child injury

diarrhoea

birth asphyxia

ARI

malnutrition

child development

HIV/AIDS

pneumonia

measles

A New Approach for Systematic Priority Setting

zinc deficiency

neonatal

malaria

In Child Health Research Investment

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A New Approach for Systematic Priority Setting In Child Health Research Investment

Authors

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Setting Priorities in Child Health Research Investments for South Africa
Mark Tomlinson, Mickey Chopra, David Sanders, Debbie Bradshaw, Michael Hendricks, David Greenfield and Igor Rudan

Setting Health Research Priorities to address Millennium Development Goal 4 and reduce Child Mortality at the Global Level
Olivier Fontaine, Jose Martines, Rajiv Bahl, Andre Briend, Lulu Muhe, Shams El Arifeen, Robert E Black and Igor Rudan

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Contents

Foreword

The contribution of health research to early detection, treatment and prevention of disease has been remarkable. Today's health research is tomorrow's health service. The importance of research is often underestimated, because the results cannot be implemented immediately. However, without research we would not achieve eradication of smallpox, elimination of poliomyelitis, control of measles, rubella, tetanus, diphtheria or haemophilus influenza. Even when highly effective interventions exist, research is still needed to identify effective and efficient delivery mechanisms. Today, millions of children are dying from diseases like diarrhea and pneumonia, although highly cost effective interventions exist to prevent most of these deaths. Clearly, available interventions are not reaching the children who need them most. One of the main reasons for this failure is lack of knowledge about effective and efficient context-specific delivery mechanisms for available interventions.

Currently, there is a large discrepancy between resource flows for health research and the diseases and conditions that account for the greatest share of disease burden in children. The 1990 Commission on Health Research for Development showed that less than 10% of global health research funding was spent on diseases and conditions accounting for 90% of the world's disease burden. With limited funding resources for health research, and with many diseases and factors contributing to mortality and morbidity in children under five years of age, it is important to develop a systematic methodology that could prioritize the investments into health research to achieve equitable reduction of the global disease burden.

Adopting the strengths of the previous approaches to priority setting in health research, CHNRI has developed a new model for priority setting. The advantage of the new methodology is that it doesn't consider generating new knowledge as the sole endpoint of research, but it rather addresses several components of a research option, such as likelihood that the results of research would lead to effective and deliverable intervention. It also incorporates the views of both technical experts and stakeholders (donors and recipients in health research). Involving the stakeholders in priority setting process is very important, as research priorities defined by the scientists are often different from those defined by the donors or the recipients of the conducted health research.

A Systematic Methodology for Setting Priorities in Child Health Research Investments

Igor Rudan[1,4,5], Shams El Arifeen[1,2], Robert E. Black[1,3]

Abstract

The Child Health and Nutrition Research Initiative (CHNRI) developed a systematic priority-setting methodology that builds on existing methodologies to identify research priorities in child health and nutrition. The major conceptual advance in this initiative is the recognition that there should be a broader definition of health research option as an activity that is not only limited to producing new knowledge, but also has a vision of implementation of this knowledge which, in the end, should help to reduce disease burden present today. The methodology addresses the dimensions of answerability in an ethical way, effectiveness, deliverability and affordability, maximum potential to reduce disease burden and impact on equity. We applied the new methodology to assess research priorities for several individual diseases and conditions of major importance in global child health: pneumonia, birth asphyxia and zinc deficiency. We also conducted a pilot study at the national level, setting priorities in child research investments for South Africa. The proposed priority-setting methodology compares a larger list of systematically defined competing research options and assigns a quantitative "research priority score" to each of those options, based on technical experts' assessment of likelihood of each option to address each of the 5 criteria. Weights and thresholds are then placed on those intermediate scores, and they are defined by the larger reference group stakeholders who assist the priority-setting process, to ensure that their values are also taken into account. The cost of research per weighted "research priority score" enables subsequent marginal analysis and reallocation of the existing resources or optimal allocation of newly available resources. This process ensures more fairness and transparency in balancing between long-term investments in basic research and short-term gains achievable by investing in implementation and delivery research. The application of this new and systematic methodology for priority setting highlighted the importance of research investments in health policy and systems research. It is shown that very large gains in terms of disease burden reduction could be achieved with existing interventions if more support was given to research on more creative implementation of the existing child health interventions in low-resource settings of developing countries.

Introduction

The World Health Organization recently highlighted the continuing scandal of unacceptably high levels of maternal and child deaths in developing countries in their World Health Report for 2005 (1). This shows that 30,000 children under 5 years of age still die each day. In recent years malaria, TB and HIV /AIDS have received global attention in high profile scientific publications and major international disease control initiatives (for example the Roll Back Malaria, Stop TB, DOTS and "3 by 5" programmes) (2-4). This international response has been reinforced by significant new funding mechanisms and sources such as the Global Fund to fight AIDS, TB and Malaria and the major financial contributions from the Bill and Melinda Gates Foundation to the development of new vaccines against these scourges. However, these conditions account for about 11% of all child deaths globally, while pneumonia, diarrhoea and neonatal conditions are jointly responsible for the majority of all child deaths (5). This is almost twice the number of deaths from smoking, four times the total

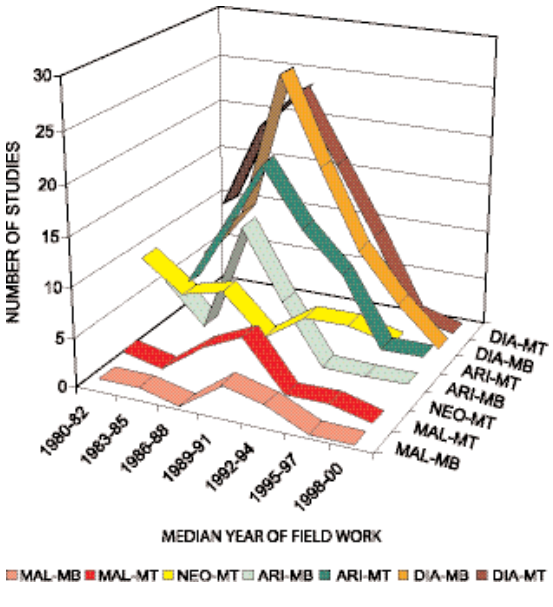

Figure 1: Number of papers with policy-relevant information on epidemiology of specific childhood illnesses in developing countries identified by WHO Child Health Epidemiology Reference Group shows depleting interest in diseases that continue to kill most children (Rudan et al., 2005) (MAL - malaria; NEO - neonatal causes; ARI - acute respiratory infections; DIA - diarrhoea; MB - morbidity; MT - mortality)

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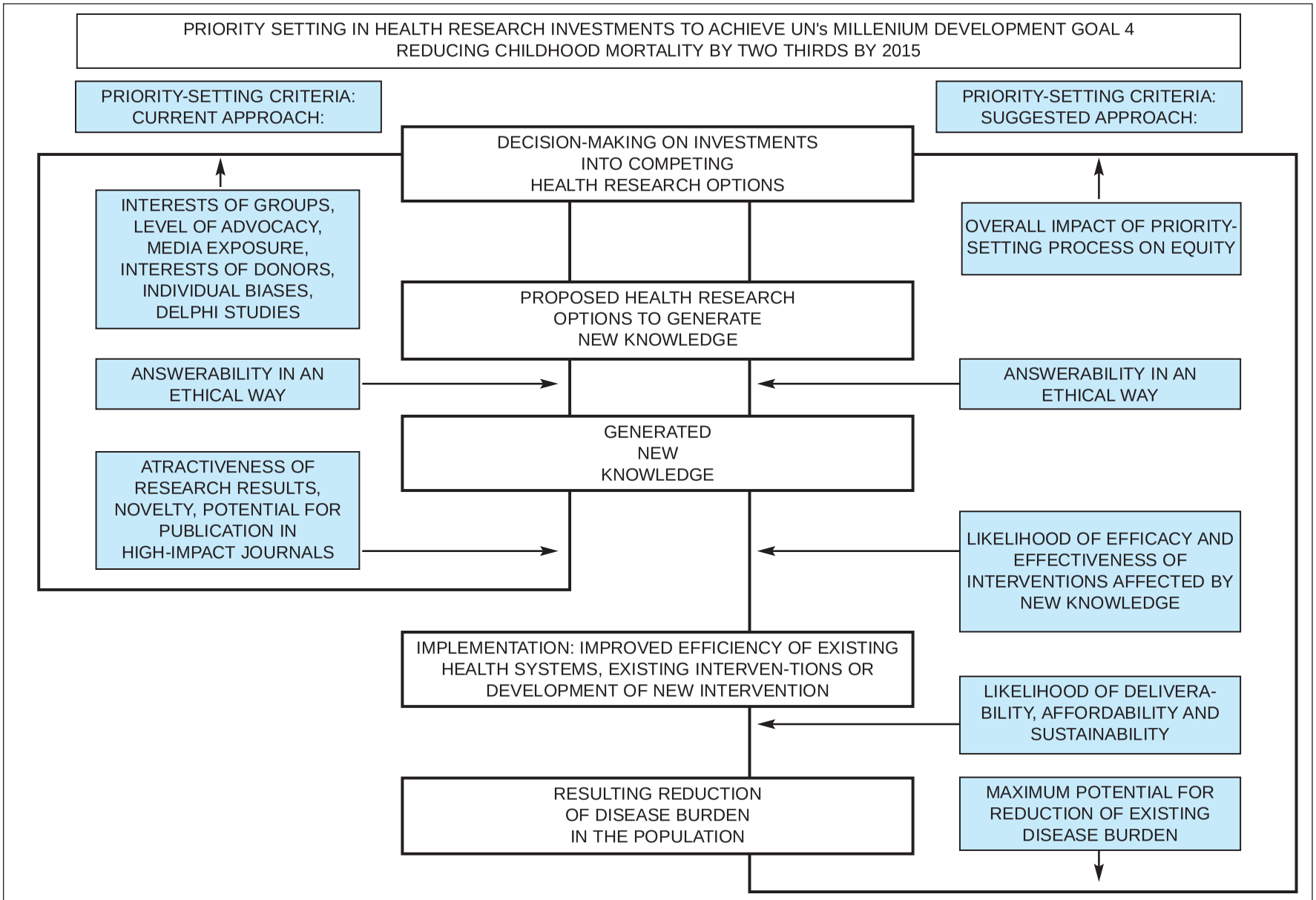

Figure 2: A diagram showing the criteria used in setting priorities in global health research investments: the current approaches (left), and the approach proposed by CHNRI (right).

number of deaths from HIV/AIDS and is 50 times the number of deaths from war globally. Despite this huge mortality, we recently found a steep decreasing trend in research publications on the global extent of these problems reflecting reduced research interest and investment over the past 2 decades (6) (Figure 1). This was in line with the report of the Global Forum for Health Research for 2004, where it was shown that diarrhoea and pneumonia research receive markedly lower investments that those allocated to other diseases that contribute significantly to global child mortality (7).

Why should there be depleted scientific interest in field studies trying to better understand the leading causes of child mortality at a time when the WHO has again shown that these remain two of the most important causes of global burden of disease in children? Why do pneumonia and diarrhoea continue to be responsible for almost half of all child deaths globally, when interventions exist to prevent most of these deaths, interventions that were developed and proven highly cost-effective more than two decades ago (8,9)? It is clear that these interventions are not being delivered to the children who most need them (10). Programmes aiming to deliver these interventions have been inadequately funded, of poor quality, not sustained and not expanded from initial pilots often in least deprived regions (11). Our failure in delivering the interventions is caused by our lack of understanding of how to do it efficiently and creatively in low resource settings, and it is a challenge for research to generate the required knowledge.

We propose that a major reason for these failures has been the lack of recognition that low coverage is a challenge for health research, to identify effective and efficient context-specific delivery mechanisms in health services of countries with limited resources. The development and proof of effective interventions has been seen in the past as the legitimate endpoint of research. Implementation research that needs to follow (including health policy and systems research and delivery research) is methodologically challenging and may require long-term studies. It has not been ranked as highly by the scientific community or by most funding agencies as new work in basic science or intervention development. This has tragic consequences. It has been shown that up to two thirds of under-five child deaths globally could be prevented today if available and cost-effective interventions were delivered to those in need (10). This would achieve UN's Millennium Development Goal 4, and is affordable within current global financial resources (10,12).

We believe that this experience with these two forgotten killers is a good predictor of what can be expected to occur in the future if the current research investment model is to persist (Figure 2). Effective new interventions such as vaccines against AIDS, TB or malaria may be developed in the coming decade, but the same challenge will then be faced: how to make those vaccines cheaper and more cost-effective, and how to deliver them to those most in need? The potential public health impact of these new interventions will not be realised without research on implementation.

