Use of systematic reviews of the evidence in public health nutrition

Proceedings of an informal consultation held
18 October 2011 in Geneva, Switzerland
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Acknowledgements

This meeting report was prepared by Dr Francesco Branca, Dr Luz Maria De-Regil, Dr Nancy Jennings Aburto, Dr Chizuru Nishida and Dr Juan Pablo Peña-Rosas. The meeting was convened by the Department of Nutrition for Health and Development, in collaboration with the Aga Khan University, Pakistan. We are grateful to the meeting participants for their active participation. We acknowledge logistic support from Mrs Anne Ryan-Rohrich and Ms Jo-Anne Muriel.

Financial support

The Bill & Melinda Gates Foundation provided financial support for travel of participants to the meeting in Geneva, Switzerland. WHO thanks the International Micronutrient Malnutrition Prevention and Control (IMMPaCt) Programme, Centers for Disease Control and Prevention (CDC), Atlanta, USA for the support provided to publish this report.
Background

As of 2010, all the public health recommendations published by World Health Organization (WHO) have to strictly comply with the methodology described in the *WHO handbook for guideline development* (1). This process, which is followed for nutrition guidelines, has been recently summarized (2) and includes several steps ranging from establishing steering and guideline groups and prioritizing needs, to planning the implementation and updating the guidelines. Systematic reviews following the Cochrane methodology (3) are used to assess the evidence for outcomes that are critical for decision-making. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology is used to assess the overall quality of evidence and establish the strength of the recommendations, considering the balance among risks and benefits, values, preferences, and costs (4–6). These guidelines, along with systematic reviews of the evidence, are made available to all countries through the WHO electronic Library of Evidence for Nutrition Actions (eLENA, http://www.who.int/elena/en/), which was launched in August 2011.

The leadership role of WHO in the area of evidence-informed nutrition guidelines, and the current high level of attention being given to nutrition through several commitments such as the 2008–2013 Action plan for the global strategy for the prevention and control of noncommunicable diseases (7), the Global strategy on diet, physical activity and health, as endorsed by the Fifty-seventh World Health Assembly resolution WHA 57.17 (8), and the Comprehensive implementation plan on maternal, infant and young child nutrition, as endorsed by the Sixty-fifth World Health Assembly resolution WHA 65.6 (9), have helped the field of public health nutrition progress more quickly.

The WHO Department of Nutrition for Health and Development, in collaboration with Aga Khan University, convened a technical informal consultation to discuss current methods being used for the development of nutrition-related systematic reviews and to review potential options to improve their quality and their utility for public health. The meeting also aimed to discuss coordination in the update and development of nutrition-related systematic reviews. The consultation was held on 18 October 2011 in Geneva, Switzerland, and included representatives from WHO internal partners, some United Nations agencies, the Cochrane Collaboration, the Campbell Collaboration, interested donor agencies and selected members of some academic and research institutions with an interest and experience in systematic reviews in this area.

Summary of presentations

Seven presentations were made and discussed during the course of this one-day meeting (Annex 1). Each presentation was followed by an open period of questions and answers and comments. The format was a round-table discussion, with all participants having equal opportunity to participate and contribute.
Overview of systematic reviews on nutrition: gaps and implications for future research

Dr Zulfiqar Bhutta and colleagues presented and discussed an unpublished background paper, *Overview of systematic reviews on nutrition: gaps and implications for future research*. This document includes a situation analysis of the status of systematic reviews in some illustrative areas relevant to nutrition; a description of those currently involved in conducting systematic reviews, including their affiliations and geographical location; and the methods used by the authors of systematic reviews. The “assessment of multiple systematic reviews” (AMSTAR) method (10), was used to assess the quality of existing systematic reviews. Authors preliminarily classified the reviews into four illustrative areas: preventive and promotive interventions; therapeutic nutrition interventions; fortification strategies; and delivery platforms. The results indicated that over the period 2006–2011, the Cochrane Collaboration had published approximately 50% of all systematic reviews in the field of nutrition and that nutrition-focused journals have published relatively few. The systematic reviews published by the Cochrane Collaboration were generally of better quality than reviews published outside of that collaboration. Among the methodological problems identified, the use of non-standardized definitions of conditions such as acute respiratory infections was discussed.

