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Social networks and health policy: The case of misoprostol and the WHO model essential medicine list



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ABSTRACT

The WHO Essential Medicines List (EML) was established to help countries prioritise medicines according to their health care needs. Selection for the List is based on rigorous scrutiny of public health relevance, evidence on efficacy and safety, and comparative cost effectiveness. The WHO ideal is that a medicine and its efficacy are based on science, but in reality a medicine has a social life and the acceptance of a pharmaceutical intervention involves the interaction of a wide array of governmental and civil society organisations, and industry. Misoprostol is a medicine widely used for both abortion and prevention of postpartum haemorrhage in low income countries. Although the evidence for the latter is highly contested it was nevertheless added to the WHO EML in 2011. We use social network analysis to examine the social, political and economic field surrounding the WHO EML applications and health policy. We describe a chronology of the drug's use and of the applications to the WHO EML and carry out a social network analysis of the organisations and individuals involved in the applications, research and dissemination. The research identified a network of 238 organisations and individuals involved in the promotion of misoprostol for postpartum haemorrhage and present at the time of the WHO EML applications. There is a strong interdependency between the funding bodies, civil society organisations, researchers and clinician organisations. The research was part of an EU FP7 funded project on Accessing Medicines in Africa and South Asia (2010–2013).

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1. Introduction

The WHO Model Essential Medicines List (EML) is intended to enable countries to serve priority health care needs of populations (WHO, 2002). According to WHO a medicine is only selected having undergone rigorous scrutiny of public health relevance, evidence on efficacy and safety, and comparative cost effectiveness. The WHO ideal is that decisions about a medicine and its efficacy are based on science, but in reality a medicine has a social life and the acceptance of a pharmaceutical intervention often involves the interaction of a wide array of governmental agencies, clinicians, civil society organisations, and industry. This paper uses a chronological approach combined with social network analysis to assess the connection between this social field and health policy. The paper addresses the research question: is health policy based solely on science and evidence based medicine, or is this process

influenced by wider social, political and economic factors? The case study is the promotion of misoprostol for the prevention and treatment of postpartum haemorrhage and its addition to the WHO EML in 2011.

2. The millenium development goal five and the maternal health case for misoprostol

Misoprostol is a synthetic analogue of naturally occurring prostaglandin E1 which was developed by Searle Pharmaceutical Inc., (now a division of Pfizer) in 1973 (Collins, 1990). Searle received approval from the U.S. Food and Drug Administration in 1988 to prevent gastric ulcers associated with nonsteroidal anti-inflammatory drugs and the drug is licensed and has been marketed to this day under the trade name Cytotec.

Misoprostol, like other prostaglandins, causes contractions of the uterus, and since the 1990s has been increasingly used for a range of off label maternal health indications, including: medical abortion, cervical ripening, induction of labour, and as a uterotonic agent in the management of third stage labour. Misoprostol has

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certain advantages over conventional uterotonic drugs. Oxytocin and ergometrine are heat sensitive and require parenteral administration. The need for cold storage and administration in clinical settings means that these are not suitable in low income countries since most births occur in rural settings. Misoprostol on the other hand is relatively inexpensive, stable at room temperature, and can be administered orally, sublingually, rectally and vaginally. For these reasons it is thought to be ideal in low resource settings where the majority of maternal deaths occur through PPH. The question is does it actually work?

The growing interest in the potential benefits of misoprostol in maternal health must be seen in the context of Millennium Development Goal Five (MDG5), in which United Nations Member States have agreed to the aim of reducing the maternal mortality ratio (the number of maternal deaths per 100,000 live birth) by three quarters and achieving universal access to reproductive health over the period from 1990 to 2015. According to WHO latest estimates the reduction in maternal deaths from 543,000 in 1990 to 287,000 in 2010 (WHO, 2012) is only a little over half the rate of decline needed to achieve the MDG target. Most of these deaths occur in developing countries, where women deliver at home and have little or no access to obstetric care. In 2005 there were an estimated 535,900 maternal deaths, 50% of which were concentrated in sub-Saharan Africa and 45% in Asia (Hill et al., 2007). A quarter of these deaths is associated with postpartum haemorrhage (PPH) (WHO, 2007), which is defined by WHO as blood loss of greater than or equal to 500 ml within 24 h following birth.

