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Research prioritization of interventions for the primary prevention of preterm birth: An international survey

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A R T I C L E   I N F O

A B S T R A C T

Objective: To identify research priorities of interventions for the primary prevention of preterm birth (PTB), by conducting an international stakeholder survey.
Study design: A prospective cross-sectional online survey was conducted in November 2016. Fifteen interventions to prevent spontaneous PTB were identified and ranked by stakeholders (n = 159) in the field of maternal and perinatal health research, using nine equally weighted criteria. Medians and interquartile ranges (IQRs) were calculated and the interventions ranked accordingly.
Results: Respondents to the survey were from 46 different countries, mostly from low and middle-income countries (62%, 99/159) and were mainly clinicians (80%, 127/159). Of the fifteen interventions ranked, the following five were identified as research priorities in the primary prevention of PTB: dietary counselling and nutritional education, risk scoring, vitamin D supplementation, exercise and antioxidant supplementation.
Conclusion: We have identified research priorities of interventions to prevent spontaneous PTB through a global stakeholder survey. The interventions prioritized in this exercise can be used by researchers, grant funding bodies and research-policy decision makers to inform calls on future clinical trials or individual patient data meta-analyses on the primary prevention of PTB.

Introduction

Preterm birth (PTB), defined as a live birth at less than 37 completed weeks of gestation, occurs in approximately 10.6% of all births worldwide [1], and most of this occurs in low and middle income countries (LMIC) [2–5], which suggests clinically significant disparities in risk factors and health care delivery across sociodemographic settings. PTB accounts for about a million neonatal deaths annually, as well as an additional 125,000 deaths in children before they are five years old, making it the leading cause of both neonatal and childhood mortality [2,3].

Interventions for the primary prevention of spontaneous PTB are those directed at the population level to all women, and implemented before or during pregnancy to reduce the risk of PTB [6–8]. Examples include smoking prevention campaigns, treatment with vitamin supplements, and weight optimization [7,8]. Secondary prevention strategies on the other hand are focused on reducing the risk in women with known or identified risk factors [6,8]. A hypothetical intervention that can delay PTB by a week across all gestational age categories could reduce the annual childhood healthcare cost of prematurity by a third [9].

With limited resources available for research, it is important to establish priorities in health research to inform future efforts and better utilize scarce resources [10,11]. The top research priority of a recent James Lind Alliance priority setting partnership for PTB was the need to identify the most effective interventions to prevent PTB [12]. There is currently large literature reporting different

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interventions for the primary prevention of preterm birth as applied in different contexts [8,13]. It is therefore important for those who are in a position to fund or deliver research projects on PTB prevention, or implement results of its findings, to prioritize which available interventions to further assess in clinical trials or individual patient data meta-analyses.

This study aimed to identify such research priorities by a diverse sample of international stakeholders.

Materials and methods

Design and study sample

We established a database of healthcare providers, academics, lay representatives, public health specialists and policy makers from existing networks of maternal and perinatal health research from a range of both higher- and lower-income countries. Public health specialists and policy makers were identified from WHO networks, while healthcare providers, academics, and lay representatives were identified from the database of participants in the PTB core outcome set development group [14].

An introduction to the study and an invitation to participate in an online research prioritization survey was sent by email to all contacts on the list. The email invitations contained a link to participate in a web-based survey. Access to a computing device and internet services was therefore required for participation in the survey. Email reminders were sent two weeks after the invitation email if no response was received, and then a week afterwards with the survey remaining open for a total of four weeks in November 2016.

To be eligible for inclusion, participants had to be fluent in either of English, Spanish, French or Italian languages, as the survey was translated into these languages. There were no other eligibility requirements, and invitees could decline participation. Consent was assumed through agreement to participate in and complete the survey. With no definitive standard or agreement on survey sample size, we chose to target a wide group of responders, because a diverse sample of stakeholders are less likely to show significant differences in responses [15].

