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Title	Respiratory syncytial virus-related outcomes from an abbreviated palivizumab dose regimen in children with congenital heart disease: a descriptive analysis
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Reviewer 1	Wendy Vaudry
Institution	Department of Pediatrics, University of Alberta, Edmonton, Alta.
General comments (author response in bold)	Very clear presentation of a program evaluation of shortened RSV prophylaxis implementation at the population level. For efficiency, I have organized my comments as responses to each of the specific questions. Responses are in italics. Please see the comments in the attached file. Does the background accurately represent current knowledge in this field? • The last sentence in the first paragraph should be referenced, or delete this sentence as it is stated more specifically in paragraph 2. **This sentence has been removed.** • Paragraph 2, line 22; do you mean currently? **The comment is not as applicable now that the paragraph has been rewritten.** • It would be appropriate/preferable to reference the CPS guidelines with or without the AAP guidelines **CPS added (page 3).** Do the authors explain why they conducted the study? **Yes** Is there a clear research question? **Yes** Is the study design appropriate? Are the methods described in enough detail? Did you find anything confusing? You may wish to consider: participants, intervention, exposure, comparator, outcome, confounders, bias **Thank you for the suggestions. We have re-organized the methods as such.** Are the results reasonable? Interesting? Surprising? • The child positive for s. pneumo by PCR from upper airway is irrelevant and should be included as RSV cases **This has been corrected (and is included in RSV cases).** • Given that three admissions occurred before the program started; should consideration be given to extending the season earlier? **The 3 admissions occurred before the children were referred to the Program, not because the season started late. This has been clarified in the result section (Page 5): "Among the 17 RSV-confirmed hospitalizations, two occurred after the start of the season, on November 19 and November 27, but before a Program application had been received from the treating physician."** **The Program reviews its season start date every year. Since the mid-1990s, our season has been consistent based on 16 years of data (as specified Ref #13). Nonetheless, we feel that discussing these details in this article is too out of scope, and are unable to include this within the word limit.** Is the interpretation supported by data in the results? **• Three of the cases occurred before the dosing period began so I'm not sure the statement in the second sentence of the first paragraph of interpretation is correct.** **The sentence has been revised: "all but one (96%) of RSV-related hospitalizations occurred before the end of the 4-dose period, not as a result of starting immunoprophylaxis late in the RSV season. So these cases were also not the result of a schedule failure" (Page 6).** • As you mention the CPS guidelines in the interpretation, they should also be mentioned in the guidelines; if word count is an issue remove the AAP references **CPS guidelines are now included in citations.** Do tables and figures accurately represent the data? Would some other visual be more helpful? **• Yes they are good** Are any important limitations not mentioned? • I think more emphasis should be placed on the potential variability in onset of the season as a limitation of a shortened season especially when a fixed date of onset is used. For example when the season starts much later many children could be unprotected. Using a shorter course may be more feasible if it is paired with onset of doses at the start of RSV season locally; a fixed onset date may not be as effective when using a shorter course. **We acknowledge that this a major point. To address this, we have added the following comment, 1st paragraph of discussion (page 6): "We show that in a geographical area where the RSV season consistently spans from early November to late April, all but one (96%) of RSV-related hospitalizations occurred before the end of the 4-dose period, not as a result of starting immunoprophylaxis late in the RSV season. So these cases were also not the result of a schedule failure." and insist in the limitation section (page 7) that 'our experience may not apply to areas where RSV epidemics occur in a non-seasonal manner'** **We also added a reference by Weinberger referred to in the introduction (Page 3) and second paragraph of the interpretation section (Page 6).** Did you spot any fatal flaws? That is, errors you do not believe the authors could overcome. Please explain clearly. **No** For whom are these findings relevant?

