

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Missed Opportunities for Vaccination (MOV) in children up to 5 years old in 19 Médecins Sans Frontières-supported health facilities: a cross-sectional survey in six low resource countries.
<b>AUTHORS</b>	Borras-Bermejo, Blanca; Panunzi, Isabella; Bachy, Catherine; Gil-Cuesta, Julita

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Shenton, Luke University of Michigan School of Public Health, Epidemiology
<b>REVIEW RETURNED</b>	03-Jan-2022

<b>GENERAL COMMENTS</b>	<p>Introduction: objectives of paper were clear Are there any available estimates of MOV prevalence more recent than 1993?</p> <p>Methods How were the health facilities surveyed chosen? As MSF works in more than these 6 countries and MOV is an issue in other countries what was the rational for choosing these ones.</p> <p>Results I'd be curious to see some breakdown of your analysis by country (or even facility). Any major differences in rates or reasons for MOV Did survey look at any factors that may be related to MOV that have been shown to be related to lower vaccinations in various countries. Number of children, maternal education, wealth, etc.</p> <p>Discussion: Well written</p>
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<b>REVIEWER</b>	Danovaro-Holliday, M Carolina Organisation mondiale de la Sante, IVB
<b>REVIEW RETURNED</b>	13-Jan-2022

<b>GENERAL COMMENTS</b>	<p>Peer-review "Missed Opportunities for Vaccination in Médecins Sans Frontières supported health facilities: eldest children urge for a second chance"</p> <p>The study summarizes findings of missed opportunities for vaccination (MOV) studies targeting caregivers of children 0-59 months of age done in six low-income countries between 2011 and 2015. The manuscript is succinct and clear. However, the results only present data on overall MOVs but miss presenting data by country and getting into more details on which vaccine-doses had</p>
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	<p>the most MOVs. The authors found more MOVs among elder children, but they did not describe if this was more marked for all vaccines and also what % had cards by age group.</p> <p>Comments by section</p> <p>Throughout – I suggest listing the countries alphabetically (unless there is reason to do otherwise) and consistently</p> <p>Throughout – EPI being only for infants is suggested throughout; this is changing. The authors may want to clarify this point, or say that the only infant schedule is the case in many low-income countries, but less and less so with the introduction of measles second dose and booster doses.</p> <p>Title – I am unsure if the use of the verb “urge” is clear</p> <p>Strengths and limitations of this study – other limitations include that % card availability declines with age, and this may weaken the association seen between age and MOVs. Also, the study is relatively old, and with the introduction of vaccine-doses in the second year of life the occurrence of MOV may have changed.</p> <p>Introduction – please include vaccination schedule for study countries at the time of surveys. I don’t think all countries had rotavirus or PCV for example. Also, data collection happened before IPV was widely used and in some studies this vaccine dose is one of the most missed ones.</p> <p>Introduction - Consider including the most recent recommendations from WHO on catch-up vaccination: World Health Organization. Leave no one behind : guidance for planning and implementing catch-up vaccination. 2021. April 1 2021.  <a href="https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination">https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination</a> It highlights the issue of not limiting the age for vaccination</p> <p>Methods – provide more details on calculation definitions, etc. It is really difficult to ascertain MOVs in general, there are many nuances. How did the authors handle birth doses? (see <a href="https://pubmed.ncbi.nlm.nih.gov/27195759/">https://pubmed.ncbi.nlm.nih.gov/27195759/</a> ) Interval between vaccine doses to ascertain eligibility? How about rotavirus, this vaccine is often restricted (at least in Africa - <a href="https://pubmed.ncbi.nlm.nih.gov/33958225/">https://pubmed.ncbi.nlm.nih.gov/33958225/</a>) though WHO position paper recommends otherwise.</p> <p>Please add more documentation. See supplemental material of this article <a href="https://www.mdpi.com/2076-393X/9/7/795/htm">https://www.mdpi.com/2076-393X/9/7/795/htm</a> for some examples of further documentation. Making the analytical code available would be important for reproducibility</p> <p>Methods – Why was only fever considered as a contraindication? There are more for DTP-containing especially.</p> <p>Methods – provide info by country, # of facilities, types, dates, etc</p> <p>Methods – indicate profile of people checking cards to understand risk of misclassifying needs for various vaccine-doses. This is important as there are many sites over a long period and it unclear how the determination of eligibility vis-à-vis ages and schedules is done and how big is the risk of misclassification as new vaccines were introduced for example</p> <p>Results – include information on parents/caregivers approached vs accepted, before the availability of a card was ascertained</p> <p>Results – the authors state “The most common reason for visiting the health facility was curative consultation (831, 30.7%)”...but what about the other almost 70% then?</p>
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	<p>Discussion – I suggest updating to include the Immunization Agenda 2030 (IA2030) endorsed by the World Health Assembly in 2020 – see <a href="https://www.immunizationagenda2030.org/">https://www.immunizationagenda2030.org/</a></p> <p>Conclusion – GVAP ended a while ago. I suggest opting for IA2030 putting the finding towards what needs to be done in the future</p> <p>Conclusion – Add most recent recommendations for catch-up as a reference for last statement (<a href="https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination">https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination</a>)</p> <p>Reference 15 – paper not found in link provided. Please update.</p> <p>Reference 16 – May want to link to landing page, as pdfs are updated periodically <a href="https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables">https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables</a></p> <p>Reference 28 – paper not found in link provided. Please update.</p> <p>Reference 29 – broken link. Please update.</p> <p>Child questionnaire – it is unclear if the schedule was the same everywhere through the study period or the form included was used only in some places.</p>
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<b>REVIEWER</b>	Ndwandwe, Duduzile South African Medical Research Council, Cochrane South Africa
<b>REVIEW RETURNED</b>	24-Jan-2022

