UNIVERSITAT AUTÒNOMA DE BARCELONA
Facultat de Medicina
Departamento de Pediatría, d'Obstetrícia i Ginecologia i de Medicina Preventiva

"ANÁLISIS Y GENERACIÓN DE EVIDENCIAS CIENTÍFICAS EN RELACIÓN A LA SALUD MATERNA"

Tesis doctoral

Doctoranda: Evelina Chapman Heller
Director: Dr. Xavier Bonfill i Cosp
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Evelina Chapman Heller

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Memoria de Tesis presentada en la modalidad de compendio de publicaciones realizadas por Evelina Chapman Heller para optar al grado de Doctor en la Universitat Autònoma de Barcelona bajo la dirección del Dr. Xavier Bonfill i Cosp y la Co-dirección de la Dra. María José Martínez Zapata

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INDICE

1. RESUMEN, ABSTRACT, ABREVIATURAS, SIGLAS Y ACRÓNIMOS

Resumen

Introducción

La morbimortalidad materna ocurrida durante el embarazo, parto o el puerperio, pone en serias dificultades las metas del objetivo de desarrollo del milenio 5 (ODM 5). Teniendo en cuenta que la mayoría de las muertes maternas son prevenibles y evitables y que ocurren en contextos de pobreza, se hace necesario el abordaje de este problema. Uno de los factores que podrían tener influencia en esta carga de mortalidad es el escaso uso de investigación en las decisiones sanitarias.

Este proyecto pretendió construir a partir de análisis de revisiones sistemáticas un mapa en el que quede reflejado cuáles son las lagunas de conocimiento científico existente sobre intervenciones destinadas a reducir -directa o indirectamente- la mortalidad materna. En segundo lugar, identificar que preguntas de investigación se consideran prioritarias a responder con más estudios. El tercer objetivo fue evaluar la calidad de los estudios contenidos en las revisiones sistemáticas de la Colaboración Cochrane mediante la herramienta riesgo de sesgo, así como su variación en el tiempo.

Cada etapa fue publicada y forman parte de un compendio de tres publicaciones secuenciales e interrelacionadas.

Métodos

Se realizó una búsqueda sistemática de las revisiones sistemáticas en la biblioteca Cochrane publicadas o actualizadas de enero 2006 a marzo de 2011. Se

seleccionaron todas aquellas que tuvieran que ver con salud materna. Se evaluó la sección 'Implicaciones para la investigación' para identificar lagunas de investigación y se elaboraron preguntas de investigación con formato PICO, las cuales se clasificaron según determinantes de mortalidad materna. Se elaboró una encuesta online, se enviaron las 319 preguntas resultantes del mapeo en 12 grupos de encuestas a participantes seleccionados de 4 grupos de la Colaboración Cochrane, que directa o indirectamente tienen alguna relación con salud materna. Se hicieron 2 rondas de consulta tanto para refinar, como para agregar nuevas preguntas y priorizar. Se usó una escala tipo Likert para la priorización. Se envió la encuesta a 155 participantes entre autores, referees y consumidores; además se enviaron cuatro recordatorios. La primera ronda se hizo entre el 5 y 31 de agosto 2011. La segunda ronda se llevó a cabo entre el 11 de noviembre y 22 de diciembre 2011 con tres recordatorios. Se enviaron las preguntas priorizadas en la primera vuelta a 2.121 participantes.

Para evaluar la calidad de los ensayos clínicos aleatorizados (ECAs) incluidos en las revisiones Cochrane se analizó la base de datos de revisiones sistemáticas Cochrane del número 12 del año 2012 por considerase la mas actualizada al momento de este estudio. Se seleccionaron de manera independiente y se incluyeron ECAs que al menos tuvieran un dominio de la herramienta riesgo de sesgo (RdS) informado.

Todos los dominios de RdS se evaluaron según diferencias en el tiempo en cuatro estratos de acuerdo a fecha de publicación en a) 2006-2012, b) 2000-2005, c) 1990 - 1999, y d) ≤ 1,989. Teniendo en cuenta la cantidad de datos a manejar, a priori se determinó evaluar cuatro dominios relevantes: generación de la secuencia, ocultación

de la asignación, el cegamiento y los datos de resultados incompletos. Se hizo además modelaje estadístico usando regresión logística para evaluar la asociación entre la presencia de bajo riesgo de sesgo según el dominio y el año de publicación del ensayo, el tipo de intervención, el tamaño de la muestra y el país del ECA.

Resultados

Se localizaron 204 RS y se incluyeron 178 RS. Se mapearon en total 319 preguntas en la primera etapa. Finalmente 62 preguntas de investigación se priorizaron como muy relevantes. La mayoría fue de políticas y sistemas de salud, embarazo no planificado y aborto, hemorragia postparto y trastornos hipertensivos. Los tipos de intervención más frecuentemente implicados fueron drogas en un 31%, seguido por intervenciones relacionadas con políticas y sistemas de salud (27%). La tasa de respuesta global fue del 47 % en la primera ronda y del 17% (363/2121) en la segunda. En la segunda ronda sólo el 12% (253/2121) de los participantes respondieron el cuestionario. Más mujeres (235) que hombres (128) participaron en la encuesta. Las mujeres sin embargo proporcionaron respuestas más incompletas que los hombres (49% versus 35%, p= 0,01). También se encontraron diferencias estadísticamente significativas (ES) al comparar el grupo de preguntas muy relevantes según sexo del participante en seis preguntas; la mitad de ellas relacionados con diabetes. No se encontraron diferencias ES al comparar el grupo de preguntas muy relevantes por tipo de entrevistado ni país de procedencia ni número de ronda.

Para la evaluación del riesgo de sesgo de los ECAs contenidos en las revisiones sistemáticas se incluyeron 1.732 ECA de 97 SR. Los ECAs juzgados como de bajo y alto RdS aumentaron significativamente en el tiempo, mientras que las tasas de RdS

poco claro disminuyeron con el tiempo en varios dominios. Los ECAs publicados después de 2007 tuvieron las tasas más altas de bajo RdS acompañados de una disminución de las tasas de las categorías de alto y poco claro RdS como la mayoría de los dominios. Los ECAs que incluían drogas como intervención fueron más propensos a mostrar un menor riesgo de sesgo para 4 de los 6 dominios evaluados. El RdS para los dominios de cegamiento cuando se comparan exclusivamente los medicamentos frente a otros tipos de intervenciones fue significativo. Estas diferencias no fueron significativas para los demás dominios de RdS.

Discusión

La utilización de la evidencia científica en las decisiones sanitarias es cada vez más frecuente. Para un uso efectivo y ético de las mismas en primer lugar se necesita saber con qué evidencias se cuentan y en segundo lugar, su calidad.

Bajo la hipótesis principal de este trabajo de tesis de que falta bastante por conocer sobre aspectos muy relevantes a la mortalidad materna, tanto sobre sus factores causales como en las intervenciones para abordarlas, nuestro primer trabajo consistió en mapear estas lagunas. Un segundo paso consistió en priorizarlas bajo forma de preguntas de investigación para conocer además, la percepción de los expertos. Por último, analizar si estas evidencias que se producen en esta misma fuente fueron mejorando su calidad en el transcurso del tiempo. Una explicación parcial del por qué la mortalidad materna no alcanzaría la meta del ODM5 vendría dada por la profunda laguna de conocimiento existente, y que fue puesta de manifiesto través de más de 300 preguntas de investigación que necesitan respuesta. Una característica a remarcar es que los sistemas de salud aparecen como determinantes relevantes de la

salud materna; tanto en el proceso de mapeo como en su priorización. Una de las ventajas a resaltar de estas dos etapas es que se usó una misma fuente y bajo los mismos estándares. La desventaja principal fue la baja tasa de respuesta. No encontramos patrones de oro para priorizar investigación en salud materna, incluso este trabajo de tesis hasta donde sabemos fue un primer intento global. Creemos que nuestro proceso simple en el diseño pero complejo en la ejecución, nos permitió tener un *ranking* de más de 60 preguntas. Parte de esas respuestas también se muestran en los anexos de esta tesis. La propia autora está participando en la elaboración de dos revisiones sistemáticas relevantes al campo de salud materna después de obtener estos resultados. Por ultimo decir que algunos esfuerzos internacionales para mejorar la calidad de los estudios están dando sus frutos. Hemos mostrado también que los ensayos clínicos que componen las revisiones sistemáticas mejoraron su calidad en el tiempo.

Conclusiones

Es posible identificar lagunas de investigación en salud materna mediante el uso de las revisiones sistemáticas como fuente de las mismas. Es posible también priorizar estas lagunas con la participación de distintos actores relevantes. Es importante que quienes desarrollen investigaciones en este campo no solo cuenten con un mapa de preguntas priorizadas sino también tengan en consideración a los sistemas de salud como determinantes. Merece destacarse que las investigaciones que se están produciendo en diferentes campos de la salud en forma de ECAs han mejorado su reporte y mejorado en su validez.

Abstract

Introduction

Maternal morbidity and mortality during pregnancy, childbirth or the puerperium jeopardize the goals of the Millennium Development Goal 5 (MDG 5). The majorities of maternal deaths are preventable and avoidable, and besides occur in contexts of poverty, so it is imperative to address this problem. Among other factors, the limited use of research in health decision could influence the burden of mortality.

This project aims to build a map that reflect the gaps of scientific knowledge on interventions addressed to reduce directly or indirectly maternal mortality, also identify priority research questions that need be answered with more research and, evaluate the quality of the studies included in the systematic reviews of the Cochrane Collaboration through risk of bias tool and, its variation over time.

Each stage was published and they are part of a compendium of three sequential and interrelated publications.

Methods

A systematic search for systematic reviews in the Cochrane Library published or updated from January 2006 to March 2011. We selected all those that had to do with maternal health. The 'Implications for research' section was evaluated to identify

research gaps and research questions were developed with PICO format, which were classified in determinants of maternal mortality. An online survey was elaborated, 319 questions were mapping and we built 12 groups of domains and 12 surveys. Four groups of the Cochrane Collaboration with tight relation with maternal health were invited to participate. Two rounds of consultation were made, both to refine, to add new questions, and prioritize. The first round was held between 5 to 31 of August 2011, A Likert scale was used for prioritization. We survey to 155 participants between authors, referees and consumers and we sent four reminders. The prioritized questions in the first round were sent to 2,121 participants in the second round between November 11 and December 22, 2011 three reminders were sent.

To assess the quality of randomized clinical trials (RCTs) included in systematic reviews of Cochrane database, the number 12 of the year 2012 of this given database was used and the RCTs were selected and included independently. The inclusion criteria was that at least one domain of risk of bias (RoB) tool had to be informed.

All RoB domains were assessed for differences into four strata according to date of publication: a) 2006-2012 b) 2000-2005, c) 1990 - 1999, d) ≤ 1.989. Considering the amount of data to be handled, were determined a priori evaluate four relevant domains: sequence generation, allocation concealment, blinding and incomplete outcome data. Statistical modeling was done using logistic regression to assess the association between the presence of low risk of bias according to domain and year of publication of the trial, the type of intervention, sample size and country of ECA.

Results

204 SR were located and included 178 RS. We mapped a total of 319 questions. Finally 62 research questions were prioritized as highly relevant. The majority was of policies and health systems, unintended pregnancy and abortion, postpartum hemorrhage and hypertensive disorders. The types of intervention most commonly implicated were drugs in 31%, followed by policies and health systems interventions (27%). The overall response rate was 47% in the first round and 17% (363/2121) in the second. In the second round only 12% (253/2121) of participants completed the questionnaire. More women (235) than men (128) participated in the survey. Women however provided incomplete answers more than men (49% versus 35%, p = 0.01). Statistically significant differences (ES) were found when comparing the group of very relevant questions by sex of participant on six questions; half of them related to diabetes. No differences were found when comparing the ES group of very important questions by type of respondent, or country or number of round.

For the assessment of risk of bias, we included 1,732 RCTs from 97 SR. The ECA judged low and high RoB increased significantly over time, while rates RoB unclear decreased over time in several domains. RCTs published after 2007 had the highest rates of low RoB accompanied by a decrease in the rates of the categories of high and unclear RoB like most domains. RCTs that included drugs as intervention were more likely to show a lower risk of bias for 4 of the 6 domains assessed. The RoB for blinding domains when compared only drugs versus other types of interventions was significative. These differences were not significant for the other domains RoB.

Discussion

The use of scientific evidence in health care decisions is becoming common. For effective and ethical use it is needed to know what evidence exists and its quality.

One of the hypotheses of this thesis is that there are important gaps in the knowledge about maternal mortality, both on their causal pathways and interventions. To address them, the first step was to map these gaps. A second step was to prioritize using experts. Finally, to analyze if the evidences produced in the same source were improving in quality over time. Part of the explanation of why maternal mortality did not achieve the target of MDG 5 could be understood by the deep gap we found, expressed through more than 300 research questions that need answering. One remarkable feature found in this research, was that health systems were described as important determinants of maternal health, both in the mapping as well in the prioritization process. One advantage to highlight these two stages is that they use the same source and the same standards. The main disadvantage was the low response rate. We found no gold standards to prioritize maternal health research, including this project to our knowledge, was the first comprehensive attempt. This design with simple design and complex implementation process, allowed us to have a ranking of more than 60 questions (see annexes). Finally we conclude that some international efforts to improve the quality of the studies are paying off. The clinical trials included in systematic reviews have improved their quality over time.

Conclusions

It is possible to identify research gaps in maternal health through the use of systematic reviews as a source of them. It is also possible to prioritize these gaps with the participation of different participants belonging to the same source. It is important that

those who conduct research in this field not only have a map of prioritized questions but also take into consideration the health systems as determinants. It is noteworthy that the RCTs taking place in different areas of health have improved reporting and enhanced in its validity.

Abreviaturas, siglas, acrónimos

CHNRI: Child Health and Nutrition Research Initiative

COHRED: Council on Health Research for Development

ENHR: Essential National Health Research

EPOC: Effective Practice and Organization of Care Group

ODM: Objetivos de desarrollo del milenio

PICO: población (P), intervención (I), comparación (C) y resultado (O de Outcome)

ES: estadísticamente significativas

RdS: Riesgo de sesgo

RoB: Risk of bias

OR: Odds ratio

ECA: ensayo clínico aleatorizado

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

CONSORT: Consolidated Standards of Reporting Trials

AMSTAR: A measurement tool to assess systematic reviews

RS: Revisión sistemática

2. INTRODUCCIÓN

Introducción

Pasaron más de 20 años del informe de la Comisión de Investigaciones Sanitarias para el Desarrollo desde donde se lanzó la emblemática *brecha 10/90* que planteaba la gran disparidad que existe entre los escasos recursos aplicados a la investigación (10% del presupuesto global de investigación) dirigidos a las necesidades de la población de los países menos desarrollados y la magnitud de sus necesidades de salud (el 90%) [1,2,3,4,5,6] . En respuesta a ese problema, se han implementado

[1] Frenk J, Chen L. Overcoming gaps to advance global health equity: a symposium on new directions for research. Health Res Policy Syst. 2011 Feb 22;9:11. doi: 10.1186/1478-4505-9-11.

[2] Commission on Health Research for Development: Health Research: Essential Link to Equity in Development. Oxford: Oxford University Press; 1990.

[3] World report on knowledge for better health : strengthening health systems. World Health Organization 2004. Disponible en: http://www.who.int/rpc/meetings/en/world_report_on_knowledge_for_better_health2.pdf . Con acceso el 15 de Junio de 2013.

distintas iniciativas a nivel internacional que promocionan métodos transparentes y válidos para establecer prioridades de investigación para la salud y que direccionaran la producción de conocimiento científico hacia estas prioridades. También se ha establecido que esta no es la única laguna a mejorar. Existen otras lagunas relacionadas con la producción de conocimiento científico como son por ejemplo, las relacionadas con la diversidad de disciplinas de investigación (sistemas biomédicos, clínicos, epidemiológicos, de salud) o los diferentes enfoques entre los campos clínicos y de salud pública; las asimetrías entre las inversiones públicas y privadas; entre estudios de eficacia y efectividad, o entre conocimiento científico y la traducción en acciones [1,[7]]. Está claro que el mayor consenso que existe es que para mejorar la salud a nivel mundial se requiere tanto incrementar producción del conocimiento científico como asegurar su traducción en acciones para la salud, el desarrollo y equidad [[8]].

[4] Haines A et al. Bridging the implementation gap between knowledge and action for health. Bull WHO 2004;82:724-732

[5] Dopson S, Fitzgerald L eds. Knowledge to action? Evidence-based health care in context. Oxford: Oxford University Press, 2005.

[6] Pang T et al. From Bangkok to Mexico: towards a framework for turning knowledge into action to improve health systems . Bull WHO 2004;82:720.

[7] McCoy D, Storeng K, Filippi V, Ronsmans C, Osrin D, Borchert M, Campbell OM, Wolfe R, Prost A, Hill Z, Costello A, Azad K, Mwansambo C, Manandhar DS. "Maternal, neonatal and child health interventions and services: moving from knowledge of what works to systems that deliver" [International Health 2 (2010) 87-98]. Int Health. 2010 Sep;2(3):228. doi: 10.1016/j.inhe.2010.03.005. Epub 2010 Jun 1.

[8] Oxman AD, Lavis JN, Lewin S, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP) 1: What is evidence-informed policymaking? Health Res Policy Syst. 2009 Dec 16;7 Suppl 1:S1. doi: 10.1186/1478-4505-7-S1-S1.

Hace poco más de 20 años también surgió la Colaboración Cochrane cuyos principios se armonizan con estos movimientos, fundamentalmente para incrementar la producción de conocimiento científico de calidad que sirva para las decisiones en salud en todos los niveles. Precisamente su mayor producto son las revisiones sistemáticas que hoy no solo son el mayor insumo para facilitar los procesos de toma de decisiones, sino también para mostrar lagunas de conocimientos que estimulen el ciclo de producción de más y mejores investigaciones para la salud [9].

La comunidad científica se había adelantado y sembrado el camino para que en el año 2004 se reunieran los ministros de todo el mundo con el fin de plantear la necesidad de más investigación acorde a las necesidades de salud de las poblaciones y a la mejor utilización de los resultados con el fin de avanzar también las metas de los objetivos de desarrollo del milenio (ODM). Precisamente, en la cumbre ministerial sobre investigación en salud celebrada en México y la resolución WHA58.34 aprobada durante la 58ª Asamblea Mundial de la Salud en 2005 se llamó la atención sobre la necesidad de producir y utilizar más conocimiento científico para mejorar la salud de las personas y los sistemas de salud, reclamando además los recursos necesarios para cubrir esta laguna [10]. Por su parte la Organización Mundial de Salud (OMS) publicó el *World report on knowledge for better health* en donde revela además, que 6

9 Chalmers I, Hedges LV, Cooper H. A brief history of research synthesis. Evaluation & the Health Professions, 2002, 25:12-37. doi: http://dx.doi.org/10.1177/0163278702025001003 PMID:11868442.

10 Task Force on Health Systems Research. Informed choices for attaining the Millennium Development Goals: towards an international cooperative agenda for health-systems research. Lancet, 2004, 364:997-1003. doi: http://dx.doi.org/10.1016/ S0140-736(04)17026- PMID:15364193.

millones de niños morirían en estos países debido a causas prevenibles que podrían evitarse con la implementación de medidas simples y probadamente efectivas [3].

A partir de estos hitos se han producido otras reuniones de alto nivel así como documentos relevantes para guiar la disminución de las lagunas mencionadas. Merece destacarse la Estrategia de la OMS sobre investigaciones para la salud. En ella se expresa que para que un sistema de investigaciones sea eficaz debe cumplir cuatro funciones: definir prioridades; desarrollar capacidades, incluyendo la recaudación de fondos; establecer estándares y utilizar los resultados de investigación para orientar las políticas [[11]].

Por su parte, los Institutos Nacionales de Salud de los Estados Unidos (en inglés NIH) sugieren que los procesos de priorización de investigaciones deben responder a las necesidades de salud pública y, al igual que lo planteado por la OMS las investigaciones priorizadas deben seguir estándares de calidad, ser potenciales para el progreso científico, expandir las fronteras de investigación y contar con adecuado soporte de infraestructura [[12]].La Colaboración Cochrane cobró tanta relevancia que desde el año 2011 tiene un lugar formal como ONG socia de la OMS con el rol

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[11] Función y responsabilidades de la OMS en las investigaciones sanitarias. Proyecto de estrategia de la OMS sobre investigaciones en pro de la salud Informe de la Secretaría. A63/22, 25 de marzo de 2010. Disponible en: http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_22-sp.pdf. Acceso el 3 de Septiembre de 2013.

[12] Scientific opportunities and public needs: improving priority setting and public input at the National Institutes of Health. Institute of Medicine. National Academy Press 2101 Constitution Avenue, N.W. Washington, D.C. 20418, 1998 Setting Research priorities at the National Institutes of Health). Disponible en: http://www.nap.edu/openbook.php?record_id=6225&page=1. Con acceso el 7 de Septiembre de 2013.

especifico de contribuir a mejorar las políticas de salud mediante la inclusión de las evidencias científicas que allí se producen.

2.1 Las lagunas de investigación en salud materna

Un tema particularmente relevante para países de ingresos bajos y medios es la salud materna. Si bien la mortalidad materna ha disminuido aproximadamente un tercio entre 1990 y 2011, la mayoría de los países en desarrollo llevarán más tiempo de lo esperado para alcanzar la meta del Objetivo de Desarrollo del Milenio 5 (ODM 5) [13]. Son relativamente pocas las revisiones sistemáticas que aborden los impactos directos de las intervenciones sobre la mortalidad materna, en parte porque este evento es en sí mismo raro [14]. Muchos países han establecido que la salud materna y, en concreto, la disminución de la mortalidad materna es una prioridad en sus agendas de investigación en salud nacionales [15,16]. Sin embargo, la producción insuficiente de la investigación relevante en áreas de bajos recursos [3,17,18], y la pobre

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13 Lozano R, Wang H, Foreman KJ, Rajaratnam JK, Naghavi M, Marcus JR, et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. Lancet 2011;378(9797):1139-65.

14 Evidence from Systematic Reviews to Inform Decision-Making Towards Achieving the Millennium Development Goals for Reducing Maternal and Child Mortality. A Background Document prepared for An International Dialogue on Evidence-informed Action to Achieve Health Goals in Developing Countries (IDEAHealth). Khon Kaen, Thailand. 13-16 December 2006.

15 Martínez-Martínez E, Zaragoza ML, Solano E, Figueroa B, Zúñiga P, Laclette JP. Health research funding in Mexico: the need for a long-term agenda. PLoS One. 2012;7(12):e51195]

16 Reveiz L, Elias V, Terry RF, Alger J, Becerra-Posada F. Comparison of national health research priority-setting methods and characteristics in Latin America and the Caribbean, 2002–2012. Rev Panam Salud Publica. 2013;34(1):1–13

17 Byskov J, Bloch P, Blystad A, Hurtig AK, Fylkesnes K, Kamuzora P, Kombe Y, Kvåle G, Marchal B, Martin DK, Michelo C, Ndawi B, Ngulube TJ, Nyamongo I, Olsen OE,

transferibilidad de los resultados de investigaciones desde escenarios de altos ingresos son factores que también contribuyen a las lagunas de investigación existentes [10].

En la última década se han realizado ejercicios de mapeo para detectar lagunas de investigación o vacíos de conocimiento de distintos problemas sanitarios [19,20,21,22].

Robinson et al. [23] define como "laguna de investigación" a un tema o área a la cual le falta o tiene información insuficiente que limita a los investigadores a sacar una

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Onyango-Ouma W, Sandøy IF, Shayo EH, Silwamba G, Songstad NG, Tuba M. Accountable priority setting for trust in health systems--the need for research into a new approach for strengthening sustainable health action in developing countries. Health Res Policy Syst. 2009 Oct 24;7:23.

18 Montorzi G, de Haan S, IJsselmuiden C. (2010) Priority setting for research for health: a management process for countries. Council on Health Research for Development. Disponible en: http://www.cohred.org/downloads/Priority_Setting_COHRED_approach_August_2010.pdf. Con acceso el 11 de enero de 2011.

19 Li T, Vedula SS, Scherer R, Dickersin K. What comparative effec- tiveness research is needed? A framework for using guidelines and systematic reviews to identify evidence gaps and research priorities. Ann Intern Med 2012;156:367e77.

20 Nasser M, Welch V, Tugwell P, Ueffing E, Doyle J, Waters E. Ensuring relevance for Cochrane reviews: evaluating processes and methods for prioritizing topics for Cochrane reviews. J Clin Epidemiol. 2013 May;66(5):474-82.

21 de Vet HC, Kroese ME, Scholten RJ, Bouter LM. A method for re- search programming in the field of evidence-based medicine. Int J Technol Assess Health Care 2001;17(3):433e41.

22 Clarke L, Clarke M, Clarke T. How useful are Cochrane reviews in identifying research needs. J Health Serv Res Policy 2007;12:101e3.

23 Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for determining research gaps during systematic reviews. Methods Future Research Needs Report No. 2. AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2011.

conclusión para una pregunta determinada. Definen también la “necesidad de investigación” como una laguna que limita la posibilidad de tomar decisiones.

Una publicación reciente muestra un estudio piloto para identificar las necesidades de investigación desde una revisión sistemática en diabetes mellitus gestacional [24]. Mientras que el estudio piloto sólo utilizó una revisión sistemática, los autores desarrollaron un modelo conceptual que incluye una serie de pasos como son la identificación de lagunas en la investigación; la retroalimentación de los autores de la revisión; la traducción de lagunas de investigación en problemas a investigar; la retroalimentación de los actores locales, rondas Delphi; priorización de los resultados y refinamiento de las preguntas finales de investigación. Una de sus conclusiones fue que los autores de las revisiones sistemáticas deben incluir la identificación de las necesidades específicas de investigación como un objetivo primordial del proceso de revisión sistemática.

Expertos en este campo consideran que las intervenciones relacionadas con los sistemas y políticas de salud son determinantes importantes de la salud materna, y también plantean la forma de quebrar estos determinantes con preguntas específicas que requieren una respuesta urgente en relación con el logro de los ODM 5. Todos estos resultados están en línea con el creciente consenso de tener en cuenta los

[24] Saldanha IJ, Wilson LM, Bennett WL, Nicholson WK, Robinson KA. Development and pilot test of a process to identify research needs from a systematic review. J Clin Epidemiol. 2013 May;66(5):538-45

determinantes de la salud relacionados con los sistemas, programas, políticas de salud en el campo de la salud materna e infantil [19,[25],[26],[27],[28]].

Para lograr este ODM en salud materna, existe entonces gran consenso sobre la necesidad de contar con políticas publicas específicas, tener acceso a la mejor evidencia disponible sobre las intervenciones que se sabe que funcionan -o podrían ser potencialmente útiles- e incorporar además, el mejor conocimiento disponible sobre los sistemas de salud, incluyendo su desempeño e impacto de sus políticas [[29],

[25] Ranson k, Law tj, Bennett s. (2010) establishing health systems financing research priorities in developing countries using a participatory methodology. soc sci med. 70(12):1933-42.

[26] Althabe F, Bergel E, Cafferata ML, Gibbons L, Ciapponi A, Alemán A, Colantonio L, Palacios AR. Strategies for improving the quality of health care in maternal and child health in low- and middle-income countries: an overview of systematic reviews. Paediatr Perinat Epidemiol. 2008 Jan;22 Suppl 1:42-60.

[27] Gonzalez-Block MA. Health policy and systems research agendas in developing countries. Health Res Policy Syst. 2004 Aug 5;2(1):6.