The major cause of PPH is uterine atony. Following a healthy birth, the uterus contracts and compresses the blood vessels and prevents blood loss. Uterine atony occurs when the muscles of the uterus lose their tone and the uterus fails to contract. Uterotonic drugs are used to prevent this condition. A Cochrane review in 2000 (Prendiville et al., 2000) showed that the use of active management of third stage labour (AMTSL) can significantly decrease blood loss following delivery. This formed the basis of the WHO guideline (2007) which recommends the use of AMTSL by skilled birth attendants. Active management comprises three interventions: prophylactic administration of a uterotonic drug, early cord clamping and cutting, and cord traction. The uterotonic drug of choice is oxytocin followed by ergometrine.

2.1. Evidence in support of misoprostol for prevention of PPH

The first study which indicated the potential benefits of misoprostol for the prevention of PPH was a study published in el-Rafaey et al. (1996), however questions of its efficacy still remained. Unusually, four Cochrane reviews on the efficacy of prostaglandins for the prevention of postpartum haemorrhage were undertaken in rapid succession: Gülmezoglu et al. (2002, 2004, 2007), Tunçalp et al. (2012). The first two reviews conclude that misoprostol is not as effective as oxytocin in preventing PPH and has more side effects. The conclusion of the last two reviews on the efficacy of misoprostol remained unchanged but a comment was added that it may be used where no injectable uterotonic is available.

A further WHO guideline (2009) recommends the use of misoprostol for the prevention of PPH in situations where oxytocin is not available. This has been the position of the International Federation of Gynaecology and Obstetrics (FIGO, 2012a) since 2006. However a systematic review published in Chu et al. (2012) of the evidence of the efficacy of misoprostol in community settings did not support the WHO position. In our view the scientific evidence underpinning this review has not been successfully challenged although following its publication a debate ensued in the letters section of the journal (Derman, 2012; Kerr, 2012; Pollock and

Brhlikova, 2012; Potts et al., 2012) and a number of key organisations put out leaflets with counterclaims (FIGO, 2012b Pathfinder International, 2012).

By the time this critical review was published misoprostol had a central role in national and international health programmes with the aim of meeting the targets of the MDG5. When in 2011, misoprostol was added to the seventeenth WHO EML for the prevention of PPH, the action was widely applauded by the growing number of civil society organisations who had been actively promoting its use in low resource settings. For key organisations promoting the use of misoprostol in maternal health, such as Gynuity Health Projects, and FIGO, the question was no longer solely a matter of providing evidence; the new concern was how to translate the already existing evidence into practice (Starrs and Winikoff, 2012).

3. Misoprostol and the WHO model essential medicines list

The WHO description of essential medicines has three components: a definition, the selection criteria and purpose. Essential medicines are defined as 'those that satisfy the health care needs of the population', they are 'selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness', and their intended purpose is 'to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford' (WHO, 2002:15). WHO first established a Model Essential List of Essential Medicines in 1977. Since that time a WHO EML Committee has met every two years to consider applications for inclusion, changes or deletion. The first Report of the WHO Expert Committee published in 1977 included 186 medicines. The current Report, which is the eighteenth, was published in 2013; it contains 374 medicines. The WHO EML has a powerful influence on the medicine policy of low income countries; once a medicine is added to the WHO EML it acts as a signal to countries to follow suit. The EML also serves as a model for medicine procurement by United Nations organisations and NGOs.

The WHO EML has two components. The core list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed.

Following criticisms about transparency, in 2002 the process for creating and updating the List was revised; information about each application is now made available on the WHO website, and the decision to add or delete a medicine now follows the procedures of evidence based medicine (Laing et al., 2003). This approach which became the dominant model in health science in the 1990s gives prime position to evidence derived from systematic reviews of the existing literature and further data derived through meta-analysis. In health research the principal source of systematic reviews is the Cochrane Collaboration. The Cochrane reviews have played a crucial role within the network of organisations promoting misoprostol.

