Setting priorities for development of emerging interventions against childhood pneumonia, meningitis and influenza

Citation for published version:

Digital Object Identifier (DOI):
10.7189/jogh.02.010304

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Journal of Global Health

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acute lower respiratory infections, which broadly
include pneumonia and bronchiolitis, are still the
leading cause of childhood mortality. ALRI contrib-
uted to 18% of all deaths in children younger than five
years of age in 2008 [1], and the main pathogens respon-
sible for high mortality were Streptococcus pneumoniae, Haem-
ophilus influenzae and respiratory syncytial virus [2-4]. In
addition, meningitis was estimated to contribute up to
200 000 deaths each year, and influenza anywhere between
25 000 and 110 000 [1,5]. It is widely acknowledged that
a major portion of this mortality should be avoidable if uni-
versal coverage of all known effective interventions could
be achieved. However, some evaluations of the implemen-
tation of World Health Organization’s (WHO) Integrated
Management of Childhood Illness (IMCI) strategy , which
promotes improved access to a trained health provider who
can administer “standard case management”, have shown
somewhat disappointing results [6-8]. Only a minority of
all children with life-threatening episodes of pneumonia,
meningitis and influenza in developing countries have ac-
cess to trained health providers and receive appropriate
treatment [6-8]. Thus, novel strategies for control of pneu-
monia that balance investments in scaling up of existing
interventions and the development of novel approaches,
technologies and ideas are clearly needed.

EMERGING INTERVENTIONS AGAINST
CHILDHOOD PNEUMONIA, MENINGITIS
AND INFLUENZA

Several recent studies quantified the burden of child mor-
tality due to childhood infections [1] and sub-divided it
further according to the causing infectious pathogens [2-5].
In a series of papers that followed, we systematically re-
viewed the available information relevant to the emerging
We conducted an expert panel exercise to assess feasibility and potential effectiveness of 29 emerging health interventions against childhood pneumonia, meningitis and influenza. 20 leading international experts from international agencies, industry, basic science and public health research took part in a CHNRI priority setting process. They used 12 different criteria relevant to successful development and implementation and showed most collective optimism towards improving low-cost pneumococcal conjugate vaccines, antibiotic pediatric formulations, the development of common-protein pneumococcal vaccines and multivalent meningococcal vaccines.

interventions against childhood pneumonia, meningitis and influenza [9-14]. We defined the list of emerging interventions of interest as follows: (i) the first set of emerging interventions was suggested by the officers from the Bill and Melinda Gates Foundation (BMGF) and it was based on strategic priorities that were being discussed at the Foundation in the year 2009; (ii) additional ideas were proposed by our team at the University of Edinburgh, after provisionally reviewing the literature on emerging interventions against childhood infections; (iii) the third set of emerging interventions was suggested by the 20 international experts invited to take part in the CHNRI expert panel meeting (see later). We eventually agreed to evaluate 29 emerging interventions that seemed feasible for reaching the implementation within a 10-year period (Table 1). We aimed to be inclusive and open-minded in their selection because some of them may still be far from implementation.

THE EXPERT OPINION EXERCISE

The CHNRI methodology for priority setting in health research (and technologies) investments was proposed as a systematic tool that can be used by those who develop research policy and/or invest in health research [15-18]. It should assist them to understand (i) the full spectrum of research investment options; (ii) the potential risks and benefits that can result from investments in different research options; and (iii) the likelihood of achieving reductions of persisting burden of disease and disability through investments in health research and health technologies. The CHNRI methodology has 3 stages: input from investors/policy-makers (who define the context and criteria for priority setting); input from technical experts (who propose, list in a systematic way, and then score different research investment options against a pre-defined set of criteria); and input from other stakeholders (weighing the criteria according to wider societal system of values). The method has been described in detail elsewhere and many examples of its implementation are publically available [19-22].