[28] Bennett WL, Robinson KA, Saldanha IJ, Wilson LM, Nicholson WK. High priority research needs for gestational diabetes mellitus. J Womens Health (Larchmt). 2012 Sep;21(9):925-32. doi: 10.1089/jwh.2011.3270. Epub 2012 Jul 2.

[29] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

[30], propiciando además que los resultados de las investigaciones se hagan visibles y accesibles para ser implementados [14,29,[31],[32], [33], [34],[35],[36]].

2.2 La definición de prioridades

La definición de prioridades de investigación implica procesos basados en métodos estandarizados. No existen métodos únicos ni ideales pero cada vez se están desarrollando más metodologías, fundamentalmente bajo el principio de eficiencia que nos habla de la necesidad de una mejor inversión de los limitados fondos disponibles para investigación. [[37]]

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[30] Institute of Medicine. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, editor(s). Clinical practice guidelines we can trust. Washington (DC): National Academies Press; 2011. 2p. Disponible en: http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust/Standards.aspx. Con acceso el 15 de diciembre de 2012.

[31] Rudan I et al. Evidence-based priority setting for health care and research: tools to support policy in maternal, neonatal, and child health in Africa. PLoS Medicine, 2010, 7:e1000308.

[32] Villar J, Carroli G, Gulmezoglu AM. The gap between evidence and practice in maternal healthcare. Internal Journal of Gynaecology and Obstetrics 2001; 75 (Suppl 1):S47-S54.

[33] Bhutta ZA, Chopra M, Axelson H, Berman P, Boerma T, Bryce J. Countdown to 2015 decade report (2000–10): taking stock of maternal, newborn, and child survival. Lancet 2010;375:2032–2044.

[34] Belizán JM, Buekens P, Althabe F, Bergel E. Maternal survival: more research is needed. Lancet. 2006 Dec 16;368(9553):2123-4.

[35] Purgato M, Barbui C, Cipriani A. Assessing risk of bias in randomized controlled trials. Epidemiol Psichiatr Soc. 2010 Oct-Dec;19(4):296-7.

[36] Graham B. Clinical Practice Guidelines: What Are They and How Should They Be Disseminated? Hand Clin. 2014 Aug;30(3):361-365.

[37] World Health Organization. The world health report 2013: research for universal health coverage. Geneva: World Health Organization; 2013

Los ejemplos mejor documentados de metodologías de priorización son los que abordan específicamente temas de salud específicos (OMS) [31,[38],[39]]. Más recientemente, otros autores examinaron de manera sistemática la forma de establecer prioridades considerando los métodos empleados, la documentación y legitimidad del enfoque, la intervención de las partes interesadas, el proceso de revisión y apelación, y el liderazgo [[40]]. También se generaron listas de chequeo para asegurar que sea una buena práctica, tan sistemática como transparente [[41],[42]].

Debemos considerar que los procesos de priorización de investigaciones son procesos dinámicos y complejos que deben ser revisados y actualizados cuando sea necesario [[43]]. Una amplia variedad de metodologías existen con respecto a estos procesos [18,24,25,40,[44],[45],[46],[47],[48]].

[38] Ghaffar A et al. The 3D Combined Approach Matrix: an improved tool for setting priorities in research for health. Geneva, Global Forum for Health Research, 2009.

[39] Okello D, Chongtrakul P, COHRED Working Group on Priority Setting. A manual for research priority setting using the ENHR strategy. Geneva, Council on Health Research for Development, 2000.

[40] Tomlinson M et al. A review of selected research priority setting processes at national level in low and middle income countries: towards fair and legitimate priority setting. Health Research Policy and Systems, 2011, 9:19.

[41] Viergever RF et al. A checklist for health research priority setting: nine common themes of good practice. Health Research Policy and Systems, 2010, 8:36.

[42] Terry RF et al. Mapping global health research investments, time for new thinking - a Babel Fish for research data. Health Research Policy and Systems, 2012, 10:28.

[43] Dr Myint Htwe. Regional Health Forum. Regional Health Forum WHO South-East Asia Region(Volume 3). Disponible en: http://www.searo.who.int/en/Section1243/Section1310/Section1343/Section1344/Section1351/Section1687_7202.htm. Con acceso el 1 de abril de 2012.

[44] COHRED. (2000). Priority setting for health research: lessons from developing countries. The Working Group on Priority Setting. Health Policy Plan., 5(2):130-6.

A pesar de ello, no existe ningún patrón oro porque priorizar - proceso de selección y clasificación de prioridades- depende del contexto e implica numerosos participantes, disciplinas, y escenarios. Como resultado de esto, los responsables políticos, los financiadores y los propios investigadores experimentan múltiples obstáculos, fundamentalmente la incertidumbre [49,50]. Varios factores contribuyen a estos obstáculos a la hora de definir prioridades. En primer lugar, la definición de los criterios son inconsistentes. Mientras algunos los definen basados en enfermedades,

45 Institute of Medicine (US) Committee on the NIH Research Priority-Setting Process. (1998). Scientific Opportunities and Public Needs: Improving Priority Setting and Public Input at the National Institutes of Health. Washington (DC): National Academies Press (US).

46 Viergever, R. (2010). Health research prioritization at WHO: an overview of methodology and high level analysis of WHO led health research priority setting exercises. The World Health Organization.

47 Uhm S, Alderdice F, Chambers B, Gyte G, Gale C, Duley L, James C, David A, McNeill J, Turner M, Shennan A, Deshpande S, Crowe S, Chivers Z, Brady I, Oliver S. PPO.23 Top 15 research priorities for preterm birth with clinicians and service users' involvement - outcomes from a James Lind Alliance priority setting partnership. Arch Dis Child Fetal Neonatal Ed. 2014 Jun;99 Suppl 1:A158.

48 The Working Group on Priority Setting. (2010). Priority setting for health research: lessons from developing countries. Health Policy Plan.15(2):130-6.

49 Mitton C, Smith N, Peacock S, Evoy B, Abelson J. Public participation in health care priority setting: A scoping review. Health Policy. 2009 Aug;91(3):219-28.

50 Reveiz L, Tellez DR, Castillo JS, Mosquera PA, Torres M, Cuervo LG, Cardona AF, Pardo R. Prioritization strategies in clinical practice guidelines development: a pilot study. Health Res Policy Syst. 2010 Mar 6;8:7.

necesidades y disponibilidad de recursos [51], otros consideran cuestiones políticas y técnicas [39,40].

En segundo lugar, la selección de la perspectiva es variable. Por ejemplo, los enfoques compuestos o combinados se basan en datos históricos, mientras que los enfoques prospectivos se basan en datos proyectados [18].

En tercer lugar, la selección de participantes no es estandarizada. Algunas metodologías apoyan los enfoques multidisciplinarios con representantes de diversos sectores, mientras que otras apoyan un enfoque en el cual los participantes se seleccionan por la variedad de sus experiencias personales [40].

En cuarto lugar, la naturaleza de la participación es ambigua. Mientras que algunas metodologías apoyan la participación amplia de las partes interesadas, otros restringen la toma de decisiones a grupos de trabajo más pequeños [50,51,52]. Por último, la dinámica de grupo puede resultar en conflicto debido a las diferentes perspectivas, agendas y fuerzas de poder.

La principal hipótesis de este proyecto es que se necesita más investigación en los escenarios de bajos y medianos ingresos para comprender mejor y abordar todas las circunstancias alrededor de las muertes maternas, incluyendo una nueva revisión del

51 Dujardin JC, Herrera S, do Rosario V, Arevalo J, Boelaert M, Carrasco HJ, Correa-Oliveira R, Garcia L, Gotuzzo E, Gyorkos TW, Kalergis AM, Kouri G, Larraga V, Lutumba P, Macias Garcia MA, Manrique-Saide PC, Modabber F, Nieto A, Pluschke G, Robello C, Rojas de Arias A, Rumbo M, Santos Preciado JI, Sundar S, Torres J, Torrico F, Van der Stuyft P, Victoir K, Olesen OF. Research priorities for neglected infectious diseases in Latin America and the Caribbean region. PLoS Negl Trop Dis. 2010 Oct 26;4(10):e780.

52 Sibbald SL, Singer PA, Upshur R, Martin DK. Priority setting: what constitutes success? A conceptual framework for successful priority setting. BMC Health Serv Res. 2009 Mar 5;9:43.

impacto que los sistemas de salud y las políticas tienen sobre ellos. Con el fin de reducir estas lagunas de conocimiento, las prioridades de investigación deben ser identificadas, priorizadas y dirigidas y los resultados de las investigaciones deben hacerse visibles, disponibles y accesibles para una implementación adecuada y oportuna [3,6,37,[53],[54]].

Al revisar la literatura encontramos que existen numerosas metodologías de priorización. Podemos citar ejemplos de metodologías de priorización encontrados como son el enfoque de investigación nacional esencial en salud (ENHRA en inglés), la matriz de estrategias combinadas y el enfoque de prioridades de salud del niño [18].

En nuestra tercera hipótesis planteamos que la elaboración de investigaciones prioritarias no solo debe pensarse para disminuir la laguna de conocimiento-acción sino que las mismas deben cumplir con estándares de calidad asumiendo que la misma está relacionada directamente con la fuerza de las recomendaciones para la toma de decisiones.

2.3 Las revisiones sistemáticas y su rol en la reducción de las lagunas

La toma de decisiones en salud basadas en evidencias es un imperativo que cobró impulso a partir de las mencionadas reuniones e iniciativas globales y propician cada vez más que esas lagunas tanto de producción como de uso se enfoquen fundamentalmente en las revisiones sistemáticas. Actualmente es bien conocido que -comparadas con otras fuentes de evidencia- las revisiones sistemáticas ofrecen – al

[53]Belizán JM, Buekens P, Althabe F, Bergel E. (2006) Maternal survival: more research is needed. Lancet. 368(9553):2123-4.

[54] Evans JR. (1990) Essential national health research. A key to equity in development. N Engl J Med. 323(13):913-5.

menos – 4 ventajas: i) reducen la posibilidad de que los tomadores de decisión sean "mal aconsejados" por los hallazgos de la investigación si se utilizan métodos sistemáticos y transparentes para la identificación, selección, evaluación y síntesis de la evidencia; ii) aumentan la confianza que ellos puedan tener respecto de lo que se puede esperar de una intervención, debido al incremento en el número de "unidades incluidas"; iii) permiten que los tomadores de decisión utilicen su escaso tiempo en evaluar la aplicabilidad local de los hallazgos y la aceptabilidad y factibilidad de las intervenciones más que en la búsqueda y análisis crítico de la información (que ya fue realizado por los revisores); y iv) permiten que los diferentes grupos de interés, incluyendo aquellos de la sociedad civil, puedan discutir en forma constructiva la evidencia presentada [55].

Con frecuencia se ha afirmado que las revisiones sistemáticas de ensayos controlados aleatorios (ECA) son la fuente más confiable de evidencias para las decisiones clínicas, de gestión y de las políticas sanitarias [29,30,56]. También es importante mencionar que junto con la producción de revisiones sistemáticas y la utilización de ensayos controlados aleatorizados como principal insumo para su elaboración en los comienzos de la Colaboración Cochrane [57], se fueron incorporando posteriormente otros diseños, fundamentalmente estudios

55 Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP) 8: Deciding how much confidence to place in a systematic review. Health Res Policy Syst. 2009 Dec 16;7 Suppl 1:S8.

56 Higgins JPT, Green S, editors. Cochrane handbook for systematic re- views of interventions version 5.0.1. The cochrane collaboration. Disponible en: www.cochrane-handbook.org. Con acceso el 6 de Septiembre de 2013.

57 Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Medicine, 2010, 7:e1000326.

cuasi-experimentales y observacionales analíticos. Asimismo la comunidad científica fue desarrollando estándares de calidad, tanto para la producción de investigación (primaria y secundaria) como para su reporte, a través de herramientas como por ejemplo, la evaluación de riesgo de sesgo, el CONSORT, AMSTAR y el propio registro internacional de ensayos clínicos [56,[58], [59], [60], [61]].

Las revisiones sistemáticas de la Colaboración Cochrane se caracterizan por realizarse bajo estándares uniformes. Sin embargo, aunque los métodos para la elaboración de estas revisiones son rigurosos y detallados, una serie de factores pueden influir en la confianza que los usuarios de estas revisiones sistemáticas tienen en las estimaciones de los riesgos y beneficios de las intervenciones de salud en el campo clínico o de políticas públicas [56]. Un campo recientemente incluido en estas revisiones, además de los ya existentes "implicaciones para la práctica y para la investigación", es la utilización de la herramienta metodológica "riesgo de sesgo"

[58] Campbell MK, Piaggio G, Elbourne DR, Altman DG; CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012 Sep 4;345:e5661.

[59] Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, Henry DA, Boers M. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009 Oct;62(10):1013-20.

[60] World Health Organization. World Health Organization international clinical trials registry platform. New standards for registration of hu- man medical research. Geneva, Switzerland: World Health Organiza- tion; 2005. Disponible en: http://www.who.int/ictrp/en/. Con acceso el 6 de Septiembre de 2013.

[61] Hróbjartsson A, Boutron I, Turner L, Altman DG, Moher D. Assessing risk of bias in randomised clinical trials included in Cochrane Reviews: the why is easy, the how is a challenge [editorial]. Cochrane Database of Systematic Reviews 2013;4:ED000058. dx.doi.org/10.1002/14651858.ED000058.

cuyo fin es evaluar la calidad de los estudios individuales incluidos en las mismas [56], por lo cual los ECAs incluidos en las revisiones Cochrane pueden ser juzgados.

El riesgo de sesgo (RdS) se define como el riesgo de "un error sistemático o desviación de la verdad, en los resultados o inferencias" [56] y los ECAs incluidos en las revisiones Cochrane pueden ser juzgados como de alto riesgo, de bajo riesgo o de riesgo poco claro [62,63,64].

En 2008, la Colaboración Cochrane comenzó a utilizar la herramienta riesgo de sesgo como el método recomendado para evaluar todos los ECAs incluidos en las revisiones sistemáticas Cochrane. Este instrumento consta de seis dominios (sesgo de selección, sesgo de realización, sesgo de detección, sesgo de deserción, el sesgo de notificación, y otros sesgos). La herramienta se actualizó en 2011, después de una nueva evaluación para incluir modificaciones tales como la evaluación de cegamiento de los participantes y el personal, separados del sesgo relacionado; también el cegamiento de la evaluación de resultados e incluyendo además la

62 Crocetti MT, Amin DD, Scherer R. Assessment of risk of bias among pediatric randomized controlled trials. Pediatrics. 2010;126(2):298-305.

63 Reveiz L, Sangalang S, Glujovsky D, Pinzon CE, Asenjo Lobos C, Cortes M, Cañón M, Bardach A, Bonfill X. Characteristics of Randomized Trials Published in Latin America and the Caribbean According to Funding Source. Plos One 2013;8(2):e56410.

64 Savović J, Jones H, Altman D, Harris R, Jűni P, Pildal J, Als-Nielsen B, Balk E, Gluud C, Gluud L, Ioannidis J, Schulz K, Beynon R, Welton N, Wood L, Moher D, Deeks J, Sterne J. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. Health Technol Assess. 2012;16(35):1-82.

suspensión precoz de un ECA en el dominio “otras fuentes de sesgo" [56,[65]] [Ver tabla 1].

El número creciente de revisiones sistemáticas Cochrane en la última década, elaboradas con estándares uniformes ha permitido que estas sean objeto de estudio y que puedan ser utilizadas no solo de manera individual para la toma de decisiones, sino de forma integral. Estas externalidades de la Colaboración Cochrane sirvieron también para la elaboración de este proyecto.

Tabla 1: Métodos para la evaluación del riesgo de sesgo en los estudios. Fuente Manual Cochrane 5.1.0.

[65] Boutron I, Ravaud P. Classification systems to improve assessment of risk of bias. J Clin Epidemiol. 2012;65(3):236-8.

Dominio	Descripción	Valoración de los revisores
Sesgo de selección.		
Generación de la secuencia.	Describir el método utilizado para generar la secuencia de asignación con detalle suficiente para permitir una evaluación de si la misma produjo grupos comparables.	Sesgo de selección (asignación sesgada a las intervenciones) a causa de una generación inadecauda de la secuencia de aleatorización.
Ocultamiento de la asignación.	Describir el método utilizado para ocultar la secuencia de asignación con detalle suficiente para determinar si las asignaciones a la intervención se podían prever antes o durante el reclutamiento.	Sesgo de selección (asignación sesgada a las intervenciones) a causa de una ocultación inadecuada de las asignaciones antes de asignarlas.
Sesgo de realización.		
Cegamiento de los participantes y del personal *Se debería evaluar cada resultado principal (o cada clase de resultado).*	Describir todas las medidas utilizadas, si se utilizó alguna, para cegar a los participantes y al personal del estudio al conocimiento de qué intervención recibió un participante. Proporcionar cualquier información con respecto a si el cegamiento propuesto fue efectivo.	Sesgo de realización a causa del conocimiento por parte de los participantes y del personal durante el estudio de las intervenciones asignadas.
Sesgo de detección.		
Cegamiento de los evaluadores del resultado *Se debería evaluar cada resultado principal (o cada clase de resultado).*	Describir todas las medidas utilizadas, si se utilizó alguna, para cegar a los evaluadores del resultado del estudio al conocimiento de qué intervención recibió un participante. Proporcionar cualquier información con respecto a si el cegamiento propuesto fue efectivo.	Sesgo de detección a causa del conocimiento por parte de los evaluadores de los resultados de las intervenciones asignadas.
Sesgo de desgaste.		
Datos de resultado incompletos *Se debería evaluar cada resultado principal (o cada clase de resultado).*	Describir la compleción de los datos de resultado para cada resultado principal, incluidos los abandonos y las exclusiones del análisis. Señalar si se describieron las los abandonos y las exclusiones, los números en cada grupo de intervención (comparados con el total de participantes asignados al azar), los motivos de las deserciones/exclusiones cuando se detallaron, y cualquier reinclusión en los análisis realizada por los revisores.	Sesgo de desgaste a causa de la cantidad, la naturaleza o el manejo de los datos de resultado incompletos.
Sesgo de notificación.		
Notificación selectiva de los resultados. Se debería evaluar	Señalar cómo los revisores examinaron la posibilidad de la notificación selectiva de los resultados, y qué encontraron.	Sesgo de notificación a causa de la notificación selectiva de los resultados.
Otros sesgos.		
Otras fuentes de sesgo.	Señalar alguna inquietud importante acerca del sesgo no abordada en los otros dominios del instrumento. Si en el protocolo de la revisión se prespecificaron preguntas/ítems particulares, se deberían proporcionar las respuestas para cada pregunta/ítem.	Sesgo debido a otros problemas no abordados en los apartados anteriores.

2.4 Justificación

Aunque muchos países han establecido la salud materna como prioridad en sus programas nacionales de investigación en salud, no se han hecho muchos esfuerzos para identificar las lagunas específicas de investigación que deben ser abordados para disminuir la mortalidad materna en países de bajos y medianos ingresos. Consideramos entonces necesario un enfoque diferente para la identificación de estas lagunas y las prioridades de investigación en salud materna para lograr las metas del ODM5.

Como ya mencionamos, las revisiones Cochrane tienen la característica de resumir la mejor investigación disponible sobre un tema específico y son una fuente de

información clave para decisores. Por ejemplo, la sección estandarizada ya mencionada "Implicaciones para la investigación" es el lugar en donde los autores identifican las lagunas de conocimiento. Pensamos que una manera de promover las políticas y prácticas basadas en evidencias es "mapeando" lagunas investigación y priorizando las necesidades de investigación como una forma de ser más eficientes y de reducir las desigualdades de salud en lugares de escasos recursos.

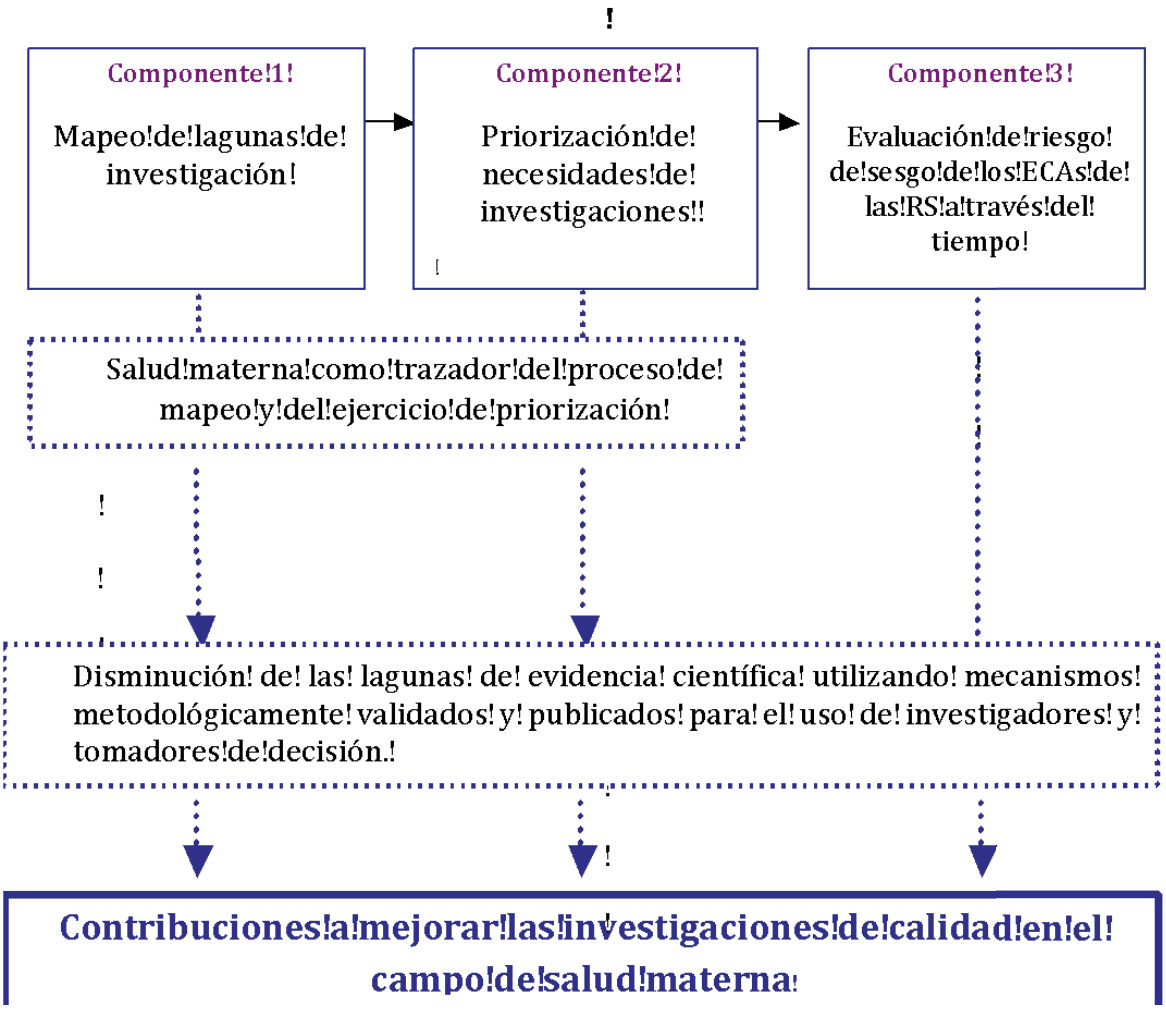
Además, es un imperativo ético producir investigaciones prioritarias y de calidad para tomar las decisiones dirigidas a problemas sanitarios relevantes y con la confianza del efecto que se quiere alcanzar.

2.5 Etapas de este proyecto

Este trabajo de tesis se diseñó en tres etapas que básicamente consisten en el mapeo de las lagunas de investigación, la priorización de las mismas y la evaluación de la calidad de las investigaciones que se producen en el tiempo. El trabajo se focalizo en salud materna, como una contribución global para el cumplimiento de la meta del ODM5.

En la figura 1 se resumen las etapas y componentes del mismo.

Figura 1: Esquema del proyecto y del impacto esperado


Componente 1
Mapeo de lagunas de investigación
Componente 2
Priorización de necesidades de investigaciones
Componente 3
Evaluación de riesgo de sesgo de los ECAs de las RS a través del tiempo
Salud materna como trazador del proceso de mapeo y del ejercicio de priorización
Disminución de las lagunas de evidencia científica utilizando mecanismos metodológicamente validados y publicados para el uso de investigadores y tomadores de decisión.
Contribuciones a mejorar las investigaciones de calidad en el campo de salud materna

3. HIPÓTESIS

Hipótesis

Tal como se ha mencionado, los supuestos que guiaron esta tesis son los siguientes:

1. La sistematización y visibilidad de las lagunas de evidencia científica sobre intervenciones necesarias para mejorar la salud materna se pueden realizar a partir de las revisiones sistemáticas.

2. Las preguntas de investigación construidas a partir de las lagunas detectadas sobre intervenciones para mejorar la salud materna se pueden priorizar con los mismos grupos relevantes productores de revisiones sistemáticas.

3. La herramienta “Riesgo de sesgo” utilizada para la evaluación de estudios primarios contenidos en las revisiones sistemáticas permite mostrar que la producción de investigaciones de calidad están mejorando en el tiempo.

4. OBJETIVOS

4.1 Objetivo general de la tesis

Contribuir a la gobernanza de la investigación en salud materna a través de dos ejes importantes de la misma como son la producción de investigaciones sanitarias prioritarias y bajo estándares de calidad.

4.2 Objetivos específicos

1. Mapear lagunas de investigación en el campo de salud materna.
2. Revisar metodologías de priorización de investigaciones y seleccionar una de ellas para ejecutarla.
3. Evaluar la evolución temporal del riesgo de sesgo de los ensayos clínicos controlados contenidos en las revisiones sistemáticas mediante la herramienta Cochrane “evaluación del riesgo de sesgo”.

5. METODOLOGÍA

Los tres objetivos específicos ya mencionados condujeron a la realización de tres trabajos diferentes y complementarios que dieron lugar además a sendos artículos publicados que han conformado esta tesis con la modalidad de compendio de publicaciones.

A continuación se resume la metodología de cada trabajo. Mayores detalles pueden encontrarse en las respectivas publicaciones.

5.1 Primer trabajo

Diseño: Estudio descriptivo.

Muestra: todas las revisiones sistemáticas publicadas en la Biblioteca Cochrane desde Diciembre 2006 hasta Marzo 2011.

Criterios de inclusión: todas las revisiones sistemáticas de la biblioteca Cochrane que contengan algún componente relacionado con intervenciones preventivas, terapéuticas y de sistemas y políticas de salud, en el campo de salud materna y que contribuyan al cumplimiento de ODM5.

Criterios de exclusión: fecha de publicación anterior a diciembre de 2006 con excepción de las RS del grupo Effective Practice and Organization of Care Group (EPOC); sin límite (a los fines de contar con la mayor cantidad de revisiones en el tópico sobre políticas y sistemas de salud).

Se elaboró una estrategia para búsqueda electrónica para revisiones sistemáticas en la biblioteca Cochrane y se utilizaron términos de búsqueda manual para el sitio de Mc Master Health Forum (Health system evidence: http://www.healthsystemsevidence.org)

Se analizaron los campos "implicaciones para la práctica" y "implicaciones para la investigación". A partir de este último principalmente se elaboraron las preguntas de investigación. Las preguntas se construyen con formato PICO: población (P), intervención (I), comparación (C) y resultado (O de Outcome) [23]. Se construyó una base de datos en Excel ® con los siguientes campos: referencia, fecha de búsqueda, implicaciones para la práctica, implicaciones para la investigación, población/paciente, intervención, comparación, resultado, lugar de la investigación, la/s pregunta/as, dominios y comentarios.

