

SAGE Working Group on Vaccine Hesitancy – Literature Review

21 March 2013

A review of vaccine hesitancy

A literature review was undertaken to “explore vaccine hesitancy in different settings including its context-specific causes, its expression and its impact” as outlined in the SAGE Working Group’s terms of reference. Specific objectives were to:

- 1) Identify factors that act as either barriers or promoters of vaccination; and
- 2) Map these onto the “Model of determinants of vaccine hesitancy” as developed by the SAGE WG to assess its relevance and guide its further development.

This literature review was undertaken by researchers of *The Vaccine Confidence Project* (VCP)¹, based at the London School of Hygiene and Tropical Medicine, with input from members of the working group.

Key Findings:

- Research about trust and confidence in, and hesitancy towards, vaccines and vaccination programmes has doubled in the last five years;
- Issues around trust, confidence and hesitancy are of global interest – studies from all WHO regions were identified – although studies about the WHO EUR and AMERICAS regions dominate the field. Of concern is the limited research available in regions where the majority of the world’s population of children live;
- A variety of factors are identified as being associated with vaccine hesitancy but their independent and relative strength of influence is complex and context-specific – varying across time, place and vaccines;
- The literature does not yet quantify the overall impact of vaccine hesitancy;
- There are no established metrics for vaccine hesitancy. Factors examined in the quantitative literature are often drawn from the core theoretical constructs of classic social cognitive models (e.g., Health Belief Model, Theory of Planned Behaviour), which do not adequately account for the influence of broader contextual features and limit interpretation around the complex multi-factorial relationships at play.

¹ <http://www.vaccineconfidence.org/>

A literature review of vaccine hesitancy: its causes, its expression and its impacts

Introduction

Vaccination is often heralded as one of the most important achievements of public health; however, this success has always been accompanied by opposition to its practice (1). Historical reasons for objection have never been singular nor straight-forward, drawing motivation from several frames of reference including religious, scientific and political (2,3). Present day issues around vaccination share the same diversity but are arguably, more complex, as more vaccines are available, and the world takes on a more global profile (4). One observed impact of this growing complexity is an increase in the expression of public concerns and sense of uncertainty around vaccines; both have been linked in developed countries to an increase in the number of people seeking alternative vaccination schedules (5,6) and decisions to delay or even refuse vaccination (7).

In recent years, this phenomenon has been labelled and investigated as 'vaccine hesitancy' (8-10). Vaccine-hesitant individuals have been defined as a heterogeneous group in the middle of a continuum ranging from total acceptance to complete refusal; these individuals may refuse some vaccines, but agree to others; delay vaccines or accept vaccines but are unsure of doing so (11,12).

Several systematic reviews offer insight into the factors that influence vaccine hesitancy across different populations and vaccines (13-16). However, there is also evidence to suggest that not all potentially relevant factors have been identified or thoroughly investigated (17,18). As such, the purpose of this first-phase literature review is to adopt a more panoramic lens in order to frame a broad selection of factors that have been identified as potential influencers of vaccine hesitancy and help bring into focus what these factors look like globally.

Figure 1. Overview of SAGE Working Group (WG) “Model of determinants of Vaccine Hesitancy”



Methods

Search strategy and selection criteria

The *Vaccine Confidence Project* (VCP) is currently running a global systematic review investigating public trust in vaccines and vaccination programmes (Part A). Given the broad scope of this review, which includes vaccine hesitancy and confidence, a subset of studies was extracted to support the SAGE WG literature review (Part B and C).

Part A

VCP Systematic Review

Published articles in all languages were identified using multidisciplinary mainstream and regional electronic databases (*Table 1*).

Table 1. Electronic databases searched

Database	Date Range
Medline	1946 – November Week 2 2012
Embase Classic & Embase	1947 - 2012 November 19
PsychInfo	1806 - November Week 2 2012
Cochrane	1993 - 12 November 2012
CINAHL Plus	1937 – 12 November 2012
Web of Science	1970 – November Week 1 2012
IBSS	1951 – November Week1 2012
LILACS	1982 – November Week 1 2012
AfricaWideInfo	19 th century – 19 November 2012
IMEMR	1984 – 12 November 2012

The search strategy included an extensive list of keywords (*Table 2*) and related MeSH/subject headings in an effort to capture the many dimensions and expressions of trust, as well as related subject headings adjusted accordingly to each database. The search strategy was first developed in Medline and then adapted as necessary across each database; the full search strategy, including MeSH terms, is laid out in Appendix 2. The search first run in October 2011 and updated on 19 July 2012.

Table 2. Keywords used in search strategy for literature review on vaccine hesitancy

vaccin*	AND	anxiety	doubt*	trust	intent*	dilemma*
		attitude*	distrust	mistrust	controvers*,	objector*
		awareness	dropout*	Perception*	misconception*	uptake
immunis*		behavi*r	exemption*	refus*	misinformation	barrier*
		belief*	fear*	rejection	opposition	choice*
immuniz*		criticis*	hesitanc*	rumo*r	delay	mandatory
		accept*	concern*	compulsory	knowledge	
		confidence	decision making	anti-vaccin*	parent* con*	

Once retrieved, articles were screened by title and abstract according to a set of inclusions and exclusion criteria (*Box 1*). After an initial round of screening using this set of criteria, articles that were purely about knowledge and awareness were also excluded as it was felt that these elements did not sufficiently investigate nor represent the complex nature of trust on their own.

Box 1. Inclusion and exclusion criteria applied to articles for literature review

Inclusion Criteria

- Articles that include research on the following:
 - Public trust/distrust, perceptions, concerns, confidence, attitudes, beliefs about vaccines and vaccination programmes by individuals (such as parents, health care workers), groups or communities.
- Peer reviewed research
- Location: Global
- Publication Years: Up to November 2012
- Study period: Any
- Vaccine: All vaccines and vaccination programmes of communicable diseases.
- Concerns: All concerns
- Populations: All

Exclusion Criteria

- Not about vaccines
- Non-Human vaccines
- Vaccines not currently available, such as HIV vaccine.
- Non-peer reviewed papers such as editorials, letters, comment/opinion, protocol (no data), pilot studies (E.g. MMWR, Med let CDC FDA, New York Times)
- Research and Development; unless about public trust, confidence or concern.
 - Safety research
 - Serologic investigations
 - Immunogenicity Studies
 - Efficacy trials
 - Pre-clinical trial research
 - Cost-benefit analysis or cost effectiveness trials
 - Evaluations of mandates
 - Knowledge and awareness as sole variables investigated
- Papers without abstracts

Part B

SAGE WG literature review on dealing with vaccine hesitancy

The above search and screening was repeated in November 2012 to bring the body of studies to be included in the literature review up-to-date. A subset of articles was extracted, limited to the publication date period January 2007 – November 2012 and restricted to the six UN languages – Arabic, Chinese/Mandarin, English, French, Russian and Spanish. The keywords of the search strategy were also translated into French and run across the following databases: Medline (via PubMed), Embase, PsychInfo, CINAHL, Cochrane, IBSS, IMEMR, REPERE, Academic search premier and JSTOR.

Summary descriptive analyses

All articles (all UN languages) were screened and coded by year of publication, country, WHO region (Appendix 4), vaccine, study group and population methodology (i.e., statistical analyses employed) and theoretical approach. Study group was identified using either keyword searches in RefWorks (reference management software) or manually. Keywords included: multivariate, multivariable, regression, factor analysis, systematic, qualitative, focus group, mixed method, univariate, bivariate and descriptive. To assess the degree to which different facets of vaccine hesitancy had been investigated, keyword searches, also using RefWorks, were run across all articles. Keywords included: Hesitan*, accept* barrier, delay, missed, partial, refus*, timeliness, unsure, confidence. Descriptive analyses of all articles were run to enable an appreciation of the global distribution of research on this topic.

Factor analysis – Barriers and Promoters of Vaccination

Multivariate studies were reviewed to identify any factors found to be significantly associated with vaccination behaviour as either barriers or promoters. Each significant factor was then mapped onto the vaccine hesitancy model developed by the SAGE Working Group in order to position them within an overarching framework. This was an important step as the concept of vaccine hesitancy is complex and much of the research tends to focus on one or only a few model elements rather than the entire scope. For this first-phase review, all studies on childhood vaccines (all vaccines administered ≤ 7 years old) were reviewed. However, in order to reflect vaccine hesitancy across a broad range of the public and vaccines, this reach will be extended to include both seasonal influenza and the human papilloma virus (HPV) vaccines in subsequent stages.