Table 1 The consolidated list of 29 emerging interventions against childhood pneumonia, meningitis and influenza

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low-cost polysaccharide conjugate vaccines for <em>Pneumococcus</em> (low-cost: US$ 3.50 per dose)</td>
</tr>
<tr>
<td>2</td>
<td>Low cost, cross-protective common protein vaccines for <em>Pneumococcus</em></td>
</tr>
<tr>
<td>3</td>
<td>Low cost, cross-protective common protein vaccines for seasonal influenza (existing flu vaccines should be considered as a current intervention)</td>
</tr>
<tr>
<td>4</td>
<td>Monoclonal antibodies for passive immunization against RSV</td>
</tr>
<tr>
<td>5</td>
<td>Anti-RSV vaccine for use in infants</td>
</tr>
<tr>
<td>6</td>
<td>Anti-RSV vaccine for use in pregnant women</td>
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<tr>
<td>7</td>
<td>Meningitis A conjugate vaccine</td>
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<tr>
<td>8</td>
<td>Multivalent meningococcal vaccines</td>
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<tr>
<td>9</td>
<td>Combination vaccines: meningococcal + other vaccines</td>
</tr>
<tr>
<td>10</td>
<td>Needle-free versions of current measles vaccines</td>
</tr>
<tr>
<td>11</td>
<td>Heat stable versions of current measles vaccines</td>
</tr>
<tr>
<td>12</td>
<td>Oxygen delivery systems for low-resource settings</td>
</tr>
<tr>
<td>13</td>
<td>Low cost ventilatory support</td>
</tr>
<tr>
<td>14</td>
<td>Non-liquid pediatric antibiotic formulations for use in large scale programmes in appropriate dose</td>
</tr>
<tr>
<td>15</td>
<td>Vaccines against <em>S. aureus</em></td>
</tr>
<tr>
<td>16</td>
<td>Passive immunization against <em>S. aureus</em></td>
</tr>
<tr>
<td>17</td>
<td>Combination vaccines against multiple respiratory viruses</td>
</tr>
<tr>
<td>18</td>
<td>Maternal vaccination to protect neonates against neonatal sepsis: <em>E. coli</em> and <em>Klebsiella</em></td>
</tr>
<tr>
<td>19</td>
<td>Maternal vaccination to protect neonates against neonatal sepsis: <em>Streptococcus B</em> and <em>S. aureus</em></td>
</tr>
<tr>
<td>20</td>
<td>Rapid diagnostic test for bacterial infections in children</td>
</tr>
<tr>
<td>21</td>
<td>Rapid multiplex assay for etiology-specific diagnosis in children</td>
</tr>
<tr>
<td>22</td>
<td>Rapid multiplex assay for etiology-specific diagnosis in young infants</td>
</tr>
<tr>
<td>23</td>
<td>Rapid diagnostic test to predict severe outcome of pneumonia episodes</td>
</tr>
<tr>
<td>24</td>
<td>Maternal vaccination for infectious agents relevant in infants (eg, PC, Hib, influenza)</td>
</tr>
<tr>
<td>25</td>
<td>Effective mucosal (oral or rectal) antibiotics for neonatal infections</td>
</tr>
<tr>
<td>26</td>
<td>Immunomodulating agents to stimulate innate immunity</td>
</tr>
<tr>
<td>27</td>
<td>Surfactant replacement therapy</td>
</tr>
<tr>
<td>28</td>
<td>Novel interventions to reduce indoor air pollution</td>
</tr>
<tr>
<td>29</td>
<td>Water-free solution for hand disinfection to reduce transmission of respiratory pathogens</td>
</tr>
</tbody>
</table>

RSV – respiratory syncytial virus, PC – pneumococcus, Hib – *Haemophilus influenzae* Type B
The expert opinion exercise focused only on emerging interventions and a broad, long-term (downstream) context/vision. We invited 20 leading international experts from international agencies, industry, basic science and public health research to Dubrovnik, Croatia, in September 2009. The invited experts provided opinion on how the 29 chosen emerging interventions satisfy a number of criteria relevant to prioritization of support to emerging interventions against childhood infections. Based on a modified CHNRI’s conceptual framework, 12 criteria for prioritization were developed for emerging interventions: (i) answerability (in an ethical way); (ii) low development cost; (iii) low product cost; (iv) low implementation cost; (v) likelihood of efficacy and effectiveness; (vi) likelihood of deliverability; (vii) likelihood of affordability; (viii) likelihood of sustainability; (ix) maximum potential impact on mortality burden reduction; (x) likelihood of acceptability to health workers; (xi) likelihood of acceptability to end users; (xii) predicted impact on equity. Further details about the modified CHNRI framework with the 12 criteria used for the expert panel meeting in Dubrovnik in 2009, and the process of the expert opinion exercise, are available from the corresponding author upon request.