El proceso de generación de preguntas implicó múltiples rondas con el equipo, revisión de pares y un tercer investigador ayudó a resolver discrepancias. La discusión no solo se hizo sobre las cualidades que debían tener las mismas durante el proceso de construcción (Formato PICO, claridad, coherencia, sin errores ortográficos, etc.) sino que debían clasificarse en los distintos campos de causas potenciales de muerte materna y de intervenciones para evitarlas o disminuirlas (llamamos dominio a los fines de esta investigación). Esta clasificación fue fundamental para la siguiente etapa de

selección de expertos para la priorización. Este proceso fue también fue realizado por pares.

Con el listado de preguntas se realizó clasificación por campos (dominios) buscando independencia entre ellos a los fines de poder realizar el proceso de priorización en la segunda etapa. Preguntas similares se integraron en una sola.

Análisis estadístico: se realizó análisis descriptivo de los principales dominios (determinantes de mortalidad materna) y una clasificación por intervenciones. Se usó distribución de frecuencias y se calcularon las proporciones usando el mismo programa en el que se armó la base (Excel ®).

5.2 Segundo trabajo

Para realizar nuestro proceso de priorización hicimos análisis comparativos y además sobre factibilidad y pertinencia de las metodologías. En el anexo 1 y 1 bis se resumen los diferentes métodos de priorización en salud evaluados críticamente en cuanto a su uso específico y ventajas y desventajas así como también un cuadro ampliado sobre los tres métodos más utilizados en procesos de priorización elaborado por el área de información, evidencias e investigaciones de la OMS. Nuestro proceso de priorización incluye consultas a expertos y finalmente solo tomamos algunos elementos de método Delphi. Hemos utilizado un grupo diferente de expertos (en lugar de repetir el proceso con el mismo grupo de expertos como en el clásico método Delphi) en dos rondas de consultas. Se dirigieron las preguntas de investigación a expertos técnicos (revisores y

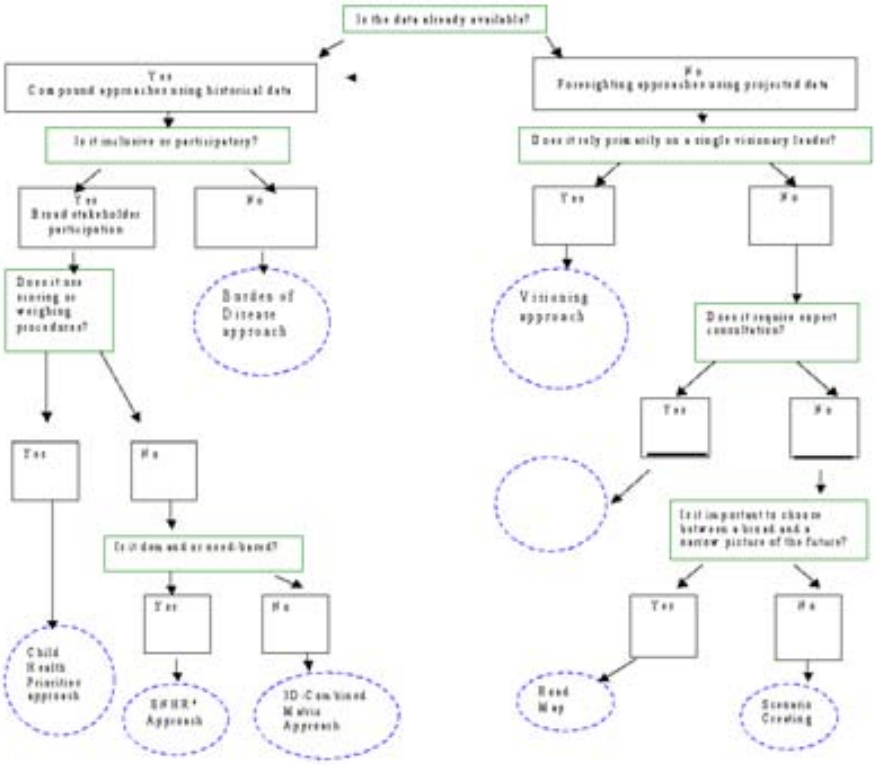
editores de 4 grupos de Colaboración Cochrane) y también a los responsables de consumidores de cada grupo.

En el flujograma de la figura 2 se muestra el camino que seguimos para decidir por esta metodología tomando conceptos del COHRED y otras fuentes y el análisis crítico mencionado [18].

Diseño: Estudio de corte transversal con 2 rondas de consulta para proceso de priorización.

Muestra: Se usaron las 319 preguntas de investigación resultantes de la primera etapa y se mapearon 2.121 participantes de los siguientes 4 grupos de la Colaboración Cochrane (CC) a través de la base Archie ®: a) Pregnancy and Childbirth Group, b) Public Health Group, c) Fertility Regulation Group y d) Effective Practice and Organization of Care Group.

Figura 2: Flujograma de selección de metodología de priorización



Primera ronda

El objetivo de la primera ronda fue refinar las preguntas y agregar más preguntas por parte de los expertos.

a) Instrumento: cuestionario

Se desarrollaron 12 grupos de encuestas en Survey Monkey® clasificados de acuerdo con las causas de la mortalidad materna. Diez grupos estaban directa o indirectamente relacionados con las causas de morbimortalidad materna; otro grupo incluyó intervenciones para la prevención del embarazo mientras que el último se relacionó con políticas y sistemas de salud usando la taxonomías desarrollada en el

sitio Web de Health System Evidence (Arreglos de gobernanza, financieros, provisión de servicios y consideraciones de implementación).

Cada cuestionario se dividió de tres secciones. La primera dirigida a conseguir los datos demográficos y filiatorios de los participantes; en la segunda se presentaban las preguntas de acuerdo a cada una de las categorías. Cada pregunta se evaluó de acuerdo a cuatro criterios (magnitud y urgencia, el potencial para maximizar la reducción de la mortalidad materna y la morbilidad impacto, viabilidad y futuro) y en una escala tipo Likert de 1 a 5 (donde 1 = no es importante en absoluto y 5 = muy importante). La tercera parte estaba destinada a agregar más preguntas y a poner comentarios generales o particulares del cuestionario.

Antes de iniciar la primera ronda tres epidemiólogos y una enfermera de salud pública evaluaron la validez de fachada del cuestionario.

b) Participantes

Los participantes fueron seleccionados de la base de datos de la CC de los grupos antes mencionados. Se armó base con datos personales y filiatorios y se eliminaron duplicados. Se enviaron a los participantes seleccionados 319 preguntas construidas a partir de 178 revisiones sistemáticas Cochrane. Se envió la encuesta a 155 participantes entre autores, referees y consumidores; además se enviaron cuatro recordatorios. La participación fue voluntaria tras aceptación mediante consentimiento informado. La primera ronda se hizo entre 05 de agosto y 31 de agosto 2011.

Segunda ronda

El objetivo de la segunda ronda fue dar prioridad a los temas de investigación más relevantes de acuerdo con el potencial de ejecutar la intervención propuesta.

a) Instrumento: Cuestionario

Después de la primera ronda, noventa y cuatro preguntas de investigación fueron identificadas como "relevantes" o "muy relevantes" y seis preguntas fueron sugeridas por los expertos. En esta ronda las preguntas se re-agruparon en cinco categorías y se utilizaron 4 criterios de priorización. De acuerdo a la percepción de importancia, cada una de las preguntas se calificó de acuerdo con una escala de cuatro puntos como "muy relevante" para el 4 y el 1 para las "no relevante"; una quinta posibilidad fue "No se puede responder" por existencia de incertidumbre o falta de conocimiento suficiente participante.

b) Participantes

En la segunda ronda se envió una invitación a los participantes de la CC que habían participado en la primera ronda. Ellos fueron el primer grupo de la segunda ronda. Como se había pensado de antemano una tasa baja de respuestas, luego de filtrar nombres, direcciones, y participantes previos, se enviaron las preguntas priorizadas en la primera vuelta de la segunda ronda a 2.121 participantes. La misma se llevó a cabo entre el 11 de noviembre y 22 de diciembre 2011 con tres recordatorios. El resumen de las rondas se puede encontrar en la publicación correspondiente.

Análisis

a) Primera ronda

Los cuatro criterios fueron ponderados igualmente en un 25%. Se clasificó las puntuaciones en orden ascendente y se calculó su distribución por percentiles. Esto nos permitió generar los siguientes estratos de categorías: "bajo" e "intermedio" (cuartiles primero y segundo), "alto" y "muy alto" para los cuartiles superiores. Se incluyeron para la segunda ronda solo aquellas con prioridad alta o muy alta.

b) Segunda ronda

Los cuatro criterios utilizados en la segunda ronda se consideraron igualmente ponderados en un 25% mientras que las distribuciones se calcularon y expresaron en percentiles generándose los siguientes estratos: "no muy relevante" y " poco relevante" para aquellas en los rangos de los cuartiles primero y segundo, y "relevante" y "muy relevante" para aquellas en los cuartiles superiores. Una pregunta se consideró como de la mayor relevancia cuando el 75% o más de los participantes la calificaron como "muy relevante".

Análisis estadístico

Los datos fueron analizados con Stata 12 ®. La prueba exacta de Fisher en el nivel <0,05 fue realizada para evaluar la significancia estadística al evaluar si la puntuación

de relevancia se asoció con el tipo de entrevistado, el país de procedencia (alto, mediano, bajo ingresos) y el sexo del participante.

5.3 Tercer trabajo

Diseño: estudio de corte transversal

Población y muestra: Todos los ECAs incluidos en las revisiones sistemáticas de la base de datos de revisiones sistemáticas Cochrane del número 12 del año 2012 por considerase la mas actualizada al momento de este estudio.

Criterios de inclusión: todos los ECAs que tengan al menos informado un dominio de los 6 de la herramienta; publicados en texto completo o resumen.

Criterios de exclusión: otros diseños (observacionales o cuasi-experimentales)

Instrumento de evaluación: La herramienta de riesgo de sesgo consta de seis dominios: generación de la secuencia de aleatorización; ocultación de la secuencia de aleatorización; cegamiento; reporte incompleto de los resultados; reporte selectivo de los resultados y otros sesgos. La descripción de cada dominio brinda la evaluación general del riesgo de sesgo de cada uno de los ECAs contenidos en las revisiones sistemáticas [29, 35].

Base de datos: Se elaboró una base en Excel ® con los siguientes campos: referencia de la revisión sistemática, del ECA, grupo Cochrane, tipo de publicación, año de publicación, país de afiliación, tamaño muestral, financiamiento, tipo de intervención

(drogas, procedimientos, modificación de conductas, educación, consejería, vacunas, dispositivos, mixtas y otras) los 6 dominios de riesgo de sesgo (incluyendo resultados subjetivos y objetivos) según fuera alto, bajo o poco claro.

Selección de ECAs y extracción de datos: La selección de los ECAs desde las revisiones sistemáticas fue realizada por 2 investigadores independientemente, se hizo chequeo de la extracción de datos y los mismos fueron volcados en una base Excel ® prediseñada.

Análisis estadístico

Con el fin de evaluar las diferencias según la herramienta riesgo de sesgo (RdS), se calculó el número y la proporción de ECAs que describen cada elemento. Todos los dominios de RdS se evaluaron según diferencias en el tiempo. Para evaluar la asociación entre variables categóricas se usaron los estadísticos Chi cuadrado y la prueba exacta de Fisher de 2 colas. Una diferencia se consideró estadísticamente significativas cuando $P < 0,05$. Los ECAs fueron divididos en cuatro estratos de tiempo de acuerdo a fecha de publicación en a) 2006-2012, b) 2000-2005, c) 1990 - 1999, y d) ≤ 1,989. Teniendo en cuenta la cantidad de datos a manejar, a priori se determinaron evaluar cuatro dominios relevantes: generación de la secuencia, ocultación de la asignación, el cegamiento y, los datos de resultado incompletos. Se hizo además modelaje estadístico usando regresión logística para evaluar la asociación entre la presencia de bajo riesgo de sesgo según el dominio y el año de publicación del ensayo, el tipo de intervención, el tamaño de la muestra y el país del ECA. El análisis estadístico de todos los ECA evaluados se realizó con Stata 12.1 ©.

6. RESULTADOS

6.1 Publicaciones presentadas en esta tesis

Publicación 1

Chapman E, Reveiz L, Chambliss A, Sangalang S; Bonfill X. Cochrane systematic reviews are useful to map research gaps for decreasing maternal mortality. Journal of Clinical Epidemiology 2013;66(1):105-112

Publicación 2

Chapman E, Reveiz L, Sangalang S; Manu C; Bonfill X; Muñoz S; Abalos E. Global research priorities for decreasing global maternal mortality and morbidity: an international survey. Journal of Clinical Epidemiology. Manuscript Number: JCE-13-137

Publicación 3

Reveiz L, Chapman Asial A, Munoz A, Bonfill X, Alonso P. Risk of bias of randomized trials over time. Journal of Clinical Epidemiology 2014; proof-13:39:27

6.1.1 Publicación 1

Chapman E, Reveiz L, Chambliss A, Sangalang S; Bonfill X. Cochrane systematic reviews are useful to map research gaps for decreasing maternal mortality. Journal of Clinical Epidemiology 2013;66(1):105-112

Factor de impacto 2013: 5.478 *Journal of Clinical Epidemiology* ranks 6th of 160 journals in the Public, Environmental & Occupational Health category.

Resumen

Objetivo: mapeo de revisiones sistemáticas para evaluar la utilidad de las revisiones Cochrane en la identificación de lagunas de investigación de la salud materna.

Se plantea una metodología secuencial de mapeo y formulación de preguntas de investigación a partir de los vacíos de información localizados en las revisiones Cochrane, proceso de priorización con expertos en el tema, conciliación con estudios en curso, actualización del proceso.

Se realizó una búsqueda exhaustiva de las revisiones sistemáticas Cochrane publicadas o actualizadas de Enero 2006 a marzo de 2011. Se evaluó los campos "Implicaciones" al final de cada revisión tanto para investigación como para la práctica para detectar las lagunas.

La estrategia de búsqueda identificó 695 referencias; Se localizaron 204 RS y finalmente quedaron incluidas 178 RS que identifican al menos una laguna de investigación.

Hemos formulado 319 preguntas de la investigación en formato PICO, que se clasifican en 11 categorías diferentes en función de las causas directas e indirectas como determinantes de la mortalidad materna: hemorragia posparto, aborto,

trastornos hipertensivos, infección/sepsis, cesárea, diabetes, prevención del embarazo, trabajo de parto prematuro, otro causas directas, causas indirectas, y lagunas en políticas y sistemas de salud. Esta clasificación fue fundamental; el proceso fue iterativo hasta lograr preguntas claras, sin ambigüedad, sin duplicación de lagunas. La clasificación fue realizada por 2 autores de manera independiente y las discrepancias se resolvieron involucrando a un tercer investigador. La mayoría de las preguntas de investigación fueron sobre la efectividad de intervenciones clínicas, que incluyeron medicamentos (42,6%), intervenciones no farmacológicas (16,3%), y del sistema de salud (14,7 %).

Nuestra principal conclusión es que es posible identificar lagunas de investigación en salud materna y también en otros problemas sanitarios a partir de las revisiones Cochrane y mediante esta estrategia.

Journal of Clinical Epidemiology 66 (2013) 105e112

Cochrane systematic reviews are useful to map research gaps for decreasing maternal mortality

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Abstract

Objectives: To use an ''evidence-mapping'' approach to assess the usefulness of Cochrane reviews in identifying research gaps in the maternal health.

Study Design and Setting: The article describes the general mapping, prioritizing, reconciling, and updating approach: (1) identifying gaps in the maternal health research using published systematic reviews and formulating research questions, (2) prioritizing questions using Delphi method, (3) reconciling identified research priorities with the existing literature (i.e., searching of ongoing trials in trials registries), (4) updating the process. A comprehensive search of Cochrane systematic reviews published or updated from January 2006 to March 2011 was performed. We evaluated the ''Implications for Research'' section to identify gaps in the research.

Results: Our search strategy identified 695 references; 178 systematic reviews identifying at least one research gap were used. We formulated 319 research questions, which were classified into 11 different categories based on the direct and indirect causes of maternal mortality: postpartum hemorrhage, abortion, hypertensive disorders, infection/sepsis, caesarean section, diabetes, pregnancy prevention, preterm labor, other direct causes, indirect causes, and health policies and systems. Most research questions concerned the effectiveness of clinical interventions, including drugs (42.6%), nonpharmacologic interventions (16.3%), and health system (14.7%).

Conclusion: It is possible to identify gaps in the maternal health research by using this approach.

Keywords: Health priorities; Research gaps; Maternal mortality; Maternal health; Survey; Review

1. Introduction

For a woman living in a developing country, the risk of maternal death during her lifetime is roughly 36 times greater than that for a woman living in a developed country [1]. Maternal mortality continues to be a health indicator that demonstrates the wide gap between the rich and poor within a country, showing the inequalities in maternal health outcomes between the rich and poor countries [1,2]. Maternal mortality also has signifi t economic implications because of the high costs of treating and managing obstetric complications [3,4]. Although recent estimates suggest that progress is being made toward significant decreases in maternal mortality, the achievement of Millennium Development Goal 5 (MDG-5) is still uncertain [5]. Recently, the United Nations Human Rights Council stated (Resolution R.11/8) that maternal mortality and morbidity are preventable and comprise a variety of determinants linked to the health, development, human rights, and fundamental freedoms [6,7]. According to the 2011 Millennium Development Goals Report, ''the vast majority of maternal deaths are avoidable,'' but the lack of adequate access ''to proven interventions that could prevent disability or death during pregnancy and childbirth remains a major burden in many developing countries'' [5].

Conflict of interests: The authors declare that they do not have any conflict of interest. The views expressed by the authors reflect their personal expert views and do not necessarily reflect the official position or policy of their employers. E.C. is a PhD candidate at the Universitat Autònoma de Barcelona. A.C. and S.S. contributed to the project during their internship at the Pan American Health Organization.

Author's contribution statement: E.C. and L.R. planned the protocol and searched for studies; all the authors extracted, evaluated, and summarized the data from trials and also drafted the final review.

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The low utilization of evidence-based research in clinical decisions and in the design of health policies and systems could influence the magnitude of maternal mortality [8e18]. The existing maternal health research fails to adequately address the maternal health disparities affecting childbearing women, especially those living in low-resource areas [19]. The insufficient production of relevant research principally in low-resource areas [12,13,20e22] and the poor transferability of available research to developing-country settings are the contributing factors [19,23].

Although many countries have established maternal health and, specifically, the decrease of maternal mortality as priorities in their national health research agendas, no deliberate efforts have been made to identify the specific research gaps that should be addressed to decrease maternal mortality in low- and middle-resource areas. Therefore, a different approach for identifying the maternal health research gaps and priorities is needed to achieve MDG-5 and decrease maternal mortality and morbidity. Similar mapping exercise using systematic reviews or guidelines have been developed and tested in the last decade [24e27].

High-quality systematic reviews summarize the best available research on a specific topic and are a key source of information in clinical, health policies, and health systems decision making [28,29]. The Cochrane Collaboration is an independently operated and well-recognized organization providing high-quality evidence for health care decision making. In addition, Cochrane reviews have a standardized ''Implications for Research'' section, in which the review authors identify gaps in the research. Robinson et al. [29] defines a ''research gap'' as ''a topic or area for which missing or inadequate information limits the ability of reviewers to reach a conclusion for a given question,'' whereas a ''research need'' was defined as ''a gap that limits the ability of health care decision makers (patients, physicians, policy makers, etc.) from making decisions.''

The aims of this study were to assess the usefulness and feasibility of a new approach to identify gaps and priorities in the maternal health research, generate a list of maternal health research questions based on the Implications for Research section of Cochrane systematic reviews, and adapt questions to Problem/Population, Intervention, Comparison, Outcome (PICO) format to create research questions for use in a future prioritization exercise with experts and other stakeholders.

1. Methods

1.1. Objectives

1. To introduce a methodology for identifying and prioritizing gaps in the maternal health research.
2. To identify gaps in the maternal health research and areas in which future research could lead to reductions in maternal mortality through health care interventions (preventive and therapeutic) and health policy and system interventions.
3. To formulate the maternal health research questions using the PICO format and classify these research questions according to different direct and indirect causes of maternal death.

1.2. Definition

Maternal death is defined by the World Health Organization as the ''death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes'' [30].

1.3. General description of the mapping, prioritizing, reconciling, and updating approach

Our approach includes a number of phases (Fig. 1). The present article describes in detail the methods and findings associated with the first phase (mapping the evidence). A future publication will focus on the subsequent phases (prioritization phase is ongoing).

1.3.1. Mapping the evidence

This phase involved a review of the literature, including a comprehensive search for systematic reviews on the specified topic (i.e., clinical, health policies, or systems interventions aiming at decreasing maternal mortality). As Cochrane systematic reviews include specific sections for Implications for Practice and Implications for Research, we focused our search on articles published in the Cochrane Library of Systematic Reviews. Although other systematic reviews frequently discuss research gaps, we only extract

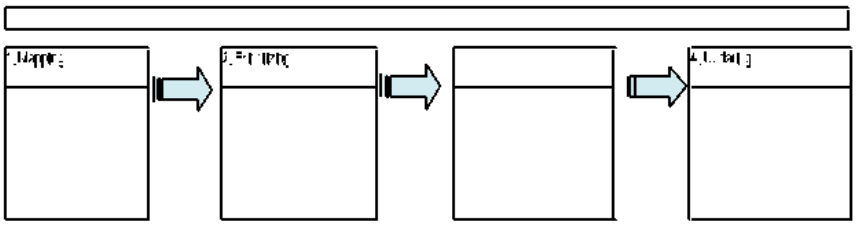

Fig. 1. Description of the mapping, prioritizing, reconciling, and updating approach phases.

information from Cochrane reviews. Also, a recent article proposed the standardization of the process for identifying research gaps in systematic reviews [29]. After extracting the Implications for Research section of selected systematic reviews, research questions were formulated using the PICO format [31].

1.1.1. Prioritizing research questions

There are numerous methodologies to choose from when prioritizing research [18,32e39]. For this project, we used a mixed approach that included a two-round Delphi survey. We also developed a number of criteria for prioritizing research questions, including the magnitude and urgency, potential to maximize the reduction of maternal mortality and morbidity, feasibility, and future impact. We surveyed technical experts (Cochrane reviewers and editors from the Cochrane Collaboration), policy makers, and Cochrane consumers (Consumer referees are consumers who comment on Cochrane Reviews to represent the perspectives and concerns of people having similar conditions). We will use the results of these surveys to compile a list of research topics identified as "high priority." Findings of these surveys will be presented in a subsequent publication.

1.1.2. Reconciling priorities with the existing literature

The third phase involves the identification of research studies that could potentially respond to highly prioritized research questions and that were not identified during the development of the research questions in the previous phases (i.e., any trials that were missing from systematic reviews, studies completed after the publication of the last review, and studies identified after searching for ongoing trials in the International Clinical Trials Registry Platform). This phase ensures that duplication of work and inefficient use of time and resources are avoided, facilitating the dissemination of highly relevant global health questions to be used by funders and developers of trials.

1.1.3. Updating the process

This phase involves the ongoing monitoring and evaluation of the progress made with respect to maternal health research prioritization. The reasons for this phase include to identify and assess new research evidence, to make modifications to the methodology as needed, to ensure that any progress made is maintained, and that research findings are disseminated. We recognize that prioritization is a dynamic and complex process. Therefore, ongoing monitoring and evaluation are necessary to address issues with possibly unequal access to resource allocation and distribution and with health disparities.

2.4. Detailed description of phase 1 in the study: mapping the evidence

A number of key steps in the mapping process were performed in our study (Fig. 2).

2.4.1. Search strategy and systematic reviews inclusion

We performed an advanced search strategy in PubMed that was limited to the Cochrane Database of Systematic Reviews (Appendix A at www.jclinepi.com). We included reviews if they were published or updated between January 2006 and March 2011.

Systematic reviews were excluded if the topic was not related to direct or indirect causes of maternal mortality, if the review did not include a description of gaps in research in the Implications for Research section, or if the review had been "withdrawn" by the Cochrane Library. We also evaluated all Cochrane reviews published in the Cochrane Effective Practice and Organization of Care (EPOC) and Public Health groups to identify systematic reviews on health systems and health policies related to maternal health, regardless of the date of publication. The following inclusion criteria were used for the selection of systematic reviews for data extraction: (1) discussion of intervention(s) that aimed to improve the maternal health and/or decrease the maternal mortality (both direct and indirect causes [30]) and (2) discussion of intervention(s) that were potentially relevant to improving maternal health or decreasing maternal mortality through health systems and policies, involving changes in delivery arrangements, governance arrangements, financial arrangements, and implementation strategies according to taxonomy proposed by Lavis et al. [16,40].

Two authors independently assessed the systematic reviews for eligibility. Disagreements were resolved by consensus between the reviewers or by decision by a third researcher. All four authors reviewed the final list of included and excluded studies.

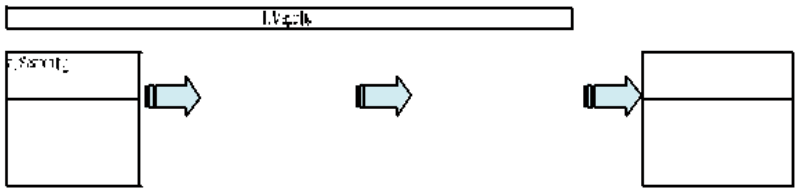

Fig. 2. Mapping phase of the mapping, prioritizing, reconciling, and updating approach. PICO, Problem/Population, Intervention, Comparison, Outcome.

2.4.1. *Developing the PICO format questions*

We designed a worksheet in Excel to facilitate the formulation of each research question according to the PICO format. We recorded the following information in the Excel worksheet: the complete reference, Implications for Practice section, Implications for Research section, PICO, category (i.e., direct or indirect causes of maternal mortality), and complete PICO research question. When difficulties arose in formulating a particular research question, we read the full text of the systematic review.

2.4.2. *Refinement and classification of PICO questions*

The process of refining the research questions involved multiple rounds of discussion and revision by the team. Discrepancies were resolved by consensus. Clarity and adherence to the PICO format were taken into account when refining each research question. Subsequently, each research question was classified according to different areas of potential causes of maternal death and types of interventions. This classification was central to the subsequent stage, in which experts were selected for the prioritization of the research questions. When similar gaps in research were identified in multiple Cochrane reviews, research questions were integrated in a single question. Two authors classified the research questions, and discrepancies in the classification were resolved by a third researcher.

1. Results

Our search strategy identified 695 Cochrane systematic reviews from PubMed, and we retrieved 204 Cochrane systematic reviews related with direct or indirect causes of maternal mortality. In addition, we identified 25 additional reviews from the EPOC and the Public Health groups from the Cochrane Library. Of the 204 Cochrane systematic reviews, 178 systematic reviews identified at least one research gap and were used to formulate research questions. The flow diagram of the process of identifying and selecting the relevant systematic reviews is shown in Fig. 3.