<b>GENERAL COMMENTS</b>	The authors can include the number with the percentage of MOV per age category so that it is in line with table 1 figures. Overall the paper brings an important discussion around assessment of MOV in children above 24 months.
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<b>REVIEWER</b>	Nic Lochlainn, Laura World Health Organization
<b>REVIEW RETURNED</b>	26-Jan-2022

<b>GENERAL COMMENTS</b>	<p>Congratulations on writing a very clear and interesting manuscript. The findings are in line with more recent MOV publications and will greatly add to the body of evidence on reasons for MOV.</p> <p>One thing regarding the analysis, it would have been interesting to see the MOV prevalence by country, for countries in which you had a large sample size.</p> <p>Please see general feedback and comments below: Abstract Conclusion</p> <p>I agree that MOV are an important problem in low resource settings and children beyond the Expanded Program of Immunization target are particularly vulnerable for MOV. However, the issue is that national immunization policies often do not allow for children beyond a certain age to receive vaccines. So, in your concluding statement, this is an important point to make. Also, it is important to mention the low availability of vaccination cards. This is a major impediment to children being caught up with vaccinations. Finally, as you also found in your study, the lack of vaccination in hospitals is an issue in many countries that leads to MOV - an important point to mention.</p> <p>Line 2: suggest to remove this term – global advisory group</p>
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	<p>Line 9: change to assessments not surveys</p> <p>Line 39: add reference for MOV tool</p> <p>Line 54: It would be better to have the full definition for MOV in the introduction, as it is half described in lines 4-5.</p> <p>Line 65: This categorization description isn't easy to follow, consider revising. Also, are you sure that for all countries, children were only eligible for vaccination &lt;12 months. I would have thought that some of these countries would have introduced a second dose of measles during the time period of the surveys.</p> <p>Line 77: Although this ensures children are caught up, please note that this is not recommended in revised WHO guidance as it can introduce bias into the survey e.g. health workers may change practices if caregivers return with children who had MOV identified. Suggest you add this approach taken as a limitation.</p> <p>Line 89: typo - change to were</p> <p>Line 92: simpler to say "experienced a MOV during their health facility visit"</p> <p>Line 161: This strategy is highlighted in this guidance <a href="https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination">https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination</a></p> <p>Line 162: There are no upper age limits in the summary tables, apart from rotavirus vaccination which is not recommended beyond the first year of life due to decreased risk of disease. The problem that needs to be emphasized is that national immunization programmes and technical advisory groups need to extend their policies to ensure children can be caught up, and that these policies are disseminated to the health facility level.</p> <p>Line 168: A similar finding was also found in a MOV assessment in Timor Leste.</p> <p>Line 187: Please note that this should already happen as part of Integrated Management of Newborn and Childhood Illnesses (IMNCI) - please check if the countries that were assessed have an IMNCI policy in place.</p> <p>Line 192: add "they had"</p> <p>Lines 192-194: I think a sentence is missing, as this sentence doesn't complement the previous statement.</p> <p>Line 198-199: I don't understand this point? Also, as mentioned in the abstract, an important finding of this study was the low proportion of vaccination card availability. It should be endorsed that caregivers bring the vaccination card to every health contact to ensure that they child can be screened for all health interventions.</p> <p>Line 200: Suggest you mention the bias that may have been introduced by caregivers returning to the health facility whose children had a MOV identified.</p> <p>Line 213: Good point, MOV will continue to require attention. Now that there is a new global Immunization Agenda (Immunization Agenda 2030) that supersedes GVAP, MOV is a key area of strategic priority 4 of the Immunization Agenda 2030.</p> <p>Line 218: See earlier comment about IMNCI, also make note of the importance of the vaccination card.</p> <p>Line 223: As previously mentioned, emphasis should be placed on immunization programmes having policies to vaccinate older children.</p>
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Mr. Luke Shenton, University of Michigan School of Public Health

Thank you very much for your valuable time reviewing the manuscript, especially in the context of the COVID-19 pandemic. We really appreciate your comments which have improved the manuscript.

Comments to the Author:

Introduction:

objectives of paper were clear

Comment: Are there any available estimates of MOV prevalence more recent than 1993?

Response: Thank you for pointing this out. There is a systematic literature review from 2014 that found an estimated MOV prevalence of 32% that was cited in the discussion, and now is added in the introduction. Lines 12-14

“...and despite increases in routine vaccination coverage since then, MOV remain as high as 32% in the last systematic review performed in 2014 (3).

Methods

Comment: How were the health facilities surveyed chosen? As MSF works in more than these 6 countries and MOV is an issue in other countries, what was the rationale for choosing these ones?