The presenter concluded that his team at the Aga Khan University would like to use the information from their paper to set the stage for discussing the possibility of creating a support platform for development of systematic reviews in nutrition, to improve quality assurance, enhance technical methods and establish an editorial process that brings in contextual and qualitative evidence and multistakeholder input. Such a platform could also help streamline the commissioning, as well as the quality, of reviews that are of relevance to public health and policy.

Use of systematic reviews in the guideline development process – lessons learnt

Dr Luz Maria De-Regil presented and discussed the WHO evidence-informed nutrition guideline development process. Mapping of available systematic reviews is an initial step for gathering the evidence in the WHO guideline development process. It helps identify reviews that may require updating to include either recently published trials or critical outcomes identified during the WHO nutrition guidelines development process and summarized in PICO (population, intervention, comparison and outcome) format. Registered trials, protocols and systematic reviews are sought in various databases, including the Cochrane Database of Systematic Reviews and the international prospective register of systematic reviews, PROSPERO (http://www.crd.york.ac.uk/NIHR_PROSPERO/), which includes Cochrane and non-Cochrane systematic reviews. Other resources are also searched, including Evidence Health Canada, which supports evidence-informed decision-making in public health organizations by providing easy access to current review-level research evidence through a searchable online registry, organisational assessments of readiness for using research to guide decision-making, customized knowledge broker consultation and support.

The Department of Nutrition for Health and Development has worked with the editorial office and various groups within the Cochrane Collaboration. The Cochrane Collaboration is an international network of more than 28 000 people from over 100 countries working together to help health-care providers, policy-makers, and patients, their advocates and carers, make well-informed decisions about health care. This
collaboration hosts the Cochrane Library and CENTRAL, the largest collection of records of randomized controlled trials in the world. Currently, the collaboration has 53 review groups, which publish reviews that fall within their scope in the Cochrane Library. The collaboration also includes many other Cochrane entities that support the work of the review groups, 16 of which cover methodological issues. Some examples are the bias methods, equity methods, comparing multiple interventions methods, individual participant data meta-analysis methods and non-randomised studies methods. On 24 January 2011, WHO awarded the Cochrane Collaboration a seat on the World Health Assembly, allowing the collaboration to provide input on WHO health resolutions.

One of the significant joint projects that WHO and the Cochrane Collaboration have developed is the WHO Reproductive Health Library. This is an electronic journal covering sexual and reproductive health, produced by WHO’s Department of Reproductive Health and Research, using the best available evidence from Cochrane reviews. This initiative has helped millions of women and babies in developing countries through practice recommendations on neonatal health, pregnancy and childbirth, and sexually transmitted infections. The Cochrane Collaboration and WHO also work jointly in eLENA. Cochrane contributors have identified relevant Cochrane reviews and updated or conducted new Cochrane reviews in response to WHO’s priorities in nutrition. This helps facilitate the development of sound, evidence-based guidelines on nutrition issues that are relevant to WHO Member States and other partners. These systematic reviews in nutrition are made open access through eLENA, by means of an agreement with the publisher John Wiley & Sons Ltd.

WHO has also collaborated with the Campbell Collaboration, a sibling organization to the Cochrane Collaboration that prepares, maintains and promotes the accessibility of systematic reviews in areas such as education, criminal justice, social policy and social care. The Campbell Collaboration was formally established in 2000. The collaboration currently has six coordinating groups: crime and justice, education, international development, methods, social welfare, and users’ group. The users’ group is responsible for the production, scientific merit and relevance of Campbell systematic reviews. Each coordinating group has two representatives on the steering group. Campbell’s International Secretariat is now located in Oslo, Norway and is hosted by the Norwegian Knowledge Centre for the Health Services.