We developed 319 research questions using the PICO format. The research questions were classified into 11 different groups based on direct and indirect causes of maternal mortality. Ten of the categories were related directly or indirectly to the causes of maternal mortality and morbidity during the pre-, intra-, and postpartum periods: postpartum hemorrhage, abortion, hypertensive disorders, infection/sepsis, caesarean section, diabetes, labor, preterm labor, other direct causes, and indirect causes; we also considered pregnancy prevention. The final category concerned health policies and systems (relating to governance, financial and delivery arrangements, and implementation considerations) that may indirectly relate to the causes of maternal mortality (Table 1). The categories that included the highest number of research questions included labor and health policies and systems (30.4%). Most research questions concerned

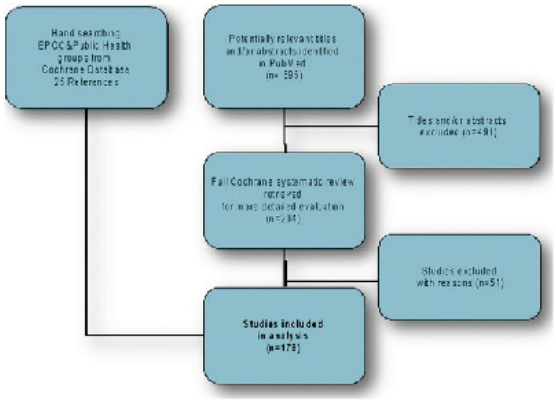

Fig. 3. Flow chart of the process of identifying and selecting the relevant systematic reviews. EPOC, Effective Practice and Organization of Care.

the effectiveness of clinical interventions, including drugs (42.6%), nonpharmacologic interventions (i.e., diagnostic tests) (16.3%), and health system (14.7%) (Table 2). Few systematic reviews raised qualitative research questions (7.2%). Few a priori selected questions are available in Table 3. The entire set of research questions are available in Appendix B (www.jclinepi.com).

2. Discussion

2.1. *Main findings*

Our findings show that it is possible to identify the maternal health research gaps by using this approach. The assessment of the Cochrane systematic reviews highlighted both progress and lags in the maternal health research and provided insight into areas in which future maternal health

Table 1. Classification of PICO research questions according to the causes/determinants of maternal mortality

Domain	Total	%
Labor	57	17.9
Health policy and system[a]	40	12.5
Infection	28	8.8
Indirect causes	27	8.5
Postpartum hemorrhage	26	8.2
Hypertensive disorders in pregnancy	26	8.2
Caesarean section	24	7.5
Abortion	24	7.4
Pregnancy prevention	23	7.2
Preterm birth	23	7.2
Diabetes	13	4.1
Other direct causes	8	2.5
Total	319	100

Abbreviation: PICO, Problem/Population, Intervention, Comparison, Outcome.

[a] Includes governance, financial and delivery arrangements, and implementation strategy.

Table 2. Classification of PICO research questions according to interventions

Interventions	Drugs	Behavior/education	Devices	Other[a]	Health system	Procedures[b]	Mixed	Total
Total	136	23	9	52	47	28	24	319
%	42.6	7.3	2.8	16.3	14.7	8.8	7.5	100

Abbreviation: PICO, Problem/Population, Intervention, Comparison, Outcome.
[a] For example, diagnostic test, exercise, and so forth.
[b] For example, symphysiotomy, surgical techniques, and so forth.

research could lead to reductions in maternal mortality. Numerous and large gaps in knowledge related to maternal mortality and morbidity are persistent and overwhelming. To minimize the burden of maternal mortality in resource-constrained areas, more research is needed to identify the gaps in the maternal health research and prioritize areas for future maternal health research. This future work is not only important to strengthening research and health care systems but it is also critical to achieving MDG-5 [23].

In their study, Robinson et al. reviewed the research gap identification practices of different organizations involved with evidence synthesis. Based on their findings, they developed a framework for identifying research gaps that included the characterization of the gap using PICO elements and identification of the reasons why the gap exists [29]. Their study also included an assessment of the difficulties associated with applying the proposed framework and of the differences in the specificity of research gaps identified by different persons [29].

Different authors have previously assessed the usefulness of concept mapping in knowledge acquisition, comprehension, and translation [41e43]. In the health sciences, concept mapping has been used in research related to a variety of topics, such as health equity [44], public health reporting [45], and quality management [46]. Concept mapping has been especially useful in better understanding the topics that are complex and involve diverse relationships, interactions, and social determinants [47,48]. De Vet et al. described a method used for programming research on the efficacy of therapeutic interventions for chronic benign pain disorders [26]. Recently, Li et al. [24] developed and tested a framework for identifying evidence gaps using systematic reviews and clinical practice guidelines and prioritizing research by using a two-round Delphi survey. We are proposing an additional step that comprises the reconciliation of priorities with the existing literature (includes searching ongoing trials in the use of the World Health Organization International Clinical Trial Registry Platform (ICTRP). As a health topic, maternal healthdspecifically maternal mortality and morbidityd involves similar challenges for researchers. Moreover, questions relating to maternal health are not always easy to answer, and research findings from one setting are not easily transferred to different settings. This is because maternal health interventions, whether clinical or nonclinical, greatly depend on the context. Often, it is not enough to understand the problem, population, and outcome. Other factors, such as health services, systems, and policies, are also important determinants of maternal health outcomes. Because the endeavor of researching maternal mortality and morbidity is sometimes characterized by ambiguity and increasing complexity, a deliberate and well-organized approach is needed to effectively address gaps in knowledge. For this reason, concept mapping, with its use of visual representations of complex interactions and relationships, was a logical choice to serve as the theoretical basis for this project.

This study was based on three major assumptions. First, the mechanisms how interventions work on improving maternal health are not fully understood. Therefore, it is not always easy to judge whether enough research is conducted or more research in other contexts are needed. Also, because the results of research cannot be implemented immediately, the importance of research is often underestimated [23]. More research is needed to better understand and address the causes of maternal death, including the

Table 3. Examples of identified PICO questions

PICO question	Classification
What behavioral issues contribute to the failure of women of reproductive age to use emergency contraception to prevent unwanted pregnancy, even if emergency contraception is readily available?	Pregnancy prevention
What are maternal and professional views and experiences on elective caesarean section for nonmedical reasons?	Caesarean section
What are the effects of dietary advice interventions on gestational diabetes mellitus prevention in healthy pregnant women and overweight or obese pregnant women?	Diabetes
What is the effectiveness and cost-effectiveness of prelicensure interventions in increasing the supply and quality of health professionals and improving maternal health outcomes in low- and middle-income countries?	Health policy and system
What are effective interventions for the control of primary postpartum hemorrhage (PPH) after home deliveries, particularly in developing countries?	PPH
When is the optimal time to give magnesium sulphate to women with pre-eclampsia?	Hypertensive disorders in pregnancy

Abbreviation: PICO, Problem/Population, Intervention, Comparison, Outcome.

important role of health systems and policies, especially in low- and middle-income countries. To close the knowledge gaps in the maternal health, systematic research must be promoted (especially in low-resource areas) and research findings must be made visible, available, and accessible. Clearly, more research is needed to effectively address health disparities in maternal mortality and morbidity. Qualitative methods can improve understanding about health beliefs and behaviors, all which play a significant role in health education and adherence to preventive or therapeutic interventions. Cochrane systematic reviews usually focus on intervention studies rather than qualitative studies. Thus, more qualitative research is needed to develop culturally sensitive and context-specific maternal health interventions that are acceptable, feasible, and sustainable [49e53].

Second, it was assumed that such gaps in knowledge can be bridged and maternal outcomes can be improved through research production and utilization through evidence-based policy and practice. Third, it was assumed that one way to promote evidence-based policy and practice is to "map" research (identify gaps and implications) and prioritize research needs (select and rank research priorities) as a way to enhance efficiency and reduce the health inequalities in resource-scarce settings.

1.1. Strength and limitations of the study

We consider that the primary strength of this study is its potential contribution to the fields of maternal health and health policy. Locally, findings from this study can provide guidance as to how to identify research gaps and rank research priorities. This is helpful not only for researchers but also for policy makers, funders, and health care consumers. For policy makers and members of government agencies, the study provides support for evidence-based decision making related to health policies and systems. Study findings can inform discussions and help direct action related to policy development, program implementation, service delivery, and governance. Globally, study findings can be used to facilitate effective communication and knowledge dissemination for individuals and organizations working internationally. Outcomes of this study can promote collaborative efforts, which include knowledge sharing and group decision making. Perhaps the most significant contribution the study can make is to promote ethical research activities, including health systems research, which lead to safe, cost-effective, and efficacious interventions that prevent death and disability during pregnancy and childbirth.

Other strengths of this study include the use of systematic and transparent methods that could be used for other health problems. The use of high-quality Cochrane systematic reviews helped us to determine the available research evidence and identify the relevant gaps in research in a systematic manner. This allowed us to develop research questions using the PICO format with the assurance that the duplication of research questions is unlikely because Cochrane systematic reviews are not repeated. The prioritization of these research questions could help to inform the process of maternal health research agenda setting, nationally and internationally. This will be the aim of the next stage of our research.

Limitations of the study included the use of a single database to search for systematic reviews and restrictive search criteria, which likely excluded some relevant articles from being reviewed. This decision was taken to guarantee a greater homogeneity and quality among selected systematic reviews. As we used Cochrane systematic reviews as our starting point, the topic selection process for the Cochrane systematic review could have affect the list of research gaps (i.e., there is no Cochrane review on a priority topic). Although some authors have suggested frameworks for formulating research recommendations, the implication for research section of Cochrane reviews can vary in their structure and content [54,55]. The lack of adequate reporting of research gaps could imply missing important topic. We will address this issue by allowing participants of the Delphi survey to include additional research questions.

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Appendix

Supplementary material

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jclinepi.2012.09.005

References

[1] Global Health Observatory (GHO). Available at: http://www.who.int/gho/maternal_health/en/. Accessed on May, 2011.

[2] Report of the Secretary-General: UN General Assembly. Fifty-eight session. Item 61 of the provisional agenda: Follow-up to the outcome of the Millennium Summit. Implementation of the United Nations Millennium Declaration: NY; 2 September 2003.

[3] Konje J, Obisesan K, Ladipo O. Health and economic consequences of septic induced abortion. Int J Gynaecol Obstet 1992;37(3):193e7.

[4] Castiel D, Brèchat P, Benoît B, Nguon B, Gayat E, Soyer P, et al. Complete cost of surgery for postpartum hemorrhage. Gynecol Obstet Fertil 2008;36(5):507e15.

[5] The Millennium Development Goals Report 2011. United Nations New York, 2011. Available at: http://www.un.org/millenniumgoals/11_MDG%20Report_EN.pdf. Accessed on May, 2011.

[6] Pan American Health Organization. Strategic objective 7: to address the underlying social and economic determinants of health through policies and programs which enhance health equity and integrate

pro-poor, gender-responsive, and human rights based approaches. 27th Pan American Sanitary Conference; 2007 Oct. 1e5; Washington (DC), US. Washington (DC): PAHO, 2007. Available at: http://www.paho.org/english/gov/csp/csp27 -od328-e.htm. Accessed on February, 2012.

[7] United Nations International Covenant on Civil and Political Rights. Twenty-first session of the United Nations General Assembly. New York: UN; 1966. Available at: http://www2.ohchr.org/english/law/ccpr.htm. Accessed on February, 2012.

[8] Black R, Morris S, Bryce J. Where and why are 10 million children dying every year? Lancet 2003;361:2226e34.

[9] Schuster M, McGlynn E, Brook RH. How good is the quality of health care in the United States? Milbank Q 1998;76:517e63.

[10] McGlynn E, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;348:2635e45.

[11] Ford L, Kaluzny AD, Sondik E. Diffusion and adoption of state-of-the art therapy. Semin Oncol 1990;4:485e94.

[12] Dopson S, Fitzgerald L, editors. Knowledge to action? Evidence-based health care in context. Oxford, UK: Oxford University Press; 2005.

[13] Haines A, Kuruvilla S, Borchert M. Bridging the implementation gap between knowledge and action for health. Bull World Health Organ 2004;82:724e32.

[14] Tunis SR, Stryer DB, Clancy CM. Practical clinical trials. Increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003;290:1624e32.

[15] Villar J, Carroli G, Gulmezoglu AM. The gap between evidence and practice in maternal healthcare. Int J Gynaecol Obstet 2001;75 (Suppl 1):S47e54.

[16] Lavis JN, Wilson MG, Oxman AD, Grimshaw J, Lewin S, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP). 5. Using research evidence to frame options to address a problem. Health Res Policy Syst 2009;7(Suppl 1):S5.

[17] Global Forum for Health (2008). Monitoring financial flows for health research 2008. Available at: http://announcementsfiles.cohred.org/gfhr_pub/assoc/s14888e/s14888e.pdf. Accessed on February, 2012.

[18] Viergever R, Olifson S, Ghaffar A, Terry R. A checklist for health research priority setting: nine common themes of good practice. Health Res Policy Syst 2010;8:36.

[19] Evidence from systematic reviews to inform decision-making towards achieving the millennium development goals for reducing maternal and child mortality. A background document prepared for an international dialogue on evidence-informed action to achieve health goals in developing countries (IDEAHealth). Khon Kaen, Thailand. 13e16 December 2006. Draft for discussion Available at: http://evipnet.bvsalud.org/lildbi/docsonline/1/4/041-MCH_Brief_exec.pdf. Accessed on January, 2011.

[20] Commission on Health Research for Development, Health Research, Essential Link to Equity in Development (1990). Available at: http://www.cohred.org/downloads/open_archive/ComReports_0.pdf. Accessed on January, 2012.

[21] World Health Organization. World report on knowledge for better health: strengthening health systems. Geneva: World Health Organization; 2004. Available at: http://www.who.int/rpc/meetings/en/world_report_on_knowledge_for_better_health2.pdf. Accessed on January, 2012.

[22] Pang T, Pablos-Mendez A, IJsselmuiden C. From Bangkok to Mexico: towards a framework for turning knowledge into action to improve health systems. Bull World Health Organ 2004;82:720.

[23] Piaggio G, Ba'aqeel H, Bergsjø P, Carroli G, Farnot U, Lumbiganon P, et al. The practice of antenatal care: comparing four study sites in different parts of the world participating in the WHO Antenatal Care Randomised Controlled Trial. Paediatr Perinat Epidemiol 1998;12(Suppl 2):116e41.

[24] Li T, Vedula SS, Scherer R, Dickersin K. What comparative effectiveness research is needed? A framework for using guidelines and systematic reviews to identify evidence gaps and research priorities. Ann Intern Med 2012;156:367e77.

[25] Nasser M, Lodge M, Fedorowicz Z. The relevance of Cochrane reviews to the cancer priorities in Iran. 15th Cochrane Colloquium 23e27 October 2007, Sao Paulo, Brazil. Available at: http://www.imbi.uni-freiburg.de/OJS/cca/index.php?journal5cca&page5article&op5view&path%5B%5D55059. Accessed on January, 2012.

[26] de Vet HC, Kroese ME, Scholten RJ, Bouter LM. A method for research programming in the field of evidence-based medicine. Int J Technol Assess Health Care 2001;17(3):433e41.

[27] Clarke L, Clarke M, Clarke T. How useful are Cochrane reviews in identifying research needs. J Health Serv Res Policy 2007;12:101e3.

[28] Lavis JN, Oxman AD, Grimshaw J, Johansen M, Boyko JA, Lewin S, et al. SUPPORT Tools for evidence-informed health Policymaking (STP). 7. Finding systematic reviews. Health Res Policy Syst 2009; 7(Suppl 1):S7.

[29] Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for determining research gaps during systematic reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I). AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed November 2011.

[30] International Classification of Diseases (ICD). International Classification of Diseases, 10th Revision. Geneva: World Health Organization; 2004.

[31] Understanding Clinical Trial Design: A Tutorial for Research Advocates Authored by Jane Perlmutter, PhD for Research Advocacy Network's Advocate Institute. (2007). Available at: http://fightcolorectalcancer.org/download/RAT2008/CTTutorial.pdf. Accessed on 15 January 2012.

[32] COHRED. Priority setting for health research: lessons from developing countries. The Working Group on Priority Setting. Health Policy Plan 2000;5(2):130e6.

[33] Institute of Medicine (US) Committee on the NIH Research Priority-Setting Process. Scientific opportunities and public needs: improving priority setting and public input at the National Institutes of Health. Washington (DC): National Academies Press (US); 1998.

[34] Montorzi G, de Haan S, IJsselmuiden C. Priority setting for research for health: a management process for countries. Available at: http://www.cohred.org/downloads/Priority_Setting_COHRED_approach_August_2010.pdf. Accessed on March 2012.

[35] Tomlinson M, Chopra M, Hoosain N, Rudan I. A review of selected research priority setting processes at national level in low and middle income countries: towards fair and legitimate priority setting. Health Res Policy Syst 2011;9:19.

[36] Viergever R. Health research prioritization at WHO: an overview of methodology and high level analysis of WHO led health research priority setting exercises. Available at: http://www.who.int/rpc/publications/Health_research_prioritization_at_WHO.pdf. Accessed on March 2012.

[37] The Working Group on Priority Setting. Priority setting for health research: lessons from developing countries. Health Policy Plan 2010;15(2):130e6.

[38] Ranson K, Law T, Bennett S. Establishing health systems financing research priorities in developing countries using a participatory methodology. Soc Sci Med 2010;70(12):1933e42.

[39] Doyle J, Waters E, Yach D, McQueen D, De Francisco A, Stewart T, et al. Global priority setting for Cochrane systematic reviews of health promotion and public health research. J Epidemiol Community Health 2005;59:193e7. J Epidemiol Community Health 2005;59:193e197, March 1, 2005 (10.1136/jech.2003.019547).

[40] Lavis JN. How can we support the use of systematic reviews in policymaking? PLoS Med 2009;6(11):e1000141. 10.1371/journal.pmed.1000141.

[41] Anthony MK, Higgins PA. Maximizing the utility of interorganizational data using concept mapping. J Nurs Adm 2006;36(5):233e40.

[42] Kassab SE, Hussain S. Concept mapping assessment in a problem-based medical curriculum. Med Teach 2010;32(11):926e31.
[43] Noble C, O'Brien M, Coombes I, Shaw PN, Nissen L. Concept mapping to evaluate an undergraduate pharmacy curriculum. Am J Pharm Educ 2011;75:55.
[44] Ridde V. Equity and health policy in Africa: using concept mapping in Moore (Burkina Faso). BMC Health Serv Res 2008;8:90.
[45] van Bon-Martens MJ, Achterberg PW, van de Goor IA, van Oers HA. Towards quality criteria for regional public health reporting: concept mapping with Dutch experts. Eur J Public Health 2011;22(3): 337e42.
[46] Minkman M, Ahaus K, Fabbricotti I, Nabitz U, Huijsman R. A quality management model for integrated care: results of a Delphi and Concept Mapping study. Int J Qual Health Care 2009;21(1): 66e75.
[47] Nalavany BA, Carawan LW, Rennick RA. Psychosocial experiences associated with confirmed and self-identified dyslexia: a participant-driven concept map of adult perspectives. J Learn Disabil 2011;44(1):63e79.
[48] Scahill SL, Harrison J, Carswell P. What constitutes an effective community pharmacy?dDevelopment of a preliminary model of organizational effectiveness through concept mapping with multiple stakeholders. Int J Qual Health Care 2010;22(4):324e32.
[49] Wichaidit W, Kaewkungwal J, Sirivichayakul C, Taechaboonsermsak P, Suvithayasiri V. Maternal and child health in a marginalized community along the Thai-Myanmar border. Southeast Asian J Trop Med Public Health 2011;42(1):152e60.
[50] Chia LR, Schlenk EA, Dunbar-Jacob J. Effect of personal and cultural beliefs on medication adherence in the elderly. Drugs Aging 2006;23(3):191e202.
[51] Cooper V, Moyle GJ, Fisher M, Reilly G, Ewan J, Liu HC, et al. SWEET (Simplification With Easier Emtricitabine Tenofovir) group, UK. Beliefs about antiretroviral therapy, treatment adherence and quality of life in a 48-week randomised study of continuation of zidovudine/lamivudine or switch to tenofovir DF/emtricitabine, each with efavirenz. AIDS Care 2001;23:705e13.
[52] Harvey JN, Lawson VL. The importance of health belief models in determining self-care behaviour in diabetes. Diabet Med 2009;26:5e13.
[53] Belizàn JM, Buekens P, Althabe F, Bergel E. Maternal survival: more research is needed. Lancet 2006;368:2123e4.
[54] Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. BMJ 2006;333:804e6.
[55] Gonzàlez U, Pinart M, Reveiz L, Rengifo-Pardo M, Tweed J, Macaya A. Designing and reporting clinical trials on treatments for cutaneous leishmaniasis. Clin Infect Dis 2010;51:409e19.

6.1.2 Publicación 2

Chapman E, Reveiz L, Sangalang S; Manu C; Bonfill X; Muñoz S; Abalos E. Global research priorities for decreasing global maternal mortality and morbidity: an international survey. Journal of Clinical Epidemiology. Manuscript Number: JCE-13-137

Factor de impacto 2013: 5.478 *Journal of Clinical Epidemiology* ranks 6th of 160 journals in the Public, Environmental & Occupational Health category.

Resumen

El objetivo de este estudio fue identificar y priorizar lagunas investigación con el objeto de contribuir a la salud maternal y disminuir la mortalidad materna.

Se ha llevado a cabo una encuesta en dos etapas. Proporcionamos a los participantes (expertos de la Colaboración Cochrane) una lista de 319 preguntas de investigación en formato PICO construidos a partir de 178 revisiones sistemáticas Cochrane (ya mencionado en el primer trabajo). Las preguntas se clasificaron en función de los determinantes directos e indirectos de muerte materna. Los encuestados de la primera ronda refinaron las preguntas de investigación, eliminaron las que consideraron de baja prioridad y de acuerdo con cuatro criterios y también incluyeron preguntas adicionales. En la segunda ronda, los encuestados priorizaron 62 preguntas [Anexo 2]. En esta ronda las preguntas se re-agruparon en cinco categorías y se utilizaron otros 4 criterios de priorización.

Las tasas de respuesta global para la primera y segunda rondas fueron del 47 % (73 /155) y 17 % (363/2121), respectivamente. Los participantes clasificaron 62 de las preguntas de investigación como "muy relevante". Aproximadamente el 20 % de todas

las preguntas que se identificaron en las revisiones Cochrane y dos tercios de las preguntas de la segunda ronda fueron considerados de "alta prioridad". Más mujeres (235) que de hombres (128) participaron en la encuesta. Las mujeres sin embargo proporcionaron respuestas más incompletas que los hombres (49% versus 35%, p= 0,01). También se encontraron diferencias estadísticamente significativas (ES) al comparar el grupo de preguntas muy relevantes según sexo del participante en seis preguntas; la mitad de ellas relacionados con diabetes. No se encontraron diferencias ES al comparar el grupo de preguntas muy relevantes por tipo de entrevistado ni país de procedencia ni número de ronda.

Se pudieron identificar prioridades de investigación mediante el mapeo y la mejora de la comprensión de las necesidades de investigación para entornos de bajos y medianos ingresos a nivel internacional.

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ORIGINAL ARTICLE

A survey study identified global research priorities for decreasing maternal mortality

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Abstract

Objectives: The aim of this study was to identify and prioritize research gaps to help decrease maternal mortality.

Study Design and Setting: We conducted a two-stage survey. We provided participants (Cochrane Collaboration experts) with a list of 319 problem/population, intervention, comparison, and outcome questions built from 178 Cochrane systematic reviews. Questions were classified according to causes of maternal death. Respondents of the first round refined the research questions and prioritized them by eliminating those that were considered of low priority, according to four criteria. They also included additional questions. In the second round, respondents prioritized 62 questions.

Results: The overall response rates for the first and second rounds were 47% (73 of 155) and 17% (363 of 2,121), respectively. Participants ranked 62 of the research questions as "very relevant." Approximately 20% of all questions that were identified in Cochrane reviews and two-third of questions of the second round were considered of "very high priority." More women (235) than men (128) participated in the survey. We did not find statistically significant differences when comparing the groups of very relevant questions by the type of respondent, income, country, and round.

Conclusion: We identified research priorities by mapping and improving the understanding of research needs in low- and middle-income settings internationally.

Keywords: Prioritization; Maternal mortality; Research; Survey; MDGs; Systematic review

1. Introduction

Although maternal mortality has declined approximately one-third from 1990 to 2011, for most low- and middle-income countries, achieving the targets of the Millennium Development Goals (MDGs) will take longer than expected [1,2]. Although most cases of maternal deaths can potentially be avoided if some of the well-known interventions that were proved to be effective are available to women, it is essential to discern the effects of those different clinical and public health interventions in different contexts to understand the best way of delivering those interventions and address barriers to implementation [2e7]. Making informed decisions to achieve the MDG5 (reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio) depends on not only the access to the best available evidence but also how to incorporate this knowledge into the complexity of the health systems, often with limited resources [8,9].

More research from low- and middle-income countries is needed to better understand and address all the circumstances around maternal deaths, including further review of the impact that health systems and policies have on them. To reduce these knowledge gaps, research priorities must be identified, prioritized, and addressed, and research

Conflict of interest: The authors declare that they do not have any conflicts of interest. The views expressed by authors reflect their personal expert views and do not necessarily reflect the official position or policy of their employers. E.C. is a PhD candidate at the Universitat Autonoma de Barcelona. S.S. contributed to the project during her internship at the Pan American Health Organization (PAHO). C.M. contributed to the project during her internship at the PAHO.

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What is new?

- Cochrane reviews can be systematically used to identify research questions for priority settings; Cochrane Collaborators from 29 countries participated in this prioritization exercise to identify global research needs.
- Relevant research needs in maternal health were identified from Cochrane systematic reviews and prioritized by Cochrane collaborators from low, middle and high-income countries.
- This exercise allowed identifying health policies and systems research as an important determinant for improving maternal health.
- Although the "implication for research" section of Cochrane reviews were useful to identify research questions for any health topic, authors of Cochrane and non-Cochrane systematic reviews should ensure that they include the EPICOT format for reporting research recommendations (Evidence; Population; Intervention; Comparison; Outcome; Time stamp) in their reviews.
- More research is needed to assess its usefulness to researchers and research funders and to define and evaluate strategies to implement global research agendas.

findings must be made visible, available, and accessible for appropriate and timely implementation [10e14].

In a previous article, we have identified gaps in maternal health research through the evaluation of the section "implications for research" of 178 Cochrane systematic reviews (SRs) in which the authors stated that the available evidence to guide clinical practice was insufficient and further research was needed. This study identified 319 research problem/population, intervention, comparison, and outcome (PICO) format questions that were classified into 12 different categories based on the causes of maternal deaths [15].

The aim of this study was to prioritize these research needs, to contribute with the building of a global research agenda for better use of resources to reduce maternal mortality.

1. Methods

1.1. Design

Our approach includes a number of phases that were described in a previous article [15] (Fig. 1). For the prioritization exercise, we conducted a two-round survey using as the main input the questions previously identified as research gaps related with MDG5. The first round had the objective of refine (or redefine) the research questions, and the second round was the proper prioritization exercise.

2.1.1. *Round 1: refining research questions*

2.1.1.1. *Questionnaire.* As mentioned, we provided participants with an initial list of 319 questions (in a PICO format) built from 178 Cochrane SRs [15]. The specific objective of the first round was to refine the proposed research questions and include additional ones to be used in the prioritization exercise (round 2). We grouped these questions into 12 different groups, according to the causes of maternal deaths; 10 were directly or indirectly related to the main causes of maternal mortality and morbidity; another group included interventions for pregnancy prevention, and the last one was related to health systems and policy interventions as defined by the Health System Evidence Web site taxonomy (ie, governance, financial and delivery arrangements, and implementation considerations; Table 1). Given the large number of questions found in some groups, a decision was made to create two separate surveys for the "labor group" and "health policies and systems group." Thus, a total of 14 surveys were created using SurveyMonkey Data Analysis tool.