Prior to 2002, most applications to the List were made by WHO programme staff and pharmaceutical companies (Laing et al., 2003). Since 2002, any individual or organization can make an application. The application is first reviewed internally by the relevant WHO department and then made publicly available on the WHO website. An external expert review is conducted, usually by a nominated member of the committee, and comments are also received from the relevant WHO department. The public, including patient advocacy groups and representatives of the health care

industry are also invited to comment on the application and make recommendations. Presently, in order to ensure the 'full scientific independence' of the Committee, with the exception of an initial open public session, the Committee reviews the evidence and makes its final decision in a private session (WHO, 2002). The revised List is published as a WHO Technical Report and made available on the WHO website along with all the application material. The Reports also give an account of any revision made to the List.

Up to 2011, when misoprostol was added to the core list for the prevention of PPH there had been five misoprostol applications to the WHO EML Committee for PPH. The first PPH application was in 2003; it was rejected due to limited registration of misoprostol for gynaecological and obstetric indications (WHO, 2003). The applications in 2005 and 2009 were rejected due to lack of evidence for efficacy (WHO, 2005, 2009). The decision to add misoprostol to the List in 2011 (WHO, 2011) for the prevention of PPH was based on evidence provided in four studies (Walraven et al., 2005; Høj et al., 2005; Derman et al., 2006; Mobeen et al., 2011), which in the view of the Committee demonstrated that misoprostol was effective when used by traditional birth attendants trained in its use at home deliveries. Nevertheless oxytocin still remained the drug of choice and there is a note under the misoprostol entry stating that it should only be used if oxytocin is not available or cannot be safely used. The 2012 review (Chu et al.) found the studies that formed the basis of the WHO decision to be deficient in a number of areas; they all had limitations with regard to study design, exclusion criteria, intervention and controls, and use of outcomes, and none of them demonstrated a strong case for efficacy or effectiveness in community settings. This review was submitted as the basis of an application to delete misoprostol from the list in 2013. The application was rejected because in the view of the committee it do not constitute new evidence (i.e. trials) (Millard et al., 2014). A further review claiming efficacy was also shown to be flawed as the conclusions did not reflect the findings of the study (Hundley et al., 2012, Pollock, 2013). The lack of clear cut scientific evidence for misoprostol for PPH led to this present study which aims to map out the concurrent development of social networks and WHO health policy.

4. Key agencies in the network and their misoprostol programmes

4.1. *Venture Strategies for Health and Development (VSHD) and Venture Strategies Innovations (VSI)*

VSHD was one of the first civil society organisations to promote the use of misoprostol for maternal health. VSHD was established in 2000 by Martha Campbell who had previously directed the population program at the David and Lucile Packard Foundation. According to information provided on their website they began their misoprostol programme at the request of three leading African obstetricians/gynaecologists, Khama Rogo of Kenya, Godfrey Mbaruku of Tanzania, and Friday Okonofua of Nigeria, who asked them for assistance in making misoprostol legally available for PPH.

Their programme involves a range of activities which includes: carrying out small scale studies to make governments aware of misoprostol in saving women's lives, sponsoring government policy meetings, managing the regulatory process, and importing and distributing the drug. Working in collaboration with Zizhu, a pharmaceutical company based in Beijing, they achieved the first registration of misoprostol for PPH in Nigeria in 2006. Soon after, with their help, misoprostol registration was achieved in several other African countries. In 2008, VSHD created its partner organisation, VSI, to take over the misoprostol programme. As we show, in

a short period VSI and VSHD became key nodes in the network. VSHD is now a think tank working in close collaboration with the Bixby Center for Population, Health and Sustainability at Berkeley's School of Public Health.

VSI's misoprostol programme is organised around three fundamental components: registration, introduction and availability. They achieve their goals by working with local partners which includes ministries of health and policy makers, local NGOs and pharmaceutical companies. Their work involves: developing implementation policies; conducting research; managing the registration process; negotiating low prices; training providers; and facilitating the availability of misoprostol through commercial and public channels. The research they have undertaken involves collaboration between VSI, Berkeley's Bixby Center for Population and local partners, and focuses on issues related to implementation. They currently have programmes in twenty countries in Africa and South Asia.

