Author’s response to reviews

Title: An economic analysis of human milk supplementation for very low birth weight babies in the USA

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Editor

Comment: We note that your submission says that you received industrial support for these studies, please state (as per journal guidelines) the role the funder played in design and publication.

Response: Apologies for this omission. The following text has been added: Martin Lee at Prolacta Bioscience provided advice throughout the study and read the final paper before submission (no edits were made). The sponsor did not dictate the study design or the analysis or interpretation of data, nor did they contribute to the writing of the report.

Dmitry Dukhovny (Reviewer 1)

1) Patient population - the title suggests US cohort, but you are only putting 1,000 (rather than roughly 60,000 VLBWs annually) through the model

Response: Cohort is this context is used to explain the hypothetic patients in the economic model, and 1,000 is the number typically used, although mathematically it makes no difference to the outcomes (per-patient). Whilst this is commonly used language for economic models, we agree that it may cause confusion. We have therefore replaced this mention of ‘cohort’ with the word ‘population’.

2) The base line parameters:
NEC rates in the trials mentioned are higher than overall rate - the table with the parameters for the models should have the references within the table to help reader to easier identify the sources (and it would help to make the text more concise when the authors go on to explain it)

Response: Whilst other data is available (Rees et al., 2007; Battersby 2018) on the incidence of NEC in this population, it does not differentiate between babies receiving bovine-based fortifier and an EHMD. Therefore we believe that the data utilised is the best available for use in this base case. This input value is then varied in the sensitivity analyses.

The numbers in square brackets in the table represent the references.

3) Sensitivity analyses - visual graphics of one way and multi-way sensitivity analyses would be helpful

Response: Thank you for this helpful suggestion. Please see new Figures 2 and 3.

4) Economic evaluation

- Please explicitly state in the methods the time horizon up front (it's presumed one year, but it's not really stated clearly until the end of the methods)

- The statement in the conclusion about cost-effectiveness does not account for the sensitivity analyses (95% CI from bootstrap/probabilistic Sn analyses) nor is there iCER table in the manuscript

- While the authors discussion on QALYs is correct, it can still be modeled under certain assumptions and may help bring multiple outcomes together

Response: Thank you – we have added this information up front in the first paragraph of the methods section.

We have also extended the statement in the conclusion, adding the following text: The finding of dominance holds in both the ‘best’ and ‘worst’ case scenarios which are based on alternative data from the literature. Cost savings increase when wider societal costs are included, and remain positive as long as the baselines incidence of NEC is 9% or above.

You note that ICERs are not presented – this is because we are using a variant of economic analysis called cost-consequences analysis, which does not involve producing ICERs (please see Neumann et al. 2017 for more details). In addition, it is not possible to calculate ICERs in a dominant scenario, as reported here (note that negative ICERs are meaningless).
We investigated the possibility of modelling QALYs, but given the paucity of data the calculation would be at best inaccurate, and at worst completely misleading. Given that the EHMD is clinically beneficial across all outcomes we know that the QALY gain would be positive, and as such the conclusion would be the same, i.e. that EHMD is clinically beneficial and cost-saving.

Reviewer 2

Comment: This paper addresses an important research question: is the exclusive human milk diet (EHMD) cost effective compared to the cow milk-based products among very low birth weight (VLBW) infants. The authors improved the decision models by including more complications and life-time costs. Using the clinical evidence from randomized controlled trial improves the model estimation. Sensitivity analyses also have been conducted. The results can have direct implications for VLBW infants care in NICU and other clinical settings.

Response: Thank you.

Comment: The decision model in Figure 1 is very simple. More details are needed to illustrate the transition of the states of VLBW infants with two different milk products.

Response: Thank you. The Figure has been extensive revised to clarify this. Please see revised Figure 1.

Comment: Moreover, the paper does not include any validation exercise of the model, which is necessary for conducting further simulations. The results in Table 3 are puzzling. The incremental benefits are number of cases or the percentage? If it is number of cases, then the results are too good to be true. For example, among 1,000 infants, human milk diet can reduce mortality by 131 cases, which is hard to believe. Therefore, the authors need to demonstrate the validity of the decision model with extensive calibration exercises.

Response: Thank you for raising this. We do believe that the results make sense.

Assuming an estimate of 16.7% probability of NEC in the routine practice group and a relative risk of 0.31 for NEC when receiving a EHMD compared to routine practice (see Table 1), it stands to reason that around 167 babies in the routine practice group would get NEC, and around 52 babies in the EHMD group would get NEC. This is a difference of 115. The difference between this 115 and the 131 reported in the paper is due to differences in mortality (not accounted for in this simple illustration). This data is the best available to represent these parameters.
We have amended Table 3 to make this clearer and added the following text to the discussion: The clinical benefits calculated by the model are substantial and in line with expectations based on the input data and published literature in this area [3-6].