes of neonatal, childhood, adult pneumonia (including severe disease).	Priority A
		Long-term consequences of pneumonia.	Priority B
4.	**Pathogenesis/ host response**	Adverse immune responses and immunomodulation (host directed therapies).	Priority B/C
5.	**Immune response**	Effects of HIV disease progression, treatment response and vaccine responses.	Priority B/C
6.	**Diagnosis and tracking**	Point-of-care rapid portable diagnosis tests for selection of patients for antibiotics or referral to hospital (Pulse oximetry).	Priority A
		Pathogen-specific tests (testing for multiple pathogens).	Priority B
		Portable ultrasound for diagnosing LRTIs (particularly pneumonia).	Priority A
		Host-response specific tests.	Priority B/C

	Topic	Description	Priority
7.	**Treatments**	Antibiotic choice for specific clinical situations (more data on aetiology were needed first): - Neonatal pneumonia - Childhood pneumonia - Adult pneumonia - Nosocomial pneumonia.	Priority B
8.	**Prevention**	Novel non-capsular antigen vaccines for pneumococcus.	Priority A
		Role of conjugated pneumococcal vaccines in adults.	Priority A
		Respiratory syncytial virus vaccination.	Priority B
		Targeting mothers-to-be for prevention of neonatal disease (increased occurrence of pertussis in mothers highlighted).	Priority B
		Group B Streptococcus-targeted vaccines.	Priority B
9.	**Cultural aspects**	Vaccine uptake.	Priority C
		Reasons for failure to access health care.	Priority C
10.	**Behavioural aspects**	Vaccine uptake.	Priority C
		Reasons for failure to access health care.	Priority C
11.	**Implementation & evaluation of control measures**	Cost-effectiveness studies.	Priority B
		Other implementation issues raised include: - Better management for antibiotic administration and monitoring; - Optimal treatment of HIV-associated LRTIs.	Priority B Priority B
12.	**Critical infrastructure needs**	Optimal oxygen and ventilation strategies for severe LRTIs.	Priority B
		Increased training of local laboratory scientists/staff identified as a critical need, as well as good laboratories and collection of baseline data for LRTIs.	Priority B

Appendix 2 - Participants

Name	Institution	Country
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