4.2. *Gynuity Health Projects (GHP)*

The third major agent in the misoprostol social network is GHP. Founded in 2003 by Beverly Winikoff. Information on its website states that its vision is to conduct clinical, service delivery and social science research on reproductive health, and to disseminate this information to policy makers and reproductive health professionals. Whereas the prime focus of VSI's programmes is on implementation, GHP focuses on research and technical assistance. They also have programmes devoted to contraception, medical abortion, pre-eclampsia, pregnancy failure, miscarriage and HIV.

GHP's PPH program has two phases, both of which are funded by the Gates Foundation. The first phase which commenced in 2004 involved evaluating misoprostol for the treatment and prevention of PPH and publicising its potential in low resource settings. A number of research projects were initiated during the first phase which resulted in several publications. One of these publications was a literature review of articles published on PPH treatment before 2007 (Blum et al., 2007). This review found little evidence to support the treatment of PPH with misoprostol; yet it still recommended its use in contexts when other treatments have failed or are unavailable. Later studies were more optimistic. A randomised controlled trial with 1119 women enrolled was carried out in Pakistan from 2006 to 8 in collaboration with Aga Khan University; this study showed a twenty-four percent reduction in PPH rate (Mobeen et al., 2011).

The second phase of GHP's misoprostol programme commenced in 2009 with a five year grant from the Gates Foundation of \$25 million. As stated on their website, under this grant the program includes: developing studies on the safe and effective use of misoprostol for the treatment and prevention of PPH; developing an evidence based policy and advocacy agenda in partnership with key international and regional organisations; creating new clinical knowledge on misoprostol for PPH indications; collaboration with pharmaceutical organisations to ensure greater availability of misoprostol; and encouraging policy change at national and international levels.

Part of the money awarded to GHP was channelled to FIGO to fund the FIGO Misoprostol for PPH in Low Resource Settings Initiative (2010–2014) that advocates for misoprostol use and disseminates evidence-based information on misoprostol for PPH for health care providers and policy makers. FIGO state that the initiative is part of a global project that is using scientific research on misoprostol to affect health policies and practices. The initiative has several components. A major concern is to publish relevant scientific articles in FIGO's official journal, *The International Journal of Gynaecology and Obstetrics*; this journal is an outlet for GHP's

own research findings on the subject. Another activity is producing guidelines, protocols and training material. A further focus is to organise expert panel sessions in national and international workshops. The 2012 FIGO World Congress of Gynaecology and Obstetrics in Rome included two panel sessions on 'Misoprostol for the Prevention and Treatment of PPH' with representatives from several key organisations in the misoprostol network.

GHP has been helped in its misoprostol promotional activities by Family Care International who received a \$6.5 million grant from the Gates Foundation in 2003 to support misoprostol promotion for PPH. Another major funder is the Susan Thompson Buffet Foundation who provided a \$12.5 million grant to VSI as stated in VSI's 2011 990 Finance form.

5. Misoprostol social network analysis

Alongside its pharmacological life, a medicine also has a social life (Whyte et al., 2002). The MDG5 has seen intense activity around the promotion of misoprostol with a dramatic increase in government and civil society organisations promoting its use and a growing body of research on its safety and efficacy. A search we carried out in 2012 identified 82 RCTs that had been carried out on the use of misoprostol for the prevention of PPH involving 287 researchers from across the globe; this itself is a strong indication of the lack of evidence for efficacy. Since misoprostol came off patent in 2001 there has also been an increase in pharmaceutical companies manufacturing generic forms of the drug (Fernandez et al., 2009).

The progressive development in the number of organisation involved in misoprostol applications to the WHO EML is shown in Chart 1. In 2000, when misoprostol came off patent the social network surrounding misoprostol consisted of a small number of entities: Searle, FIGO, the American Congress of Obstetricians and Gynaecologists, the International Confederation of Midwives, WHO, the Cochrane Collaboration and a growing number of researchers, mainly physicians. GHP, VSHD and VSI are key communicators and facilitators in the misoprostol network. Some of the individuals and organisations involved in the applications sent short supporting letters, others were signatories to collective supporting letters. A few organisations sent long supporting letters stating the public health need and the importance of misoprostol in meeting this need. For example, FIGO in its letter points to 'a wealth of scientific evidence, which includes numerous randomised clinical trials and several clinical guidelines' all supporting the use of misoprostol. There is also a supporting letter from Sigma Pharmaceutical Industries which speaks of their concern to prioritise the needs of the consumer; they state that as a WHO Good Manufacturing Practices approved manufacturer of misoprostol they are committed to keeping the cost as low as possible.