Part C

Qualitative analysis – AFR region (Childhood, Adolescent and Adult vaccines)

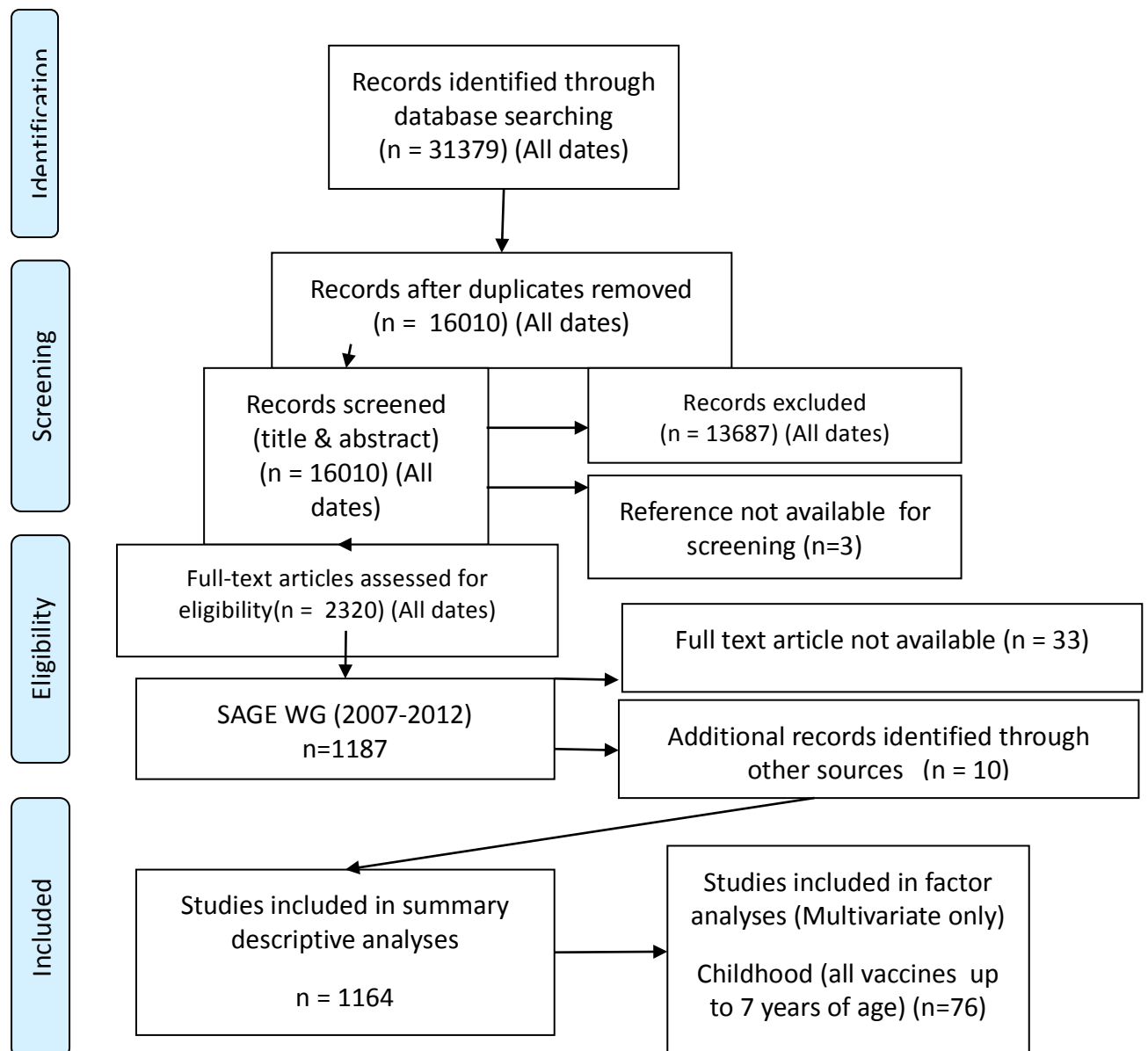
A small, nested analysis of qualitative studies about the WHO AFR region was performed to complement the larger literature review. This study was undertaken because of the paucity of peer-reviewed quantitative research from this region and it was hoped that the qualitative data could add to the understanding of vaccine confidence, hesitancy and barriers to the use of vaccines in the region.

Papers were identified using the original literature review search and filtered by year of publication (2007-2012), WHO region (AFR) and Study group (qualitative and mixed method). The themes from each study were examined and the arising common themes from the 19 papers were selected. These themes were then grouped according to the three primary domains of the model of determinants of vaccine hesitancy: Contextual influences, vaccine and vaccination-specific issues and individual/social group influences.

Results

31,379 records (all languages) were identified from the databases using the combined searches (*Figure 2*). After the removal of duplicates, 16,010 records were shortlisted for screening by title and abstract, of which 2,320 were included for full-text assessment. Once the additional criteria were applied for the purposes of the SAGE Working Group literature review, 1,187 articles remained, of which 33 were not available in full text. An additional 10 articles were added from other sources, which summed to a total of 1,164 articles on public trust, confidence or hesitancy to be analysed in this literature review. All of these articles were included in the summary descriptive analyses. For the factor analyses, in order to focus on the most robust and relevant articles, only those articles that used multivariate analyses were included (n=76 for childhood vaccines).

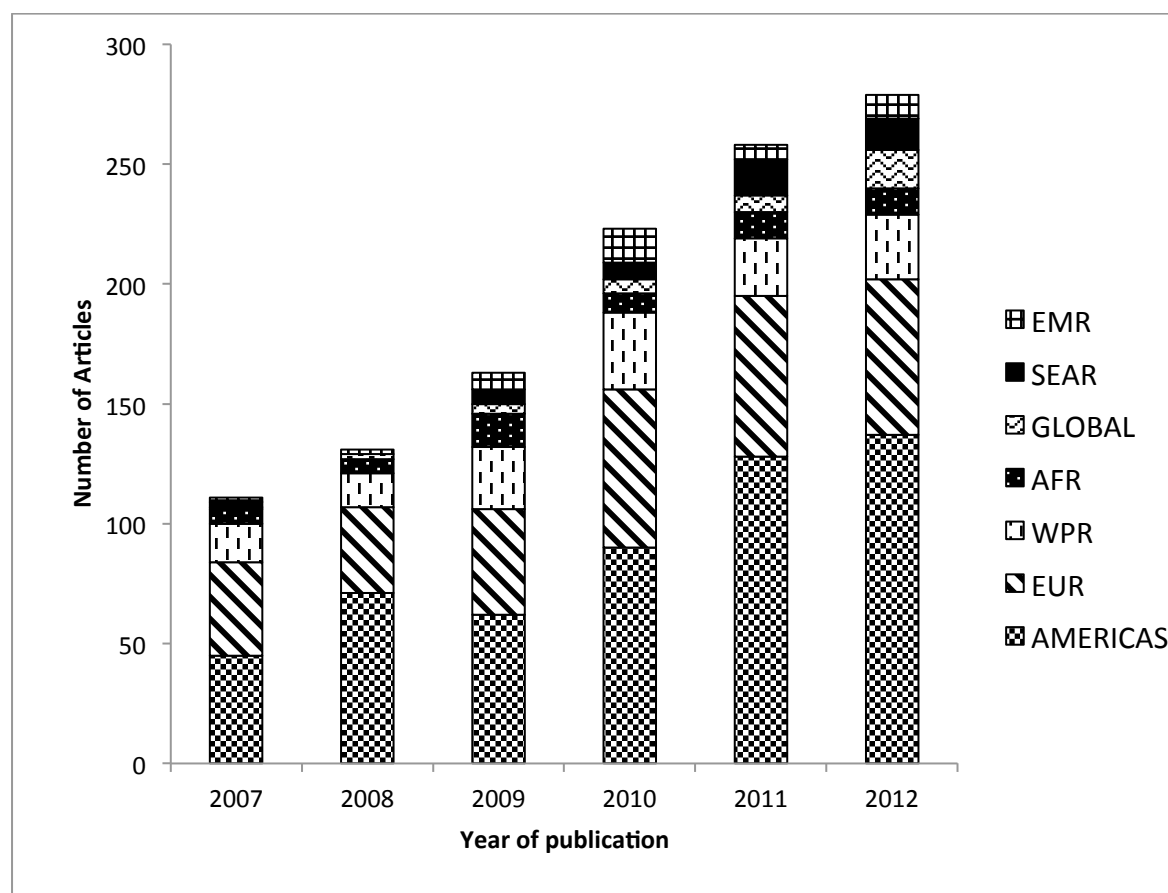
Figure 2. Flow diagram for systematic review on public trust in vaccines incorporating subset for SAGE literature review



Summary descriptive analyses

Research on the many different facets of public confidence in vaccines and vaccination programmes were found across all WHO regions but the majority originated from the AMERICAS, EUR and WPR regions (*Figure 3*). Over the period 2007-2012, there has been a marked increase in research on this topic, particularly within the AMERICAS and EUR regions. The full concept and expression of ‘vaccine hesitancy’ is however relatively new, especially as a core topic, with only 6 articles found using this term in either the title or abstract, most of which were published in the last two years (8-10,19-21). Historically, it has been more common for issues of vaccination behaviour to be discussed in terms of acceptance, barriers and refusals with some covering middle-continuum aspects of vaccine hesitancy including delay, missed, partial and timeliness.