Questionnaires had three sections. Section A contained questions about the participant's gender, main role in the Cochrane Collaboration (CC; author, consumer coordinator, consumer referee, or external referee), and "income country" (further classified as high, middle, or low level).

Section B presented a list of questions (according to the prespecified category) to be evaluated for magnitude and urgency, potential to maximize the reduction of maternal mortality and morbidity, feasibility, and future impact by

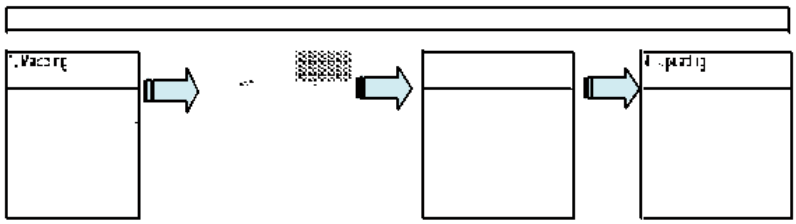


Fig. 1. Description of the mappingeprioritizingereconcilingeupdating (MPRA) approach phases.

Table 1. Number of PICO classified according to the causes of maternal death

Category	Total	%
Labor	57	17.9
Health policies and systems	40	12.5
Infection	28	8.8
Indirect causes	27	8.5
Postpartum hemorrhage	26	8.2
Hypertensive disorders	26	8.2
Cesarean section	24	7.5
Abortion	24	7.4
Unplanned pregnancy	23	7.2
Preterm birth	23	7.2
Diabetes	13	4.1
Other direct causes	8	2.5
	319	100

Abbreviation: PICO, problem/population, intervention, comparison, and outcome.

ranking each criterion on a Likert-type scale of 1 to 5 (where 1 indicates not important at all and 5 indicates very important). Three epidemiologists and a public health nurse evaluated the face validity of the instrument in July 2011 stating that the questions were clear, unambiguous, logical, and free of excess wording. Besides that, free-text fields for open responses were also provided in section C for participants to comment on any aspect of the survey and make suggestions for additional research questions. See the sample in Fig. 2.

2.1.1.1. Sampling. Participants were selected from the CC's database of Cochrane review authors of the Pregnancy and Childbirth Group, the Public Health Group, the Fertility Regulation Group, and the Effective Practice and Organization of Care Cochrane Group. Reviewers having published more than one Cochrane review related to maternal health were selected. A list of Cochrane participants with a valid e-mail address was created with the following information: name, Cochrane group, role (author, consumer coordinator, consumer referee, and external referee as defi in the Cochrane handbook) [16], e-mail, affi , country, and gender.

2.1.2. Round 2: prioritizing highly relevant research questions

2.1.2.1. Questionnaire. The aim of the second round was to prioritize the most relevant research questions according to their potential of implementation. The research questions identified as "important" or "very important" in the first round and all new questions suggested by experts were grouped into five new categories according to causes/determinants of maternal mortality (Table 2) using four criteria (acceptable, deliverable, equitable, and feasible). According to its perceived importance, each of the questions was scored independently by evaluators using a Likert-type scale of 1 to 5 varying from "very relevant" to "not relevant" with a fifth judgmentd"can't answer"dfor those research questions that could not be answered because of uncertainty or lack of sufficient knowledge from the respondent. See sample in Fig. 2.

2.1.2.2. Sampling. In the second round, an invitation to contribute was sent to the CC review authors who had participated in the first round. As we anticipated a low response rate, all other CC authors, consumer coordinators, consumer referees, and external referees identified from the same Cochrane Groups were contacted [16].

2.2. Analysis

2.2.1. First round

All four criteria were equally weighted (25% each). We sorted scores in ascending order and calculated their distribution by quartiles. This allowed us to generate four strata grading the questions in the following categories: "low" and "intermediate" importance for those in the first and second quartiles and "high" and "very high" importance for the upper quartiles. Only those having high or very high importance were included in the second round.

2.2.2. Second round

All four criteria were equally weighted, each one being worth 25%. Scores were sorted in ascending order, and distributions were calculated and expressed in quartiles, grading questions as follows: "not very relevant" and "slightly relevant" for those in the first and second quartiles and "highly relevant" and "very relevant" for those in the upper quartiles. A question was considered to be "most relevant" when 75% or more of the participants scored the question as "very relevant."

2.2.3. Statistical data analysis

Data were analyzed with Stata (version 12; STATA Corporation) Fisher's exact test at level !0.05 was performed for statistical significance to evaluate whether relevance score was associated with respondent's role, type of country of residence, and gender.

1. Results

1.1. First round

One hundred fifty-five Cochrane review authors were contacted and four reminders were sent. The overall response rate was 47% (73 of 155) with some differences between groups that were categorized according to causes/determinants of maternal death. From these, 60% (44 of 73) completed the whole questionnaire. The "postpartum hemorrhage" group had the highest response rate (67%; 8 of 12), whereas the "preterm delivery" group had the lowest response rate (23%; 3 of 13). Regarding the evaluation of the research questions, 29.5% (94 of 319) were ranked as "important" or "very important," and six additional questions were suggested (Fig. 3).

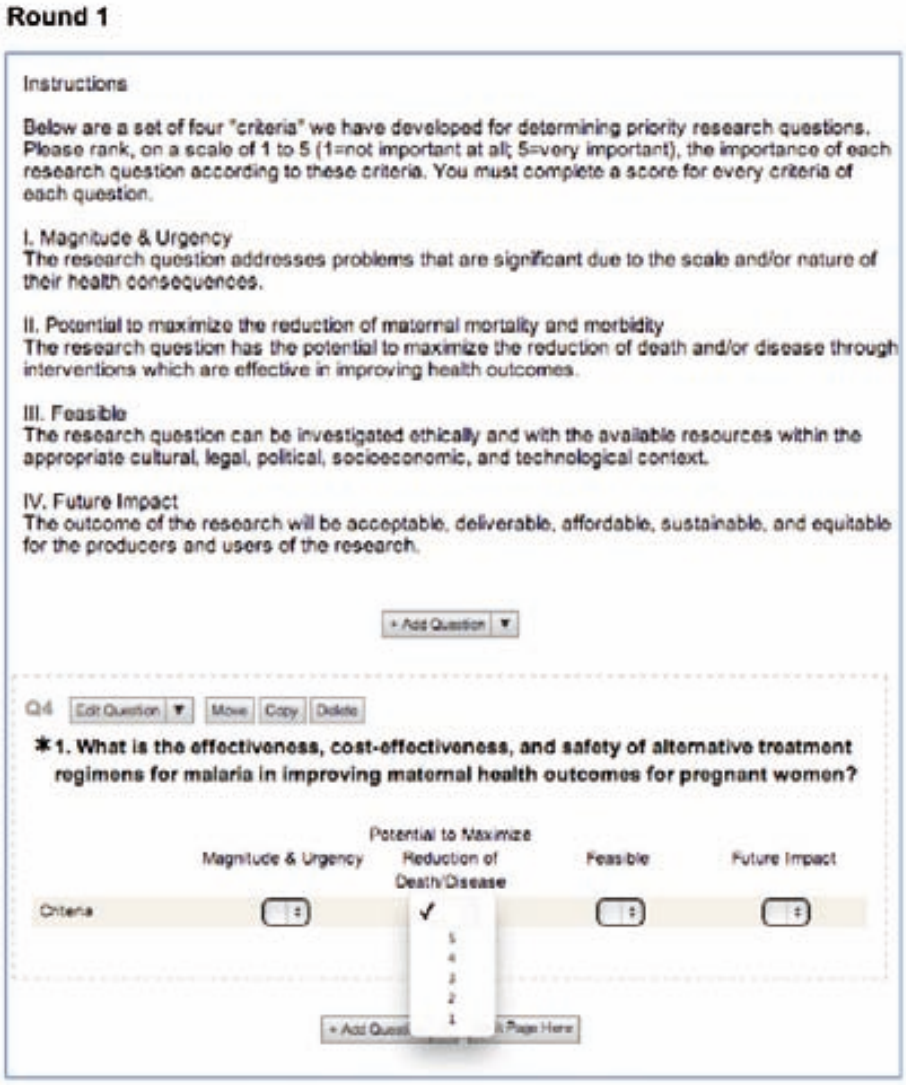


Fig. 2. Sample of two rounds in SurveyMonkey.

1.1. Second round

Finally, 2,165 individuals were invited to participate (44 e-mails were bounded); three reminders were sent. The summary of rounds is shown in Fig. 3 and summary description of participants is shown in Table 3. The overall response rate was 17% (363 of 2,121), and 69% (253 of 363) of participants answered the whole questionnaire. The groups categorized by causes/determinants of maternal death having the highest rate of complete responses were the "health systems and services" (24.2%; 88 of 253), "diabetes and other causes" (12.7%; 46 of 253), and "labor and cesarean" (12.9%; 47 of 253).

Two-third (62 of 100) of the questions from the second round were considered to be of very high priority (for the complete list of research questions see Appendix). Most questions of the "health policy and systems," "abortion and unplanned pregnancy," and "postpartum hemorrhage and hypertensive disorders" were highly ranked in the second round (Fig. 4). The interventions involved drugs (31%) health systems (27%), behavior modification, education, and counseling (16%), mixed (13%), and others such as devices, nutrition, and diagnostic tests (13%).

More women (235) than men (128) responded in the survey; however women more frequently provided incomplete

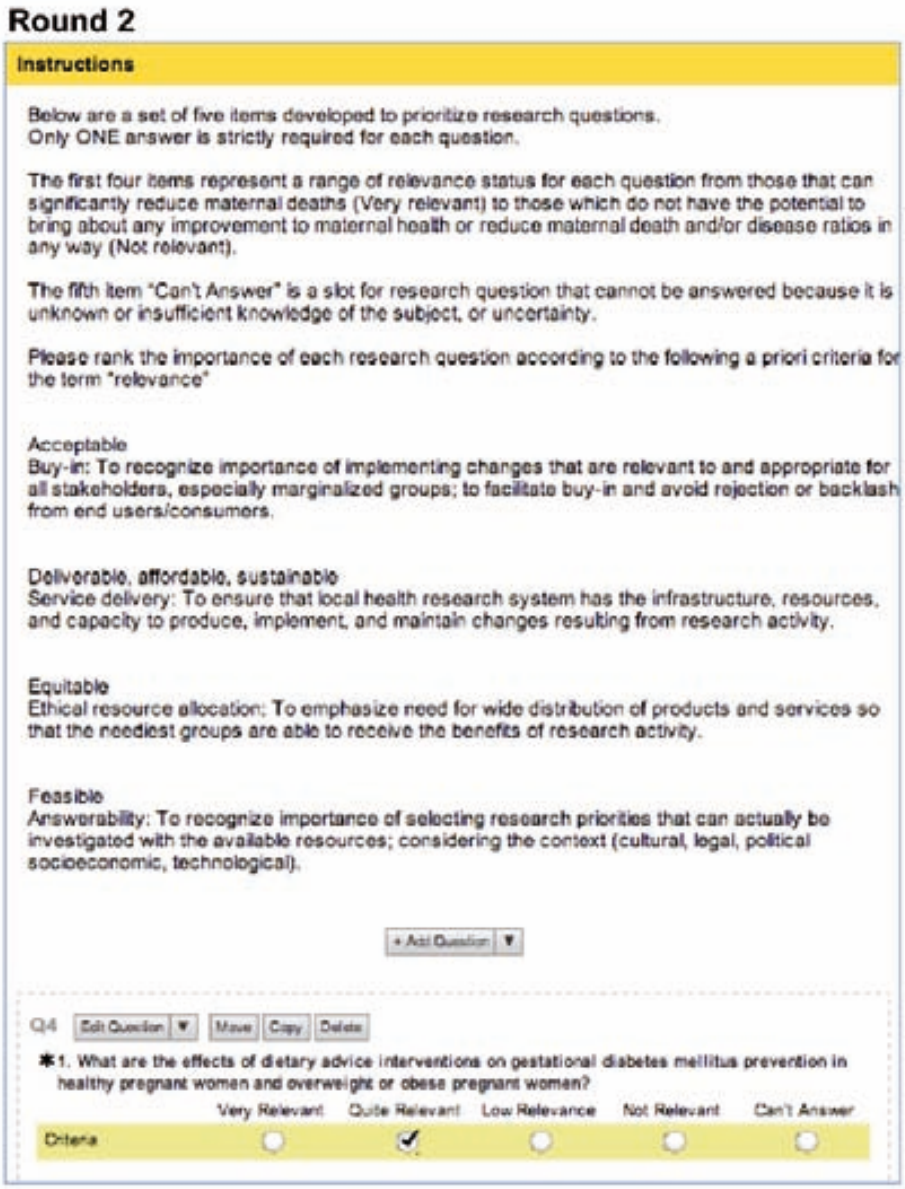


Fig. 2. *continued*

responses than men (49% vs. 35%, P 5 0.01; Table 4). We did not find statistically significant differences when comparing the group of very relevant questions by the type of respondent (author, consumer, or external referees), the country's income level, and between rounds (rounds 1 and 2). However, a significant difference was found when comparing a small number of the ''very relevant'' questions according to the respondent's gender (Table 5).

1. Discussion

We conducted an explicit exercise of prioritization, guided by a broader analysis of the research gaps drawn from the most up-to-date evidence (or lack of) from SRs. Our previous work consisted in mapping research gaps, from unanswered questions about interventions reviewed in Cochrane SRs, which helped us build 319 questions

Table 2. Number of PICO-formatted questions categorized according to the cause of maternal mortality used for Delphi round 2

Category	Total	%
Abortion and unplanned pregnancy	23	23
Diabetes and other causes[a]	19	19
Labor and cesarean	18	18
Postpartum hemorrhage and hypertensive disorders	15	15
Health policy and system	25	25
	100	100

Abbreviation: PICO, problem/population, intervention, comparison, and outcome.

[a] Include obesity, HIV, malaria, anemia, violence, and so on.

(research needs) in a systematic manner [15]. The prioritization process of these research questions was the main objective of this article to inform the maternal health research agenda at a global level.

Although previous prioritization exercises have looked for research gaps in maternal mortality, the approach described in this study is, to our knowledge, one of the first attempts to use an important number of Cochrane SRs to identify research questions and obtain expert opinion from multiple stakeholders groups [17]. Saldanha et al. [18] recently published a pilot study to identify research needs using a SR in gestational diabetes mellitus. Although the pilot study only used one SR, the authors developed a conceptual model that included a number of steps: the identification of research gaps; feedback from authors of SR; translation of research gaps into researchable questions; feedback from local stakeholders and online, in-person and external stakeholder feedback; Delphi rounds; prioritization of outcomes; and refinement of final research questions. One of their conclusions was that the authors of SRs should include the identification of specific research needs as a primary objective of the SR process. Our exercise included a larger number of SRs and focused on prioritizing research questions at the global level.

Although there is an increasing consensus that stronger health systems are the key for achieving better health outcomes, there is much less agreement on how it works [19]. We found that the gap (unanswered questions) about interventions related to health systems and policy remained the top priority over the two rounds in our prioritization exercise. This also could reflect that experts have incorporated this issue as a determinant for maternal health that needs to be explored.

Many countries have established that maternal health and, specifically, the decrease of maternal mortality is a priority in their national health research agendas [20,21]. However, the insufficient production of relevant research in low-resource areas [12,22,23] and the poor transferability of available evidence from high resource settings are contributing factors to the existing research gaps [9]. Health research prioritization is a dynamic process that is influenced by multiple factors. It was found to be context dependent, which was consistent with findings in the literature [24,25]. For instance, our prioritization process depended on external factors such as participant's gender, role, and country of residence as well as internal factors such as the length of the survey, the readability of the survey questions, and incidents of technical difficulties with the survey's electronic format.

Fig. 3. Summary of the two rounds.

Table 3. Participants of Cochrane Collaboration

Name of the group	Number of participants	Consumer coordinators	Consumer referees	External referees
	Number with e-mail			
Pregnancy and Childbirth Group				
Total	1,075	2	66	338
With e-mail	987	2	24	98
Public Health Group				
Total	134	0	5	31
With e-mail	123	0	4	29
Effective Practice and Organization of Care Group				
Total	734	0	0	12
With e-mail	691	0	0	10
Fertility Regulation Group				
Total	140	0	0	98
With e-mail	121	0	0	96
Total with e-mail	1,922	2	28	233

E-mails were bounced in 64 participants. Hence, 2,121 were final participants.

Rate of response was another critical issue in our exercise. We had an average of 47% and 17% of responses in the first and second rounds, respectively. Participants of the first round were the most knowledgeable in the maternal health field (predefined as those with more publications in a specific area). They were the first filters in this effort to identify the most relevant questions. The lower response rate in the second round could be explained because it included all members of the four CC groups.

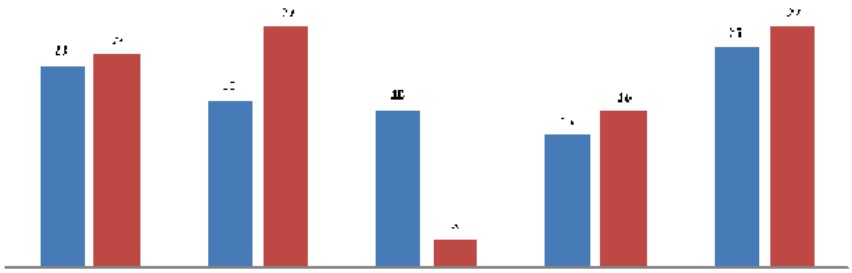
We had more answers for questions related to postpartum hemorrhage most likely because it is the leading cause of maternal death globally. Other priority research questions found to be relevant by participants were abortion and unplanned pregnancy and hypertensive disorders (Fig. 3) maybe because abortion is the leading cause of maternal death in many countries and adolescent childbearing is a public health concern [26].

Stakeholders think that health systems and policy-related interventions are important determinants for maternal health and also how to break them down into specific questions that need an urgent response in relation to the achievement of MDG5. All these findings are aligned with the growing consensus of taking into account the determinants of health related to systems, programs, and health policy in the field of maternal and child health [27e33].

We found no plausible explanation as to why nearly twice as many more women than men responded to the survey or why the responses of men were significantly more complete than those of women (65% vs. 51%). More research is needed to better understand why these differences exist. Future studies should explore prioritization from the perspective of different groups of individuals, particularly policy makers, politicians, economists, healthcare administrators, health-care providers, and patients.

4.1. *Limitation of the study*

This study has a number of limitations. We contacted a sample of international experts from a range of countries. The response rate varied according to the round: it was higher on the first round in which the expertise of respondents, as per their publications in the field, was presumably stronger. It also varied according to the category or group of causes of maternal deaths, and we cannot exclude the possibility that some groups of interventions were underrepresented. As data of nonrespondents were not available, we could not perform any comparison with those responding the survey. The time allocated to complete and submit the surveys was brief and possibly insufficient even with the use of reminders; some studies have found that reminder notifications have a positive effect on response rates for Web surveys [34]. There were also some technical questions, yet no reference text was included to provide background information. It was assumed that all participants had sufficient level of expertise to answer the questions accurately, although the complexity of the survey particularly for the first round was high. In addition, the balance



For 2nd round: * 10% and ** 17,5 % (Include HIV, Malaria, Anemia, Violence, etc)

Fig. 4. Summary of questions as results of Delphi round 2 (first and second rounds).

Table 4. Complete and incomplete responses for Delphi round 2, by participant sex

	Female			Male		
Category	Complete	Incomplete	% Incomplete	Complete	Incomplete	% Incomplete
Diabetes and other causes	30	11	37	16	1	0.6
Labor and cesarean section	24	14	58	23	7	30
Health policies and systems	53	25	47	35	14	40
Postpartum hemorrhage and hypertensive disorders	26	15	58	10	5	50
Abortion and pregnancy prevention	25	12	48	11	6	55
Total	158	77	49	95	33	35

on the role of participants and the interest the topic might have for them could affect the response, as all were Cochrane experts in different fields.

Although the CC is an international network of more than 31,000 dedicated people from over 120 countries, we did not include non-Cochrane participants (ie, stakeholders or attending physicians); this fact might decrease the external validity of our findings. Another technical issue would be related to misclassifications of some questions, or research questions that could be applicable to more than one group and, arbitrarily, were allocated to one only.

4.1. *Strengths*

Strengths of the study include the selection of research questions that were based on the structured ''implication for research'' section of Cochrane SRs, the utilization of feedback based on expert opinion from a variety of stakeholder groups, and the application of a specific selection procedure to identify experts and verify their expertise. The main advantage of this approach is that experts from all over the world were able to participate anonymously and meaningfully in the prioritization exercise without incurring additional expenses, which proved to be a well-structured mean of effective communication and group decision making; furthermore, no significant differences were found when comparing high-, medium-, and low-income level countries. In addition, the implementation of continuous monitoring and evaluation of the prioritization exercise by the research team provided the following advantages: prompt identification and resolution of technical problems and prompt and personalized response to participant feedback.

Table 5. Example of relevant questions with statistical difference by the sex of the participant

1. Do interventions to reduce weight and obesity in pregnant women have any effect on improving maternal health outcomes?
2. What is the effectiveness of maternity waiting home (MWH) facilities in improving maternal health outcomes in low-resource countries?
3. What are the indicators to better assess the short- and long-term outcomes of caesarean section and vaginal birth?
4. Which are the best strategies for management of gestational diabetes, including alternative management strategies?
5. What is the effectiveness and safety of various interventions (such as administration of oral anti-diabetics drugs, combined nutrition and glucose self-monitoring, and continuous glucose monitoring) in improving maternal health outcomes in pregnant women with pre-existing diabetes type 2?
6. Compared with insulin or dietary and lifestyle control, what is the effectiveness and safety of various oral anti-diabetic agents in improving maternal health outcomes and glycaemic control parameters for women with pre-existing diabetes mellitus, impaired glucose tolerance, or previous gestational diabetes mellitus, who are pregnant or who are planning a pregnancy?

5. Conclusion

It is possible to select and rank maternal health research priorities using this approach, which was found to be innovative and useful in obtaining expert opinion from a variety of stakeholder groups using only one database. The highest priority research questions identified in this study can potentially have a major impact on maternal mortality if they are considered when new research is planned and produced. That could be innovative in the global research agenda, particularly for selected interventions on determinants related with health systems and policy.

This is especially important for governments and aid agencies supporting research efforts in developing countries, which are already overburdened and extremely resource limited. More research is needed to fine-tune this prioritization process to better serve the needs of not only researchers but also policy makers, funders, and consumers.

5.1. *Ethical considerations*

This prioritization exercise was considered a Public Health Practice aiming at monitoring public health research priorities [35]. All participants have consented to participate in the survey; responses were treated and analyzed anonymously.

Acknowledgments

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References

[1] Lozano R, Wang H, Foreman KJ, Rajaratnam JK, Naghavi M, Marcus JR, et al. Progress towards Millennium Development Goals

4 and 5 on maternal and child mortality: an updated systematic analysis. Lancet 2011;378:1139e65.

[2] The Millennium Development Goals Report (2011). United Nations New York. Available at http://www.undp.org/content/dam/undp/library/MDG/english/MDG_Report_2011_EN.pdf. Accessed September 4, 2013.

[3] World Health Organization. World Health Report 2005: make every mother and child count. Geneva, Switzerland: WHO; 2005:Available at http://www.who.int/whr/2005/en/index.html :Accessed December 15, 2011.

[4] World Health Organization. Trends in maternal mortality: 1990 to 2008. Estimates developed by WHO, UNICEF, UNFPA and The World Bank. 2010. ISBN: 978 92 4 150026 5. Available at: http://www.who.int/reproductivehealth/publications/monitoring/9789241500265/en/. Accessed March 14, 2012.

[5] Shennan AH, Redman C, Cooper C, Milne F. Are most maternal deaths from pre-eclampsia avoidable? Lancet 2012;379:1686e7.

[6] Bhutta ZA, Chopra M, Axelson H, Berman P, Boerma T, Bryce J, et al. Countdown to 2015 decade report (2000e10): taking stock of maternal, newborn, and child survival. Lancet 2010;375:2032e44.

[7] Khan K, Wojdyla D, Say L, Gülmezoglu A, Van Look P. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066e74.

[8] Alliance for Health policy and Systems Research. Evidence from systematic reviews to inform decision-making to wards achieving the millennium development goals for reducing maternal and child mortality. A background document prepared for an international dialogue on evidence-informed action to achieve health goals in developing countries (IDEAHealth). Khon Kaen, Thailand: 2006. Draft for discussion. Available at: http://www.who.int/rpc/meetings/MCH_Brief.pdf. Accessed September 4, 2013.

[9] Piaggio G, Ba'aqeel H, Bergsjø P, Carroli G, Farnot U, Lumbiganon P, et al. The practice of antenatal care: comparing four study sites in different parts of the world participating in the WHO Antenatal Care Randomised Controlled Trial. Paediatr Perinat Epidemiol 1998;12(Suppl 2):116e41.

[10] Belizán JM, Buekens P, Althabe F, Bergel E. Maternal survival: more research is needed. Lancet 2006;368:2123e4.

[11] Evans JR. Essential national health research. A key to equity in development. N Engl J Med 1990;323:913e5.

[12] World Health Organization. World report on knowledge for better health: strengthening health systems. Geneva: World Health Organization: 2004. Available at. http://www.who.int/rpc/meetings/pub1/en/:Accessed September 4, 2013.

[13] Pang T, Pablos-Mendez A, Jsselmuiden C. From Bangkok to Mexico: towards a framework for turning knowledge into action to improve health systems. Bull World Health Organ 2003;82:720e1.

[14] World Health Organization. The World Health Report 2013: research for universal health coverage. Geneva, Switzerland:World Health Organization; 2013:Available at http://apps.who.int/iris/bitstream/10665/85761/2/9789240690837_eng.pdf :Accessed September 4, 2013.

[15] Chapman E, Reveiz L, Chambliss A, Sangalang S, Bonfill X. Cochrane systematic reviews are useful to map research gaps for decreasing maternal mortality. J Clin Epidemiol 2013;66:105e12.

[16] Higgins JPT, Green S (editors). Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. UK: The Cochrane Collaboration; 2011. Available at: www.cochrane-handbook.org. Accessed November 14, 2013.

[17] Sridhar D. Who sets the global health research agenda? The challenge of multi-bi financing. PLoS Med 2012;9(9):e1001312.http://dx.doi.org/10.1371/journal.pmed.1001312 .

[18] Alliance for Health policy and Systems Research. Evidence from systematic reviews to inform decision-making to wards achieving the millennium development goals for reducing maternal and child mortality. A background document prepared for an international dialogue on evidence-informed action to achieve health goals in developing countries (IDEAHealth). Khon Kaen, Thailand: 2006. Draft for discussion. Available at: http://www.who.int/rpc/meetings/MCH_Brief.pdf. Accessed September 4, 2013.

[19] Travis P, Bennett S, Haines A, Pang T, Bhutta Z, Hyder AA, et al. Overcoming health-systems constraints to achieve the Millennium Development Goals. Lancet 2004;364:900e6.

[20] Reveiz L, Elias V, Terry RF, Alger J, Becerra-Posada F. Comparison of national health research priority-setting methods and characteristics in Latin America and the Caribbean, 2002e2012. Rev Panam Salud Publica 2013;34(1):1e13.

