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**Title Page**

**Title:** A Cost Analysis of Salbutamol Administration by Metered-Dose Inhalers with Spacers versus Nebulization for Patients with Wheeze in the Paediatric Emergency Department: Evidence from Observational Data in Nova Scotia

**Running header:** Cost Analysis of Salbutamol by Metered-Dose Inhalers vs Nebulization in the Paediatric ED

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**Word Count: ~~2484~~**

**Abstract**

**Background:**
Despite evidence demonstrating the advantages of metered-dose inhalers with spacers (MDI-s), nebulization (NEB) remains the primary method of asthma treatment in some paediatric emergency departments (PED). There is a perception that delivering salbutamol by MDI-s is more costly than by NEB. This research evaluates the relative costs of MDI-s and NEB using local, hospital-specific, patient-level data.

**Methods:**
Regression models estimated associations between the salbutamol inhalation method and costs, length-of-stay (LOS) in the PED and hospital, and the probability of admission. Our population was a random sample of 822 patients presenting with wheeze to the PED in 2008/2009. Control variables included age, sex, triage acuity, time of PED visit, other medications, and vitals. Costs were calculated using the prices and quantities of medical resources used per treatment. Probabilistic sensitivity analysis was used.

**Results:**
Treatment with MDI-s versus NEB was associated with an absolute decrease in hospitalization of 4.4% ($p<0.05$) and a 25 hour ($p<0.001$) reduction in average inpatient stay. This resulted in savings of $24/patient in the PED and $180/patient overall ($p<0.001$). Inpatient care accounted for most of total patient costs (96% in NEB and 92% in MDI-s).

**Conclusions:**
Our results suggest economic gains associated with MDI-s for salbutamol inhalation in PEDs. Sensitivity analyses show that this conclusion is not affected by changes in model parameters that may differ by jurisdiction. Since most facilities already collect the data used for this study, our methods could be adopted for a cross-jurisdictional account of the cost effectiveness of MDI-s.

**Introduction:**

Wheeze leads to frequent presentations to paediatric emergency departments (PEDs).[1] Salbutamol, a beta-agonist often used to treat wheeze, was traditionally administered by nebulization (NEB). However, evidence shows that salbutamol administered by metered-dose inhalers with valved spacers (MDI-s) offers advantages to paediatric patients.[2] Salbutamol administered by MDI-s is associated with less tachycardia and tremor, decreased PED length-of-stay (LOS), and decreased risk of admission.[2] MDI-s also results in increased child and parent treatment satisfaction and may reduce staff and caregiver risk during respiratory epidemics.[3-5] Although PEDs in Canada are now accepting MDI-s as the route of choice for salbutamol inhalation,[6] one of the factors linked to resistance to switching salbutamol inhalation methods ~~has been linked to~~is the ~~a~~ perception of increased costs.[7,8]

The cost-effectiveness of MDI-s versus NEB has been documented,[4,9-12], but no published Canadian study has used local clinical and administrative data in their analysis. One Canadian study estimated cost-savings of $155 per PED visit associated with salbutamol delivery via MDI-s.[10] Doan and colleagues used hospital-level data for medication, labour and equipment costs, but drew on a systematic review of randomized controlled trials for patient outcomes.[2] While cross-regional extrapolation of epidemiological outcomes is commonly accepted in health economic evaluations, clinical outcomes such as LOS and hospitalization rates may be less generalizable because of jurisdictional variations in socioeconomic status, practice variability, and supply of health care resources.[13-15] Our objective was to conduct an economic evaluation of both salbutamol inhalation methods based on local, hospital-specific patient-level outcome and cost data.

**Methods:**

Approval was obtained from the Research Ethics Board of the IWK Health Centre (#1012427, September 28, 2012). Consolidated Health Economic Evaluation Reporting Standards (CHEERS) were used in the development of this paper.[16]

*Data Collection*

The setting was the IWK Health Centre, the tertiary care paediatric facility for Maritime Canada. The IWK PED sees approximately 28,000 children per annum, with approximately 2000 (7.1%) presenting with an acute wheeze-related illness. Our cohort was established in a previous study.[17] A randomized sample of 1376 children were chosen from the 4140 patients diagnosed with asthma (J45), bronchiolitis (J21), other respiratory disorders (J98.8) or wheeze (R06.2) (International Statistical Classification of Disease and Related Health Problems, 10th Revision, Canada) between January 1, 2008 - December 31, 2009.