Response: Countries and health facilities were chosen on a convenient basis following operational reasons. The selection was based on the projects in which MSF was already supporting routine vaccination and where we were able to perform MOV training to local staff in those health facilities. We clarified it within the text and now it reads (Lines 33-36): “Countries, health facilities and time of the assessments were chosen on a convenient basis following operational reasons. Facilities included were chosen because MSF was already supporting routine vaccination and where MOV training to local staff was feasible in those health facilities.”

Results

Comment: I'd be curious to see some breakdown of your analysis by country (or even facility). Any major differences in rates or reasons for MOV

Response: We appreciate your suggestion on presenting MOV data by Country. However, we think it would divert attention to make clear the main manuscript message. Nevertheless, we agree with the reviewer that this information would support to better understand results, thus we have decided to present this data as supplementary material.

Line 143: “Differences in MOV by country can be consulted at Supplementary table 3.”

Comment: Did survey look at any factors that may be related to MOV that have been shown to be related to lower vaccinations in various countries. Number of children, maternal education, wealth, etc.

Response: As you pointed out, latest evidence (32) suggests many factors are related to MOV such as maternal educational level, living in rural areas, number of children and other economic inequalities. Unfortunately, our survey was based on routinely collected data and did not explore them.

Following the reviewer suggestion, we have included this point as a limitation, lines 269-271: “Also, we could not explore other factors that have been previously related to MOV such as maternal education, living in rural areas, number of children and other economic inequalities (32).”

(32) Duduzile Ndwandwe, Olalekan A. Uthman, Abdu A. Adamu, Evanson Z. Sambala, Alison B. Wiyeh, Tawa Olukade, Ghose Bishwajit, Sanni Yaya, Jean-Marie Okwo-Bele & Charles S. Wiysonge (2018) Decomposing the gap in missed opportunities for vaccination between poor and non-poor in sub-Saharan Africa: A Multicountry Analyses, *Human Vaccines & Immunotherapeutics*, 14:10, 2358-2364, DOI: 10.1080/21645515.2018.1467685

Discussion:

Well written

Thank you again for your valuable comments and your time revising the manuscript.

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Reviewer: 2

Dr. M Carolina Danovaro-Holliday, Organisation mondiale de la Sante

Thank you very much for your valuable time reviewing the manuscript, especially in the context of the COVID-19 pandemic. We really appreciate your comments which have improved the manuscript.

Comments to the Author:

Peer-review "Missed Opportunities for Vaccination in Médecins Sans Frontières supported health facilities: eldest children urge for a second chance"

Comment: The study summarizes findings of missed opportunities for vaccination (MOV) studies targeting caregivers of children 0-59 months of age done in six low-income countries between 2011 and 2015. The manuscript is succinct and clear. However, the results only present data on overall MOVs but miss presenting data by country and getting into more details on which vaccine-doses had the most MOVs. The authors found more MOVs among elder children, but they did not describe if this was more marked for all vaccines and also what % had cards by age group.

Response: We appreciate your suggestion on presenting MOV data by country. However, we think it would divert attention to make clear the main manuscript message. Nevertheless, we recognize that the information suggested by the reviewer would support to better understand the results, thus we have decided to present this data as supplementary material.

Line 143: "Differences in MOV by country can be consulted at Supplementary table 3."

We agree that detailed data on MOV by vaccine/antigen would bring more light on the reasons affecting MOV. However, such an analysis is beyond the scope of the objectives of the study, and when adding it, the messages get diluted. This is why we would like to keep our message straight and clear.

Regarding relation of age with possession of vaccination card: is it true that possession of vaccination card could decline with age, which is also reflected in our data (we added more data to supplementary material).

Lines 123-124: "Characteristics of children not presenting vaccination cards can be consulted at Supplementary table 1"

Nevertheless, when assessing the relation between MOV and age including those with and without vaccination card we obtain same results (Supplementary table 2).

To address your comment, we have added to the discussion this point and the paragraph reads as follows from line 272:

"Third, we excluded from the analysis almost half of the children whose caregivers could not present a vaccination card. This may mean that we underestimated MOV prevalence in our target population, since not presenting a vaccination card has shown to be associated with MOV (1)(3)(33). On one hand, not relying on self-reported data helped avoid potential recall bias, which is a limitation in vaccine coverage studies in low-resource settings (34). On the other hand, possession of vaccination card declines with age (10) (a relation also observed in our study, Supplementary table 1); what could result in an overestimated prevalence of MOV in older children. Nevertheless, when assessing the relation between MOV and age including those with and without vaccination card, we obtain similar results (Supplementary table 2)."

#### Comments by section

Comment: Throughout – I suggest listing the countries alphabetically (unless there is a reason to do otherwise) and consistently.

Response: Order has been updated as suggested (Afghanistan, Democratic Republic of the Congo, Mauritania, Niger, Pakistan and South Sudan) and applied throughout the document.

Comment: Throughout – EPI being only for infants is suggested throughout; this is changing. The authors may want to clarify this point, or say that the only infant schedule is the case in many low-income countries, but less and less so with the introduction of measles second dose and booster doses.

Response: Thanks for the useful suggestion. We acknowledge it was confusing to understand EPI target throughout the manuscript. It has now been clarified through the following changes:

Lines 72-75: “Most of National immunization programs allowed vaccination until 12 months of age by the time of the assessments. Nevertheless, MSF supported vaccination of children up to 5 years of age in each of these facilities.”

Lines 96-98: For the bivariate analysis, age was categorized as below and above 12 months of age as this was the main target of the National program schedules in countries included by date the survey was performed.

