Title and study registration

Title: Vitamin D In the prevention of Viral-induced Asthma in preschoolers: a randomized controlled multi-center trial (DIVA trial)

Protocol #: DIVA 2017

Date of protocol version approval : February 28, 2022

Funding sources for the study (including grant numbers) : Canadian Institutes of Health Research (CIHR).

Is the study registered in a public register? Y/N : Y
Registration number(s) : Clinicaltrials.gov #: NCT03365687
Registered protocol last updated: 2024-05-21

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Version control

Version number	Date	Contributed by	Brief description of the updates
V 1.1		Mi-Suk Kang Dufour	Initial draft of the SAP
V 1.2	2025-03-10	Anna Smyrnova	1. Version control table has been added; 2. Appendix 1 added: List of variables/conditions for primary outcome calculations; 3. Clarifications added to the following Sections: • Data source(s) and time frame; • Primary outcome definition; • Secondary outcome definitions;
V 1.3	2025-03-14	Francine Ducharme Mi-Suk Kang Dufour	1. Clarification for Asthma Symptoms score calculation; 2. Clarification on definitions
V 1.4	2025-03-27	Anna Smyrnova	All previous modifications accepted. Clarification added: 1. Definition of phenotype 2. Definition of atopic status 3. Calculation of BMI (WHO) 4. Definition of Step therapy Secondary outcomes added 1. Treatment intensification at V2 and V3 2. Total duration of β2-agonist use
V 1.5	2025-05-15	Anna Smyrnova	Added: 1. Definition of Step Therapy (GINA, Canadian guidelines) 2. *Ad hoc* analysis: definition of 3 additional *ad hoc* subgroup variables to consider (Type 2 inflammation, Step Therapy, Past morbidity);
V 1.6	2025-05-23	Mi-Suk Kang Dufour	Accepted previous modifications. Updated table of contents Reformatted to move coding details to appendix Added detail to the statistical analysis section
V 1.7	2025-05-27	Francine Ducharme	Updated table of contents Added definition of duration of B2 agonists use by diary, acute care visits by diary, and Global parental functional status Harmonized the list and order of subgroup analyses in different sections. Deleting Appendix 4 Added page numbers

Final version 1.7 on 2025-05-07 approved by Francine Ducharme

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List of abbreviations

AE Adverse event
AUC area under the curve
CHUSJ Centre Hospitalier Universitaire de Saint-Justine
CI Confidence interval
CRF Case report form
ED Emergency department
kg Kilogram
MD Medical doctor
MedDRA Medical dictionary for regulatory activities
mg Milligram
Min Minimum
OR Odds ratio
SAE Serious adverse event
SAP Statistical analysis plan
SD standard deviation

Introduction

Background: Preschoolers have the highest rate of acute care visits and hospitalisations of all age groups. Most exacerbations are triggered by upper respiratory tract infections (URTI), mainly in the fall/winter. New evidence suggests significant long-term sequelae of preschool asthma: irreversible lung obstruction by 6 years and chronic obstructive lung disease in adulthood. Risk factors of sequelae include frequency and severity of exacerbations, specific viral URTIs, and atopy. Prevention is the best approach to reduce morbidity. Vitamin D insufficiency is highly prevalent in Canadian preschoolers with recurrent asthma exacerbations (75%), increases further in winter, and is associated with more URTI and OCS use, indicative of moderate/severe exacerbations. A systematic 2016 review of randomised controlled trials (RCT) concluded that vitamin D supplements significantly decreased asthma exacerbations requiring rescue OCS (rate ratio: 0.63, high-quality evidence) with insufficient data to firmly conclude that findings apply to preschoolers with moderate/severe exacerbations.

Specific Objectives: To determine if vitamin D3 supplementation will reduce by 25% the number of exacerbations requiring rescue OCS per child (primary outcome), URTIs, and other markers of exacerbation frequency and severity, compared to placebo in preschoolers with moderate/severe exacerbations.

Design: A Phase III, randomised, triple-blind, placebo-controlled, parallel-group multicentre trial of vitamin D3 supplementation. Overall, 323 (of the target of 865) children aged 1-5 years, with asthma triggered by URTI, ≥4 URTIs in past year (or ≥ 2 URTIs in past 12 months if pertaining to the pandemic period) and ≥1 OCS in the past 6 months (12 months since February 2022) were recruited in 9 or more Canadian centers over a 7-year period in this high-intensity 7-month protocol. Year-round, children were randomly assigned to one of the two following study arms: (1) Intervention— two oral boluses of 100,000 IU vitamin D3 (3.5 months apart) with 400 IU daily vitamin D3 or (2) Control— identical placebo boluses with daily placebo dose.

Research question: Can vitamin D3 supplementation decrease the number of asthma exacerbations per child requiring rescue OCS (predominantly physician-initiated) vs placebo?

Randomisation was implemented through the Applied Clinical Research Unit (ACRU), at the CHUSJ, under the direction of the study statistician, Dr. Mâsse. A computer-generated random list was utilized, with randomisation stratified by site to ensure balanced allocation across different locations. Children were allocated to either the vitamin D3 or placebo group in a 1:1 ratio using a permuted block randomisation method, which enhanced allocation concealment. Group allocation codes for each site were securely stored with restricted access by the Central Pharmacy (CHUSJ) and the independent biostatistician. The active vitamin D3 and placebo preparations, provided by the manufacturer Europharm, were identical in appearance and taste, ensuring blinding. The allocated treatment numbers were forwarded to site pharmacies, which prepared the bolus in coded syringes and the coded bottles containing the daily dose and dispensed the study drugs in masked kits to maintain the integrity of the randomisation process.

Analysis objectives

The primary objective of this analysis is to evaluate whether vitamin D3 supplementation leads to a 25% relative reduction in the mean number of exacerbations requiring oral corticosteroids (OCS) per child over a 7-month period compared to placebo. We hypothesized that the number of OCS per child would approximately follow a Poisson distribution.

The secondary objectives are to assess differences between the treatment groups in:

- Mean number and type of laboratory-confirmed respiratory infections during asthma exacerbations.
- Severity of asthma symptoms during exacerbations.
- Duration of asthma symptoms during exacerbations.
- Duration of use of rescue β2-agonists during exacerbations
- Intensity of use of rescue β2-agonists during exacerbations.
- Parents' functional status during asthma exacerbations.
- Mean number of emergency department (ED) visits for asthma exacerbations.
- De-intensification of preventive asthma therapy at scheduled clinic visits.
- Cost-effectiveness of the intervention.
- Proportion of children with clinically significant hypercalciuria, hypercalcemia, serum 25OHD >250 nmol/L, and adverse health events.

The exploratory objectives are to examine differences between the treatment groups in:

- Gene expression changes between baseline and 3.5 months.
- White blood cells' response to infections between baseline and 3.5 months.
- Serum and nasal metabolome and blood cell composition over 7 months.
- Distribution of laboratory-confirmed respiratory infections.
- Viral load
- Lung function changes measured by respiratory resistance at 7 months.
- Markers of bone remodeling.
- Identification of responders to vitamin D in peripheral blood mononuclear cells (PBMC) or gene polymorphisms.

Finally, subgroup analyses based on baseline variables are planned to identify potential modulators of response and subgroups that may experience greater benefits from the treatment.

Data source(s) and time frame

Main REDCap database: Data was collected directly in the participant's electronic Case Report Forms (eCRF) or recorded on paper CRF before being entered into the eCRF during the study follow-up period (7 months). The set of eCRFs in the REDCap database includes the following instruments:

1. Pre Screening Form

2. Confirmation Of Eligibility And Willingness To Participate prior to randomisation (CEWP)
3. Calcium Intake
4. Vitamin D Intake
5. Pharmacy Report (verification of eligibility, documented OCS dispenses)
6. OCS documented in medical records (verification of eligibility, documented OCS administration in clinic/hospital)
7. Medical Examination (performed and completed at Clinic Visits 1,2,3)
8. Comorbidity
9. Randomization
10. Urine Collection
11. Blood Collection (clinic)
12. Blood collection (home)
13. Nasal swab (clinic)
14. Nasal swab reception (from parents) - (documented returns of nasal swabs taken by parents during cold between the clinic visits)
15. Baseline Demographics
16. Allergy and Environnement
17. Visit and Phone Contact
18. Additional Cold or Asthma Flareup
19. Sun Exposure Questionnaire
20. Bolus Administration
21. Daily Supplement Provision
22. Daily Supplement Bottles Return
23. Respiratory resistance (collected in children aged 3 years and older in selected sites having the required equipment)
24. Safety Markers (completed with assessment of normality or action to be taken if not normal)
25. Complete Blood Count (collected in all children at selected sites)
26. Discontinuation or End of study
27. Pharmacy Report / End of Study
28. OCS documented in medical records / End of study
29. Blinding Verification Form (Parents)
30. Blinding Verification Form (Physician)
31. Blinding Verification Form (Research Nurse)
32. Adverse Health Event
33. Serious Adverse Event
34. Protocol Deviation

Data were entered into the REDCap database by each Site Coordinator, using:

- information collected during the visit,
- information taken from source documents (lab results, pharmacy reports, medical records, etc.)
- Information obtained from parents via follow-up phone call.

Secondary REDCap database

The second database, REDCap3 (DIVA - Asthma Flare-Up Diary), is designed to collect information directly from parents (reminders are sent by text/email). Parents were asked to complete the Asthma Flare-Up Diary for Young Children symptoms (ADYC) at the onset of the first sign of a cold or an asthma flare-up and to continue daily until 24 hours without asthma symptoms. At the end of a flare up, they were then asked to complete two summary CRFs for that flare up; the Effects of a Young Child's Cold or Asthma Flare-up on Parents (ECAP) questionnaire, and the Summary of a cold or asthma flare-up. This sequence was repeated at each new cold or asthma flare-up throughout the study.
Parents could choose to access to the electronic diary CRF or to complete the forms on paper, in which case the research coordinator would transcribe the information in the REDCap3 database. The list of CRFs collected through the secondary database includes:

1. AdycSMS (sent automatically to participants)
2. AdycEMAIL (sent automatically to participants)
3. Cold and Asthma Flare Up Diary For Young Children (ADYC) (completed by parents)
4. Adyc Report (generated automatically, presents summary of documented ADYCs)
5. Effects of a Young Child's Cold or Asthma Flare-up on Parents (completed by parents)
6. Summary of an asthma flare-up or cold (completed by parents)

Source documents

Source documents anonymized and retained in the patient study binder include pharmacy records, medical records, relevant information from Dossier de Santé du Québec (DSQ) or similar databases if obtained by the treating physician, laboratory results, and pulmonary function test results.

