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Strategies for addressing vaccine hesitancy – A systematic review

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A B S T R A C T
The purpose of this systematic review is to identify, describe and assess the potential effectiveness of strategies to respond to issues of vaccine hesitancy that have been implemented and evaluated across diverse global contexts.

Methods: A systematic review of peer reviewed (January 2007–October 2013) and grey literature (up to October 2013) was conducted using a broad search strategy, built to capture multiple dimensions of public trust, confidence and hesitancy concerning vaccines. This search strategy was applied and adapted across several databases and organizational websites. Descriptive analyses were undertaken for 166 (peer reviewed) and 15 (grey literature) evaluation studies. In addition, the quality of evidence relating to a series of PICO (population, intervention, comparison/control, outcomes) questions defined by the SAGE Working Group on Vaccine Hesitancy (WG) was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria; data were analyzed using Review Manager.

Results: Across the literature, few strategies to address vaccine hesitancy were found to have been evaluated for impact on either vaccination uptake and/or changes in knowledge, awareness or attitude (only 14% of peer reviewed and 25% of grey literature). The majority of evaluation studies were based in the Americas and primarily focused on influenza, human papillomavirus (HPV) and childhood vaccines. In low- and middle-income regions, the focus was on diphtheria, tetanus and pertussis, and polio. Across all regions, most interventions were multi-component and the majority of strategies focused on raising knowledge and awareness. Thirteen relevant studies were used for the GRADE assessment that indicated evidence of moderate quality for the use of social mobilization, mass media, communication tool-based training for health-care workers, non-financial incentives and reminder/recall-based interventions.

Overall, our results showed that multicomponent and dialogue-based interventions were most effective. However, given the complexity of vaccine hesitancy and the limited evidence available on how it can be addressed, identified strategies should be carefully tailored according to the target population, their reasons for hesitancy, and the specific context.

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1. Introduction

The dynamic and challenging period of indecision around accepting a vaccination – often referred to as “vaccine hesitancy” 5 – is being increasingly studied. Given the growing concern in many countries about vaccine hesitancy, the Strategic Advisory Group of Experts (SAGE) Working Group (WG) on Vaccine Hesitancy 6 asked that a review focused on strategies to address hesitancy be undertaken.

The purpose of this systematic review was to identify strategies that have been implemented and evaluated across diverse global contexts in an effort to respond to, and manage, issues of vaccine hesitancy. This review was conducted to inform the

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5 Some of the authors are World Health Organization staff members. The opinions expressed in this article are those of the authors and do not necessarily represent the decisions, official policy or opinions of the World Health Organization.

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5 Vaccine hesitancy “refers to delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is complex and context spec-

6 http://www.who.int/immunization/sage/sage_wg_vaccine_hesitancy_apr12/en/ [accessed 02.02.15].
recommendations of the SAGE WG, building on the previous review of determinants of vaccine hesitancy [1].

2. Methods

2.1. Search strategy

For the peer-reviewed literature, the following databases were searched for the period of January 2007–October 2013: Medline, Embase, PsychInfo, Cochrane, CINAHL Plus, Web of Science, LLILACS, Africa-Wide Information (for these, the search range was 2007 to 9 October 2013); IBSS (2007 to 19th July 2013) and IMEMR (2007 to 10 October 2013). The applied search strategy was kept deliberately broad to try to capture the multiple facets of vaccine hesitancy and incorporated MeSH or equivalent terms [Appendix 1]. References in relevant papers were searched for further relevant studies.

For grey literature, an open-dated search ending, in October 2013, was conducted across several databases and organizational websites, which included: OpenGrey, New York Academy of Medicine, Global Health, National Institute for Health and Care Excellence (NICE), Department for International Development (DFID), the Communication Initiative Network and the Polio Communication Initiative Network [see search terms in Appendix 2]. Direct email requests were sent to individuals/organizations identified by the SAGE WG.

2.2. Study selection – Part A (Identification, scope of literature and effect of evaluated interventions)

For peer-reviewed literature, studies were included against the following criteria: (i) contained research on vaccine hesitancy; (ii) included any of the keywords in the title or abstract: “strategy”, “intervention”, “campaign”, “evaluation”, “approach” or “program”; (iii) described or evaluated an intervention addressing hesitancy and reported a measure of the primary outcome, i.e. indicating a change in vaccination uptake or the secondary outcome, i.e. indicating a change in knowledge/awareness and/or attitudes; (iv) published between January 2007 and October 2013; (v) pertaining to any vaccines and vaccination programmes; (vi) published in any of the six official UN languages (Arabic, Chinese, English, French, Russian and Spanish).