Data from the patient chart review, Discharge Abstract Database (DAD) and National Ambulatory Care Reporting System (NACRS) were linked to provide a patient-level data set. Each record represents a visit to the PED and captures age, sex, visit date and time, triage acuity, vitals, salbutamol inhalation method, total dosage, other medications given (ipratropium bromide and dexamethasone), PED and hospital LOS, and disposition. (Table 1)

We excluded patients whose data did not match between chart review, DAD and NACRS (n=191), patients who received both or neither methods of salbutamol inhalation (n=245) and those with missing or invalid data values (n=118). Our final sample numbered 822 visits.

*Study Perspective and Discounting*

Our analysis takes the hospital's perspective. That is, our analysis did not include private or societal costs and benefits. Physician costs were not included as PED physicians at the IWK are paid a rate per shift which is not dependent on patient volume or treatment choices. We did not perform present-value discounting as all costs and clinically relevant outcomes occurred shortly after treatment.

*Calculating Cost of Treatment*

Patient-level costs were calculated using data on treatment method, dosage and disposition with local information on the cost of supplies, nursing time[11] and inpatient care. Table 2 describes the supplies and time required for each round of treatment including the monetary cost per treatment. We used the patient's recorded dosage of salbutamol and the IWK Health Centre's Asthma Care

Map (available on request) to derive the total number of treatments received by a patient while in the PED.

All costs and prices were converted to 2010 constant Canadian dollars prior to calculating costs of treatment. Cost estimates were also converted into U.S. dollars. We also compared our cost estimates to others found in the literature. Where appropriate, citations of treatment costs from international jurisdictions were converted into Canadian dollars using foreign/Canadian exchange rates for the year of publication (http://fxtop.com), and then adjusted to 2010 constant dollars.

*Analytic Methods*

We describe our data set using sample counts by selected patient groups. Means (95% confidence intervals) were calculated for the both patient groups. Regression models were used to estimate differences in outcomes and costs between groups. Because admissions and LOS in both the PED and hospital are significant drivers of treatment costs, all three clinical measures were used as dependent variables. Control variables included age, sex, triage acuity, patient vitals (e.g. respiratory rate, oxygen saturation, heart rate), date~~/time~~ of PED visit, and the use of other medications. Baseline heart, respiratory rates, and oxygen saturation were converted to age-based CTAS categorical scales prior to their inclusion in the regression models.[18]

Logistic regressions were used to estimate admission probabilities, while Poisson regressions were used for PED and inpatient LOS. Generalized Linear Models (GLM) with log-link and Gamma distribution were used to model inpatient and PED costs. Since 85% of visits to the PED resulted in a discharge and, therefore, zero inpatient costs, we adopted a two-part model for evaluating inpatient costs. In this case, we separately modelled the probability of inpatient admission and the level of inpatient costs among hospitalized patients. The estimates generated from these two models were combined to derive a single estimate of the difference in inpatient cost between the two treatment groups.

All analyses were conducted using Stata12.1 (www.stata.com).

*Sensitivity Analysis*

We performed two sensitivity analyses to explore the sensitivity of our results to changes in the parameter values used to calculate the costs. First we used a scenario in which we assumed that baseline parameter values were biased in favour of MDI-s. Under an alternative scenario, we replaced baseline MDI-s parameters with higher prices and more intensive resource use values, whereas baseline NEB parameters were replaced with lower prices. The second sensitivity analysis used a multi-way (probabilistic) sensitivity approach. In this case, parameter values were selected at random from probability distributions and then used to re-calculate patient costs. Once these costs were produced, we re-estimated our regression models. This procedure was replicated 10,000 times to derive a simulated distribution of cost differences between groups.

**Results**

*Clinical and Demographic Characteristics*

Of the 822 patients analyzed, 644 were in the MDI-s group and 158 in the NEB group. Patients in the NEB group were 1.1 years younger and presented to the PED with more severe clinical symptoms as measured by triage acuity (Table 3).