The first task for the experts was to read the background information assembled about the 29 emerging interventions in a 285-page landscape review, later published as a series of papers [9-14]. The second task was to participate in the expert panel meeting where, over the course of 5 days and a total of 10 discussion sessions, the experts were told why each of the 12 criteria was chosen, and then they discussed how to apply them to each of the 29 emerging interventions. They were free to challenge all information provided to them in a background document and to share further personal knowledge or opinion with the group. Notes of their input were taken and the landscape review was being continuously amended. After each discussion session the experts were invited to score, independently of each other, all emerging interventions according to the 12 agreed CHNRI criteria. For each of the 29 emerging interventions and each criterion, each expert answered questions targeted to assess the likelihood of the proposed emerging interventions to comply with the priority-setting criterion. A summarized version of those questions is presented in Table 2. The full version of questionnaires that were used is available upon request from the corresponding author.

<table>
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<tr>
<th>Table 2</th>
<th>A summarized version of questions used to assess whether proposed 29 interventions satisfy the 12 priority-setting criteria</th>
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<tbody>
<tr>
<td><strong>Answerability (1 for Yes; 0 for No; 0.5 for Undecided)</strong></td>
<td>• Do we have a sufficient research and development capacity to make the intervention available on the market by 2020? • Do we have a sufficient level of funding support to make the intervention available on the market by 2020? • Would you say that it is likely that the remaining technical hurdles can be overcome to make the intervention available on the market by 2020?</td>
</tr>
<tr>
<td><strong>Cost of Development (in US$) (1 for Yes; 0 for No; 0.5 for Undecided)</strong></td>
<td>• How much will it cost to get from the current stage of development to commercial availability of each emerging intervention below? a.&lt;US$1 billion, b.&lt;US$ 500 million, c.&lt;US$ 100 million</td>
</tr>
<tr>
<td><strong>Likelihood of Efficacy (0%-100%)</strong></td>
<td>• Please assess the likelihood (0%-100%) that adequately powered randomized controlled trials of the interventions listed below (ROWS), conducted in developing countries, would consistently show statistically significant reduction in cause-specific mortality from each of the four causes of death listed below (COLUMNS). a. Pneumonia, b. Meningitis, c. Neonatal sepsis, d. Influenza</td>
</tr>
<tr>
<td><strong>Likelihood of Maximum Potential Impact on Disease Burden</strong></td>
<td>• Please predict, for each of the 4 causes of death below (COLUMNS), the proportion of deaths in children under five years of age due to that cause that could be averted if the complete coverage with the emerging interventions listed below (ROWS) could be achieved? a. Pneumonia, b. Meningitis, c. Neonatal sepsis, d. Influenza</td>
</tr>
</tbody>
</table>
| **Delivery of the Intervention at Time of Introduction (1 for Yes; 0 for No; 0.5 for Undecided)** | • Taking into account (i) the infrastructure and resources required to deliver emerging interventions listed below (eg, human resources, health facilities, communication and transport infrastructure); (ii) the resources likely to be available to implement the emerging interventions at the time of introduction; (iii) overall capacity of the governments (eg, adequacy of government regulation, monitoring and enforcement; governmental intersectoral coordination), and (iv) internal and external partnership required for delivery of interventions (eg, partnership with civil society and external donor agencies), would you say that the emerging interventions would be? a. Deliverable at the time of introduction, b. Affordable at the time of introduction, c. Sustainable for at least 10 y after the time of introduction Assessing Readiness of Health Systems to take Existing and Emerging Interventions to High Coverage Globally (90% urban / 80% Rural) at this Point and at the Time of their Introduction (**1** – we are ready (or we will be ready); **0.5** – we may be getting closer, but are not quite ready; **0** – we will not be ready;)
| **Acceptability and Equity (1 for Yes; 0 for No; 0.5 for Undecided)** | • Taking into account the overall context, intervention complexity, health workers’ behavior and the end-user population at the time of introduction, a. Would health workers be likely to comply with implementation guidelines? b. Would end-users be likely to fully accept the intervention? c. Would you say that the proposed intervention has the overall potential to improve equity after 10 y following the introduction? |
The second level of priority was assigned to improvements in existing vaccines to enable needle-free delivery and heat stability, and to evaluations of maternal immunization, improved use of oxygen systems and the development of combination vaccines and vaccines against major viral pathogens. Passive immunization, action on risk factors such as indoor air pollution or poor sanitation, or development of vaccines against sepsis-causing bacterial pathogens received the lowest scores. The exercise suggested that most of the emerging interventions are still not feasible.
in existing vaccines (eg, measles or H. influenzae type b) to enable needle-free delivery and heat stability. Similar overall scores were given to evaluations of maternal immunization, improved use of oxygen systems and the development of combination vaccines and vaccines against major viral pathogens. The next level of priority was assigned to various diagnostic tools, the impact of which is currently limited with sub-optimal levels of access to care, care-seeking behavior and the availability of 1st and 2nd line antibiotics. Interventions that proposed passive immunization, action on risk factors such as indoor air pollution or poor sanitation, or development of vaccines against sepsis-causing bacterial pathogens such as S. aureus or E. coli received the lowest scores (Table 3).

