Vaccine 32 (2014) 6870–6879

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

A systematic literature review of missed opportunities for immunization in low- and middle-income countries

Shruti Sridhar[1], Nadira Maleq[2], Elise Guillermet[2], Anais Colombini, Bradford D. Gessner*

Agence de Médecine Preventive, 164 Rue de Vaugirard, Paris 75015, France

ARTICLE INFO

Article history:
Received 24 August 2014
Received in revised form 18 October 2014
Accepted 21 October 2014
Available online 4 November 2014

Keywords:
Immunization
Missed opportunity
Vaccine
Vaccine hesitancy
Systematic review
Meta-analysis

ABSTRACT

Background: Missed opportunities for immunization (MOIs) may contribute to low coverage in diverse settings, including developing countries.
Methods: We conducted a systematic literature review on MOIs among children and women of childbearing age from 1991 to the present in low- and middle-income countries. We searched multiple databases and the references of retrieved articles. Meta-analysis provided a pooled prevalence estimate and both univariate and multivariate meta-regression analysis was done to explore heterogeneity of results across studies.
Results: We found 61 data points from 45 studies involving 41,310 participants. Of the 45 studies, 41 involved children and 10 involved women. The pooled MOI prevalence was 32.2% (95% CI: 26.8–37.7) among children – with no change during the study period – and 46.9% (95% CI: 29.7–64.0%) among women of child-bearing age. The prevalence varied by region and study methodology but these two variables together accounted for only 12% of study heterogeneity. Among 352 identified reasons for MOIs, the most common categories were health care practices, false contraindications, logistic issues related to vaccines, and organizational limitations, which did not vary by time or geographic region.
Conclusions: MOI prevalence was high in low- and middle-income settings but the large number of identified reasons precludes standardized solutions.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

After the Global Advisory Group of the World Health Organization (WHO) recommended the strategy of immunizing at every opportunity in 1983, protocols were developed for evaluating the magnitude and risk factors for missed opportunities for immunization (MOI) by WHO [1]. It defined a missed opportunity as an occasion when a person eligible for immunization and with no valid contraindication visits a health service facility and does not receive all recommended vaccines. Following the publication of a systematic review on missed opportunities during 1993 [2], the goal was set to achieve full immunization of 90% of the world's children by 2000. This goal has not been achieved as of 2013, and one of the major contributors is MOIs [3].

The objective of our study was to perform a systematic literature review to assess the prevalence of missed immunization opportunities in low- and middle-income countries since publication of the last summary review during 1993. We focused on children and women of child-bearing age – as these are the target groups for publicly funded immunization programs in the evaluated countries – and assessed the importance of temporal and geographic variations.

2. Materials and methods

2.1. Database search

Two authors (SS and NM), conducted the database search and data extraction. We included searches of the following: PubMed, Cochrane, Popline, WHO regional databases (LILACS: Latin American and Caribbean; IMSEAR: Index Medicus of South East Asian

Abbreviations: AJOL, The African Journal Online; IMEMR, Index Medicus Eastern Mediterranean region; IMSEAR, Index Medicus of South East Asian Region; LILACS, Latin American and Caribbean; MOI, missed opportunity for immunization; PAHO, Pan American Health Organization; UNICEF, United Nations International Children's Emergency Fund; WHO, World Health Organization; WPRIM, Western Pacific Region Index Medicus.

* Corresponding author at: 164 Rue de Vaugirard, Paris 75015, France. Tel.: +33 1 5386 8920.
E-mail addresses: shrutilion@gmail.com (S. Sridhar), bgessner@aamp.org, bdgessne@yahoo.com (B.D. Gessner).

[1] Worked for Agence de Médecine Preventive while performing this work. Currently, she is an independent contractor.
[2] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.vaccine.2014.10.063
0264-410X/© 2014 Elsevier Ltd. All rights reserved.

Region; PAHO: Pan American Health Organization; WPRIM; Western Pacific Region Index Medicus; IMEMR: Index Medicus Eastern Mediterranean region), the African Journal Online (AJOL), and Google Scholar. Databases requiring paid access (EMBASE, CINAHL etc.) were not included because of budget constraints; despite this, after consultation with the WHO librarian, the authors considered that the included databases were likely to have identified all or the great majority of relevant manuscripts.

Our goal was to include immunization terms combined with practices, services and type of study. Our search terms included "immunization" OR "vaccination" (or any of numerous synonyms) in combination with "Health Knowledge, Attitudes, Practice" OR "Attitude of Health Personnel" OR "Immunization/trends" OR "Immunization/utilization" OR "Immunization/physiology" OR "Vaccination/psychology" OR "Vaccination/trends" OR "Vaccination/utilization" OR "Preventive Health Services/trends" OR "Health Services/trends" OR ("Health Services/utilization" AND "Epidemiologic Studies") OR "Follow-Up Studies" OR "Health Surveys" OR "Data Collection". For PubMed, MeSH (Medical Sub-headings) was used to help expand the search. These terms were then combined with the names of individual low- and middle-income countries. Additional manuscripts in French papers were searched on Google using the terms ([Opportunité] AND [manquée/perdue] AND [vaccination/immunization]) OR (Perte AND opportunité AND vaccination).

2.2. Inclusion criteria and selection process

We included studies that measured the magnitude or described the reasons for missed opportunities in children (0–18 years) or woman of childbearing age in low- or middle-income countries (as defined by the World Bank during 2013) after 1991. Only studies in English, Spanish, French and Portuguese were included based on staff translation capacity.

Following pilot testing of the selection form, two independent reviewers reviewed in a stepwise fashion the title, abstract, and full text using Distiller Software (Fig. 1). Discrepancies were resolved through consensus. The references of all included manuscripts were searched for additional manuscripts. As indicated in Fig. 1, we had three ancillary searches. The African Journal Online database was searched for the terms "missed" AND "immunization" AND "opportunities"; this led to 53 results, of which three manuscripts were included after title abstract and full text screening. The Google search for French references yielded 30 results, of which four manuscripts eventually were included. Lastly, a secondary PubMed search using the term "missed immunization opportunities" led to 307 results and seven included manuscripts.

2.3. Quantitative data extraction

Of 59 [4–62] identified manuscripts, 45 [4–48] were included in quantitative analysis. These 45 studies included data on the number of persons with MOI as well as the total population under study eligible for vaccination (N), regardless of study methodology. Study participants were considered to have a MOI if they visited a healthcare facility, were not up-to-date on recommended immunizations, and did not receive recommended immunizations irrespective of the number of visits. The total population (N) eligible for vaccination equaled the sum of persons who were fully or partially vaccinated, those who had false contraindications for vaccination, and those with missed opportunities. Some manuscripts provided more than one data point, for example data for multiple countries (one report from South America had information on 10 countries) or for both women and children. For these cases, we included each data point separately in analysis (Table 1).

2.4. Qualitative data extraction

Qualitative data included reporting source, definition of missed opportunities, reasons for MOIs, and limits and quality of data.

2.5. Statistical analysis

All analyses were carried out in Stata version 12. Prevalence was calculated directly from manuscripts as a ratio of the number of children or women with MOIs divided by the total eligible population and the standard error calculated. Pooled estimates were calculated during meta-analysis using the *metan* command [63] in Stata on the prevalence and standard error. Heterogeneity was explored statistically using *Cochrane Q* and *I2* values, a statistic that quantifies the degree of inconsistency across studies in a meta-analysis on a scale ranging from 0 to 100%. A random effects model was used for weighting because of a high level of heterogeneity between studies. Results were stratified by WHO region, year of the study (time trend), methodology, and age group of children.