The dominant model of research priority setting is resulting in gross under-achievement of potential disease burden reduction and is actually generating further health inequity. Current major global funding initiatives favour the areas of research interest of the scientists involved in basic research, thus investing into options which have received the greatest level of advocacy and media coverage and whose future potential outputs appear most attractive to these communities and the agencies which support them. This is further encouraged by the greater potential for publications in high-impact journals, which is a major indicator of research quality, and also funding in the current research policy model (Figure 2). When these new research avenues lead to the successful development of new interventions, the initial beneficiaries usually are those who can afford the results of the research. More complete coverage of the population in need often lags decades behind (12-14). It is apparent that global research priorities and media pressure fuelled by an interest in highly unusual individual cases or emerging but uncertain threats are bound to generate ever increasing inequity. We believe that a major underlying problem is lack of clear principles for health research investment based on a vision of what the end-points of such investments should be. We need a framework which values investment not only in generating new knowledge, but also in research that seeks to define how to implement and make better use of the existing knowledge leading to public health impact on burden of disease

Method: A New Model of Priority Setting for Global Health Research Investments

The Commission on Health Research for Development was the most significant initial development in setting research priorities globally (15). It reviewed global health needs and priorities for health research in 1990 and concluded that "...less than 10% of global health research funds is devoted to 90% of the world's health problems" (13). A number of subsequent initiatives addressed this problem by attempting to set priorities in global health research, including the recommendations from the Ad Hoc Committee on Health Research Relating to Future Intervention Options in 1996 (16), The Council on Health Research and Development in 2000 (17), "The Grand Challenges" in Global Health supported by The Gates Foundation that emerged from World Economic Forum in 2003 (18), and the Combined Approach Matrix tool by the Global Forum for Health Research in 2004 (19). Another initiative is now underway by The Lancet itself to identify health research priorities to address UN Millenium Development Goals 4 and 5 through a two-stage Delphi study. All these approaches have in common that they are very useful for gathering information relevant to setting research priorities, but the process itself then eventually depends on a limited number of technical experts who collect this information and then recommend priorities, which makes it highly sus

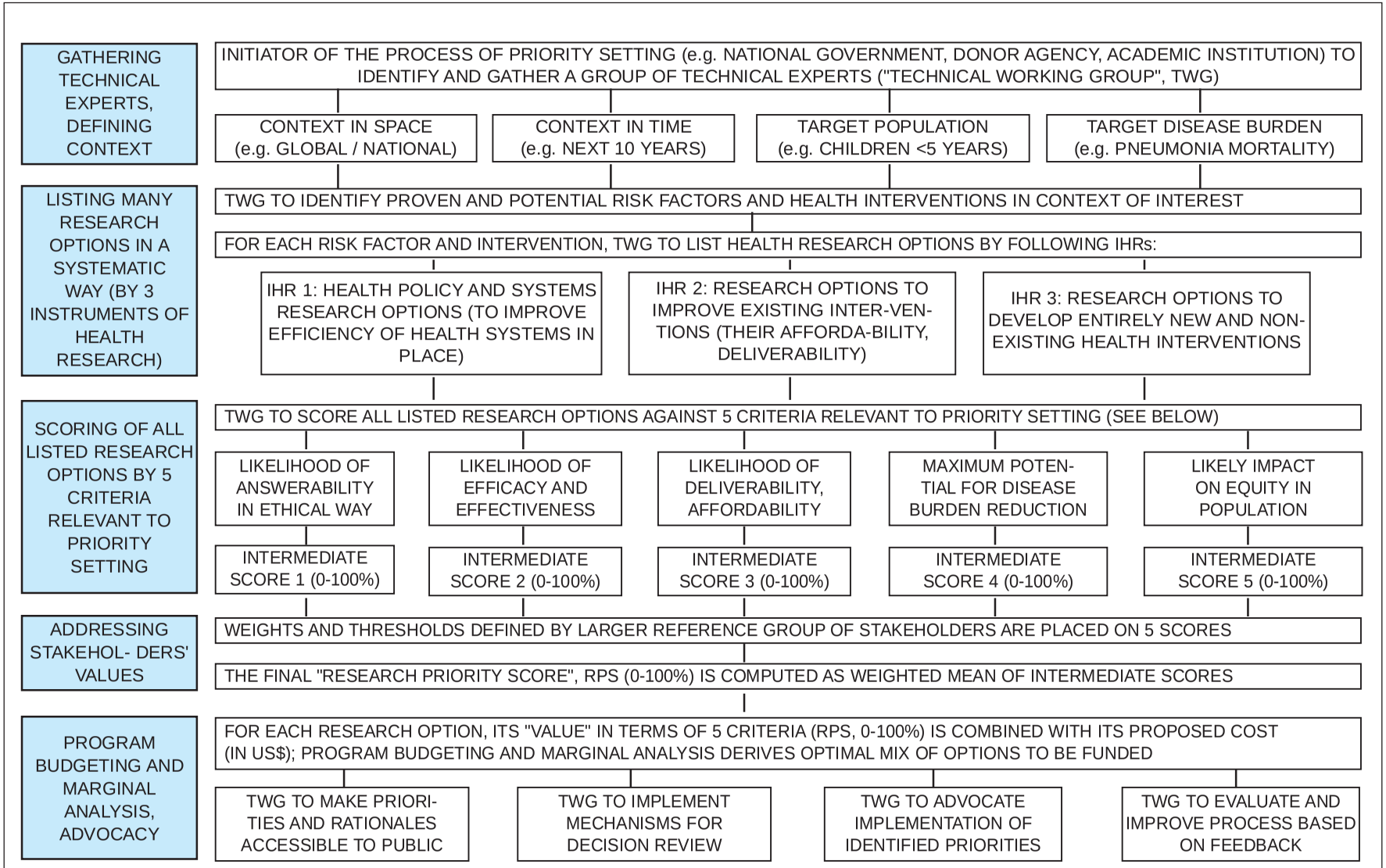

Figure 3: A figure showing all the steps of proposed CHNRI methodology at a glance: gathering a working group of technical experts who are expected to define the context (space, time, population and disease burden addressed); list research options systematically based on potential risk factors, interventions and 3 instruments of health research (IHR); score the competing research options independently and in a highly structured way, according to 5 criteria relevant to priority setting; address the input from stakeholders; and perform program budgeting and marginal analysis, to define the optimal mix of assessed overall value of research for invested funding.

ceptible to their own individual opinions and personal interests and biases.

The Child Health and Nutrition Research Initiative (CHNRI), an initiative of the Global Forum for Health Research, is now leading a project which seeks to overcome these concerns. The major conceptual advance in this initiative is the recognition that there should be a broader definition of health research option as an activity that is not only limited to producing new knowledge, but also has a vision of implementation of this knowledge which, in the end, should help to reduce disease burden present today. From this it follows that it is important not to consider the endpoint of research as "generating new and interesting knowledge or insight", because this necessarily favours more fundamental research. Rather, the process of research priority setting should have a clear theoretical framework based on multiple endpoints coupled to a systematic process of scoring and ranking competing research options. In **Figure 2**, we illustrate the alternative model proposed by CHNRI, which addresses several components of a research option that can be used as criteria for setting research priorities: (i) likelihood that research option would be answerable in ethical way; (ii) likelihood that resulting intervention would be effective in reducing disease burden; (iii) deliverability, affordability and sustainability of resulting intervention; (iv) maximum potential of intervention to reduce disease burden; and (v) effect of disease burden reduction on equity in population. We believe it is also important to acknowledge that there are three different instruments of health research (IHRs, **Figure 3**). For example, health policy and systems research will reduce disease burden by improving efficiency of health systems in delivering the interventions, implementation research will aim to improve existing non-affordable interventions to make them feasible and affordable in low-income settings, while other types of research will seek new and non-existing interventions. The former two types of research are not as innovative and attractive as the latter one, and their results are unlikely to be publishable in journals of high impact, but they nevertheless carry a significant potential to reduce the existing disease burden.

Figure 3 presents the elements of the methodology at a glance. In the first step, the initiators of the process of setting research priorities should gather a group of leading technical experts in the area of interest in child health. The experts then define the context in space, time, target population and target disease burden. In the next step (Figure 3), TWG members are expected to systematically create an exhaustive list of the competing research options by addressing main risk factors and possible interventions through 3 main instruments of health research. The next step involves scoring of all research options by technical experts, in which they assess the likelihood of each research option to address each of the 5 criteria relevant to priority setting - answerability in an ethical way, efficacy and effectiveness, deliverability and affordability, maximum potential to reduce the existing disease burden and predicted effect on equity in the population. In the next step of the methodology, weights and thresholds are placed on the five intermediate scores to reflect the values of stakeholders' representatives from the larger reference group (LRG). In this way, the methodology ensures that the scientific assessment of the research priorities is combined with a view of the wider society in which the priorities should be implemented. Although the stakeholders can't be expected to set research priorities based on their scientific merit and the above 5 criteria, they can still declare which of those criteria they see as more important than the others. This forms a basis for the involvement of the larger reference group in this process. Weighted means of intermediate scores are then computed to derive the final "research priority score" for each research option. It is then expected from technical experts to use the derived scores for the final steps shown in Figure 3: to perform program budgeting and marginal analysis at the country level, to make the results accessible to public, to implement mechanisms for reviewing the scores and decisions, to advocate and implement the identified priorities and to evaluate and improve this process based on feedback information.

Results: Experiences with Implementation of the Methodology

This methodology has been recently implemented at both global and national levels. At the global level, CHNRI and WHO Child and Adolescent Health Department are now working together using this methodology and global childhood mortality burden estimates (provided recently by WHO Child Health Epidemiology Reference Group) to define research priorities for each of the 8 main causes of child deaths (5). Some preliminary results for pneumonia are presented in **Table 1**, while results of addressing the research priorities for birth asphyxia globally are presented in **Table 2** and zinc deficiency as a risk factor in **Table 3 (Rudan I and Campbell H, personal communication; Brown K and Hess S, personal communication; Lawn J and Darmstadt G, personal communication).** The three tables present unweighted research priority scores for the top and bottom 10 research options. This methodology has also been applied recently at the national level **(Tomlinson M and Chopra M, personal communication).** A total of 63 health research options addressing 7 main causes of child deaths in South Africa were listed (9 options per cause of death) and scored by local technical experts, with their results adjusted by local stakeholders. In Table 4, we present final (weighted) research priority scores and rankings of top 10 and bottom 10 research options. The priorities identified in all 4 examples were dominated by health policy and systems research options to increase the coverage of the simplest and most cost-effective interventions, which in South Africa case included hand-washing, breastfeeding and increased usage of antibiotic treatment of pneumonia **(Tables 1-4)**.

Discussion

We are concerned that the current research priority decision making is not driven by an explicit framework and value system and thus is too open to research interest bias

Top 10 child health research options - Pneumonia

RPS (x100)	Rank	Disease	IHR	Research option
80	1/44	Pneumonia	1	Health policy and systems research (HPSR) to achieve increased measles immunization coverage
79	2/44	Pneumonia	1	HPSR to improve breastfeeding practices
77	3/44	Pneumonia	1	HPSR to achieve increased usage of antibiotic treatment
76	4/44	Pneumonia	1	HPSR to improve existing ways of training health workers to deliver pneumonia standard case management
75	5/44	Pneumonia	1	HPSR to increase pertussis immunization coverage
75	5/44	Pneumonia	1	HPSR to increase hand-washing with soap in villages and communities
75	5/44	Pneumonia	1	HPSR to improve the access to appropriate health care for management of pneumonia
74	8/44	Pneumonia	1	HPSR to achieve increased care-seeking behaviour
73	9/44	Pneumonia	1	HPSR to improve supportive supervision for ARI SCM
71	10/44	Pneumonia	1	HPSR to achieve increased child spacing intervals

Bottom 10 child health research options - Pneumonia

RPS (x100)	Rank	Disease	IHR	Research option
51	35/44	Pneumonia	1	HPSR to reduce direct transmission and crowding
51	36/44	Pneumonia	3	Developing "common protein" pneumococcal vaccine
50	37/44	Pneumonia	2	Developing zinc delivery solutions with longer duration of effect
49	38/44	Pneumonia	2	Evaluating the impact of polysaccharide pneumococcal vaccine in infancy on childhood pneumonia
49	39/44	Pneumonia	3	Developing RSV vaccine
49	40/44	Pneumonia	2	Developing existing vaccines with needle-free delivery
42	41/44	Pneumonia	1	HPSR to reduce nosocomial infections
41	42/44	Pneumonia	3	Developing vaccines against non-typable H. influenzae
39	43/44	Pneumonia	1	HPSR to reduce exposure of children to cigarette smoke
38	44/44	Pneumonia	3	Developing new antibiotics that would overcome bacterial resistance

Table 1: Preliminary results from research priority setting exercise to address research priorities to address pneumonia, a major cause of mortality in global child health. A total of 44 research options were proposed for scoring by global technical experts, and they addressed all three instrument of health research, IHR). The final research priority scores (RPS) were based on scoring by technical experts only.