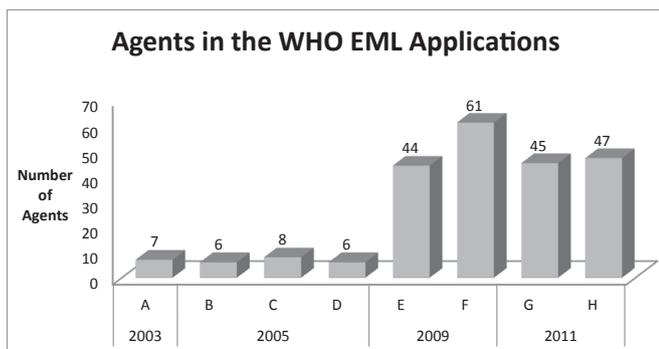


Chart 1. Agents in the WHO EML applications.

5.1. Social network methods

A key element in social network analysis is the notion of boundary. For present purposes the boundary was defined by identifying as many organisations or individuals as possible who were actively engaged in the promotion of misoprostol. The primary source for this was websites and existing academic and grey literature on misoprostol. We used a snowball sampling method starting with the organisations in the WHO EML applications. Most of the letters submitted to WHO supported the applications, but the 2009 and 2011 applications contained a small number of letters from pro-life groups who opposed its addition because in their view this would lead to it being used for abortion.

We identified 238 agents within the network including the individuals who sent letters of support to the WHO EML Committee. The list was divided into eight broad categories: civil society, which includes organisations, individuals and professional associations (total 121); governmental (total 17) and intergovernmental agencies (total 2); funding organisations (total 11); pharmaceutical companies (total 20); academic institutions (total 16); research bodies (total 6); and research studies (total 45), and each agent was allocated a reference number. In our analysis we have adopted the notion of actant from actor-network theory. An actant is any item which is endowed with the ability to act; this includes both people and material objects (Law, 1992, Latour, 1987). Research plays a crucial role in the misoprostol network and as such it has been included as an actor.

Social network analysis is based on two areas of mathematics: matrix theory and graph theory, which are two ways of representing the same data. Once the fields within the matrix have been populated, each agent is represented as a node and mathematical algorithms can be performed to evaluate its position and power within the network. There is now a wide range of computer software which can carry out this operation. The software that was used to generate the graphs and analyse the data presented in this paper was UCINET 6 and Netdraw 2. Visual Understanding Environment (VUE) was used to create the condensed sociograms enclosed in the boxes.

As data on the relationship between the nodes has been gathered solely from websites and existing literature, to categorise the relationships between the nodes in the matrix we have used a simple binary, directed measure: a relationship flowing from node A to B, has been categorised as one, as was a relationship flowing from node B to A; the absence of a relationship has been recorded as zero. The relationship is thus simplex as it represents only whether a relationship exists or not, no further information is recorded about the different kinds of relationships that might exist between two agents. We used this information to develop adjacency matrices and corresponding graphical representations (sociogram) of the entire network and each of the WHO EML misoprostol applications.

5.2. Chronology of WHO misoprostol applications and evolution of related social networks

5.2.1. 2003 application

Fig. 1 is the sociogram for the 2003 WHO EML misoprostol application and Fig. 2 is the corresponding adjacency matrix. Makerere University, Uganda, submitted the application for misoprostol's use in a range of gynaecological and obstetric indications. As evidence, they provided two research studies and a bibliography supplied by the Population Council. In the network we have included the general body of existing research on misoprostol as a node in the network; this is the source of data for the Cochrane Reviews, the applicant, and the WHO EML Committee. The nature

of the relationships between the agents in this group is represented by the flows of the arrows. Each EML application is based on evidence identified in specific research studies. These studies are presented to the WHO EML Committee by the applicant. As previously mentioned, as these research studies are central to the decision making process we have chosen to regard them as agents within the network. For this reason we have directed the research to the applicant who is submitting it and directly to the WHO EML node with a broken line, indicating that the actual direction went through the applicant.