*Patient Outcomes and Costs*

Our summary statistics (Table 4) show that MDI-s treatment is associated with lower costs and improved clinical outcomes. For example, only 11% of those in the MDI-s group were admitted after treatment in the PED, compared to one-third of those in the NEB group. Costs in the NEB group were $998 per patient-visit, compared to $173 for MDI-s. Inpatient care accounted for more than 93% of total patient costs (96% in NEB and 92% in MDI-s).

Table 3 and 4 show summary statistics which do not control for confounding influences including illness severity, additional medications and patient characteristics (e.g. CTAS, ipratropium, age).

MDI-s was also associated with lower treatment costs. Treatment via MDI-s is associated with a $180 (US$175) reduction in total costs per patient-visit. While almost 90% ($156 (US$152)) of

this reduction came in the form of lower inpatient costs, MDI-s was also associated with a $24 (US$23) reduction in PED costs.

~~Our results are not sensitive to changes in baseline parameter values. Increasing input prices and~~ higher equipment prices for MDI-s than at baseline. For example, under this scenario, it is assumed that spacers are used for 3 patients, rather than 5 as stated under our baseline assumptions. The analysis~~Our scenario analysis (Table 5, Panel C)~~ reduces but does not eliminate the cost-(US$141)~~, but does not eliminate cost-savings from MDI-s~~. As before, cost-savings are driven by with MDI-s. However, PED cost-savings for MDI-s fell by 79%, from $24 per patient visit to $5 (US$4.85).

Figure 1 displays the results of the multi-way sensitivity analysis. Each point on the figure is an estimate of the cost-savings for MDI-s under a simulated set of input prices and resource use values for each treatment. Importantly, all of the simulated estimates indicate cost-savings for MDI-s. For example, the right tail of the distribution indicates that the use of MDI-s is associated with a minimum cost-savings of approximately $160 (US$155) per patient visit.

**Discussion:**

Salbutamol inhalation by MDI-s is associated with lower admission rates and inpatient LOS, after controlling for observed differences between treatment groups in illness severity (e.g. CTAS, vitals, use of ipatropium) and patient characteristics (e.g. age, sex). ~~, after controlling for selected patient characteristics and illness severity.~~ This resulted in cost-savings of $180 ($p<0.001$) per patient, with most savings coming from lower admission rates. With approximately 2,000 patients presenting to our PED with an acute wheeze-related illness per year, even if only 75% are treated with salbutamol, the predominant use of MDI-s would realize total savings of $270,000 (US$262,000) per annum. Of these, $42,000 (US$41,000) per annum are direct savings to the PED.

While PED LOS was equivalent in both comparator groups, our model used the total treatment time as reported by the UK time and motion study [11], which was significantly higher for patients

in the NEB group. The authors of the UK study measured administration and set-up time separately and added the two to obtain total treatment time. At our PED, registered nurses perform setup and administration tasks, making total treatment time the most relevant model parameter. While PED cost differences are likely sensitive to setup time, PED costs make up only a small fraction of total patient costs at our institution.

Several studies have examined the economic impact of salbutamol inhalation procedures in emergency departments.[9,11,12] In two studies, respiratory therapist or nursing costs for both procedures were assessed.[9,11] Both studies found similar costs of drug, delivery system and staffing for both inhalation methods - savings of US$8.15 (CAN$9.87) associated with MDI-s were reported in one study[9], while a loss of US$7.33 (CAN$8.87) for a single treatment was noted by another.[11] However, the authors of the latter study noted that savings had switched in favour of MDI-s by the fourth or fifth treatment. Another study examined differences in treatment time, reporting a 25-minute reduction in treatment time for MDI-s versus NEB. Based on historical ED charges, the authors estimate time-related cost-savings of US$216 (CAN$222) per patient-visit.[12] The value of the assessment or education given in the PED when using MDI-s has yet to be assessed in ~~any~~ comparative study~~y~~ies.

In addition, two studies examined cost-savings achieved through admission rate changes associated with MDI-s.[4,10] Leversha and colleagues documented significantly decreased costs in patients aged 1 to 4 years in a New Zealand PED through reduced hospital admissions in patients using MDI-s.[4] Their savings, NZ$457 (CDN$547) per patient, are more than twice ours. A Canadian study using non-local clinical data, arrived at estimated savings with MDI-s versus NEB that is remarkably similar to ours (CDN$155 versus $180).[10]

**Strengths and Limitations:**

An important strength of our study is that it uses local patient-level clinical data, and local economic data from administrative sources. This data captures unique regional factors influencing treatment, admissions and cost of treatment. Our results may not be generalizable to other health care systems because of work flow and practice culture. However, because we used data that is

already collected in many jurisdictions, our methods can be used for cross-jurisdictional accounts of the cost-effectiveness of MDI-s.

