N°d'ordre NNT : 2017LYSE1063

**THESE de DOCTORAT DE L'UNIVERSITE DE LYON**
opérée au sein de
**l'Université Claude Bernard Lyon 1**

**Ecole Doctorale ED 341**
**Evolution, Ecosystèmes, Microbiologie, Modélisation**

**Spécialité de doctorat** :
**Pharmacologie Clinique**

Soutenue publiquement le 04/04/2017, par :
**Perrine Janiaud**

# The rational use of available evidence before extrapolating the benefit risk ratio from adults to children

Devant le jury composé de :

| | |
|---|---|
| Pr TRUFFERT, Patrick, PU-PH, CHRU de Lille | Président |
| Pr BOUTRON, Isabelle, PU-PH, AP-HP | Rapporteur |
| Dr LAPORTE, Silvy, MCU-PH, Université Jean Monet | Rapporteur |
| Pr RHEIMS, Sylvain, PU-PH, CHU de Lyon | Examinateur |
| Dr BIDAULT, Roselyne, PharmD, Laboratoire GlaxoSmithKline | Examinatrice |
| Pr KASSAI, Behrouz, PU-PH, CHU de Lyon et UCBL 1 | Directeur de thèse |
| Dr CORNU, Catherine, PH, CHU de Lyon | Co-directrice |
| Dr CUCHERAT, Michel, MD, Consultant en pharmacologie clinique | Invité |

# UNIVERSITE CLAUDE BERNARD - LYON 1

| | |
|---|---|
| **Président de l'Université** | **M. le Professeur Frédéric FLEURY** |
| Président du Conseil Académique | M. le Professeur Hamda BEN HADID |
| Vice-président du Conseil d'Administration | M. le Professeur Didier REVEL |
| Vice-président du Conseil Formation et Vie Universitaire | M. le Professeur Philippe CHEVALIER |
| Vice-président de la Commission Recherche | M. Fabrice VALLÉE |
| Directeur Général des Services | M. Alain HELLEU |

## *COMPOSANTES SANTE*

| | |
|---|---|
| Faculté de Médecine Lyon Est – Claude Bernard | Directeur : M. le Professeur J. ETIENNE |
| Faculté de Médecine et de Maïeutique Lyon Sud – Charles Mérieux | Directeur : Mme la Professeure C. BURILLON |
| | Directeur : M. le Professeur D. BOURGEOIS |
| Faculté d'Odontologie | Directeur : Mme la Professeure C. VINCIGUERRA |
| Institut des Sciences Pharmaceutiques et Biologiques | Directeur : M. le Professeur Y. MATILLON |
| Institut des Sciences et Techniques de la Réadaptation | Directeur : Mme la Professeure A-M. SCHOTT |
| Département de formation et Centre de Recherche en Biologie Humaine | |

## *COMPOSANTES ET DEPARTEMENTS DE SCIENCES ET TECHNOLOGIE*

| | |
|---|---|
| Faculté des Sciences et Technologies | Directeur : M. F. DE MARCHI |
| Département Biologie | Directeur : M. le Professeur F. THEVENARD |
| Département Chimie Biochimie | Directeur : Mme C. FELIX |
| Département GEP | Directeur : M. Hassan HAMMOURI |
| Département Informatique | Directeur : M. le Professeur S. AKKOUCHE |
| Département Mathématiques | Directeur : M. le Professeur G. TOMANOV |
| Département Mécanique | Directeur : M. le Professeur H. BEN HADID |
| Département Physique | Directeur : M. le Professeur J-C PLENET |
| UFR Sciences et Techniques des Activités Physiques et Sportives | Directeur : M. Y.VANPOULLE |
| Observatoire des Sciences de l'Univers de Lyon | Directeur : M. B. GUIDERDONI |
| Polytech Lyon | Directeur : M. le Professeur E.PERRIN |
| Ecole Supérieure de Chimie Physique Electronique | Directeur : M. G. PIGNAULT |
| Institut Universitaire de Technologie de Lyon 1 | Directeur : M. le Professeur C. VITON |
| Ecole Supérieure du Professorat et de l'Education | Directeur : M. le Professeur A. MOUGNIOTTE |
| Institut de Science Financière et d'Assurances | Directeur : M. N. LEBOISNE |

# Résumé


## L'utilisation rationnelle des données disponibles avant d'extrapoler la balance bénéfice risque de l'adulte à l'enfant

Les médicaments sont évalués et reçoivent une autorisation de mise sur le marché (AMM) avant d'être prescrits. Ils sont généralement évalués chez des patients adultes, et utilisés chez les enfants en extrapolant les résultats obtenus chez les adultes. L'extrapolation de la balance bénéfice risque de l'adulte à l'enfant intervient lors du développement clinique du médicament et lorsqu'il est prescrit (dans l'AMM ou hors AMM, ce qui est fréquent chez l'enfant). Ceci est dû aux contraintes de la recherche clinique en pédiatrie, qui conduit à un manque de données chez l'enfant. Une recommandation sur l'extrapolation est en cours de finalisation par l'Agence Européenne du Médicament (EMA). En utilisant une approche méta-épidémiologique, nous avons exploré les similitudes ou différences du bénéfice, de la balance bénéfice risque et de l'évolution sous placebo entre adultes et enfants à partir de méta-analyses d'essais randomisés en double aveugle contre placebo, ayant inclus des adultes et des enfants dans des indications et avec des médicaments identiques, et présentant des données séparées chez l'adulte et l'enfant. Par la suite, nous avons construit le modèle d'effet à partir des données adultes et l'avons utilisé pour prédire l'effet du traitement et calibrer la taille de l'essai clinique pédiatrique. Ces travaux mettent en avant l'importance d'utiliser toutes les données disponibles avant d'extrapoler la balance bénéfice risque de l'adulte à l'enfant et de justifier les nouvelles études au regard des connaissances existantes. Cette démarche permet de réduire les répétitions inutiles d'essais cliniques, de mieux affecter les ressources destinées à la recherche, d'identifier les domaines pour lesquels les connaissances sont insuffisantes et ainsi optimiser la recherche clinique en pédiatrie. De manière plus globale, cela s'applique à tous types de recherche et permet d'éviter le gâchis au niveau du temps et des ressources investis.