Questionnaire development

The survey was piloted internally and then modified based on feedback received to improve the clarity of the questions. The final version consisted of six demographic questions: gender, age, professional status, years of experience, main country of residence and main work setting. The questionnaire evaluated primary prevention strategies for PTB, identified in an ongoing review of systematic reviews [16], against nine criteria (Table 1). The review of reviews is still ongoing, however access to unpublished results was provided through shared authorship [17]. Of the spontaneous PTB primary prevention interventions identified in the review, we excluded those where large trials already existed with at least

fifteen thousand participants, and those that were going to be recommended against with high certainty evidence, in the WHO antenatal care guidelines [18,19].

Participants were asked to indicate their level of agreement to statements on a 6-point Likert scale anchored between 1 ('Strongly Disagree') and 6 ('Strongly Agree'). We chose a 6-point Likert scale to avoid neutrality in response to questions by participants. A free text box was provided at the end of the questionnaire for responders to suggest interventions not already considered in the survey for prioritization.

There was no need for review of the study by an ethics board [20]. We used SmartSurvey to develop and administer our online survey, which also randomized the order of questions received by invitees [21].

Statistical analysis

We performed descriptive analyses to summarize participant characteristics and calculated median and interquartile range (IQR) for each criteria assessed, along with an overall summary score for the intervention. These were presented as boxplots to aid visualization. Analysis were done on completed questionnaires. We weighted equally all the assessed criteria and *a priori* identified an IQR of ≤ 1 to indicate consensus between responders [22]. The final prioritization and ranking of interventions were based on a summary score of ≥ 5 indicating overall importance with the assessed intervention and an IQR ≤ 1. All analysis were done using SPSS version 24 (IBM SPSS Statistics for Windows) [23] and figures were produced with Microsoft Office Excel 2016.

Results

An ongoing review of systematic reviews identified fifteen promising interventions that were effective or potentially effective for primary prevention of spontaneous preterm birth (Table 2) [16]. A total of 445 individuals were contacted to participate in the survey. Of these, about a third (36%, 159/445) responded and took part in the prioritization exercise.

Participants from 46 countries completed the prioritization survey (19 LMICs contributed with 62% of participants, while 27 high-income countries contributed with 38% of participants). Responders were mainly clinicians (80%, 127/159), made up of obstetricians (68%, 86/127); neonatologists (24%, 30/127); nurses/midwives (7%, 9/127) and general practitioners (2%, 2/127). Researchers, epidemiologists, consumers, policy makers and representatives of non-governmental organizations (NGOs) and funding bodies also participated in the prioritization exercise (Table 3).

Eight (8/15, 53%) interventions were scored as being important (Fig. 1), while the others (7/15, 47%) were scored as only being slightly important (summary score of 4) in the prioritization exercise (Fig. A1). Summary scores showed minimal variation (IQR ≤ 1) for five of the important interventions namely: dietary

Table 1
Scoring criteria for setting research priorities.

1	**Affordability to women**	The intervention will be affordable to women
2	**Affordability to HCP**	The intervention will be affordable to health care providers
3	**Acceptability to women**	The intervention will be acceptable to women
4	**Acceptability to HCP**	The intervention will be acceptable to health care providers
5	**Implementation**	The intervention can be implemented
6	**Sustainability**	The intervention can be sustained in the long-term
7	**Equity**	The intervention will reach the most vulnerable groups and reduce health inequity
8	**Effectiveness of an RCT**	An RCT on this intervention is likely to demonstrate desirable or beneficial effects
9	**Feasibility of an RCT**	An RCT on this intervention would be feasible

HCP – Health Care Providers, RCT – Randomised Controlled Trial.

Table 2
Interventions identified from systematic review on the primary prevention of preterm birth.