[21] Martínez-Martínez E, Zaragoza ML, Solano E, Figueroa B, Zúñiga P, Laclette JP. Health research funding in Mexico: the need for a long-term agenda. PLoS One 2012;7(12):e51195.

[22] Commission on Health Research for Development. Health research, essential link to equity in development. 1990. Available at http://www.cohred.org/downloads/open_archive/ComReports_0.pdf . Accessed March 22, 2011.

[23] Priority Setting for Research for Health: a management process for countries. Montorzi G, de Haan S, Usselmuiden C. Council on Health Research for Development (COHRED); 2010. Available at : http://www.cohred.org/wp-content/uploads/2011/02/Priority-Setting-Approach_ENG_-2010.pdf. Accessed November 15, 2013.

[24] Tomlinson M, Chopra M, Hoosain N, Rudan I. A review of selected research priority setting processes at national level in low and middle income countries: towards fair and legitimate priority setting. Health Res Policy Syst 2011;9:19.

[25] Viergever RF, Olifson S, Ghaffar A, Terry RF. A checklist for health research priority setting: nine common themes of good practice. Health Res Policy Syst 2010;8:36.

[26] The millennium development goals report 2012. United Nations New York. 2012. Available at http://www.un.org/en/development/desa/publications/mdg-report-2012.html. Accessed May 2, 2012.

[27] USAID's Global Health Strategic Framework. Better health for development. Executive summary. U.S. Agency for International Development; 2012:FY 2012eFY 2016. Washington DC: Available at: http://vet.osu.edu/sites/vet.osu.edu.global/files/documents/USAID-gh_framework2012-2016.pdf. Accessed November 14, 2013.

[28] Ranson K, Law TJ, Bennett S. Establishing health systems financing research priorities in developing countries using a participatory methodology. Soc Sci Med 2010;70(12):1933e42.

[29] Althabe F, Bergel E, Cafferata ML, Gibbons L, Ciapponi A, Alemán A, et al. Strategies for improving the quality of health care in maternal and child health in low- and middle-income countries: an overview of systematic reviews. Paediatr Perinat Epidemiol 2008;22(Suppl 1):42e60.

[30] Gonzalez-Block MA. Health policy and systems research agendas in developing countries. Health Res Policy Syst 2004;2(1):6.

[31] Bennett WL, Robinson KA, Saldanha IJ, Wilson LM, Nicholson WK. High priority research needs for gestational diabetes mellitus. J Womens Health (Larchmt) 2012;21(9):925e32.http://dx.doi.org/10.1089/jwh.2011.3270 .

[32] Robinson KA, Saldanha IJ, McKoy NA. Development of a framework to identify research gaps from systematic reviews. J Clin Epidemiol 2011;64:1325e30.http://dx.doi.org/10.1016/j.jclinepi.2011.06.009 .

[33] Li T, Vedula SS, Scherer R, Dickersin K. What comparative effectiveness research is needed? A framework for using guidelines and systematic reviews to identify evidence gaps and research priorities. Ann Intern Med 2012;156:367e77.http://dx.doi.org/10.1059/0003-4819-156-5-201203060-00009.

[34] Kaplowitz M, Hadlock T, Levine RA. Comparison of web and mail survey response rates. Public Opin Q 2004;68(1):94e101.

[35] Pan American Health Organization/ World Health Organization. Ethics Review Committee Standard Operating Procedures for submitting research proposals. 2009 ed. ISBN 9 789275 130537. Available at: http://new.paho.org/hq/dmdocuments/2009/074_ENG.pdf . Accessed September 12, 2012.

6.1.3 Publicación 3

Reveiz L, Chapman Asial A, Munoz A, Bonfill X, Alonso P. Risk of bias of randomized trials over time. Journal of Clinical Epidemiology 2014; proof-13:39:27

Factor de impacto 2013: 5.478 *Journal of Clinical Epidemiology* ranks 6th of 160 journals in the Public, Environmental & Occupational Health category.

Resumen

Objetivo: evaluar la variación en el riesgo de sesgo (RdS) de ensayos controlados aleatorizados (ECA) en el tiempo.

Se analizaron todos los ECA incluidos en revisiones sistemáticas (RS) publicados en la edición 12 (2012) de la base de revisiones sistemáticas de la Cochrane. Se extrajo la evaluación de cada dominio de RdS realizada por los autores y otras características de los ECAs. Se utilizó regresión logística multivariada para evaluar la asociación entre la presencia de un bajo riesgo de sesgo según dominios de RdS y otras características.

Se incluyeron 1732 ECAs de 97 RS. Los ECA juzgados como de bajo y alto RdS aumentaron significativamente con el tiempo, mientras que las tasas RdS poco claro disminuyeron en varios dominios. El aumento de las tasas de bajo RdS fueron consistentes cuando se considera el tipo de intervención (medicamentos vs otras intervenciones), el tamaño de la muestra y el nivel de ingresos del país. El análisis multivariado con regresión logística mostro que los ECAs publicados entre 2006-2012, en comparación con los publicados antes de 1990, fueron más propensos a ser considerados con bajo RdS para la generación de secuencia de aleatorización (OR =

3,96 IC 95 % 2,29-6,87), para el ocultamiento de la asignación (OR = 3,56; 1,96-6,46), para los datos de incompletos (resultados objetivos) (OR 1,89 ; 01.13 a 03.15) y para los dominios de reportes selectivos (OR = 4,14 ; 2,35-7,29).

Los ECAs han mejorado el reporte y disminuyeron la incertidumbre para la evaluación de RdS en las últimas décadas.

El tercer artículo fue aceptado el 1 de Junio de 2014 y se encuentra en imprenta. Se copian a continuación carta del co-editor y el artículo en etapa de revisión para su publicación:

From: ees.jce.b.29a9b5.1e2c6f3b@eesmail.elsevier.com
[mailto:ees.jce.b.29a9b5.1e2c6f3b@eesmail.elsevier.com] On Behalf Of Laura Fitzpatrick
Sent: Tuesday, June 03, 2014 11:47 AM
To: Reveiz, Dr. Ludovic (WDC)
Subject: JCE-13-484R1: Final Decision

Ms. Ref. No.: JCE-13-484R1
Title: Risk of bias of randomized trials over time
Journal of Clinical Epidemiology

Dear Dr. Reveiz,

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Journal of Clinical Epidemiology - (2014) -

ORIGINAL ARTICLE

Risk of bias of randomized trials over time

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Abstract

Objectives: To determine the variation in the risk of bias (RoB) of randomized controlled trials (RCTs) in time.

Study Design and Setting: We reviewed all included RCTs from systematic reviews (SRs) published in the issue 12 (2012) of the Cochrane Databases of Systematic Reviews. We extracted the RoB author's evaluation per domain and other RCT characteristics. Multivariate logistic regression was used to evaluate association between the presence of a low RoB according to RoB domains and other characteristics.

Results: We included 1,732 RCTs from 97 SRs. The rates of RCTs judged as having low and high RoB significantly increased over time, whereas the rates of unclear RoB decreased for several domains. Increased rates of low RoB were consistent when considering the type of intervention (drugs vs. others), sample size, and country income level. Multivariate logistic regression shows that RCTs published between 2006 and 2012, compared with those published before 1990, were more likely to be considered at low RoB for sequence generation (odds ratio [OR] 5 3.96; 95% confidence interval [CI]: 2.29, 6.87), allocation concealment (OR 5 3.56; 95% CI: 1.96, 6.46), incomplete outcome data (objective outcomes; OR 5 1.89; 95% CI: 1.13, 3.15), and selective reporting (OR 5 4.14; 95% CI: 2.35, 7.29) domains.

Conclusion: RCTs have improved reporting during the last decades decreasing the uncertainty for the RoB assessment.

Keywords: Randomized controlled trials; Risk of bias; Systematic reviews; Methods; Research design; Quality improvement

1. Introduction

Systematic reviews (SRs) of randomized controlled trials (RCTs) provide the most reliable source of evidence and are at the core of clinical practice guidelines recommendations and clinical and policymakers' decisions [1e3]. Although rigorous and detailed methods have been developed and used by systematic reviewers (ie, Cochrane Collaboration handbook), a number of factors may influence the confidence that users of those SRs have in the estimates of risk and benefit of clinical or public health interventions [2].

The GRADE working group approach proposed a system for rating quality of evidence in SRs and guidelines. According to GRADE, the ''quality of evidence reflects the extent to which confidence in an estimate of the effect is adequate to support recommendations.'' Although RCTs are considered high-quality evidence to evaluate the efficacy of health care interventions [1,2], GRADE proposes several reasons to lower our confidence in this type of design, including; risk of bias (RoB), imprecision, inconsistency, indirectness, and magnitude of effect [4].

RoB is defined as the risk of ''a systematic error or deviation from the truth, in results or inferences'' [2], and RCTs included in Cochrane SR are frequently judged as having high or unclear RoB [5e7]. Such bias may lead to an overestimation or underestimation of the true effectiveness of interventions. Many tools have been developed to evaluate the RoB or the quality of RCTs [1,2]. In 2008, the Cochrane Collaboration introduced the RoB tool as

Conflict of interest: S.A. participated in this study during his internship at the Pan American Health Organization. The Pan American Health Organization does not assume responsibility for the statements contained therein. E.C. is a Ph.D. candidate at the Universitat Autonoma de Barcelona. P.A. is funded by a Miguel Servet research contract from the Instituto de Salud Carlos III (CP09/00137).

reporting bias, and other bias); the tool was updated in 2011 after a further evaluation to include modifications such as assessing blinding of participants and personnel separately from bias related to blinding of outcome assessment and including early stop of a trial in the "other sources of bias" domain [2,8]. Although it is difficult to objectively determine the amount of bias in a study or to what extent biases have affected the result of RCTs, evaluators can recognize the RoB that a study has by identifying certain failures; for example, if an RCT is not blinded, it will probably have more RoB than the one that is blinded, particularly for subjective outcomes [1,2]. The evaluation is typically performed independently by two systematic reviewers, and disagreements are usually solved by consensus or by a third reviewer [2].

Another source of concern that could also introduce bias to the assessment of the RCTs is the quality of research reporting. The Consolidated Standards of Reporting Trials (CONSORT) statement published in 1996 [9], updated in 2001 [10] and in 2010 [11], standardizes the reporting of RCT findings. Although the impact of CONSORT recommendations is difficult to measure, the overall quality of reporting during the post-CONSORT period seems to have improved [12–14]. An overview of reviews assessing the quality of RCTs between 1987 and 2007 found that although there is an important variability in assessing the quality of RCTs, the reporting of the methodology seems to have improved over time [13,14].

Although a number of studies have evaluated the impact of reporting guidelines, or assess the RoB in specific subset of RCTs [5,6], to the best of our knowledge, no study has explored the variation of RoB in RCTs over time. We therefore evaluated this issue in a cohort of Cochrane SRs.

2. Methods

2.1. Study design

Methodological survey of all included RCTs in the Cochrane SRs published in 2012 (issue 12) in the Cochrane Databases of Systematic Reviews.

2.2. Sample

2.2.1. Eligibility

Inclusion criteria: all included RCTs in Cochrane SRs published in 2012 (issue 12) in the Cochrane Databases of Systematic Reviews that reported at least one domain of the RoB tool. Exclusion criteria: other type of designs (eg, observational or quasiexperimental studies). We included both studies published as full text or abstracts.

2.2.2. Selection of RCT reports and data extraction

The full report of all SRs was assessed by one reviewer (S.A.) and checked by others (L.R. and F.C.). Data were extracted from full articles that were deemed appropriate for inclusion. A prespecified format was used to collect data.

2.3. Outcomes

Descriptive variables were RCT year of publication; country of affiliation of the main investigator; type of country income; type of publication (full text, abstract, and so forth); whether the RCT was multinational or not; sample size; type of interventions (drugs, procedures, behavior modification, education, counseling, vaccines, devices; mixed; and others).

Analytic variable was RoB measured by the instrument proposed by the Cochrane Collaboration [2]. Each domain is classified, according to RoB, as high, low, or unclear, and some of those domains have subcategories according to the type of outcome (objective or subjective outcomes). We checked the information provided for each trial regarding the type of outcome (objective or subjective); when the information was not state, we classified the type of outcomes based on the Cochrane Handbook guidance [2].

2.4. Statistical analysis

To assess differences according to the RoB instrument, we calculated the number and proportion of reports describing each item. All RoB domains were assessed for differences according to the time. Chi-square (χ^2) statistics and two-tailed Fisher exact tests were used to examine the significance of the association between categorical variables. A difference was considered to be statistically significant when $P < 0.05$. RCTs were divided a priori in four strata according to the period of publication (2006–2012; 2000–2005; 1990–1999; and ≤1989). Taking into account the important amount of data, the authors agreed a priori on four domains thought most likely to represent potential biases: sequence generation; allocation concealment; blinding; and incomplete outcome data. Multivariate logistic regression (for each RoB domain, ≤1989 period was considered basal category) was used to evaluate association between the presence of a low RoB according to domain and the year of trial publication, type of intervention, study sample size (≤50; 51–100; 101–200; and >200), and the type of income of the country where the RCT was conducted (main country for the following categories: Organization for Economic Cooperation and Development members; other high, medium, and low income countries). Statistical analysis of all evaluated RCT was performed using Stata 12.1.

3. Results

3.1. Characteristics of included studies

The search identified 119 reviews of which 22 were excluded for considering only observational studies or not

Table 1. Low risk of bias assessment by time

Year period or domain	Judgment	Sequence generation, % (n)	Allocation concealment, % (n)	Blinding participants, personnel (objective outcomes), % (n)	Blinding participants, personnel (subjective outcomes), % (n)	Blinding outcome assessors (objective outcomes), % (n)	Blinding outcome assessors (subjective outcomes), % (n)	Incomplete outcome data reporting (objective outcomes), % (n)	Incomplete outcome data reporting (subjective outcomes), % (n)	Selective outcome reporting, % (n)	Other sources of bias, % (n)
<1989	Low risk vs. others[a]	20.6 (48)	16.74 (39)	36.05 (84)	9.44 (22)	31.33 (73)	6.87 (16)	32.19 (75)	3.43 (8)	21.46 (50)	33.48 (78)
1990–1999	Low risk vs. others	32.99 (127)	25.45 (98)	32.73 (126)	10.91 (42)	32.73 (126)	9.35 (36)	41.56 (160)	8.83 (34)	35.06 (135)	24.16 (93)
2000–2005	Low risk vs. others	30.50 (147)	27.39 (132)	28.01 (135)	4.98 (24)	29.88 (144)	5.19 (25)	49.59 (239)	4.98 (24)	44.40 (214)	20.12 (97)
2006–2012	Low risk vs. others	44.93 (275)	36.93 (226)	27.29 (167)	6.70 (41)	31.21 (191)	7.68 (47)	50.16 (307)	5.88 (36)	44.44 (272)	24.18 (148)
Total	Low risk vs. others	34.87 (597)	28.91 (495)	29.91 (512)	7.54 (129)	31.19 (534)	7.24 (124)	45.62 (781)	5.96 (102)	39.19 (671)	24.30 (416)
P-value	Low risk vs. others	0.0001	0.0001	0.037	0.005	0.846	0.122	0.0001	0.027	0.0001	0.002

[a] Others include unclear + high risk of bias categories.

including any RCTs. Finally, 1,732 RCTs were included for analysis (Appendix A). The country where the RCT was primarily conducted was not available from reviews in 53% of the cases. Of those that were available most were undertaken in high income (38.9%) countries. Most RCTs were published as full-text articles (96.8%). The proportion of assessed RoB domains in Cochrane reviews varied greatly. Missing assessment was more frequent for the "other sources of bias" domain (Appendix B).

3.2. *RoB assessment over time*

The rates of RCTs judged as having low RoB significantly increased over time in four domains (sequence generation, allocation concealment, incomplete outcome data reporting [objective outcomes] and selective outcome reporting; Table 1; Fig. 1). On the other hand, the rates of RCTs judged as having high RoB also significantly increased in four domains (sequence generation, allocation concealment, blinding participants and personnel [objective outcomes], blinding outcome assessors [objective outcomes]) and other sources of bias categories (Table 2; Fig. 2).

The rate of RCTs judged as having unclear RoB significantly decreased over time in all domains (Fig. 3). The decrease in the rate of RCTs judged as having unclear RoB for most domains was consistent when considering across type of intervention (drugs vs. other), sample size (≤50; 51–100; 101–200; and >200), and country income level where the RCT was primarily conducted (Appendix C).

Multivariate logistic regression showed that RCTs published between 2006 and 2012, compared with those published before 1990, were more likely to show a low RoB in four domains (sequence generation [odds ratio {OR} = 3.96; 95% confidence interval {CI}: 2.29, 6.87], allocation concealment [OR = 3.56; 95% CI: 1.96, 6.46], incomplete outcome data reporting [objective outcomes; OR = 1.89; 95% CI: 1.13, 3.15], and free of selective reporting [OR = 4.14; 95% CI: 2.35, 7.29]). Studies having sample sizes larger than 100 were more likely to be judged as having low RoB for allocation concealment (OR = 1.95; 95% CI: 1.21, 3.14 and OR = 2.26; 95% CI: 1.35, 3.79, respectively) than smaller RCTs. In addition, RCTs of drug interventions were more likely to show lower RoB for five of seven evaluated domains (blinding participants, personnel [objective outcomes; OR = 5.13; 95% CI: 3.48, 7.58], blinding outcome assessors [objective outcomes; OR = 3.18; 95% CI: 2.23, 4.55], incomplete outcome data reporting [objective outcomes; OR = 3.10; 95% CI: 2.23, 4.29], free of selective reporting [OR = 3.16; 95% CI: 2.25, 4.43], and other sources of bias domains [OR = 1.69; 95% CI: 1.15, 2.48]). Detailed information is presented in Table 3. Figures 1 and 2 also show that RCTs published after 2007 were judged as having the highest rates of low RoB accompanied by a decrease of the rates of both high and unclear RoB categories for most domains.

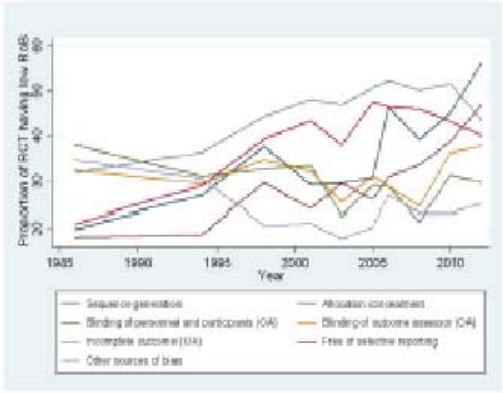

Fig. 1. Low risk of bias domain rates in the included Cochrane reviews per year. RCT, randomized controlled trial.

Table 2. High risk of bias assessment by time

Year period or domain	Judgment	Sequence generation, % (n)	Allocation concealment, % (n)	Blinding participants, personnel (objective outcomes), % (n)	Blinding participants, personnel (subjective outcomes), % (n)	Blinding outcome assessors (objective outcomes), % (n)	Blinding outcome assessors (subjective outcomes), % (n)	Incomplete outcome data reporting (objective outcomes), % (n)	Incomplete outcome data reporting (subjective outcomes), % (n)	Selective outcome reporting, % (n)	Other sources of bias, % (n)
<1989	High risk vs. others*	7.73 (18)	7.73 (18)	20.60 (48)	1.72 (4)	15.02 (35)	1.72 (4)	20.17 (47)	4.29 (10)	18.03 (42)	7.30 (17)
1990–1999	High risk vs. others	7.27 (28)	10.39 (40)	15.84 (61)	3.64 (14)	13.25 (51)	5.19 (20)	8.57 (33)	5.51 (22)	11.69 (45)	12.47 (48)
2000–2005	High risk vs. others	22.41 (108)	24.07 (116)	30.71 (148)	3.73 (18)	29.46 (142)	3.32 (16)	9.13 (44)	2.49 (12)	15.77 (76)	17.43 (84)
2006–2012	High risk vs. others	18.95 (116)	22.39 (137)	29.41 (180)	4.25 (26)	27.61 (169)	4.41 (27)	9.31 (57)	4.74 (29)	14.22 (87)	13.56 (83)
Total	High risk vs. others	15.77 (270)	18.17 (311)	25.53 (437)	3.62 (62)	23.19 (397)	3.91 (67)	10.57 (181)	4.26 (73)	14.60 (250)	13.55 (232)
P-value	High risk vs. others	0.0001	0.0001	0.0001	0.372	0.0001	0.137	0.0001	0.110	0.144	0.002

* Others include unclear + low risk of bias categories.

4. Discussion

4.1. Main findings

In our methodological study, we observed that an increasing significant proportion of studies were judged as having both low and high RoB for several domains over time. In addition, we observed that larger studies and those evaluating drug interventions were more likely to be judged as low RoB for some of the domains. A significant decreasing rate of RCTs was judged as having unclear RoB over time; this decrease being consistent across types of interventions, sample size, and country income level.

Our findings are consistent with previous research in relation to the overall high proportion of RCTs having unclear and high RoB [5,6,15]. In addition, a number of studies have also reported significant differences on trial quality or RoB domains according to the sample size and the type of interventions among other characteristics. For example, the lack of blinding in RCTs has been associated with more exaggerated estimated intervention effects, particularly for subjective outcomes [16–18].

Ensuring the "quality of evidence" by all different agents (researchers, health personnel, participants, policymakers, consumers, institutions, funders, governments, and so forth) at different stages of development involves a complex adaptive systems thinking approach. The development, implementation, monitoring, and evaluation of several regulations, norms, policies, and standards at the national, regional, or global level and the creation of varied institution governing health research among many others factors implies "a dynamic network of agents acting in parallel, constantly reacting to what the other agents are doing, which in turn influences behavior and the network as a whole" [19]. Global declarations, reports, and initiatives have been developed and implemented in the last decades to ensure the integrity of the scientific process and reduce the risk of making incorrect conclusions about interventions effects; this includes the Declaration of Helsinki and its subsequent updates [20], the Belmont Report [21], the guidelines for good clinical practice [22–24], the World Association of Medical Editors [25], the CONSORT statement [10–12], the prospective clinical trial registration initiative [26–29], the reporting of research results [30]; the Cochrane Collaboration standards for SRs [7], and the GRADE working group approach for guidelines [4]. However, the impacts of those initiatives at different levels are not obviously related, and the collective behaviors of the "research system" and its interaction in each environment over time are difficult to establish.

While planning this study, we anticipated the occurrence of a significant increase in the rate of RCTs having low RoB and a decrease in both unclear and low categories over time. A key obstacle in the assessment of the RoB is the

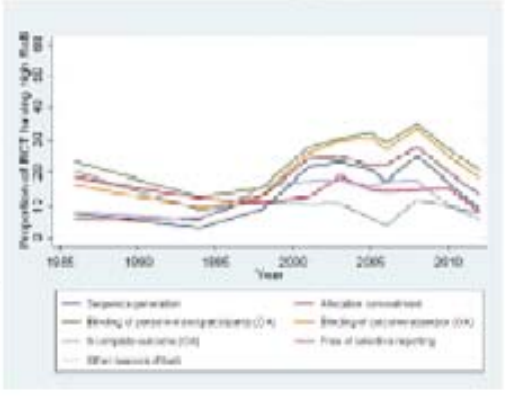

Fig. 2. High risk of bias domain rates in the included Cochrane reviews per year. RCT, randomized controlled trial.

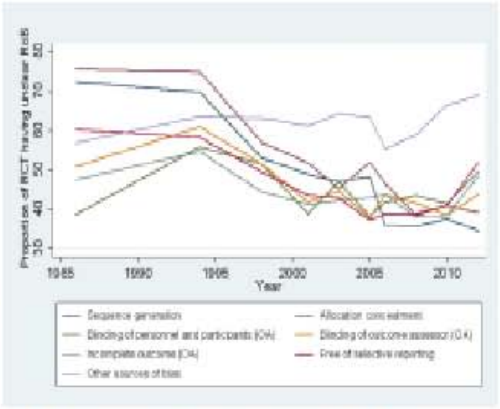

Fig. 3. Unclear risk of bias domain rates in the included Cochrane reviews per year. RCT, randomized controlled trial.

lack of available information about the design, conduct, and analysis of the study and the fact that reports do not necessarily reflect the way the trial was conducted. In a SR of RCT for which both the protocol and the publication were available, Mhaskar et al. found that poor quality of reporting did not reflect the actual high methodological quality of RCTs [31]. Cochrane reviewers probably selected to judge as "unclear RoB" studies with missing or poorly reported information. From our point of view, there are various possible explanations for the decrease on the level of uncertainty about the RoB. Initiatives such as The CONSORT statement have improved the quality of reporting in the last decade, and this finding could be directly linked to this improvement [13,14]; the adequate reporting of RCTs facilitates the interpretation of the design and results of the study. In addition, the number of published RCTs, as well as the number of journals publishing such studies worldwide, importantly increased in the last decade. It could be argued that the homogenization of CONSORT standards worldwide in the last decade as well as the announcement of the International Committee of Medical Journal Editors in 2004 that all trials should be registered in a prospective database (accompanied by the development of international standards for registration of clinical trials) [25–28] could have contributed to the increased rate in the low RoB and a decrease in both the unclear and high RoB assessment from 2008. It is also interesting to note the visual "homogeneity" of the high RoB over time between domains (Fig. 2), which contrasts with the visualized heterogeneity of RCTs judged as having low RoB (Fig. 1).

4.2. Strengths and limitations of study

Our study has several limitations. First, our sample is not a random sample of RCTs. We relied on a sample from a cohort of SRs published in 2012 in the Cochrane Library. Therefore, our results might not be representative of the real RoB of RCTs over time. However, we think that this is unlikely given the number of SRs included and the breadth of topics covered. Second, we relied on the RoB results reported in the SRs rather than performing our own evaluation. Although the RoB tool has been widely used in recent years, some studies have found low reliability of the instrument between individual reviewers and across consensus assessments of reviewer pairs [14,15,32]. In a cohort of cancer RCTs, Vale et al. found that assessing RoB from the publication alone could be unreliable,

Table 3. Logistic regression models for low risk of bias

Low risk of bias (domain)	Sequence generation, OR (95% CI)	Allocation concealment, OR (95% CI)	Blinding participants, personnel (objective outcomes), OR (95% CI)	Blinding outcome assessors (objective outcomes), OR (95% CI)	Incomplete outcome data reporting (objective outcomes), OR (95% CI)	Free of selective reporting, OR (95% CI)	Other sources of bias, OR (95% CI)
Year							
≤1989	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1990–1999	1.35 (.76, 2.37)	1.39 (.75, .58)	1.10 (.64, 1.91)	1.05 (.62, 1.77)	2.14 (1.28, 3.69)	2.45 (1.41, 4.25)	.78 (.44, 1.38)
2000–2005	1.50 (.87, 2.60)	1.49 (.82, .72)	1.02 (.55, 1.75)	.67 (.39, 1.13)	2.37 (1.43, 3.92)	3.03 (1.76, 5.23)	.80 (.46, 1.40)
2006–2012	3.96 (2.28, 6.86)	3.56 (1.96, .48)	1.44 (.82, 2.52)	1.12 (.66, 1.90)	1.89 (1.13, 3.15)	4.14 (2.35, 7.29)	1.36 (.77, 2.39)
Sample size							
≤50	1.00	1.00	1.00	1.00	1.00	1.00	1.00
51–100	1.13 (.71, 1.79)	1.63 (.98, 2.70)	1.34 (.85, 2.09)	1.23 (.79, 1.92)	.96 (.62, 1.49)	.85 (.55, 1.32)	.62 (.39, .99)
101–200	1.59 (.99, 2.55)	2.26 (1.35, 3.79)	.91 (.56, 1.48)	1.10 (.68, 1.76)	.76 (.48, 1.19)	.88 (.55, 1.39)	.62 (.38, 1.02)
>200	1.36 (.88, 2.09)	1.95 (1.20, 3.14)	.63 (.40, 1.00)	.92 (.59, 1.43)	1.36 (.90, 2.06)	.63 (.41, .96)	.34 (.21, .55)
Intervention							
Other interventions	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Drugs	.56 (.40, .77)	1.20 (.84, 1.70)	5.13 (3.47, 7.57)	3.18 (2.22, 4.55)	3.10 (2.23, 4.29)	3.16 (2.25, 4.43)	1.69 (1.15, 2.49)
Country level							
OECD	1.00	1.00	1.00	1.00	1.00	1.00	1.00
High income	1.18 (.83, 1.68)	.59 (.41, .85)	.83 (.57, 1.20)	1.09 (.76, 1.57)	.83 (.59, 1.17)	.72 (.51, 1.01)	.58 (.40, .86)
Other	.89 (.55, 1.43)	.40 (.24, .67)	.57 (.35, .92)	.95 (.59, 1.52)	.91 (.58, 1.44)	.46 (.29, .73)	.91 (.56, 1.48)

Abbreviations: CI, confidence interval; OECD, Organization for Economic Cooperation and Development; OR, odds ratio.

particularly for those RCT assessed as unclear risk [15]. Cochrane review groups usually require that the composition of an SR authoring team include a coauthor who has experience of Cochrane methodology or statistical analyses. Judgments on the RoB assessment are usually made independently by at least two reviewers with discrepancies frequently solved by consensus or by a third reviewer. In this regard, we included recently published Cochrane reviews as there has been a learning curve process for reviewers and editors for using the RoB tool. Finally a proportion of Cochrane reviews had missing data for some trial characteristics (ie, country where it was conducted) or for particular RoB domains. We also included a large number of RCTs from 97 SRs having a broad range of topics.