Grey literature was selected based on the following inclusion criteria: (i) contained any of the keywords “immunisation/immunization”, “vaccine”, “vaccination”, “strategy”, “intervention”, “evaluation”, “hesitancy”, “refusal”, “trust”, “confidence”, “acceptance”, “engagement”, “anxiety”, “concern”, “distrust”, “barrier”, “rejection”, “fear”; (ii) published anytime up to October 2013; (iii) English only. Literature was excluded if it was: (i) about non-human vaccines or vaccines not currently available (e.g. HIV); (ii) related to research and development of vaccines (e.g. efficacy trials) unless explicitly about public trust, confidence, concern or hesitancy.

The screening of titles and abstracts was shared between at least two authors; a sample of studies was independently coded by authors to ensure consistency.

2.3. Data extraction

2.3.1. Part A

A data extraction form was developed by the authors and reviewed by the SAGE WG. For evaluation studies, information extracted included details about the specific hesitancy issue; type of intervention (dialogue-based, incentive-based, reminder–recall based or multi-component), the type of participants, setting and target vaccine; and the findings related to the outcomes of interest.

2.3.2. Part B (PICO & GRaDE) – Study selection, risk of bias & analysis

The SAGE WG identified 15 PICO (Population, Intervention, Comparator, Outcome) questions [2][Appendix 3] a priori, to examine population features likely to influence the effect of different interventions and to assess the quality of evidence for each PICO question using GRaDE (Grading of Recommendations, Assessment, Development, and Evaluation) [3]. The primary outcome of interest was defined as the uptake of all vaccines included in routinely recommended immunization.

The 15 PICO questions were developed under three intervention themes: (1) Dialogue-based, (2) incentive-based (non-financial), and (3) reminder–recall. Following an extensive discussion by the WG at the December 2013 meeting, it was decided to focus on the impact of single component approaches and exclude multi-component approaches. However, data were included where a multi-component intervention provided suitable data to assess the effect of its individual component parts.

Theme categories for PICO questions:

i) Dialogue-based, including the involvement of religious or traditional leaders, social mobilization, social media, mass media, and communication or information-based tools for health-care workers (HCW);

ii) Incentive-based (non-financial), including the provision of food or other goods to encourage vaccination, and;

iii) Reminder/recall-based, including telephone call/letter to remind the target population about vaccination.

Evaluated primary studies identified earlier (Part A) were included if they provided direct evidence relevant to one or more PICO questions and reported data for comparison groups. Reasons for excluding studies are presented in Characteristics of excluded studies [4].

2.3.3. Assessment of risk of bias

The Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies [5] was applied to determine the risk of bias of all eligible studies. Two reviewers independently conducted the risk of bias assessment and data extraction; disagreements were settled through discussion.

2.3.4. Data analysis

For studies which included pre- and post-control and intervention groups, only post-data were used to more accurately represent the effect of the intervention. Outcomes reported varied between studies, so available data were entered into Review Manager software as individual studies. The fixed-effects model was used for analysis and results reported as risk ratios between intervention and control groups.

3. Results

3.1. Part A – Identification, scope of literature and effect of evaluated interventions

The search of peer-reviewed publications identified 33023 peer reviewed articles. After removing duplicates and screening for inclusion criteria, 1149 articles were included by full-text. Of these, 166 [6–172] evaluated and 983 described, but did not evaluate, an intervention. Among the evaluated studies included from the peer reviewed literature, 115 related to Outcome 1, 37 to Outcome 2, and 14 to both [Fig. 1].
Fig. 1. Search process flow chart (peer reviewed literature) – Vaccine hesitancy.

The grey literature search identified 4896 records. After removing duplicates and screening for inclusion criteria, 59 articles were included by full text. Of these, 15 evaluated [172–186] and 44 only suggested an intervention. Among the evaluated studies included from the grey literature, nine reported on Outcome 1, three on Outcome 2, and three on both [Fig. 2].