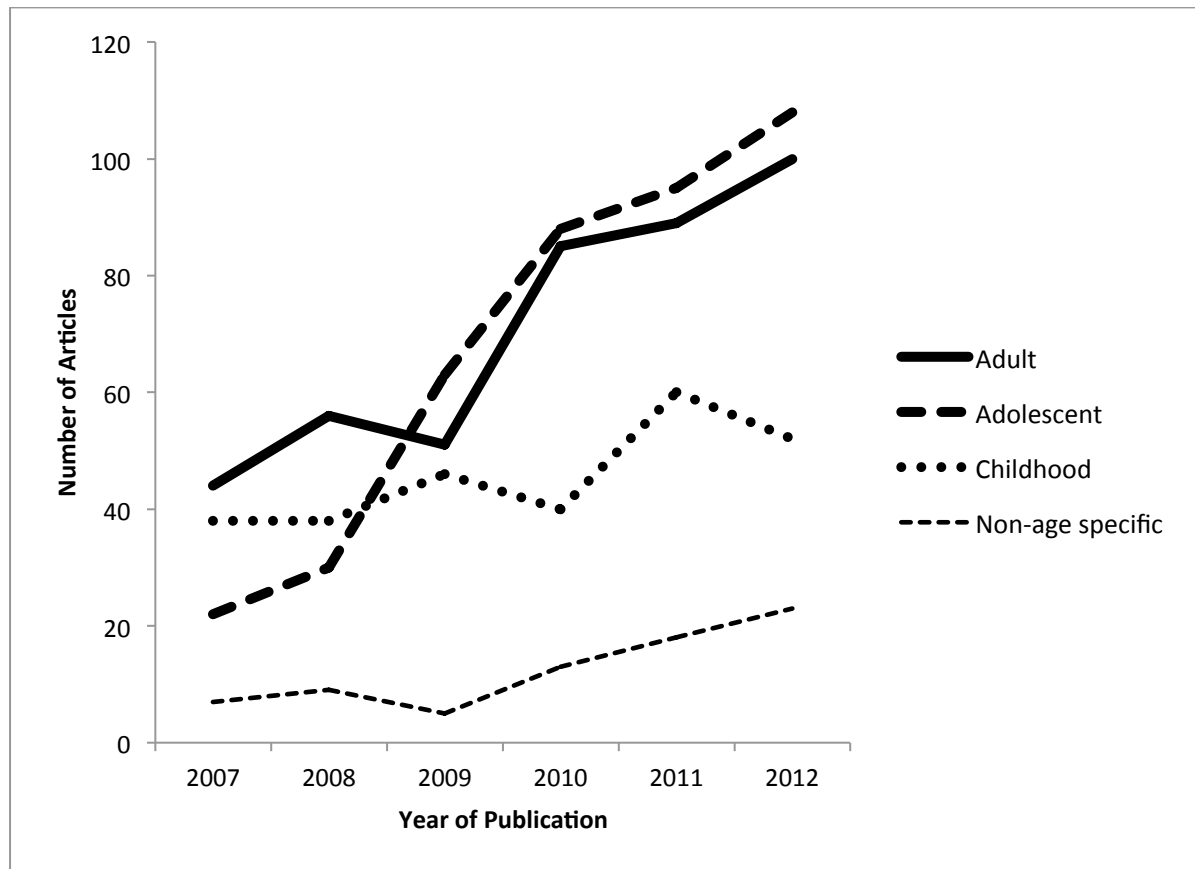
Figure 3. Articles about public trust, confidence or hesitancy in vaccines by year (2007-2012) and WHO region (n=1164)



NB: Number exceed total number of articles reviewed as some articles discuss more than one region. Data is non-cumulative.

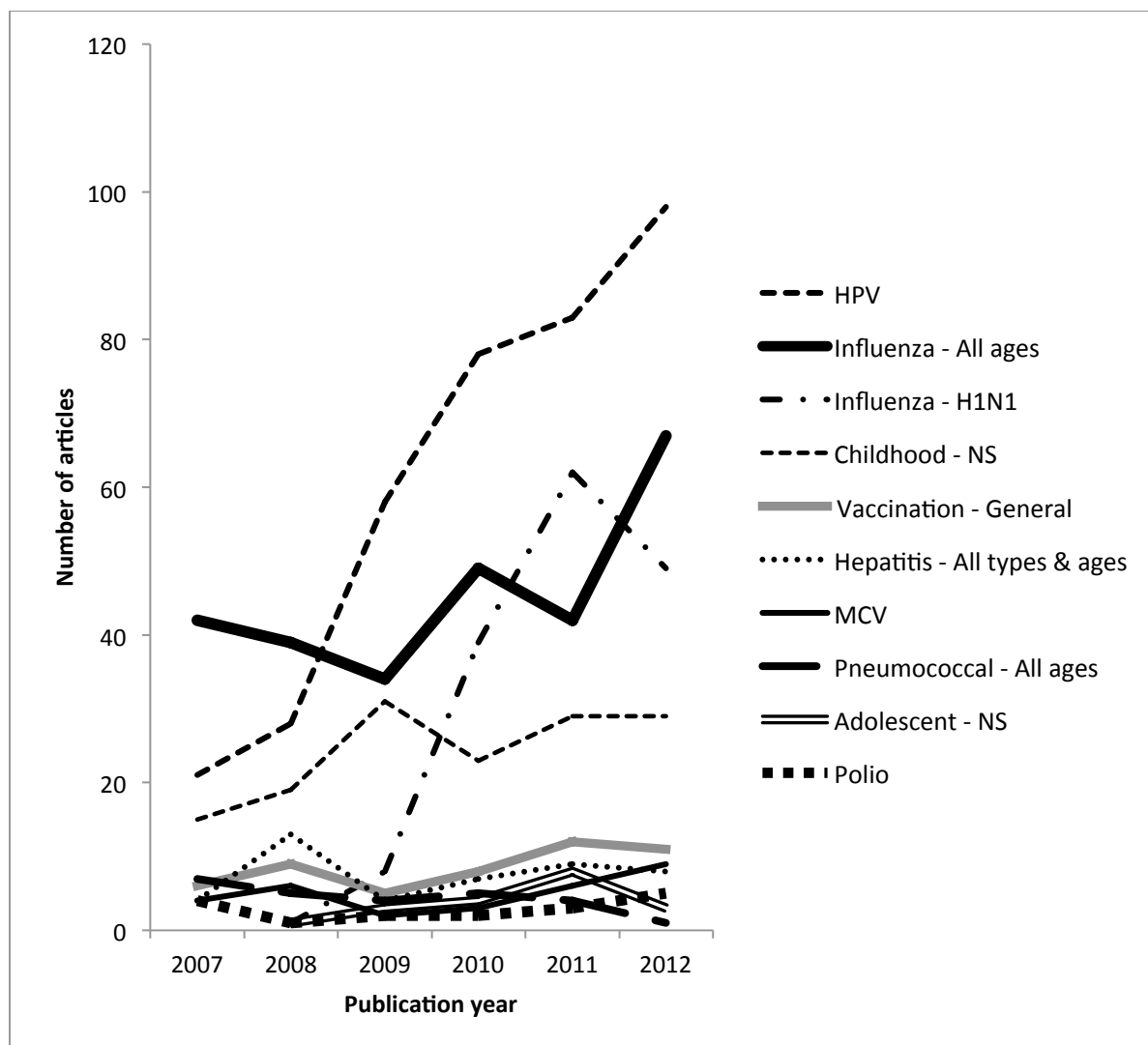
Across all WHO regions over the period 2007-2012, there has also been an interesting shift in vaccines of interest. Childhood vaccines have remained a steady focal point with an increase in the last couple of years as well as non-age specific (i.e., studies about vaccination in general), but the real divergence was seen for both adult and adolescent vaccines (*Figure 4*). For these age groups there has been a special interest in influenza vaccines – both pandemic and seasonal – and the newly introduced HPV (*Figure 5*). There have been a greater proportion of articles published on adult and adolescent vaccines in the more developed regions – AMERICAS, EUR and WPR; whereas childhood vaccines continue to be the mainstay of in this area in less developed regions – AFR, SEAR and EMR (*Figure 6*). Importantly, the introduction of HPV and the expanded recommendations for Influenza (H1N1) led to a three-fold increase in the literature around issues of acceptance and barriers to vaccination during the period 2006-2011. Taking a retrospective view, this increase reflects the widespread challenges faced around uptake of the pandemic (H1N1) vaccine and the varied debates around the introduction of the HPV vaccines and the implications for vaccine confidence.