The data is organized in a tabular format within REDCap, with each row representing a participant observation (one row per event per person) and each column representing a specific data field. Data exports are available in CSV, Excel, and XML formats. The data fields include various types such as text, number, date, and multiple choice. The data dictionary is accessible within the REDCap project and provides detailed descriptions of each data field, including field names, types and allowed values.

Samples and Laboratory Databases:

- Biobank log (xlsx file, managed by the study Coordination Centre)
- CHUSJ Lab results for urine and blood (xlsx file, uploaded directly to OwnCloud),
- McMaster University Lab results for nasal swabs (xlsx file, uploaded directly to OwnCloud),
- Oscillometry results (data exported from the Tremoflo software, managed by the study Coordination Centre)

The detailed description of samples/data transfer and storage is described in the Data Management Plan.

Analysis sets/Populations/Subgroups

The target population for this study includes children aged 1-5 years with physician-diagnosed asthma, who have experienced recurrent, moderate/severe viral-induced exacerbations in the

preceding year. These children were treated with daily or pre-emptive inhaled corticosteroids (ICS) alone or with adjunct therapy as the standard of care from randomization onwards, and were randomized to receive either vitamin D3 supplementation or placebo. The sampling frame consists of potentially eligible children seen in one of the 9 participating pediatric institutions. Recruitment occurred in the fall over 3 months (Sept to Nov) for 1 year (2018), over 5 months per year (from Sept to January) for 3 years (2019-2021), than year-round for another 3 years (2022-2024), over a total period of 7 years. The analysis sample (n=323) includes all randomized participants regardless of adherence to the intervention protocol or whether they completed the study (intention-to-treat analysis). Of note, the consent form allowed data collection of the primary outcome until 7 months post-randomization, even in case of withdrawals or loss to follow-up.

Inclusion criteria:

- Age 1-5 years
- Physician-diagnosed asthma (as per the 2015 Canadian Position Paper on the diagnosis of preschool asthma)
- ≥1 asthma exacerbation requiring rescue oral corticosteroids (OCS) in the past 6 months or ≥2 in the past 12 months from 2018 until 2020; then ≥1 asthma exacerbation requiring rescue oral corticosteroids (OCS) in the past 12 months, starting from the fall of 2020 (pandemic) onwards (as documented by pharmacy/medical records)
- ≥4 upper respiratory tract infections (URTIs) in the past 12 months (as per parental report) or ≥ 2 URTIs in past 12 months, starting from the fall of 2020 (pandemic) onwards
- URTIs as the main asthma trigger (as per parental report).

The inclusion criteria target a high-mordidity population, at risk of consequences from asthma exacerbations, ensuring they are the most likely to benefit from the treatment.

Exclusion criteria:

- Intake > 400 IU/day of vitamin D3 supplements or fish oil in the past 3 months
- Intention to use > 400 IU/day of vitamin D3 supplements or fish oil in the fall and winter
- Extreme prematurity (< 28-week gestation)
- No vitamin D supplementation (if breast-fed in the last 6 months)
- Vitamin D restrictive diets, that is, minimal intake of vitamin D fortified milk (<250 mL/day for 1-3 years or <375 mL/day for 4-6 years AND no other (or <200 IU/day) vitamin D supplement
- Recent immigrants from regions at high risk of rickets (in the past 12 months)
- Recent refugees (in the past 12 months)
- Undernourished children
- Other chronic respiratory disease (e.g. Cystic fibrosis, Bronchopulmonary dysplasia) or chronic kidney, gastrointestinal, endocrinological or cardiac diseases, or sickle cell anemia
- History of bone disorder disease (e.g. rickets, osteomalacia)
- Intake of oral anti-epileptic, diuretic or anti-fungal medications
- Anticipated difficulty with follow-up or with adherence to the intervention or the procedures.

These criteria exclude participants prone to vitamin D deficiency, which could lead to hypocalcemia during vitamin D supplementation. They also exclude children already taking or planning to take over 400 IU/day of vitamin D, to prevent dilution of the treatment effect. Additionally, conditions or circumstances that could interfere with vitamin D metabolism or study follow-up are excluded to ensure reliable results.

The **ITT sample** includes all participants who are randomized into the study, regardless of whether they adhere to the study protocol or complete the study. The **per protocol sample** includes participants who adhered strictly to the study protocol without major deviations. This means they received the correct Study drug, swallowed more than 50% of Study Bolus, missed daily supplement intake for fewer than 40 days (or less than 20% of expected intake), did not experience unblinding of the study treatment and were eligible at randomization. For patients with a low daily Ca intake (< 350mg if aged 1-3 years; < 500 mg if aged 4-6 years), the bolus was administered only after receiving normal results for Ca, Ph, and ALP analyses. Additionally, there were no deviations impacting patient safety, rights, welfare, or data integrity.

The **complete case sample** includes all participants who completed the 7-month study period and provided the necessary data for primary and secondary endpoints. This includes participants who may have experienced major protocol deviations, such as incorrect study drug administration or missed daily supplements for up to 40 days, as well as minor deviations, such as delayed urine sample collections, as long as they did not withdraw from the study and their data is available for analysis.

Seven **subgroup analyses** were pre-specified at the start of the study as being of interest because of the potential for the relationship between vitamin D and asthma related outcomes to be modified by these characteristics. These include; Serum 25OHD Levels, ICS Therapy (Pre-emptive vs. Daily), Clinical Asthma Phenotype, Sex, Atopy, BMI category at baseline, Skin color according to the 6 category Fitzpatrick scale. An additional three variables were identified before analysis by group or unblinding, for exploration of subgroup effects. These include: Type 2 inflammation, OCS in the past 12 months, and step therapy using the GINA 2024 definitions.

Exposure(s), Endpoint(s) and Covariates

Exposure(s) of interest

The exposure of interest is the administration of vitamin D3 as defined in the protocol intervention. Specifically, this involves receiving two 2mL oral boluses of 50,000 IU/mL (total dose of 100,000 IU) vitamin D3 (cholecalciferol) during 2 clinic visits (randomisation and 3.5 ± 0.5 months later), along with a daily dose of 400 IU vitamin D3. The control group receives 2 identical placebo boluses and a daily placebo dose. The intervention is designed to ensure a rapid and sustained increase in serum vitamin D levels, providing maximal group separation. Hence, the exposure variable will be binary, indicating whether a participant is in the intervention group or the control group.

The research nurses (or auxiliary nurses) were responsible for administering the oral bolus doses and providing the daily doses to participants. They ensured adherence to the bolus dose by administering it in the clinic. The bolus doses were prepared in 2 mL coded syringes, and the daily doses were provided in coded bottles, all dispensed in masked kits to maintain blinding. Adherence to the daily vitamin D3 administration was monitored by weighing returned bottles and parental report.

Endpoint(s)

Participants will attend three clinic visits (0, 3.5±0.5, and 7±0.5 months), each coinciding with their usual medical visit. The enrolment visit (visit 1) was usually be conducted in-person, but the following visits 2 and 3 could be conducted in-person or remotely at the discretion of the physician and parents' preference in accordance to the child's health status, particularly during and after the pandemic.

Covariates

As the randomization was stratified by clinical site, the site of enrollment will be considered as a covariate in the analyses. Several baseline covariates will be considered as potential effect modifiers in subgroup analyses (e.g., BMI, atopy, serum 25OHD levels, asthma phenotype, sex, skin color, pre-emptive vs. daily ICS therapy, past morbidity, type 2 vs.non-type 2 inflammation and prescribed Step therapy using GINA 2024) and assessed at baseline. The quantity of vitamin D3 effectively administered to each participant will be ascertained after baseline covariates have been collected. Serum values for vitamin D during follow up may be considered as a marker of effective adherence in per-protocol analyses.

Adherence and protocol deviations

Adherence to the protocol will be defined as participants having no major protocol deviations, as specified in the protocol's list of major deviations (see 'per-protocol sample'). Specifically, participants must have received at least 50% of the correct bolus dose under nursing supervision in the clinic and consistently taken the daily supplement as prescribed. In the pilot trials, adherence to the bolus dose was ensured by nursing administration in the clinic, and median adherence to daily supplement administration was over 92%, based on the weighing of returned bottles.

Major protocol deviations that will be reported and may result in changes to the analysis include instances where the wrong study drug was administered, the study bolus was not administered or less than 50% was swallowed, daily supplement bottles were not provided or collected, patients missed the daily supplement for 40 or more days, unblinding of study treatment occurred, ineligible patients were randomized, or bolus administration occurred without necessary lab results or despite abnormal results in patients with low calcium intake. Any deviation impacting patient rights, safety, welfare, or the integrity of the study data will also be considered.

Handling of missing values and other data conventions

A nested loop of imputation of missing values with regression (to adjust for baseline variables) and bootstrapping (to estimate uncertainty) will be used. This approach reduces bias, ensures imputed values reflect baseline differences, and provides robust estimates of variability and confidence intervals, thereby minimizing the impact of missing data and ensuring robust and reliable results.

Loss to follow-up occurs when participants who were initially enrolled in the study become unreachable or unresponsive at subsequent follow-up points, resulting in missing data. In this study, a high retention rate (>92.5%) was anticipated due to the provision of a ±2-week window for scheduling return visits, like the NEJM trial, which had a 6.9% loss to follow-up over 10 months (pro-rated at 5% over 7 months). Moreover, the consent enabled documentation of the main outcome until projected end-date in participants who withdrew or were lost to follow-up prior to the last visit. To address loss to follow-up, we will use the same comprehensive approach as for other missing values. This includes multiple imputation to estimate missing data, regression techniques to adjust for baseline variables, and bootstrapping to estimate the uncertainty of the imputed values.

Outliers will be identified and reviewed for data entry or measurement errors, with appropriate adjustments made in the analysis. Non-compliance will be addressed through sensitivity analyses, comparing per-protocol and intention-to-treat populations to assess its impact. Withdrawals will be documented, including the reasons for withdrawal, to identify any patterns or biases. The impact of withdrawals on study outcomes will also be evaluated using sensitivity analyses.

Outcome(s)

Primary outcome

The primary outcome is the **number of asthma exacerbations per child treated with rescue oral corticosteroids** over the time frame of 7 months. To be reported as group difference in the mean number of exacerbations treated with rescue oral corticosteroids/child.
Information on exacerbations and OCS use was collected throughout the study and recorded at endpoint. OCS was documented through multiple sources including; medical records (if given in ED/hospital), pharmacy records (if given at home), and self-reported information about OCS administration/prescription collected via from parents [CRFs: “Visit and Phone Contact”, “Additional Cold or Asthma Flareup” (REDcap database); “Cold and Asthma Flare Up Diary For Young Children” and “Summary of an asthma flare-up or cold (REDCap3 database)].
Information was preferentially taken from documented medical records as preferred means (as it also mentioned the diagnosis associated with OCS administration) or second means, from the pharmacy records (no diagnosis); the third level of certainty was based on information provided by parents to the research coordinator with reports of the drug, posology and diagnosis. However, If self-reported information was not confirmed in the Medical records or Pharmacy report, information on the OCS was reviewed by an independant adjudicator with clinical expertise in asthma.