	Intervention	Classification	Description
1	**Antioxidants** [24]	**Supplementation**	Regular antenatal dietary supplementation of one or more antioxidants such as vitamin C
2	**Vitamin D** [25]	**Supplementation**	Regular antenatal dietary supplementation of vitamin D either alone or in combination with other supplements
3	**Vitamin E** [26]	**Supplementation**	Regular antenatal dietary supplementation of vitamin E either alone or in combination with other supplements
4	**Omega-3/fish oil** [27]	**Supplementation**	Regular antenatal dietary supplementation of Omega-3/fish oil capsules
5	**Zinc** [28]	**Supplementation**	Regular antenatal dietary supplementation of zinc either alone or in combination with other supplements
6	**Aspirin** [29]	**Supplementation**	Low-dose aspirin therapy with or without dipyridamole
7	**Probiotics** [30]	**Supplementation**	Regular administration of probiotics as pessaries, capsules, tablets or powder
8	**Antibiotics prophylaxis** [31]	**Treatment of infection**	Routine antibiotics given during the second and third trimesters to prevent vaginal or cervical infections
9	**Screening and treating genital tract infection or BV** [32]	**Treatment of infection**	An infection screening and treatment programme for all women during routine antenatal care, regardless of whether they present with symptoms
10	**Dietary counselling and nutritional education** [33,34]	**Lifestyle management**	Dietary counselling and nutritional education provided to women throughout pregnancy
11	**Exercise** [35]	**Lifestyle management**	Antenatal advice and support in promoting exercise changes throughout pregnancy
12	**Group antenatal care** [36]	**Models of care**	Antenatal care provided in groups of 8-12 women at usual scheduled visits
13	**Telephone support** [37]	**Models of care**	Regular antenatal telephone calls from antenatal clinical nurse or midwife specialists to assess signs and symptoms of preterm labour
14	**Risk scoring** [38]	**Prediction and Risk Reduction**	A scoring system of risk factors associated with preterm birth to identify pregnancies that are at higher risk
15	**Digital cervical examination** [39]	**Prediction and Risk Reduction**	A finger examination of the cervix done routinely during pregnancy to detect any changes, which might indicate preterm labour

Table 3
Characteristics of 159 participants who participated in the survey.

Characteristic	No. (%) of responders
Language	
English	141 (89)
French	5 (3)
Spanish	10 (6)
Italian	3 (2)
Sex	
Male	97 (61)
Female	62 (39)
Age (years)	
<35	5 (3)
35–45	29 (18)
46–55	53 (33)
56–65	55 (35)
>65	17 (11)
Experience (years)	
<5	2 (1)
5–9	6 (4)
10–20	44 (28)
>20	107 (67)
Resident country classification	
Low and Middle Income Country	99 (62)
High Income Country	60 (38)
Work setting	
Rural	15 (9)
Urban	130 (82)
Suburban	14 (9)
Professional status	
Obstetrician	86 (54)
Neonatologist	30 (19)
Nurse/Midwife	9 (6)
General Practitioner	2 (1)
PTB Researcher	9 (6)
Epidemiologist	12 (8)
Patient/Client	2 (1)
Policy maker	5 (3)
Staff of NGO	3 (2)
Staff of funder	1 (1)

NGO – Non-Governmental Organisation, PTB – Preterm Birth.

counselling and nutritional education, risk scoring, vitamin D supplementation, exercise and antioxidant supplementation. There was less difference in median scores across interventions for the assessed criteria of affordability to women, affordability to health care professionals, implementation of the intervention, reducing health inequity and feasibility as a RCT (Randomized Controlled Trial). Acceptability of the interventions to women and health care professionals, and the sustainability and effectiveness of an RCT had less congruent median scores (Fig. A2).

Fifty-two (33%) responders suggested fourteen additional interventions for further research. We excluded interventions that were not primary prevention strategies, or had previously been excluded from this prioritization exercise based on the available level of evidence [16,18,19]. Suggested interventions for further research were within three main categories. These were preconception counselling (e.g., birth spacing and family planning), universal antenatal cervical length screening by ultrasound, and behavioral interventions, such as smoking cessation programs, partner involvement in antenatal care and incentives to seek or attend antenatal care.