Top 10 child health research options - Birth Asphyxia

RPS (x100)	Rank	Disease	IHR	Research option
89	1/28	Birth Asph.	3	Behav. package to prepare for birth, newborn care and emergency (funds, transport) - "Birth preparedness"
88	2/28	Birth Asph.	1	Identification of a limited number of high risk conditions/danger signs by community worker
86	3/28	Birth Asph.	3	Behavioural/community participation, infrastructure package to improve recognition and acting on simplified danger signs for mother in labor (transport and phone/radio communication)
84	4/28	Birth Asph.	1	Behavioural research to promote optimal (at least 24 months) birth spacing in various cultural contexts
82	5/28	Birth Asph.	2	Protocols, training, audit to increase quality of intrapartum monitoring and speed of intervention
79	6/28	Birth Asph.	1	Promoting the use of doulas (including relatives) to increase acceptance/use of facility birth
78	7/28	Birth Asph.	2	Testing simpler recognition and management algorithms for babies who require resuscitation
74	8/28	Birth Asph.	1	Behavioural research to delay age of first pregnancy in various cultural contexts
72	9/28	Birth Asph.	2	Operationalising Maternity Waiting Homes in various cultural contexts
72	10/28	Birth Asph.	2	Development low cost, robust, simple fetal heart monitors that count beat to beat variability for the user

Bottom 10 child health research options - Birth Asphyxia

RPS (x100)	Rank	Disease	IHR	Research option
46	19/28	Birth Asph.	2	Simplify protocols for identification and care of newborns with neonatal encephalopathy assessing mortality and long term neurodev outcomes (specific sub questions eg fluid restriction, anticonvulsants etc)
46	20/28	Birth Asph.	3	Address micronutrient deficiencies (iodine etc) and/or anaemia synergistic with asphyxial outcomes
42	21/28	Birth Asph.	1	Behavioural research to address unhealthy behaviours in pregnancy eg smoking and drug abuse
40	22/28	Birth Asph.	2	Nutrition of the girl child to reduce later risk of obstructed labor and asphyxia-related outcomes
32	23/28	Birth Asph.	3	Interventions to address the synergy of infections/ maternal pyrexia with neonatal encephalopathy (NE)
31	24/28	Birth Asph.	2	Adapting the procedure of amnio infusion to lower resource settings
30	25/28	Birth Asph.	3	Early identification of babies who have development problems following NE and provision of support
30	26/28	Birth Asph.	2	Appropriate management of meconium aspiration in low resource settings (suction or not, who to do etc)
27	27/28	Birth Asph.	2	Adapting head cooling/body cooling to be feasible/lower cost for low resource settings
10	28/28	Birth Asph.	3	Novel approaches to reducing cerebral damage after insult (magnesium, nitrates, allopurinol etc)

Table 2: Preliminary results from research priority setting exercise to address research priorities to address birth asphyxia, an important cause of mortality in global child health. A total of 28 research options were proposed for scoring by global technical experts, and they addressed all three instrument of health research, IHR). The final research priority scores (RPS) were based on scoring by technical experts only.

Top 10 child health research options - Zinc

RPS (x100)	Rank	Disease	IHR	Research option
85.3	1/31	Zn deficien.	1	Determine effectiveness of scaling up zinc as treatment for diarrhea and pneumonia in high risk regions
84.4	2/31	Zn deficien.	1	Determine efficacy and effectiveness of zinc when delivered alone or with other single (e.g. iron) or multiple micronutrients between meals or with foods
79.7	3/31	Zn deficien.	1	Determine optimal dose and duration of zinc supplements provided for treatment of diarrhea or pneumonia
79.6	4/31	Zn deficien.	1	Investigate the effectiveness of different delivery systems (growth monitoring, EPI, community-based organi zations) to provide preventive zinc supplements
79.3	5/31	Zn deficien.	1	Undertake cost-effectiveness and cost-benefit analysis of zinc interventions to improve case for advocacy
79.2	6/31	Zn deficien.	1	Determine optimal efficacious and safe dose of preventive zinc supplements for different age groups
76.1	7/31	Zn deficien.	3	Demonstrate efficacy of complementary food-based zinc intervention
75.3	8/31	Zn deficien.	1	Assess the impact of zinc internventions on malaria incidence and severity
73.6	9/31	Zn deficien.	1	Determine bioavailability of different chemical forms of zinc from different food vehicles
73.1	10/31	Zn deficien.	1	Develop appropriate reference values for serum zinc concentration of infants and pregnant women

Bottom 10 child health research options - Zinc

RPS (x100)	Rank	Disease	IHR	Research option
63.0	22/31	Zn deficien.	3	Efficacy and effectiveness of agricultural interventions (appropriate fertilizers, selective breeding for high-zinc cultivars) on dietary zinc intake and zinc status
62.6	23/31	Zn deficien.	1	Investigate whether parasites cause increased risk of zinc deficiency
58.4	24/31	Zn deficien.	3	Develop genetically modified staple crops with both a high zinc content and a low phytate content.
56.0	25/31	Zn deficien.	2	Increase the availability (improved access, storage) to increase the consumption of zinc-rich foods
55.0	26/31	Zn deficien.	3	Develop an innovative public private-partnership and/or new business model to make fortified complementary foods available to lowest income groups
54.4	27/31	Zn deficien.	1	Investigate the impact of preventive zinc supplementation of term AGA, term SGA, and premature infants
53.8	28/31	Zn deficien.	3	Develop zinc solutions to include in EPI injections for mother during pregnancy and for infants, to serve as slow release depot infections of zinc
52.6	29/31	Zn deficien.	1	Investigate safe upper limits of zinc intake for different population groups (by age, physiological status)
50.9	30/31	Zn deficien.	3	Develop innovative zinc intervention strategy to provide slow release zinc
33.5	31/31	Zn deficien.	3	Investigate the relationship between zinc deficiency and risk of obesity (excess body fat)

Table 3: Preliminary results from research priority setting exercise to address research priorities to address zinc deficiency, as a major risk factor in global child health. A total of 31 research options were proposed for scoring by global technical experts, and they addressed all three instrument of health research, IHR). The final research priority scores (RPS) were based on scoring by technical experts only.

Top 10 child health research options - South Africa

RPS (x100)	Rank	Disease	IHR	Research option
88.6	1/63	Malnutrition	1	Health policy and systems research (HPSR) to achieve increased vitamin A supplementation coverage
87.8	2/63	Diarrhoea	1	Health policy and systems research to increase hand-washing with soap
87.7	3/63	Pneumonia	1	HPSR to achieve increased usage of antibiotic treatment for pneumonia
87.7	4/63	HIV/AIDS	1	HPSR to increase coverage of PMTCT interventions
84.2	5/63	Diarrhoea	1	HPSR and education/behaviour modification research to increase exclusive breastfeeding in first 6 months
83.5	6/63	Pneumonia	1	HPSR to improve existing ways of training health workers to deliver pneumonia standard case management
83.3	7/63	Diarrhoea	1	HPSR to increase awareness of indications for treatment and access to ORS sachets at all times and sites
83.0	8/63	Malnutrition	1	HPSR to improve management of severe malnutrition
82.4	9/63	Malnutrition	1	HPSR to achieve increased zinc supplementation coverage
80.3	10/63	Diarrhoea	2	Research to reduce costs /improve deliverability and sustainability of piped safe water systems

Bottom 10 child health research options - South Africa

RPS (x100)	Rank	Disease	IHR	Research option
52.6	54/63	Acc. & Inj.	3	Developing innovative solutions to protect the pedestrians
52.4	55/63	Neonatal	2	Adapting head cooling/body cooling to be feasible/lower cost for low resource settings
52.3	56/63	Con. / Gen.	3	Developing cost-effective diagnostic tool for detecting cong. heart disease after birth in a commun. setting
52.0	57/63	Neonatal	1	HPSR to achieve increased child spacing intervals
51.9	58/63	Con. / Gen.	3	Develop. cost-effective diagnostic tool for early detect. of cong. anomalies during pregnancy in a com. set.
49.7	59/63	Pneumonia	2	Research to reduce the costs of oxygen therapy and make it more available to the general public
49.6	60/63	Con. / Gen.	3	Making catheter interventions for congenital heart disease more affordable
49.3	61/63	Con. / Gen.	2	Making community genetics screening tests more affordable and cost-effective
45.6	62/63	Neonatal	2	Adapting the procedure of amnio infusion to lower resource settings
30.8	63/63	Con. / Gen.	1	HPSR to increase the coverage of screening for genetic conditions in the population (community genetics)

Table 4: Preliminary results from research priority setting exercise to address South African child health research priorities (covering 7 major causes of child deaths in the country: HIV/AIDS, malnutrition, neonatal problems, diarrhoea, pneumonia, congenital and genetic disorders, accidents and injuries). For each cause of death, 9 research options were proposed for scoring by local experts (3 for each of the three instrument of health research, IHR). The final research priority scores (RPS) were based on scoring by technical experts and adjusting the scores according to the system of values of 30 members of larger reference group representing the stakeholders in the country.

of individuals who influence funding priorities in large donor agencies without an unbiased vision focused on reducing disease burden and improving global health inequities. The six main advantages of the CHNRI methodology presented in **Figure 3** over the alternative approaches are: (i) it is systematic, and technical experts involved the process to set research priorities are asked to list and score competing research options in a highly structured way; this limits the influence of their own personal biases on the outcome, which is frequently a problem in Delphi studies; (ii) the methodology is entirely transparent; all rationales for decision making and input from each person involved from the initial to the final stages are recorded, displayed and can be viewed and challenged at any later point in time; (iii) the experts submit their input into the process independently from each other, and the results are based on their collective opinion in a true sense, thus avoiding the possibility of some individuals among them directing the process; (iv) the final result is a simple quantitative outcome ("research priority score"), which measures the "value" of each research option when all the criteria and stakeholders' views are taken into account; this "value" can then be combined with the proposed cost of research in order to perform program budgeting and marginal analysis and derive an optimal mix of research options to be funded from a fixed budget; (v) the methodology is well suited to simultaneously evaluate and score different types of research (e.g. health policy and systems research, implementation research and research on new interventions) using the same set of criteria; (vi) unlike all previous approaches, this methodology incorporates an efficient means of considering the voice of stakeholders and wider public, who are given the power to place thresholds and weights upon intermediate scores (which are based on collective opinion of technical experts) and in this way considerably shape the final outcome (see **Figure 3**).

Although all initiatives aiming to set priorities and invest in child health research in developing countries are welcome, it is important to understand that without an explicit consideration of the issues listed above, the health gains that can be achieved will be limited. There are signs that these issues are beginning to gain attention. Some examples include the Research Assessment Exercise in the UK, a major driver of research priorities in public sector, debating how to respond to criticisms that the system undervalues health systems research; the European Commission, announcing that there will be a new funding stream for Health Policy and Systems Research in the forthcoming 7 year research programme (FP7) and, in the field of pneumonia, the grants by the Global Alliance for Vaccines and Immunisation for public-private partnerships and related research to accelerate the achievement of high levels of population coverage of immunisation with the new Hemophilus influenzae type b and pneumococcal protein conjugate vaccines. These initiatives are welcome but there is a need for a new framework for global health research priority setting, especially in child health research. We believe that only in this way will proper attention be given to delivery of proven interventions to reduce the high childhood mortality due to causes such as pneumonia, diarrhoea and neonatal conditions.

In summary, we feel that the implementation of CHNRI methodology for setting priorities in health research investments in the four examples shown in Tables 1-4 was a very useful exercise. Among those involved, it enabled much better understanding of the key criteria that qualify some research option as a funding priority over the others. Its transparency ensured that all rationales for decision making and input from each person involved from the initial to the final stages were recorded and can be viewed and challenged at any later point in time. In South Africa example, it also considered the voice of stakeholders and wider public, who were given the power to place thresholds and weights upon intermediate scores. Although several possibilities for further improvement of the methodology were identified, we feel that these features of the methodology used to set research investment priorities represent substantial advantages over the existing approaches and that it could be of help to policy makers in their decisions on investments in health research.