Lines 175-176: “To our knowledge, this is one of the few studies that assessed MOV in children beyond 23 months of age”. Instead of “EPI target”.

Lines 187-189: “Thus, we believe that overall MOV prevalence is being seriously underestimated, as assessments do not include children beyond the EPI age target for most vaccines, that is, above 23 months of age.”

Line 195-197: “Age as a risk for having MOV may be explained by older children having been perceived as “too old” to be eligible (13), as most National immunization programs only target children below one year of age.”

Lines 306-308: “National immunization programs should allow to administer missing dose regardless the age of the child, as the EPI has expanded its vaccination recommendations during second year of life and beyond”

Lines 284-286: “Also, MOV prevalence estimates may have improved over the last ten years, as WHO has lately reinforced EPI vaccination during the second year of life.”

Comment: Title – I am unsure if the use of the verb “urge” is clear

Response: Title and abstract have been revised to match journal requirements and previous statement was eliminated. The title now reads “Missed Opportunities for Vaccination (MOV) in children up to 5 years old in 19 Médecins Sans Frontières-supported health facilities: a cross-sectional survey in six low resource countries.”

#### Strengths and limitations of this study

Comment: – other limitations include that % card availability declines with age, and this may weaken the association seen between age and MOVs.

Response: We agree and have updated the text.

We added this limitation in lines 277-284: "... On the other hand, possession of vaccination card declines with age (10) (a relation also observed in our study, Supplementary table 1); what could result in an overestimated prevalence of MOV in older children. Nevertheless, when assessing the relation between MOV and age including those with and without vaccination card, we obtain similar results (Supplementary table 2).

Comment: Also, the study is relatively old, and with the introduction of vaccine-doses in the second year of life the occurrence of MOV may have changed.

Response: Thanks. Following on your comment we have inserted the following. Line 284: "Also, MOV prevalence estimates may have improved over the last ten years, as WHO has lately reinforced EPI vaccination during the second year of life.

Comment: Introduction – please include vaccination schedule for study countries at the time of surveys. I don't think all countries had rotavirus or PCV for example. Also, data collection happened before IPV was widely used and in some studies this vaccine dose is one of the most missed ones.

Response: Thank you for this suggestion. We have added Figure 2 with immunization schedule and clarified information on methodology to ascertain MOV.

Line 77: "Only widely introduced vaccines in each country were considered to ascertain MOV. Year of vaccine introduction in each country can be consulted here (9)."

Also, clarified at Figure 2 that OPV and not IPV was considered.

Comment: Introduction – Consider including the most recent recommendations from WHO on catch-up vaccination: World Health Organization. Leave no one behind : guidance for planning and implementing catch-up vaccination. 2021. April 1 2021. <https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination> It highlights the issue of not limiting the age for vaccination

Response: Thanks for the important suggestion. We have added the reference in Line 19: "...strengthens routine vaccination services regardless the age of the child, following WHO recommendations (7)"

Comment: Methods – provide more details on calculation definitions, etc. It is really difficult to ascertain MOVs in general, there are many nuances. How did the authors handle birth doses? (see <https://pubmed.ncbi.nlm.nih.gov/27195759/> ) Interval between vaccine doses to ascertain eligibility? How about rotavirus, this vaccine is often restricted (at least in Africa - <https://pubmed.ncbi.nlm.nih.gov/33958225/>) though WHO position paper recommends otherwise. Please add more documentation. See supplemental material of this article <https://www.mdpi.com/2076-393X/9/7/795/htm> for some examples of further documentation.

Response: Thank you for your suggestion.

We have included the vaccination schedule in Figure 2 for clarification, with information about upper age limits, minimum interval between doses and country specifications.

We have improved MOV ascertaining methodology as follows in lines 67-81:

"We classified children as having a MOV as per standard WHO's definition (6) according to each national vaccination schedule: a MOV occurs when a child eligible for vaccination (without contraindication) remains unvaccinated or partially vaccinated (not up to date) at the end of any visit to a health facility (Figure 1). Surveyors determined if the child was eligible that day of the assessment for at least one vaccine dose according to age and National immunization schedules (Figure 2), and whether the child had received all the recommended vaccines during that visit. Most of



National immunization programs allowed vaccination until 12 months of age by the time of the assessments. Nevertheless, MSF supported vaccination of children up to 5 years of age in each of these facilities. In our study, surveyors considered a MOV if a child did not receive the indicated vaccines even if they were above the recommended age to receive them according to the country policy, to the exception of BCG and Rotavirus (Figure 2). Only widely introduced vaccines in each country were considered to ascertain MOV. Year of vaccine introduction in each country can be consulted here (9)”

Comment: Making the analytical code available would be important for reproducibility

Response: Instead of sharing the analytical codes, we in MSF have the policy to publish at open access and share the study data in a repository: <https://doi.org/10.17605/OSF.IO/SFXDK> Reference (37).

Comment: Methods – Why was only fever considered as a contraindication? There are more for DTP-containing especially.

Response: We missed to indicate other contraindications for vaccination considered in the study, as severe allergic reaction to a previous dose of DTP-containing or measles-containing vaccine was considered as a contraindication for vaccination with those vaccines. They have now been indicated in Lines 61-62.