In the case of multiple exacerbations with OCS use, events were considered separate events if they were separated by 7 days or more. In cases where conflicting information was collected from different sources, or there were multiple reports within a short window of time clinical records were reviewed by the independent adjudicator to determine the number of separate events.

It was considered that there was OCS use if at least one dose of OCS was administered, prescribed or dispensed to the patient. This outcome was chosen because it is a clinically meaningful efficacy measure that has been shown to important for family, health care providers, and payers, to influence practice, and the metric (counting all OCS per patient) was preferred by parents.

Documented OCS events will be considered part of the study period if they were administered or prescribed after randomization (providing that the time of administration of OCS is documented after randomization and after the randomization visit, that is, was not prescribed on Med Examination at randomization *(CRF "Medical Examination", Q9. Are you prescribing or recommending any systemic (oral, iv, im) corticosteroids today for the management of a CURRENT exacerbation?, variable [medex_rec_sys_cort]).* All OCS administered or dispensed on the day of randomization were reviewed by an independent adjudicator. OCS administered or prescribed throughout the study period were considered, including those administered or prescribed on the last day of the follow up period. The end of follow up window is defined as the date of visit 3 (CRF "Discontinuation or End of study", variable [disendstud_last_sche_cont], 3. Date of last scheduled contact completed) or, if the visit 3 did not occur (e.g. lost to follow-up), at 7 months from the randomization date. As per the informed consent, the main outcome was meant to be obtained from medical and pharmacy records until the end of follow-up or at 7 months, even in participants dropped out or were lost to follow-up.

Detailed information on the coding of the primary outcome variable is provided in appendix 1.

Secondary outcomes

Detailed information on the coding and definitions for secondary outcome varibables is provided in appendix 2.

Number of laboratory-confirmed respiratory infections per child

The number of laboratory-confirmed viral respiratory infections over the time frame of 7 months, quantified through a polymerase chain reaction (PCR) analysis of the nasal sample collected in clinic if the child was sick or by parents during colds and/or asthma exacerbations will be summarized for each child.

Number of reported viral infections

Total number of reported viral infection will be collected through verbal and written parental report (with each means of recording considered as a separate outcome).

Number of reported asthma exacerbations

Total number of reported asthma exacerbations will be collected through verbal and written parental report (with each means of recording considered as a separate outcome).

Number of acute-care visits / hospital admissions

The number of urgent care events during the 7-month study follow up period will be calculated as the number of times an acute care visit or hospital admission for asthma or asthma-like diagnosis was reported by verbal report of a parent and confirmed by the research coordinators either from the medical records or from parental reports (including the diary) or (ii) written report on diary (with each means of recording considered as a separate outcome). Urgent care events within 7 days of each other will be merged and considered as one event.

Children with at least one acute care visit for asthma, children requiring at least one course of oral corticosteroids for asthma and children with at least one hospitalisation for asthma will also be reported

Treatment intensification at Visit 2 & 3

Treatment intensification (vs. no change or treatment de-intensification) at V2 (3.5 months) and V3 (7 months) time points is reported by the treating physician. Intensification is defined as an increase in the total daily dose of ICS of more than 50 ug/day, the addition of an additional daily preventive drug, or an increase of more than 200 ug/day in the dose of ICS if given pre-emptively at the onset of an exacerbation.

Duration of asthma symptoms

Duration of asthma symptoms for each exacerbation event will be collected through verbal and written parental report (with each means of recording considered as a separate outcome). For each child the average duration of symptoms during exacerbations will be calculated for reported events.

Total duration of β2-agonist use

Total duration of β2-agonist use will be collected through verbal and written parental report (with each means of recording considered as a separate outcome). This will be defined as total number of days when β2-agonist (the rescue bronchodilator - ventolin, bricanyl - blue inhaler) was used during each cold/asthma flare-up.

Number of lost parental workdays

The impact of flare-ups on the number of lost parental workdays as documented through verbal and written parent reports (with each means of recording considered as a separate outcome). This will be summarized as the total number of days that a parent reports that he/she missed work due to a

cold or asthma flare up or to take care of his/her child related to an asthma flare up. Only one parent is surveyed for each flare-up.

Family expenses

Family expenses during exacerbations associated to medications, ED visits, hospitalisations, as well as income loss were recorded at each study contact (phone or visit) by research nurses. The total amount of expenses reported during follow up will be summarized for each child.

Health care cost

Health care cost, calculated by assigning unit costs to ED visits, hospital admissions, medication use, and physician visits whereas the cost of intervention was determined through drug manufacturer, nursing time, and facility's resources, documented in a random sample of 100 children.

Severity of asthma symptoms

The sum of the daily scores as a measure of the severity of asthma symptoms during exacerbations, completed daily by parents using the validated 17-item, each scored from 1 (best) to 7 (worst), Asthma Flare-Up Diary for Young Children symptoms (ADYC) and standardized over 7 days using the method pubished in Ducharme et al 2016.

Intensity of use of rescue B2-agonists

Intensity of use of rescue β2-agonists during asthma exacerbations, defined as:

- Cumulative rescue bronchodilator use: ∑ daily number of puffs from the first day until last day of use until last day of use, inclusively. Units [puffs/episode]
- Average rescue bronchodilator score = Cumulative rescue bronchodilator use ÷ duration of use, units [average puffs/day]

Parental functional status

This is a measure of the parental report of how much he/she was affected by each asthma flare up reported (i) on the Effect of a Child Asthma flare-up on Parents (ECAP) comprising 21 questions, where the ECAP score for each episode is the mean of values for non-missing items collected on a seven-point scale (1 :Not at all to 7 : Extremely) and (ii) as Global parental functional status**,** on a 7-point likert scale to the question *Overall, how much did this asthma flare-up affect you*? Each means of recording is considered as a separate outcome. Only one parent is surveyed for each flare-up.

Subgroups

Subgroups of interest were chosen based on the potential for the response to vitamin D to vary by baseline characteristics that are hypothesized to modify the effect of vitamin D on asthma related outcomes. These subgroups were defined based on the values of the baseline covariates. Detailed

information on the coding and definitions for secondary outcome varibables is provided in appendix 3. Each of these will be considered as binary variables separating participants into two groups for analysis as described below.

Planned subgroup analyses

In this study, seven baseline variables are *a priori* hypothesized to be potential effect modifiers:

- Baseline 25OHD serum level dichotomized (<75 vs. ≥75 nmol/L)
- Atopy (specific multiallergen IgE ≤0.35 or >0.35kUa/L),
- Asthma phenotype (viral-induced vs. multi-trigger),
- ICS therapy (pre-emptive vs. daily),
- Body mass index (< 85%ile vs. ≥ 85%ile)
- Biological sex assigned at birth (male/female)
- Skin color (6 categories of Fitzpatrick scale, dichotomized for analysis as 1, 2 or 3 vs 4, 5 or 6)

Subgroups to consider (ad hoc)

Three additional variables were added to the set of potential subgroups to consider. These variables were added to the analysis plan prior to the start of analysis, in light of recent scientific knowledge since the beginning of the study

- Type 2 high vs. Type 2 low inflammation (Phadiatop ≥0.35 kUa/L) OR Eosinophils ≥300 cells/µL vs. neither)
- Past morbidity (≤ 2 vs > 2 OCS in past year)
- Prescribed GINA 4 Step-therapy at index visit (dichotomized as Step 1-2-3 vs 4)

Safety outcomes

The urine calcium:creatinine ratio, as a marker of normal calcium metabolism, was the primary safety outcome to assess the individual safety profile. Urine samples to test for hypercalciuria was systematically collected for immediate on-site analysis at baseline, 3.5 and 7 months, and at 10 days after each bolus. Site- and age-specific reference values were used for interpretation locally. In case of an elevated urine calcium:creatinine ratio, a site endocrinologist/bone specialist, blinded to group allocation, interpreted results and, if necessary, requested further analysis (urine or blood samples). Serious and non-serious adverse health events were ascertained at each visit and phone call.

The proportion of children with ≥1 occurrence of clinically significant:

- Hypercalciuria, clinically significant hypercalcemia (>2.63 mmol/L), documented in the Safety Markers eCRF and Adverse effects eCRF; Q 3.3.1 Serum Ca Value (mmol/L) [safmark_biomark_caval].
- Elevated serum 25OHD (>250 nmol/L—measured at the CHUSJ; exceptionally, if measured as part of investigation of adverse events, it may be documented in safety markers eCRF and

Adverse effects eCRF;

- Serious and non-serious adverse health events ascertained at each visit by Adverse effect eCRF and Serious adverse effect eCRF (and Visit and Phone eCRF and Medical Examination eCRFl.

Exploratory outcomes

Group difference in:

1. Change in gene expression levels in peripheral blood mononuclear cells (PBMC) in a subset of patients, analyzed using whole transcriptome analysis by next-generation sequencing (RNAseq or equivalent), in some patients (from CHUSJ and MCH) at 0, 10 days, and 3.5 months.
2. Change in monocytes and lymphocytes' response to infection, namely to bacterial and viral products as well as responsiveness to corticosteroids (in vitro studies), examined at 0, 10 days, and 3.5 months in a subgroup of children.
3. Potential signature of responders vs. non-responders to vitamin D in PBMC and in gene polymorphisms from DNA or by patient and treatment characteristics.
4. Change in serum and nasal metabolome
5. Change in blood cell composition (specifically eosinophils) over the 7-month study.
6. Change in serum osteocalcin, telopeptides C, and other markers of *bone metabolism*.
7. The distribution of specific respiratory pathogens and virus load detected by qPRC.
8. Change from baseline in preschool lung function (respiratory resistance), when available at the specific institutions, documented in cooperative patients aged ≥3 years to assess a potential impact of vitamin D3 on lung growth.

Statistical procedures

Description of study cohort and positivity checks:

To ensure a comprehensive understanding of our study population, we will provide detailed descriptions of the clinical variables measured at inclusion for each group, summarized in a baseline characteristics table. This will encompass key baseline characteristics such as serum 25OHD levels, ICS therapy (daily ICS vs. Preventive ICS), clinical asthma phenotype, sex, atopy status, body mass index, skin color, type 2 inflammation, OCS use in preceding 12 months, Step therapy. We will also document the proportion of missing data for each variable.