5. Conclusion

RCTs have improved reporting during the last decades decreasing the uncertainty for the RoB assessment. Consequently, this has likely been the cause of an increase in the proportion of RCTs judged to be at low and high RoB. RCTs published after 2008 were judged as having the highest rates of low RoB accompanied by a decrease of the rates of both high and unclear RoB categories for allocation concealment and sequence generation domains. Further studies should confirm that these findings are encouraging as they could reflect more rigorous scientific processes. A standard conclusion of this study could be that there *is room for improvement in the design and reporting of RCTs*. However, the control of bias is the raison d'être for RCTs because of its potential to reduce bias. Therefore, it is an ethical imperative to improve the quality of the planning, conduction, and reporting of research to reduce the vulnerability of RCTs to many types of bias.

Acknowledgment

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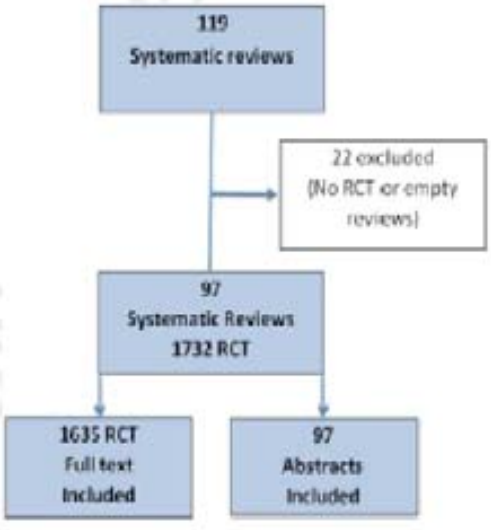
Author contributions: L.R. and E.C. had the original idea and all authors conceived and designed the study. E.C., S.A., and L.R. extracted the relevant data. S.M., E.C., and L.R. performed the statistical analyses, and all authors interpreted the data. L.R. and E.C. wrote the manuscript, and all authors revised it critically for content and approved the final version.

Appendix A.

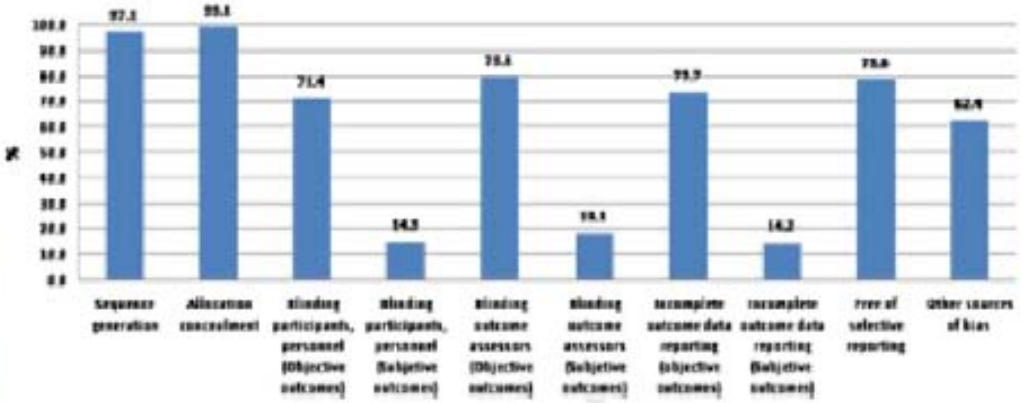
Flowchart



RCT, randomized controlled trial.

Appendix B.

Proportion of informed risk of bias domains in Cochrane reviews, n = 1,732 RCTS



Appendix C.

Tables for unclear risk of bias assessment

Table 1. Rate of randomized controlled trials having unclear risk of bias over time according to type of interventions

Domain or year period	Sequence generation, % (n)	Allocation concealment, % (n)	Blinding participants, personnel (objective outcomes), % (n)	Blinding outcome assessors (objective outcomes), % (n)	Incomplete outcome data reporting (objective outcomes), % (n)
Drugs					
<1989	73.10 (125)	77.14 (135)	27.40 (40)	45.45 (70)	34.48 (50)
1990–1999	56.30 (134)	59.58 (146)	17.58 (32)	30.93 (60)	25.81 (48)
2000–2005	41.64 (137)	40.24 (134)	17.27 (48)	21.31 (62)	18.41 (51)
2006–2012	39.19 (136)	39.77 (138)	16.78 (48)	18.67 (56)	17.38 (49)
Total	49.03 (532)	50.23 (553)	18.83 (168)	26.41 (248)	22.25 (198)
*P*value					
Other interventions					
<1989	65.52 (38)	70.69 (41)	20.59 (7)	47.83 (22)	38.64 (17)
1990–1999	62.22 (84)	72.66 (101)	51.32 (39)	55.21 (53)	37.50 (33)
2000–2005	53.68 (73)	65.97 (95)	26.39 (19)	40.63 (39)	26.92 (21)
2006–2012	27.71 (69)	39.61 (101)	25.85 (38)	34.83 (62)	18.63 (30)
Total	45.67 (264)	56.71 (338)	31.31 (103)	42.31 (176)	27.22 (101)
*P*value					

Other interventions include devices, procedures, vaccines, educational and behavior, mixed, and so forth.

Table 2. Rate of randomized controlled trials having unclear risk of bias over time according to country income level*

Year period or domain	<1989	1990–1999	2000–2005	2006–2012	Total
Organization for Economic Cooperation and Development countries					
Sequence generation, % (n)	70.21 (33)	60.66 (37)	59.38 (38)	27.71 (23)	51.37 (131)
Allocation concealment, % (n)	64.00 (32)	59.38 (38)	56.72 (38)	31.33 (26)	50.76 (134)
Blinding participants, personnel (objective outcomes), % (n)	22.73 (10)	25.49 (13)	13.64 (6)	30.77 (16)	23.56 (45)
Blinding outcome assessors (objective outcomes), % (n)	40.43 (19)	42.59 (23)	23.64 (13)	32.81 (21)	34.55 (76)
Incomplete outcome data reporting (objective outcomes), % (n)	23.40 (11)	22.64 (12)	2.22 (1)	9.09 (5)	14.50 (29)
High income countries					
Sequence generation, % (n)	58.70 (27)	53.13 (51)	33.83 (45)	27.42 (27)	39.35 (157)
Allocation concealment, % (n)	74.47 (35)	65.35 (66)	43.61 (58)	38.21 (47)	50.99 (206)
Blinding participants, personnel (objective outcomes), % (n)	17.86 (5)	24.59 (15)	17.53 (17)	24.00 (18)	21.07 (55)
Blinding outcome assessors (objective outcomes), % (n)	39.02 (16)	39.11 (23)	19.47 (22)	29.00 (29)	27.03 (90)
Incomplete outcome data reporting (objective outcomes), % (n)	48.84 (21)	27.16 (22)	17.27 (19)	18.48 (17)	24.23 (79)
Medium and low income countries					
Sequence generation, % (n)	66.67 (4)	62.07 (18)	45.00 (18)	44.64 (25)	49.62 (65)
Allocation concealment, % (n)	83.33 (5)	60.00 (18)	58.54 (24)	52.63 (30)	57.46 (77)
Blinding participants, personnel (objective outcomes), % (n)	20.00 (1)	36.84 (7)	31.58 (12)	39.58 (19)	35.45 (39)
Blinding outcome assessors (objective outcomes), % (n)	33.33 (2)	28.57 (8)	40.00 (16)	39.22 (20)	36.80 (46)
Incomplete outcome data reporting (objective outcomes), % (n)	—	25.00 (7)	30.00 (12)	30.77 (16)	27.78 (35)

* Data from low and middle income countries were analyzed together because of the small number of trials. Data were not available from Cochrane review tables for 878 trials.

Table 3. Rate of randomized controlled trials having unclear risk of bias over time according to sample size

Year period or domain	<1989	1990–1999	2000–2005	2006–2012	Total
≤50					
Sequence generation, % (n)	76.24 (77)	71.76 (94)	47.76 (64)	31.03 (45)	54.79 (280)
Allocation concealment, % (n)	79.21 (80)	74.24 (98)	50.37 (68)	47.59 (69)	61.40 (315)
Blinding participants, personnel (objective outcomes), % (n)	27.59 (24)	29.47 (28)	16.22 (18)	19.66 (23)	22.68 (93)
Blinding outcome assessors (objective outcomes), % (n)	44.32 (39)	46.00 (46)	21.67 (926)	24.79 (30)	32.87 (141)
Incomplete outcome data reporting (objective outcomes), % (n)	37.04 (30)	36.67 (33)	19.44 (21)	24.56 (28)	28.50 (112)
51–100					
Sequence generation, % (n)	75.86 (44)	57.29 (55)	45.10 (46)	39.52 (49)	51.05 (194)
Allocation concealment, % (n)	79.66 (47)	68.35 (66)	48.15 (52)	39.20 (49)	54.45 (214)
Blinding participants, personnel (objective outcomes), % (n)	21.74 (10)	28.95 (22)	19.51 (16)	19.80 (20)	22.30 (68)
Blinding outcome assessors (objective outcomes), % (n)	48.00 (24)	37.04 (30)	25.88 (22)	20.59 (21)	30.50 (97)
Incomplete outcome data reporting (objective outcomes), % (n)	25.53 (12)	28.75 (23)	29.87 (23)	18.18 (18)	25.08 (975)
101–200					
Sequence generation, % (n)	64.71 (22)	51.67 (31)	36.14 (30)	37.00 (37)	43.32 (120)
Allocation concealment, % (n)	63.89 (23)	60.61 (40)	44.32 (39)	44.34 (47)	50.34 (149)
Blinding participants, personnel (objective outcomes), % (n)	32.00 (8)	17.14 (6)	16.92 (11)	21.92 (16)	20.71 (41)
Blinding outcome assessors (objective outcomes), % (n)	46.43 (13)	27.50 (11)	25.68 (19)	27.16 (22)	29.15 (65)
Incomplete outcome data reporting (objective outcomes), % (n)	32.14 (9)	21.05 (8)	19.12 (13)	21.05 (16)	21.90 (46)
>200					
Sequence generation, % (n)	53.13 (17)	39.73 (29)	42.74 (53)	30.89 (59)	37.62 (158)
Allocation concealment, % (n)	66.67 (22)	47.95 (35)	40.32 (50)	31.58 (60)	39.76 (167)
Blinding participants, personnel (objective outcomes), % (n)	20.00 (4)	25.53 (12)	16.05 (13)	15.45 (19)	17.71 (48)
Blinding outcome assessors (objective outcomes), % (n)	41.94 (13)	36.21 (21)	30.00 (27)	28.67 (41)	31.68 (102)
Incomplete outcome data reporting (objective outcomes), % (n)	46.67 (14)	23.33 (14)	13.19 (12)	11.94 (16)	17.78 (56)

References

[1] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[2] Higgins JPT, Green S, editors. Cochrane handbook for systematic [illegible] of interventions version 5.0.1. The Cochrane Collaboration; 2[illegible] Available at: www.cochrane-handbook.org. Accessed December 2012.

[3] Institute of Medicine, In: Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, editors. Clinical practice guidelines we can trust. Washington, DC: National Academies Press; 2011:2. Available at: http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust/Standards.aspx.

[4] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.

[5] Crocetti MT, Amin DD, Scherer R. Assessment of risk of bias among pediatric randomized controlled trials. Pediatrics 2010;126(2):298−305.

[6] Reveiz L, Sangalang S, Glujovsky D, Pinzon CE, Asenjo Lobos C, Cortes M, et al. Characteristics of randomized trials published in Latin America and the Caribbean according to funding source. PLoS One 2013;8(2):e56410.

[7] Savović J, Jones H, Altman D, Harris R, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. Health Technol Assess 2012;16:1−82.

[8] Boutron I, Ravaud P. Classification systems to improve assessment of risk of bias. J Clin Epidemiol 2012;65:236−8.

[9] Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA 1996;276:637−9.

[10] Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663−94.

[11] Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.

[12] Turner L, Shamseer L, Altman DG, Schulz KF, Moher D. Does use of the CONSORT statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. Syst Rev 2012;1(1):60.

[13] Dechartres A, Charles P, Hopewell S, Ravaud P, Altman DG. Reviews assessing the quality or the reporting of randomized controlled trials are increasing over time but raised questions about how quality is assessed. J Clin Epidemiol 2011;64:136−44.

[14] Hróbjartsson A, Boutron I, Turner L, Altman DG, Moher D. Assessing risk of bias in randomised clinical trials included in Cochrane reviews: the why is easy, the how is a challenge. [editorial]. Cochrane Database Syst Rev 2013;ED000058. http://dx.doi.org/10.1002/14651858.ED000058.

[15] Vale CL, Tierney JF, Burdett S. Can trial quality be reliably assessed from published reports of cancer trials: evaluation of risk of bias assessments in systematic reviews. BMJ 2013;346:f1798.

[16] Pildal J, Hróbjartsson A, Jørgensen KJ, Hilden J, Altman DG, Gøtzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol [illegible]36:847−57. Q10

[17] [illegible] L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 2008;336:601−5.

[18] Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. Agency for healthcare research and quality methods guide for comparative effectiveness reviews. AHRQ Publication, 2012 No. 12-EHC047-EF. Available at www.effectivehealthcare.ahrq.gov/.

[19] The Evidence Centre on behalf of the Health Foundation. Research [illegible] complex adaptive systems. 2010. Available at http://www.health.org.uk/public/cms/75/76/313/2590/Complex%20adaptive%20systems.pdf?realName=jlaj8CP.pdf. Accessed June, 2014.

[20] World Medical Association. WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. Available at http://www.wma.net/en/30publications/10policies/b3/. Accessed June, 2014.

[21] Belmont Report. 1979. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. Available at hhs.gov/ohrp/humansubjects/guidance/belmont.html. Accessed June, 2014.

[22] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Available at http://www.ich.org/. Accessed June, 2014.

[23] European Medicine Agency. Available at http://www.ema.europa.eu/ema/. Accessed June, 2014.

[24] U.S. Food and Drug Administration. Science and Research. Available at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm. Accessed June, 2014.

[25] World Association of Medical Editors. Available at http://www.wame.org/. Accessed June, 2014.

[26] De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med 2004;351:1250−1.

[27] De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. N Engl J Med 2005;352:2436−8.

[28] World Health Organization. The Mexico Statement on Health Research. Knowledge for better health: strengthening health systems. Geneva, Switzerland: WHO; 2011.

[29] World Health Organization. The World Health Organization announces new standards for registration of all human medical research. Geneva, Switzerland: WHO; 2011.

[30] Krleža-Jerić K, Chan AW, Dickersin K, Sim I, Grimshaw J, Gluud C, Ottawa Group. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa Statement (part 1). BMJ 2005;330:956−8.

[31] Mhaskar R, Djulbegovic B, Magazin A, Soares HP, Kumar A. Published methodological quality of randomized controlled trials does not reflect the actual quality assessed in protocols. J Clin Epidemiol 2012;65:602−9. http://dx.doi.org/10.1016/j.jclinepi.2011.10.016.

[32] Hartling L, Hamm MP, Milne A, Vandermeer B, Santaguida PL, Ansari M, et al. Testing the risk of bias tool showed low reliability between individual reviewers and across consensus assessments of reviewer pairs. J Clin Epidemiol 2013;66:973−81. pii:S0895-4356(12)00217-X. Q11

7. DISCUSIÓN

El uso de la evidencia científica en las decisiones sanitarias es un proceso cada vez más necesario y fundamental en países de bajos ingresos, no solo para contribuir a resolver los problemas de salud sino también las desigualdades. Para poder llevar a cabo aquel objetivo se necesitan algunos requisitos, entre ellos la producción de más evidencias y poner en marcha mecanismos para su uso. La utilización de pruebas científicas en la toma de decisiones implica trabajar en distintas modalidades de plataformas de traducción de conocimiento (*Knowledge translation* en la lengua inglesa) con el fin que decisores, investigadores y otros interesados lleven a cabo esta tarea y puedan mejorar las prácticas y políticas de salud.

A pesar de que el rol de la investigación en mejorar los resultados en salud ha sido bien establecido, un punto clave en el necesario proceso de traducir los resultados de las investigaciones en políticas y prácticas es determinar cuáles son las lagunas de conocimiento y cómo priorizarlas para producir las investigaciones relevantes. La necesidad de establecer un orden de importancia de potenciales investigaciones relevantes se fundamenta en que los recursos económicos y humanos para investigación son siempre escasos. Por último, no solo se necesita producir las investigaciones necesarias sino que además, éstas sean realizadas con los adecuados estándares de calidad.

Esta tesis está orientada a los procesos de producción de evidencias en el campo de salud materna. La mejora de la salud materna está incluida como meta del ODM 5 y la preocupación global es no lograrla. Decidimos tomar la salud materna para este proceso de identificación de lagunas de conocimientos porque es un indicador de

desigualdades existentes y además, es un trazador del respeto (o no) de los derechos humanos y de la propia salud como derecho [13, [66]].

7.1 El mapeo de lagunas de investigación

Es bien conocido que la morbilidad y mortalidad maternas son prevenibles y comprenden una variedad de determinantes vinculados a la salud, al desarrollo, a los derechos humanos y a las libertades fundamentales [33,[67]].

Intervenir en salud materna y evitar la morbi-mortalidad específica implica retos importantes para los investigadores. Las cuestiones relativas a la salud materna no siempre son fáciles de responder y los resultados de las investigaciones no se pueden transferir fácilmente a los diferentes escenarios. Esto se debe a que las intervenciones de salud materna, ya sean clínicas o no clínicas, dependen en gran medida del contexto. No es suficiente entender el problema, la población y el resultado. Otros factores, tales como las creencias de la población, los servicios de salud, los sistemas y las políticas de salud también son determinantes importantes de la salud materna. Los esfuerzos de producir investigación en este campo a veces se caracterizan por la ambigüedad y la creciente complejidad, por lo que se hace necesario un enfoque bien organizado para abordar eficazmente las lagunas de conocimiento. Por esta razón el mapeo sistemático por pares, la clasificación de las preguntas de investigación en

[66] TheMillennium DevelopmentGoals Report (2011).UnitedNations New York. Disponible en: http://www.undp.org/content/dam/undp/library/MDG/english/MDG_Report_2011_EN.pdf. Con acceso el 4 de septiembre de 2013.

[67] Khan K, Wojdyla D, Say L, G€ulmezoglu A, Van Look P. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066e74

dominios fue una elección lógica para servir como la base instrumental a este proyecto.

Muchos países han establecido que la salud materna y la disminución de la mortalidad materna son prioridades en sus agendas nacionales de investigación sanitaria [68,69]. Sin embargo, la producción insuficiente de la investigación relevante en zonas de bajos recursos [2,3,18] y la pobre transferibilidad de las evidencias disponibles de países altos ingresos serían factores que contribuyen a las lagunas de investigación existentes [70,71].

El mapeo de lagunas de investigación en salud materna se basó en tres supuestos. El primero de ellos es que los mecanismos de cómo las intervenciones trabajan para mejorar la salud materna no se entienden completamente, por lo tanto no es tan simple juzgar si se están desarrollando investigaciones suficientes o si es más necesaria en otros contextos. También asumimos que los resultados de investigaciones no se pueden implementar inmediatamente, además de ser muchas veces subestimados

68 Doyle J, Waters E, Yach D, McQueen D, De Francisco A, Stewart T, Reddy P, Gulmezoglu AM, Galea G, Portela A. Global priority setting for Cochrane systematic reviews of health promotion and public health research. J Epidemiol Community Health. 2005 Mar;59(3):193-7.

69 Sheppard AJ, Hetherington R. A decade of research in Inuit children, youth, and maternal health in Canada: areas of concentrations and scarcities. Int J Circumpolar Health. 2012 Jul 26;71:18383.

70 Piaggio G, Ba'aqeel H, Bergsjø P, Carroli G, Farnot U, Lumbiganon P, Pinol A, Villar J. The practice of antenatal care: comparing four study sites in different parts of the world participating in the WHO Antenatal Care Randomised Controlled Trial. Paediatr Perinat Epidemiol. 1998 Oct;12 Suppl 2:116-41.

71 Burchett HE, Dobrow MJ, Lavis JN, Mayhew SH. The applicability and transferability of public health research from one setting to another: a survey of maternal health researchers. Glob Health Promot. 2013 Mar;20(1):16-24.

por parte de los decisores, y que se necesita más investigación para comprender y abordar mejor las causas de muerte materna. Numerosas lagunas de conocimientos relacionados con la morbi-mortalidad materna son todavía persistentes y abrumadoras. Nosotros hemos mapeado más de 300 preguntas de investigación que nos están marcando las lagunas mencionadas.

En segundo lugar asumimos que estos vacíos en el conocimiento pueden ser mejorados a través de una mayor producción y utilización de evidencias tanto para la práctica clínica como para las políticas.

Por último, se supuso que una manera de promover la política y la práctica basada en evidencias es '"mapeando" (identificando lagunas y sus implicaciones) y priorizando las necesidades de investigación como una forma de mejorar la eficacia y reducir las desigualdades de salud en entornos de escasos recursos.

Para el proceso de mapeo de lagunas y la transformación de ellas en preguntas de investigación hemos usado las revisiones sistemáticas de la biblioteca Cochrane y específicamente el campo “Implicaciones para la investigación”. Según nuestro conocimiento, es el primer estudio que realiza este proceso en salud materna. Las ventajas de esta metodología fue la disponibilidad del insumo (revisiones Cochrane) estandarizado y de calidad. El proceso de construcción de preguntas en formato PICO [población (P), intervención (I), comparación (C) y resultado (O de *Outcome*)] [23] fue un proceso iterativo y laborioso pero finalmente logramos desagregar hasta la laguna más impensable y visualizar por primera vez al propio sistema de salud y sus políticas como determinantes de la salud materna y de la mortalidad.

Esta metodología sencilla es posible de usar y las preguntas están disponibles no solo para seguir en el tiempo la cobertura de estas lagunas sino para actualizarlas y priorizarlas. De hecho, en el anexo 13.3 se encuentran 2 protocolos de revisiones Cochrane como contribuciones futuras de la autora desde este trabajo de tesis, a las lagunas de investigación que existen en el campo de salud materna.

7.2 Sobre el proceso de priorización

La primera etapa de la ejecución de esta tesis nos permitió confeccionar un mapa de 319 preguntas que sirvieran de insumo para el proceso siguiente de priorización y para mostrar lo que sospechábamos al inicio del proyecto, esto es, que existen todavía muchas lagunas de conocimiento en el campo de salud materna [70]. El proceso de priorización de estas preguntas de investigación fue el paso siguiente con el fin de visibilizar e informar la agenda de investigación de la salud materna a nivel mundial.

Aunque ejercicios previos de priorización han buscado lagunas de investigación en el campo de mortalidad materna, el enfoque descrito en nuestro estudio es a nuestro entender y como ya fue expresado, uno de los primeros intentos de utilizar un número importante de revisiones Cochrane para identificar preguntas de investigación y obtener la opinión de expertos de múltiples grupos de interés [[72]]. Saldanha y Col., han publicado recientemente un estudio piloto para identificar las necesidades de investigación usando una revisión sistemática para la diabetes gestacional [24] en un proceso similar al nuestro. Sin embargo, nuestro ejercicio incluyó un mayor número de

[72] Sridhar D (2012) Who Sets the Global Health Research Agenda? The Challenge of Multi-Bi Financing. PLoS Med 9(9): e1001312.

revisiones sistemáticas y se centró en dar prioridad a las preguntas de investigación a nivel mundial abarcando un espectro muy amplio para salud materna.

Aunque existe un consenso creciente de que los sistemas de salud en toda su amplitud son la clave para lograr mejores resultados de salud, hay mucho menos acuerdo sobre cómo funcionan [[73]]. Se encontró que las lagunas sobre las intervenciones relacionadas con los sistemas y las políticas de salud seguían siendo la máxima prioridad en las dos rondas en nuestro ejercicio de priorización. Esto también podría reflejar que los expertos han incorporado este tema como un factor determinante para la salud materna y debe ser explorado y abordado.

Debemos comprender que la priorización de investigaciones para la salud son procesos dinámicos que están influidos por múltiples factores. Nuestros hallazgos mostraron la influencia del contexto, muy consistente con los hallazgos en la literatura [40,41]. Por ejemplo, nuestro proceso de priorización dependió tanto de factores externos como por ejemplo, el sexo de los participantes, el rol y país de residencia, así como también de factores internos como la duración de la encuesta, la legibilidad de las preguntas de la misma, y en algunos casos las dificultades técnicas relacionados al formato electrónico de la encuesta.

La tasa de respuesta fue otro tema fundamental en nuestro ejercicio. Tuvimos un promedio de 47 % y el 17 % de las respuestas en la primera y segunda ronda, respectivamente. Los participantes de la primera ronda fueron los más entendidos en el campo de la salud materna (pre-definidas como aquellas con mayor número de

[73] Travis P, Bennett S, Haines A, Pang T, Bhutta Z, et al. (2004) Overcoming health-systems constraints to achieve the Millennium Development Goals. Lancet. 364(9437):900-6.

publicaciones en un área específica). Ellos fueron los primeros filtros en este esfuerzo para identificar las cuestiones más relevantes. La menor tasa de respuesta en la segunda ronda podría explicarse porque incluía a todos los miembros de los cuatro grupos de la Colaboración Cochrane (CC) ya mencionados en el apartado de metodologia.