Comment: Methods – provide info by country, # of facilities, types, dates, etc

Response: Thanks for the useful suggestion. Following your suggestion, we have added the information by country at Supplementary material

Line 143: “Differences in MOV by country can be consulted at Supplementary table 3.”

Comment: Methods – indicate profile of people checking cards to understand risk of misclassifying needs for various vaccine-doses. This is important as there are many sites over a long period and it unclear how the determination of eligibility vis-à-vis ages and schedules is done and how big is the risk of misclassification as new vaccines were introduced for example

Response: We hope that now MOV methodology is clearer with Figure 2 and information added at lines 67-81.

Comment: Results – include information on parents/caregivers approached vs accepted, before the availability of a card was ascertained

Response: Thank you for this insightful suggestion. Unfortunately we are not able to show this data.

Comment: Results – the authors state “The most common reason for visiting the health facility was curative consultation (831, 30.7%)”...but what about the other almost 70% then?

Response: Thanks for the suggestion. It has now been completed in lines 133-136: “Reasons for visiting the health facility were distributed among curative consultation (31%), followed by unspecified reason (26%), vaccination (16%), nutrition (16%), mother and child health visit (10%) and accompanying an adult (1%).”

Comment: Discussion – I suggest updating to include the Immunization Agenda 2030 (IA2030) endorsed by the World Health Assembly in 2020 – see <https://www.immunizationagenda2030.org/>

Response: Thank you for your comment. Following your suggestion it has been updated and reads as follows (line 201): “But efforts are being made to ‘Leave No One Behind’(15)...”

Comment: Conclusion – GVAP ended a while ago. I suggest opting for IA2030 putting the finding towards what needs to be done in the future.

Response: We fully agree, thanks for your suggestion. The conclusion has been updated accordingly and it now reads in line 289-290: “Avoiding MOV should remain a priority where access to health care is limited, in line with the new 2030 Immunization Agenda (15).”

Lines 309-311: “National immunization programs should allow to administer missing doses regardless the age of the child, as the EPI has expanded its vaccination recommendations during second year of life and beyond. Strengthening the implementation of second-year-of-life visits, as recommend by WHO, with catch-up vaccination strategies(7) would provide additional opportunities to receive missed vaccine doses and leave no one behind.”

Comment: Conclusion – Add most recent recommendations for catch-up as a reference for last statement (<https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination>)

Response: Thanks. The reference has been added, now reference (7).

Reference 15 – paper not found in link provided. Please update. The link has now been updated. It is now the reference (20)

Reference 16 – May want to link to landing page, as pdfs are updated periodically

<https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables>. Thanks. The link has been updated.

Reference 28 – paper not found in link provided. Please update. The link has been updated. Now reference (34)

Reference 29 – broken link. Please update. The link has been updated. Now reference (35)

Comment: Child questionnaire – it is unclear if the schedule was the same everywhere through the study period or the form included was used only in some places.

Response: Thank you for your comment. We added in line 55 “A structured questionnaire was created (Annex 1) and used in all assessments”.

We included the vaccination schedule in Figure 2 for clarifying, with information about upper age limits and country specifications.

Thank you again for your valuable comments and your time revising the manuscript.

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Reviewer: 3

Dr. Duduzile Ndwandwe, South African Medical Research Council

Thank you for your time in reviewing the manuscript, we appreciate your comments.

Comments to the Author:

Comment: The authors can include the number with the percentage of MOV per age category so that it is in line with table 1 figures. Overall the paper brings an important discussion around assessment of MOV in children above 24 months.

Response: As per your suggestion, we have added the number of children with MOV in lines 140-142, so now it is consistent with Table 1.

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Reviewer: 4

Dr. Laura Nic Lochlainn, World Health Organization

Comments to the Author:

Dear authors,

Congratulations on writing a very clear and interesting manuscript. The findings are in line with more

recent MOV publications and will greatly add to the body of evidence on reasons for MOV.

Thank you very much for your valuable time reviewing the manuscript, especially in the context of the COVID-19 pandemic. We really appreciate your constructive and detailed comments which have improved the manuscript.

Comment: One thing regarding the analysis, it would have been interesting to see the MOV prevalence by country, for countries in which you had a large sample size.

Response: We appreciate your suggestion on presenting MOV data by country. However, presenting it in the body of the results would divert attention to make clear the main message. Nevertheless, we recognize that this information was missing to better understand results, thus we have decided to present this data as supplementary material.

Line 143: "Differences in MOV by country can be consulted at Supplementary table 3."

Please see general feedback and comments below:

Abstract / Conclusion

Comment: I agree that MOV are an important problem in low resource settings and children beyond the Expanded Program of Immunization target are particularly vulnerable for MOV. However, the issue is that national immunization policies often do not allow for children beyond a certain age to receive vaccines. So, in your concluding statement, this is an important point to make. Also, it is important to mention the low availability of vaccination cards. This is a major impediment to children being caught up with vaccinations. Finally, as you also found in your study, the lack of vaccination in hospitals is an issue in many countries that leads to MOV - an important point to mention.

Response: We have incorporated at the conclusion how essential is to strengthen checking vaccination status at every encounter through promotion and possession of vaccination cards. We have also clarified that vaccination beyond 12 months of age should be allowed.

