Childhood Pneumonia and Diarrhoea: Setting our Priorities Right

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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 and diarrhoea are jointly responsible for nearly half of all child deaths (5). This is about the same as the number of deaths from smoking, double the total number of deaths from HIV/AIDS and is 25 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 these two conditions – childhood pneumonia and diarrhoea - 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 these two diseases 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 endpoints 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

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 susceptible 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.

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 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).

This methodology has been recently implemented with success at both international 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). This methodology has also been applied recently at the national level. 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 (*Tomlinson M, Chopra M and Rudan I, personal communication*). In Table 1, we present final scores and rankings of those research options that addressed pneumonia and diarrhoea. Eight research options addressing those two diseases were placed among the top 13 research priorities, thus correctly recognizing the magnitude of their effect on mortality burden in South Africa. Furthermore, the priorities identified were dominated by health policy

and systems research options to increase the coverage of the simplest and most cost-effective interventions, such as hand-washing, breastfeeding and increased usage of antibiotic treatment of pneumonia (Table 1).

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 pneumonia and diarrhoea.

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Legends to figures and a table

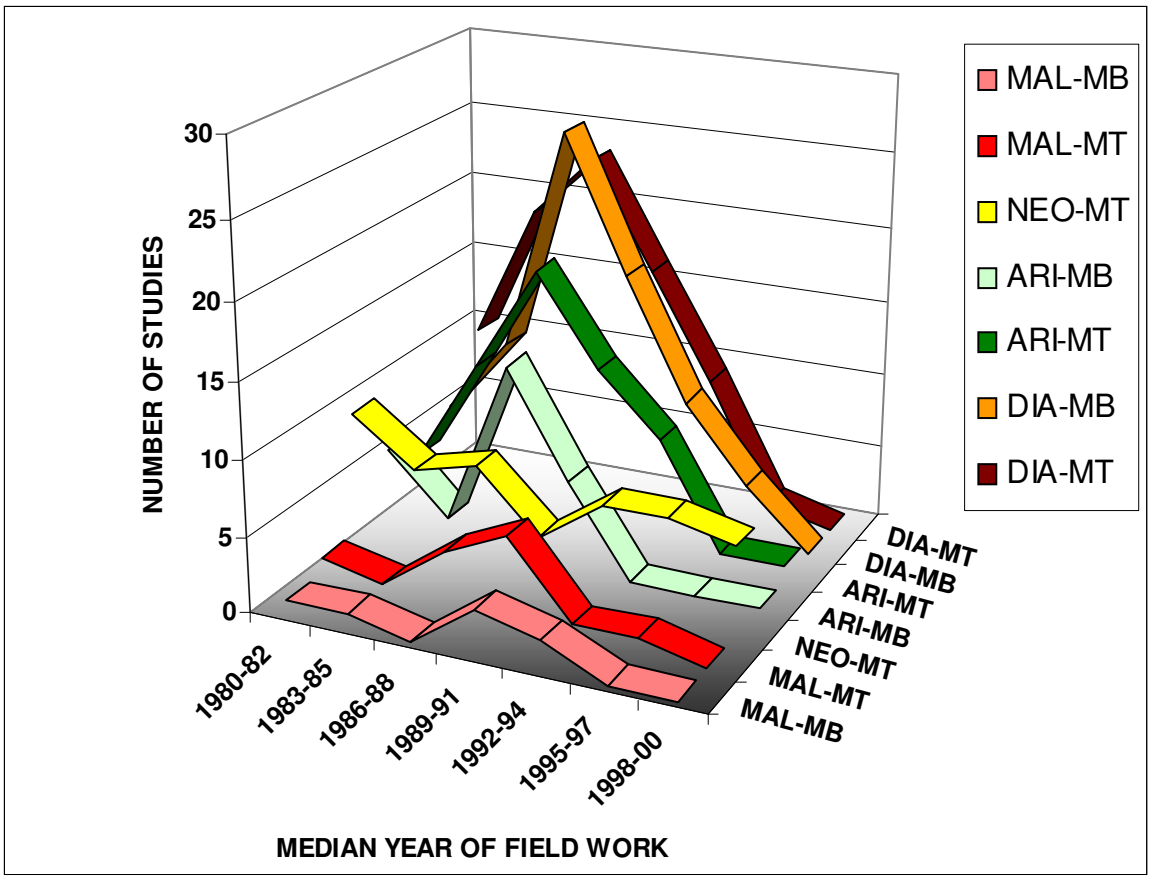
Figure 1: Number of papers with policy-relevant information on epidemiology of specific childhood illnesses in developing countries identified by WHO Child Health Epidemiology Reference Group shows depleting interest in diseases that continue to kill most children (Rudan et al., 2005) (MAL - malaria;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