An important methodological limitation of our study is sample size hindering our ability to assess differences in costs and outcomes by patient sub-groups. The data is derived from paper-based medical records. To validate the accuracy of the abstraction process, a randomly selected 10% of the medical record reviews were repeated by an independent researcher.[17] Kappa (κ) for the inter-rater reliability test was 0.97. Our data does not include patient co-morbidities or validated measures of asthma severity, and may be limited by other unmeasured confounding such as variations in physician choice of initial therapy in the PED and inpatient treatment. ~~Instead, we used CTAS to group patients into severity groups, and hospitalization as a proxy for~~

We did not include administration costs involved in ordering drugs and supplies. Our time estimate for each visit is based on a UK time and motion study and may exclude the teaching time done in our PED to reinforce patient and caregiver MDI-s technique. Our study did not deal with the many advantages offered by, or technical and physical differences of using MDI-s instead of NEB for the delivery of salbutamol. These differences have been addressed elsewhere.[19,20] Data limitations also precluded an assessment of patient relapse/readmission.

**Conclusions:**

We show that use of MDI-s for salbutamol inhalation in PEDs is associated with significant economic gains. Compared with NEB, MDI-s was associated with a 4.4% absolute reduction in admission to hospital and reduced costs by $180 per patient visit. These results suggest that broader adoption of MDI-s by other PEDs could result in substantial cost-savings.

Our study uses local data on patient outcomes, treatment protocols and input costs, thereby capturing unique regional factors influencing treatment, admissions and costs. While these data are less transferable to other settings, we show, using sensitivity analyses, that our conclusions are

not affected by changes in model parameters, such as treatment times or prices of medical supplies. Since most facilities collect the data used for this study, our methods could be adopted more widely for a cross-jurisdictional account of the cost effectiveness of MDI-s.

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**Conflict of Interest:**
The opinions, views and major findings from this project are those of the primary author and do not represent the views of the IWK PED. The authors have no conflicts of interest.

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Table 1: Data Sources and corresponding variables and model parameters.

Commented [1]:
Are we still adding links in the notes?

| Data Sources | Variables and Model Parameters |
|---|---|
| The National Ambulatory Care Reporting System (NACRS) | Patient's age, sex, triage level, time and date (year and quarter) of PED visit |
| Patient chart review | Respiratory rate, oxygen saturation, heart rate, other drugs administered, PED length of stay |
| Discharge Abstract Database (DAD) | Inpatient length of stay |
| Nova Scotia Nurses Union | Wages and salaries for registered nurses (RN-2 pay scale) |
| Time and motion study by Mason et al, 2006 | Time used by nurses to perform MDI-s and NEB procedures |
| Pharmacy inventory data, IWK Health Centre | Unit cost of salbutamol nebule, mask, tubing, spacer, and MDI |
| Canadian Institution of Health Information Patient Cost Estimator for 2010-2011 | Inpatient costs for asthma patients aged 1-7 years in Nova Scotia |
| Statistics Canada CANSIM Table 326-0020 | Consumer Price Index |

PED = Paediatric Emergency Department; MDI = metered-dose inhaler; MDI-s = metered-dose inhaler with valved spacer; NEB = wet nebulization

Table 2: Baseline resource use and unit cost parameters used to calculate cost per treatment

| | Resource Use | CDN$[1]/Unit | CDN$/Patient, 1 treatment |
|---|---|---|---|
| **MDI-s** | | | |
| MDI[2] | 1 unit /patient | 2.95/Unit | 2.95[3] |
| Spacer[4] | 1 unit/5 patients | 33.07/Unit | 6.61 |
| Nursing Time[5] | 140.4 seconds/treatment | 31.88/hour | 1.24 |
| | | | Total=10.80 |
| **NEB** | | | |
| Mask | 1 unit/patient | 0.97/Unit | 0.97 |
| Tubing | 1 unit/patient | 0.27/Unit | 0.27 |
| Nebule | 1/treatment | 0.43/Unit | 0.43 |
| Nursing Time[5] | 1256.6 seconds/treatment | 31.88/hour | 11.13 |
| Salbutamol[6] | 5 mg/treatment | 0.06/mg | 0.30 |
| | | | Total=13.10 |
| **MDI-s and NEB** | | | |
| Inpatient Cost | - | 1,077/day | - |