Figure 4. Articles about trust, confidence or hesitancy grouped by age over time (2007-2012) (n=1164)



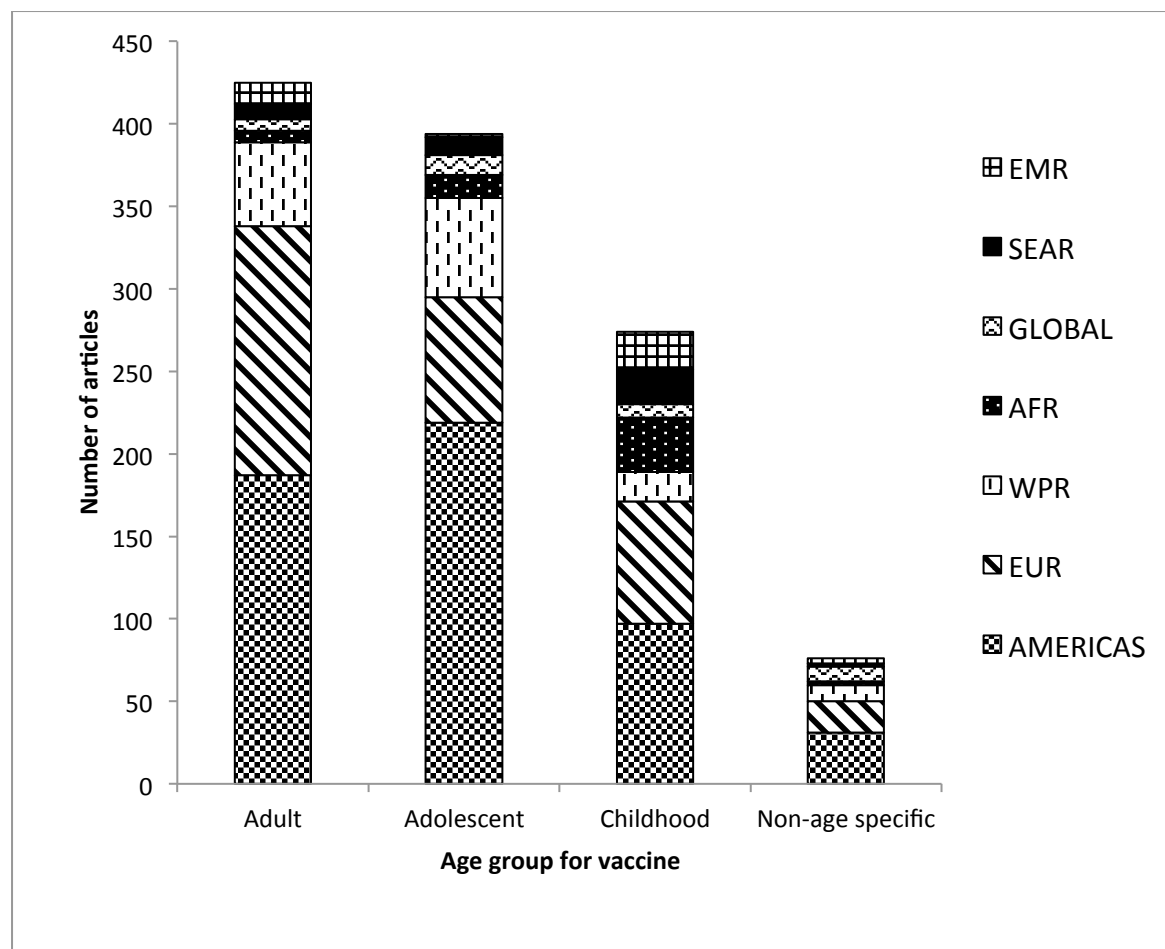
NB: Data is non-cumulative.

Figure 5. Articles on all vaccines (over 15 articles) grouped by year of publication (2007-2012)



NB: NS = Non-specific – vaccines in general; Influenza – All ages = Seasonal influenza only across all age groups; Influenza – H1N1 = Pandemic vaccine only

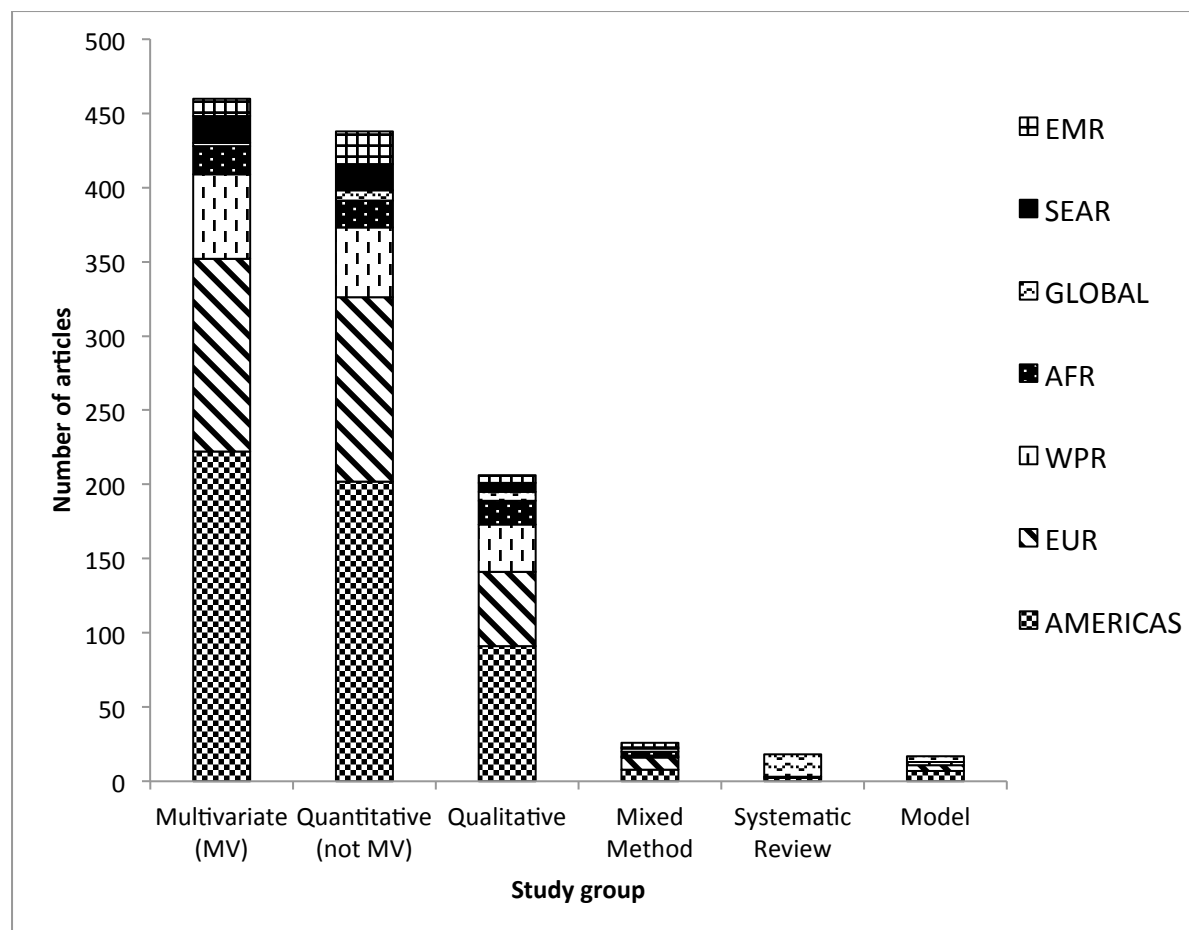
Figure 6. Articles about trust, confidence or hesitancy in vaccines grouped by WHO region and by age (2007-2012) (n=1164)



NB: Number exceeds total number of articles reviewed as some articles discuss vaccines across more than one age group.

A review of the methodological approaches used in the articles analysed showed that the majority of studies were multivariate, followed by other quantitative and qualitative methods (*Figure 7*). A higher proportion of all these studies have been conducted about the AMERICAS and EUR regions with much less representation from the other regions.

Figure 7. Articles about trust, confidence or hesitancy in vaccines grouped by WHO region and study type (2007-2012) (n=1164)