Positivity checks will be performed to verify the effectiveness of randomization and ensure that baseline characteristics are balanced across the study arms. The probability of intervention conditional on baseline variables will be calculated for all observations. These probabilities will be graphed to confirm that there are no violations of positivity. Should there be any violations, the statistician will investigate and characterize participants with a less than 5% or greater than 95% probability of intervention. The statistician will then notify the investigators and discuss whether a restriction of the analysis is necessary.

Descriptive analysis of serum vitamin D

Vitamin D values were measured at baseline, visit 2 and visit 3. Additional home visit measures were available for some participants. Vitamin D was assessed using Serum 25OHD testing at a central laboratory. These values will be summarized by study visit and intervention group.

Descriptive analysis of primary and secondary outcome measures:

Empirical distributions of primary and secondary outcomes will be generated overall and comparatively by intervention arm using graphical representations. Additionally, summary statistics, including measures of central tendency (e.g., mean) and variability (e.g., standard deviation), will be calculated and reported overall and by intervention arm for:

- The number of oral corticosteroids (OCS) courses per child
- The number of laboratory-confirmed viral upper respiratory tract infections (URTIs)
- Total number of viruses (all viruses included in all positive swabs) detected per child (this could include more than 1 virus identified in a given swab)
- Total number of swabs with at least 1 virus detected, thus number of 'positive' swabs per participant;
- At least one nasal swab detection of virus types in one of the following 10 viruses groups:
    - Rhino/Entero
    - InfluenzaA
    - InfluenzaB
    - Parainfl1
    - Parainfl2
    - Parainfl3
    - HMPV

    - RSV
    - Adeno
    - SARSCoV2
- Mean number of ED visits with/without hospital admissions for asthma exacerbations per child over 7 months study period
- Proportion of children with intensification of preventive asthma therapy at visit 2, visit 3, or either.
- Mean duration of asthma symptoms per child reported verbally or documented on the validated written 'Asthma Flare-up Diary for Young Children' over the time frame of 7 months (with each means of recording considered as a separate outcome).
- Mean duration of use of β2-agonist was used during each cold/asthma flare-up reported verbally or documented on the validated written 'Asthma Flare-up Diary for Young Children' over the time frame of 7 months (with each means of recording considered as a separate outcome).
- Mean of out-of-pocket asthma related expenses per exacerbation
- The sum of the daily ADYC scores as a measure of the severity of asthma symptoms during exacerbations, completed daily by parents using the validated 17-item, each scored from 1 (best) to 7 (worst), Asthma Flare-Up Diary for Young Children symptoms (ADYC) and standardized over 7 days
- Mean intensity of β2-agonist use reported on the diary as
    - Cumulative rescue bronchodilator use: ∑ daily number of puffs from the first day until last day of use until last day of use, inclusively. Units [puffs/episode]
    - Average rescue bronchodilator score = Cumulative rescue bronchodilator use ÷ duration of use, units [average puffs/day]
- Mean parents' functional status during exacerbations per child
    - Reported as the mean ECAP score
    - Reported as Global functional status on a 7-point likert scale from 1-not at all, to 7-extremely

Primary Efficacy Analyses

A Poisson regression model, will be estimated, using an ITT approach, including only randomization group as a predictor and adjusting only for the stratification of randomization by clinical site. This model will be used to estimate the incidence rate ratio comparing the mean number of oral corticosteroids (OCS) per child during the 7-month follow-up by study group. If overdispersion is present, a negative binomial model will be used. If there are large variations in person-time an adjustment using an offset term will be made. Two sensitivity analysis are planned; 1) the incidence rate ratio will be stratified by the month of recruitment to explore the possibility of effect modification by seasonality and 2) the incidence rate ratio will be stratified by year of the pandemic (2000-2001) to assess the possibility of effect modification by exposure to the COVID-19 pandemic period. The original analysis plan included a fixed effect for each site. However, for sites with a very small number of recruited patients, these small sites may be grouped together.

Secondary outcome analyses

Secondary outcomes will be analyzed using the same modeling strategy as the primary efficacy analysis. For outcomes collected as count variables (e.g. number of laboratory-confirmed viral upper respiratory tract infections (URTIs), days with asthma symptoms, days of rescue B agonist use, number of lost parental workdays) we will again use a Poisson or negative binomial model for differences by intervention group and adjusted only for study site.

For continuous outcomes including: severity of symptoms, duration of asthma symptoms per exacerbation, duration and intensity of rescue β2-agonists use per exacerbation, and functional status we will compare outcomes by treatment group using a generalized linear regression model approach. For outcomes with repeated measures, a GEE method will be used adjusting for the clustering of events in individual children and if indicated an offset variable for variations in person-time if relevant.

For binary outcomes, including treatment intensification, a generalized linear model with a log-linear link function will be used, again including a GEE method to adjust for repeated measures. All confidence intervals will be constructed using robust standard errors. No adjustment for multiple outcomes is planned.

Safety Outcomes:

The Mantel-Haenszel method, stratified by clinical site, will be used to compare dichotomous outcomes including:

- The proportion of children with at least one clinically significant occurrence of hypercalciuria and hypercalcemia,
- The proportion of children with one or more occurences of elevated serum 25OHD (>250 nmol/L)
- Proportion of children experiencing an adverse event
- Proportion of children experiencing a serious adverse event

Documented adverse and serious adverse events will be summarized according to type using MEDRA classifcations.

Significance thresholds:

A two-tailed alpha of 5% will be used for all statistical tests, ensuring that the results are assessed for significance on both ends of the distribution. One interim analysis was planned once 50% of patients have been recruited and their primary endpoint assessed. The O'Brien-Fleming stopping rules were meant be applied, with p-values for the two looks (one interim and one final) set at 0.003051 and 0.046946, respectively. As nearly all the nominal alpha is preserved for the final look, no adjustment to sample size is needed.

Subgroup Analyses

Potential modification of the effect of study intervention with vitamin D on primary and secondary outcomes will be assessed using the addition of interaction terms to the regression models. If there is a significant effect of the intervention, we will consider there as evidence of potential effect modification if inclusion of the interaction improves the overall model fit (using AIC/BIC criteria or R squared metrics), and if the interaction term is significant at an alpha of 0.20 or lower.

Statistical software and versions

The statistical analyses will be conducted using R 4.3.1 on Rstudio Server 2023.03.0. The following R packages are likely to be used based on the analysis requirements: base, stats, MASS, glm2, car, dplyr, tidyr, ggplot2, mice, Amelia, boot, heemod, BCEA.

Ancillary studies:

The economic evaluation will use standard trial-based economic evaluation methods. The intention is to provide the expected value of the intervention cost versus health care and family cost of exacerbations, effectiveness, and cost-effectiveness ratio with uncertainty around such values in terms of credible intervals.

References:

Ducharme FM, Jensen ME, Mendelson MJ, Parkin PC, Desplats E, Zhang X, Platt R. Asthma Flare-up Diary for Young Children to monitor the severity of exacerbations. J Allergy Clin Immunol. 2016 Mar;137(3):744-9.e6. doi: 10.1016/j.jaci.2015.07.028. Epub 2015 Sep 2. PMID: 26341275.

GINA 2024:www.ginasthma.com with ICS Doses based on Canadian Thoracic Society 2021 Guideline

Yang CL, et al. 2021 Canadian Thoracic Society Guidelines. Can J Resp Crit Care Sleep Med. 2021:1-41

Appendix 1: Primary outcome variable coding

Primary outcome (OCS)

Suggested wording for use in manuscripts:

The primary outcome was number of short courses of systemic corticosteroids (OCS) prescribed for asthma during the 7-month intervention period, as confirmed by hospital and/or pharmacy records (or exceptionally, reported by parents and determined to be credible by an independent clinician).

Sources of OCS events

OCS could be documented in a number of places in the study CRFs including:

REDCap database:

- Med Examination CRF (to be considered administered or prescribed prior to randomization);
- Visit and Phone Contact CRF;
- CRF OCS in Medical Records (Clinic visit 1) – should contain info about OCS dated PRIOR to Randomization, to be verified in case any typos/mistakes have been done during the data entry;
- CRF OCS in Medical Records at end of study;
- CRF Pharmacy Report (Clinic visit 1) – should contain info about OCS dated PRIOR to Randomization, to be verified in case any typos/mistakes have been done during the data entry;
- CRF Pharmacy Report at end of study;
- CRF Additional cold or asthma flareup (main redcap).

REDCap3 database (parent-reported):

- CRF Cold and Asthma Flare Up Diary For Young Children;
- CRF Summary of an asthma flare-up or cold.

Validation of OCS events

Timing:

To be considered an outcome, an OCS must be administered or prescribed after randomization but could include the day of randomization, provided it was not prescribed on the MEDEX par the study physician and there was credible information of its administration/prescription after the time of reandomization, until (and including) the last day of the follow up window. For the purposes of OCS use, the end of the follow up window is either the date of visit 3, or if the visit 3 did not occur, the randomization date plus 7 months.

Completeness of the data:

The complete information about OCS includes the name of the medication, dose, daily frequency, duration, and route as well as reason.

Relationship with an asthma exacerbation:

(1) Inclusion
- OCS use requires a medical documentation (MedRec CRF) or by the parental report (verbally recorded in VPC or on ADYC) that the reason for its use is asthma related, defined as:
    i. Asthma flare-up, Asthma-like diagnoses (bronchospasm, airway hyperactivity, bronchiolitis, bronchitis, wheezing, pneumonia , etc.);
    ii. Other diagnosis (Pneumonia, Otitis) as such indication would suggest a co-existing diagnosis of asthma
    iii. Unknown: Handling of unconfirmed reasons of OCS use. Unless otherwise confirmed, all OCS uses will be assumed to be for asthma (i.e., pharmacy dispensing of OCS without parental report or medical record of reason for use), given the high prior probability of this reason in included participants.

(2) Excluded:
- OCS administered for treatment of conditions or other respiratory conditions (e.g. cutaneous conditions, adrenal insufficiency, anaphylaxis (anaphylactic shock), kidney disease, serum sickness, surgery, croup' or 'laryngitis'etc.) as documented in eCRF OCS documented in the medical Record (1st priority), Visit and phone contacts (less priority as self-reported) or ADYC will be excluded. Of note, if prescribed in Med examination (eCRF), then it is clearly for asthma.