Eight variables in the dataset were reported commonly enough to be evaluated as potential covariates. Bivariate regression analysis was performed to establish the association between each of these variables and the prevalence estimate. Variables associated with missed opportunity prevalence with a p-value <0.05 on bivariate analysis were included in a meta-regression analysis [64]. Meta-regression was performed with the "metareg" command using prevalence as the outcome variable. All analyses were done separately for women and children.

2.6. Quality assessment

No standard method exists for assessing data quality in descriptive reports. Consequently, we developed the following methodological quality scoring system based on four variables:

- Location: health center based but no details given as to the nature of the site = 0; retrospective community-based = 1; health center based and details provided = 2.
- Methodology: recall/no immunization cards = 0; immunization cards = 1; exit interviews/health center records = 2.
- Definition of missed opportunity used in the study: non-WHO definition = 1; WHO definition = 2.
- Sample size: ≤500 = 0, 501–1000 = 1, >1000 = 2.

The study authors developed the scoring system and information for all variables was extracted from the manuscripts themselves. The scoring system was developed as a means of standardizing bias assessment and to account for the lack of explicit bias assessment in most of the included studies. We considered that community-based household surveys due to their retrospective nature were more susceptible to recall bias than studies conducted in health centers. With respect to study methodology, we considered that exit interviews combined with health center records had the least bias in assessing immunization status. With respect to MOI definition, we considered that use of the WHO definition was less biased than an ad hoc definition, although we recognize no empiric data support this decision. These first three variables were used as measures of study validity, while the final variable was used as a measure of study precision. To calculate the total score, we summed values for these four variables.

3. Results

We identified 59 studies from 31 countries and 6 WHO regions (Supplemental Table 1). Of these, 45 studies (containing 61 data

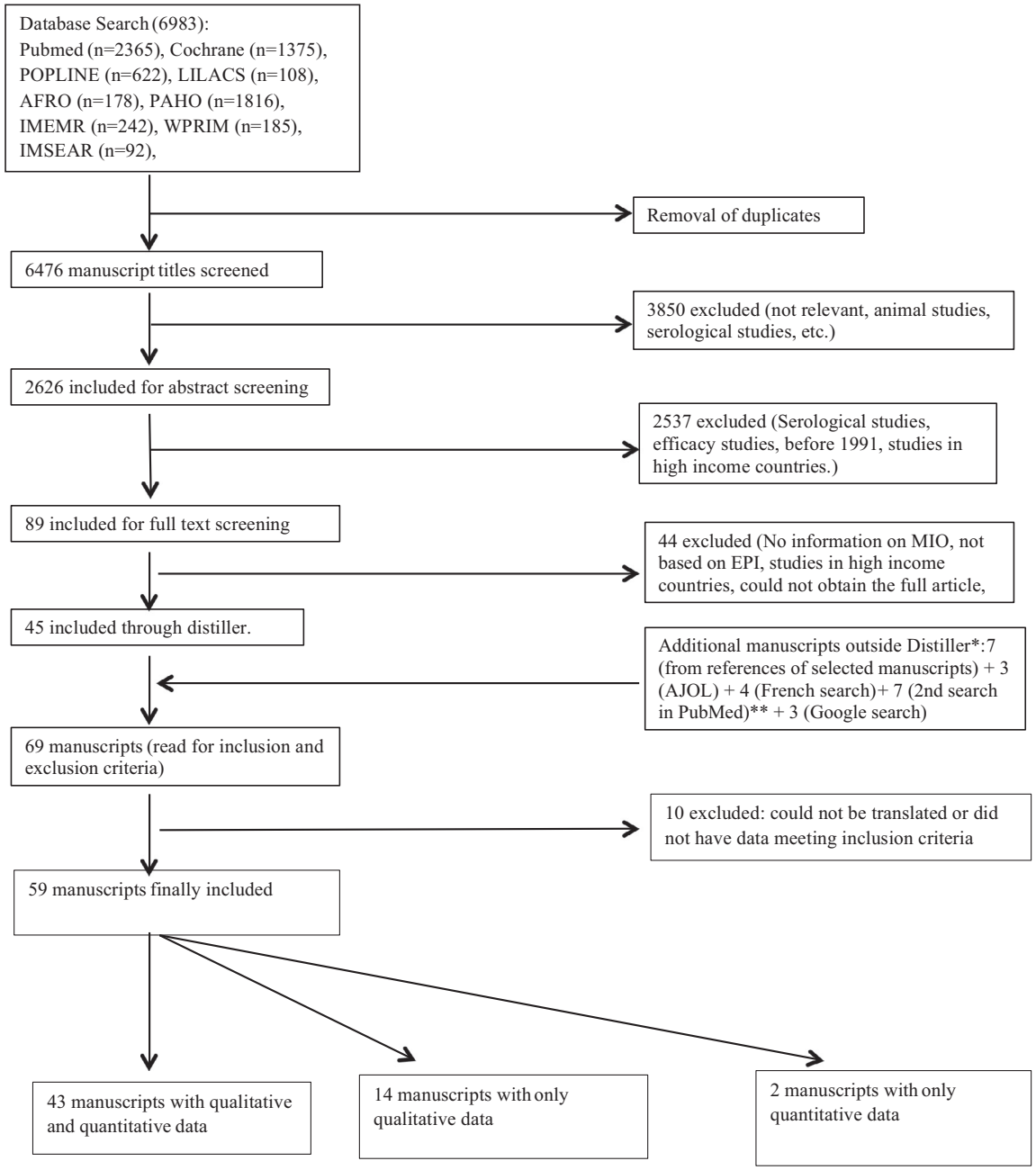

Fig. 1. Flow chart representing results of the systematic review.

Table 1
The prevalence of missed opportunities for immunization by vaccine type.

Country	Setting	BCG (%)	DPT (%)	Measles (%)	OPV (%)
India [45]	Population based	37.1	31.2	–	–
Ghana [22]	Not specified	–	–	75	–
South Africa [20]	Mixed[a]	–	–	15.7	–
Papua New Guinea [46]	Tertiary hospital	15	36	26	36
South Africa [17]	Population based	5.1	35.8	35.8	35.8
Guinea [16]	Population based	8	18	15	18
South Africa [15]	Mixed	–	–	16.2	–
Brazil [34]	Tertiary hospital	0.4	19	6.4	13.4
India [43]	Population based	–	–	15.3	–
Philippines [47]	Tertiary hospital	0.3	4.9	4.9	3
Nigeria [25]	Tertiary hospital	5	48	70	46.7

[a] Mixed refers to mix of various types of hospitals (primary, secondary and tertiary care centers).