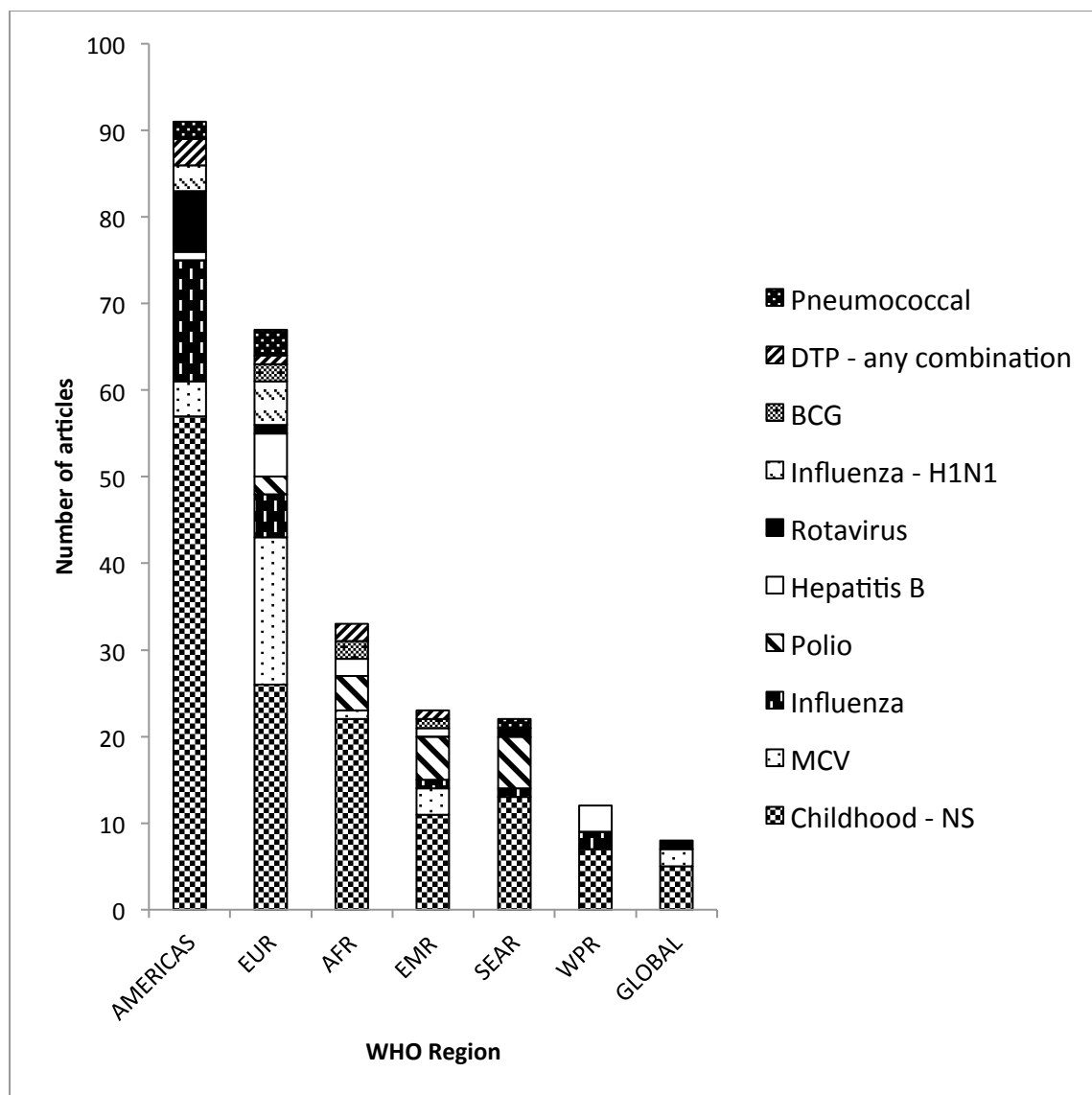


NB: One article was also identified as a 'Survey instrument' but not included on this graph; Mixed Method = both qualitative and quantitative approaches were applied; Quantitative = all quantitative methods other than those employing multivariate analyses e.g., descriptive, bivariate.

Vaccine-specific analyses - Childhood

Among the studies on childhood vaccines, the majority looked at vaccines in general and were not specific to one vaccine (*Figure 8*). Vaccine-specific studies were mostly about Influenza and Rotavirus in the AMERICAS, and measles in EUR. Polio was a key vaccine of interest across AFR, EMR and SEAR regions. Most of the studies were conducted with parents / primary caregiver (n=60). 16 studies examined the perspectives of healthcare workers (e.g., general practitioners, paediatricians and nurses on childhood vaccines, and the extent to which different factors influenced their intention or practice of recommending vaccines.

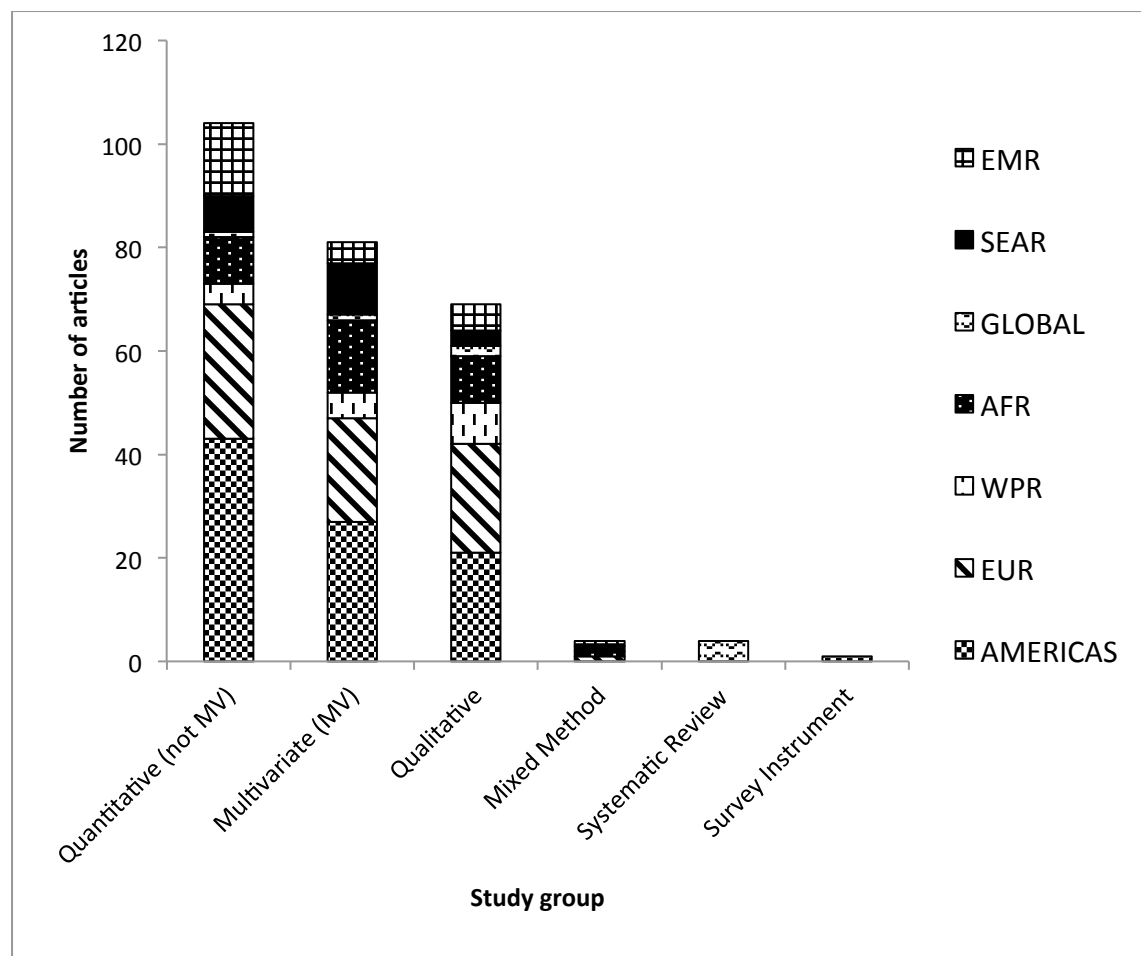
Figure 8. Articles about trust, confidence or hesitancy in childhood vaccines by WHO region and Childhood vaccines (2007-2012)



NB: One article could apply across multiple VPD groups; Includes only VPDs covered in six or more articles (n=256) from a total of 262.

For childhood vaccines, the majority of studies across all regions were quantitative (70%) (Figure 9). Multivariate analyses were used in 44% of the quantitative studies, and identified across all regions.

Figure 9. Articles about trust, confidence or hesitancy in childhood vaccines, by WHO region and study group (2007-2012) (n=262)



Quantitative factor analysis – Childhood vaccines

Several determinants of vaccine hesitancy were frequently observed in relation to childhood vaccines (Appendix 3). These predominantly clustered around the core constructs of popular social cognitive models (e.g., Health Belief Model and Theory of Planned Behaviour) as more often than not, these were the approaches adopted to explore the issues around vaccination behaviour. With respect to Objective 2 of this review, these findings help validate the inclusion of these factors as determinants of vaccine hesitancy but due to the framing of questions in these models (e.g., HBM, TPB), they risk missing other important factors captured in the broader vaccine hesitancy model.

1. Contextual influences

Socio-economic

Level of income/Socio Economic Status (SES) was identified as a significant explanatory factor in eight studies across three regions. In two studies about the USA (AMERICAS), both high (22) and low (23) income/SES were indicated as barriers to vaccination. In Nigeria (AFR), low income/SES was identified as both a barrier (24) and promoter (25), and in Burkino Faso (AFR), two studies identified high income/SES as a promoter (26,27). In India (SEAR), higher income was noted as a promoter (28) and in Bangladesh (SEAR), both high and low income/SES was found to promote vaccination and middle income was non-significant (29). The reasons why this factor is of influence are not always explained, and when they are, it is usually not in isolation. For example, lower income in the USA was linked to issues of trust with the health provider (23) and in Nigeria (24) it was a barrier because it related to both low education, and therefore a lack of knowledge of childhood diseases, as well as access issues, as poorer women are less likely to hold decision-making power.

Level of education presents an equally mixed set of results. Six studies about India (SEAR) consistently found caregivers' higher education to be a promoter (28,30-34). Studies about China (WPR) (35), Lebanon (EMR) (36), Israel (EUR) (37), Bangladesh (SEAR) (29) and USA (AMERICAS) (22) all identified higher education as a potential barrier, whereas studies about Greece (EUR) (38), The Netherlands (39), Nigeria (AFR) (40) and Pakistan (EMR) (41,42) identified it as a promoter of vaccination. Low education was identified as a barrier in studies about Nigeria (AFR) (24,25,43,44), India (SEAR) (30,45), China (WPR) (46), Kyrgyzstan (EUR) (47), and as both a promoter (48) and barrier (49) in the USA (AMERICAS). In the DR Congo (AFR), both high and low education were represented as barriers (50). It is interesting to note that low education manifests different effects; in India, illiteracy indicates more of an issue with knowledge whereas in Nigeria and Kyrgyzstan, low education was associated with higher levels of anti-vaccination attitudes. The evidence from this review suggests that factors should not be considered in isolation as contextual influences are at play.