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Setting Priorities in Child Health Research Investments for South Africa

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Abstract

It is estimated that nearly 100,000 children under 5 years of age still die each year in South Africa (SA). The aim of this paper was to define health research priorities at the national level to address this persisting problem of unacceptably high mortality. The authors applied the methodology for setting priorities in health research investments recently developed by Child Health and Nutrition Research Initiative (CHNRI) of the Global Forum for Health Research. Two working groups were assembled: a group of 6 national technical experts and a larger reference group (LRG) of 30 representatives of stakeholder groups. For each of the seven main causes of child deaths in SA (HIV/AIDS, pneumonia, diarrhea, neonatal conditions, malnutrition, accidents and injuries, congenital and genetic disorders), technical experts proposed 9 research options that they considered research priorities. This was done in a structured way to ensure that the proposed research options equally address all three instruments of health research (health policy and systems research, research on improving the existing health interventions and research on developing new interventions). Technical experts scored 63 proposed research options independently, assessing the likelihood of their answerability, effectiveness, deliverability, maximum potential to reduce mortality burden, and likely impact on equity. The 30 members of LRG placed weights on those five intermediate scores through a separate survey, according to their own system of values. The weighted mean of the intermediate scores, or the "research priority score", ranged from 88.6 to 30.8 and ranked the 63 research options according to their overall value in addressing the five priority-setting criteria and values of the stakeholders. The identified research priorities within the existing SA context were dominated by health policy and systems research activities to generate new knowledge on how to improve delivery of the simplest and most cost-effective existing interventions, such as vitamin supplementation, hand-washing, antibiotics for pneumonia, prevention of mother-to-child HIV transmission (PMTCT) and exclusive breastfeeding.

Introduction

The number of possible avenues in health research is growing continuously and the proposals for research funding far exceed the potential of the countries to fund them. This is especially the case in developing countries, where health needs are large and health research budgets are small. Therefore, guidelines are needed to assist decisions on defining the priorities for health research investments. An early attempt at the global level to define health research priorities was made through Commission on Health Research for Development in 1990. The Commission promoted the concept of Essential National Health Research (ENHR), in which countries take responsibilities to delineate a research agenda by themselves (1). It also reviewed global health needs and priorities for health research in 1990 and concluded that "...less than 10% of global health research funds is devoted to 90% of the world's health problems" (2). A number of subsequent initiatives addressed this problem by attempting to set priori

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ties in global health research, including the recommendations from the Ad Hoc Committee on Health Research Relating to Future Intervention Options in 1996 (3), The Council on Health Research and Development in 2000 (4), "The Grand Challenges" in Global Health that emerged from World Economic Forum in 2003 supported by The Gates Foundation (5), and the Combined Approach Matrix tool by the Global Forum for Health Research in 2004 (6).

Child health in developing countries has been recognized as one of the main focuses of health research priority initiatives at the global level in the past. This is mainly due to persisting unacceptable burden of child mortality of 10.6 millions each year, as estimated by World Health Organization's Child Health Epidemiology Reference Group (CHERG) (7). About three quarters of those deaths in children younger than 5 years are caused by pneumonia, diarrhoea, malaria, neonatal pneumonia or sepsis, preterm delivery and asphyxia at birth (8,9). One of the eight "Millennium Development Goals" is to reduce child mortality by two-thirds between 1990 and 2015 (10). Although the cost-effective health interventions and the financial support needed to achieve this goal both seem available (11,12), substantial gains in terms of mortality reduction have not been observed during recent years in most of the developing countries, especially those in sub-Saharan Africa (13). One of the recently proposed contributing factors to this situation is poor prioritization of health research investments (14). There is limited funding and interest in research on how to implement cost-effective interventions in the context

of health services in countries with limited resources. Implementation research is not ranked highly by the scientific community nor by most funding agencies. As it is rarely considered as a research priority, research on new interventions far exceeds that on delivery (14).

The Child Health and Nutrition Research Initiative (CHNRI), an initiative of the Global Forum for Health Research, is now leading a project that seeks to identify research priorities to address UN's Millennium Development Goal 4 (15). CHNRI developed a systematic methodology for setting priorities in health research investments that can be applied at different levels (global, national) and for different purposes (addressing a disease, group of diseases, risk factors, etc.) (16-19). The proposed major conceptual advance of CHNRI's methodology is the recognition that there should be a broader definition of health research option as an activity that is not only limited to generating new knowledge, but also has a vision of implementation of this knowledge which should help to reduce present disease burden. This methodology should be particularly useful when applied at the national level, as the results derived from the input of the main national technical experts and representatives of all the major national stakeholders could have a direct impact on the research investment policy. In a recent systematic review of existing national health priorities for child health research in sub-Saharan Africa, Swingler et al. concluded that few systematically developed national research priorities exist, and that in rare cases where they do, children's interests may be distorted in processes that combine all age groups (20). They saw this as particularly concerning in the light of the fact that 65% of the disease burden in sub-Saharan Africa in 1990 was attributable to conditions found in children (20). In this paper, we attempt to apply CHNRI methodology to systematically and transparently address child health research priorities in South Africa, where nearly 100,000 children a year are estimated to die before the age of five.

Materials and Methods

Methodology for setting health research priorities - activities of technical working group (TWG)

The methodology used to set research priorities was developed recently by the Child Health and Nutrition Research Initiative (16-19). The rationale, conceptual framework, application guidelines and strategies to address the needs of the stakeholders have all been described in great detail elsewhere (16-19). This paper reports on the first application of the methodology at the national level, and South Africa was chosen for the pilot study as the only country in sub-Saharan Africa that has sufficiently well developed mechanisms for the collection and analysis of burden of disease statistics, thus offering a particularly favorable setting for application of the methodology (21). **Table 1** presents the elements of the methodology at a glance. In the first step, the initiators of the process of setting research priorities (in this case, an academic institution - Health Policy and Systems Research Unit of the Medical Research Council in Cape Town, South Africa) identified and gathered a group of leading South African technical experts in the area of child health. The six experts who agreed to participate and form a technical working group (TWG) came from the Medical Research Council (Health Policy and Systems Research Unit and Burden of Disease Research Unit), University of Western Cape, and University of Cape Town. They defined the context in space as national (South Africa), context in time as next 10 years (the year 2015, by which UN Millennium Development Goals should be met), target population as children below 5 years of age, and target disease burden as all cases of child deaths in expected to occur within that period in under-fives in South Africa.

In the next step (**Table 1**), it was first suggested that TWG members list up to 100 research options by addressing main risk factors and possible interventions through 3 main instruments of health research. A justification to limit the exercise to 100 research options was the fact that a simulation of scoring showed that in this case each member of TWG would need to spend up to 10 hours (more than 1 full working day) scoring the options, which was agreed as the upper limit of time that could realistically be asked from them for this pilot study. However, a further suggestion was that the 100 research options should be listed so that they address causes of death proportionally to the number of deaths that they cause. This was then dismissed, as it was soon realized that one of the criteria to set priorities is "maximum potential for disease burden reduction", so those options would already have an expected advantage over the others based on that criterion and further advantages should not be introduced artificially.

Eventually, an agreement was reached among technical experts to limit the exercise to 7 leading causes of deaths, which jointly account for more than 90% of child deaths in South Africa: HIV/AIDS, pneumonia, diarrhea, neonatal causes, malnutrition, accidents and injuries and congenital and genetic disorders. Furthermore, for each of 7 selected causes of death, it was decided that equal number of research options addressing 3 instruments of health research would be proposed for scoring, to avoid favoring any of the instruments (e.g., research on health policy and systems, research on improving the existing interventions, and research to develop new interventions). A survey was then conducted among the experts in each of the 7 causes of death within South Africa, in which they were asked to agree on the selection of 3 research options for each of the instrument of health research that would, in their opinion, stand the best chance to be considered a research investment priority when evaluated against the research options addressing other causes of death. This led to having a total of 63 research options to score (7 causes of death x 3 instruments of health research x 3 research options proposed), which was still a demanding and labor-intensive task.

As shown in **Table 1**, the next step included scoring of all research options and the 6 technical experts performed the

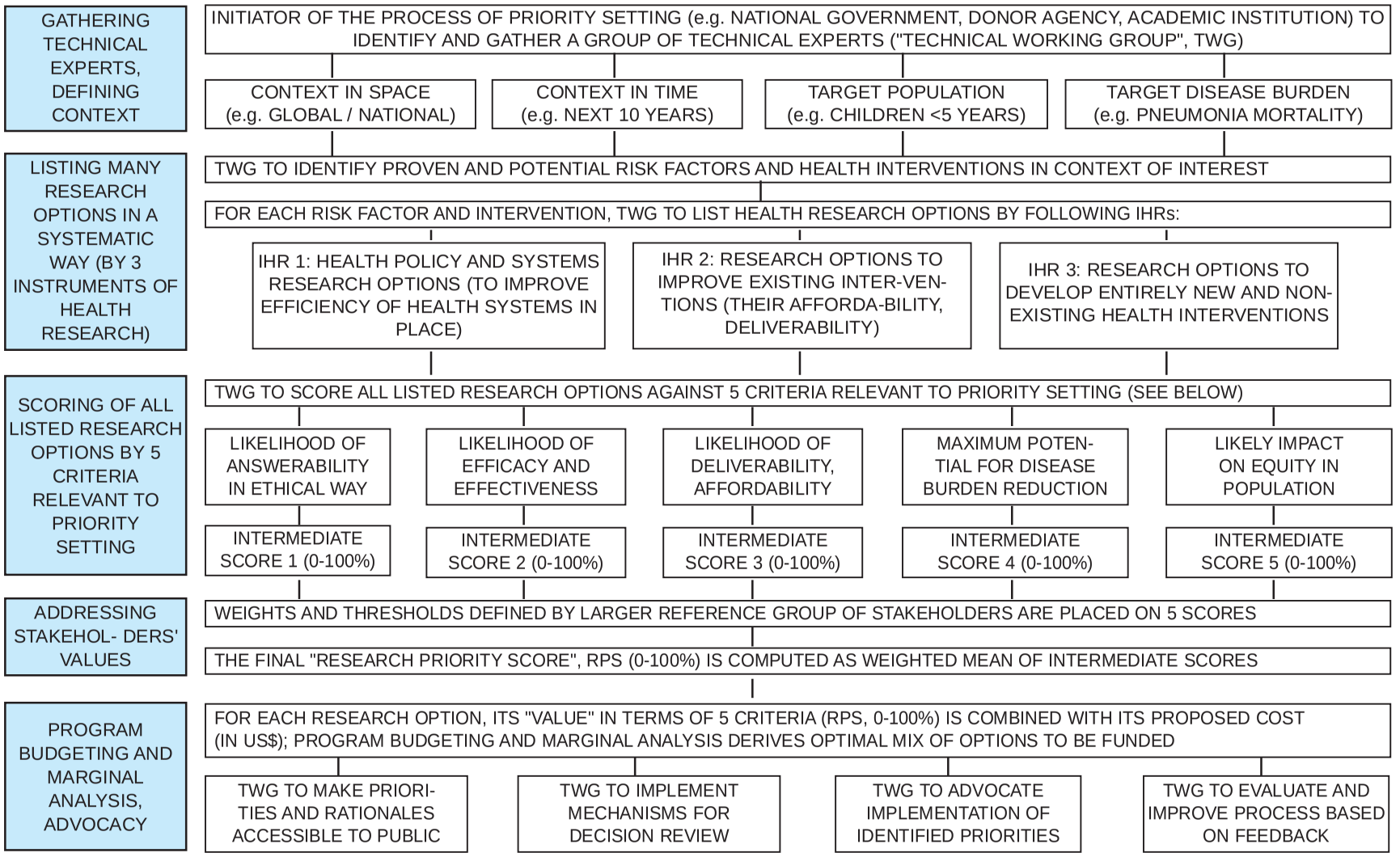

Figure 3: A figure showing all the steps of proposed CHNRI methodology at a glance: gathering a working group of technical experts who are expected to define the context (space, time, population and disease burden addressed); list research options systematically based on potential risk factors, interventions and 3 instruments of health research (IHR); score the competing research options independently and in a highly structured way, according to 5 criteria relevant to priority setting; address the input from stakeholders; and perform program budgeting and marginal analysis, to define the optimal mix of assessed overall value of research for invested funding.

scoring independently. For each of the 63 research options, they assessed their likelihood of answerability in an ethical way, efficacy and effectiveness, deliverability and affordability, maximum potential to reduce the existing child mortality burden and predicted effect on equity in the population. Assessment was mad by answering 3 questions per each criterion according to conceptual framework developed by Rudan et al. (17). This yielded 5 intermediate scores, all ranging between 0-100%. The exact methods of the computations of intermediate scores were explained elsewhere (18).