Handling of Special cases

Denied administration of prescribed or dispensed OCS by parents:
If parents deny administration of identified OCS prescribed or dispensed by pharmacy, the OCS will be counted as an OCS use for the primary outcome, as per the physician intention for the child to use OCS, as this intention is the marker of moderate or severe exacerbation. (qu 10 et 11)

Delayed administration of prescribed or dispensed OCS by parents
If parents credibly report of an alternate start date than that documented in pharmacy records (for example, medication dispensed ahead of time for subsequent use as part of an action plan or prior to travel), the actual date of OCS use will be reported by parents in VPC CRF (or ADYC), and this date will be considered for primary outcome calculation. Such credible report should be documented in VPC CRF by the nurse. In this case, the concordance between the information provided verbally (VPC) or in writing (ADYC) by parents regarding the reason for, and information about, the OCS prescription will be cross-verified with the documentation of the original prescription in med records CRF (reason, name and dosage)—preferred approach— and/or Pharmacy report (OCS name, dose, duration) — secondary approach as the Pharmacy report that does not provide the reason for its prescription. If

the date of initiation has not occurred before or at Visit 3, the OCS would not considered as OCS use during the study period. (qu 10.2.6.2)

If **pharmacy records were never obtained**, we will consider accepting the OCS medications as described in the Clinic and Phone contacts eCRF, provided that the information is considered credible by the nurse and the reported reason is concordant with other document (med records or parental resport) about the OCS.

Of note, given the potential subjectivity of the judgement of 'credibility', these approaches will be independently coded by two biostatisticians, to identify any rule resulting in discrepancy. Any rule resulting in discrepancies will be identified; and all OCS events in which these rules applied would be independently assessed by an independent adjudicator, whose decision will be final.

Events with multiple 'courses'

Each record of a possible OCS course will be extracted from the CRFs and added to a long file with a source, reason for administration, type of documentation, start and end date.
Once all CRF sources have been extracted, OCS courses will be evaluated to determine if they represent one event or multiple events.

Any occurrence of two or more 'courses' (whether administration, prescription, dispensing, or parent-administered), initiated with a 7-day period (between the beginning of 1st course and the beginning of the 2nd course) or within a 2-day period (between the end of a 1st course and the beginning of the 2nd course) which ever if longest, will be counted only once (and assumed to be for the same exacerbation). These approaches will be independently coded by two biostatisticians, to identify any rule resulting in discrepancy Any rule resulting in discrepancies will be identified; and all OCS events in which these rules applied would be independently assessed by an independent adjudicator, whose decision will be final.

Following the double-coding approach, the team of Dre Ducharme will prepare the list of documented OCS, in a wide format, showing all sources of OCS reporting:

- Medical Examination,
- OCS in Medical records,
- Pharmacy Report
- Visit and Phone Contact,
- Additional cold and asthma flare-up (ACAFU)
- Asthma Flare-up Diary for Young Children (ADYC) (REDCap3)
- Summary of an asthma flare-up or cold (SAF) (REDCap3)

The information from REDCap3 (ADYC and Summary CRF) will be merged with the main list of the OCS to detect special cases when information is credibly reported in REDCap3, but missing in REDCap main database.

The list of variables related to the primary outcome calculation, including conditions to verify, is available in the Appendix.

CRF specific coding rules:

- Visit and Phone Contact
  phcon_steroid, phcon_steroid_2, phcon_steroid2 and phcon_steroid2_2 = 1 were used to select records where an OCS was indicated
  Exclude records where reason for systemic steroids was = 2 (other condition)
  ocs_start=phcon_steroid_startdat,
  ocs_end=phcon_steroid_endat,
- Med Examination
- OCS in Medical Records
  ocsdoc_v1_syst_yn used to select records where an OCS was indicated
- OCS in Medical Records end of study
  ocsdoc_end_syst_y used to select records where an OCS was indicated
  Exclude records where reason for systemic steroids was not 1, 2 or 4, (3 was Laryngitis) [ocsdoc_end_reason] assuming for this source that
  - if OCS is only administered, then the start date is the administration date and the duration should consider the total number of days administered as reported in qu1.1.6 (# days administered or given) including the start date
  - if only prescribed, start date is prescription date and end date calculated with the duration of prescription including prescription date.
  - if both administered and prescribed, then start date is the administration date, the total number of days considered administered is 1.1.6 (# days administered or given) and the start day of prescription is included in the duration of the prescribed medication.
  - if only prescribed, then total number of days considered date prescribed + #days prescribed - 1

  if both administered and prescribed, provide information (name, duration, etc) for each OCS
- Pharmacy Report
- Pharmacy Report end of study reporting OCS name, dose, date and number of days of prescription
- Additional cold or asthma flareup (REDCap)
- Asthma Flare-up Diary for Young Children (ADYC) (REDCap3)
- Summary of an asthma flare-up or cold (SAF) (REDCap3)

Specific variables used by CRF source

Visit and Phone Contact CRF

Variable / Field Name /	Field Attributes (Field Type,	Required

Field Label	Validation, Choices)	
10. Is the child currently taking, or have he/she taken oral, intravenous, or intramuscular STEROIDS since the last contact? [phcon_steroid_2]	1: Yes 0: No	Should be yes
10.1 What was the reason for SYSTEMIC STEROIDS due to: [phcon_steroid_reas]	1: a. Asthma flare-up 4: b. Asthma-like diagnoses (broncho-spasm, airway hyperreactivity, bronchio-litis, or wheezing) 2: c. Other condition: (record in AHE) 3: d. Unknown	Should not be a missing value
10.1.1 Other condition: [phcon_steroid_4]	text	Should include "bronchospasm, airway hyperactivity, bronchiolitis, bronchitis, wheezing, pneumonia , otitis".
10.2 Medication (Use the generic name(s), NOT trade name(s)): (To be documented when interviewing parents, but the generic name MUST be entered before submitting the form): [phcon_steroid_mednam]	1: Prednisone tablet 2: Prednisolone (Pediapred®) 3: Dexamethasone (solution or tablet) 4: Methylprednisolone (solution or tablet) 5: Solucortef 6: Other	Should not be a missing value
10.2a If other, specify: [phcon_steroid_mednam_2]	text	Should not include cefodox / magnesium sulfate / hydrocortisone, other cutaneous, nasal, ophthalmic (etc.) preparation.
10.2.1 Route: [phcon_steroid_medrout]	1: Oral 2: IV 3: IM	Should not be a missing value

10.2.2 mg per dose *_ _ _ . _mg* [phcon_steroid_meddos]	text (number)	Should not be a missing value
10.2.3 Frequency (#times/day): [phcon_steroid_medfreq]	1:1 2:2 3:3 4:4	Should not be a missing value
10.2.4 Start date: [phcon_steroid_startdat]	text (date_ymd)	Should not be a missing value
10.2.5 End date: [phcon_steroid_endat]	text (date_ymd)	Should not be a missing value
10.2.6 According to parents, the medication was administered or served by (Both answers are possible) Selon les parents, le médicament a-t-il été administré ou servi par (les deux réponses sont possibles)	[phcon_steroid_servby___1]1: Pharmacy [phcon_steroid_servby___2]1: Hospital	Should not be a missing value
10.2.6.1 Confirmation of dispensing obtained by pharmacy records: *If awaiting until the end of study to obtain pharmacy records, leave this question unanswered until then* [phcon_sterconfby_pharm]	1: Yes 2: No 3: Pharmacy records never obtained	Should not be a missing value
10.2.6.2 Date of dispensing based on [phcon_steconfby_pharm_date	1: Pharmacy records 2: Credible report by parents of an alternate start date than that documented in pharmacy records (for example, medication dispensed ahead of time for subsequent use as part of an action plan) 3: Credible report by parents of denied administration of prescribed or dispensed 4: Unconfirmed as pharmacy	Should not be a missing value

	records NEVER obtained	
10.2.6.3 Confirmation of administration with/without dispensing obtained from hospital: *If awaiting until the end of study to obtain hospital/clinic records, leave this question unanswered until then* [phcon_sterconfby_hrec]	1: Yes 2: No 3: Hospital/clinic Records NEVER obtained	Should not be a missing value
10.2.6.4 Date of administration/dispensing confirmation based on [phcon_steconfby_hosp_date]	1: Hospital/clinic records 2: Credible report by parents of an alternate start date (for example, medication dispensed ahead of time for subsequent use as part of an action plan) 3: Credible report by parents of denied administration of prescribed or dispensed medication 4: Unconfirmed as hospital / clinic records NEVER obtained	Should not be a missing value

Comment: the same coding should be applied to Q11- Q11.2.6.4.
Comment 2: in case of missing values, consider imputation if feasible (for example, the missing value for Route can be imputed based on the name of the medication).

Medical Examination CRF

Variable / Field Name / Field Label	Field Attributes (Field Type, Validation, Choices)	Required
9. Are you prescribing or recommending any systemic (oral, iv, im) corticosteroids today for the management of a CURRENT exacerbation? If Yes, specify name of the drug, dose, frequency and duration of treatment.	1: Yes 0: No	Should be Yes

[medex_rec_sys_cort]		
9. a) Systemic Corticosteroids (SCS) [medex_rec_cort_list]	1: Prednisone tablet 2: Prednisolone (Pediapred®) 3: Dexamethasone (solution or tablet) 4: Methylprednisolone (solution or tablet) 5: Other oral corticosteroids (solution or tablet)	Should not be a missing value
9.1 Name of medication [medex_rec_sys_cort_oth]	text	Should not include hydrocortisone or other unrelated medications
9. b) mg per dose, mg [medex_rec_cort_strength]	text, Required	Should not be a missing value
9. c) Frequency (#times/day) [medex_rec_cort_freq] *#times/day*	text	Should not be a missing value
9. d) Duration of treatment [medex_rec_cort_dur]	1: 1 day 2: 2 days 3: 3 days 4: 4 days 5: 5 days 6: >5 days	Should not be a missing value

Additional Cold or Asthma Flare-up CRF

Variable / Field Name / Field Label	Field Attributes (Field Type, Validation, Choices)	Required
8.1.1 What was the reason for SYSTEMIC STEROIDS due to: [acafu_steroid_reas]	1a. Asthma flare-up, specify episode # below 2b. Asthma-like diagnoses (bronchospasm, airway hyperreactivity, bronchiolitis, bronchitis, wheezing, or pneumonia) 3c. Other condition: (record in AHE) 4d. Unknown	Should not be a missing value