Notes:
[1] Monetary values are expressed in 2010 constant Canadian dollars. [2] An MDI contains 10,000 mcg of salbutamol or 100 puffs. Since the dosage for each treatment is 10 puffs (or 5 puffs for under age 5), each MDI contains a maximum of 10 treatments (or 20 treatments for under age 5). Patients in the MDI-s group did not exceed the maximum number of treatments per MDI; therefore each patient in the MDI-s group was allocated the full cost of an MDI. In this case, we allocate the value of $2.95 to each patient regardless of the number of treatments.[3] Since each patient uses one MDI, costs for MDIs are given as costs per patient rather than costs per treatment (see note 2). [4] At the IWK, spacers are used up to five times across multiple patients, with sanitation occurring between uses. [5] Nursing time parameters are extracted from a previous time and motion study conducted in the United Kingdom (Mason et al[11]). Our baseline values are the midpoints of the interquartile ranges for total treatment time that were reported in

this study. Total treatment time includes treatment setup and administration times. A nurse performs the setup and treatment administration in our setting.[6] The dosage for each NEB treatment is 5.0 mg (or 2.5 mg for under age 5)
MDI = metered-dose inhaler; MDI-s = metered-dose inhaler with valved spacer; NEB = wet nebulization

Table 3: Selected Clinical and Demographic Patient Grouping

| **Patient Group** | **MDI-s (n)** | **NEB (n)** | **Treated with MDI-S (%)** |
|---|---|---|---|
| All patients | 664 | 158 | 81 |
| Female patients | 230 | 62 | 79 |
| Male patients | 434 | 96 | 82 |
| Age ≤ 2 years | 295 | 97 | 75 |
| Age > 2 years | 369 | 61 | 86 |
| Triage I-II* | 218 | 88 | 71 |
| Triage III-IV* | 446 | 70 | 86 |
| Hospitalized | 74 | 54 | 58 |
| Discharged from PED | 590 | 104 | 85 |
| Use of dexamethasone | 513 | 89 | 85 |
| Use of ipratropium | 65 | 31 | 68 |

MDI-s = metered-dose inhaler with spacer, NEB = wet nebulization, PED = Pediatric Emergency Department, *Triage = Canadian Triage and Acuity Scale (CTAS)

Table 4: Summary Statistics of Selected Clinical and Demographic Characteristics, Dependent Variables, and Costs

| Variables | MDI-s[1] | NEB[1] | P-Value of Difference |
|---|---|---|---|
| Percent Admission to Inpatient Care | 11 (9, 14) | 34 (27, 42) | 0.0000 |
| LOS in ED (Hours) | 3.05 (2.95, 3.15) | 2.62 (2.43, 2.81) | 0.0000 |
| LOS inpatient (Hours) | 31.98 (26.01, 37.94) | 62.62 (41.19, 84.04) | 0.0024 |
| Total Cost (CDN$) | 173.18 (127.83, 218.53) | 997.87 (613.19, 1382.55) | 0.0021 |
| Inpatient Cost (CDN$) | 159.92 (114.65, 205.20) | 960.33 (574.99, 1345.67) | 0.0000 |
| ED Cost (CDN$) | 13.26 (13.06, 13.45) | 37.54 (33.09, 41.99) | 0.0000 |
| Time Cost (CDN$) | 3.69 (3.50, 3.89) | 31.43 (27.75, 35.11) | 0.0000 |
| Drug Cost[2] (CDN$) | 2.95 | 0.52 (0.45, 0.59) | 0.0000 |
| Equipment Cost[3] (CDN$) | 6.61 | 4.69 (4.14, 5.24) | 0.0000 |

| Variables | MDI-s[1] | NEB[1] | Difference (MDI-s-NEB) |
|---|---|---|---|
| Percent Admission to Inpatient Care | 11 (9, 14) | 34 (27, 42) | -23*** |

**Commented [2]:**
I think it looks cleaner and easier for this audience to understand as p-values. I would favour changing the p-values as you did in the footnote: *p<0.05, **p<0.01, ***p<0.001

**Commented [3]:**
We have been told by editors not to do leave p values of 0.0000 but instead to make it less than 0.00001. Paul what do they do in economics?