WHO has followed various approaches to retrieve, synthesize and assess the evidence. One approach has been to use existing systematic reviews and contact the authors for updating them if they are not current. An alternative has built on the use of systematic reviews developed by other groups, or commissioned “tailored” systematic reviews by external experts. WHO has also taken the lead in promoting multicountry multidisciplinary review teams to undertake the systematic reviews. The latter approach has been the most cost effective (see Table 1). It allows the inclusion of authors with multiple expertise, and tailoring of the reviews to answer priority questions in line with prespecified inclusion and exclusion criteria and defined interventions. It further builds on a thorough systematic search, and facilitates timely delivery of the systematic reviews for guideline meetings. It is also less expensive and keeps WHO staff up to date in their areas of work.
Table 1
Factors related to the development of tailored systematic reviews for nutrition

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pros</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review team</td>
<td>WHO promotes the formation of multidisciplinary review teams that include a methodologist, content experts and graduate students.</td>
<td>WHO staff time may be overcommitted. An efficient number of authors may not allow the process to be sufficiently inclusive of different views.</td>
</tr>
<tr>
<td></td>
<td>WHO provides technical and financial support at the time staff are up to date on the topic.</td>
<td>Perceived or real conflicts of interest of any of the authors cannot be completely ruled out.</td>
</tr>
<tr>
<td>Capacity-building</td>
<td>Their use allows for training of future independent reviewers (i.e. capacity-building on authors from low- and middle-income countries).</td>
<td>As the systematic reviews are published in English, the formation of future reviewers is limited to those that are fluent in this language.</td>
</tr>
<tr>
<td>Usefulness</td>
<td>Reviews are tailored to answer WHO priority questions in terms of populations, interventions, comparisons and outcomes.</td>
<td>Question items that are not deemed as a priority by a guideline development group may not be addressed by the reviews.</td>
</tr>
<tr>
<td></td>
<td>The results of the review are limited by the definitions, comparisons and outcomes used in the trials and they may not be appropriate to respond to the priority questions.</td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td>The reviews permit standardization over the inclusion and exclusion criteria, search and methods.</td>
<td>Not all authors are willing to accept the standardized methods required by WHO.</td>
</tr>
<tr>
<td>Timeliness</td>
<td>Information is available for guideline development meetings.</td>
<td>WHO timelines are not always aligned with Cochrane editorial and publication timelines.</td>
</tr>
<tr>
<td></td>
<td>External authors, who commonly have other priorities, may not comply with deadlines.</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Less expensive.</td>
<td>Differences in costs associated with systematic reviews may not allow appropriate budget planning.</td>
</tr>
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</table>

* Tailored systematic reviews are those specifically commissioned for WHO nutrition guidelines development and can be conducted in-house with direct involvement of WHO technical staff and technical support from external experts.
Evidence gaps for nutrition-sensitive agriculture

Dr Marie Ruel discussed the evidence gaps for nutrition-sensitive agriculture. She addressed the complex relationship between agriculture and nutrition and a recently published systematic review on agriculture and nutrition. It is now widely recognized that nutrition outcomes are determined by a complex interaction among preconditions, including individual dietary intake and health status; household food security; caring capacity and practice; access to adequate health services; and a healthy environment – all of which are reinforced by deeper social, economic and political processes that drive and enable them. It is difficult to handle all the complex pathways between agriculture and nutrition when conducting a systematic review of the evidence. Most reviews on agriculture and nutrition in the last 10 years have looked at the same studies, using different approaches yet with very similar results. Overall conclusions are generally that nutrition impact is mixed and is improved with behavioural-change communications. Many nutritional outcomes are not the focus of these studies and therefore nutrition outcomes are not commonly measured. There is a general belief that agriculture programmes are too complex to be measured systematically.

It was highlighted that a systematic review of the evidence in this area would probably be more useful to draw conclusions if the studies evaluated were more rigorous. This is an area that needs more evidence in place of more reviews. One issue discussed referred to the lack of rigorous evaluations and the premise that there is not much publication bias because rigorous evaluations are generally published. The systematic review is valuable to identify the gaps and acknowledge when there are few studies addressing a question.