Lines 293-311: "We recommend integrating systematic vaccination screening into routine health care services, regardless of the reason for the visit, the type of facility and the age of the child. To promote maintaining and providing vaccination cards at every health care visit will help to reinforce vaccination screening and better identification of eligible children.

We identified that children above 23 months of age are particularly vulnerable for MOV. Thus, we would recommend including children beyond 23 months of age in the current WHO methodology for MOV assessments in order to avoid underestimation of MOV. National immunization programs should allow to administer missing dose regardless the age of the child, as the EPI has expanded its vaccination recommendations during second year of life and beyond. Strengthening the implementation of second-year-of-life visits, as recommended by WHO, with catch-up vaccination strategies(7) would provide additional opportunities to receive missed vaccine doses and leave no one behind."

Also updated at the Abstract.

Line 2: suggest to remove this term – global advisory group. Eliminated, Line 2

Line 9: change to assessments not surveys. Changed, Line 15.

Line 39: add reference for MOV tool. Line 50 reference (8) is added.

(8) Sato, P. A & WHO Expanded Programme on Immunization. (1988). Protocole pour l' évaluation des occasions manquées de vaccination / Paul Sato. Organisation mondiale de la Santé.  
<https://apps.who.int/iris/handle/10665/58643>

Line 54: It would be better to have the full definition for MOV in the introduction, as it is half described in lines 4-5. Thanks for the suggestion. We have included it, Lines 4-7: “A Missed Opportunity for Vaccination (MOV) occurs when a child eligible for vaccination (without contraindication) remains unvaccinated or partially vaccinated (not up-to-date) at the end of the visit, so the consultation does not result in the children receiving all the vaccine doses for which he or she was eligible.”

Line 65: This categorization description isn't easy to follow, consider revising. Thanks. Following the suggestion, it has been clarified, Lines 87-93. Now reads: “We calculated the prevalence of MOV among children eligible for a vaccination, excluding those with a reported contraindication. Among children with a MOV we calculated the proportion of caregivers who would have accepted vaccination if it had been proposed on the day of the visit and the proportion of caregivers who knew their date of next vaccination appointment.”

Comment: Also, are you sure that for all countries, children were only eligible for vaccination <12 months. I would have thought that some of these countries would have introduced a second dose of measles during the time period of the surveys.

Response:

We included the vaccination schedule in Figure 2 for clarifying, with information about upper age limits, minimum interval between doses and country specifications. Despite some countries had introduced a second dose of measles, this was not considered to ascertain MOV in our study.

We have further clarified the MOV ascertaining methodology as follows in lines 67-81:

“We classified children as having a MOV as per standard WHO's definition (6) according to each national vaccination schedule: a MOV occurs when a child eligible for vaccination (without contraindication) remains unvaccinated or partially vaccinated (not up to date) at the end of any visit to a health facility (Figure 1). Surveyors determined if the child was eligible that day of the assessment for at least one vaccine dose according to age and National immunization schedules (Figure 2), and whether the child had received all the recommended vaccines during that visit. Most of National immunization programs allowed vaccination until 12 months of age by the time of the assessments. Nevertheless, MSF supported vaccination of children up to 5 years of age in each of these facilities. In our study, surveyors considered a MOV if a child did not receive the indicated vaccines even if they were above the recommended age to receive them according to the country policy, to the exception of BCG and Rotavirus (Figure 2). Only widely introduced vaccines in each country were considered to ascertain MOV. Year of vaccine introduction in each country can be consulted here (9).

Line 77: Although this ensures children are caught up, please note that this is not recommended in revised WHO guidance as it can introduce bias into the survey e.g. health workers may change practices if caregivers return with children who had MOV identified. Suggest you add this approach taken as a limitation.

Thank you for your comment. If a MOV was identified and could be resolved by returning to the facility, it was prioritized over introducing bias in the survey. Nevertheless, we agree with the potential bias of interviewing those children again on MOV estimates, so we have included it among limitations.

Lines 282-283: “Finally, as children with identified MOV were sent back for vaccination when possible, it could have introduced a bias in MOV prevalence if these children were inadvertently interviewed again.”

Line 89: typo - change to were. "where" is corrected to "were" Line 126

Line 92: simpler to say "experienced a MOV during their health facility visit" Applied, Line 129

Line 161: This strategy is highlighted in this guidance <https://www.who.int/publications/i/item/leave-no-one-behind-guidance-for-planning-and-implementing-catch-up-vaccination> Thank you, the reference is now included (7) Line 210

Line 162: There are no upper age limits in the summary tables, apart from rotavirus vaccination which is not recommended beyond the first year of life due to decreased risk of disease. The problem that needs to be emphasized is that national immunization programmes and technical advisory groups need to extend their policies to ensure children can be caught up, and that these policies are disseminated to the health facility level.

Thank you. We have revised the text to address your concerns and hope that it is now clearer.

Lines 201-204: "But efforts are being made to 'Leave No One Behind'(13): the latest WHO update of recommendations for routine immunization (14) emphasizes that measles vaccine should not be limited to children up to 12 months of age. Actually there are no age limits to vaccinate children (with rotavirus exception)."

Lines 211-213: "We believe this 'never too old' policy should be adopted by all national immunization programs in order to ensure children do not miss the opportunity to be fully vaccinated at any age."