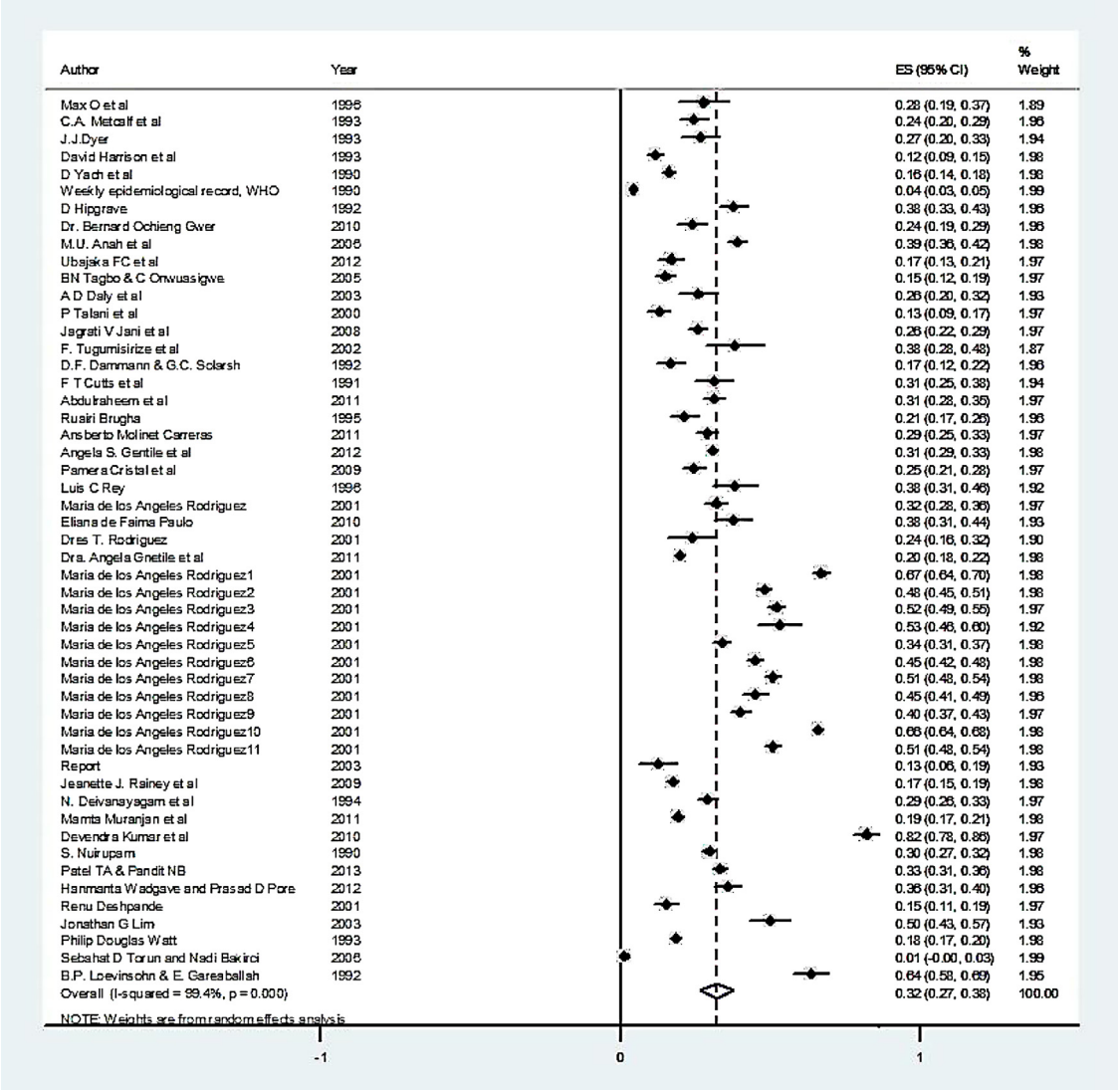

Fig. 2. Forest plot showing the pooled prevalence estimates of missed opportunities for immunization among children.

points) had data available for quantitative and 57 for qualitative analysis (Supplemental Table 2). Of the 61 data points available for quantitative analysis, 48 had data from health services-based studies (including 46 based on exit interview and 2 on hospital record surveys) while 13 were from population based studies (including 4 based on vaccination card review and 9 based on card review plus interviews). The majority of studies reported data for children (51 out of 61 data points used for quantitative analysis) and for this reason most analyses were performed only for studies with data on children.

3.1. Quantitative results in children

For the 51 data points available for children, the prevalence of MOIs ranged from 1.3% in a study in Turkey [4] to 82% in a study in India [5]. The pooled MOI prevalence estimate was 32.2% (26.8–37.7) (Fig. 2). MOI prevalence was modestly higher in the Americas than in Africa and Southeast Asia (Fig. 3). Most of the studies in the African, American, and Southeast Asian regions measured MOI prevalence using exit interviews (Fig. 4), following WHO recommendations.

We did not identify any increase or decrease in MOIs over the study period (Fig. 5). To control for potential confounding by unmeasured factors that varied by country, we evaluated three individual countries from three different WHO regions that had at least six data points. While we found a slight increase in prevalence in South Africa [10,15,17,19–21] and India [5,8,41–45] and a decrease in Brazil [31,34,35,39], none of these changes were statistically significant.

Of 26 studies with information available on setting, 19 [5,9,11,12,14,15,18,20,22–24,31,34,38,39,42,44,46,47] measured missed opportunities only in a curative setting, 4 studies only in a preventive setting [13,33,35,45] and 3 in both settings [8,10,25]. The pooled prevalence estimated in the curative setting was 33.4% (95% CI: 23.8–43.0) and in the preventive setting was 17.8% (95% CI: 9.4–26.1). When considering only the three studies that measured data in both settings, no difference in pooled prevalence was seen.

Eleven studies [15–17,20,22,25,34,43,45–47] reported MOI prevalence by vaccine type (Table 1). Of these, six studies included all of the following vaccines: BCG, DPT, measles and OPV. With the exception of one study in India, BCG (recommended for use during the newborn period) had the lowest prevalence while patterns for other vaccines varied by study.

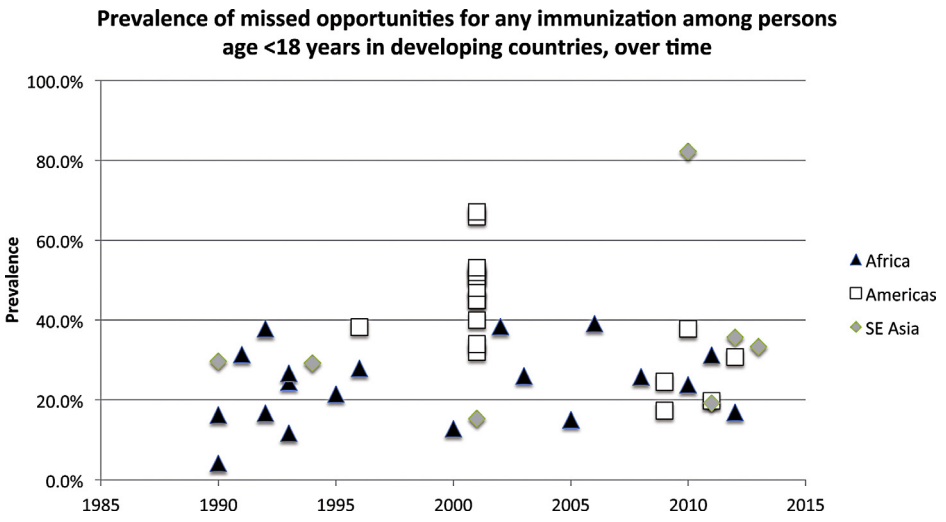

Fig. 3. Prevalence of missed opportunities for any immunization among persons age 0–18 years in developing countries, over time.

