PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Palivizumab reimbursement criteria and neonatal RSV hospitalization: a single regional retrospective review
AUTHORS	Belleudi, Valeria Marchetti, Federico Finocchietti, Marco Davoli, Marina Addis, Antonio

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. mario decurtis Institution and Country: University of Rome La Sapienza Maternal and Child Health, Italy Competing interests: None
REVIEW RETURNED	23-Dec-2020

GENERAL COMMENTS	The topic tackled by this article is interesting and several studies are trying to assess the usefulness of prophylaxis with palivizumab to prevent RSV in infants. The authors compared data on RSV infant hospitalization in three different time periods (i.e. before, during and after reimbursement limitation for infants 30-35 weeks gestational age), in the neonatal population of Lazio region. The results demonstrate that changes in reimbursement criteria were not associated with changes in neonatal RSV hospitalizations rate but with a significant impact on palivizumab use and increased costs for the Italian health service. The paper is well written and worthy of publication pending some minor points needing explanation. In addition, the findings of this article can lead to a positive and practical impact on the Italian health system. 1) I recommend indicating clearly the number of infants that have been included in this study. 2) Page 4 - Line 32: “using real-world data”. R: Please clarify the source of your data and possible limitations in data collection. Clarify criteria for diagnosis of VRS and Other Virus infection 3) Page 4 - Line 56: “RSV infection-based hospitalizations rate in the periods before, during and after AIFA-2016 limitations were 0.98% [CI95% 0.91%-1.04%], 0.85% [CI95% 0.76%-0.93%] and 1.34 [CI95% 1.24%-1.39%]”. R: Is there a significant difference between the 3 periods? 4) Page 5 - Line 42: It is also worthy to note that after the revoke of AIFA’s reimbursement limitations the prevalence of palivizumab use in infant ≤29 GA is higher than that observed in the period before the regulatory restrictions (41% vs 26%). What is the possible explanation to that?

REVIEWER	Reviewer name: Dr. Roberto Buzzetti Institution and Country: Pass IV Novembre 2, Ranica, 24020, Italy

	Competing interests: None
REVIEW RETURNED	22-Dec-2020

GENERAL COMMENTS	The paper submitted adresses a crucial problem, and proposes a reflection on the cost-effectiveness of the administration of Palivizumab to premature babies for the prevention of RSV disease. Since its first appearance [The IMpact-RSV Study Group. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. PEDIATRICS 1998 (102; 3): 531-537] a fair efficacy was clear ("Palivizumab prophylaxis resulted in a 55% reduction in hospitalization as a result of RSV (10.6% placebo vs 4.8% palivizumab") which however raised problems in terms of cost-effectiveness (NNT = 17 approximately, against a high cost of prophylaxis). The authors show the Italian data (from one single region) on the use of this prophylaxis and on hospitalizations, in three different periods: "PRE period" (two seasons before the implementation of the 2016 limitations - 2014/15-2015/16), "POST period with limitations to <30 weeks " (one season after the approval of limitations - 2016/17) and the" POST period without limitations" (two seasons following the revocation of these limitations of reimbursement - 2017/18-2018/19). In my opinion, Figure 1 and Figure 2 could be read together, assuming the use of palivizumab as an "exposure" and hospitalization for RSV as an "outcome". There is therefore a possible association, among the lower gestational age group (under 30 weeks) between exposure (increasing with an almost linear trend - 26%, 32%, 41% - in the three periods) and outcome (decreasing, also in this case almost linearly). On the other hand, there is apparently no relationship among the gestational age groups greater than or equal to 30 weeks. Of course this is a very rough suggestion that should be validated with appropriate statistical tests for the class <30 weeks, while for the upper classes things seem to go completely random. This seems to corroborate the policy of granting the drug only in case of gestational age <30 weeks. The authors very conveniently give us an estimate of the possible savings achievable following the most restrictive strategy, even if the theoretical extension of the data from a single region to all Italian newborns requires a confirmation with robust national data.