Methodology for setting health research priorities - activities of larger reference group (LRG)

In the next step of the methodology, weights were placed on the five intermediate scores to reflect the values of 30 stakeholders' representatives from the larger reference group (LRG). In this way, the methodology ensures that the scientific assessment of the research priorities is combined with a view of the wider society in which the priorities should be implemented. Although the stakeholders can't be expected to set research priorities based on their scientific merit and the above 5 criteria, they can still declare which of those criteria they see as more important than the others. This forms a basis for the involvement of the larger reference group in this process.

In recruiting a larger reference group (LRG), context can be of particular importance and in this regard a brief discussion of the South African context is needed. In South Africa, concepts such as democratic consultation, equity and transparency have a particular resonance in the light of its apartheid history. As South Africa's institutions began to be transformed post-1994, concepts such as transparency and equity, and the importance of extensive consultation with all parties, were more than simply politically correct terms, and were rather the cornerstones of the new government's policies of how the transition to a new dispensation should take place.

In this study, LRG members were recruited from a number of different sources. Whilst as broad a range of stakeholders from South Africa was sought for the larger reference group, this was not done in a systematic way. Firstly, participants at a local public health conference were approached and asked to rank the 5 criteria. Secondly, academics (from disciplines ranging from history to psychology and public health) from the three universities in the Western Cape Province and one from the University of Kwazulu-Natal were recruited. Reference group members were also sought from the two research councils with offices in Cape Town - the Medical Research Council and the Human Sciences Research Council. Other reference group members included a number of child and youth care workers, teachers, social workers, a statistician, a health journalist and finally members of the public. Eventually, LRG had 30 members: 11 researchers, 1 medical officer of an international health body, 4 University lecturers, 1 statistician, 1 professor, 2 child clinical psychologists, 1 monitoring and evaluation specialist, 2 members of the public, 2 child and youth care workers, 2 social workers, 1 teacher, 1 public health postgraduate student, 2 government representatives and 1 health journalist.

The weights for the 5 criteria used by technical experts were obtained in the following way: LRG members were simply asked to rank those 5 criteria from the most important within the South African context (rank 1) to the least important (rank 5). The criteria were listed in random order and LRG members received different lists, to ensure that the order in which the criteria are presented to them does not introduce bias. The average of suggested ranks was then computed. The criterion of equity received the highest average rank (2.31), followed by efficacy and effectiveness (2.75), deliverability, affordability and sustainability (2.94), maximum potential for mortality burden reduction (3.28), and answerability (3.72). Following the earlier discussion on South Africa's apartheid past and the contemporary emphasis on ensuring equity, it was not surprising that equity emerged as the top ranked criteria. These observed average ranks were then turned into weights by dividing the expected average rank in the situation of equal importance of all 5 criteria (which is 3.00) by the observed average rank (19). This simple procedure gives weights for the intermediate scores in a range between 3.0 (maximum) and 0.6 (minimum).

Weighted means of intermediate scores were then computed to derive the final "research priority score" for each research option. It is now the intention of the authors to use the derived scores for the final steps shown in **Table 1**: to perform program budgeting and marginal analysis at the country level, to make the results accessible to public, to implement mechanisms for reviewing the scores and decisions, to advocate and implement the identified priorities and to evaluate and improve this process based on feedback information.

Results

The final results of the scoring process are shown in **Table 2**. In this table, all 63 scored research options are ranked by their final "research priority score" (RPS) multiplied by a 100, which gives a range of score values between 0 and 100. This score took into account the scores from technical experts, based on five criteria relevant to priority setting, and the weights defined by the larger reference group. The ranks in brackets indicate research priority scores before the weighting by the larger reference group. The final research priority scores for the 63 research options ranged from 88.6 to 45.6, with the lowest score of 30.8 being an outlier. This shows substantial variation between the research options in their likelihood to address the five criteria, as assessed by technical experts and larger reference group, and indicates that the methodology has a power to discriminate many competing research options using a simple conceptual framework with 15 questions.

RPS (x100)	Rank	Cause of death	IHR	Research option
88.6	1 (1)	Malnutrition	1	Health policy and systems research (HPSR) to achieve increased vitamin A supplementation coverage
87.8	2 (3)	Diarrhoea	1	HPSR to increase hand-washing with soap
87.7	3 (3)	Pneumonia	1	HPSR to achieve increased usage of antibiotic treatment for pneumonia
87.7	4 (2)	HIV/AIDS	1	HPSR to increase coverage of PMTCT interventions
84.2	5 (5)	Diarrhoea	1	HPSR and education/behavior modification research to increase exclusive breastfeeding during first 6 months
83.5	6 (6)	Pneumonia	1	HPSR to improve existing ways of training health workers to deliver pneumonia standard case management
83.3	7 (7)	Diarrhoea	1	HPSR to increase awareness of indications for treatment and access to ORS sachets at all times and sites
83.0	8 (8)	Malnutrition	1	HPSR to improve management of severe malnutrition
82.4	9 (9)	Malnutrition	1	HPSR to achieve increased zinc supplementation coverage
80.3	10 (10)	Diarrhoea	2	Research to reduce costs /improve deliverability and sustainability of piped safe water systems
79.1	11 (11)	Acc. & Injuries	3	Develop affordable spill-proof paraffin stoves that comply with safety standards
77.6	12 (12)	Diarrhoea	2	Research to develop ways of sewage treatment systems affordable to developing countries
75.6	13 (13)	Pneumonia	1	HPSR to increase zinc supplementation coverage
74.3	14 (15)	HIV/AIDS	1	HPSR to increase access to antiretroviral treatments
73.9	15 (14)	Neonatal	3	Development and testing of low cost, robust, simple fetal heart monitors
73.7	16 (16)	Malnutrition	3	Evaluating cost-effectiveness of different strategies to increase adherence of iron supplementation in pregnancy
72.8	17 (19)	Neonatal	3	Developing the optimal strategies of implementation of post-discharge Kangaroo mother care
72.6	18 (17)	Malnutrition	2	Evaluating cost-effectiveness of cash transfer programs to improve diet quality and nutrition in poor areas
71.6	19 (20)	Malnutrition	3	Developing new cheap appropriate complementary foods
71.1	20 (18)	HIV/AIDS	1	Behavioral research to reduce HIV risky behaviors
69.3	21 (22)	Congen./ Genet.	1	HPSR to increase supplementation of folic acid, beans, oranges and green leafy vegetables in pregnant women
69.2	22 (21)	HIV/AIDS	2	Research to make CD4 count cheaper and easier
68.6	23 (23)	Congen./ Genet.	2	Developing zinc delivery solutions with longer duration of effect
68.4	24 (28)	Diarrhoea	3	Low cost no electrical/no fuel consuming refrigerators to storage food at home level
68.3	25 (24)	Diarrhoea	2	Increasing availability of appropriate complimentary foods
67.5	26 (26)	Pneumonia	2	Reducing the cost of Hib vaccine
67.5	27 (26)	HIV/AIDS	2	Reducing the cost of second-line treatment
67.1	28 (25)	Acc. & Injuries	1	HPSR to improve the access to the existing trauma care systems
66.7	29 (29)	Acc. & Injuries	3	Developing "safe community network programme" adapted for low-resource setting
66.5	30 (33)	HIV/AIDS	3	Developing solutions to prevent mother-to-child transmission
66.2	31 (30)	Neonatal	3	Developing new and improved antibiotic solutions for treating neonatal sepsis

Table 2: The final research priority scores and ranks of 63 research options after application of CHNRI methodology for setting priorities in child health research investments to address the burden of child mortality in the present South African context

Table 2: (Continued)

RPS (x100)	Rank	Cause of death	IHR	Research option
65.8	32 (31)	Malnutrition	3	New technologies for measuring micronutrient status applicable in low-resource settings
64.8	33 (34)	Acc. & Injuries	2	Developing more affordable solutions for accommodating the needs of the injured and disabled
64.6	34 (35)	Neonatal	1	Behavioral research to delay age of first pregnancy in various cultural contexts
63.6	35 (32)	Acc. & Injuries	1	HPSR to improve the efficiency of transfer from low to high level trauma facility
63.5	36 (36)	HIV / AIDS	2	Research to make PCR HIV testing cheaper
63.0	37 (38)	Diarrhoea	3	Develop interventions that will reduce bacterial contamination of crops irrigated with contaminated water
62.6	38 (40)	Malnutrition	3	Developing high-yield micronutrient rich crops
61.9	39 (37)	HIV/AIDS	3	Developing an HIV vaccine
61.8	40 (39)	Pneumonia	2	Developing existing vaccines with needle-free delivery
59.2	41 (43)	Diarrhoea	3	Developing shigella vaccines
58.6	42 (41)	Neonatal	1	Behavioral research to address unhealthy behaviors in pregnancy, e.g. smoking, alcohol and drug abuse
58.6	43 (45)	Neonatal	3	Investigate the role of resuscitation with 100% oxygen of newborn infants, especially premature ones
58.0	44 (42)	Pneumonia	3	Developing RSV vaccine
57.9	45 (48)	HIV/AIDS	3	Develop new generation of less toxic HIV/AIDS treatment regimes
57.1	46 (44)	Acc. & Injuries	3	Develop an innovative safety belt system for child transport in road traffic in an unsafe way
56.9	47 (47)	Pneumonia	3	Developing "common protein" pneumococcal vaccine
56.9	48 (46)	Acc. & Injuries	1	HPSR to establish effectiveness of home-visiting programs to reduce child injuries
55.8	49 (49)	Congen. / Genet.	1	HPSR to improve knowledge on availability and efficient usage of neonatal ICU for emergency surgery
55.6	50 (51)	Malnutrition	2	Evaluating the cost-effectiveness of the existing tools to screen for post-natal depression
54.8	51 (49)	Acc. & Injuries	2	Make blood alcohol testing kits for drunk drivers more affordable
54.4	52 (52)	Pneumonia	3	Developing new antibiotics that would overcome bacterial resistance
52.7	53 (56)	Congen. / Genet.	3	Developing screening tools that are non-dependent of community infrastructure and/or highly skilled personnel
52.6	54 (54)	Acc. & Injuries	3	Developing innovative solutions to protect the pedestrians
52.4	55 (57)	Neonatal	2	Adapting head cooling/body cooling to be feasible/lower cost for low resource settings
52.3	56 (55)	Congen. / Genet.	3	Developing cost-effective diagnostic tool for detecting cong. heart disease after birth in a community setting
52.0	57 (60)	Neonatal	1	HPSR to achieve increased child spacing intervals
51.9	58 (53)	Congen. / Genet.	3	Developing cost-effective diagnostic tool for early detection of cong. anomalies during pregnancy in a com. set.
49.7	59 (60)	Pneumonia	2	Research to reduce the costs of oxygen therapy and make it more available to the general public
49.6	60 (57)	Congen. / Genet.	3	Making catheter interventions for congenital heart disease more affordable
49.3	61 (59)	Congen. / Genet.	2	Making community genetics screening tests more affordable and cost-effective
45.6	62 (62)	Neonatal	2	Adapting the procedure of amnio infusion to lower resource settings
30.8	63 (63)	Congen. / Genet.	1	HPSR to increase the coverage of screening for genetic conditions in the population (community genetics)

Among the 10 research options that received the highest research priority scores (80.3 or greater), nine of them address "instrument 1" of health research, which is health policy and systems research on how to become more efficient with the interventions that are already in place. Four among the top 10 options address diarrhea, three address malnutrition, two address pneumonia and one addresses HIV/AIDS. Apparently, the priority was generally given to the research on more efficient delivery of already existing and cost-effective interventions.

Among the addressed diseases and conditions, the most represented in the top were those that contribute most tothe child mortality in South Africa. An exception to this rule was a relative under-representation of research options addressing HIV/AIDS among the top 10 research options, although HIV/AIDS is considered responsible for up to the third of child deaths in South Africa. A likely explanation for this result is the lack of cost-effective interventions to fight AIDS that could realistically achieve high population coverage, such as a long-awaited vaccine. However, a research option "Development of HIV vaccine" was ranked 37th by technical experts and 39th after adjustments of the scores according to the values of stakeholders, because its answerability and effect on equity upon its initial implementation achieved very low scores in comparison to already existing cost-effective interventions available for other diseases. Similarly, a research option "HPSR to increase coverage of PMTCT interventions" to address HIV/AIDS was ranked 2nd overall by technical experts, but then moved into the fourth place after adjustments by the stakeholders, which was again motivated by equity concerns. The second best-ranked research option to address HIV/AIDS was "HPSR to increase access to antiretroviral treatments", which was ranked 15th by the experts and 14th after adjustment by the stakeholders, e.g. it moved upwards due to its positive implications on equity.