3.2. Risk factor analysis in children

During bivariate analysis, there was an association ($p < 0.05$) between MOI prevalence and region of study, methodology, and age group of the population. Age group categories, however, were not mutually exclusive (that is, studies using differing and overlapping age group categories) making it impossible to include this variable in a multivariate analysis. In the final meta-regression, both study methodology ($p = 0.089$) and study region ($p = 0.048$) were associated with MOI prevalence to approximately the same degree. The final model R-square was 12%. A second model was created with year of study entered as a dichotomous variable based on pre-2005 and post-2005, but this did not change results.

3.3. Women of reproductive age

Ten studies provided 10 data points for women of reproductive age. The pooled MOI prevalence was 46.9% (CI: 29.7–64.0%) and ranged from 11.6% in a study in Ethiopia [6] to 88% [7] in a study in Swaziland. Six data points derived from the African region [6,7,18,23,29,30], two from the American region [31,40] and one study each from the Southeast Asian [42] and European regions [48]. Of the 10 data points, seven were collected using the exit interview methodology.

3.4. Reasons for missed opportunities for immunization

We included 57 studies in the analysis of reasons for missed opportunities. These studies reported 352 reasons for children and women of reproductive age. These reasons were categorized as related to service providers, the parents, and the immunization system (Table 2). Among children, most reported reasons were categorized as related to service providers and parents. Lack of availability of vaccines and other logistic problems were less commonly reported. Economic barriers were rarely reported.

Of the 10 articles with information on women of childbearing age, four had information exclusively on women (specifically, for tetanus toxoid vaccine). The reasons mainly revolved around healthcare practices of the providers and logistic problems.

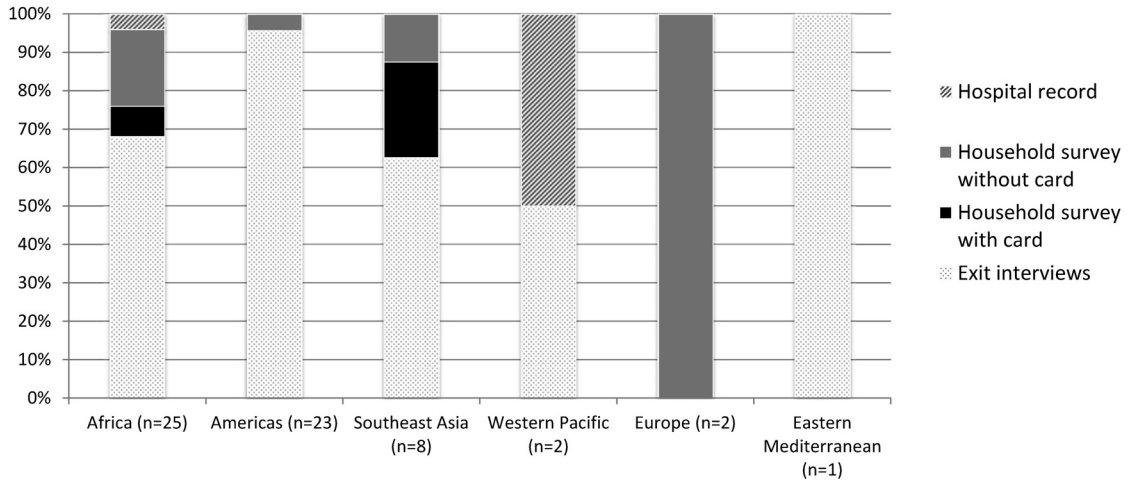

Fig. 4. Methodology used to assess missed opportunities for immunization for six World Health Organization Regions.

Table 2
Reasons for missed opportunities for immunization among children and women of reproductive age-group.

I. Children	*317*
A. Practices	75
1. Health care providers (HCP)	59
Immunization cards not reviewed	13
Immunization history not reviewed	9
HCP reluctant to open vaccine vial	8
Immunization not offered	7
Delays	4
Referral to clinics or other services	3
Lack of interaction and communication	2
Negative attitude of HCP	2
No administration of vaccines simultaneously	2
No advice to vaccinate	2
Practices (not detailed)	2
Negative attitude from the HCP	1
Not following the new policy	1
Patients discharged	1
Reminder not given by the health staff	1
Wrong immunization history	1
2. Parents	16
Immunization cards not available	10
Children did not report to the immunization staff	1
Forgetfulness in bringing the subjects to the vaccine providers	1
Maternal causes	1
No administration of vaccines simultaneously	1
Not following the new policy	1
Unavailable immunization card	1
B. Perceived contraindications	65
1. Health care providers	18
Not further detailed	6
Concurrent illness	5
Concurrent treatment for illness	2
Difficult birth	1
Low birth weight	1
Preterm birth	1
Underweight	1
Previous history of vaccine reaction	1
2. Contraindications (parents)	47
Concurrent sickness not otherwise specified	34
Concurrent infection	6
Not otherwise specified	4
Preterm birth	3
Concurrent treatment for illness	2
Under nutrition	1
C. Immunization session organization	56
Lack of time to perform immunizations given other provider duties	9
Lack of health staff	8
Long waiting time	7
Days designed for immunization limited	7
Need to separate preventive and curative services	4
Distance to center too far	3
Lack of orientation toward immunization	3
Poor communication about immunization	2
No schedule	2
Vaccination rooms not accessible	2
Lack of information	1
Lack of interaction	1
Lack of organization	1
Lack of physical space to perform immunizations	1
No days designated for immunization	1
Quality of health services	1
Schedules not communicated	1
Vaccination rooms far from consultation rooms	1
D. Logistics	33
Lack of vaccines (out of stock, not accessible to curative services)	21
Logistical problems not otherwise specified	6
Closed room	1
Cold chain failures, poor stock control	1
Irregular vaccine supply	1
Lack of adequate material	1
Lack of electricity	1
Lack of water	1

Table 2 (*Continued*)

E. Awareness, beliefs and knowledge	28
1. Awareness: health care provider	4
Lack of health care provider knowledge and awareness	3
Vaccination not seen as necessary	1
2. Awareness: parents	7
Vaccination not seen as necessary	2
Lack of awareness	1
Lack of information on vaccine availability	1
Lack of parental awareness	1
Many children	1
Vaccination not seen as necessary for older children	1
3. Beliefs: health care providers	2
Beliefs about side effects	1
Fears	1
4. Beliefs: parents	5
Concern about vaccine safety	1
Cultural plus religious reasons	1
Cultural reasons	1
Fears (unspecified)	1
Fears about side effects	1
5. Knowledge: health care providers	2
Knowledge on cold chain management	1
About prescription of vaccinations	1
6. Knowledge: parents	8
Lack of knowledge (not specified)	3
Lack of knowledge about expanded program on immunization	2
Calendars not known	2
Days designated for immunization not known	1
F. Attitudes	18
1. Health care providers	4
Negative attitude	1
Refusal	1
Refusal to deliver multiple doses	1
Vaccination not seen necessary	1
2. Parents	14
Refusal	5
Negative attitude of parents	3
Forgetfulness	2
Delays	1
Refusal of several doses	1
Stress	1
Vaccination not seen necessary	1
G. Economic barriers	8
Lack of money	5
Lack of transportation	2
Lost daily wages	1
H. Determinants	28
Other	6
Older child age	6
Lower maternal education	6
Place of delivery	3
Maternal unemployment	2
Older maternal age	1
Young maternal age	1
Child's death	1
Lower paternal education	1
Marital status of mothers	1
Women of reproductive age	*35*
A. Practices	8
1. Health care providers	7
Immunization cards not reviewed	2
Immunization history not reviewed	2
Immunization not offered	1
No advice to vaccinate	1
Referrals	1
2. Parents/recipients	1
Immunization cards not available	1
B. Attitudes	7
1. Health care providers	5