Lines 306-311: "National immunization programs should allow to administer missing dose regardless the age of the child, as the EPI has expanded its vaccination recommendations during second year of life and beyond. Strengthening the implementation of second-year-of-life visits, as recommend by WHO, with catch-up vaccination strategies (7) would provide additional opportunities to receive missed vaccine doses and leave no one behind."

Line 168: A similar finding was also found in a MOV assessment in Timor Leste. We understand reviewer is referring to Line 178 and it now reads in Line 223: "A similar finding is highlighted in a MOV assessment in East Timor (13) were Anyie J. Li et al. found..."

Line 187: Please note that this should already happen as part of Integrated Management of Newborn and Childhood Illnesses (IMNCI) - please check if the countries that were assessed have an IMNCI policy in place.

We added "This could be avoided through the proper adherence to the Integrated Management of Newborn and Childhood Illnesses (IMNCI) guidelines (18), already in place in these countries (22)." in lines 227-229.

Line 192: add "they had" Typo corrected. Thanks.

Lines 192-194: I think a sentence is missing, as this sentence doesn't complement the previous statement. Line 198-199: I don't understand this point?

We agree the previous paragraph was not clear. Thanks. It has been now clarified.

Comment: Also, as mentioned in the abstract, an important finding of this study was the low proportion of vaccination card availability. It should be endorsed that caregivers bring the vaccination card to every health contact to ensure that they child can be screened for all health interventions.

Response: We added the importance of possession of vaccination card and it now read as follows:

Line 243-248: "Caregivers should be encouraged to bring the vaccination card to every contact with health services, to facilitate and ensure that the child can be properly screened for vaccination eligibility".

Lines 293-297: We recommend integrating systematic vaccination screening into routine health care services, regardless of the reason for the visit, the type of facility and the age of the child. To promote maintaining and providing vaccination cards at every health care visit will help to reinforce vaccination screening and better identification of eligible children.

Line 200: Suggest you mention the bias that may have been introduced by caregivers returning to the health facility whose children had a MOV identified. Thank you. Added at Lines 282-284: "Finally, as children with identified MOV were sent back for vaccination when possible, it could have introduced a bias in MOV prevalence if these children were inadvertently interviewed again"

Line 213: Good point, MOV will continue to require attention. Now that there is a new global Immunization Agenda (Immunization Agenda 2030) that supersedes GVAP, MOV is a key area of strategic priority 4 of the Immunization Agenda 2030.

We agree, conclusion has been updated, aligning the finding towards the recommendation, and now reads (lines 288-292): "Despite progress in vaccine coverage, MOV remains an important problem in low-resource settings. Avoiding MOV should remain a priority where access to health care is limited, in line with the new 2030 Immunization Agenda (15). This is particularly important considering the negative impact COVID-19 pandemic is having on routine immunization programs in low and middle-income countries (35)(36)."

Line 218: See earlier comment about IMNCI, also make note of the importance of the vaccination card. We have added the importance of possession of vaccination card at lines 243-248 and 293-297.

Line 223: As previously mentioned, emphasis should be placed on immunization programmes having policies to vaccinate older children. We fully agree, thanks for the suggestion. It has been emphasized at lines 306-311: "National immunization programs should allow to administer missing dose regardless the age of the child, as the EPI has expanded its vaccination recommendations during second year of life and beyond. Strengthening the implementation of second-year-of-life visits, as recommend by WHO, with catch-up vaccination strategies(7) would provide additional opportunities to receive missed vaccine doses and leave no one behind."

Thank you again for your valuable comments and your time revising the manuscript.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Danovaro-Holliday, M Carolina Organisation mondiale de la Sante, IVB
<b>REVIEW RETURNED</b>	09-Apr-2022

<b>GENERAL COMMENTS</b>	Thank you for considering the reviews. The manuscript is clearer now. I only have a few outstanding comments: Throughout: revise spelling of Haemophilus influenzae - it is missing the last e of the species. Also, genus and species should be in
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	<p>italics, as per standard for bacterium names.</p> <p>Abstract. I suggest changing "Children beyond the Expanded Program of Immunization" to beyond their second year of life.</p> <p>Discussion. I suggest adding "in MSF supported countries, or something to qualify the use of "most" , or just remove "most" and change for "many" in the following sentence: as most of National immunization programs only target children below one year of age"</p> <p>Discussion. The age limit for rotavirus was changed many years ago, in 2013, and this is clear in the most recent WHO Position Paper (available here: <a href="https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers">https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers</a>). In fact, there is a recent study that concluded than in many African countries the practice has been to keep an age restriction in spite of this change: <a href="https://pubmed.ncbi.nlm.nih.gov/33958225/">https://pubmed.ncbi.nlm.nih.gov/33958225/</a>. In summary, please correct the statement and possibly cite these documents.</p> <p>I suggest listing additional limitations, such as "This study is not from a representative sample, and very few children were eligible in Afghanistan and Pakistan [or "in two of the six countries included"]]. We don't have information to estimate the participation rate; information on caregivers contacted for the study and enrolled was not kept."</p> <p>Figure 2. Please explain as a footnote why there was an age limit for OPV. For BCG and rotavirus, you explained in the text that you used an age limit, but not for OPV. In any case, why would OPV be restricted?</p> <p>For Supplementary Table 1, I don't quite understand how eligibility was assessed for children without cards??</p>
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<b>REVIEWER</b>	Nic Lochlainn, Laura World Health Organization
<b>REVIEW RETURNED</b>	19-Apr-2022