REVIEWER	Reviewer name: Dr. Mitchell Goldstein Institution and Country: Loma Linda Univ, 11175 Campus Street, Suite #11121, Loma Linda, California, 92350, United States Competing interests: None
REVIEW RETURNED	31-Dec-2020

GENERAL COMMENTS	This is a single-center review of the RSV hospitalization rates before and after a change in the AAP 2014 policy regarding palivizumab prophylaxis. The authors cite demographic and hospitalization data regarding the impact of the subsequent adoption of this policy by the AIFA. Interestingly, although the <= 29-week group should not have been affected, there was a clear trend towards decreased admissions with the resumption of immunization. In the >= 37 weeks, which also should not have been affected by the policy, there was a trend towards increased hospitalizations. But when we look at the actual use of palivizumab, it actually increased in the <=29 by 15 percentage

	points throughout the study. This number should not have been affected by a change in the policy unless the implications of the policy were more far-reaching in so far as the unintended effect on the improvement of immunization rates in a group that was not receiving appropriate coverage. Regardless, for this study to be clinically, as opposed to statistically meaningful, the raw numbers of patients in each epoch and each stratification need to be reported.

REVIEWER	Reviewer name: Dr. Amanda M. Kong Institution and Country: IBM Watson Health, 75 Binney Str Cambridge, Massachusetts, 02142-1123, United States Competing interests: None
REVIEW RETURNED	28-Dec-2020

GENERAL COMMENTS	Even with the limited word count, I think it's important to include at least some details on the methods and limitations so the data can be interpreted. Specific comments are: What are the sample sizes? What is the data source? Should the proportions of hospitalizations be rates? Is the denominator of the proportions all infants who were <6 months old during the RSV season? Could infants contribute different amounts of person-time? Is there any reason to think these results would be different in other regions since RSV circulation is different by geographic regions? You note that your study is consistent with one very small US based analysis. That study consisted of 91 patients. You should also cite additional analyses that have found an impact and explain why those results may be different than yours. Are these levels of palivizumab use enough to influence hospitalization rates? These rates seem low. Most people aren't following the guidelines before the change.

VERSION 1 – AUTHOR RESPONSE

Dear Editor,

Please find here below the response points by points to the requests from reviewers

Reviewer: 1

Comments to the Author

The paper submitted addresses a crucial problem, and proposes a reflection on the cost-effectiveness of the administration of Palivizumab to premature babies for the prevention of RSV disease. Since its first appearance [The IMpact-RSV Study Group. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in

High-risk Infants. PEDIATRICS 1998 (102; 3): 531-537] a fair efficacy was clear ("Palivizumab prophylaxis resulted in a 55% reduction in hospitalization as a result of RSV (10.6% placebo vs 4.8% palivizumab") which however raised problems in terms of cost-effectiveness (NNT = 17 approximately, against a high cost of prophylaxis).

The authors show the Italian data (from one single region) on the use of this prophylaxis and on hospitalizations, in three different periods: "PRE period" (two seasons before the implementation of the 2016 limitations - 2014/15-2015/16), "POST period with limitations to <30 weeks " (one season after the approval of limitations - 2016/17) and the" POST period without limitations" (two seasons following the revocation of these limitations of reimbursement - 2017/18-2018/19).

In my opinion, Figure 1 and Figure 2 could be read together, assuming the use of palivizumab as an "exposure" and hospitalization for RSV as an "outcome". There is therefore a possible association, among the lower gestational age group (under 30 weeks) between exposure (increasing with an almost linear trend - 26%, 32%, 41% - in the three periods) and outcome (decreasing, also in this case almost linearly). On the other hand, there is apparently no relationship among the gestational age groups greater than or equal to 30 weeks. Of course this is a very rough suggestion that should be validated with appropriate statistical tests for the class <30 weeks, while for the upper classes things seem to go completely random.

This seems to corroborate the policy of granting the drug only in case of gestational age <30 weeks. The authors very conveniently give us an estimate of the possible savings achievable following the most restrictive strategy, even if the theoretical extension of the data from a single region to all Italian newborns requires confirmation with robust national data.