8.1.1.1 Other condition: [acafu_steroid_oth]	text	Should include “bronchospasm, airway hyperactivity, bronchiolitis, bronchitis, wheezing, pneumonia , otitis”.
8.1.2 Medication (Use the generic name(s), NOT trade name(s)): (To be documented when interviewing parents, but the generic name MUST be entered before submitting the form): [acafu_steroid_mednam]	1Prednisone tablet 2Prednisolone (Pediapred®) 3Dexamethasone (solution or tablet) 4Methylprednisolone (solution or tablet) 5Solucortef 6Other	Should not be a missing value
8.1.2.1 If other, specify: [acafu_steroid_mednam_oth]	text	Should not be a missing value
8.1.3 Route: [acafu_steroid_medrout]	1Oral 2IV 3IM	Should not be a missing value
8.1.4 mg per dose: [acafu_steroid_meddos] *_ _ _ . _mg*	text (number)	Should not be a missing value
8.1.5 Frequency (#times/day): [acafu_steroid_medfreq]	11 22 33 44	Should not be a missing value
8.1.6 Start date: [acafu_steroid_startdat]	text (date_ymd)	Should not be a missing value
8.1.7 End date: [acafu_steroid_endat]	text (date_ymd)	Should not be a missing value
8.1.8 According to parents, the medication was administered or served by (Both answers are possible)	acafu_steroid_servby___1: Pharmacy: 1 acafu_steroid_servby___2: Hospital: 1	Should not be a missing value
8.1.8.1 Confirmation of dispensing obtained by pharmacy records: [acafu_sterconfby_pharm]	1Yes 2No 3Pharmacy records never obtained	Should not be a missing value

8.1.8.2 Date of dispensing based on: [acafu_steconfby_pharm_date]	1Pharmacy records 2Credible report by parents of an alternate start date than that documented in pharmacy records (for example, medication dispensed ahead of time for subsequent use as part of an action plan) 3Credible report by parents of denied administration of prescribed or dispensed 4Unconfirmed as pharmacy records NEVER obtained	Should not be a missing value
8.1.8.3 Confirmation of administration with/without dispensing obtained from hospital: [acafu_sterconfby_hosp] *If awaiting until the end of study to obtain hospital/clinic records, leave this question unanswered until then*	1Yes 2No 3Hospital/clinic Records NEVER obtained	Should not be a missing value
8.1.8.4 Date of administration/dispensing confirmation based on: [acafu_steconfby_hosp_date]	1Hospital/clinic records 2Credible report by parents of an alternate start date (for example, medication dispensed ahead of time for subsequent use as part of an action plan) 3Credible report by parents of denied administration of prescribed or dispensed medication 4Unconfirmed as hospital/clinic records NEVER obtained	Should not be a missing value

Comment: the same coding should be applied to Q8.2 – Q8.5.

OCS in Medical Records CRF

Variable / Field Name / Field Label	Field Attributes (Field Type, Validation, Choices)	Required
1. Has there been any administration and/or prescription of systemic (oral, IM, IV) corticosteroids (OCS*) documented in the medical record for asthma or asthma-like symptoms since randomization until V3 (or 7 months after randomization if premature discontinuation) ? [ocsdoc_end_syst_yn]	1Yes 0No	Should be Yes
Was the OCS: (choose all that apply)	ocsdoc_end_syst_y___1 1:administrated (or given to patient) ocsdoc_end_syst_y___2 1: prescribed (to be filled by community pharmacy)	Should not be a missing value
1.1.1 Date of administration (1st dose) [ocsdoc_end_adm_date]	text (date_ymd), Required	Should not be a missing value
1.1.2 Medication (use the generic or trade name) [ocsdoc_end_med]	1Prednisone tablet 2Prednisolone (pediapred) 3Dexamethasone (solution or tablet) 4Methylprednisolone (solution or tablet) 5Other	Should not be a missing value
1.1.2 a) If other, specify[ocsdoc_end_med_oth]	text	Should not include hydrocortisone or other unrelated medications
1.1.3 Route[ocsdoc_end_route]	1Oral 2IV 3IM	Should not be a missing value
1.1.4 mg per dose[ocsdoc_end_mg] *mg*	text, Required	Should not be a missing value
1.1.5 What was the reason for	1a) Asthma flare-up	Should not include

SYSTEMIC STEROIDS due to: [ocsdoc_end_reason]	2b) Asthma-like symptoms: bronchospasm, airway hyperactivity, bronchiolitis, bronchitis, wheezing, pneumonia 3c) Laryngitis 4d) Unknown	Laryngitis
1.1.6 Total number of doses administered or given to parents by health care provider (for example include a dose of dexamethasone to give at home by parents) [ocsdoc_end_nb_dos] *# doses*	text	Should not be a missing value
1.1.7 Was the dose accompanied by a prescription (to be filled by community pharmacy), as documented in the medical chart? [ocsdoc_end_pres]	1Yes 0No	Should not be a missing value
1.1.7.1 Date of prescription[ocsdoc_end_pres_date]	text (date_ymd), Required	Should not be a missing value
1.1.7.2 Medication (Use the generic name(s), NOT trade name(s)): [ocsdoc_end_pres_med]	1Prednisone tablet 2Prednisolone (Pediapred®) 3Dexamethasone (solution or tablet) 4Methylprednisolone (solution or tablet) 5Solucortef 6Other	Should not be a missing value
1.1.7.2 a) If other, specify[ocsdoc_end_pres_med_oth]	text	Should not include hydrocortisone or other unrelated medications
1.1.7.3 Route[ocsdoc_end_pres_route]	1Oral 2IV 3IM	Should not be a missing value
1.1.7.4 Total daily dose in mg[ocsdoc_end_pres_tot_mg]	text	Should not be a missing value

mg		
1.1.7.5 Prescription duration (# days) [ocsdoc_end_pres_dur] *days*	text	Should not be a missing value

Comment: the same coding should be applied to information about Medication 2 (Q1.2.1 - Q1.2.7.5) and Medication 3 (Q1.3.1 - Q1.3.7.5).

Pharmacy Report / End of Study CRF

Variable / Field Name / Field Label	Field Attributes (Field Type, Validation, Choices)	Required
Section Header: *Oral Corticosteroids (OCS) Medication* 1. Has there been any serving of oral corticosteroids (OCS) medication since randomization until V3 (or 7 months after randomization if premature discontinuation) ? [pharm_ocs_end]	1 Yes 0 No	Should be Yes
1.1.1 Date of dispensing [pharm_ocs_end_dat_disp_1]	text (date_ymd), Required	Should not be a missing value
1.1.2 Medication (use the generic or trade name) [pharm_ocs_end_nam_1]	1 Prednisone tablet 2 Prednisolone (pediapred) 3 Dexamethasone (solution or tablet) 4 Methylprednisolone (solution or tablet) 5 Other (specify DIN)	Should not be a missing value
1.1.2 a) Specify [pharm_ocs_end_nam_1a]	text	Should not include hydrocortisone or other unrelated medications

1.1.4 mg per dose [pharm_ocs_end_dos_1] *mg*	text, Required	Should not be a missing value
1.1.5 Frequency (#times/day) [pharm_ocs_end_freq_1] *#times/day*	text	Should not be a missing value
1.1.6 Prescription duration (#days) [pharm_ocs_end_dur_1] *days*	text	Should not be a missing value
1.1.7 Date of the prescription [pharm_ocs_end_date_1]	text (date_ymd), Required	Should not be a missing value

Comment: the same coding should be applied to information about Medications 2 - 6 (Q1.2.1 - Q1.2.7; up to Q1.6.1 - Q1.6.7).

Appendix 2: Secondary Outcome coding

Number of laboratory-confirmed respiratory infections per child

1. **Timing**: exacerbations documented in REDCap after the Randomization over the period of study follow-up will be considered.
   1.1. Nasal swabs collected during Clinic Visit 1 – to be disregarded
   1.2. Nasal swabs collected during Clinic Visit 2, CRF "Nasal swab (clinic)":
   - If routine swab collection and no exacerbation reported (Q1. According to parents, is the child sick (cold or asthma)? = "No") – to be disregarded;
   - If exacerbation reported "Q1. According to parents, is the child sick (cold or asthma)? = "Yes" – included in calculation;

   1.3. The swabs collected by parents at home during cold or exacerbations and documented in the CRF "Nasal swab reception (from parents)", brought back at Clinic Visit 2 and Clinic Visit 3 - to be included in calculations;
2. **Lab results** will be provided by McMaster Lab, the xlsx file with the data and the codebook will be uploaded directly to the URCA OwnCloud.
3. The **biobank log**, showing the correspondence between the nasal swabs collected/received and lab results provided by McMaster Lab is managed by the Study Coordination Centre.

List of viruses to explore/report:

1. Rhino/Entero_Result
2. InfluenzaA_Result
3. InfluenzaB_Result
4. Parainfl1_Result
5. Parainfl2_Result
6. Parainfl3_Result
7. HMPV_Result
8. RSV_Result
9. Adeno_Result
10. SARSCoV2_Result

Number of ED or acute-care visits / hospital admissions

Number of reported and/or documented ED or acute –care visits and hospitalisations for asthma and asthma-like diagnosis, obtained throughout the 7-month study period from:

REDCap – verbal parental report:

- Visit and Phone contact CRF (9 timepoints, self-reported, completed by Coordinator);
    - Q 3. Did the flare-up result in an UNSCHEDULED visit to an acute care centre due to respiratory difficulty (includes pneumonia, asthma)? – up to Q 3.4.1;
    - Q 3.5 Was the subject admitted to the hospital? – up to Q 3.5.5.4a;
    - Q 4. Did the flare-up result in any other UNSCHEDULED visit to an acute care centre due to respiratory difficulty (includes pneumonia, asthma)? – up to Q 4.4.1;
    - Q 4.5 Was the subject admitted to the hospital? – up to Q 4.5.5.4a;

- Additional Cold or Asthma Flareup CRF (As needed, self-reported, completed by Coordinator); (the same structure as VPC CRF, Q 3, Q 3.5, Q 4, Q4.5)

REDCap3 – written parental report:

- Summary of an asthma flare-up or cold (REDCap3, final summary CRF for each episode) completed by parents at the end of each the episode:
    - Section: Was your child taken to the Emergency Department or any other acute care facility? [sum_emerg_yn] – up to Q [sum_emerg_doctor_autre_2];
    - Section: Was your child hospitalized (which implies leaving the emergency room for another hospital unit)? [sum_hospit_yn].

Of note, coordinators were instructed to check medical records and parents' summary of an asthma flare-up or cold, at the end of the follow-up to identify any acute care centre visit or hospitalization for asthma or asthma-related diagnosis and recorded it in VPC; the distribution of the means of confirmiation of the event (Q3.4.1; 4.4.1) will be described. In addition to serving to confirm the diagnosis at such visit, this systematic verification at the end of the follow-up (or 7 months in case of drop-outs or loss to follow-up) was intended to maximise the documentation of all events, to avoid

omission or data loss due to study discontinuation prior to Visit 3.