There were a total of 181 articles that evaluated interventions from the peer reviewed and grey literature search, combined.

The number of peer reviewed studies evaluating interventions peaked in 2011 (at 32 studies) and has remained relatively stable since (28 in 2012 and 25 in 2013) [Fig. 3].

Very few evaluated interventions were identified in the grey literature with one or two articles annually at most from 1996 to 2012. In 2013, eight relevant articles (47% of those identified through the grey literature search) were found [Fig. 4].

Across all the literature reviewed (1208 articles), only five (0.4%) used the actual term ‘hesitancy’ or ‘hesitant’ with reference to vaccines/vaccination [94,173–176]. These were all found in the peer-reviewed literature and were all published in 2013. Only one of these articles evaluated an intervention. This intervention was carried out in AMR and focused on childhood vaccines, targeting vaccine hesitant parents using a multi-component strategy that focused on education techniques. More often articles used terms such as “refusal”, “distrust” and “acceptance” to discuss vaccination behaviour. This reflects the relative newness of the term “hesitancy”.

The majority (58%) of evaluation studies in the peer reviewed and grey literature were based in AMR[7] (110/189[8]), and primarily focused on influenza, HPV and childhood vaccines. In low- and middle-income regions, particularly SEAR and AFR, the focus was on Diphtheria, Tetanus, Pertussis (DTP) and polio. All regions had evaluated studies anticipating or researching acceptance of the newly introduced HPV vaccine.

[7] The World Health Organization (WHO) divides the world into six WHO regions, for the purposes of reporting, analysis and administration: WHO African Region (AFR), WHO Region of the Americas (AMR), WHO South-East Asia Region (SEAR), WHO European Region (EUR), WHO Eastern Mediterranean Region (EMR) and WHO Western Pacific Region (WPR).

[8] The total number of articles is more than (n = 166) (peer reviewed) and (n = 15) (grey literature) as some articles report on more than one WHO region.
Most interventions (primarily in AMR and EUR) targeted parents, health-care workers (HCWs) and the local community. Interventions in the grey literature from AFR largely focused on the local community and religious leaders.

When mapped against the SAGE WG model of determinants of vaccine hesitancy [Appendix 4], interventions addressing individual and social group influences, particularly knowledge and awareness raising, were most common in both the peer reviewed and grey literature (157/341, 46%). Vaccine delivery and the role of the HCWs were the primary focus of vaccine and vaccination-specific interventions (123/341, 36%). The engagement of religious and other community leaders was most commonly used to address contextual influences such as religion, culture and gender [Fig. 5].

In both the peer reviewed and grey literature, across all regions, most interventions (97/127, 76%) were multi-component. Dialogue-based interventions were common in all regions except EMR; reminder–recall approaches featured predominantly in higher-income regions; and incentive-based interventions were

Fig. 2. Search process flow chart (grey literature) – Vaccine hesitancy.

Fig. 3. Evaluated peer reviewed strategies by publication year (2007–2013) and WHO region (n = 172)*. "Total number of articles is more than (n = 166) as some articles report on more than one WHO region."
3.2. Which interventions have been most successful?

The most effective interventions employed multiple strategies. The interventions with the largest observed increases (>25%) in vaccine uptake (Outcome 1) were those that (not in order of importance): (1) directly targeted unvaccinated or under-vaccinated populations [13]; (2) aimed to increase vaccination knowledge and awareness [20]; (3) improved convenience and access to vaccination [116]; (4) targeted specific populations (e.g. HCW) [9]; (5) mandated vaccinations or sanction against non-vaccination [46]; and (6) engaged religious or other influential leaders to promote vaccination [177]. The greatest increases (>20%) in knowledge, awareness or attitudes (Outcome 2) were observed with education initiatives, particularly those embedding new knowledge into routine processes (e.g. hospital procedures), which were most successful at increasing knowledge and changing attitudes [105]. For both outcomes, those that tailored interventions to specific populations and their specific concerns were most effective [23,38].
3.3. Which interventions have been least successful?

Interventions associated with a less than 10% increase in uptake included those that focused on quality improvement at clinics (e.g. improved data collection and monitoring, extended clinic hours [8, 98], passive interventions (e.g. posters, websites [19, 41]) and incentive-based interventions using conditional or non-conditional cash transfers. It must be noted that incentive-based interventions usually targeted general preventive health and not just vaccination [96, 98]. Lastly, reminder–recall interventions were associated with variable changes in uptake [57, 75, 88].