As suggested by the reviewer our study shows a possible association between the increase of palivizumab use and a decrease of RSV hospitalization rates for infants with gestational age less than 30 weeks. The possible benefit of palivizumab in this population seems to corroborate AAP 2014 guidelines and initial AIFA policy, narrowing the access to the drug for the populations with an increased risk and severity of RSV disease. In fact, even if not included in the SPC of the drug, AIFA recommended reimbursement by the NHS also for prophylaxis with palivizumab for children: (iv) ≤1 year of age and with severe congenital malformations (e.g., neuromuscular, cardiac); (v) ≤2 years of age in children with primitive or secondary immunodeficiencies.

However, further studies with a different study design need to evaluate palivizumab effectiveness in this subpopulation as well as a national study on the impact of AIFA policy at the national level could confirm our results.

Reviewer: 2

Comments to the Author

The topic tackled by this article is interesting and several studies are trying to assess the usefulness of prophylaxis with palivizumab to prevent RSV in infants.

The authors compared data on RSV infant hospitalization in three different time periods (i.e. before, during, and after reimbursement limitation for infants 30-35 weeks gestational age), in the neonatal population of the Lazio region.

The results demonstrate that changes in reimbursement criteria were not associated with changes in neonatal RSV hospitalizations rate but with a significant impact on palivizumab use and increased costs for the Italian health service.

The paper is well written and worthy of publication pending some minor points needing explanation. In addition, the findings of this article can lead to a positive and practical impact on the Italian health system.

1) I recommend indicating clearly the number of infants that have been included in this study.

According to your suggestion, we indicated the number of infants included in the study both in the text and in Figures 1/2.

2) Page 4 - Line 32: “using real-world data”. R: Please clarify the source of your data and possible limitations in data collection. Clarify criteria for the diagnosis of VRS and Other Virus infection

We thank the reviewer for this comment; we added details on data sources and possible limitations.

3) Page 4 - Line 56: “RSV infection-based hospitalizations rate in the periods before, during and after AIFA-2016 limitations were 0.98% [CI95% 0.91%-1.04%], 0.85% [CI95% 0.76%-0.93%] and 1.34 [CI95% 1.24%-1.39%]”. R: Is there a significant difference between the 3 periods?

Yes, in particular, the higher hospitalization rate observed in period 3 is mainly related to infants with gestational age >= 37 weeks, which not have been affected by the policy. However, this could indicate a variation in the intensity of RSV epidemics in the last period.

4) Page 5 - Line 42: It is also worthy to note that after the revoke of AIFA’s reimbursement limitations the prevalence of palivizumab use in infant ≤29 GA is higher than that observed in the period before the regulatory restrictions (41% vs 26%).

What is the possible explanation for that?

We think that a possible explanation for this data is that AIFA’s reimbursement limitation has recall the attention on a target subpopulation for palivizumab (infant ≤29 GA) that was not receiving appropriate coverage.

Furthermore, the impossibility to track palivizumab administration during hospitalizations could slightly underestimate palivizumab prevalence.

Reviewer: 3

Comments to the Author

Even with the limited word count, I think it's important to include at least some details on the methods and limitations so the data can be interpreted. Specific comments are:

What are the sample sizes? What is the data source?

In the new version of the manuscript, we have added details on infants included in the study and data sources.

Should the proportions of hospitalizations be rates? Is the denominator of the proportions all infants who were <6 months old during the RSV season? Could infants contribute different amounts of person-time?

For each period, all infants aged <6 months at the beginning of RSV season or born during it were considered as denominator: denominators are similar in the three periods.

Is there any reason to think these results would be different in other regions since RSV circulation is different by geographic regions?

Our analysis is based on data from one single Italian central region and may not reflect hospitalization trends seen in another geographical area. However, to the best of our knowledge, this is the largest European study evaluating the impact of the guidance on palivizumab based on a population representing 10% of Italian infants. Furthermore, we are not aware of any epidemiological or other reasons why a national regulatory decision, such as the one taken by the Italian Medicine Agency, should work differently in different regions. In Italy, all regions follow the same drug reimbursement rules by the National Health Service.