Table 1 provides network macro measures and levels of centrality for the 2003 application. The left half of the table gives macro measures that relate to the network as a whole. The network size is seven; this relates to the number of agents or nodes in the network. The number of ties relates to the number of links present; a line with an arrow on both ends represents two ties. The total possible ties in this network is seven multiplied by seven, minus the seven diagonals which denote self-ties and as such are discounted. This gives a total of forty-two. The density is measure as the proportion of existing ties to all possible ties, expressed as a percentage, which in this case is $18/42 = 43\%$. This is a moderate level of density with nearly half of all possible ties present. The geodesic distance is the length of the shortest existing path between two nodes measured by the number of edges between the two nodes. For example the shortest possible distance between the nodes 'population council' and 'evidence submitted', following the flows of the arrows, is two edges, which is a geodesic distance of two; in the sociogram there are seventeen geodesic distances at a distance of two. The diameter of a network is defined as the largest geodesic distance, which in this network is four. In the tables the geodesic distance is also expressed as a percentage of the total number of geodesic paths in the network (eg Table 1 total geodesic paths is 42, $18/42 = 42.9\%$).

The right half of the table provides figures on centrality. The outdegree figures in the table represent the number of relationships that a node has which are directed towards other nodes. This can be taken as a reflection of the power that the node has within the network. The indegree figure represents 'sinks' or nodes which are subject to inflowing connections of other nodes. The first column gives the number of directed lines and the second column gives this as a percentage of the total nodes in the network. As this is a small network there is little variation between the figures for outdegree and indegree. Centrality, in terms of outgoing connections, is equally distributed amongst four nodes: 4, 189, 180, and 188. The WHO EML Committee is surrounded by the highest degree of connections with 67% of all flows directed towards it.

5.2.2. 2005 applications

In 2005, three misoprostol applications were made to the WHO EML Committee. An application was made by the Geneva Foundation for Medical Education and Research through the WHO Department of Reproductive Health and Research, for the use of mifepristone combined with misoprostol for first trimester medical abortion. A second application was made by BMJ knowledge through the WHO Department of Reproductive Health and Research, for misoprostol low dose usage for labour induction at term. And a third application was made by the WHO Department of Reproductive Health and Research for the use of misoprostol for the treatment of PPH. Fig. 3 shows the sociograms of each of these applications. Fig. 4 is the sociogram of the 2005 applications combined together and Table 2 provides network macro measures and levels of centrality.

Compared to the 2003 application the network has almost doubled in size involving now 13 nodes. The density of the network is considerably less than in the 2003 application. This indicates that most of the action in the network is centred on a small number of

nodes. We can see this in the right side of Table 6 where the nodes 192, 193, 188, 189 and 139 have the highest outdegree and indegree scores. Both the organisations that made the applications have relatively high outdegree and indegree; this indicates their power in the network as collectors of information and facilitators. The Cochrane Collaboration also has relatively high influence in the network due to its role as a major source of evidence for all the applications. The surrounding connections towards the WHO EML Committee has increased since the 2003 application reaching an indegree of 10; this means that 83% of all nodes in the network are directed towards it.

5.2.3. 2009 applications

In 2009 the WHO Essential Medicines List Committee considered 2 applications. An application was made by Gynuity Health Projects (GHP) and Venture Strategies for Health and Development (VSHD) for the inclusion of misoprostol for the prevention of PPH, and an application was made by GHP for the inclusion of misoprostol for the treatment of incomplete abortion. Fig. 5 shows the sociograms for each of these applications. Fig. 6 is the sociogram of these applications combined, and Table 3 provides figures for macro measures and centrality.