	Public health program planners, vaccine policy developers, clinicians Do the authors place their findings in the context of the literature? **Yes**
Reviewer 2	Chandrakant Lahariya
Institution	Department of Community Medicine, Gajara Raja Medical College, Gwalior, India
General comments (author response in bold)	None
Reviewer 3	Bernhard Resch
Institution	Department of Pediatrics Medical University of Graz, Graz, Austria
General comments (author response in bold)	The authors retrospectively investigated a 4-dose-palivizumab regime in a total of 325 children with CHD who had received 406 palivizumab courses. Seventeen RSV-confirmed hospitalizations occurred; 8 additional cases were not tested for RSV, for a maximum rate of hospitalizations for RSV-confirmed or unknown of 6.2 per 100 approvals (95%CI: 4.0 to 9.0%). Twenty-four of the 25 hospitalizations occurred before the 4th palivizumab dose. Only one RSV-confirmed hospitalization occurred (52 days) after the 4th palivizumab dose. Clinical characteristics of children with RSV-confirmed hospitalizations (n=17) were similar to those with RSV-unrelated hospitalizations (n=40). The manuscript is well written, findings are of interest, and the study complies with the STROBE criteria. There are some concerns: Despite palivizumab prophylaxis the authors found a high rehosp. rate between 5.2 – 7.6% (Proven and calculated, resp.). Please comment within the discussion section (low compliance rate or other reasons?). **We respectfully disagree with the reviewer's comment. Our hospitalization rate is inflated with the fact that we include RSV-undetermined cases in our conservative hospitalization estimates, which may differ from other studies. Regardless, our results are well within the statistical interval comparing to the only RCT in babies with congenital heart disease, or other Canadian or non-Canadian studies (e.g. using 95%CI) as presented on Page 6-7 (interpretation section), so it appears that our hospitalizations are comparable to other population of infants with CHD receiving palivizumab.** **As for compliance, 89% of intended palivizumab courses were completed (i.e. 361 / 406; figure 2), so I am not sure that our compliance rates are any worse than other population, though this has been insufficiently studied. The majority of hospitalizations occurred within the peak of viral exposure (Dec-Jan), and given that palivizumab only reduces hospitalizations by about 50% or so, to state that our cases of hospitalizations is due to missed doses or poor compliance is inaccurate. See first discussion (Page 6).** When did the RSV infections occur in regard to palivizumab injections? I suspect that the majority of rehospitalizations happened between 1. and 2. Injection. What about cardiac surgery in the context of RSV season and palivizumab doses regimen and rehosp.? **Correct, as in other Programs the majority of infections occurred in December/January, the peak incidence for respiratory virus exposure. We did not quantify the relative risk of hospitalizations relative to viral exposures. Infants who underwent cardiac surgery during the season received a post-pump dose. We have not analyzed in details the risk of RSV in relation to cardiac surgery mainly due to the major confounder or viral exposure/load at different times in the season.**
Reviewer 4	H. Cody Meissner
Institution	Department of Pediatrics, Tufts University School of Medicine, Boston, Mass.
General comments (author response in bold)	Several issues might be addressed by the authors that would strengthen this submission: • The authors need to clarify the objective of this report. Are they suggesting 4 monthly doses offer the same protection as 5 monthly doses of palivizumab? Why not 3 monthly doses? Three doses will likely offer significant reduction in RSV hospitalization. Even two doses would almost certainly provide some degree of protection. The reader is left wondering about the issue of relative efficacy for a schedule of less than 5 doses? Without some comparator group, the reader is unable to draw a conclusion about efficacy. Clearly, a 4 dose series has a number of advantages over 5 doses. But what is the consequence on reducing RSV hospitalizations? The authors imply 4 doses are adequate, but some evidence or at least discussion should be offered. If there is only a modest increase in RSV hospitalizations from 4 doses (compared to 5 doses), then that is likely to be acceptable. Both benefits and risks of a shorter course should be discussed. **To be clear, the 4-dose program is standard in BC for any approvals other that 29 to 34 weekers for who 3-doses is standard. That is, no infant receives 5 or more doses intentionally (omitting the extra dose given immediately after bypass blood exchange). Our objective was to report outcomes from infants enrolled in our 4-dose program, in an intention-to-treat population-based analysis. Our objective was not to compare the efficacies of 4 vs 5 dose programs in our population, as we do not have that data. In the article, we do place our data in the context of the Feltes trial and data from jurisdictions who use a standard 5 dose regime as we feel this indirect comparison is valuable, but we cannot determine how many cases would be avoided should we have used a 5-dose regime. Because 96% of cases occur before the 4th dose and only ONE case occurred after the 4th dose 35-day maximal interval period it is extremely unlikely that the use of a 5 dose regime would have changed the outcome in any meaningful way. On the other hand, we discuss the benefits of a 4th dose regime on reducing the need for clinic visits and injections, which is an important benefit.