Information needs for policy briefs on nutrition-sensitive development

Dr Meera Shekhar addressed the information needs for policy notes on nutrition-sensitive development. Policy notes require that evidence be retrieved and evaluated first. There are efforts to address the gap when the evidence is lacking and to identify ways to build the evidence base. There is interest in developing support for agricultural and larger programmes for improving health and nutrition, as well as increased policy interest in nutrition. The Scaling Up Nutrition (SUN) movement is for all countries whose populations experience undernutrition and for all stakeholders committed to providing support. Over one billion people in the world today are undernourished. Proven solutions are available and are ready to be scaled up. SUN brings together over 100 organizations and governments committed to working together to fight hunger and undernutrition. The SUN framework, which began with direct nutrition interventions, is now looking at “nutrition-sensitive” interventions as a way to address the fact that nutrition interventions are not all direct nutrition interventions. There is a lot of “faith” behind this idea but very little actual evidence available. Issues that would move forward the agenda around nutrition-sensitive interventions include understanding the evidence needed to convince policy-makers regarding the utility of these interventions, as well as addressing outcomes and indicators that are relevant for decision-making, such as nutritional health and women’s equity. The questions related to nutrition are different from those for which agricultural and social welfare programmes were designed. It was

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1 The United Nations defines nutrition-sensitive policies as “policies that enable all people to enjoy good nutrition”. 

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discussed that WHO may not be the appropriate convening body for all groups, for all work in the entire field of nutrition. WHO is interested in the development of synergies and partnerships to simultaneously move various agendas forward. The World Bank communicates the message to countries that they can work with individual countries to develop the evidence around SUN actions in nutrition-sensitive interventions, but must be careful not to give wrong advice. It is important to provide options and say “let’s evaluate together”, as opposed to giving recommendation where there is no evidence. There is a need to have experts in agriculture and social protection as part of the dialogue related to SUN, which currently focuses on public health stakeholders.

**Quality control in Cochrane systematic reviews**

Prof Geraldine Macdonald presented the editorial process of the Cochrane Library for publication of high-quality systematic reviews. The Cochrane Collaboration has a handbook for systematic reviewers of interventions (3), which “provides guidance to authors for the preparation of Cochrane Intervention reviews”. The Cochrane handbook outlines eight general steps for preparing a systematic review: defining the review question and developing criteria for including studies; searching for studies; selecting studies and collecting data; assessing the risk of bias in included studies; analysing data and undertaking meta-analyses; addressing reporting biases; presenting results and “summary of findings” tables; and interpreting results and drawing conclusions.

Before work starts, all Cochrane systematic reviews must be registered as titles with a Cochrane review group. Registering a title is important to prevent duplication of effort with other authors, and to make sure the topic is appropriate for a Cochrane review. There are 53 review groups that each focus on a particular area of health, coordinated by an editorial team that edits and publishes completed reviews in the Cochrane Library. Coordination between groups is required and potential titles are shared among groups’ editors before registration, to ensure there is not extensive overlap. Attempts are made to keep titles of a similar topic within an appropriate group, but this may not always be accomplished.

Unlike other journals, the Cochrane review group provides support and advice throughout the iterative review process. When assessing the pertinence of a title for registration, it is important to consider the mix of authors, who should have the appropriate skill set to complete the review, especially statistical competencies. Cochrane reviews must be undertaken by more than one person. Review teams should include people with expertise in the topic area being reviewed, as well as someone with experience in the methodology of systematic review. The protocol development reviewed by editors may go through several iterations before going to external review. Protocols for Cochrane reviews are published before the completed systematic review in the Cochrane Database of Systematic Reviews. Changes in the protocol should be documented and reported in the “Differences between protocol and review” section of the completed review, and, when possible, sensitivity analyses exploring the impact of deviations from the protocol should be undertaken.

Preparing a Cochrane review is complex and involves many judgements. Since Cochrane reviews, by their nature, analyse data that have already been collected, it is important that the methods to be used are established and documented in advance. The
Cochrane Collaboration advises authors to collaborate with others with the correct skill set for the particular topic. Publication of a protocol for a review prior to knowledge of the available studies reduces the impact of review authors’ biases, promotes transparency of methods and processes, reduces the potential for duplication, and allows peer review of the planned methods. However, conducting a systematic review may be a long and cumbersome process for the authors. In some cases where the review is deemed as of poor quality or is replaced by an updated version, it may be necessary to withdraw titles (protocols or reviews) previously registered or published so that new teams are able to produce a systematic review of high quality. Importantly, once a full review has been published, it can never be removed from The Cochrane Library; it will appear in the “Other versions” section of The Cochrane Library record.

