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Conjugated and polysaccharide anti-pneumococcal vaccines

Dear Editor,

With respect of the article published by Di Nuzzo & Fonseca[1] we would like to point out that the information provided on the subject of immunization against pneumococcal diseases require correction, as described below.

In this article, four conjugated pneumococcal vaccines are presented. In Brazil, however, there is just one conjugated pneumococcal vaccine, the 7-valent vaccine conjugated with the CRM197 diphtheria toxin (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), which is indicated for administration from 2 months of age onwards (and not just from 2 months to 2 years) and can be given up to 5 years of age. Children who are first vaccinated with the 7-valent vaccine can later be given a dose of the 23-valent vaccine in special cases (high risk).[2,3]

Immunodepressed children over 2 years of age should be given two doses of the 7-valent vaccine (with a 2-month interval) and a single dose of the 23-valent vaccine (2 months after the last dose of the 7-valent vaccine).

Recent studies of the efficacy and immunogenicity of the vaccine for premature patients, and also for older children requiring protection from non-invasive diseases (e.g. acute otitis media) are the references that have been used to widen the indications and the target-population of the vaccine.[4-7]

With respect of the 23-valent vaccine, this should be classified among the polysaccharide vaccines, composed of purified antigens from the polysaccharide capsules of 23 serotypes, being only available in our country for administration from 2 years of age onwards.

The 9 and 11-valent conjugated vaccines are not yet available commercially being in the final phases of research.

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Lung deposition, efficacy and effectiveness of spacer devices

Dear Editor,

We read with great interest the article written by Rocha Filho et al.[1] and now we would like to make some comments and questions about it:

1) In large-volume spacer devices, aerosol particles remain in suspension before being inhaled; thus, for better drug delivery, it is recommendable that the inhalation time should be exactly the same as that one used for smaller devices (often 30 instead of 10 seconds, as mentioned in the article).

2) As three-year-old preschoolers have a different respiratory dynamics from seven-year-old schoolchildren, it seems more appropriate to assess deposition according to age group instead of including these patients in the same analysis; what would the mean age of these groups have been?

3) Since it is a test of hypotheses, the type and extent of the difference to be tested are not indicated when sample size is described; do the differences lie between means or proportions of pulmonary deposition? What were the values? If the difference is between the means, what was the value for the pooled variance on which the sample size calculation was based?

4) In the absence of these assumptions – which are essential in analyzing the power of the study – we employ the mathematical formula for the differences between the means and we obtain the approximate sample size necessary to ensure a power of 80% indicated in the methodology; thus, in order to detect differences in the means of deposition between Inalair® and Flumax® nearly 20 children and 34 adults[2] would be necessary; therefore, we ask: what is the actual power of the study?

5) Besides p value, it is recommendable to include the upper and lower limits of the 95%CI, thus allowing for the better understanding of the statistical significance and its consequent interpretation from a clinical point of view; what were these values? As the analysis of Figure 2 suggests overlapping of pulmonary deposition ranging between the tested spacer devices, shouldn't these results be further developed in the discussion? What are the internal and external validities of the investigation? The results obtained allow the authors to state that "*our study clearly demonstrates that small-volume spacer devices are superior to large-volume ones*?"

6) In addition, in the randomized clinical trial cited in the references,[3] the large-volume spacer device consisted of a 500-ml mineral water bottle that was as efficacious as the nebulizer in the treatment of acute asthma despite the fact that 95.8% of the patients analyzed comprised preschool and school-aged children; are large-volume spacer devices always less efficacious in these age groups?

7) Since inaccuracy cannot be dissociated from any semiquantitative method, would the deposition of technetium phytate *per se* correspond to the actually inhaled proportion of bronchodilators and/or corticosteroids whose molecules were or were not radiolabeled? What would the actual limitations be in case of *in vivo* semiquantitative studies? Should these aspects be further developed in the discussion?

8) We understand that the electrostatic charge of plastic spacer devices should be discussed in more detail: do different types of plastic contain the same electrostatic charge? Would Flumax®, which is made of PVC, has the same results as Aerochamber® and other spacers made of polycarbonate? Are there largely accepted methods that could be used to reduce this electrostatic charge? What is the role of household detergents in this case? Do the differences in deposition between metal and plastic spacer devices increase or decrease when plastic devices are coated with these detergents? Would it be methodologically recommendable to coat the tested plastic spacer devices before analyzing pulmonary deposition?

9) As our study was cited (reference 10), it should be stressed that, as an inseparable part of the semiquantitative study we carried out with Flumax,® we included a clinical evaluation, and we obtained favorable results even when the mean age of the analyzed children was 5.5 years; how can this be explained if large-volume spacer devices should be reserved for adolescents and adults? Should this finding be included in the discussion of the commented article?