Research options addressing neonatal causes of death were also underrepresented at the top of the Table 2 relative to their share in child mortality burden in South Africa. This was again due to the lack of existing cost-effective interventions that could be delivered at the level of population and achieve high coverage. This resulted in all 3 of the proposed health policy and systems research options that addressed neonatal causes of death being ranked in the bottom half of the table. This also explains why the most highly ranked research options addressing neonatal causes of death, at rank 15 and 17, were research options addressing the development of entirely new interventions, in this case "Development and testing of low cost, robust, simple fetal heart monitors" and "Developing the optimal strategies of implementation of post-discharge Kangaroo mother care", respectively.

With most of the research options addressing HIV/AIDS and neonatal causes of death clearly lacking potential to achieve high scores for all five priority-setting criteria, which was mainly due to low answerability, deliverability and affordability of related new interventions and uncertain effect on equity of the existing ones, the top of the table was clearly dominated by the research options addressing malnutrition, diarrhea and pneumonia with existing highly cost-effective approaches. Nine of top 10 (90%) and 14 of top 20 (70%) research options addressed those 3 conditions. All the five research options that achieved the highest research priority scores were health policy and systems research options offering to improve coverage of the simplest and most cost-effective existing interventions: vitamin supplementation, hand-washing, antibiotics for pneumonia, PMTCT and breast feeding.

This group of priorities is followed by research on improving those interventions that could become highly efficient if they could be made more affordable, deliverable and sustainable, such as, e.g., retroviral treatments to address HIV/AIDS or piped safe water systems or sewage treatment systems to address diarrhea. Another large group of highlighted priorities includes those addressing diseases and conditions with large effect on mortality burden, but for which there are no existing interventions that could achieve very high population coverage in an equitable way. In such cases, an attempt to develop such entirely new interventions was given greater priority than research on creative scaling up or improving of the existing interventions. As mentioned before, the best examples of this were neonatal causes of death, but also accidents and injuries, with a research option "Develop affordable spill-proof paraffin stoves that comply with safety standards" being the overall highest-ranked research option on development of an entirely new intervention, at 11th place.

The middle third of the rankings was occupied by a mixture of highly valued research options that addressed diseases or conditions of lesser impact on the mortality burden, or moderately valued research options addressing diseases with greater impact on the overall mortality. Some good examples of the former case are research options "HPSR to increase supplementation of folic acid, beans, oranges and green leafy vegetables in pregnant women" to address prevention of neural tube defects, i.e. a group of congenital anomalies and genetic disorders, and "Developing 'safe community network programme' adapted for low-resource setting" to address accidents and injuries. The examples of the latter case were research options "Developing solutions to prevent mother-to-child transmission" for HIV/AIDS and "Developing existing vaccines with needle-free delivery" for pneumonia.

It was of interest to analyze which suggested research options found themselves at the bottom end of the score range, and what were the main reasons for their low rankings. Among the 21 research options from the bottom third of the table, seven (1 in 3) addressed congenital and genetic causes of child deaths, while further four addressed accidents and injuries. It is clear that a relatively low contribution of those two causes of deaths to the total disease burden coupled with low answerability, affordability and deliverability of the possible interventions were the main causes underlying this unfavorable outcome, which is

especially the case with genetic disorders. It is of greater interest, however, to understand why four research options addressing pneumonia and another four research options addressing neonatal conditions received low scores, despite having much greater potential to reduce the existing mortality burden.

In case of research options addressing pneumonia, the four research options placed in the lower third of the table were "Developing RSV vaccine", "Developing "common protein" pneumococcal vaccine", "Developing new antibiotics that would overcome bacterial resistance" and "Research to reduce the costs of oxygen therapy and make it more available to the general public" (ranks 44, 47, 52 and 59, respectively). An analysis of the scores for individual criteria shows that the main concerns over the proposed research to develop new interventions to address pneumonia were answerability, affordability and impact on equity. In addition, the particularly low score for the proposed oxygen therapy research option was due to very low predicted potential on overall childhood mortality reduction. Unlike pneumonia, the research options of very low priority score addressing neonatal causes of deaths were not those proposing the development of new intervention, but rather more efficient delivery and improvement of existing interventions: e.g. "Adapting head cooling/body cooling to be feasible/lower cost for low resource settings", "HPSR to achieve increased child spacing intervals" and "Adapting the procedure of amnio infusion to lower resource settings" (ranks 55, 57 and 62, respectively). Those scores reflect very low confidence of technical experts in the potential value of health interventions that already exist to address neonatal causes of death.

Discussion

We presented the application of CHNRI methodology to set research priorities to address child mortality in South Africa. The most important message of this exercise was that the priorities within the existing context are health policy and systems research activities to generate new knowledge on how to improve delivery of the simplest and most cost-effective existing interventions against malnutrition, diarrhoea, pneumonia and HIV/AIDS. This was the first application of the CHNRI methodology at the national level, and many valuable lessons have been learned in the process.

Initially, there was a concern that the methodology, through its proposed five criteria for priority setting, may end up favoring certain types of health research instruments or certain diseases/conditions over the others. However, the application showed that this is not the case, and that the methodology was able to discriminate between the competing research options in an entirely transparent way. Although the top of the rankings in Table 2 was dominated with health policy and systems research options, we argue that the main reason for this is the context in which methodology was applied, in which the highlighted research options do indeed represent research priorities, and not the general preference of the methodology for this type of research. There are two arguments to support this statement. Firstly, in the context of the high remaining burden of child mortality in South Africa in presence of cost-effective interventions and sufficient available resources to implement them, it was expected that the methodology should highlight the issues of improved delivery and increased coverage of those interventions as an immediate priority. As an alternative example, in Scandinavian countries, where the context is entirely different, health policy and systems research options would achieve extremely low scores on their potential to further reduce disease burden. The remaining burden of disease would be best tackled through research on entirely new interventions, which would therefore dominate the top of the ranking list in that context. Secondly, among the 16 research options at the bottom of the list of rankings, 4 of them (25%) are health policy and systems research options (including the outlier at the bottom), despite their high representation at the top of the table. This shows that neither technical experts nor the stakeholders showed preference for this type of research in their scoring, unless it was addressing an intervention for which there was confidence in its overall potential to reduce mortality burden in an equitable way.

The second concern was that a specific disease or condition could be strongly favored over the others through this methodology based on the proposed criteria. However, this was again not the case. For example, the criterion of maximum potential for disease burden reduction was expected to favor research options addressing HIV/AIDS, which has the highest overall contribution to child mortality burden in South Africa. However, the failure of the proposed research options addressing HIV/AIDS to satisfy the other criteria (e.g. answerability, effectiveness, deliverability and the predicted impact on equity) left many of them outside of the highest priority scores. The similar scenario was also observed with neonatal causes of death. The methodology showed that, if mortality reduction due to these two causes is to be achieved in an equitable way, the research priorities would be to develop new and better interventions that would be cost-effective and could achieve high population coverage in an equitable way, rather than insisting on further research on the existing interventions.

It is very important to also understand the dynamic role of the time factor and the impact that the overall context has on the results. The application of this methodology in South Africa showed the way to reduction of child mortality burden by optimizing health research investments within the present context. However, once the expected health gains are achieved though the proposed research investment prioritization, some problems will be reduced (e.g., deaths caused by diarrhea, pneumonia and malnutrition). This will have a feedback effect on the list of priorities: the potential of currently identified priorities to reduce disease burden and improve equity would substantially decrease, affecting their present scores and moving them down in the rankings. The list would then begin to change, and the research options that were identified as the "second-line" priorities

would surface and represent the new research priorities in the changed context. In this way, over a long period of time, optimal sequence of investments into health research would have a substantial potential to reduce the burden of child mortality in a country of interest.

A number of useful observations were made during this process that should be taken into account in further applications of CHNRI methodology at the national level. Technical experts had two main tasks: to systematically list and score research options. In this exercise, it was realized that the listing of research options should be limited in some way, given the time consuming nature of scoring each option afterwards and busy schedules of technical working group members. Therefore, the imperative was to ensure that the list of research questions was not an endless one. This was handled by deciding collectively to address only the top 7 causes of death in South Africa, which were jointly responsible for more than 90% of annual child deaths. Furthermore, for each selected cause of death, it was decided that equal number of research options addressing 3 instruments of health research would be proposed for scoring, to avoid favoring any of the instruments (e.g., research on health policy and systems, research on improving the existing interventions, and research to develop new interventions). A survey was then conducted among the experts in each of the 7 causes of death within South Africa, in which they were asked to agree on the selection of three research options for each of the instrument of health research that would, in their opinion, stand the best chance to be considered a research investment priority when evaluated against the research options addressing other causes of death. This led to having a total of 63 research options to score, which was still a demanding task, but some technical experts managed to complete scoring process during a 1-day workshop, while the remaining experts completed and submitted their scores within a week. Therefore, it is our opinion that the process, as conducted in South Africa, was highly feasible, but would not recommend more than 100 research options to be scored within a single exercise at the national level, as this would be excessively tedious and time-consuming for the technical experts involved in the process.

During the workshops that were held with the 6 members of the technical working group (TWG), it became apparent that in the case of a study at the national level (as opposed to the application at the global or local level when a single condition is addressed, e.g. pneumonia or neonatal causes of death), technical experts involved in the TWG will not possess the knowledge necessary to answer the questions on all the diseases and conditions that are being covered by the exercise. This is particularly exacerbated for questions addressing the maximum potential for disease burden reduction. The allowed scores of 0.5 for undecided but informed answer, and blanks for uninformed answers, allayed this concern to some extent (18). However, there was still some discomfort among the experts that was evidenced by a considerable relative share of 0.5 scores and several answers left blank.

A number of less general technical concerns surfaced during the process of scoring. For example, questions were raised on how would the possible negative impact of an intervention addressed by the research be considered (as, for example, new vaccines may carry some risk, whereas hand washing does not). Another point raised was that the focus on child mortality burden in the context of South Africa is clear, but there would be other areas in which research prioritization is also necessary, but the focus on outcome would be much less clear (e.g. morbidity from asthma or mental illness in developing country context, or child development in general). When it comes to program budgeting and marginal analysis that should follow the process of scoring the research options and in which the priority scores should be combined with the predicted costs of research, there were concerns on how to estimate the cost that should be proposed for development of new interventions at the national level (e.g., HIV vaccine).

When technical experts were presented with the 5 criteria that would be used for setting priorities, a proposal was put forward that perhaps there should be an additional criterion at the national level of South Africa, that would take into account the existing government priorities, i.e. the prevailing political ethos. This idea should be welcomed, as the overall political context and governmental programs and priorities are critical to consider in most countries, and CHNRI methodology is well suited to include more criteria in addition to the 5 that are presented initially (17). Eventually, it was decided that some of this ethos would be captured through involvement of the larger reference group that would be given the power to place weights on the scores addressing individual criteria, and in this way affect the outcomes. There was a feeling among the technical working group that care needed to be taken to ensure that the stakeholders who are asked to provide input on weights are indeed representative of a wide variety of stakeholders. A concern was also expressed that involving lay members of the public in larger reference group would just reproduce prevailing notions. It was also felt that, when building a larger reference group, a purposive sampling of people with critical beliefs should perhaps be a priority (e.g., People's Health Movement).

In selection of larger reference group, a number of factors specific of South African context needed to be taken into account. Pre-1994, South Africa's health system and institutions were managed with scant regard for stakeholder input and a vertical chain of command with little or no input horizontally. When engaging with a larger reference group it was very important to recognize the ideological environment within which one is operating, and to keep this in mind when targeting a larger reference group. In a political climate such as this, it was likely that certain criteria may have a different meaning and resonance than they might in a country in the developed world or even another country within the developing world. By way of example, equity in the South African context has multiple meanings. In many developed countries, the predominant meaning of equity may be that of gender equity. In other countries with wide

disparities between rich and poor equity may primarily refer to such inequities and to attempts to redress such imbalances. In South Africa, while gender and wealth inequities are central, equity in this context also refers to attempts to redress the racial determination of access to health care and services. Furthermore, in conditions of scarce resources, it is often assumed that cost effectiveness is the determining factor of people's values with regard to assigning priorities. Ubel and Loewenstein make the point, however, that cost effectiveness does not capture people's values for setting health care priorities but that fair distribution is considered more important (22). This is reflected in the South African data where equity and efficacy are both given more weight than affordability. There is also a possibility however, that affordability may have scored even lower in the South African larger reference group were it a separate criteria rather than being grouped with deliverability and sustainability.