Discussion

We conducted a research prioritization exercise on interventions for the primary prevention of spontaneous preterm birth. Validated and robust methods were applied, and we prioritized the interventions through multidisciplinary engagement, involving clinicians, researchers, lay representatives, and policy makers in the field. The detailed and transparent reporting of the process of prioritizing interventions for the primary prevention of spontaneous PTB highlights important areas around which research questions can be developed.

The results reported here represent the consensus view of a large sample of stakeholders, and highlights the most relevant interventions to be considered by researchers, policymakers and other stakeholders when developing clinical trials or conducting further knowledge syntheses. The methods used to obtain these results are well recognized for use in setting research priorities. The list of interventions evaluated were identified through a
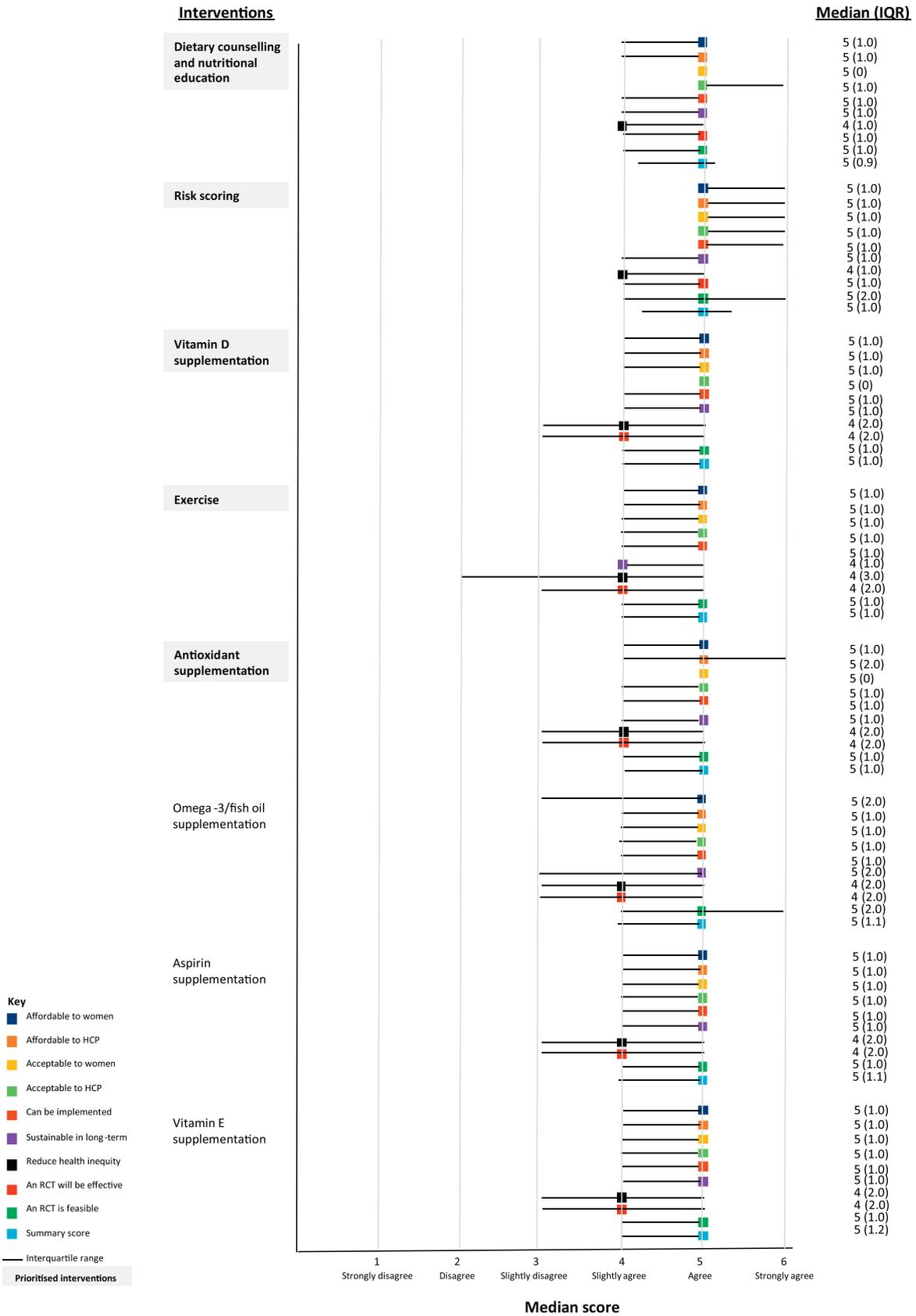
Fig. 1. Research interventions prioritised for the primary prevention of preterm birth.