** • One option would be to compare their results (4 doses) with the results obtained in the randomized trial (5 doses) in reference #4, Feltes et al. Historical controls are difficult because definitions will differ but at least it is some comparative measure. **The hospitalization outcomes in the Feltes trial are mentioned in the introduction (page 3) and are entirely comparable to our study. We also reviewed other population-based outcomes in the Supplementary Table 1 that demonstrate comparable hospitalization rates.** • Why did the authors select 4 doses? They imply it is because pharmacokinetics show palivizumab accumulation after 4 doses and that higher serum concentration of palivizumab after the 4th dose will offer protection for more than 4 months. This is very likely to be true, but the authors have not proven that or even clearly stated that. **This is now more clearly stated in the introduction (page 3), hoping it is satisfying. More details of the**

	pharmacokinetic comparisons are detailed in the references. • The best reference regarding palivizumab pharmacokinetics is Antimicrobial Agents and Chemotherapy 2012;56(9):4927, which is not cited. This reference (study published by the manufacturer) shows that at least for 30 days after the 4th dose, protective serum levels are present for most subjects. This should be discussed as it strongly supports the author's position. **We appreciate the suggestion. This reference, from Medimmune (the company selling palivizumab) does not support an abbreviated regime. However, others have contradicted these estimations (references in the introduction, Page 3). In this article, we feel that it would be outside the scope of the article to directly get in the middle of the controversy of who has the right pharmacokinetic modelling. Rather, we have made a choice in the BC RSV Program in 2012 and hope that simply reporting clinical outcomes from this unique real-life experience will better inform readers about the usefulness of this approach.** • Suggest some discussion of RSV season in British Columbia to assist the reader in understanding how the start and end of monthly prophylaxis was established. **We have worked to clarify that the fixed season start and end dates is based on 16 years of consecutive data in BC (methods section, Page 3). We have previously reported this data in Ref #15. This data cannot be repeated here but citation has been included in the methods.** • Reference #3 is now 36 years old and has no relevance today because of changes in many things, including time and types of cardiac surgery. Suggest better reference **Thank you, we have added another more recent reference (#3). To the best of our knowledge, very few authors have directly compared types of cardiac lesions in terms of RSV risk and these 2 references are the most notable to us.** • Many would not agree that children with Down syndrome without CHD or "severe immunodeficiency" are at "particularly at risk". Suggest supporting references. **Correct. Though we feel that the most recent data, especially the studies that have compared infants with Down syndrome with or with prematurity/CHD do suggest that Down syndrome increase the severity of RSV infections we have removed the reference to this patient group to avoid distracting from the focus of our study.** • Discussion of RSV and non-RSV related hospitalization is confusing. The numbers are difficult to figure out. This is important because of observations showing palivizumab prophylaxis results in an increase in non-RSV related hospitalization for LRI that equals the reduction in RSV hospitalization. Reference: Faber et al. Pediatrics, Aug 2016, 138 (2) e20160627 **We are very receptive about ways we could make this clearer. The result section of the manuscript has been revised, including figure 2, hoping that this will clarify the matter.** • Page 9, line 5, reference to AAP recommending less than 5 doses is not quite correct. AAP refers to infants born after start of RSV season. **Correct. We have added this precision (2nd paragraph page 6).** • This reviewer strongly supports shorter courses of palivizumab. Suggest some changes to this submission to make a greater impact on the reader. **We truly appreciate suggestions from all 3 reviewers.**