**Getting the best of observational data**

Dr Vivian Welch discussed issues related to getting the best of observational data. The Campbell and Cochrane Equity Methods Group is registered with the Campbell and the Cochrane Collaborations. Both the Cochrane and Campbell Collaborations are international, not-for-profit and independent organizations. The Equity Methods Group encourages authors of both Campbell and Cochrane reviews to include explicit descriptions of the effect of the interventions not only on the whole population, but also on the disadvantaged, and/or their ability to reduce socioeconomic inequalities in health and to promote their use to the wider community. Ultimately, this will help build the evidence base on such interventions and increase the capacity to act on the health gap between rich and poor.

This Campbell and Cochrane Equity Methods group has addressed methodological issues that could be applied to examine equity issues in systematic reviews. The group has developed a list of crucial components for equity-relevant systematic reviews and proposes the use of GRADE summary of findings for communicating the results. The use of Supporting Policy-relevant Reviews and Trials (SUPPORT) tools (11) for summary leads the discussion of applicability. It is useful for authors to follow the Cochrane handbook (3), to justify the choice of included study designs, to assess the risk of bias using accepted tools, and to join working groups on methodological innovation.

**The generation of data on impact evaluation**

Ms Birte Snilstveit discussed how improved impact evaluations could be useful for more relevant systematic reviews of the evidence. Theory-based systematic reviews can answer not only whether an intervention works but also why it does. Programme theory is used to conduct a causal chain analysis when possible. It often requires additional search with different criteria to supplement the data of the original review, so it may be very labour intensive. There are resources available that would be useful for systematic reviews, including providing information from the process, information to enable the calculation of effect size, and information to assess the risk of bias. In terms of incentives, funding agencies can create pressure for programmes to conduct process evaluation and to have better impact evaluations. It is important to advocate for standard methods but because studies are limited by time, money and infrastructure, this may not always be feasible. Work should also be done on the methodology, to synthesize data from varying outcomes or different indicators of the same outcome.
Discussion

Key characteristics of high-quality systematic reviews were outlined. Understanding the effectiveness and efficacy of nutrition interventions is an important consideration during the interpretation of the results of systematic reviews, and depends on the questions scoped by the guideline group. Transparency throughout the review process is paramount. The representatives from the Cochrane Collaboration highlighted the steps that Cochrane has in place to increase transparency and overall quality, namely: (i) the registration of the title and publication of the protocol; (ii) peer review to make sure the reviews are conducted according to the Cochrane handbook for systematic reviews of interventions (3) and are sound in terms of a particular topic; (iii) use of “summary of findings tables”; (iv) checklists of common problems; (v) withdrawal of titles if needed; and (vi) insistence that authors collaborate with others with the correct skill set. Additionally, the Campbell Cochrane Equity Methods Group recommends that authors (i) follow the Cochrane handbook for systematic reviews of interventions (3); (ii) justify the choice of included study designs; (iii) assess the risk of bias using accepted tools; and (iv) join working groups on methodological innovation.

Representatives from both the Cochrane Collaboration and the Campbell Collaboration described the methods followed to continuously improve the quality of systematic reviews. The Cochrane Collaboration is a living, dynamic organization and methods continue to improve, to increase flexibility and to adapt to the available evidence in various fields. Both Campbell and Cochrane are continuously working to improve methods for the use of observational data in all the reviews.

The evidence that has been retrieved and synthesized in a systematic review needs to be assessed for quality. Quality of evidence is defined as the “extent to which one can be confident that an estimate of the effect or association is correct”. WHO uses the GRADE approach to assess the quality of a body of evidence and develop and report recommendations. GRADE methods are used by WHO because they represent internationally agreed standards for making transparent recommendations. Assessing the evidence and developing evidence summaries is a specialized task that is best done by a methodological expert. WHO guideline development groups usually include methodologists, who may be GRADE experts or methodologists from the Cochrane Collaboration. WHO guideline development group members who have no previous experience of working with GRADE require briefing on the process by WHO prior to the guideline meeting. Several WHO staff are members of the GRADE working group and bring to this group’s attention issues encountered in the development of evidence-informed guidelines. Some challenges and opportunities for the use of GRADE methodology for evaluation of the quality of evidence were discussed. Some areas of opportunity regarding the use of the results of systematic reviews were discussed.