3.4. Part B – PICO & GRADE

Of 129 studies available, only 13 studies met the inclusion criteria for GRADE evaluation. The methodological quality (risk of bias) of each is set out in Appendix 5. Further study details are presented in Appendix 6.

The delivery of interventions varied as did the outcomes. Consequently only one outcome (two studies) for a single vaccine was pooled; meta-analysis was not feasible for any other outcome [64, 66]. Summary of relative risk ratios (RR) and evidence quality (GRADE) for each question are presented in Appendix 3. Of the 15 PICO questions, only 10 could be addressed, often with only 1 study with evidence.

4. Dialogue-based interventions

Eleven studies evaluated by PICO and GRADE deployed dialogue-based interventions (explained below). There was appreciable variability in the quality of evidence supporting the use of these interventions and their impact varied considerably, by type of intervention, by vaccine and by setting.

For polio, the involvement of religious or traditional leaders in populations with low baseline uptake indicated a large, positive effect (RR 4.12 [3.99, 4.26]) on vaccine uptake but the evidence quality was assessed as very low [65] (Nigeria). The grey literature also reinforced that religious and traditional leader involvement can have a positive impact [3.5, 177, 178] as in west and central francophone African countries, Afghanistan, India and Europe.

Four studies using social mobilization among parents in low-income settings found a positive effect on measles (RR 1.63 [1.39, 1.91]) [78] (Pakistan), DTP3 (RR 2.17 [1.8, 2.61]) [78] (Pakistan), DTP1 (RR 1.54 [1.1, 2.15]) [106] (Nigeria), and polio (RR 1050.00 [147.96, 7451.4]) [66] (Pakistan) [64] (India) vaccine uptake. The quality of evidence for each outcome ranged from moderate (measles, DTP3), to low (polio) and very low (DTP1). Two studies targeting polio vaccination referrals reported large increases in uptake. In the grey literature, inclusion of social mobilization as a component appeared to have a positive, albeit varied effect and was not always quantified.

Two studies evaluating social media interventions found a positive effect on uptake for MCV4/Dtap (RR 2.01 [1.39, 2.93]) [102] (Australia) and seasonal influenza (RR 2.38 [1.23, 4.6]) [157] (Australia) although the evidence was assessed as low and very low quality. In the grey literature, one study [178] in Slovenia reported on the use of social media with other strategies for A(H1N1), however its effect was not independently measured, achieved low utilization, and became a source of negative social media rumors.

A study on mass media to target parents with low awareness of health services found an association with increased uptake of all routinely recommended vaccines (RR 1.57 [1.4, 1.75]) [179] (India). The quality of evidence was moderate. Three grey literature studies reported on the use of mass media for A(H1N1) [178] (Europe), routine childhood immunization [177] (west and central francophone African countries) and polio [3] (Afghanistan) but their impact was not independently measured from other intervention components.

Communication tool-based training for health-care workers had a positive impact on uptake of EPI vaccines (RR 3.09 [2.19, 4.36]) [92] and DTP3 (RR 1.54 [1.33, 1.79]) [79] in India and Pakistan respectively, among rostered patients; evidence quality was assessed as moderate and low respectively.

One study [10] (Turkey) assessed the impact of information-based training for health-care workers on uptake for rostered patients, with varying results. There was little or no increase in uptake of DTP/OPV-1 (RR 0.99 [0.93, 1.06]), DTP/OPV-2 (RR 1.04 [0.97, 1.12]), BCG (RR 1.01 [0.95, 1.08]) and measles (RR 1.02 [0.96, 1.09]), a moderate increase in uptake of HepB-2 (RR 1.63 [1.49, 1.79]), HepB-3 (RR 1.89 [1.74, 2.04]) and DTP/OPV-3 (RR 1.42 [1.33, 1.51]), and a substantial increase in uptake of HepB-1 (RR 2.83 [2.6, 3.08]); but the evidence quality was very low for all.

5. Non-financial incentives

The evidence for non-financial incentives for parents/communities located in low-income settings (India) was moderate for a large, positive effect on EPI vaccine uptake (RR 2.16 [1.68, 2.77]) [92].