Table 2 (*Continued*)

Immunization not seen as a priority	1
Lack of motivation	3
Negative attitude of health care provider	1
2. Parents/recipients	2
Carelessness	1
Fear of being vaccinated during pregnancy	1
C. Awareness, beliefs and knowledge	7
1. Awareness: health care providers	1
Lack of awareness/knowledge	1
2. Awareness: parents/recipients	1
Lack of awareness/knowledge	1
3. Beliefs: health care providers	1
Vaccination not seen necessary	1
4. Knowledge: health care providers	2
Lack of knowledge	1
Schedules for immunization not known	1
5. Knowledge: parents/recipients	2
Lack of knowledge (purpose, schedules)	1
Lack of knowledge about number of doses	1
D. Organization	7
Days designed for immunization limited	2
Lack of information	2
Lack of time	2
Lack of communication	1
Lack of productivity	1
E. Contraindications	2
Concern for the safety of women during early pregnancy	1
Menstruation	1
F. Logistics	2
Inefficient immunization record keeping system	1
Lack of vaccines	1
G. Economic barriers	1
Lack of money	1
H. Determinants	1
Pregnant and no previous children or only one child	1
Total	352

There were 173 reasons for MOIs cited before 2005 and 179 after 2005 (total = 352). Reasons remained fairly constant over time except that before 2005, 27% ($n = 173$) of identified reasons were related to health care provider practices whereas after 2005, this number decreased to 11% ($n = 179$). In the African region, 30% of cited reasons were categorized as perceived contraindications whereas in the Americas, this reason accounted for 11%. Among all cited reasons in a curative setting, 24% were related to health care provider practices; among all cited reasons in a preventive setting, were related to parental perceived contraindications.

3.5. Quality assessment

Of the 61 data points, the mean quality assessment score was 6.0 out of a possible 8: three data points (5%) came from studies with a score of 2 or 3; 15 (23%) had a score of 4 or 5; 32 (52%) a score of 6 or 7; and 11 (18%) a score of 8. The mean score for children was 6.1 (range 2–8) and for women of reproductive age 5.2 (range 3–7). The mean score for data points in Africa was 5.4 (range 4–8) compared to 6.8 (range 4–8) for the Americas and 6.0 (range 2–8) for Southeast Asia. Three of our data assessment score categories evaluated bias; when considering only these three categories, the mean score was 5.3 out of a possible 6 (range, 3–6). The remaining score category measured precision; the mean score for this single category was 0.7 out of a possible 2.

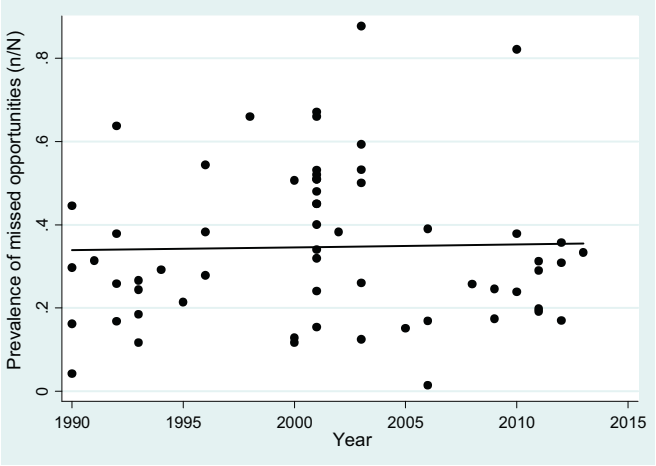

Fig. 5. Scatter plot showing trend in the prevalence of missed opportunities for immunization over time since 1991 (line shows fitted value).

4. Discussion

During 1993, WHO released its first report on missed immunization opportunities globally, which identified a median prevalence of 41% (range; 0–99%) in developing countries [2]. Several strategies then were adopted to address this issue. In 2005, WHO and UNICEF together published the Global Immunization Vision and Strategy (GIVS) for the decade 2006–2015 [65]. According to this, there was an increase in quantities of WHO prequalified vaccines offered to UNICEF after 2003. However, assessment of individual vaccine procurement by UNICEF shows a varying picture. Since 2003, the DTP procurement per year has been steadily falling and in 2013, there was a reported shortage of 5 million doses which was requested to be supplied [66]. By contrast the procurement of *Haemophilus influenzae* type b conjugate and hepatitis B vaccines from WHO increased since 2003 [67]. Also, by mid-2005, 53 countries, mostly in Asia and Africa, had begun implementing the RED (Reaching Every District) strategy, which takes the district as its primary focus and aims to improve equity in access to immunization by targeting difficult-to-reach populations [65]. This strategy focused on training for good immunization practices, timely collection of data on vaccine coverage and other vaccine-related activities (logistics, supply, and surveillance), proper supervision of immunization health workers, and involvement of communities in the planning and delivery of immunization services.

Given these substantial efforts, it would have been reasonable to expect a substantial decrease in the number of missed opportunities. However, the median prevalence for missed opportunities among children in our review was 32%, which is only modestly lower than the 1993 estimates. Moreover, no improvement could be documented over the 22-year time horizon of the current study. While studies from 2005 and later showed some decrease compared to earlier studies, methodological differences make conclusions difficult. This point is emphasized by the evaluation of individual countries, which show no evidence of declining MOI prevalence.

Additionally, efforts to increase immunization coverage do not equate with efforts to reduce MOIs because these are in part separate issues. For example, at the extreme, an area with high curative care use combined with high but delayed coverage delivered entirely in preventive settings could lead to both high MOI prevalence and high coverage.

We found higher MOI prevalence in the Americas than Africa, despite the much greater level of economic advancement and immunization infrastructure in the former area. The main reasons

for missed opportunities were immunization services practices, organization, and logistical barriers; all of these in theory should drive prevalence higher in more disadvantaged African settings. Methodological issues could explain some of the observed difference. For example, studies in the Americas were more likely to use exit interviews; additionally, studies only included persons who presented to health care facilities and thus by definition had enough resources for health care access. However, it may also be that missed opportunities do not occur primarily for economic reasons in lower income settings where most persons receive vaccines free of charge through national immunization programs, even if other cost barriers to attending an immunization clinic exist. Consistent with this observation, individual financial constraints were rarely reported as a cause of MOIs.