Tuvimos más respuestas a las preguntas relacionadas con hemorragia postparto, muy probablemente debido a que es la principal causa de muerte materna en todo el mundo. Otras cuestiones prioritarias de investigación que se consideren pertinentes por los participantes fueron los trastornos hipertensivos, el aborto y el embarazo no planeado, tal vez porque el aborto es la principal causa de muerte materna en muchos países y la maternidad adolescente es planteada como un problema de salud pública [74].

Los participantes consideraron que las intervenciones relacionadas con los sistemas y políticas de salud son determinantes importantes de la salud materna, y también el cómo convertirlas en preguntas específicas que requieren una respuesta urgente en relación a alcanzar las metas del ODM 5. Todos estos resultados están en línea con el creciente consenso de tener en cuenta a los determinantes de la salud relacionados con los sistemas, con programas y con las políticas de salud en el campo de la salud materna e infantil [23,25-28,[75],[76]].

[74] The Millennium Development Goals Report 2012. United Nations New York (2012). Disponible en: http://www.un.org/en/development/desa/publications/mdg-report-2012.html. Con acceso el 2 de mayo de 2012.

[75] USAID's Global Health Strategic Framework. Better health for development. Executive summary. U.S. Agency for International Development.(2012) FY 2012–FY

No encontramos ninguna explicación plausible de por qué casi el doble de mujeres más que hombres respondieron la encuesta, ni por qué las respuestas de los hombres fueron significativamente más completas que las de las mujeres (65 % versus 51 %). Se necesita más investigación para comprender mejor por qué existen estas diferencias. Los estudios futuros deben explorar el establecimiento de prioridades desde la perspectiva de los diferentes grupos de personas, en particular los responsables de formular políticas, los políticos, economistas, administradores de salud, los proveedores de salud y los pacientes.

7.3 La calidad de las investigaciones en el tiempo

Originalmente habíamos pensado en analizar los ECAs contenidos en las revisiones Cochrane relacionadas con salud materna. Durante el proceso de mapeo y priorización anticipamos que no iba a ser factible conseguir un número suficiente de estudios para mostrar las diferencias de riesgo de sesgo en el tiempo (o la evolución temporal de la calidad de los mismos), por lo que decidimos tomar una muestra general de ECAs de la base de las revisiones Cochrane asumiendo que de manera indirecta podrían mostrarnos una tendencia general de calidad.

En nuestros resultados se observó un aumento significativo de estudios juzgados tanto como de bajo como de alto riesgo de sesgo para varios dominios en el tiempo. A su vez, el alto riesgo de sesgo para algunos dominios disminuyó en los estudios más

2016. Disponible en: http://transition.usaid.gov/our_work/global_health/home/Publications/docs/gh_framework_es2012.pdf. Con acceso el 2 de mayo de 2012.

[76] Owlia P, Eftekhari MB, Forouzan AS, Bahreini F, Farahani M, Ghanei M. Health research priority setting in Iran: Introduction to a bottom up approach. J Res Med Sci. 2011 May;16(5):691-8.

grandes y en aquellos que incluían intervenciones con drogas. Se encontró además una tasa de disminución significativa de riesgo de sesgo incierto o poco claro en el tiempo que fue relevante cuando se incluyeron tipos de intervenciones, tamaño de muestra y el nivel de ingreso del país. Estos resultados son consistentes con investigaciones previas en relación con el alto porcentaje de ECA con alto riesgo y también con riesgo de sesgo incierto [77, 78, 79].

Además, un número de estudios también informaron diferencias significativas en la calidad de los ensayos o en el riesgo de sesgo de los dominios de acuerdo con el tamaño de la muestra y el tipo de intervenciones, entre otras características. Por ejemplo, la falta de cegamiento en los ECAs se ha asociado con estimación de efectos más exagerados y en particular para resultados subjetivos [80,81,82].

77 Sinha YK, Craig JC, Sureshkumar P, Hayen A, Brien JA. Risk of bias in randomized trials of pharmacological interventions in children and adults. J Pediatr. 2014 Aug;165(2):367-371.e1.

78 World Health Organization. The World Health Organization announces new standards for registration of all human medical research. Geneva: WHO; c2011.

79 Vale CL, Tierney JF, Burdett S. Can trial quality be reliably assessed from published reports of cancer trials: evaluation of risk of bias assessments in systematic reviews. BMJ. 2013 Apr 22;346:f1798

80 Pildal J, Hróbjartsson A, Jørgensen KJ, et al. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol 2007;36:847–57.

81 Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: metaepidemiological study. BMJ 2008;336:601–5.

82 Viswanathan M, Berkman ND, Dryden DM, Hartling L. Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Aug.

En las ultimas décadas se han ido desarrollado e implementado reportes globales, informes e iniciativas para garantizar la integridad del proceso científico y reducir el riesgo de llegar a conclusiones erróneas sobre los efectos de las intervenciones, como son por ejemplo, las recomendaciones para la buena práctica clínica [[83], [84], [85]], la declaración CONSORT [60], la iniciativa de registro de ensayos clínicos prospectivos [[86],[87]], los reportes de resultados de la investigación [[88]], las normas de la CC para las revisiones sistemáticas [29] y los criterios del marco metodológico GRADE [[89]].

Sin embargo, los impactos de estas iniciativas en diferentes niveles no están estrechamente relacionados y los comportamientos colectivos de los "sistemas de

[83] European Medicine Agency. Disponible en: http://www.ema.europa.eu/ema/. Con acceso el 3 de junio de 2013.

[84] U.S. Food and Drug Administration. Science and Research. Disponible en: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm. Con acceso el 3 de Junio de 2013.

[85] Turner L, Shamseer L, Altman DG, Schulz KF, Moher D. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. Syst Rev. 2012;1(1):60.

[86] De Angelis C, Drazen JM, Frizelle FA, Haud C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351:1250-1.

[87] Stegemann H. [The International Clinical Trials Registry Platform - ICTRP]. Arch Latinoam Nutr. 2007 Dec;57(4):311-2.

[88] Krleža-Jeric K, Chan AW, Dickersin K, Sim I, Grimshaw J, Gluud C for the Ottawa Group. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa Statement (part 1). BMJ. 2005;330:956-8.

[89] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.

investigación" y su interacción en cada ambiente a través del tiempo, son difíciles de establecer.

Durante la planificación de este estudio, esperábamos encontrar un aumento significativo en la tasa de ECAs con bajo riesgo de sesgo y una disminución en las categorías tanto para el alto sesgo como para el RdS poco claro o incierto. Uno de los obstáculos clave para evaluar el riesgo de sesgo es la falta de información disponible sobre el diseño, realización y análisis del estudio y el hecho de que las publicaciones no reflejan necesariamente la forma en que fue desarrollado el ECA. Probablemente, los revisores Cochrane tomaran la decisión en estos casos, de evaluar como riesgo de sesgo poco claro. Por otra parte, la disminución en el tiempo del riesgo de sesgo incierto o poco claro como fueron los hallazgos de esta tesis, podría estar relacionada con la mejora del reporte propuesta por el CONSORT [[90], 61,[91]]. El uso de la herramienta permite facilitar la interpretación del diseño del estudio y los resultados. Otro factor que podría haber contribuido a la mejora de RdS en general como informamos en nuestros resultados, es que desde 2008 el Comité Internacional de Editores de Revistas Médicas (ICMJE) en 2004 determinó que todos los ECAs deben registrarse [[92],[93],[94]].

[90] Dechartres A, Charles P, Hopewell S, Ravaud P, Altman DG. Reviews assessing the quality or the reporting of randomized controlled trials are increasing over time but raised questions about how quality is assessed. Journal of Clinical Epidemiology 2011;64:136- 144.

[91] Turner L, Shamseer L, Altman DG, Schulz KF, Moher D. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. Syst Rev. 2012 Nov 29;1:60.

[92] World Association of Medical Editors. Disponible en: http://www.wame.org/. Con acceso el 3 de junio de 2013.

[93] Roehr B. FDA given new powers over data reporting to national clinical trials registry. BMJ. 2012 Oct 2;345:e6629.

[94] World Health Organization. The Mexico Statement on Health Research. Knowledge for better health: strengthening health systems. Geneva: WHO; c2011.

95 Rada G, Pérez D, Capurro D. Epistemonikos: a free, relational, collaborative, multilingual database of health evidence. Stud Health Technol Inform. 2013;192:486-90.

10. ANEXOS

Anexo 10.1 Resumen de métodos de priorización que fueron evaluados críticamente [18, 40, 41, 44,46-48].

Tabla 1. Metodologias de establecimiento de prioridades. (Se dejaron los nombres en ingles para evitar malas interpretaciones)

Compound Approaches

(using historical data)

* Essential National Health Research Approach (ENHRA)
* Burden of Disease
* 3D Combined Matrix Approach
* Child Health Priorities Approach

Foresighting Approaches

(using projected data)

* Visioning
* Scenario Creating
* Delphi
* Roadmaps

Tabla 2. Metodologias de ranking de prioridades

Direct Valuation

* Comparison in Pairs
* Anchored Rating Scale

Indirect Valuation

* Hanlon Method

* ENHR Method

* Incluyen procesos, no un “método”

Anexo 10.1 bis. Resumen de los tres métodos más usados para el establecimiento de prioridades de investigación.

Tomado de “Priority Setting Methodologies in Health Research: A workshop convened by WHO's Cluster on Information, Evidence and Research (IER), its Department for Research Policy and Cooperation (RPC) and the Special Programme for Research and Training in Tropical Diseases (TDR)” (2008). http://www.tropika.net/report/Chinnock20080612ReportPrioritySetting/workshop_summary_and_conclusions.pdf

Tabla 3. Resumen de los tres métodos más usados para el establecimiento de prioridades de investigación.

Resumen

Fortalezas

Debilidades

Aplicaciones y referencias

Essential National Health Research (ENHR) approach

- Defines who sets priorities and how to get participants involved, the potential functions, roles and responsibilities of various stakeholders, information and criteria for setting priorities, strategies for implementation and indicators for evaluation
- Specifies broad research avenues
- Detailed listing of priority possibilities/options
- Involvement of a broad range of stakeholders
- Significant engagement with experts

- Discussion and decisions on funding based on participants’ own views and knowledge
- Identified interventions and research questions are not compiled in a truly systematic way

Country experiences

- Philippines
- South Africa
- Brazil
- Alan B Feranil (2004) http://www.globalforumhealth.org/
- Department of Health, Directorate Research Coordination and Management (1996), South Africa
- Reinaldo Guimarães, Cuadernos de Saúde et al. Ministry of Health (2005). Brasil. ISBN 85-334-0827-3

Combined Approach Matrix (CAM)

- Systematic classification, organization and presentation of large body of information
- Incorporates many dimensions
- Recently included gender and poverty dimensions
- Specifies broad research avenues
- Identifies gaps in knowledge and future challenges
- Systematic listing of all relevant information so that decisions made by the members of committees based on all relevant and available information, rather than their own personal knowledge and judgment
- Does not, in itself, represent an algorithm for making decisions on the priorities by ranking competing investment options, or differentiating the two alternative research strategies according to their priority
- Identified interventions and research questions are not compiled in a truly systematic way
- Consensus reached by panels of experts and danger is that decisions may be driven by research interest bias of individual experts
- Diarrhoeal diseases research in India
- Pakistan's National Action Plan for noncommunicable disease: prevention, control and health promotion
- Application of the CAM to a disease: The example of schizophrenia
- Application of the CAM to a risk factor: The example of indoor air pollution
- Perinatal and neonatal care in Pakistan

Child Health and Nutrition Research Initiative (CHNRI) approach

- Principles of legitimacy and fairness
- Detailed listing of individual questions
- Individual questions scored against pre-defined criteria. Technical experts independently score each research option
- Stakeholder input is sought and used to provide relative weight of the criteria
- Systematic listing of individual research questions
- Everything that led to the final list of priorities is recorded, is repeatable, can be reviewed, can be challenged and can be revised at any time based on feedback

- Weights and thresholds may be revised to address the changes in a dynamic political, economic, social and cultural environment
- May be too specific for some purposes
- Role of non-experts limited to selection and weighting of criteria
- Consensus building is incorporated in methods (eg selection of areas of research, weights given to criteria) but not formally after the priorities are set
- National level: South Africa (Tomlinson et al., PLoS Med, 2007)
- Global level: Pneumonia, Diarrhoea, Malaria, Neonatal conditions, Undernutrition and HIV/AIDS with WHO (Rudan et al., Lancet Inf Dis, 2007) Zinc, Falls injuries (Hyder et al., Acta Paediatrica, 2007; Brown et al., Public Health Nutr, in press) Mental health (Chisholm et al., Lancet, 2007)

Anexo 10.2. Lista de las 62 preguntas priorizadas

Fuente: Chapman E, Reveiz L, Sangalang S; Manu C; Bonfill X; Muñoz S; Abalos E. Global research priorities for decreasing global maternal mortality and morbidity: an international survey. Journal of Clinical Epidemiology. Manuscript Number: JCE-13-137

1 Compared to the conventional start of hormonal contraceptives, what is the effectiveness and safety of immediate start of hormonal contraceptives in reducing unintended pregnancies?

2 What behavioral issues contribute to the failure of women of reproductive age to use emergency contraception to prevent unwanted pregnancy, even if emergency contraception is readily available?

3 What are the behavioral issues surrounding the failure to use emergency contraception when needed, even when it is readily available?

4 What is the effectiveness and cost-effectiveness of enhanced counseling, use of intensive reminders (for one's next appointment), and dosing in improving adherence and acceptability of hormonal contraceptive use, among women of reproductive age, without medical contraindications to hormonal methods of contraception?

5 What strategies are most effective in increasing adherence to different methods of contraception according to consumers?

6 What is the effectiveness and safety of immediate postpartum insertion (within ten minutes of delivery of the placenta), vs. delayed postpartum or interval insertion, of an intrauterine device (IUD) to prevent pregnancy and/or spontaneous expulsion?

7 Which interventions based in theory (such as the social cognitive theory) are most effective in preventing unwanted pregnancy in low-resource areas and in clinical settings?

8 Should antibiotics be routinely used in cases of incomplete abortion?

9 When used in combination with misoprostol for induction of a mid-trimester abortion, what is the additional value, safety, optimal dose, and timing of mifepristone?

10 What is the effectiveness and safety of misoprostol for medical treatment of early fetal death?

11 What is the optimal route of administration and optimal dose, as well as the potential side effects, of misoprostol during medical treatment of early fetal death?

12 What is the optimal dose, frequency, and route of administration of misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death?

13 What is the effectiveness and safety of various medical interventions (such as misoprostol, expectant care, and surgery) for the treatment of incomplete miscarriage for pregnant women between 13 to 24 weeks gestation?

14 What is the comparative effectiveness and safety of the use of medical treatments (by the various routes) with expectant care versus surgery in women with incomplete abortion between 13 and 24 weeks?

15 What is the most effective and safe method for preventing and/or controlling pain in conscious women having uterine interventions without general anaesthesia?

16 Compared with a policy of delayed delivery (expectant management), what is the effectiveness of a policy of early delivery by induction of labour or by caesarean section for women with severe preeclampsia in improving maternal and neonatal outcomes?

17 Compared with all three components of active management of the third stage of labor (Controlled cord traction, uterine massage of the placenta after delivery, and administration of an uterotonic soon after delivery of the baby) what is the effectiveness, cost-effectiveness, and safety of administrating various uterotonic drugs in order to reduce bleeding in the mother?

18 Compared with routine active management of the third stage of labor (Controlled cord traction, uterine massage of the placenta after delivery, and administration of an uterotonic son after delivery of the baby), is management by a single uterotonic drug effective in reducing bleeding and improving health outcomes for women after delivery?

19 What is the effectiveness and safety of sustained uterine massage after delivery of the placenta (with or without the use of uteronics) for the prevention of postpartum haemorrhage in pregnant women in the third stage of labour?

20 What are effective interventions for control of primary postpartum haemorrhage (PPH) following home deliveries, particularly in developing countries?

21 What is the optimum method of expectant management of the third stage of labor that results in the lowest rates of PPH?

22 Should a loading dose of magnesium sulphate be used for women with pre-eclampsia at primary care level before they are transferred to hospital?

23 What is the minimum effective dose of magnesium sulphate for women with pre-eclampsia?

24 What is the optimal duration of magnesium sulphate therapy for women with pre-eclampsia?

25 When is the optimal time to give magnesium sulphate to women with pre-eclampsia?

26 What is the effectiveness, safety, lowest effective dose for routine use, and optimal route of administration of misoprostol for routine third stage of labour management when conventional uterotonics are not available?

27 What is the effectiveness of partogram use in the first stage of labor on health outcomes (of women with singleton pregnancies and cephalic presentations who are in spontaneous labour at term), stratifying participants according to parity, use of services

associated with low and high perinatal mortality, and use of interventions (low vs. high intervention rates), compared to no partogram use?

28 Within the context of common medical and obstetrical practices, such as epidurals and oxytocin stimulation; is it effective and safe to give women during labor foods and fluids such as water and carbohydrate drinks compared to restricting them?

29 What are the effects of dietary advice interventions on gestational diabetes mellitus prevention in healthy pregnant women and overweight or obese pregnant women?

30 What is the effectiveness and safety of various interventions (such as administration of oral antidiabetics drugs, combined nutrition and glucose self-monitoring, and continuous glucose monitoring) in improving maternal health outcomes in pregnant women with pre-existing type 2 diabetes?

31 Compared with insulin or dietary and lifestyle control, what is the effectiveness and safety of various oral anti-diabetic agents in improving maternal health outcomes and glycaemic control parameters for women with pre-existing diabetes mellitus, impaired glucose tolerance, or previous gestational diabetes mellitus, who are pregnant or who are planning a pregnancy?

32 What are the effects of screening and subsequent management of gestational diabetes?

33 Which are the best strategies for management of gestational diabetes, including alternative management strategies?

34 What is the safety and effectiveness of exercise in preventing long-term diabetes complications for women with gestational diabetes and possibly type 2 diabetes?

35 What is the effectiveness, cost-effectiveness, and safety of alternative treatment regimens for malaria in improving maternal health outcomes for pregnant women?

36 What are the benefits of combining intermittent preventive treatment (IPT) and insecticide-treated nets (ITNs) in a multipronged approach to prevent malaria in pregnant women (especially in Asia and Latin America)?

37 What is the effectiveness, cost-effectiveness and safety of various antiretrovial regimens (ZDV, 3TC, NVP, Zidovudine monotherapy) aimed at preventing mother-to-child transmission and improving maternal health outcomes for pregnant women with HIV?

38 What is the effectiveness, cost-effectiveness and safety of different doses, regimens, and routes of administration for commonly-used treatments for anemia in improving short- and long-term maternal and neonatal health outcomes in pregnant women with severe and moderate anemia in poorly-resourced settings?

39 What is the effectiveness, cost-effectiveness and safety of various psychological and/or educational interventions in reducing consumption of alcohol among pregnant women, or women planning a pregnancy, and improving maternal and neonatal health outcomes?

40 What is the effectiveness of preconception counseling, delivered at different reproductive life stages, in influencing pregnancy planning behavior and improving pregnancy outcomes for women with epilepsy (WWE)?

41 Do interventions to reduce weight and obesity in pregnant women have any effect on improving maternal health outcomes?

42 What is the effectiveness and cost effectiveness of interventions to reduce weight gain before second or subsequent pregnancies to reduce maternal mortality?

43 What is the effectiveness of advocacy interventions to reduce violence and abuse on pregnant women conducted within healthcare settings?

44 What is the effectiveness of advocacy interventions to reduce violence and abuse on pregnant women conducted outside healthcare settings?

45 What is the effectiveness of advocacy interventions to reduce violence and abuse on pregnant women compared with usual care or no care at all?

46 Compared with traditional delivery of health care services, what is the effectiveness and costeffectiveness of conditional cash transfer (CCT) programs in helping overcome barriers (financial, cultural) in access to maternal health services, including services that are not free?

47 What are the effects of different interventions on increasing the proportion of health care professionals practicing in rural and other under-served areas?

48 What models of training for providers of labour support are most effective and cost-effective in resource-poor settings?

49 What are the benefits of alternative models of antenatal care compared to standard models of antenatal care for high risk vs. low risk populations?

50 Compared with routine provision of services, does integration of health services at the point of delivery improve health care delivery (in relation to outputs, service quality, and cost), improve health status of users (in relation to nutritional status, morbidity, and mortality), and make it easier for communities to access and use health services?

51 What are the effects of alternative settings vs. conventional settings on birth outcomes?

52 What is the effectiveness of maternity waiting home (MWH) facilities in improving maternal health outcomes in low-resource countries?

53 Compared with planned hospital birth, what is the effectiveness and safety of planned home birth? (in reducing prepartum, intrapartum, and postpartum complications, the number of interventions, and mortality among pregnant women)?

54 What is the effectiveness of various methods to improve initial home-based management (first aid stabilization), safe referral to care, and maternal health outcomes for pregnant women?

55 What is the effectiveness and cost-effectiveness of various methods of training traditional birth attendants (TBAs) in improving maternal health behaviors, thought to mediate positive pregnancy outcomes, and in improving maternal health outcomes for mothers cared for by TBAs?

56 Compared to usual care, what is the safety, effectiveness, and cost-effectiveness of interventions involving lay health workers (LHWs) in improving maternal health outcomes?

57 Compared with professional healthcare providers, what is the effectiveness, safety, and costeffectiveness of having lay health workers (LHWs) provide interventions in the fields of health education, promotion, and disease management in improving maternal health outcomes?

58 Is critical incident audit and feedback effective in reducing the perinatal mortality rate, the maternal mortality ratio, and severe neonatal and maternal morbidity?

59 What are the indicators to better assess the short- and long-term outcomes of caesarean section and vaginal birth?

60 Compared with other models of care for childbearing women and their infants, what is the effectiveness of midwife-led models of care in improving access to care,

continuity of care, and improving maternal health outcomes, among pregnant women classified as low- or high-risk for complications?

61 Compared with other models of midwife-led care, what is the effectiveness and cost-effectiveness of the community-based ‘‘case load model’’ of midwife-led care in improving maternal health outcomes, continuity of care, and satisfaction among pregnant women?

62 What is the most effective and cost-effective way to organize midwife-led care to improve maternal health outcomes under varying conditions?

10.3 ARTÍCULOS ADICIONALES

Protocolos de revisiones Cochrane encaminados a cubrir las brechas que surgieron en este estudio.

Primer protocolo

Segundo protocolo

Otra publicación relacionada

7.4 Fortalezas y limitaciones

Fortalezas

Los hallazgos de este trabajo de tesis muestra la utilidad de las revisiones sistemáticas para identificar lagunas de investigación en el campo de salud materna. Al mismo tiempo permiten desarrollar de manera directa preguntas de investigación en formato PICO con la seguridad de que es improbable que se dupliquen los temas de investigación porque las revisiones sistemáticas Cochrane no se repiten. Por otra parte, la priorización de esas preguntas de investigación podría ayudar a informar el proceso de establecimiento de la agenda de investigación en salud materna, a nivel nacional e internacional, siendo esto útil no sólo para los investigadores sino también para los responsables políticos, financiadores y consumidores de atención médica. Pensamos también que el uso de estos métodos sistemáticos y transparentes podría ser de utilidad para otros problemas de salud.

Las revisiones sistemáticas no solo contribuyen a mostrar las lagunas de conocimiento sino el espectro de evidencia disponible y además, cómo va evolucionando en el tiempo la calidad de los estudios individuales contenidos en las mismas. Otra contribución relevante es promover la investigación en sistemas de salud que conduzcan a intervenciones que prevengan la muerte y la discapacidad durante el embarazo y el parto.

Limitaciones

Las revisiones sistemáticas no obedecen a ningún proceso de ordenamiento de prioridades de salud por lo que pueden existir algunas lagunas que no se reflejan en los trabajos recolectados. El hecho usar una sola fuente de revisiones sistemáticas también podría haber limitado el mapeo de lagunas de conocimiento que pudieran estar en otras fuentes.

Con respecto a la administración de las encuestas para el proceso de priorización, no fue posible obtener las características de aquellos participantes que no respondieron la encuesta por lo que no se pudo comparar sus características con aquellos que si lo hicieron, lo que la hace susceptible a potencial sesgo de selección. La distribución desigual de los participantes de cada grupo Cochrane y el interés que el tema podría tener para ellos podría haber afectado la respuesta, ya que todos eran expertos pero en diferentes campos. Otra cuestión técnica se relacionó con errores de clasificación de algunas preguntas, o preguntas de investigación que podrían ser aplicables a más de un grupo y, arbitrariamente, fueron asignados a uno solo.

Finalmente, hay que señalar que no fueron incluidos en el proceso de priorización otros actores tales como usuarios (organizaciones o individuos) y gestores de salud, como por ejemplo los encargados ministeriales o locales de programas de salud relacionados con el tema. Su inclusión probablemente nos hubiera dado un espectro mas completo de las brechas, aunque la idea inicial de este proyecto fue incluir solo participantes de los cuatro grupos Cochrane que sumaban mas de dos mil participantes y en los que también se incluyen consumidores.

8. CONCLUSIONES

8.1 Implicaciones para la práctica

- Las revisiones sistemáticas permite descubrir los vacíos de conocimiento sobre un tema específico, en este caso la salud materna. Este trabajo de tesis ha validado su utilización como recurso para determinar aquellas lagunas de conocimiento que deben completarse para alcanzar objetivos sanitarios.
- Es importante que aquel proceso se haga con la construcción de preguntas de investigación estructuradas que permiten mayor especificidad y no sobre grandes temas que podrían impedir una mayor profundización y definición del problema o laguna a estudiar.
- Hacer un proceso de priorización de las lagunas de conocimiento detectadas con la participación de los principales actores del tema en estudio puede favorecer que el proceso sea de alta calidad. Sin embargo, es necesario garantizar el conocimiento de algunos antecedentes minimos que permitan comparar el grupo de respondedores con aquellos que no lo hicieron. Debería también incluirse de manera explícita a decisores, proveedores y usuarios del

sistema de salud en el proceso, lo cual permitiría una mirada más amplia al problema y no solo desde el punto de vista de los investigadores.

8.2 Implicaciones para la investigación

- Es necesario idear estrategias de cómo mejorar los procesos de priorización de investigaciones a través de recursos en línea como por ejemplo Internet.
- El hecho de que las revisiones Cochrane como las del grupo Pregnancy and Chilbirth tengan al mes de septiembre de 2014 cerca de 600 revisiones sistemáticas, nos inclina a pensar que están cubriendo un gran espectro de lagunas de conocimiento en salud materna. Sin embargo, seria importante indagar los contenidos temáticos de otras revisiones no Cochrane para evaluar el impacto de nuestro trabajo en el tiempo, usando herramientas de búsqueda como por ejemplo, la de la iniciativa Epistemonikos [95].
- Deberían también estimularse que todas las revisiones sistemáticas que se produzcan señalen de manera explícita y lo más específica posible las implicaciones para futuras investigaciones, las cuales serán la base para delimitar los vacíos existentes.
- Indagar la calidad de los estudios que se incluyen en las revisiones sistemáticas y su relación con la subestimación de dichos vacíos por la presencia de sesgos, podría ser un punto relevante.
- Para la producción de más investigación, el listado de preguntas derivadas de las lagunas de investigación debería compartirse con organizaciones que están interesadas en la salud pública, especialmente de países de menores recursos, como por ejemplo la Organización Mundial de la Salud.

- Finalmente, seria importante realizar un seguimiento temporal acerca de si el nuevo conocimiento producido en base a estos ejercicios de priorizacion, se traduce en acciones sanitarias y en un impacto positivo en la salud publica, el desarrollo y la equidad.

9. BIBLIOGRAFÍA