10) What matters to clinicians is all that occurs in real life and this can be analyzed in effectiveness studies; in two different studies that assessed the asthma program implemented in Belo Horizonte, in which children only used a large-volume spacer device (Flumax®), 2,141[4] and approximately 700[5] children were evaluated, of which 75% were younger than 5 years, and a reduction of respectively 75.8% and 89% was obtained for the hospitalization rate, and 85 and 91% for emergency room visits, respectively; how can these results be explained in a population that basically consists of preschool children?

11) Finally, according to Anderson,[6] "*there is no 'best' outcome or 'gold standard' in the assessment of inhaled drug delivery …. We need more trials comparing in vitro with in vivo outcomes …; in the final analysis, however, there is no substitute for clinical trials in patients"*. Should these aspects be further developed in the article?

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Author's reply

Dear Editor,

We appreciate the interest of Professors Camargos and Rubim in our study[1] as well as their comments. It should be recalled that the aim of our study was to assess the pulmonary deposition of radioisotope-labeled aerosol. Therefore, the data presented do not allow making any conclusions about the clinical efficiency of the spacer devices analyzed. We agree that pulmonary deposition varies with the type of medication used. However, we did not find any evidence in the literature for the hypothesis that aerosol particles remain in suspension for a longer time in large-volume spacer devices, requiring a longer inhalation time. Why 30 seconds instead of 20, 25 or 15 seconds?

Our opinion is that the major factors related to the pulmonary deposition of a certain aerosol are the size of the particles, more specifically, the median mass diameter of these particles, and the inspiratory flow. When, besides the variables mentioned above, spacer devices are used, the electrostatic charge and the patient's tidal volume (8 to 10 ml/kg) are of paramount importance. Therefore, a child weighing 15 kg has a tidal volume around 120 to 150 ml. Two breaths with the small-volume spacer and five breaths with the large-volume spacer should be enough for the entire content of the spacer to be inhaled. In fact, one co-author (Simal CJR) observed that, regardless of age, almost all the radioisotope-labeled aerosol within the spacer was inhaled during the first two breaths with the spacer (personal communication). It is the same co-author of the study conducted by Rubim et al.,[2] in which a similar technique was used to assess pulmonary deposition. Therefore, we do not believe that 30 seconds of inhalation with large-volume spacers would bring any additional benefits.

The electrostatic charge also has a remarkable effect on pulmonary deposition. We agree that the electrostatic charge may vary with the type of material used. A spacer made of PVC such as Flumax® is likely to have a different electrostatic charge from spacers made of polycarbonate such as Aerochamber®. Moreover, the electrostatic charge is influenced by the climate and by the volume in the spacer device. It is inversely proportional to air humidity and to the size of the spacer. Therefore, the electrostatic charge is higher in drier conditions and in small-volume spacers, reducing the amount of aerosol particles. Anyway, no matter which material which the spacer is made of, the electrostatic charge will always be smaller in metal spacers, since this type of material has no electrostatic charge. This important difference can be overcome when spacers are rinsed with a neutral detergent, thus eliminating the electrostatic charge from PVC or polycarbonate spacer devices. The aim of our study was to assess the effect of this electrostatic charge on different spacer devices, so we were not supposed to eliminate it by rinsing the spacer with detergent. We also believe that metal spacers are more practical in emergency care because they do not have to be rinsed with neutral detergent after being used by the patient.

The power of the sample was based on the fact that the size of the three comparison groups is equal to 9, considering a significance level of 0.05, a common standard deviation of 8.7 and a mean variance of 68.756. These data are necessary to calculate the power of the study when we have three or more comparison groups. In our opinion, the comment about the p value is unfounded since confidence intervals were not calculated. Figure 2 shows the boxplots for pulmonary deposition in three spacer devices according to age and not to confidence intervals. The crux of the matter is not whether the difference between the three groups is significant. A small difference can be statistically significant and have no clinical relevance. The extent of the difference is what really matters.

We should highlight that large-volume spacers have been used on a smaller scale, even in Brazil. While numerous small-volume spacers are available, Flumax® is the only large-volume spacer available in the Brazilian market. Large-volume spacers are cumbersome and unwieldy, not easily mounted, and contain electrostatic charge. At no moment was it documented that large-volume spacers are better than small-volume ones. Our study is in line with several other literature studies that indicate the superiority of small-volume spacers which, contrary to their sizable counterparts, can be used at any age. At the last Brazilian Congress on Pediatric Pulmonology held in Rio de Janeiro in April 2004, Dr. Hawm Tildden analyzed pulmonary deposition, using a more sophisticated method than the one employed by us, and confirmed a low pulmonary deposition when he tested Flumax® at his laboratory in the Netherlands (personal communication).