6. Reminder–recall interventions

Two studies assessed the impact of reminder–recall interventions in low-income and under-vaccinated populations. The impact of reminder–recall interventions in low-income settings was positive for DTP3 (RR 1.26 [1.13, 1.42]) [146] (Pakistan) with moderate quality evidence. For settings with low baseline uptake, the effects were large and positive for scheduled childhood vaccines (RR 3.22 [1.59, 6.53]) [86] (Switzerland) but the quality of evidence was very low.

7. Discussion

7.1. Part A – Identification, scope of literature and effect of evaluated interventions

While there has been an increase in the number of articles on the issue of vaccine hesitancy, of those that include a discussion on interventions or strategies to address hesitancy, few go as far as evaluating them. Furthermore, the specific term “vaccine hesitancy” has only recently been used and the only evaluated intervention that explicitly addressed “hesitancy” comes from the United States.

Overall, many of the interventions were not different from traditional strategies to increase vaccine acceptance, with the majority focusing at individual and social group level and interventions being largely on knowledge and awareness raising. While knowledge and awareness raising strategies are important, they are inadequate, as evidenced by the finding that the most effective interventions used multi-component strategies. Furthermore the most effective interventions were tailored to specific populations and addressing specific concerns, pointing to the importance of understanding the drivers of vaccine hesitancy to inform the interventions.

The increasingly recognized domain of vaccine hesitancy needs new interventions to address new issues. In particular, the dearth of interventions identified in low-income countries needs attention.

7.2. Part B – PICO & GRADE

Despite the few studies available for GRADE and variability in the quality of the evidence, several interventions showed some
positive impact on vaccination uptake, including: social mobilization, mass media, communication tool-based training for HCW, non-financial incentives, and reminder–recall activities. None of these interventions were without shortcomings, and given the variability in context, target population and outcome, the potential application of these interventions must be cautiously considered when applying them in different circumstances.

8. Dialogue-based interventions

The impact of religious or traditional leader involvement in populations with low baseline uptake merits further investigation and evaluation. This type of intervention is important as it addresses one of the more difficult determinants of vaccine hesitancy, namely, misconceptions and community distrust. This intervention aligns itself with natural community processes—seeking out community leaders, and encouraging dialogue across multiple levels to both inform and influence. The success of the intervention could be attributed to the efforts made to understand the target audience, facilitate open dialogue, and integrate activities with familiar processes and systems.

The success of social mobilization interventions for populations refusing polio vaccination could also be attributed to the targeting of, and dialogue with, a clearly defined population. By comparison, the social mobilization interventions for measles and DTP were much less targeted; although positive outcomes appear to be due to meaningful dialogue at both the group and individual level.

Social media intervention studies suggest that this approach might work well for those who have already started their vaccination schedule, or who are familiar with social media in other aspects of their lives. However, there is important evidence that social media are also very open to exploitation if not managed well. Also those who initiate vaccination are probably not the most hesitant of populations and those with access to social media are not the most marginalized.

The use of mass media to target populations with low awareness of health services appears to be effective, however; the limited impact also suggests that there may be other underlying issues affecting the impact that need investigation and more tailored supporting interventions.

The provision of communication tool-based training for HCW generally had a positive effect (for EPI vaccines, DTP3) but the size of the effect and evidence quality varied. The observations about this example and mass media suggest that interventions that adopt a unidirectional (top down) approach to communication may be successful among some individuals and groups, but not all; success is dependent on the nature and degree of hesitancy.

The impact of information-based training for HCW on uptake of several vaccines for rostered patients was generally poor. A possible explanation for these results is that there was no clear understanding of the underlying reasons for the low vaccination uptake and as such, the intervention was not appropriately targeted. Nonetheless, the intervention did achieve good success with HepB (all doses) and DTP/OPV (dose 3); one possible reason for this is that the HCW exhibited greater confidence but it is not clear whether this was an issue prior to the intervention.

9. Non-financial incentives

The moderate to large effect of non-financial incentives for parents/communities located in low-income settings on vaccination uptake is promising. In this study the target group was very disadvantaged and the food-based incentive, so closely linked with basic survival, was readily received. Furthermore, the baseline vaccination rates were very low (2%), and more likely to show greater outcome changes with an intervention. It is possible that by addressing basic needs, this intervention simultaneously built confidence and reduced vaccine hesitancy because the target population felt that their other critical needs were being addressed. This approach could be particularly important for underserved groups.