Treatment intensification at Visit 2 & 3

Treatment intensification (vs. no change or treatment de-intensification) at V2 (3.5 months) and V3 (7 months) time points is reported by the treating physician. Intensification is defined as an increase in the total daily dose of ICS of more than 50 ug/day, the addition of an additional daily preventive drug, or an increase of more than 200 ug/day in the dose of ICS given pre-emptively at the onset of an exacerbation.

To identify any deterioration, the asthma controller regimen prescribed in detail at each visit was categorized by the treating physician in representing

- A treatment intensification defined as an increase in the TOTAL daily DOSE of ICS of >50 ug/day OR the ADDITION of another daily preventive drug OR an INCREASE >200 ug/day in the dose of ICS given pre-emptively at onset of exacerbation
- NO substantial change OR
- A treatment deintensification defined as decrease in the TOTAL daily DOSE of ICS of >50 ug/day OR the CESSATION of another daily preventive drug OR a DECREASE >200 ug/day in the dose of ICS given pre-emptively at onset of exacerbation.

REDCap Codebook:
[medex_best_opt_man_2] At Visit 2 and Visit 3:
10. Compared to the last visit, today's recommendations represent (record the best option):
1: no substantial change;
2: a treatment intensification;
3: a treatment desintensification.
of previous management (please disregard the management of a current exacerbation in this assessment).

Duration of asthma symptoms

Duration of asthma symptoms for each exacerbation event will be collected through verbal and written parental report. For each child the average duration of symptoms during exacerbations will be calculated for reported events. Information will be collected from the two REDCap databases as follows:

- REDCap database - verbal parental report: Visit and Phone Contact CRF and Additional cold or asthma flareup CRF (verbal report),
    - Where Q2. According to the parent(s)/guardian(s), does the child presently have an ASTHMA flare up (with/without a cold)? [phcon_flarup] =1 (yes) and
    - the duration is defined as Date of end of asthma symptoms (e.g. Q2.3 End of asthma symptoms [phcon_flarup_onset_knw]) -Date of beginning of asthma symptoms (e.g.

Q2.2 Date of onset of asthma symptoms [phcon_flarup_onset_knw]). Take note of the similar questions for additional events in the eCRF or the Additional cold and asthma flare-up CRF.

- REDCap3 database - written parental report: Duration of asthma symptoms defined as the number of days with symptoms, obtained from the REDCap3 database, parental diary:
    - Valid Asthma Flare-Up Diary for Young Children symptom's diary (ADYC) diary as defined above, in which each day is examined for whether it fits the definition of a Day with asthma symptom
    - A Day with asthma symptom if defined as at least one symptom is documented, that is if at least two variables among the 7 items in qu 1 to qu 7 [adyc_cough_freq] to [adyc_skin_pull_freq] is ≥ 2 (i..e, excluding 1: Never). Values of 8 (Cannot answer) are considered as missing after recoding as documented above.
    - Duration is the time elapsed between the first and last day with asthma symptom

Total duration of β2-agonist use

Total duration of β2-agonist use will be collected through verbal parental report and written report on the diary. This will be defined as total number of days when β2-agonist (the rescue bronchodilator - ventolin, bricanyl - blue inhaler) was used during each cold/asthma flare-up.

- REDCap database - verbal parental report: Information will be collected from the Visit and Phone Contact CRF in REDCap as follows:

If according to the parent(s)/guardian(s), does the child presently have a cold:
(phcon_cold_lascon_2 = Yes)

[phcon_rescue_bronch] 8. During the present cold/flare-up, was the rescue bronchodilator (ventolin, bricanyl) - blue inhaler used at home?
1 Yes
0 No

If according to the parent(s)/guardian(s), has the child had a cold, since the last contact?
(phcon_cold_lascon == Yes)

[phcon_rescue_bronch_2] 8. During the present or past cold/flare-up, was the rescue bronchodilator (ventolin, bricanyl) - blue inhaler used at home?
1 Yes
0 No

[phcon_rescue_bronch_dur] 8.1 Total duration of β2-agonist use (Days):

- REDCap3 database - written parental report: Duration of β2-agonist use defined as the number of days with of β2-agonist use, obtained from the REDCap3 database, parental diary:

A valid diary set was defined as least 2 or more consecutive days with valid reporting of B2-agonist use, with no more than one missing day of recording between the first and last day of reporting. If a daily value is missing between the first and the last day of bronchodilator use, the score will be imputed using the last score carried forward.

- Q: Has your child taken Ventolin (or blue inhaler) (salbutamol, Bricanyl®, terbutaline but NOT Zenhale)? [adyc_blue_inh]
- Q: Which? [adyc_blue_inh_choice]
    - 1 : Ventolin® ou salbutamol
    - 2 : Bricanyl® ou terbutaline
- Q: If Yes, and No. puffs (or nebules) / 24hrs [adyc_blue_inh_ify] is not missing
    - If 1. ventolin, then dose =number of puffs x 1
    - If 2. bricanyl , then dose = number of puffs x2
    - If number of puffs missing, impute from previous day.

Duration is the time elapsed between the first and last day with rescue B2-agonists

Number of lost parental workdays and productivity

The impact of flare-ups on the number of lost parental workdays as documented through verbal and written parent reports. This will be summarized as the total number of days that a parent reports that he/she missed work due to a cold or asthma flare up or to take care of his/her child related to an asthma flare up. Only one parent is surveyed for each flare-up. Reports will be collected from the verbal and written parent CRFS as follows:

Verbal parental report

REDCap, CRF Visit and Phone contact (Section 7):

- From Q 7. Since the last contact, has any of the child's parents or guardians missed work due to the child's cold or asthma flare-up?
- Up to Q 7.1.1 and 7.2.1 and 7.3.1 etc.

Written parental report

REDCap3, CRF Effects of a Young Child's Cold or Asthma Flare-up on Parents(ECAP), completed by parents after each exacerbation.

- Q 23. How many days of work or regular planned activities did you miss because you had to take care of your child? [aep_days_work]
- Q 24. To what extent were you able to go about performing your work or regular planned activities? [aep_ext_perf_percent] (0-100%)

Family expenses

Family expenses during exacerbations associated to medications, ED visits, hospitalisations, as well as income loss were recorded at each study contact (phone or visit) by research nurses. The total amount reported during follow up will be summarized for each child as the sum of all ammounts reported on the following CRFS:

REDCap, Visit and Phone contact CRF (Section 6):

[phcon_expenses] 6. Have there been any out-of-pocket expenses related to your child's colds or asthma flare-up since the last contact? (Yes/No)

[phcon_expenses_y] 6a. Specify any expenses for (choose all that apply)

1. Prescription drugs Médicaments sur ordonnance;
2. Non-prescription medication/product Médicaments ou produits sans ordonnance;
3. Transport to or parking at medical care facilities Transport ou stationnement aux centres médicaux.

[phcon_insur_cover] 6.2 Did a public or private drug insurance help cover part of the cost of this medication? (Yes/No)

Health care cost

Health care cost, calculated by assigning unit costs to ED visits, hospital admissions, medication use, and physician visits whereas the cost of intervention was determined through drug manufacturer, nursing time, and facility's resources, documented in a random sample of 100 children.

Severity of asthma symptoms

The sum of the daily scores as a measure of the severity of asthma symptoms during exacerbations, completed daily by parents using the validated 17-item, each scored from 1 (best) to 7 (worst), Asthma Flare-Up Diary for Young Children symptoms (ADYC) and standardized over 7 days using the method published in Ducharme et al. 2016.

Parents are asked to record any asthma symptoms child has experienced during the past 24 hours, the diary should be completed every evening from the first day of cold symptoms until 2 days with no asthma symptoms.
Data source: REDCap3 – written parental report, CRF "Cold and Asthma Flare Up Diary For Young Children (ADYC)"

Q1 - Q7, the Symptoms over last 24 hours:
1 (Never) to 7 (All the time), with "Cannot answer" (coded as 0 (zero)) and should be considered as missing.

Q8 – Q14, the Degree to which each symptom has been a problem observed
1 (Not at all) to 7 (Extremely), with "Cannot answer" (coded as 0 (zero)) and should be considered as missing.

Q15-Q17 the Degree to which the child responsed to rescue bronchodilator – special cases:
1 (Not at all) to 7 (Extremely), with "Cannot answer" should be considered as missing or 1, conditional on the response to the question: Has your child taken Ventolin (or blue inhaler) (salbutamol, Bricanyl®, terbutaline but NOT Zenhale)? [adyc_blue_inh] (1:Yes, 0:No)

The logic is:

- If Ventolin was not taken, all 3 questions should be considered as absence of negative symptoms, thus recoded for 1 (Not at all) category;
- If Ventolin was taken, the documented responses for 3 questions should be considered fur further score calculation.

Which is in terms of coding:

1. If [adyc_blue_inh] == 0 (No), then tree questions: Q15 (Does not respond as well to Ventolin® (or blue inhaler) as usual), Q16 (Does not respond as rapidly to Ventolin® (or blue inhaler) as usual) and Q17 (The effect of Ventolin® (or blue inhaler) does not last as long as usual) are not applicable and should be considered as absence of negative effects, recorded as 1 (Not at all):
   - Q15: [adyc_respondness_vent_deg] = 1;
   - Q16: [adyc_rapidness_vent_deg] = 1;
   - Q17: [adyc_last_vent_deg] = 1

2. If [adyc_blue_inh] == 1 (Yes), then documented values for all 3 questions, Q15, Q16 and Q17 should be used for calculations.

Definition of a valid ADYC day

- At least 9 items out of 17 must be answered, after recording of Questions 15 to 17 in case of no use of bronchodilator (see above); otherwise, the daily score will be set to missing.
- If there are more than 8 missing items (out of 17) on ADYC day 1, then all computations described below will start on ADYC day 2.

Identification of a valid ADYC set (event)

- At least 2 or more consecutive days with a valid ADYC day.

Symptom score calculation

- For each valid ADYC day, the **daily symptom score** will be computed as the mean of all (max of 17) non missing items. The minimum score will therefore be 1 (all non-missing responses

equal 1) and the maximum score will be 7 (if all non-missing responses equal 7).

Cumulative and average symptom score during an episode

- Cumulative episode symptom score = ∑ daily ADYC score from the first day with symptom until last day with symptoms, inclusively. Standardized over 7 days value to be reported.

- Average episode symptom score = Cumulative symptom score ÷ duration of symptoms, units [score/day] (see below) Min = 1, max = 7
  This includes ADYC days that did not fulfil the definition of asthma symptom days.