While studies evaluated missed opportunities in preventive and curative services, only three studies simultaneously evaluated both, and these studies found no difference by setting [8–10]. Nevertheless, we found different categories of reasons in the two settings, suggesting that intervention strategies will need to be tailored. Additionally, while the prevalence of missed opportunities may be similar in each setting, the bulk of immunizations are delivered in preventive settings and the barriers to implementing more complete immunization should be less in settings designed for this purpose. Finally, if immunization delivery in preventive settings functioned perfectly at all levels, no reason would exist to deliver immunization in curative settings. Consequently, we think the bulk of intervention efforts should focus on immunization clinics.

While some reasons for missed opportunities were more common than others, no single reason, or even category of reason, accounted for more than 25% of the total. This indicates that efforts to decrease missed opportunities must be multifaceted. Efforts to increase card retention would be useful and some strategies have been successful [68]; alternatively, new technologies such as rapid detection of biomarkers may identify children in need of vaccination [69,70]. Prefilled syringes or single-dose vials can overcome reluctance to open multi-dose vials [71]. Social messaging and provider training may address perceived contraindications. However, in settings with high mortality, not vaccinating children with serious acute or chronic illness may do more good for the immunization program as a whole even if it does not serve the interests of the individual child; this is because deaths temporally but not causally related to immunization nevertheless may be perceived as causally related by parents or community members. Opportunities exist to design better immunization systems that facilitate immunization delivery both for providers and recipients. Examples include SMS messaging [72], improved outreach strategies [73], and better organization of immunization sessions with adequate staff, time, and immunization rooms. For eligible countries, the GAVI Alliance financing window for health system strengthening could be used to support some of these activities. While we did not identify large differences in categories of reasons between Africa and Asia, it is likely that specific issues will be heavily influenced by the local cultural context, especially with regards to attitudes and beliefs.

While much overlap existed in reasons for missed opportunities between the current review and that conducted during 1993 [2], differences also were found. In particular, the 1993 review found that a substantial proportion of missed opportunities resulted from failure to administer vaccines simultaneously or patient refusal while more recent studies rarely reported these reasons. Polyvalent vaccines could have contributed to a decline in the former, as could better training of health care providers. Vaccine refusal or hesitancy has been attributed to various factors and the reasons range from individual or personal beliefs to contextual factors like wars to vaccine specific adverse events. WHO has addressed vaccine refusal over the last decade, which might have resulted in studies infrequently citing patient refusal as a reason for MOI in our study [74]. Regardless, the decline in two major reasons for missed opportunities combined with little evidence of an overall decrease in missed opportunities prevalence emphasizes the dynamic nature of this phenomenon. Consequently, decreasing missed opportunities is likely to require ongoing monitoring for new causes, particularly with the advent of social media, which can greatly amplify the speed and penetration of concerns related to immunization.

The main limitation of the current review was the highly varied methodology. Identified studies varied in the definition of missed opportunities, sample size, method of measurement, population, location, and other features. The lack of a gold standard methodology for conducting such studies also made it difficult to assess the degree to which methodology impacted differences between studies. Many studies reported reasons for missed opportunities as isolated events, whereas it is likely that in most cases missed opportunities resulted from a dynamic web of interrelated processes including system integration, communication between actors, culturally based concepts of immunization, differing health and economic priorities, and other issues. We identified a relatively small number of studies, which prevented more robust comparisons by region, age, and study methodology. We do not know the representativeness of studies we evaluated for other regions; in particular, studies tend to be conducted in urban centers or countries with a richer history of research.

Studies also were subject to a variety of biases. Selection bias occurred in the selection of the study population and the selection of cases within this population. For the former, studies frequently used populations that were easily accessible even if they were not representative of the underlying population. Across the studies, the age group of the children that were studied varied considerably. None of the groups were mutually exclusive. Cases selected for inclusion varied by the definition used. While most studies used the WHO definition (55 out of 61 data points), others used their own definitions. For example, according to the standard MOI case definition, persons who refused vaccination should be excluded, but this was not done consistently across studies.

Information bias occurred in studies using different methods to ascertain immunization receipt including immunization cards or other written records as well as verbal histories. Within studies relying on verbal histories, different persons provided this information, which may have influenced data accuracy.

Lastly, despite our efforts to identify all relevant papers, a systematic review is inherently an imperfect process due to issues such as differences in language use, something that likely is accentuated with a non-standardized outcome such as missed opportunities for immunization.

5. Conclusions and recommendations

Our data leads to several conclusions and recommendations. Implementation of standardized methodology would facilitate greatly comparison over space and time. Standardization should include the study setting, population, and interview methodology; the case definition should address explicitly issues such as whether patient refusal is considered part of the definition; and valid versus perceived contraindications should be identified. The Pan American Health Organization released an implementation manual [75] which gave a detailed definition of an eligible child, vaccines to be considered, vaccination schedule, study design, sample size and study population. The manual might be improved through inclusion of information on valid contraindications and

a clear position on whether patient refusal is considered a MOI. Finally, to be effective the manual needs to be implemented widely.

More studies are needed to determine if specific vaccines or presentation characteristics lead to more or fewer missed opportunities. As public immunization programs expand outside of infancy and pregnancy, studies will be needed on new target groups such as toddlers, adolescents, and the elderly. Because of the great variety of reasons contributing to missed opportunities, immunization professionals should identify interventions that could address various issues simultaneously. Additionally, identification of a reported reason for a missed opportunity does not necessarily mean that this reason was a necessary condition and thus that appropriate intervention would have eliminated the missed opportunity; to make this link, a need exists for well-designed intervention research including randomized trials [8,11].

Conflict of interest

All authors worked for AMP at the time of the study; AMP receives unrestricted support from Sanofi Pasteur and grant specific support from Crucell, GSK, Merck, Novartis, Pfizer and Sanofi Pasteur.

Acknowledgments

AMP: Audrey Gavard-Lonchey for project management. WHO: Alina Ximena Riveros Balta, Ana Maria Henao Restrepo and Thomas Allen for assistance with study design and literature searches.

The World Health Organization (Grant no. 2013/3422963-0) – Geneva provided funding for this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.10.063.