Communication and media environment

Regular exposure to vaccination stories / messages through mass media, newspapers or community sources was identified as a promoter of vaccination in Nigeria (AFR) (24,43,51), India (SEAR)(28) and Bangladesh (SEAR) (29). This positive influence may relate to the more basic issues of low knowledge about vaccination in these countries. Exposure to news stories about vaccination, particularly negative ones, in the mass media acted as a barrier in Taiwan (WPR) (52) and Canada (AMERICAS) (53).

2. Vaccine and vaccination-specific issues

Costs

Different types of costs were identified in the studies reviewed including financial, time, administrative and general accessibility. In DR Congo (AFR) (50), having the father pay the transport fare to the vaccination clinic acted as a promoter. In Nigeria (AFR)(43), India (SEAR)(45), Pakistan (SEAR)(54) and Greece (EUR)(38), longer distances from vaccination delivery point, either real or perceived, were a significant barrier. In Nigeria, knowledge was reported as the more important barrier over different costs for any level of vaccination. However, the factors of influence were different in relation to partial and non-immunisation status. Specifically, supply-side issues such as maternal and familial availability appeared to explain partial immunisation whereas for non-immunisation, ideational and normative factors, such as parental disapproval, held sway (43). One study from the USA (AMERICAS)(55) reported several costs perceived by health providers which acted as barriers to recommendation of the rotavirus vaccine. These included extra time needed to explain safety profile with patients and additional financial and administrative burdens.

3. Individual/social group influences

Immunisation as a social norm vs immunization not needed / harmful

Encouragement from others, either social or professional (e.g., co-workers, government or health professional recommendation) or belief that immunisation should be a social, familial or workplace norm was a promoter across all studies in which immunisation as a social norm was identified as a factor. The studies were split across the USA (55-57) and Canada (53,58,59) in the AMERICAS; the UK (18) and The Netherlands (60) in EUR; as well as Taiwan (WPR) (52) and Nigeria (43,51) and DR Congo (50) in AFR. These findings suggest that perceptions of social and professional support around vaccination behaviour, whether it be positive or negative, is an important explanatory factor with universal appeal.

Beliefs, attitudes & motivation about health and prevention.

Greater health knowledge in general was found to promote vaccination in India (SEAR) (34) whereas health knowledge, influenced by myths or rumours in Nigeria (AFR) (43) or anthroposophic beliefs and alternative medicine in The Netherlands (EUR) (32,61), acted as a barrier. Belief in scientific medicine promoted vaccination in Germany (EUR) (62). Predictably, having a positive attitude to, and seeing value in vaccination was found to be a promoter in studies about Italy (EUR) (63), UK (EUR) (18), Canada (AMERICAS) (59,64), The Netherlands (EUR) (60), and Switzerland (EUR) (30,65). Similarly, feeling a sense of self-efficacy and comfort about getting vaccinated acted as a promoter in both The Netherlands (EUR) (60) and Canada (AMERICAS) (59) whereas anticipating barriers to immunization acted as a barrier in the USA (AMERICAS) (66,67) and Taiwan (WPR) (52) respectively. On the flipside, either ignoring vaccination as a health behaviour or generally opposing vaccination acted as a barrier in Senegal (AFR) (68) and Taiwan (WPR) (52). However, one study in the USA (AMERICAS) (69) showed that it is possible to have a positive attitude to vaccination yet decide for exemption.

In terms of health behaviours, studies about Nigeria (AFR) (43), India (SEAR)(30,32), Burkino Faso (AFR) (27), China (WPR) (67), practicing one or more of the following supported vaccination: Accessing antenatal care (27,28,51), giving birth at a health facility (27,30,32,43,51,67), and having an immunization card (26,51). In Senegal (AFR) (68) and China (WPR) (67), not having an immunization card acted as a barrier to vaccination. Further, accessing vaccination through a private clinic or regularly accessing healthcare were both found to be promoters in Nigeria (AFR) (70) and The Netherlands (EUR) (39). In one study in the USA (AMERICAS) (23), planning on breastfeeding was reported as a barrier, as was being a smoker in Turkey (EUR) (71).

Outside of health behaviours, a study in India (SEAR) (34) found that membership of/in a development organisation promoted vaccination.

Knowledge / awareness of why / where / what / when vaccines are needed

Two studies about Nigeria (AFR) identified awareness of a vaccine-preventable disease (VPD) as a promoter (43,51). Similarly, a perception that the VPD is dangerous promoted vaccination in Taiwan (WPR) (52) as did having had experience of or caring for someone with a VPD in DR Congo (AFR) (50). Knowledge about vaccine recommendations and schedule was acted as a promoter in India (SEAR) (28) but as a barrier in DR Congo (AFR) (50) and China (WPR) (67). Interestingly, most of the other studies identifying aspects of knowledge as explanatory factors related to health providers responsible for vaccination. Specifically, a greater sense of confidence in personal knowledge and training in vaccination was found to act as a promoter, in terms of recommending vaccines, in France (EUR) (72), Canada (AMERICAS)(64,73), New Zealand (WPR) (74) and Pakistan (EMR) (54). Perceived medical severity of the VPD by health providers was also found as a promoter in USA (AMERICAS) (75), Canada (AMERICAS) (64,73) and The Netherlands (EUR) (60), and when considered less severe, became a barrier in the USA (AMERICAS) (55).

Qualitative analysis – AFR region

20 relevant papers were identified; one of these was not available, but was a second paper on the same study already in the sample. A total of 19 papers were reviewed. The studies (n=19) came from 10 countries – only five of which are in the top ten countries for highest number of unimmunised children – including, South Africa (n=4) (76-79), Uganda (n=3) (80-82), Nigeria (n=2) (83-85), Tanzania (n=3)(86-88), Ethiopia (n=1) (89), Gabon (n=1) (90), Kenya (n=1) (91), Burkina Faso (n=1) (92), Benin (n=1) (93) and Zimbabwe (n=1) (94). The majority of papers were about childhood vaccines (non-specific) (n=7; 37%) (80,82,89,90,92-94) and HPV and preparedness for vaccine introduction (n=5 ; 26%)(77-79,81,86), followed by polio (n=3; 11%)(83-85), cholera (n=2 ; 11%) (87,88), and one each for adolescent (non-specific) (76) and Influenza – H1N1 (91). The most commonly used qualitative approaches were focus group discussion and in-depth interviews (n=13; 68%), and five (26%) studies used a mix of both quantitative and qualitative methods.

1. Contextual influences

Despite the general willingness of caregivers to have children vaccinated, the studies noted a number of barriers. Geographical distance was common to many, as well as the costs of getting to the health centre. Opportunity costs were mentioned in many papers; these were mainly the time taken to get a child vaccinated (often a whole day) when there is a lot of work to be done at home and in the fields.

Social barriers were mentioned in relation to the social support needed to take a child for

Also it is the mother who should really make sure your child is immunised. If you follow the man's advice and you don't immunise the child, when that child falls sick it is you the mother who will spend sleepless nights when the child is sick. He will be snoring and the doctors will abuse you as he is not around the hospital. Yet you followed his advice. You the mother have to stick to your guns. Let him fight with you, but after your child has been immunised.

(Older mother, Kampala, Uganda)

vaccination. If a male partner or elderly relative is against vaccination, for instance, it is difficult for a mother to then take the child for vaccination (though some mentioned doing so nevertheless). Elderly support for vaccination was mentioned a number of times. In the AFR region, given the important place of older relatives in child rearing and decision making, the elderly are an important group of people with whom to build vaccine confidence. In some cases lack of support resulted in intimate partner

violence. One woman, for instance, was reportedly put out of her house because the child became ill after being vaccinated.

Health service barriers were mentioned in a number of the papers. These related to being shamed by the health workers (and sometimes other mothers) if one was dressed poorly; if the child failed to thrive; if the child was not well dressed; if one arrived late (after having to wait for the water of a river to subside to enable crossing) or just being humiliated for no reason. Most respondents said after such an experience they would not return to complete their vaccination.

Other health service barriers included the clinic being too far away and the queues being too long. Not having a mobile clinic coming to an area was a predictor of incomplete vaccination in Malawi.

2. Vaccine and vaccination-specific issues

Poverty and the costs associated with vaccination were fairly consistent across the papers. Anxiety about the side effects of vaccination was also a common theme, though the studies found that this did not necessarily deter respondents from being (or having their children) vaccinated. The side effects mentioned were mostly localised swellings, or the child becoming ill.

Routine immunisation was preferred over mass campaigns in a few studies. Interestingly the reasons given were that the health workers could be found in case of a problem and held accountable, whereas in a campaign follow up afterwards is difficult for an individual.