What sets this application apart from the previous applications in 2003 and 2005 is the large number of organisations listed as supporting the application. There are now eight-two nodes in the network. As we can see from the sociogram all of nodes are inter-linked. These nodes represent a wide range of organisations and experts within the maternal health field, including local and international NGOs, national obstetrics and gynaecological organisations, and a range of academic institutions and research units. These organisations and individuals sent supporting material directly to the WHO EML secretariat; this is represented in the sociogram with bidirectional lines to the applicant, representing the communication between them in the application process, and directed lines to the WHO EML Committee. In this application thirty-one research studies were submitted as evidence to the WHO EML Committee, these are the nodes with the upward pointing triangle (202–232) in the bottom left corner of the sociogram. As in previous sociograms these have been directed towards the WHO EML node, with bidirectional arrows also connecting them to the applicants.

The network in this application is six times larger than in 2005, yet the density is much smaller with only 5% of all possible relationships present. The diameter is small at three with 92% of nodes connected by paths of length two. These figures can be explained by the fact that the network centres on VSHD and GHP which have outdegree and indegree scores far beyond all the other nodes. The only exception to this is the WHO EML node which is a major sink in the network with 95% of the nodes directed towards it. VSHD and GHP are the major gatherers and facilitators in this network. In the table we can see that a number of other civil society organisation have relatively high levels of indegree and outdegree; this is not related to their connection to the WHO EML committee but to their relationship with other nodes in this network. Nodes such as POPPHI, RTI International and Engender Health are nested in subgroups within the network, a point we shall return to later.

5.2.4. 2011 applications

In 2011 a further two misoprostol applications were considered by the WHO EML Committee. An application was made by GHP and VSI for the inclusion of misoprostol for the prevention of PPH and a second application was submitted by GHP for the inclusion of misoprostol for the treatment of PPH. Fig. 7 gives the sociograms for each of the 2011 EML applications, and Fig. 8 shows the sociogram for the entire 2011 application network. The nodes around the

perimeter are organisations and individuals supporting the application. The nodes in the bottom left corner with the upward pointing triangle (233–238) are research studies which were used as evidence in the application.

The measures in Table 4 largely parallel those for the 2009 applications. The network size is lower at 51, but this is because less research studies were submitted to the WHO EML Committee. The density is low with only 9% of possible connections present, yet at the same time there is a high degree of interconnection with 88.9% of geodesic distances at a level of two. The high degree of connectivity is made possible by the gathering and facilitating activity of VSI and GHP, which is represented in Table 4 by the high indegree and outdegree scores for these nodes. The WHO EML node is again a major sink with 96% of all nodes directed towards it. The centrality of these three major nodes in the network is clearly visible in the Fig. 8 sociogram.

5.3. The nesting of the WHO EML misoprostol applications within the entire network

Up to now we have only considered the agents involved in the WHO EML misoprostol applications. Even this level of data demonstrates there was some degree of social complexity surrounding the decisions of the Committee, but this is only one part of the network. Another feature of social network analysis is the notion of nesting. What we have considered so far, the WHO EML misoprostol network, is a subset nested within the entire misoprostol social network. This can be seen in Fig. 9 which provides the sociogram of the entire network. A key has been provided to identify the different categories of nodes. The four central nodes in the network have been enlarged in the sociogram.

The macro measures in Table 5 show the density of the network to be very small with only 1.5% of all possible connections present. At the same time there is still a high degree of interconnection with 88.3% of geodesic distances at three or less. The diameter is large at six but there are only six geodesic distances of this length which represents only 0.001% of the total. 231 of the total 238 nodes are interconnected. The remaining 7 nodes are pharmaceutical companies which produce generic forms of misoprostol; at the time of this research they were not connected with any of the nodes and they are the only 'isolates' in the network. The WHO EML node is still the major sink with 130 nodes directed towards it. This results from our primary focus on WHO EML applications as a source of information, nevertheless this provides insight into areas of connections in the network and clique formation.

As in the previous sociograms, the high degree of interlinkage in the network arises through the interaction of a number of key nodes which serve both as facilitators and communicators. The figures for centrality show GHP, VSI and VSHD to have much higher levels of indegree and outdegree than all the other nodes. The high levels of GHP can be accounted for by its central position in the WHO EML applications. The sociogram of the entire network also presents a clear visual representation of VSI's principal misoprostol focus which is on implementation; this is shown by the lines radiating from it to the nodes at the right and centre of the sociogram, many of which represent VSI's implementation partners.