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).

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.

Table 3: Selected results from research priority setting exercise conducted in April 2006 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. The rankings of 18 research options that addressed childhood pneumonia and diarrhoea are presented.


NUMBER OF STUDIES
30
25
20
15
10
5
0
1980-82
1983-85
1986-88
1989-91
1992-94
1995-97
1998-00
MEDIAN YEAR OF FIELD WORK
DIA-MT
DIA-MB
ARI-MT
ARI-MB
NEO-MT
MAL-MT
MAL-MB
MAL-MB
MAL-MT
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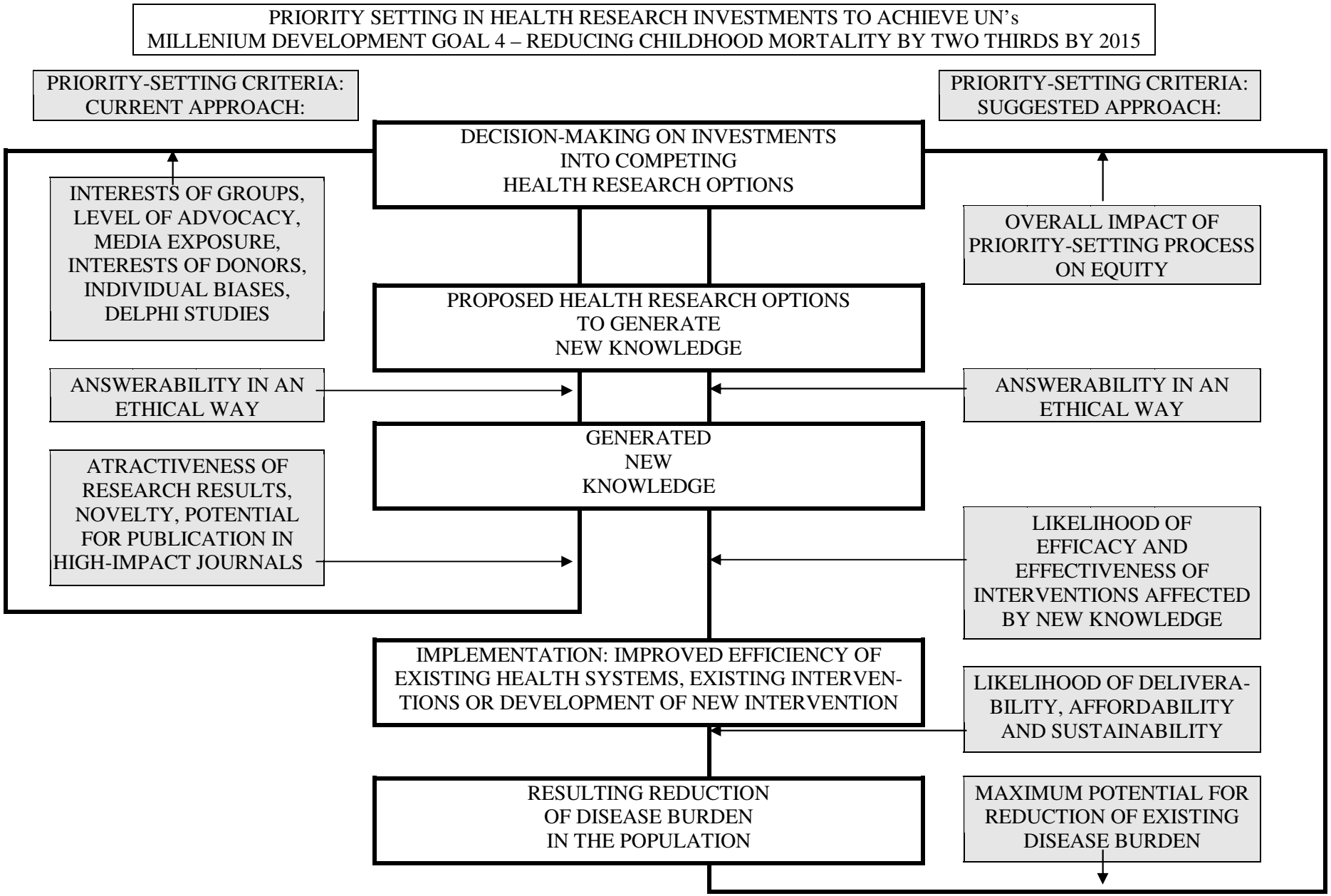
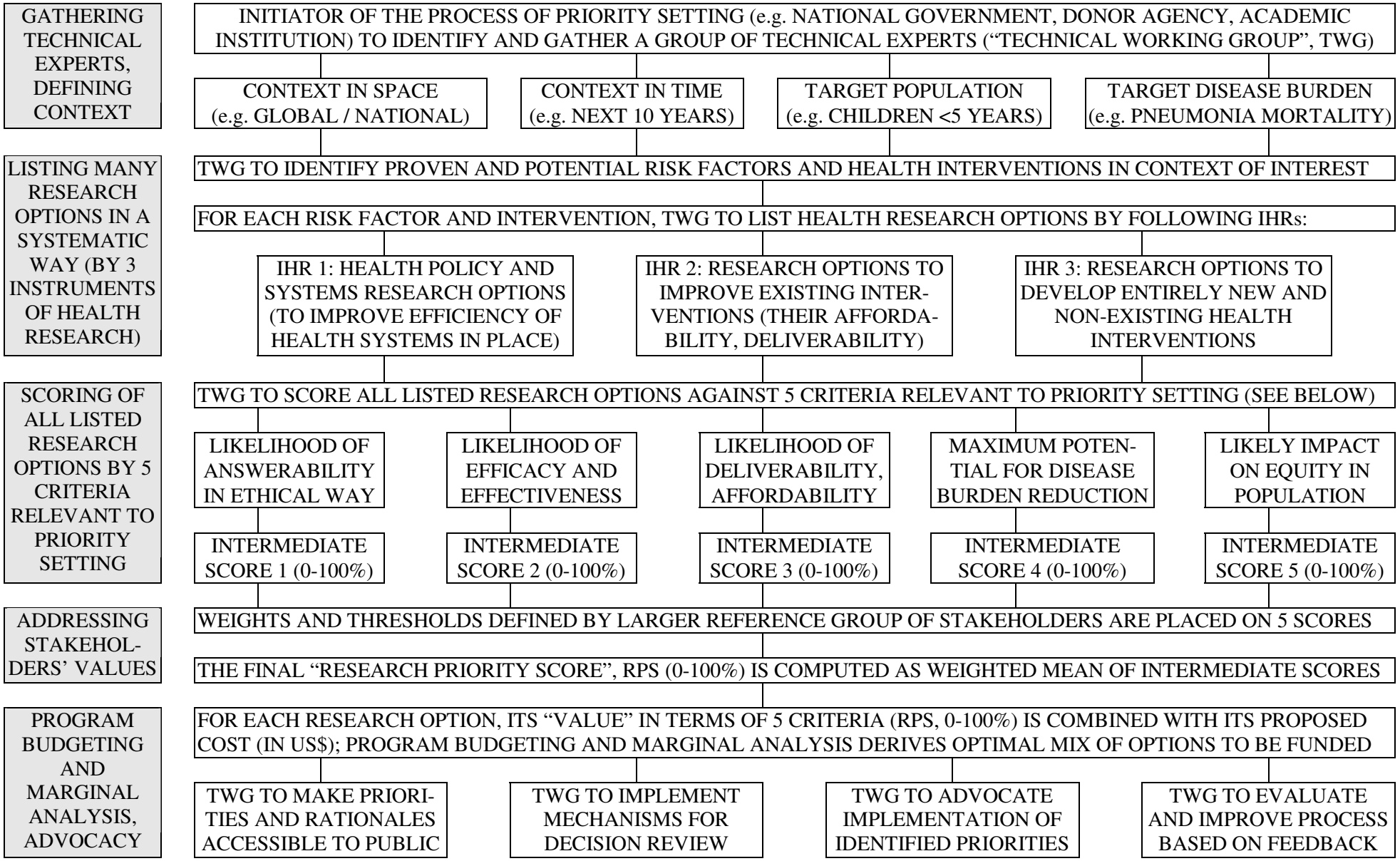