Systematic reviews summarize the trials included and make a formal assessment of the evidence therein. The overall quality of the studies summarized in the review cannot be any better than that of the studies used in the review and this needs to be ascertained in the review process. If primary studies do not follow rigorous methodology, their
quality will affect the overall body of evidence, increasing the risk of bias and affecting the overall quality of the evidence in the review. If studies do not report important characteristics of methodology or results, then additional efforts are required to evaluate the quality. Through comprehensive methods, systematic reviews could both answer whether an intervention is effective and identify some of the determinants for implementation of the intervention, but such reviews usually require extensive data on process as well as outcome, in order to conduct causal chain analysis. Therefore, monitoring and evaluation of nutrition programmes in public health require continuous support, in order to provide inputs for future reviews that incorporate programmatic experiences of implementation.

Important aspects of systematic reviews, and opportunities for their use in guideline development were also discussed. One of them is the increased political momentum for nutrition in the public health agenda, which requires the use of more rigorous processes to ensure that health-care recommendations are informed by the best available research evidence. It was noted that systematic reviews also help identify research gaps that are relevant for policy-making. The reviews may serve to inform the design of new studies and provide guidance where no evidence is available. The World Bank follows a different process than WHO for developing guidance notes; it differentiates guidance notes from policy notes, which require that the evidence has been evaluated first.

Conflicts of interests, real or perceived, cannot be ruled out when developing systematic reviews. On the one hand, authors with expertise in the topic may provide clarity to the interpretation of the findings, but they may also be perceived as biased, particularly when they have a strong position or have many publications in the area that are either original or derivative. On the other hand, while the involvement of WHO staff in the development of systematic reviews helps keep continuity and concordance throughout the guideline development process, this may also be perceived as conflicted, given the normative role of WHO.

Improvement of the use of the evidence base and systematic reviews was discussed. Some members of the Cochrane Collaboration explained the coordination mechanisms their collaboration has in place among topic area groups, to ensure there is not extensive overlap between reviews. However, full coordination may not always be accomplished. There was general consensus to support the use of the Cochrane handbook for systematic reviews of interventions (3) to improve the quality of reviews being produced. The topic of setting up a nutrition editorial board for nutrition reviews was raised, and it was thought that the usefulness and feasibility would need to be explored further. Another suggestion was to develop a portal for registration of nutrition titles but many participants felt this step would be redundant, as Cochrane, Campbell and PROSPERO are platforms for registering titles. These platforms are currently being used for the registration of systematic reviews in nutrition used in WHO evidence-informed guidelines development.
References


Annex 1. Agenda

09:00 – 09:15 Welcome and introduction of participants  
Dr Francesco Branca – WHO

09:15 – 10:15 Overview of systematic reviews on nutrition: gaps and implications for future research  
Dr Zulfiqar Bhutta – The Aga Khan University

10:15 – 10:45 Use of systematic reviews in the guideline development process – lessons learnt  
Dr Luz Maria De-Regil – WHO

10:45 – 11:00 Break

11:00 – 11:30 Evidence gaps for nutrition-sensitive agriculture  
Dr Marie Ruel – International Food Policy Research Institute

11:30 – 12:00 Information needs for policy briefs on nutrition-sensitive development  
Dr Meera Shekar – The World Bank

12:00 – 12:30 Quality control in Cochrane systematic reviews  
Prof Geraldine Macdonald – Queen’s University Belfast. Coordinating Editor of the Cochrane Developmental, Psychosocial and Learning Problems Review Group

12:30 – 13:30 Lunch

13:30 – 14:00 Getting the best of observational data  
Dr Vivian Welch – Centre for Global Health

14:00 – 14:30 The generation of data on impact evaluation  
Ms Birte Snilstveit – London International Development Centre

14:30 – 15:30 Group discussion. What can we do to harmonize methodologies?  
Dr Luz Maria De-Regil – WHO

15:30 – 15:45 Break

15:45 – 16:45 Group discussion. What can we do to coordinate the production of systematic reviews in nutrition?  
Dr Zulfiqar Bhutta – The Aga Khan University

16:45 – 17:15 Conclusions and next steps  
Dr Francesco Branca – WHO  
Dr Zulfiqar Bhutta – The Aga Khan University
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