Finally, we totally agree with professors Camargos and Rubim when they say that many of the statements made by us and them have to be corroborated by well-designed clinical studies. The clinical experience of Belo Horizonte in the treatment of asthmatic children at the public health level is an example of how these patients can benefit from a well-designed and properly conducted program. Despite the decrease in asthma hospitalization rates, we question whether the use of small-volume spacers could bring additional benefits. This seems to be the concern of the team in charge of the study, given that small-volume spacers are already available for the public in Belo Horizonte. Likewise, the aim of the study carried out by Rubim et al. was not to compare the clinical efficiency of different spacers. We did not infer that large-volume spacers are inefficient; instead, we meant that small-volume spacers are superior to the large-volume ones in terms of pulmonary deposition. Hypotheses are indeed the driving force behind the growth of knowledge. If not supported by well-designed clinical trials, these hypotheses are merely speculative. Because of that, we are carrying out a double-blind comparative study in our setting in order to assess the use of different spacer devices in approximately 200 patients. With this study, we hope to answer some of the questions raised here, since half-truths can be downright lies. Clinical impression and personal experience are certainly useful in formulating a hypothesis, but they cannot replace objective data obtained through well-designed clinical trials. A

hypothesis should be tested, but until it is not, it should not be regarded as fact.

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Comparing asthma prevalence estimates in Recife

Dear Sir,

We would like to comment on a number of methodological issues related to an article by Britto et al.[1] recently published in this journal.

One of the objectives of that study was to evaluate the diagnostic accuracy of the annual prevalence of wheezing as an indicator of asthma. To do this the authors compared answers to two different questions: question 2 (Q2) of the core asthma module of the ISAAC questionnaire - "Have you had wheezing in the past 12 months"? and question 6 (Q6) -"Have you ever had asthma?". It has been previously suggested that, in the absence of a gold standard, results obtained by administering a questionnaire of the signs and symptoms of asthma can be compared to documented diagnosis of asthma made by physicians in the same patients.[2] In our opinion, information obtained through Q6 cannot be taken as equivalent to a history of physician-diagnosed asthma (clinical examination and diagnosis made by a health professional), since participants' replies to this question will be determined by their own understanding of the term 'asthma' rather than by an objective measure of the presence of that disease. Therefore, the reported information seems to merely represent data on the agreement between answers to two separate questions rather than information on the validation of Q2. Validating this question would have required the comparison of replies to Q2 with results from either an objective test (e.g. lung function test), or a clinical examination by a physician, or documented information on a previous diagnosis of asthma from medical records.[2]

A second methodological issue is concerned with the use of the term cansaço (which in English means feeling breathless or short of breath) as part of the translation of the term "wheeze". Although the ISAAC study group had suggested that asthmatic children and their parents could be asked to describe breathing patterns during an asthma episode,[3] we think that the translation of the term "wheeze" as "cansaço" used in the present study might not be appropriate. First, the term "wheeze" included in the core module of the ISAAC questionnaire corresponds to the terms "sibilos", "piado" or "chiado", in Brazilian Portuguese. In contrast, the term "cansaço" (shortness of breath) has a broader meaning and, in the Brazilian context, it is frequently associated with several clinical conditions other than asthma. Second, the English version of the questionnaire that was used in phase I of the ISAAC only included the terms "wheeze", "cough" and "asthma" (and not "breathless" or "short of breath").[4] The term "breathless" or "short of breath" was only introduced later in the English version of the phase II ISAAC core questionnaire (module Wheeze and Breathlessness Supplementary Questionnaire).[3] It is worth noting that the term "cansaço" did also not appear in the Brazilian version of the questionnaire designed to be used in Phase I of the ISAAC in Brazil.[5] Finally, other three English versions of questionnaires designed to study respiratory diseases have used the terms "wheeze", "breathless" and "short of breath" in separate questions or as "shortness of breath with wheezing" (IUATLD, ATS and MRC).[2] And it has been shown that questions that use the terms "breathless" and "short of breath" have lower specificity in correctly identifying asthma than those using the term "wheeze".[2]

As a result, by accepting the term "cansaço" as a translation of "wheeze", Britto et al. may have obtained higher prevalence estimates than surveys based on questionnaires that did not include that term, making the results of the present study less comparable. Moreover, it is unclear whether the term "cansaço" was used in the survey conducted in 1994-1995[6] or only in the 2000 survey and, if it was not used, interpretation of the findings from this comparative study will be difficult. In conclusion, we would like to suggest that future surveys of this type use standard questionnaires (e.g. ISAAC) without modification in order to preserve comparability of results across countries and over time. If modifications are judged necessary, they should be incorporated as additional questions, allowing separate analyses, as recommended in textbooks.[7]

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