References

[1] WHO. Systematic review of missed opportunities for vaccination; 2013. Available online http://www.who.int/immunization/rfp_review_missed_opportunities_vaccination/en/index.html (accessed 05.05.14).
[2] Hutchins SS, Jansen HA, Robertson SE, Evans P, Kim-Farley RJ. Studies of missed opportunities for immunization in developing and industrialized countries. Bull World Health Organ 1993;17(5):549–60.
[3] Szilagyi PG, Rodewald LE. Missed opportunities for immunizations: a review of the evidence. J Public Health Manag Pract 1996;2(1):18–25.
[4] Torun SD, Bakirci N. Vaccination coverage and reasons for non-vaccination in a district of Istanbul. BMC Public Health 2006;6:125.
[5] Kumar D, Aggarwal A, Gomber S. Immunization status of children admitted to a tertiary-care hospital of North India: reasons for partial immunization or non-immunization. J Health Popul Nutr 2010;28(3):300–4.
[6] Yared M. Missed opportunity of tetanus toxoid immunization among pregnant women in Southern Ethiopia. Ethiop J Health Dev 2000;14(2):143–8.
[7] Daly AD, Nxumalo MP, Biellik RJ. Missed opportunities for vaccination in health facilities in Swaziland. S Afr Med J 2003;93(8):606–10.
[8] Deivanayagam N, Nedunchelian K, Mala N, Ashok TP, Rathnam SR, Ahmed SS. Missed opportunities for immunization in children under 2 years attending an urban teaching hospital. Indian Pediatr 1995;32(1):51–7.
[9] Rodriguez MA. Magnitud y causas de oportunidades perdidas en vacunacion en poblacion menor de dos anos en America. Rev CES Med 2001;15(1):71–80.
[10] Bachmann MO, Barron P. Missed opportunities for immunisation in curative and preventive services in a community health centre. A follow-up survey. S Afr Med J 1996;86(8):947–9.
[11] Loevinsohn BP, Gareaballah E. Missed opportunities for immunization during visits for curative care: a randomized cross-over trial in Sudan. Bull World Health Organ 1992;70(3):335–9.
[12] Anah MU, Etuk IS, Udo JJ. Opportunistic immunization with in-patient programme: eliminating a missed opportunity in Calabar, Nigeria. Ann Afr Med 2006;5(4):188–91.
[13] Ubajaka FC, Ukegbu AU, Okafor NJ, Ejiofor O. The prevalence of missed opportunities for immunization among children utilizing immunization services in NNAMDI AZIKIWE University Teaching Hospital, NNEWI. J Biol Agric Healthc 2012;6.(2).
[14] WHO. Expanded Programme on Immunization: missed opportunities for immunization. Wkly Epidemiol Rec 1990;65:167–70.
[15] Yach D, Metcalf C, Lachman P, Hussey G, Subotsky E, Blignaut R, et al. Missed opportunities for measles immunisation in selected western Cape hospitals. S Afr Med J 1991;79(8):437–9.
[16] Cutts FT, Diallo S, Zell ER, Rhodes P. Determinants of vaccination in an urban population in Conakry, Guinea. Int J Epidemiol 1991;20(4):1099–106.
[17] Dammann DF, Solarsh GC. The use of COSAS in the analysis of vaccination coverage in urban, peri-urban and rural populations in the Edendale/Vulindlela district of KwaZulu. S Afr Med J 1992;82(2):118–23.
[18] Hipgrave D. Missed opportunities for immunisation at Kasungu. Malawi Med J 1992;8(1):76.
[19] Harrison D, Barron P, Glass B, Sonday S, Heyde Yvd. Far fewer missed opportunities for immunisation in an integrated child health service. S Afr Med J 1993;83(8):575–6.
[20] Metcalf CA, Yach D, Beer ZJ. Missed opportunities for immunisation at hospitals in the Western Cape – a reappraisal. S Afr Med J 1994;84(3):149–52.
[21] Dyer JJ. Missed opportunities for immunisation in Natal health facilities. S Afr Med J 1993;83(8):577–9.
[22] Brugha R. Missed opportunities for immunizations at curative and preventive health care visits. Trans R Soc Trop Med Hyg 1995;89(6):698.
[23] Talani P, Nkounkou-Pika J, Mayanda H, Yala F. Les occasions de vaccination manquées à Brazzaville. Bull Soc Pathol Exot 2000;93(2):121–2.
[24] Tugumisirize F, Tumwine JK, Mworozi EA. Missed opportunities and caretaker constraints to childhood vaccination in a rural area in Uganda. East Afr Med J 2002;79(7):347–54.
[25] Tagbo BN, Onwuasigwe C. Missed immunization opportunities among children in Enugu. Nigerian J Pediatr 2005;32(4):73–6.
[26] Jani JV, Schacht CD, Jani IV, Bjune G. Risk factors for incomplete vaccination and missed opportunity for immunization in rural Mozambique. BMC Public Health 2008;8:161.
[27] Bernard OG (Ph.D. thesis) Missed opportunities for immunization in Nairobi province. University of Nairobi; 2010. Available online http://erepository.uonbi.ac.ke/ [accessed 10.04.13].
[28] Abdulraheem IS, Onajole AT, Jimoh AAG, Oladipo AR. Reasons for incomplete vaccination and factors for missed opportunities among rural Nigerian children. J Public Health Epidemiol 2011;3(4):194–203.
[29] Adeiga A, Omilabu SA, Audu RA, Sanni F, Lakehinde GP. Tetanus toxoid immunization coverage among mothers of below one year of age in difficult-to-reach area of Lagos Metropolis. Afr J Clin Exp Microbiol 2005;6(3):233–7.
[30] Edet EE, Ikpeme BM, Ndifon WO, Oyo-Ita AE. Factors associated with missed opportunities to immunise with tetanus toxoid at a tertiary health institution in Nigeria. Cent Afr J Med 1998;44(8):199–202.
[31] Rey LC. Missed opportunities for immunization in a pediatric hospital in Fortaleza, State of Ceará – Brazil. J Pediatr (Rio J) 1996;72(1):9–13.
[32] Rodriguez DT. Oportunidades perdidas en vacunacion [Missed opportunities in pediatric vaccination]. Med Infant 2001;8(1):23–5.
[33] Rainey JJ, Lacapère F, Danovaro-Holliday MC, Mung K, Magloire R, Kananda G, et al. Vaccination coverage in Haiti: results from the 2009 national survey. Vaccine 2012;30(9):1746–51.
[34] Santos PCF, Bohland AK, Paixão AC. Oportunidades perdidas de vacinação em hospital de referência pediátrica, em Aracaju (SE), Brasil [Missed immunization opportunities in a pediatric hospital in Aracaju, Sergipe, Brazil]. Rev APS 2009;12(1). Available online http://aps.ufjf.emnuvens.com.br/aps/article/view/95/185
[35] Paulo EF. Oportunidades perdidas de vacinação em crianças menores de dois anos de idade, ocorridas nas salas de vacinação, das unidades de saúde da região norte do município de São Paulo/Missed opportunities for vaccination in children under two years old, occurred in the halls of vaccination of health units in the northern region of Sao Paulo. Government Publication 2010. Report No.: category V02.500; Record number 35253; Unique identifier D022903.
[36] Gentile A, Bakir J, Firpo V, Caruso M, Lución MF, Abate HJ, et al. Delayed vaccine schedule and missed opportunities for vaccination in children up to 24 months. A multicenter study. Arch Argent Pediatr 2011;109(3):219–25.
[37] Carreras AM, León JRH. Cobertura de vacunación y su impacto en lactantes con la incorporación de Barrio Adentro en Sanare/Vaccination coverage and its impact on infants with Barrio Adentro inclusion in Sanare. Medisan 2011;15(12):1736–42.
[38] Gentile AS. Delayed schedules and missed opportunities for vaccination in children up to 2 years old. Rev Argent Salud Publica 2012;3(11):30–6.
[39] Sá SM (thesis) Oportunidades perdidas de vacinação em um hospital pediátrico de referência no Estado do Rio de Janeiro: uma análise exploratória [Lost chances of vaccination in a pediatric hospital of reference in the State of Rio de Janeiro: a exploratory analysis]. Fundação Oswaldo Cruz, Department: Escola Nacional de Saúde Pública Sergio Arouca; 2005. Available online http://www.arca.fiocruz.br/handle/icict/5458
[40] Borges de Mattos LM, Caiaffa WT, Bastos RR, Tonelli E. Missed opportunities for tetanus immunization of pregnant women in Juiz de Fora, Minas Gerais, Brazil. Rev Panam Salud Publica 2003;14(5):350–4.
[41] Wadgave HV, Pore PD. Missed opportunities of immunization in under-fives in adopted area of Urban Health Centre. Ann Trop Med Public Health 2012;5(5):436–40.