Our experience with the role of the larger reference group (LRG) did not entirely meet our initial expectations. Although the selection of group members managed to ensure wide representation (see materials and methods section) and their responses were easily obtained, it became apparent after the weighting process that the influence of the LRG on the rankings was quite limited. In most cases, the rankings that were obtained after the scoring from technical experts hardly changed. This is because the questionnaire used to gather the opinions from LRG members asked them to rank the 5 criteria from 1st to 5th, and it was shown that this approach leads to weights that are limited in range (from 3.0 to 0.6, see ref. 19). The equity was highlighted by the LRG as the criterion that should be given greater weight than the others, but the application of the weights did not have potential to change the list of priorities substantially. In the future, this notion needs to be taken into account, and other systems to derive weights from the representatives of the stakeholders possibly implemented (discussion on how this can be achieved is given in ref. 19).

In summary, we feel that the implementation of CHNRI methodology for setting priorities in child health research investments in South Africa was a very useful exercise. Among those involved, it enabled much better understanding of the key criteria that qualify some research option as a funding priority over the others. It provided insight into comparative value of research options addressing different diseases and using different instruments of health research, based on the same set of criteria. Its systematic nature enabled listing and scoring of the competing research options in a highly structured way, which limited the influence of experts' own personal biases on the outcome. Its transparency ensured that all rationales for decision making and input from each person involved from the initial to the final stages were recorded and can be viewed and challenged at any later point in time. The experts submitted their input into the process independently from each other, and the results were based on their collective opinion in a true sense, thus avoiding the possibility of some individuals among them directing the process. The final result was a simple quantitative outcome ("research priority score"), which can now be combined with the proposed cost of research in order to perform program budgeting and marginal analysis and derive an optimal mix of research options to be funded from a fixed budget. It also attempted to consider the voice of stakeholders and wider public, who were given the power to place thresholds and weights upon intermediate scores. Although several possibilities for further improvement of the methodology were identified, we feel that these features of the methodology used to set research investment priorities represent substantial advantages over the existing approaches and that it could be of help to national-level policy makers in their decisions on investments in health research.

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Setting Health Research Priorities to address Millennium Development Goal 4 and reduce Child Mortality at the Global Level

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Abstract

The WHO Child Health Epidemiology Reference Group (CHERG) recently estimated that 10.6 million children younger than 5 years still die each year. This improved characterisation of burden of mortality by specific causes among world's children can now be used to set health research priorities to address this burden. WHO's Department for Child and Adolescent Health (CAH) and Child Health and Nutrition Research Initiative (CHNRI) of Global Forum for Health Research are now using a systematic methodology developed recently by CHNRI to set health research priorities in 10 areas corresponding to leading causes of death in children globally: pneumonia, diarrhea, malaria, birth asphyxia, preterm delivery, neonatal infection or sepsis, HIV/AIDS, accidents and injuries, measles and malnutrition. Each of the 10 groups will be composed of 20-25 technical experts including clinical scientists, epidemiologists, behavioural scientists, experts with technological expertise (e.g., laboratory scientists), implementors (e.g., country program managers), representatives of non-governmental organizations, experts in ethics, and others. Four research instruments will be addressed and prioritised: basic epidemiological research, health policy and systems research, research to improve existing health interventions and research for development of new interventions. Within each of these 4 instruments, broader research avenues, more focused research options and very specific research questions will be systematically listed. They will then be evaluated according to criteria of answerability, effectiveness, deliverability, likely impact on equity and maximum potential for mortality burden reduction. In the second stage, cross-cutting research options will be addressed and the suggested priorities from all 10 groups will be merged and re-ranked, taking into account their potential to reduce disease burden from all 10 main causes of child deaths. This should lead to better understanding of the issues relevant to priority setting for child health research and to recommendations on optimising the use of health research funds to maximise health gains in an equitable way.

Introduction

Among the many problems and issues present in global child health today, the main is that 10.6 million children younger than 5 years still die each year. The high burden of disease and death in children in the developing world is due to a combination of a large number of factors, some of which include avoidable health risks that are still present in high prevalence in the population; lack of education and knowledge about management of the sick child; and a failure of local health systems to deliver interventions at high coverage, especially in low income settings.

In 2001, the World Health Organization established the external Child Health Epidemiology Reference Group (CHERG) to develop estimates of the proportion of deaths attributable to each of the main diseases that cause deaths in children under 5 years of age: pneumonia, diarrhoea, malaria, measles, and the major causes of death in the first 28 days of life. This was needed as a solid starting point for setting priorities in global child health and nutrition, as previous estimates varied widely, with certain organizations or

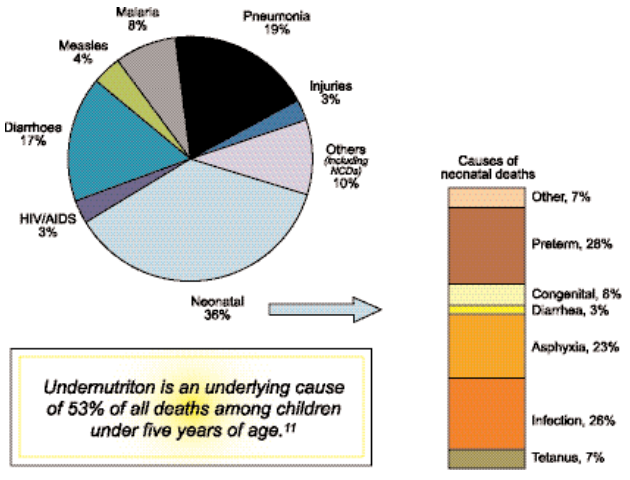

Figure 1: The most recent WHO estimates of the causes of death in children (Bryce et al., 2005)

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research groups showing a tendency to overemphasize the importance of the diseases of their interest (1). They concluded that, over the period 2000-2003, six causes accounted for 73% of deaths in children younger than 5 years: pneumonia (19%), diarrhoea (18%), malaria (8%), neonatal pneumonia or sepsis (10%), preterm delivery (10%), and asphyxia at birth (8%) (Figure 1) (2,3).

A number of interventions that could reduce the burden of disease and death in children are already available. Globally, the coverage for most of these interventions is below 50%, and the children who do not receive them are usually also the poorest, and those exposed to the multiple risk factors. Jones and colleagues estimated that, if the existing interventions for which there is sufficient or limited evidence of the effect, and which are feasible for delivery at high coverage in low-income settings, were made available universally, a disproportionately high figure of 63% of child deaths would be prevented each year (4). Subsequently, Bryce and colleagues demonstrated that there are no financial obstacles to fund such an effort given the amount of funding available, but there is lack of knowledge on how to do it: how best to reach the children who need those interventions (5).

One of the eight "Millennium Development Goals" (UN, 2001) is to reduce child mortality by two-thirds between 1990 and 2015. Although the interventions and the funding needed to achieve this goal seem available, it is increasingly apparent that this goal may still soon be out of reach. One of the reasons for this situation may lie in an inadequate way in which funding priorities are being set in global child health research. Pneumonia and diarrhoea, as an example, are jointly responsible for nearly 50% of all child deaths globally, and interventions (antibiotics and oral rehydration therapy) have been developed and have been shown to be highly cost-effective in preventing deaths from both diseases in the mid 1980's, but this appears to be where research interest ended (6). There is considerably less interest in research on how to implement these approaches in the context of health services in countries with limited resources. As it is rarely considered as a research priority, research on new interventions far exceeds that on delivery. Even if work on new research avenues proves successful, the beneficiaries are only those who can afford the results of the research success, which increases inequity. The methodology for setting investment priorities is needed which could compare and carefully balance between planning long-term investments and research on how to make better use of the existing knowledge.

Proposed Methods

Child and Adolescent Health Department of the World Health Organization (CAH WHO) will use a methodology for setting priorities in health research investments developed by Child Health and Nutrition Research Initiative (CHNRI) to address persisting high levels of child mortality at the global level. The methodology developed by CHNRI is described in detail elsewhere (7-10). WHO CAH will modify and adjust the methodology to the needs of this specific task by introducing changes related to the areas listed below.

Specifying the scope and the context

The scope of CAH WHO's exercise is to recommend priorities in health research investments to address UN's MDG 4 to reduce global child mortality by two thirds by 2015. This undertaking builds upon the 4-year work of WHO Child Health Epidemiology Reference Group (CHERG) that defined the causes of child mortality, as summarised in the introduction of this paper.

As the first step towards setting health research priorities, CHNRI methodology requires defining the context in space, time, population of interest and addressed burden. In this exercise that WHO CAH is undertaking with CHNRI, the context in space is global and the context in time is defined within UN's MDG 4 (the year 2015). Therefore, the suggested prioritisation of health research would be expected to demonstrate results within the next 10 years. The population of interest are children under 5 years of age. The addressed burden is restricted to mortality of all causes in this population.

Revising the suggested instruments of health research

Experts at WHO CAH noted that CHNRI methodology is disease burden oriented and that it proposes three instruments of health research to reduce the burden: health policy and systems research, research to improve existing interventions and research to develop new interventions. However, given the lack of understanding on the extent and underlying causes of the burden itself in many parts of the world, WHO CAH experts felt that an additional research instrument should be basic epidemiological research to define the extent of the burden, the relative risks of factors that cause it and the efficacy of available interventions to avert it.

The importance of this instrument of health research was already recognized by CHNRI experts in earlier versions of the methodology. It was referred to as "Category I" type of research, which is needed to inform the process of priority setting. However, it was omitted as such from the later versions of the methodology and merged with HPSR into "Box 2" research, as it was difficult to score using the same conceptual framework that was applied to other 3 instruments of health research. Nevertheless, for the purpose of this exercise it was agreed between the WHO CAH and CHNRI experts to improve the methodology so that it can address 4 most fundamental instruments of health research:

- Basic epidemiological research to define disease bur den, its components, relative risks of different underlying factors and efficacy of the available interventions to reduce the burden;

RESEARCH INSTRUMENT	RESEARCH AVENUE	RESEARCH OPTION ("project")	RESEARCH QUESTION ("paper")
Basic epidemiological research	Measuring the burden	(List research options within each research avenue)	(List research questions within each research option)
	Understanding risk factors		
	Evaluating the existing interventions		
Health policy and systems research	Studying system capacity to reduce exposure to proven health risks		
	Studying system capacity to deliver efficacious interventions		
Research to improve existing interventions	Research to improve deliverability of existing interventions		
	Research to improve affordability of existing interventions		
	Research to improve sustainability of existing interventions		
Research for development of new interventions	Basic research		
	Clinical research		
	Public health research		

Table 1: Listing the proposed research options and questions

- Health policy and systems research, that would gen erate new knowledge to enable more efficient use of available health care resources in reducing disease burden;
- Research to improve existing interventions that would aim to improve deliverability, affordability and sustainability of those interventions of proven efficacy.
- Research for development of new interventions, that would include all possible approaches that would lead to development of new and non existing interventions, ranging from exploring the role of possible new and unrecognised risk factors to basic molecular and genomic research that would help understand processes leading to child deaths in developing countries.

Further categorization of suggested research (research avenues, research options and research questions)

The experts from WHO CAH noted that the suggested activity of "systematic listing of competing research options" within each of the instruments of health research is a difficult task without defining the level of specificity of the proposed research. In many cases, "research options" seemed too broadly defined to address certain criteria (e.g., answerability), as research questions could be envisaged within different research options that differ in answerability. Also, it was realised that the existence of pre-defined broad "research avenues" within each of the 4 fundamental health research instruments would help technical experts list the proposed research activities in a more systematic way.

A consensus was reached that there should be 4 initial "health research instruments", and within each of them an appropriate number of pre-defined "research avenues". Then, the experts would be responsible to systematically list "research options" within each research avenue and also more specific "research questions" within each research option. The level of specificity of "research option" would be analogous to a proposal for 3-5 year research project, while "research question" would be analogous to a scope of a single research paper. In this way, these four categories of specificity of proposed research activities ("instruments", "avenues", "options" and "questions") address the needs of investors (research areas, research grants) and researchers themselves (research projects, research papers). Table 1 shows the suggested classification for initial two stages of listing the research options and questions.

In this way, the first research instrument ("Basic epidemiological research") would contain 3 broad research avenues: (i) measuring the burden; (ii) understanding risk factors; and (iii) evaluating the existing interventions. The second research instrument ("Health policy and systems research") would have 2 broad research avenues: (i) studying system capacity to reduce exposure to proven health risks; and (ii) studying system capacity to deliver efficacious interventions; the third research instrument ("Improving the existing interventions") would have 3 research avenues: (i) research to improve deliverability, (ii) affordability and (iii) sustainability of existing interventions. Finally, the fourth instrument ("Research for development of new interventions") would have 3 broad avenues: (i) basic research, (ii) clinical research and (iii) pubic health research.