review of systematic reviews of the literature [16]. The prioritization exercise was carried out via an online survey, which overcomes bias from dominant individuals within the groups if prioritization was done in small face-to-face settings. The optimal size for an online survey to generate consensus is not known, however ours is of a moderately larger size and represents a good range of opinions [15].

Our work has limitations. While we engaged with a diverse, multi-disciplinary, international group of participants, the findings are based on individual views, and thus may be influenced by their interests and areas of work. We were unable to stratify the prioritized interventions according to country income groups. It is therefore likely that the prioritized interventions are more skewed towards high-income countries, since this was the dominant group responding to the survey, based on the country of residence of responders. Although there was good response to the call to participate in the prioritization exercise by clinicians and researchers, lay representatives, policy makers and funding organizations were not so well represented. A different prioritization exercise (or different methodological approaches for prioritization) may therefore highlight other interventions as research priorities from these key groups. Finally, this prioritization exercise is time sensitive and so findings reported are relevant to the immediate period of investigation. It is likely that with the development of new interventions and evaluation of existing technologies, the prioritized interventions identified in this work may not be as relevant in the future.

One of the main challenges in spontaneous PTB prevention research is identifying which of the numerous interventions advocated to prevent spontaneous PTB is worth exploring further within the confines of scarce research resources. Many interventions are studied in clinical trials which are often underpowered and show little or no effect on PTB rates [8]. Thus, a consensus on which interventions to prioritize for research becomes essential. The exercise reported in this manuscript relates to primary prevention strategies but it is clear that researchers in this field have a predilection towards secondary prevention strategies focusing on those at high risk of preterm birth. Interventions such as progesterone, cerclage and the use of corticosteroid were repeatedly suggested in our survey as interventions to be considered for evaluation in PTB prevention research.

We did not weigh the criteria used in this exercise and have reported the prioritized list of interventions as ranked by a diverse group of stakeholders. We therefore consider this to be the best reflection of international research priorities of interventions for the primary prevention of spontaneous preterm birth.

Conclusion

We identified five research priorities of interventions for the primary prevention of spontaneous PTB, which should be considered by researchers, grant funding bodies and research-policy decision makers to inform calls on future clinical trials or individual patient data meta-analyses on the primary prevention of spontaneous PTB. We hope that in conjunction with the preterm birth research priorities identified by the James Lind Alliance, the interventions prioritized in this exercise will inform future research agenda in the primary prevention of spontaneous preterm birth.

Author contribution

All authors contributed to the study design, were involved in the critical discussion, and approved the final version of the manuscript for publication. JA and SN analyzed the data. JA and AM drafted the manuscript, which was reviewed by all authors.

This manuscript represents the views of the named authors only, and not the views of their institutions or organizations.