In contrast, the eleven funding bodies that we included and marked by diamond shaped nodes do not measure high in the network in terms of indegree and outdegree. Yet several of these organisations have real power in the network. This is because the measures of indegree and outdegree are based on direct connections, which are not the only way that a node can affect the network. These funders have influence via the organisations which they fund. For instance when the Gates Foundation gives money to GHP (see above) it is indirectly connected to all organisations GHP

uses in its promotional activities. The exponential increase shown in chart one in the number of agents involved in the applications after 2005 reflects increases in funding at that time.

5.4. Clique formation

Money coming from USAID to fund misoprostol activities provides an interesting case study for social network analysis. Just as the WHO EML application network is nested within the entire network, misoprostol programmes funded by USAID form a number of nested subgroups clustered around the nodes 70, 34 and 51; this is a classic 'clique' formation, defined in social network theory as a maximal complete sub-graph (Hanneman and Riddle, 2005). The sociograms for these subgroups are shown in Fig. 10. The top sociogram shows the network around node 70, the USAID funded Pakistan Initiative for Mothers and Newborns (PAIMAN), a programme designed to assist the government of Pakistan reduce maternal and child mortality. The programme included a one year project to test the feasibility of home administration of misoprostol. The second sociogram centres on node 34, this is the network of organisations involved in the USAID funded Postpartum Haemorrhage Prevention and Treatment Initiative (POPPHI). POPPHI was a partnership led by PATH, RTI International and Engender Health; its mandate is to promote and support the use of active management of third stage labour in low resource settings and to make uterotonic drugs available at low cost. The third sociogram shows the cluster of organisations around node 51, the Maternal and Child Health Integrated Programme (MCHIP), this is the USAID funded MaMoni programme which uses misoprostol amongst a package of measures to reduce the maternal mortality ratio in Bangladesh. Some of these agents are also present in the WHO EML applications. In the sociogram of the 2009 EML applications (Fig. 6) we can see that all the organisation of the POPPHI subgroup are present.

In the upper left corner of the 2009 WHO EML sociogram (Fig. 6) we can see a subgrouping between the nodes 188, 189 and 193. This is a research grouping/clique which persists unchanged throughout all the EML applications. It is most clearly evident in the small network in the 2003 sociogram (Fig. 4). It consists of the interlinking of the applicant, the research body, the Cochrane Collaboration, the research evidence submitted, and the WHO EML Committee. In each WHO EML application the relationship between the Cochrane Collaboration, the WHO EML Committee and the research body is reciprocated. In its evaluation of the existing evidence the WHO EML draws on the existing body of research and Cochrane Reviews and in the process identifies gaps in the literature, this establishes a feedback loop which generates more research and reviews. This is a prime mechanism through which the industry of research is maintained. The powerful presence in the network of Reviews provided by Cochrane Collaboration is represented by its relatively high indegree and outdegree measures.

6. Conclusion

This paper has shown that between 2003 and 2011 there had been 5 applications to WHO EML committee to add misoprostol for use in PPH. Up to 2011 all of these applications had been rejected due to lack of scientific evidence. In 2011 misoprostol was finally added to the list based on an evaluation of new scientific evidence provided to the committee. During the same time period, a network of organisations and individuals of increasingly complexity developed with the common purpose of promoting the use of misoprostol for PPH. This network had substantial financial backing from major private foundations. Organisations within this network have been involved in misoprostol promotion and implementation

programmes across the world. It is their explicit aim to influence government health policy in favour of misoprostol. The 2009, 2011 WHO EML misoprostol applications were made by three of the key organisation in this network, VSI, VSHD and GHP, with supporting letters provided by many other individuals and organisations. It is not clear to what extent, if any, the WHO EML committee decision was influenced by the presence of this social network. What is clear is the scientific evidence for the use of misoprostol remains contested, and as this paper has shown its addition to the WHO model list in 2011 did not occur as an isolated event.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.socscimed.2015.03.011>.

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