An extended version of the results of the CHNRI process with the current status of each emerging interventions’ development, the key challenges that remain to be addressed, the visual representation of scores given by the expert panel to each intervention and the assessment of potential effectiveness of each intervention is available in the series of papers published elsewhere [9-14]. It should be noted that the assessment of potential effectiveness (Table 3) can also range from 0%-100%, but its interpretation is different than the other 11 criteria; rather than measuring collective optimism, it actually predicts the proportion of mortality burden that could be averted through implementation.

Pneumococcal conjugate vaccines, which were treated as emerging interventions back in 2009 because of a very low uptake in low and middle income countries at the time, achieved scores over 80% for all criteria apart from “low uptake in low and middle income countries at the time,” which indeed ended up being the main point of discussion once they were introduced. In compar-
ison, common protein pneumococcal vaccines are still held back by concerns over answerability (although it is getting closer to 80%), and over all criteria related to their future cost. Other interventions show quite different score profiles. For example, anti-RSV vaccine for use in infants failed on all criteria apart from “acceptance for health workers”, whereas monoclonal antibodies for passive immunization against RSV failed entirely on product cost, affordability and sustainability concerns, although product development cost was considered feasible. The introduction of oxygen systems was considered answerable and did not suffer from major cost concerns, but these systems were not deemed sustainable, sufficiently acceptable and equitable. In comparison, common protein flu vaccines were considered sustainable, acceptable and equitable, but there were still concerns about answerability and costs of development and of the final product.

CONCLUSION

In accordance with other similar exercises with CHNRI methodology the process showed some clear advantages. The context and the criteria were transparent and the management of the process was overseen by the funding agency (BMGF) over its entire duration. This kind of partnership should result in better understanding and promote ownership and commitment to the main messages of the expert opinion exercise. The scoring process was highly systematic and structured. It was free from undue influence from prominent members within the expert group, because all the experts submitted their opinions and scores independently from each other. The varied mix of the experts from different backgrounds ensured that the scientific assessment of the research priorities is combined with a view of the broader community in which the priorities would be implemented. The entire process from the initial to the final stages was documented and can be viewed and challenged at any point in time. The final result of the process was a simple quantitative outcome (“research priority score”), which measured the “value” of each research option when all the criteria and views were taken into account. This “value” can be combined with the predicted cost of further research and development needs in order to derive an optimal mix of emerging interventions to be funded from a limited budget.

Acknowledgments: The authors express their gratitude to all the participants of the expert panel meeting in Dubrovnik in September 2009 for their time and valuable input, which allowed conduction of this unique exercise. The authors also thank their project officers for clear guidance and excellent collaboration throughout the course of the project.

Funding: Bill and Melinda Gates Foundation.

Ethical approval: Not required.

Authorship declaration: IR, ET, LZ, HN, KYC, MT, AT, ZB, TH, SEA, MC and HC prepared background reading material (a 285-page “landscape review”) and moderated different stages of the expert meeting. IR, HC, ET, HN, ZB, KYC, AT, MT and MC designed a modified CHNRI process for setting research priorities in emerging health technologies. LZ, ZB and ET conducted the analyses. IR, KYC, HC, ET, HN and LZ drafted the paper with other various authors’ contribution in revision. TH, MC and SEA provided important intellectual input at different stages of the work.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coiDisclosure.pdf (available on request from the corresponding author) and declare support from Bill and Melinda Gates Foundation for the submitted work. The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES


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