Conflict of interest

The authors declare no conflicts of interest.
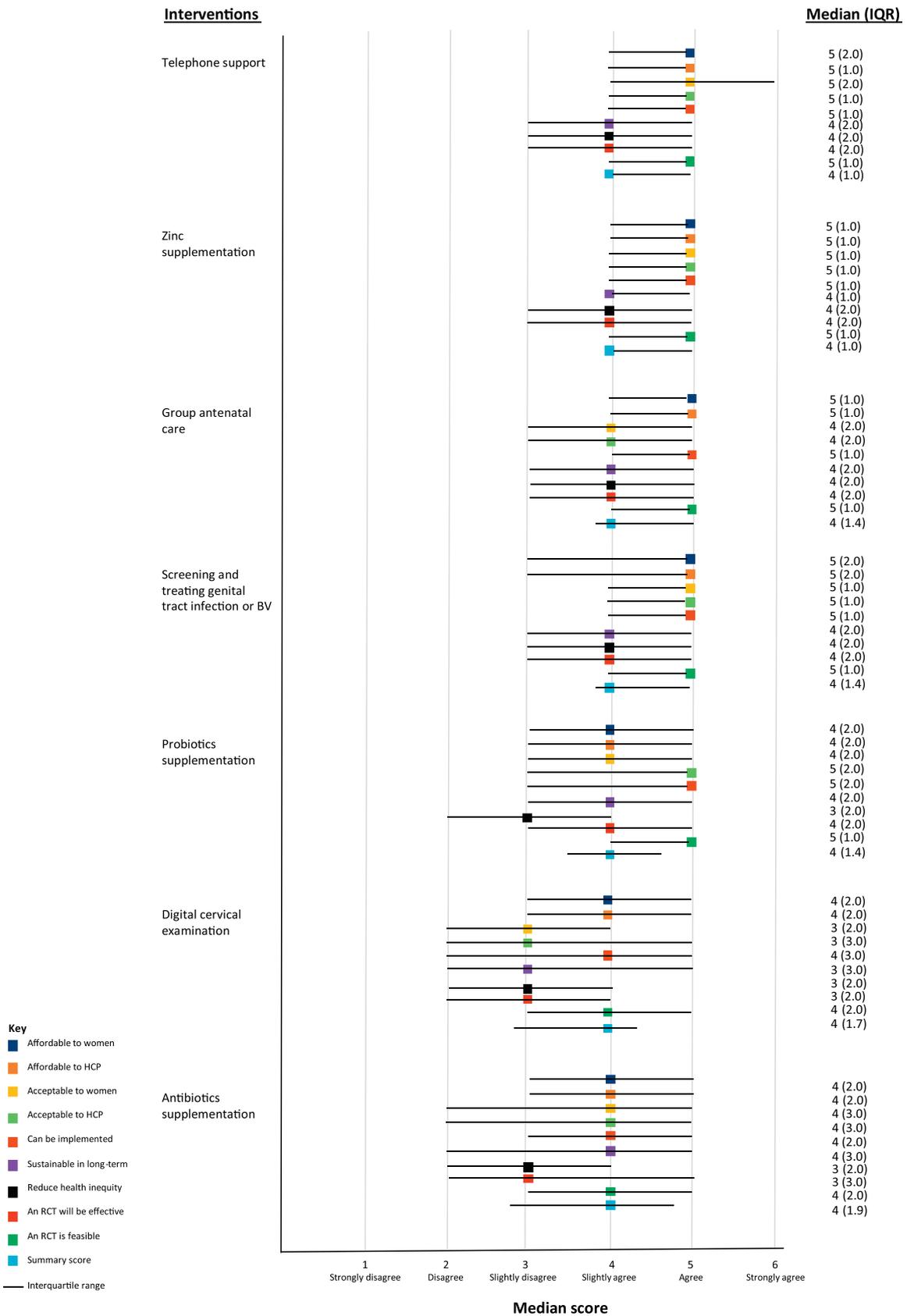
Funding