<b>GENERAL COMMENTS</b>	<p>Congratulations, this revised version of the manuscript reads very well. I only have a few minor comments which can be found below:</p> <p>Why in line 110 do you say that "During the survey, children &lt;12 months identified with MOV were sent back to the vaccination unit to receive the missing vaccine(s) if the caregiver agreed and if there was no shortage." - when earlier i line 76 you stated that MSF supported vaccination of children up to 5 years of age in each of these facilities.</p> <p>Line 224 and 234: Timor Leste is the correct country name.</p> <p>Line 224 and 226, only cite author surnames e.g. Li et al and Kabore et al.</p> <p>Line 294: the new immunization strategy is called "Immunization Agenda 20230"</p> <p>Line 310: change to - National immunization programs should allow administration of missing doses, regardless of the age of the child, as the EPI has expanded its vaccination recommendations during the second year of life and beyond.</p>
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**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 2

Dr. M Carolina Danovaro-Holliday, Organisation mondiale de la Santé

Comments to the Author:

Thank you for considering the reviews. The manuscript is clearer now.

I only have a few outstanding comments:

Comment: Throughout: revise spelling of *Haemophilus influenzae* - it is missing the last e of the species. Also, genus and species should be in italics, as per standard for bacterium names.

Response: Thanks, typo corrected.

Comment: Abstract. I suggest changing "Children beyond the Expanded Program of Immunization" to beyond their second year of life.

Response: Thank you for the suggestion, this has been changed.

Comment: Discussion. I suggest adding "in MSF supported countries, or something to qualify the use of "most", or just remove "most" and change for "many" in the following sentence: as most of National immunization programs only target children below one year of age"

Response: Suggestion applied: "most" has been replaced by "many".

Comment: Discussion. The age limit for rotavirus was changed many years ago, in 2013, and this is clear in the most recent WHO Position Paper (available here:

<https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers>). In fact, there is a recent study that concluded that in many African countries the practice has been to keep an age restriction in spite of this change: <https://pubmed.ncbi.nlm.nih.gov/33958225/>. In summary, please correct the statement and possibly cite these documents.

Response: Thanks for pointing this out. It has been clarified and references (15) and (16) added:

Lines 183-184: "For example, since 2013 WHO removed age restriction for rotavirus vaccine in the WHO African region, nevertheless, it is not implemented in many countries (15)(16)."

Line 187: the statement was removed "Actually, there are no age limits to vaccinate children (with rotavirus exception)."

Comment: I suggest listing additional limitations, such as "This study is not from a representative sample, and very few children were eligible in Afghanistan and Pakistan [or "in two of the six countries included"]. We don't have information to estimate the participation rate; information on caregivers contacted for the study and enrolled was not kept."

Response: Thank you for the suggestion. The following sentences were added:

Lines 233-234: This study is not from a representative sample, and very few children were eligible in two of the six countries included (Supplementary table 3).

Lines 243-245: as information on contacted caregivers was not kept (34) and unfortunately, we do not have information to estimate the participation rate.

Comment: Figure 2. Please explain as a footnote why there was an age limit for OPV. For BCG and rotavirus, you explained in the text that you used an age limit, but not for OPV. In any case, why would OPV be restricted?

Response: OPV upper age limit was eliminated (except for birth dose in order to respect minimum intervals between doses). It was a confusion.

Comment: For Supplementary Table 1, I don't quite understand how eligibility was assessed for children without cards??

Response: When cards were unavailable, surveyors obtained vaccination history and approximated dates from caregiver oral history. Surveyors referred to commonly used anatomical vaccination sites to help remember previously administered doses. We have incorporated a footnote in Table 1 specifying that vaccination history could be obtained through presentation of vaccination card or oral history.

Reviewer: 4

Dr. Laura Nic Lochlainn, World Health Organization



Comments to the Author:

Dear authors,

Congratulations, this revised version of the manuscript reads very well. I only have a few minor comments which can be found below:

Comment: Why in line 110 do you say that "During the survey, children <12 months identified with MOV were sent back to the vaccination unit to receive the missing vaccine(s) if the caregiver agreed and if there was no shortage." - when earlier i line 76 you stated that MSF supported vaccination of children up to 5 years of age in each of these facilities.

Response: We fully agree, thanks for the suggestion. "<12 months" was eliminated. Line 97.

Comment: Line 224 and 234: Timor Leste is the correct country name.

Response: This has been corrected, thanks. Lines 202 and 209.

Comment: Line 224 and 226, only cite author surnames e.g. Li et al and Kabore et al.

Response: This has been corrected, thanks. Lines 202-203.

Comment: Line 294: the new immunization strategy is called "Immunization Agenda 20230"

Response: Thank you, this has been modified in line 262 and in the abstract too.

Comment: Line 310: change to - National immunization programs should allow administration of missing doses, regardless of the age of the child, as the EPI has expanded its vaccination recommendations during the second year of life and beyond.

Response: Suggestion applied, thank you. Lines 272-274.

Thank you again for your valuable comments and your time revising the manuscript.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Danovaro-Holliday, M Carolina Organisation mondiale de la Sante, IVB
<b>REVIEW RETURNED</b>	16-Jun-2022
<b>GENERAL COMMENTS</b>	Comments addressed. Thank you.