PRIORITY SETTING IN HEALTH RESEARCH INVESTMENTS TO ACHIEVE UN's MILLENIUM DEVELOPMENT GOAL 4 – REDUCING CHILDHOOD MORTALITY BY TWO THIRDS BY 2015
PRIORITY-SETTING CRITERIA: CURRENT APPROACH:
PRIORITY-SETTING CRITERIA: SUGGESTED APPROACH:
DECISION-MAKING ON INVESTMENTS INTO COMPETING HEALTH RESEARCH OPTIONS
INTERESTS OF GROUPS, LEVEL OF ADVOCACY, MEDIA EXPOSURE, INTERESTS OF DONORS, INDIVIDUAL BIASES, DELPHI STUDIES
OVERALL IMPACT OF PRIORITY-SETTING PROCESS ON EQUITY
PROPOSED HEALTH RESEARCH OPTIONS TO GENERATE NEW KNOWLEDGE
ANSWERABILITY IN AN ETHICAL WAY
ANSWERABILITY IN AN ETHICAL WAY
GENERATED NEW KNOWLEDGE
ATRACTIVENESS OF RESEARCH RESULTS, NOVELTY, POTENTIAL FOR PUBLICATION IN HIGH-IMPACT JOURNALS
LIKELIHOOD OF EFFICACY AND EFFECTIVENESS OF INTERVENTIONS AFFECTED BY NEW KNOWLEDGE
IMPLEMENTATION: IMPROVED EFFICIENCY OF EXISTING HEALTH SYSTEMS, EXISTING INTERVEN-TIONS OR DEVELOPMENT OF NEW INTERVENTION
LIKELIHOOD OF DELIVERA-BILITY, AFFORDABILITY AND SUSTAINABILITY
RESULTING REDUCTION OF DISEASE BURDEN IN THE POPULATION
MAXIMUM POTENTIAL FOR REDUCTION OF EXISTING DISEASE BURDEN