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Appendix A

Fig. A1. Interventions research prioritised as slightly important for the primary prevention of preterm birth.
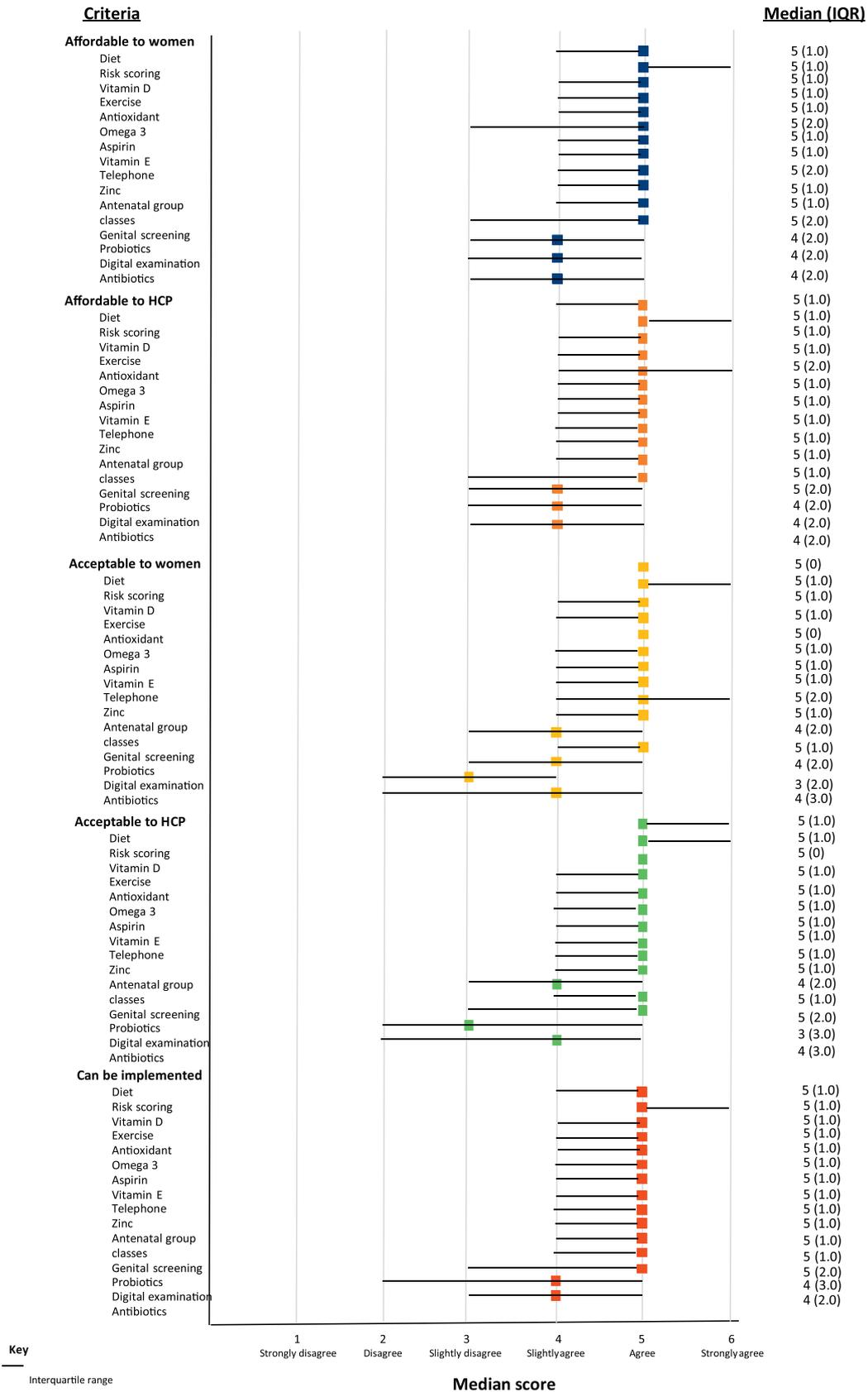
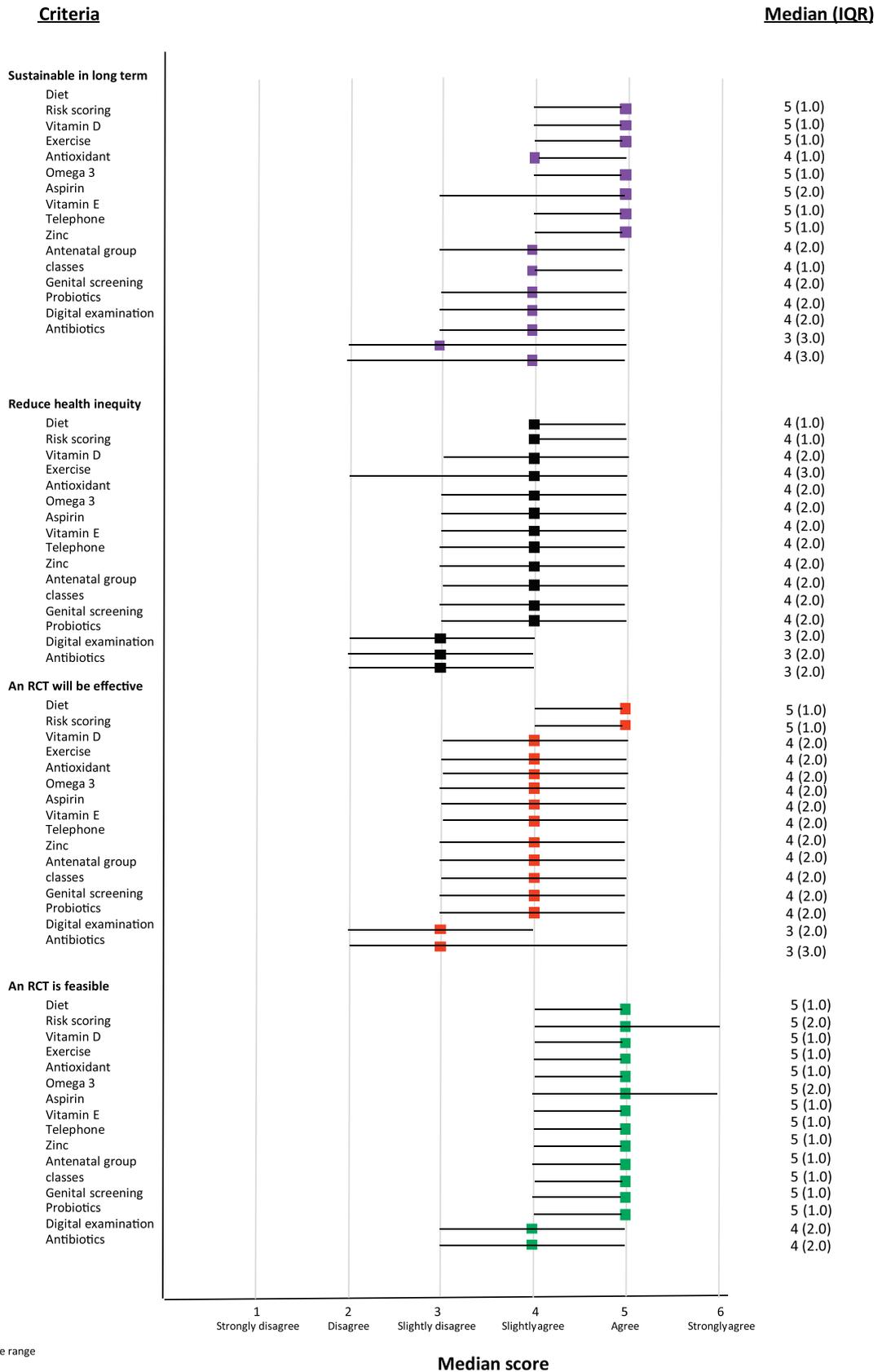Fig. A2. Ranking of interventions across criteria assessed.

Fig. A2. (Continued)

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