[42] Nirupam S, Chandra R, Srivastava VK. A survey of missed opportunity for immunization in Lucknow. Indian J Pediatr 1992;29(1):29–32.
[43] Deshpande R, Nimbalkar S, Banker N, Kapoor A. Prevalence of missed opportunities for measles immunization in rural areas of Gujarat. Indian J Pediatr 2001;68(7):609–12.
[44] Muranjan M, Mehta C, Pakhare A. An observational, health service based survey for missed opportunities for immunization. Indian J Pediatr 2011;48(8):633–6.
[45] Patel TA, Pandit NB. Why infants miss vaccination during routine immunization sessions? Study in a rural area of Anand District, Gujarat. Indian J Public Health 2011;55(4):321–3.
[46] Watt PD. Vaccination status and ward-based opportunistic immunization of children admitted to Madang General Hospital, 1985–1990. P N G Med J 1993;36(4):297–300.
[47] Lim JG. Immunization coverage and missed immunization among 1–5 year old patients seen at Chong Hua hospital, vol. 7(1). PIDSP; 2003.
[48] Kalaça S, Yalçin M, Simsek Yavuz S. Missed opportunities for tetanus vaccination in pregnant women, and factors associated with seropositivity. Public Health 2004;118(5):377–82.
[49] Cutts FT, Zell ER, Soares AC, Diallo S. Obstacles to achieving immunization for all 2000: missed immunization opportunities and inappropriately timed immunization. J Trop Pediatr 1991;37(4):153–8.
[50] Kofoed PE, Nielsen B, Rahman AK. Immunisation in a curative setting. BMJ 1990;301(6752):593–4.
[51] Downing SG, Lagani W, Guy R, Hellard M. Barriers to the delivery of the hepatitis B birth dose: a study of five Papua New Guinean hospitals in 2007. P N G Med J 2008;51(1–2):47–55.
[52] Nisar N, Mirza M, Qadri MH. Knowledge, attitude and practices of mothers regarding immunization of one year old child at Mawatch Goth, Kemari Town, Karachi. Pakistani. J Med Sciences 2010;26(1):183–6.
[53] Perry H, Weierbach R, El-Arifeen S, Hossain I. A comprehensive assessment of the quality of immunization services in one major area of Dhaka City, Bangladesh. Trop Med Int Health 1998;3(12):981–92.
[54] Borus PK. Missed opportunities and inappropriately given vaccines reduce immunisation coverage in facilities that serve slum areas of Nairobi. East Afr Med J 2004;81(3):124–9.
[55] Khatun J, Roy NC. Missed opportunities for reproductive and child health services of clients in urban NGO clinics of Bangladesh. Matern Child Health J 2006;10(6):563–70.
[56] Perry H, Weierbach R, Hossain I, Islam R. Tetanus toxoid immunization coverage among women in zone 3 of Dhaka city: the challenge of reaching all women of reproductive age in urban Bangladesh. Bull World Health Organ 1998;76(5):449–57.
[57] Singh J, Datta KK. Measles control in India: additional immunization strategies. Indian Pediatr 1997;34(7):621–6.
[58] Avila-Figueroa C, Navarrete-Navarro S, Ramirez-Galvan L, Baltazar-Lopez A, Lopez-Serrano M, Santos-Preciado JI. Inmunizaciones en ninos hospitalizados y de consulta externa: reduccion de las oportunidades perdidas de vacunacion. Bol Med Hosp Infant Mex 1992;49(5):271–4.
[59] Cutts FT, Glik DC, Gordon A, Parker K, Diallo S, Haba F, et al. Application of multiple methods to study the immunization programme in an urban area of Guinea. Bull World Health Organ 1990;68(6):769–79.
[60] Drabo KC (thesis) Evaluation des activites de vaccination dans le district sanitaire de Macina. Mali: Bamako University; 2009. Available online: http://www.keneya.net/fmpos/theses/2009/med/pdf/09M158.pdf [accessed 20.08.14].
[61] Morón-Duarte L, Espitia MT. Evaluación Rápida de Coberturas Vacunales en Bogotá, 2006. Rev Salud Publica 2009;11(1):237–46.
[62] Martins RM. Oportunidades perdidas de imunização. J de Pediatria 1996;72(1):3–4.
[63] Harris RJ, Bradburn MJ, Deeks JJ, Harbord RM, Altman DG, Sterne JAC. Metan: fixed- and random-effects meta-analysis. STATA J 2008;8(1):3–28.
[64] Harbord RM, Higgins JPT. Meta-regression in Stata. STATA J 2008;8(4):493–519.
[65] WHO, UNICEF, World Bank. State of the Vaccines and Immunization. 3rd ed. Geneva: World Health Organization; 2009. Available online: http://whqlibdoc.who.int/publications/2009/9789241563864_eng.pdf [accessed 14.07.14].
[66] UNICEF. Current DTP Supply and Outlook, UNICEF Supply Division; January 2013. Available online: http://www.unicef.org/supply/files/UNICEF_SD_DTP_Supply_Update_Jan2013.pdf [accessed 07.06.14].
[67] WHO. Developments in UNICEF Vaccine Procurement, Global Immunization Meeting UNICEF Supply Division; 2014. Available online: http://www.who.int/immunization/newsroom/190209_R_Matthews.pdf [accessed 07.06.14].
[68] Mukanga DO, Kiguli S. Factors affecting the retention and use of child health cards in a slum community in Kampala, Uganda, 2005. Matern Child Health J 2006;10(6):545–52.
[69] Friedman MG, Phillip M, Dagan R. Virus-specific IgA in serum, saliva, and tears of children with measles. Clin Exp Immunol 1989;75(1):58–63.
[70] Vyse AJ, Brown DWG, Cohen BJ, Samuel R, Nokes DJ. Detection of rubella virus-specific immunoglobulin G in saliva by an amplification-based enzyme-linked immunosorbent assay using monoclonal antibody to fluorescein isothiocyanate. J Clin Microbiol 1999;37(2):391–5.
[71] Kasi SG, Prabhu SV, Sanjay S, Chitkara A, Mitra M. Prefilled syringes versus vials: impact on vaccination efficiency and patient safety in Indian private market. Pediatr Infectious Dis 2013;5(4):181–6.
[72] Wakadha H, Chandir S, Were EV, Rubin A, Obor D, Levine OS, et al. The feasibility of using mobile-phone based SMS reminders and conditional cash transfers to improve timely immunization in rural Kenya. Vaccine 2013;31(6):987–93.
[73] Schoeps A, Ouédraogo N, Kagoné M, Sié A, Müller O, Becher H. Socio-demographic determinants of timely adherence to BCG, Penta3, measles, and complete vaccination schedule in Burkina Faso. Vaccine 2013;32(1):96–102.
[74] WHO. Underlying Issues Are Key to Dispelling Vaccine Doubts. Bull World Health Organ 2014;92:84–5. Available online: http://www.who.int/bulletin/volumes/92/2/14-030214/en/ [accessed 20.07.14].
[75] Pan American Health Organization (PAHO). Methodology for the Evaluation of Missed Opportunities for Vaccination, Washington, DC; 2013. Available online: www.paho.org [accessed 20.07.14].