In Benin a study with a number of religious sects examined the strong religious beliefs that led to their refusal to vaccinate their children. Striking about the study was the low level of formal education among all responders.

Mistrust of the vaccine was mentioned a number of times, in one context it was believed that the vaccines in Africa are not of as high standard as those in the first world. Another related to rumours and myths about infertility, illness and HIV caused by vaccines.

Some of the barriers were very specific to the country or the vaccine. For example, the study on Nigeria described the political, religious and social resistance to the polio eradication campaign in 2003. In Nigeria there were also concerns about the high number of campaigns and the belief that children could get a vaccine overdose.

3. Individual / social group influences

The most prominent theme across the studies was a general lack of knowledge – about vaccine-preventable diseases, vaccines, and the appropriate schedule of administration. Nonetheless, despite respondents' lack of knowledge, they were generally well disposed towards vaccination to prevent illness and were keen to know more.

Limitations

Quantitative analysis

This review only included peer-reviewed literature that related to stated dimensions (see Appendix 1) of vaccine trust, confidence or hesitancy. The exclusion of studies that only looked at knowledge or awareness and grey literature may have undermined a fuller examination of the explanatory factors in SEAR, especially India, and AFR regions, where issues around knowledge are recognized by experts as a very common problem. The exclusion of articles on mandates may also have influenced findings around the influence of policies and politics. There is also a clear publication bias with the majority of studies investigating populations in the EUR and AMERICAS regions. Despite regional databases being included, the database searches were only conducted in natural language for English and French which may have impacted on the sensitivity of searches for articles in other UN languages.

The majority of the studies reviewed applied cross-sectional questionnaires based on similar theoretical approaches. This presents issues in terms of ecological bias and limits the extent to which the relative strength of individual factors can be assessed and interpreted at a general level. In an effort to balance these shortcomings a set of qualitative studies from the AFR region have been included in this review, however, in order to further validate the vaccine hesitancy model and enhance understanding around explanatory factors, a review of the remaining qualitative literature and input from subject-matter experts in all regions would be extremely useful. This extension would not only help highlight gaps in knowledge and overcome the regional publication bias that currently exists, but also help qualify and quantify the extent to which vaccine hesitancy is an issue across the regions – it is essential that in exploring and directing action on vaccine hesitancy that immunisation resources allocated elsewhere are not unjustifiably put at risk.

Qualitative analysis – AFR

This extension piece highlighted that there were very few papers directly investigating the issue of vaccine hesitancy, despite including a broader range of vaccines. Further, the inclusion of adolescent and adult vaccines, whilst useful from a general perspective, made up the majority of the articles analysed so comparability with childhood-only vaccines is limited. Some of the studies also looked at health worker's perceptions of reasons for vaccine hesitancy as opposed to the more direct interrogation of parents and caregivers in the quantitative analysis, although investigation from this perspective could prove useful in relation to communication strategies. There were also some issues around sample-bias, with some studies only being facility-based, which would exclude those not able to reach the facility, and other studies purposively selected populations known to be hesitant. This means that the results need to be interpreted with this in mind.

Discussion

Quantitative analysis

Until further review of alternative studies and sources is conducted, it is difficult, and perhaps unwise, to make inferences about the relative importance of individual factors or how they are incorporated into decision-making processes. Part of the difficulty in understanding the relative importance of individual factors to vaccine hesitancy, is the definition of vaccine hesitancy itself. For example, a study on the timeliness of children's vaccination (95) – just one aspect of the vaccine hesitancy continuum – found that children's vaccinations varied widely between and within 45 low- and middle-income countries (96). Similarly, a study in Nigeria found that partial immunisation was most influenced by supply-side factors, such as maternal availability, and lack of knowledge, whereas non-immunization largely related to demand factors, such as parental disapproval (43), and in Greece (EUR) (38), socioeconomic factors, such as number of other siblings and father's education were the most important predictive factors of both under- and delayed childhood vaccination, and parental attitudes and beliefs about vaccinations were found to be non-significant in this regard. The picture by individual vaccines is no simpler; a study on MMR in the UK found that different factors or the same factors by different degrees influenced decision-making at each dose (18).

To engage with this issue in the immediate term, one option could be to perform a closer review of the hierarchy of factors identified in multivariate studies, but not without significant caveats. In addition, further consideration of the qualitative literature and a review of models around decision-making could be of use. Essentially, the dominating fact is that vaccine hesitancy is a complex issue and is driven by very context-specific factors which require a multidisciplinary approach to be better understood.

Qualitative analysis

The AFR region has high numbers of unimmunised children but there is little information about the demand side reasons for this. There is no information at all in 50% of the countries with the highest number of unimmunised children.

The most striking aspect of these data is that there were many common issues across the studies, such as the lack of knowledge about vaccination and about the illnesses under discussion, the general acceptance of the vaccines, and fear or concern about the side effects. However despite the lack of information, many papers described that the study participants were willing to learn and that they were keen to vaccinate their children to protect them from illness, often despite the many health service barriers.

There were areas of mistrust, particularly in areas where there were repeated mass immunisation campaigns. The mistrust related to believing that “western powers” wanted to sterilise the population or introduce certain diseases like AIDS.

There were different issues relating to different age groups and different vaccines, for example the issues relating to polio vaccination in Nigeria were quite specific, issues relating to cholera vaccination in Zanzibar were a little different but the difference is a matter of emphasis rather than different issues.

What is clear is that more research is needed to elucidate the confidence/ hesitancy around vaccines in the AFR region, but the limited indications are that there is not a huge problem relating to lack of vaccine confidence, and the weight of these is difficult to determine while the numerous structural barriers to immunisation persist.

Future research

Encouragingly, there are signs of expansion in the mode of approach adopted by researchers on this topic. For example, a recent study in Pakistan (EMR), sought to understand the mechanisms, or ‘pathways’ of true impact factors, through which vaccination choices are derived. Using this method the study was able to disaggregate broad factors like ‘education’ and assess its influence on health outcomes over time. In this example, the education level of the father had a greater influence on childhood immunization and that of the mother’s on longer term health outcomes, such as height and weight (97). In the same vein, a recent study in India (SEAR) (34) examined the broader influence of maternal education in terms of human, social and cultural capital, as well as empowerment, to explore the pathways in which these factors affect child health.

Similarly, studies that attempt to identify the influence of layers beyond the individual would be worthwhile. For example, one study in northern Nigeria (AFR) used the behavioural-ecological model to explore the influence of factors at five levels of BCG immunization; these included: intrapersonal, interpersonal, institutional, community and public policy (51). This approach allowed for both broad identification of relevant factors and their relative strength. In this case, maternal (e.g., use of prenatal care, knowledge about immunization) and household factors (e.g., social influence) were more important than child characteristics, and vaccine supply factors were least important. In parallel with multidisciplinary approaches, research like this, which is broad in scope but context-specific, would greatly support global understanding of vaccine hesitancy.

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Appendix 1 - Search strategy for systematic review of public trust in vaccines and vaccination programmes – Ovid MEDLINE(R) 1948 to November Week 3 2012

1. ((vaccin\$ or immunis\$ or immuniz\$) adj5 (anxiety or attitude\$ or awareness or behavior\$ or belief\$ or criticism\$ or doubt\$ or distrust or dropout\$ or exemption\$ or fear\$ or hesitancy\$ or trust or mistrust or perception\$ or refusal\$ or rejection or refusal\$ or intent\$ or controversy\$ or misconception\$ or misinformation or opposition or delay or dilemma\$ or objector\$)).ti,ab.
2. ((vaccin\$ or immunis\$ or immuniz\$) adj3 (uptake or barrier\$ or choice\$ or mandatory or compulsory or concern\$ or acceptance\$ or knowledge or parent\$ concern\$)).ti,ab.
3. (((vaccin\$ or immunis\$ or immuniz\$) adj5 confidence) not confidence interval).ti,ab.
4. ((vaccin\$ or immunis\$ or immuniz\$) adj5 decision making).ti,ab.
5. ((vaccin\$ or immunis\$ or immuniz\$) and (anti-vaccin\$ or antivaccin\$)).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. exp vaccination/
8. Vaccines/
9. Mass Vaccination/
10. Immunization/
11. exp Immunization Programs/
12. 7 or 8 or 9 or 10 or 11
13. Public Opinion/
14. Attitude to Health/
15. Attitude/
16. Health Knowledge, Attitudes, Practice/
17. "Patient acceptance of health care"/
18. Treatment Refusal/
19. Parental Consent/
20. Decision Making/
21. Prejudice/
22. Internet/
23. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 12 and 23
25. 6 or 24
26. limit 25 to humans
27. ((vaccin\$ or immunis\$ or immuniz\$) adj5 (anxiety or attitude\$ or awareness or behavior\$ or belief\$ or criticism\$ or doubt\$ or distrust or dropout\$ or exemption\$ or fear\$ or hesitancy\$ or trust or mistrust or perception\$ or refusal\$ or rejection or refusal\$ or intent\$ or controversy\$ or misconception\$ or misinformation or opposition or delay or dilemma\$ or objector\$)).ti,ab.
28. ((vaccin\$ or immunis\$ or immuniz\$) adj3 (uptake or barrier\$ or choice\$ or mandatory or compulsory or concern\$ or acceptance\$ or knowledge or parent\$ concern\$)).ti,ab.