Composition of technical working group expected to list and score research questions

WHO CAH experts noted that the guidance in CHNRI methodology on the number of technical experts that should form each technical group was rather general and that it was left to initiators of the priority setting process to choose it according to their specific needs. Therefore, it was agreed that, given the intended scope and scale of this exercise, no less than 20-25 experts should form each TWG to ensure greater legitimacy of the process. Their backgrounds should be diverse, to avoid systematic bias in their answers and preference towards a specific instrument of health research. Each TWG should ideally include clinical scientists, epidemiologists, behavioural scientists, experts with technological expertise (e.g., laboratory scientists), implementors (e.g., country program managers), representatives of non-governmental organizations, experts in ethics and others.

Validation of the outcome of the process

It is in interest of the WHO CAH to have a clear plan on how to validate the recommended priorities once the process is completed. A concern is that relatively larger number of technical experts expected to score the options against priority setting criteria (such as effectiveness, likely impact on equity or maximum potential for disease burden reduction) will not share equal level of expertise in addressing some of those criteria. A way to validate the outcome of the process is therefore to a priori define those among the experts who possess the greatest level of expertise needed to answer specific priority setting criterion. After scoring, the final results (derived from all 20-25 experts) will be compared to a situation in which only the scores of most qualified expert were taken into account for each given criterion. The comparison between the overall score and this limited version of score will validate the final outcome of the process.

Expected Results

The exercise will be conducted in two stages. In the first stage, 10 groups of technical experts (technical working groups, TWGs) will be formed. They will be assessing research priorities within the following causes of child deaths globally: (i) pneumonia, (ii) diarrhea, (iii) malaria, (iv) birth asphyxia, (v) preterm delivery, (vi) neonatal infection or sepsis, (vii) HIV/AIDS, (viii) accidents and injuries, (ix) measles and (x) malnutrition (as an underlying risk factor for about half of all child deaths). In the second stage, cross-cutting research options will be addressed, the suggested priorities of all 10 groups merged and re-ranked, taking into account their potential to reduce disease burden from all 10 main causes of child deaths.

Tables 2 and 3 show examples of lists of research options and questions for malnutrition (as an underlying risk factor for about half of child deaths) and HIV/AIDS (as a direct cause of death). Similar lists will also be formed for other main causes of child deaths by experts contracted by CHNRI (for pneumonia, malaria and diarrhea) or based at WHO CAH (for remaining diseases). It is expected that technical experts will be invited to join their respective TWGs and submit additional ideas for research options and questions, until the lists become exhaustive. When the lists are finalized, research options and questions will be scored against the 5 criteria identified as relevant to priority setting. This phase of the process is expected to be finalized towards the end of 2006.

WHO CAH also plans to undertake a survey among different groups of stakeholders (such as donors, international organizations, researchers and recipients of research results) and present the differences in their views on the relative importance of 5 criteria defined as relevant to priority setting. These views will be combined with the scores assigned by technical experts to derive the final list of research priorities.

In the final step, the results of the 10 TWGs will be merged by retaining the intermediate scores for the 4 criteria (answerability, effectiveness, deliverability and equity) given to each option from within the TWG. The intermediate

Table 2: An example of listing the proposed research options and questions addressing child mortality from undernutrition

RESEARCH INSTRUMENT	RESEARCH AVENUE	RESEARCH OPTION ("project")	RESEARCH QUESTION ("paper")
Basic epidemiological research	Measuring the burden	Identify the burden of severe malnutrition	Develop tool to identify severe malnutrition in verbal autopsy
			Measure the incidence of severe malnutrition
			Develop tool to measure the incidence of kwashiorkor
	Understanding risk factors	Identify risk factors for severe malnutrition	Assess relative risk of non-breastfeeding
			Assess relative risk of low birth weight
		Identify risk factors for moderate malnutrition	Assess relative risk of non-breastfeeding
			Assess relative risk of low birth weight
	Evaluating the existing interventions	Assess efficacy of existing supplem. feeding programs	To prevent severe wasting
			To prevent kwashiorkor
		Assess efficacy of nutrition counselling	For low birth weight
			For moderate malnutrition
		Assess efficacy of diets based on local food	For low birth weight
			For moderate malnutrition
Health policy and systems research	Studying system capacity to reduce exposure to proven health risks Studying system capacity to deliver efficacious interventions	HPSR to assess capacity of health system to detect severe malnutrition	Assess coverage of existing community-based methods to detect risk exposures
		HPSR to assess cost-effectiveness of treatment	Assess coverage of existing facility-based methods of diagnosis
			Assess cost-effectiveness of inpatient treatment
			Assess cost-effectiveness of outpatient treatment of severe malnutrition
		HPSR to assess access to treatment	Assess cost-effectiveness of outpatient treatment of moderate malnutrition
			Proportion of detected cases who get appropriate inpatient treatment
Research to improve existing interventions	Research to improve deliverability of existing interventions Research to improve affordability of existing interventions Research to improve sustainability of existing interventions	Optimalization of nutrition education messages	Proportion of detected cases who get appropriate outpatient treatment
			Compare efficacy of individual counselling vs. group counselling
		Treatment of severe malnutrition with ready to use therapeutic food	Assess efficacy of introduction of media counselling for moderate malnutrition
			Research to reduce cost of RUTF by using non-milk ingredients
		Adapting existing diets for modetare malnutrition that are based on local food	Assess the level at which RUTF can be de-centralized to become more afford.
			Research on feasibility of diets based on local food
Research for development of new interventions	Basic research	Design of low-cost multi-fortified food to replace animal source foods	Assessments of the feasibility of local foods use in different regions
			Reach consensus on nutrients that should be included in the formulation of fortified food based on biological evidence
	Clinical research	Developing interventions to prevent Kwashiorkor	Understand the biological and metabolic changes leading to Kwashiorkor
			Develop and test new treatments for Kwashiorkor
	Public health research	Improve understanding of interactions between different nutrients between themselves and anti-nutrients	Investigate the interaction between Zn and Iron in fortified food
			Investigate the effect of anti-nutrient on micronutrient absorption

Table 3: An example of listing the proposed research options and questions addressing child mortality from HIV/AIDS

RESEARCH INSTRUMENT	RESEARCH AVENUE	RESEARCH OPTION ("project")	RESEARCH QUESTION ("paper")
Basic epidemiological research	Measuring the burden	Identify the burden of HIV in women of reproductive age and children	Develop a diagnostic test that would confirm the presence of HIV infections by age groups
			Measure the incidence of HIV infection among women of reproductive age
			Measure the incidence of HIV infection among children
	Understanding risk factors	Identify risk factors for mother to child transmission	Assess the risk of breastfeeding for MTCT
			Assess the risk of poverty for MTCT
	Evaluating the existing interventions	Assess efficacy of interventions to prevent mother-to-child transmission	Assess the benefit of existing antiretroviral therapy for uninfected mothers
			Assess the benefit of existing antiretroviral therapy for infected mothers
			Assess the decrease in risk through Cesarean section
		Assess efficacy of interventions to delay mortality in children	Assess the benefit of existing antiretroviral therapy for children
			Assess the benefit of cotrimoxasole prophylaxis
Health policy and systems research	Studying system capacity to reduce exposure to proven health risks	HPSR to assess capacity of health system to make early diagnosis of HIV infection in children	Assess coverage of existing facility-based methods of diagnosis
			Assess coverage of existing community-based methods to screen and refer possibly infected children
			Assess the capacity of health system to introduce DBS method
	Studying system capacity to deliver efficacious interventions	HPSR to assess access to prevention, care and treatment	Proportion of detected cases who get appropriate prevention through cotrimoxasole prophylaxis
			Proportion of detected cases who get appropriate ART
		HPSR to assess cost-effectiveness of existing interventions	Assess cost-effectiveness of prophylaxis through cotrimoxasole
			Assess cost-effectiveness of DBS method in different contexts
			Assess cost-effectiveness of outpatient treatment of ART in different context
Research to improve existing interventions	Research to improve deliverability of existing interventions	Research to improve the preparation and design of the ART for usage in children	Research to develop ART independent of refrigerator requirement and stable in usual environment
		Research to reduce cost of ART	Research to ensure ways to sustain supply and financial resources for ART
	Research to improve affordability of existing interventions	Research to reduce cost of DBS test	Research to replace components of the test with cheaper alternatives
		Research to ensure sustained high prevalence of condom use	Research to develop behavioural interventions to avert "prevention fatigue"
	Research to improve sustainability of existing interventions		Research to improve the design of "female condoms"
Research for development of new interventions	Basic research	Research to develop HIV vaccine	Research to improve understanding of genetic basis of the viral replication
			Research to improve understanding of antigen structure of HIV
		Research to understand molecular basis of host resistance	Research to understand genetic basis of resistance to HIV infection or its slower progressing to AIDS
	Clinical research	Research to develop alternative ARV	Research to develop and test entirely new formulations of ARV
	Public health research	Research to develop new diagnostic tests	Use technological progress in basic molecular research to develop new and highly sensitive and specific diagnostic tests for use at community level

score for the fifth criterion, which is maximum potential for overall reduction in mortality, will be recalculated having in mind he potential of research to reduce mortality from several diseases and conditions at the same time. This should lead to better understanding of the issues relevant to priority setting for child health research and to recommendations on optimising the use of health research funds to maximise health gains in an equitable way.

Discussion

WHO was already involved in several exercises in priority setting in global health research investments. In 1994, WHO formed Ad Hoc Committee on Health Research Relating to Future Intervention Options (AHC). The Committee's mandate was to address priorities for health research and development, prospects for funding and institutional changes that might enhance the output of ongoing research and development investments at the time. In 1996, the Committee presented a report "Investing in Health Research and Development", that recommended policies for R&D investments of particular relevance to the poor nations (11). In 1998, the Global Forum for Health Research began its operations with the main focus on helping to correct this "10/90" gap (12). It identified priority investments ("best buys") through structured interviews, comprehensive review of the literature and a number of other methods that took into account e.g. dynamic nature of "best buys", time factor, baseline status and research intensity, gap towards the intervention development, clarity of definition of endpoints, and other, AHC identified 17 research and development priorities and grouped them into "Strategic research", "Package development and evaluation" and "New tool or intervention development".

Following this exercise, an International Conference on Health Research and Development was held in Bangkok, Thailand in 2000. The conference was spearheaded by an international organizing committee, formed by the representatives of the WHO, The World Bank, Global Forum for Health Research and the Council on Health Research and Development (COHRED). As an introduction to the conference session devoted to priority setting for health research, COHRED reviewed the experiences and lessons from developing countries (13). The issues addressed in this review were systematically categorized into the processes and methods for priority setting, assessing the results of ENHR strategy, defining who sets priorities and how to get participants involved, the potential functions, roles and responsibilities of various stakeholders, information and criteria for setting priorities, strategies for implementation and indicators for evaluation (13). Global Forum for Health Research has also developed a useful priority setting tool for health research, the "Combined Approach Matrix". It is based upon the achievements of historic initiatives from which the Global Forum for Health Research emerged, i.e. the CHRD, ENHR and Ad Hoc Committee on Health Research (AHC). The tool has proven to be highly useful for systematic classification, organization and presentation of the large body of information that is needed at the different stages of priority setting process. It incorporates an "economic" dimension in the priority setting process, defined by the five steps above, along one axis, and an "institutional" dimension along the other, thus covering the information on the determinants of health at the population level (14).

Although all initiatives aiming to set priorities in health research investments are welcome, they are not free of certain shortcomings. For example, identified interventions and research questions in the past were never compiled in a truly systematic way, using scientifically convincing conceptual framework and objective and repeatable methods. The priorities were defined, as a rule, through consensus reached by panels of experts, which makes it more difficult to present the identified priorities to wider audiences as legitimate and fair. There is growing need to make decisions on research priorities not only globally, but also at lower levels - regional, national and local community levels, and at single health facilities. Even among the existing set of leading research priorities defined at the global level, there is still a need to prioritise between them. A methodology in a form of algorithm that would enable this and that would be simple enough to gain wider acceptance is much needed, and CHNRI's effort in developing such methodology was recognized by experts at WHO CAH as potentially useful to attempt priority setting for health research to address global child mortality. The initial results of the application of this methodology will be presented at Global Forum 10 in Cairo, while the more final results are expected towards the end of 2006.

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child injury

diarrhoea

birth asphyxia

ARI

malnutrition

child development

HIV/AIDS

measles

pneumonia

zinc deficiency

neonatal

child injury

malaria

malnutrition

measles

child development

malaria

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