**Commented [4]:**
Conventionally, they assign significance stars (* ** ***) to the difference in group means, with a legend at the bottom of the table --typically * p<0.05; ** p<0.01; *** p<0.001 as in Table 5. This requires replacing the p-value column with a column of group differences in means and significance stars. For example, for % inpatient care the group difference in means is -23 (11-34); so we would write -23*** to indicate that the p-value of the difference is less than 0.001.

Some publications also add in brackets, under the group difference in means (i.e. the -23), an estimate of the standard error or t-ratio or 95% confidence interval of the group difference. However, p-values, t-ratios and confidence intervals capture similar information re: statistical significance so the significance stars should be sufficient for our case.

I've added an example below the original Table 4.

| | | | |
|---|---|---|---|
| LOS in ED (Hours) | 3.05<br>(2.95, 3.15) | 2.62<br>(2.43, 2.81) | 0.43*** |
| LOS inpatient (Hours) | 31.98<br>(26.01, 37.94) | 62.62<br>(41.19, 84.04) | -30.64** |
| Total Cost (CDN$) | 173.18<br>(127.83, 218.53) | 997.87<br>(613.19, 1382.55) | -824.69** |
| Inpatient Cost (CDN$) | 159.92<br>(114.65, 205.20) | 960.33<br>(574.99, 1345.67) | -800.41*** |
| ED Cost (CDN$) | 13.26<br>(13.06, 13.45) | 37.54<br>(33.09, 41.99) | -24.28*** |
| Time Cost (CDN$) | 3.69<br>(3.50, 3.89) | 31.43<br>(27.75, 35.11) | -27.74*** |
| Drug Cost[2] (CDN$) | 2.95 | 0.52<br>(0.45, 0.59) | 2.43*** |
| Equipment Cost[3] (CDN$) | 6.61 | 4.69<br>(4.14, 5.24) | 1.92*** |

*Notes:*
[1]Means with 95% Confidence Intervals in parentheses
[2]Since the dosage for each treatment is 10 puffs (or 5 puffs for under age 5), each MDI contains a maximum of 10 treatments (or 20 treatments for under age 5). Patients in the MDI-s group did not exceed the maximum number of treatments per puffer; therefore each patient in the MDI-s group was allocated the full cost of an MDI. In this case, we allocate the value of $3.14 to each patient regardless of the number of treatments. Consequently, the cost of drugs does not vary across patients in the MDI-s group.
[3]For the MDI-s group, the only equipment cost is the cost of the spacer. Spacers are used for up to five patients. We therefore assigned one-fifth of the cost of a spacer to each patient in the MDI-s group. Like MDI-s, the cost of the spacer does not vary across patients in the MDI-s group.

MDI = metered-dose inhaler; MDI-s = metered-dose inhaler with valved spacer; NEB = wet nebulization
Statistical significance *p<0.05, **p<0.01, ***p<0.001

Table 5: Regression Results: MDI-s Associated with Improved Clinical Outcomes and Lower Costs

| | **Effect of MDI-s**[1] | **PED**[1] | **Hospital Admission**[1] |
|---|---|---|---|
| (A) Outcome | Probability of Admission | Length of Stay (Hours) | Length of Stay (Hours) |
| | -0.044* (-0.005, -0.083) | 0.171 (-0.201, 0.543) | -24.95*** (-23.52, -26.38) |
| (B) Costs using baseline parameters | **Total** | | |
| | -180.35*** (-57.24, -303.46) | -23.55*** (-19.69, -27.41) | -156.80* (-33.38, -280.22) |
| (C) Costs assuming MDI-s is more expensive than baseline | **Total** | | |
| | -146.5** (-35.66, 257.34) | -5.38*** (-2.79, -7.97) | -141.12* (-30.05, -252.19) |

MDI-s = metered-dose inhaler with spacer, PED = Pediatric Emergency Department
Statistical significance *p<0.05, **p<0.01, ***p<0.001

[1] 95% Confidence Intervals in parentheses