Missing ADYCs - imputation

- If a daily score is missing between the first and the last day with symptoms, the score will be imputed using the last score carried forward.
- The cumulative symptom score will then be computed as the sum of all daily scores between the first and last day with symptoms.

Intensity of use of rescue B2-agonists

Intensity of use of rescue β2-agonists during asthma exacerbations, defined as:

- Cumulative rescue bronchodilator use: ∑ daily number of puffs from the first day until last day of use until last day of use, inclusively. Units [puffs/episode]
- Average rescue bronchodilator score = Cumulative rescue bronchodilator use ÷ duration of use, units [average puffs/day]

To be reported as a group difference in the mean cumulative use of rescue β2-agonists per child during exacerbations documented on the validated 'Asthma Flare-up Diary for Young Children' over the 7 months time frame.

A valid diary set was defined as least 2 or more consecutive days with valid reporting of B2-agonist use, with no more than one missing day of recording between the first and last day of reporting. If a daily value is missing between the first and the last day of bronchodilator use, the score will be imputed using the last score carried forward.

- Q: Has your child taken Ventolin (or blue inhaler) (salbutamol, Bricanyl®, terbutaline but NOT Zenhale)? [adyc_blue_inh]
- Q: Which? [adyc_blue_inh_choice]
  - 1 : Ventolin® ou salbutamol
  - 2 : Bricanyl® ou terbutaline
- Q: If Yes, and No. puffs (or nebules) / 24hrs [adyc_blue_inh_ify] is not missing
  - If 1. ventolin, then dose =number of puffs x 1
  - If 2. bricanyl , then dose = number of puffs x2
  - If number of puffs missing, impute from previous day.

Intensity of use of rescue B2-agonists (sum of daily puffs) = sum of daily rescue b2 (including 0), report as median (25%, 75%)

Parental functional status

Parents' functional status during exacerbation per child as documented on the validated 'Effect of a child's asthma flare-up on parents questionnaire'. Only one parent is surveyed for each flare-up

Documented in REDCap3, CRF Effects of a Young Child's Cold or Asthma Flare-up on Parents (ECAP), completed by parents after each exacerbation: 21 questions.

- A Valid ECAP questionnaire requires a min of 11 questions non-missing
- The **ECAP score** = is the total score was the average of all completed (non missing) items (score range, 1-7).
- **Global parental functional status assessement** = Q 22. Overall, how much did this asthma flare-up affect you? [aep_grav_3] (1 :Not at all – 7 : Extremely, with 8: Cannot answer);

Appendix 3: Coding for subgroup variables

Subgroup variables

Subgroups (pre-specified)

Seven subgroups of interest were *a priori* chosen based on the potential for the response to vitamin D to vary by baseline characteristics that are hypothesized to modify the effect of vitamin D on asthma related outcomes. These subgroups were defined based on the values of the following baseline covariates:

Serum 25OHD Levels

Subgroups: <75 nmol/L vs. ≥75 nmol/L at baseline
Objective: To evaluate if baseline vitamin D status influences the reduction in asthma exacerbations requiring OCS.

ICS Therapy (Pre-emptive vs. Daily)

Subgroups 1: Pre-emptive vs. Daily
Objective: To assess if the type of inhaled corticosteroid therapy affects the efficacy of vitamin D3 in reducing asthma exacerbations.

REDCap Codebook: Medical Examination CRF (medical_examination)

[medex_asthmcont_med] 5. Today, are you prescribing or recommending that the child take any **MAINTENANCE** ASTHMA CONTROLLER medication for asthma? If Yes, specify name of the drug, dose, frequency and duration of treatment.
1 Yes
0 No

[medex_preemptive_cont_med] 6. Are you prescribing or recommending that the child take any **PRE-EMPTIVE CONTROLLER** therapy (started by parents at onset of exacerbation, but not taken when well)?
1 Yes,
0 No

According to REDCap database, only 1 participant did not receive maintenance asthma controller medication and only 2 participants received pre-emptive – to review the original pre-emptive vs daily ICS subgroup comparison.

Clinical Asthma Phenotype

Subgroups: Viral induced vs. multi-trigger
Objective: To determine if the asthma phenotype modulates the response to vitamin D3 supplementation.

Definition of categories:

1. **Intermittent Viral-induced phenotype**:
    - Symptoms only with URTI episodes (perfectly well between episodes) **AND** One single trigger;
    - Unclear **AND** One single trigger;
2. **Persistent or Multitrigger phenotype:**
    - Intercurrent **OR** all Multiple triggers.

REDCap Codebook: Medical Examination CRF (medical_examination)

[medex_besdesc_asthm] 1. Which best describes the child's current asthma pattern?

- 1 Symptoms only with URTI episodes (perfectly well between episodes)
- 2 Intercurrent (intermittent or continuous) symptoms between episodes
- 3 Unclear

[medex_asth_trig] 2. Is the child's asthma symptoms/exacerbations triggered by:

- 1 One single trigger
- 2 Multiple triggers (2 or more)

Sex

Subgroups: Male vs. Female
Objective: To explore if there are sex-specific differences in the response to vitamin D3 supplementation.

Atopy

Subgroups: Specific multiallergen IgE <0.35 kUa/L vs. ≥0.35 kUa/L
Objective: To investigate if atopic status influences the effectiveness of vitamin D3 in reducing asthma exacerbations.

The info to be derived from the CHUSJ OptiLab data set with tests results.

Variables:

TEST_ID	NAME	Description
RPTOP	Rech: PHADIATOP	• values: <0.35, • >100.00, • various numeric values in the range of (0.35 - 100.00)
RPNEG	PHADIATOP INTERPRET. NEGATIF	values : NEGATIF if RPTOP <0.35
RPPOS	PHADIATOP INTERPRET. POSITIF	values : POSITIF if RPTOP >=0.35

Body Mass Index (BMI) at baseline

Subgroups: Normal if < 85%ile, Overweight or Obese if >= 85%ile, calculated according to WHO Child Growth Standards.
Objective: To examine if BMI impacts the response to vitamin D3 supplementation.

Body Mass Index, as well as z-score for height and weight to be calculated using the following instruments:

R package **anthro**: Computation of the WHO Child Growth Standards
Provides WHO Child Growth Standards (z-scores) with confidence intervals and standard errors around the prevalence estimates, taking into account complex sample designs. More information on the methods is available online: <https://www.who.int/tools/child-growth-standards>.

R package **anthroplus**: Computation of the WHO 2007 References for School-Age Children and Adolescents (5 to 19 Years)
Provides WHO 2007 References for School-age Children and Adolescents (5 to 19 years) (z-scores)

with confidence intervals and standard errors around the prevalence estimates, taking into account complex sample designs. More information on the methods is available online: <https://www.who.int/tools/growth-reference-data-for-5to19-years>.

Skin Color

Subgroups: 6 categories of Fitzpatrick scale, dichotomized for analysis as 1,2,3 vs 4,5,6.
Objective: To assess if skin color, as a proxy for potential differences in vitamin D synthesis, affects the treatment outcomes.

REDCap Codebook: Baseline Demographics CRF (baseline_demographics)
bd1_fitz_answer]. Using the visual Fitzpatrick scale, assess child's skin colour. Fitzpatrick scale.

Subgroups to consider (*ad hoc*)

In addition to prespecified subgroup variables, 3 new categories will be explored as *ad hoc* analysis, based on new hypotheses (arising after the beginning of the study) regarding potential modification of the effect of vitamin D on asthma related outcomes; they are mentioned post-hoc as they were voiced after the last protocol version and after considering the distribution of these variables in all randomized individuals; of note, there were added before any blinded analysis by group or after unblinding.

Type 2 inflammation

Subgroups: 2 categories, Type 2 High vs. Type 2 Low.
Objective: To assess if Type 2 inflammation affects the treatment outcomes.

Type 2 inflammation includes allergic asthma and eosinophilic asthma and is defined as:

Type 2 High: Atopy positive (Phadiatop ≥0.35 - POSITIVE) OR Eosinophils >=300 cells/µL
Type 2 Low: Atopy negative (Phadiatop <0.35 - NEGATIVE) AND Eosinophils <300 cells/µL

Past Morbidity in previous 12 months

Past morbidity is defined as the number of OCS administered in 12 months prior randomization.

Subgroups: ≤ 2 vs > 2 OCS reported.
Objective: To examine if intensity of use of rescue OCS in the 12 months prior to index visit is associated with the response to vitamin D3 supplementation.

REDCap Codebook: Baseline Demographics CRF (baseline_demographics)
Variable: [bd1_4_nbr_ocs] 6.1 Episodes with oral corticosteroids (prescribed, served and/or administered) .
Values:

- 1 Unknown
- 2 0
- 3 1
- …
- 21 19
- 22 20
- 23 more than 20

Prescribed GINA 4 Step-therapy at index visit

Subgroups: Step therapy, dichotomized as Step 1-2-3 vs 4, at baseline, based on the 2014 GINA report.
Objective: To assess if asthma severity (severe vs. non-severe) defined by the intensity of asthma maintenance therapy (daily inhaled corticosteroid therapy with/without adjunct therapy) and/or the intensity of therapy itself affects the efficacy of vitamin D3 in reducing asthma exacerbations.

Step therapy (defined by GINA 2024)

According to the updated Global Strategy for Asthma Management and Prevention (2024), for children of 5 years and younger.

Step	Daily Tx, children of 5 years and younger
STEP 1	No Rx
STEP 2	1.Low dose maintenance ICS OR 2.Daily LTRA (Montelukast)
STEP 3	1.Double low (moderate) dose maintenance ICS OR 2.Low dose ICS + LTRA 3. Low dose ICS + LABA (if age >=4 years) No other adjunct therapy (no LAMA)
STEP 4	1.Double low (moderate) dose maintenance ICS + LTRA 2. Moderate dose ICS+LABA 3. Moderate dose ICS+LAMA) 4. High dose ICS or ICS-LABA 5. Any ICS dose ICS with >=2 adjunct therapies 6. Low dose ICS + LABA (if age <4 years)

Reference: GINA 2024:www.ginasthma.com with ICS Doses based on Canadian Thoracic Society 2021 Guideline

Canadian guidelines: Preschoolers (1-5 years of age), total daily dosing is in micrograms (mcg)

Corticosteroid	Low	Medium
Beclomethasone dipropionate HFA	100 (mcg)	200 (mcg)

Ciclesonide (Alvesco)	100 (mcg)	200 (mcg)
Fluticasone propionate (Flovent)	<200 (mcg)	200-250 (mcg)

Reference: Yang CL, et al. 2021 Canadian Thoracic Society Guidelines. Can J Resp Crit Care Sleep Med. 2021:1-41