You note that your study is consistent with one very small US based analysis. That study consisted of 91 patients. You should also cite additional analyses that have found an impact and explain why those results may be different than yours.

We chose the most recent publication that supports our analysis given the limited number of references allowed in the research letter. However, several studies, undertaken in different contexts, support our results showing no differences in the prevalence of RSV infection-based hospitalizations in children aged <2 years after the implementation of the AAP-2014 guidance for palivizumab use (1-4).

Furthermore, evidence of lack of efficacy of palivizumab, measured by hospitalization in infants aged <2 years born at a GA of 29–35 weeks without comorbidities has been supported by several studies (5-6). Within all these references, we decided to add in the new version the one we believed is the most significant (3)

1. Grindeland CJ, Mauriello CT, Leedahl DD, et al. Association Between Updated Guideline-Based Palivizumab Administration and Hospitalizations for Respiratory Syncytial Virus Infections. Pediatr Infect Dis J. 2016; 35:728-32.

2. Rajah B, Sánchez PJ, Garcia-Maurino C, et al. Impact of the Updated Guidance for Palivizumab Prophylaxis against Respiratory Syncytial Virus Infection: A Single Center Experience. J Pediatr. 2017; 181:183-188.e1.

3. Farber HJ, Buckwold FJ, Lachman B, et al. Observed Effectiveness of Palivizumab for 29-36-Week Gestation Infants. Pediatrics. 2016;138. pii: e20160627

4. Buckley BC1, Roylance D, Mitchell MP, et al. Description of the outcomes of prior authorization of palivizumab for prevention of respiratory syncytial virus infection in a managed care organization. J Manag Care Pharm. 2010;16:15-22.

5. Newby B, Sorokan T. Respiratory Syncytial Virus Infection Rates with Limited Use of Palivizumab for Infants Born at 29 to 31+6/7 Weeks Gestational Age. Can J Hosp Pharm. 2017; 70:13-18;

6. Resch B, Bramreiter VS, Kurath-Koller S, et al. Respiratory syncytial virus associated hospitalizations in preterm infants of 29 to 32 weeks gestational age using a risk score tool for palivizumab prophylaxis. Eur J Clin Microbiol Infect Dis. 2017; 36:1057-1062

Are these levels of palivizumab use enough to influence hospitalization rates? These rates seem low. Most people aren't following the guidelines before the change.

We observed important variation in palivizumab use in gestational age 30-32 during the three periods considered (30.9%, 3.9%, 36.3%) but no variation in terms of RSV hospitalization rate was observed in this subpopulation.

Reviewer: 4

Comments to the Author

This is a single-center review of the RSV hospitalization rates before and after a change in the AAP 2014 policy regarding palivizumab prophylaxis. The authors cite demographic and hospitalization data regarding the impact of the subsequent adoption of this policy by the AIFA. Interestingly, although the <= 29-week group should not have been affected, there was a clear trend towards decreased admissions with the resumption of immunization. In the >= 37 weeks, which also should not have been affected by the policy, there was a trend towards increased hospitalizations. But when we look at the actual use of palivizumab, it actually increased in the <=29 by 15 percentage points throughout the study. This number should not have been affected by a change in the policy unless the implications of the policy were more far-reaching in so far as the unintended effect on the improvement of immunization rates in a group that was not receiving appropriate coverage.

Regardless, for this study to be clinically, as opposed to statistically meaningful, the raw numbers of patients in each epoch and each stratification need to be reported.

We thank the reviewer for comments; in the new version of the manuscript, we added in the Figures the number of patients in each period.

Editor in Chief

Comments to the Author:

Title amend to "Palivizumab reimbursement criteria and neonatal RSV hospitalization: a single-center retrospective review"

Given the regional perspective of this our analysis (which include several centers and hospitals, we suggest the following Title:

"Palivizumab reimbursement criteria and neonatal RSV hospitalization: a single regional retrospective review"

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. mario decurtis Institution and Country: University of Rome La Sapienza Maternal and Child Health, Italy Competing interests: None
REVIEW RETURNED	18-Jan-2021

GENERAL COMMENTS	I agree with the edits submitted by the authors