29. (((vaccin\$ or immunis\$ or immuniz\$) adj5 confidence) not confidence interval).ti,ab.
30. ((vaccin\$ or immunis\$ or immuniz\$) adj5 decision making).ti,ab.
31. ((vaccin\$ or immunis\$ or immuniz\$) and (anti-vaccin\$ or antivaccin\$)).ti,ab.
32. 27 or 28 or 29 or 30 or 31
33. exp vaccination/
34. Vaccines/
35. Mass Vaccination/
36. Immunization/
37. exp Immunization Programs/
38. 33 or 34 or 35 or 36 or 37
39. Public Opinion/
40. Attitude to Health/
41. Attitude/
42. Health Knowledge, Attitudes, Practice/
43. "Patient acceptance of health care"/
44. Treatment Refusal/
45. Parental Consent/
46. Decision Making/
47. Prejudice/
48. Internet/
49. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. 38 and 49
51. 32 or 50
52. limit 51 to humans

Appendix 2. WHO Regions and countries²

WHO Western Pacific Region	WHO African Region	WHO EURpean Region	WHO Region of the Americas	WHO Eastern Mediterranean Region	WHO South-East Asia Region
Australia	Algeria	Albania	Antigua and Barbuda	Afghanistan	Bangladesh
Brunei	Angola	Andorra	Argentina	Bahrain	Bhutan
Darussalam	Benin	Armenia	Bahamas	Djibouti	Democratic People's
Cambodia	Botswana	Austria	Barbados	Egypt	Republic of
China	Burkina Faso	Azerbaijan	Belize	Iran (Islamic Republic of)	Korea
Cook Islands	Burundi	Belarus	Bolivia (Plurinational State of)	Iraq	India
Fiji	Cameroon	Belgium	Brazil	Jordan	Indonesia
Japan	Cape Verde	Bosnia and Herzegovina	Canada	Kuwait	Maldives
Kiribati	Central African Republic	Bulgaria	Chile	Lebanon	Myanmar
Lao People's Democratic Republic	Chad	Croatia	Colombia	Libya	Nepal
Malaysia	Comoros	Cyprus	Costa Rica	Morocco	Sri Lanka
Marshall Islands	Congo	Czech Republic	Cuba	Oman	Thailand
Micronesia (Federated States of)	Côte d'Ivoire	Denmark	Dominica	Pakistan	Timor-Leste
Mongolia	Democratic Republic of the Congo	Estonia	Dominican Republic	Qatar	
Nauru	Equatorial Guinea	Finland	Ecuador	Saudi Arabia	
New Zealand	Eritrea	France	El Salvador	Somalia	
Niue	Ethiopia	Georgia	Grenada	South Sudan	
Palau	Gabon	Germany	Guatemala	Sudan	
Papua New Guinea	Gambia	Greece	Guyana	Syrian Arab Republic	
Philippines		Hungary		Tunisia	
Republic of Korea		Iceland		United Arab Emirates	
Samoa		Ireland		Yemen	
Singapore		Israel			
Solomon Islands		Italy			
Tonga		Kazakhstan			
		Kyrgyzstan			
		Latvia			
		Lithuania			
		Luxembourg			

² Source: <http://www.who.int/about/regions/en/index.html>

Tuvalu	Ghana	Malta	Haiti		
Vanuatu	Guinea	Monaco	Honduras		
Viet Nam	Guinea-Bissau	Montenegro	Jamaica		
	Kenya	Netherlands	Mexico		
	Lesotho	Norway	Nicaragua		
	Liberia	Poland	Panama		
	Madagascar	Portugal	Paraguay		
	Malawi	Republic of Moldova	Peru		
	Mali	Romania	Saint Kitts and Nevis		
	Mauritania	Russian Federation	Saint Lucia		
	Mauritius	San Marino	Saint Vincent and the Grenadines		
	Mozambique	Serbia	Suriname		
	Namibia	Slovakia	Trinidad and Tobago		
	Niger	Slovenia	United States of America		
	Nigeria	Spain	Uruguay		
	Rwanda	Sweden	Venezuela (Bolivarian Republic of)		
	Sao Tome and Principe	Switzerland			
	Senegal	Tajikistan			
	Seychelles	The former Yugoslav Republic of Macedonia			
	Sierra Leone	Turkey			
	South Africa	Turkmenistan			
	Swaziland	Ukraine			
	Togo	United Kingdom			
	Uganda	Uzbekistan			
	United Republic of Tanzania				
	Zambia				
	Zimbabwe				

Appendix 3. Determinants of vaccine hesitancy identified in relation to childhood vaccines and vaccination.

Figure 11. Factors identified as either barriers (B) to or promoters (P) of childhood vaccination and mapped onto Vaccine Hesitancy model (multivariate studies reviewed, n=76)

		ALL REGIONS		AMERICAS		EURO		WPR		AFRICA		GLOBAL		SEAR		EMRO	
		B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P
Contextual influences	Socio-economic group																
	Religion / Culture / Gender																
	Politics / policies (eg. Mandates)																
	Influential leaders and individuals																
	Communication and media environment																
	Pharmaceutical Industry																
	Historical influences																
	Geographic barriers																
Vaccine and vaccination-specific issues	Risk/benefit (scientifically based)																
	Vaccination schedule																
	Mode of administration																
	Mode of delivery																
	Introduction of a new vaccine or new formulation																
	Reliability of vaccine supply																
	Role of healthcare professionals																
	Costs																
Individual/social group influences	Tailoring vaccines / vaccination to needs																
	Experience with past vaccination																
	Risk/Benefits (perceived / heuristics)																
	Personal experience with and trust in health system and provider																
	Knowledge/awareness of why/where/what/when vaccines are needed																
	Beliefs, attitudes and motivation about health and prevention																
	Immunisation is a social norm vs immunization is not needed/harmful																

Figure 12. Breakdown of factors identified as ‘Contextual Influences’ (see above) for childhood vaccines

			ALL REGIONS		AMERICAS		EURO		WPR		AFRICA		GLOBAL		SEAR		EMRO	
			B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P
Contextual influences	Socio-economic group	Age (Adult/Caregiver)																
		Age (Physician)																
		Race/Ethnicity																
		Birthplace																
		Income / SES																
		Marital status (M) / family composition																
		Education																
		Occupation																
		Language Proficiency																
		Family decision making																
		Access to health care																
		Health status																
		Age (Child)																
		Birth Order																
		Birth interval																
		Birthweight																
		Birth Environment																
		Number of births given (parity)																
		Family Size																
	Religion / Culture / Gender	Religious affiliation																
		Cultural																
		Gender (Child)																
		Gender (Adult)																
	Politics / policies (eg. Mandates)	Politics																
		Policies																
	Influential leaders and individuals	Influential leaders and individuals																
	Communication and media environment	Access to information																
		Mass Media (Use and influence)																
	Pharmaceutical Industry	Pharmaceutical Industry																
	Historical influences	Historical influences																
	Geographic barriers	Place of residence																

Figure 13. Breakdown of factors identified as 'Vaccine & vaccination-specific issues' (see above) for childhood vaccines

			ALL REGIONS		AMERICAS		EURO		WPR		AFRICA		GLOBAL		SEAR		EMRO	
			B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P
Vaccine and vaccination-specific issues	Risk/benefit (scientifically based)	Use of evidence		I		I												
		Trust in evidence																
	Vaccination schedule	Schedule	III		II						I							
	Mode of administration	Mode of administration																
	Mode of delivery	Campaign	II		I						I							
	Introduction of a new vaccine or new formulation	Introduction of a new vaccine or new formulation																
	Reliability of vaccine supply	Supply	I								I							
		Patient communication																
	Role of healthcare professionals	Vaccination expectations																
		Organisational culture	III	I	I	I	II											
		Place of work																
		Financial	I	I	I						I							
	Costs	Time	I		I													
		Administrative	I		I													
		Access	III	III			I		I		I	II			I		I	
	Tailoring vaccines / vaccination to needs	Options	I				I											

Figure 14. Breakdown of factors identified as 'Individual / social group influences' (see above) for childhood vaccines

		ALL REGIONS		AMERICAS		EURO		WPR		AFRICA		GLOBAL		SEAR		EMRO	
		B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P
Individual/social group influences	Experience with past vaccination	Vaccination behaviour															
		Susceptibility to disease															
	Risk/Benefits (perceived / heuristics)	Disease severity															
		Vaccine safety															
		Vaccine efficacy															
	Personal experience with and trust in health system and provider	Distrust / fear of vaccine due to:															
		Satisfaction with public health system															
	Knowledge/awareness of why/where/what/when vaccines are	Knowledge - Vaccination															
		Knowledge - General Health															
		Attitude															
	Beliefs, attitudes and motivation about health and prevention	Beliefs															
		Motivation / Practices															
	Immunisation is a social norm vs immunization is not needed/harmful	Need for vaccine															