GATHERING TECHNICAL EXPERTS, DEFINING CONTEXT
INITIATOR OF THE PROCESS OF PRIORITY SETTING (e.g. NATIONAL GOVERNMENT, DONOR AGENCY, ACADEMIC INSTITUTION) TO IDENTIFY AND GATHER A GROUP OF TECHNICAL EXPERTS ("TECHNICAL WORKING GROUP", TWG)
CONTEXT IN SPACE (e.g. GLOBAL / NATIONAL)
CONTEXT IN TIME (e.g. NEXT 10 YEARS)
TARGET POPULATION (e.g. CHILDREN <5 YEARS)
TARGET DISEASE BURDEN (e.g. PNEUMONIA MORTALITY)
LISTING MANY RESEARCH OPTIONS IN A SYSTEMATIC WAY (BY 3 INSTRUMENTS OF HEALTH RESEARCH)
TWG TO IDENTIFY PROVEN AND POTENTIAL RISK FACTORS AND HEALTH INTERVENTIONS IN CONTEXT OF INTEREST
FOR EACH RISK FACTOR AND INTERVENTION, TWG TO LIST HEALTH RESEARCH OPTIONS BY FOLLOWING IHRs:
IHR 1: HEALTH POLICY AND SYSTEMS RESEARCH OPTIONS (TO IMPROVE EFFICIENCY OF HEALTH SYSTEMS IN PLACE)
IHR 2: RESEARCH OPTIONS TO IMPROVE EXISTING INTER-VENTIONS (THEIR AFFORDA-BILITY, DELIVERABILITY)
IHR 3: RESEARCH OPTIONS TO DEVELOP ENTIRELY NEW AND NON-EXISTING HEALTH INTERVENTIONS
SCORING OF ALL LISTED RESEARCH OPTIONS BY 5 CRITERIA RELEVANT TO PRIORITY SETTING
TWG TO SCORE ALL LISTED RESEARCH OPTIONS AGAINST 5 CRITERIA RELEVANT TO PRIORITY SETTING (SEE BELOW)
LIKELIHOOD OF ANSWERABILITY IN ETHICAL WAY
LIKELIHOOD OF EFFICACY AND EFFECTIVENESS
LIKELIHOOD OF DELIVERABILITY, AFFORDABILITY
MAXIMUM POTEN-TIAL FOR DISEASE BURDEN REDUCTION
LIKELY IMPACT ON EQUITY IN POPULATION
INTERMEDIATE SCORE 1 (0-100%)
INTERMEDIATE SCORE 2 (0-100%)
INTERMEDIATE SCORE 3 (0-100%)
INTERMEDIATE SCORE 4 (0-100%)
INTERMEDIATE SCORE 5 (0-100%)
ADDRESSING STAKEHOL-DERS' VALUES
WEIGHTS AND THRESHOLDS DEFINED BY LARGER REFERENCE GROUP OF STAKEHOLDERS ARE PLACED ON 5 SCORES
THE FINAL "RESEARCH PRIORITY SCORE", RPS (0-100%) IS COMPUTED AS WEIGHTED MEAN OF INTERMEDIATE SCORES
PROGRAM BUDGETING AND MARGINAL ANALYSIS, ADVOCACY
FOR EACH RESEARCH OPTION, ITS "VALUE" IN TERMS OF 5 CRITERIA (RPS, 0-100%) IS COMBINED WITH ITS PROPOSED COST (IN US$); PROGRAM BUDGETING AND MARGINAL ANALYSIS DERIVES OPTIMAL MIX OF OPTIONS TO BE FUNDED
TWG TO MAKE PRIORI-TIES AND RATIONALES ACCESSIBLE TO PUBLIC
TWG TO IMPLEMENT MECHANISMS FOR DECISION REVIEW
TWG TO ADVOCATE IMPLEMENTATION OF IDENTIFIED PRIORITIES
TWG TO EVALUATE AND IMPROVE PROCESS BASED ON FEEDBACK

RPS (x100)	Rank	Disease	IHR	Research option
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
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
80.3	10/63	Diarrhoea	2	Research to reduce costs /improve deliverability and sustainability of piped safe water systems
77.6	12/63	Diarrhoea	2	Research to develop ways of sewage treatment systems affordable to developing countries
75.6	13/63	Pneumonia	1	HPSR to increase zinc supplementation coverage
68.4	24/63	Diarrhoea	3	Low cost no electrical/no fuel consuming refrigerators to storage food at home level
68.3	25/63	Diarrhoea	2	Increasing availability of appropriate complimentary foods
67.5	26/63	Pneumonia	2	Reducing the cost of Hib vaccine
63.0	37/63	Diarrhoea	3	Develop interventions that will reduce bacterial contamination of crops irrigated with contaminated water
61.8	40/63	Pneumonia	2	Developing existing vaccines with needle-free delivery
59.2	41/63	Diarrhoea	3	Developing shigella vaccines
58.0	44/63	Pneumonia	3	Developing RSV vaccine
56.9	47/63	Pneumonia	3	Developing “common protein” pneumococcal vaccine
54.4	52/63	Pneumonia	3	Developing new antibiotics that would overcome bacterial resistance
49.7	59/63	Pneumonia	2	Research to reduce the costs of oxygen therapy and make it more available to the general public