10. Reminder–recall interventions

Although positive, the relatively low observed effect of reminder–recall interventions in low-income settings seems to reflect the limitations of using this kind of intervention alone. In this example, a complex set of issues was identified in the target population but the intervention only addressed one of them. Reminder–recall on its own is not enough to tackle multiple causes of hesitancy.

11. Limitations

This review may be subject to publication bias, in that unsuccessful interventions may be less likely to be documented in either the peer-reviewed or grey literature. Another reason for the paucity of relevant studies is that the PICO questions emphasize specific, single component strategies, but many evaluated strategies are neither designed nor presented in this way. Evaluated, multi-component interventions were identified but only overall impact data were presented. Therefore, outcome data for individual strategies to address vaccine hesitancy were not separately available.

12. Conclusion

Overall this review has found that, despite extensive literature searching, there are (1) few existing strategies that have been explicitly designed to address vaccine hesitancy; and (2) even fewer strategies that have quantified the impact of the intervention (14% (166/1149) of peer reviewed; 25% (15/59) of the grey literature). There is also an uneven geographical spread in the available literature, with most focusing on AMR and EUR.

Efforts to address issues of hesitancy are disparate. While a number of interventions did have a positive effect, wide variation was observed in the effect size between studies, settings and target populations. In addition, the high level of heterogeneity across study design and outcomes, coupled with few available studies, further limited our ability to draw many general conclusions about the effectiveness of different strategies.

Nonetheless, interventions to increase uptake that are multi-component and/or have a focus on dialogue–based approaches tend to perform better. Together, these interventions suggest that taking a comprehensive approach that targets multiple audiences and layers of social interaction are more likely to bring positive results. The evidence for non-financial incentives and reminder–recall activities was also of good quality, and carries the potential to bring positive change by addressing the more practical aspects of vaccination.

Vaccine hesitancy is a complex issue and no single strategy will be able to address it. There are some promising examples using uptake as a link, but many are incomplete and most are not directly comparable. One of the greatest drawbacks of the interventions identified is that many operate from an assumption-based rather than an evidence-based approach; appropriate evaluation is also lacking. On a more positive note, there is a growing body of research on the determinants of vaccine hesitancy which can help inform and refine currently used approaches that look promising but have not yet been fully implemented or evaluated.

Lastly, there is a clear need for more attention to understanding and addressing hesitancy at the community and social
network level – most interventions have historically focused on addressing individual level issues (e.g. knowledge, awareness) and vaccine/vaccination specific concerns (e.g. mode of delivery, vaccine risks) despite the large body of literature on the many other determinants of vaccine hesitancy.

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**Conflict of interest statements**

None of the other authors had any potential conflict of interest.

**Appendix. SAGE Working Group on Vaccine Hesitancy**

Juhani Eskola, National Institute for Health and Welfare, Finland (Chair of Working Group since April 2014); Xiaofeng Liang, Chinese Center for Disease Control, China (Member of SAGE until 2014, Chair of Working Group from March 2012 to April 2014); Mohuya Chaudhuri, Independent Journalist and Documentary Filmmaker, India; Eve Dubé, Institut National de Santé Publique du Québec, Canada; Bruce Gellin, Department of Health and Human Services, U.S.A; Susan Goldberg, Soul City: Institute for Health and Development Communication, South Africa; Heidi Larson, London School of Hygiene & Tropical Medicine, U.K.; Noni MacDonald, Dalhousie University, Canada; Mahamane Louali Manzo, Ministry of Health, Niger; Arthur Reingold, University of California at Berkeley, U.S.A.; Kinzang Tshering, Jigme Dorji Wangchuck National Referral Hospital, Bhutan; Yuqing Zhou, Chinese Centre for Disease Control, China with the WHO/UNICEF Secretariat: Robb Butler, World Health Organization, Denmark; Philippe Duclos, World Health Organization, Switzerland; Sherine Guriguis, UNICEF, U.S.A.; Ben Hickler, UNICEF, U.S.A.; Melanie Schuster, World Health Organization, Switzerland.

**Appendix B. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.vaccine.2015.04.040](http://dx.doi.org/10.1016/j.vaccine.2015.04.040)

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