**Mots clés** : Pédiatrie – Recherche clinique – Méta-épidémiologie – Balance bénéfice risque – Extrapolation – Médicament – Essais cliniques randomisés contrôlés

# Abstract

## The rational use of available evidence before extrapolating the benefit risk ratio from adults to children

Drug interventions are evaluated and receive a Marketing Authorization (MA) before being prescribed. They are generally evaluated in adult patients and then prescribed to children by extrapolating the treatment effect observed in adults. The extrapolation of the benefit risk ratio from adults to children occurs during drug development and when prescribing drugs (within the MA or off-label, which is frequent in children). This is due to the specific constraints of pediatric clinical research leading to a lack of data in children. A framework for extrapolation is currently being finalized by the European Medicines Agency (EMA). Using a meta-epidemiological approach, we explored the similarities and differences of the benefit, the benefit risk ratio and the perceived placebo effect between adults and children from meta-analyses including randomized double-blinded placebo-controlled trials evaluating a drug intervention in an indication in adults and children with separate data for both populations. We then built the effect model using adult data to predict the treatment effect in children and calibrate future pediatric clinical trials. Our research highlights the importance of using all available evidence before extrapolating the benefit risk ratio from adults to children and to justify new studies in the context of existing evidence. This approach allows to reduce unnecessary repetitions of clinical trials, to better allocate resources, to identify gaps in knowledge and thus optimize pediatric clinical research. More generally, it applies to any research allowing to avoid a waste in the time and resources invested.



**Keywords**: Pediatric –Clinical research – Meta-epidemiology – Benefit risk ratio – Extrapolation – Drug – Randomized controlled trials

# Table of Contents

Résumé ..... 3

Abstract ..... 4

Table of Contents ..... 5

List of Publications – Oral and Poster Communications ..... 7

Abbreviations ..... 11

**PREFACE ..... 12**

**SUBSTANTIAL FRENCH SUMMARY ..... 14**

**GENERAL INTRODUCTION ..... 19**

I. CLINICAL RESEARCH IN CHILDREN ..... 19

II. ACHIEVEMENT AND IMPACT OF THE US AND EU LEGISLATION ..... 23

III. EXTRAPOLATION FRAMEWORK ..... 25

**OBJECTIVES ..... 30**

**META-EPIDEMIOLOGICAL APPROACH ..... 32**

I. METHODS ..... 32

II. DESCRIPTION OF THE DATABASE ..... 34

**DIFFERENT TREATMENT BENEFITS WERE ESTIMATED BY CLINICAL TRIALS PERFORMED IN ADULTS COMPARED WITH THOSE PERFORMED IN CHILDREN ..... 38**

**THE BENEFIT RISK RATIO IN ADULTS AND CHILDREN: A META-EPIDEMIOLOGICAL STUDY ..... 52**

**IS THE PERCEIVED PLACEBO EFFECT COMPARABLE BETWEEN ADULTS AND CHILDREN? A META-REGRESSION ANALYSIS ..... 63**

**THE ADULT TREATMENT EFFECT MODEL FOR PREDICTING THE POTENTIAL BENEFIT IN CHILDREN AND CALIBRATING ADEQUATELY NEW PEDIATRIC CLINICAL TRIALS ..... 91**

**DISCUSSION .....103**

**CONCLUSION.....107**

**REFERENCES.....108**

**APPENDIX 1: RESEARCH STRATEGY FOR THE LITERATURE DATABASE .....113**

**APPENDIX 2: INCLUDED META-ANALYSIS CHARACTERISTICS AND REFERENCES .....114**

**APPENDIX 3: UNNECESSARY REPETITIONS OF PEDIATRIC CLINICAL TRIALS: CUMULATIVE META-ANALYSES .....147**

# List of Publications – Oral and Poster Communications

### *First author publications:*

**JANIAUD Perrine**, LAJOINIE Audrey, COUR-ANDLAUER Fleur, CORNU Catherine, COCHAT Pierre, CUCHERAT Michel, GUEYFFIER François, KASSAI Behrouz.
Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children.

*Journal of Clinical Epidemiology*. 2015;9(15):00334-0.
doi: 10.1016/j.jclinepi.2015.06.021

**JANIAUD Perrine**, CORNU Catherine, KASSAI Behrouz.
Extrapolation will never replace randomized clinical trials.

*Journal of Clinical Epidemiology*. 2015;4(15):00332-7.
doi: 10.1016/j.jclinepi.2015.06.019

**JANIAUD Perrine**, CORNU Catherine, LAJOINIE Audrey, DJEMLI Amina, CUCHERAT Michel, KASSAI Behrouz.
Is the perceived placebo effect comparable between adults and children? A meta-regression analysis.

*Pediatric Research*. 2016.Epub ahead of print.
doi: 10.1038/pr.2016.181

### *Other publications:*

LE Hai Ha, EL-KHATIB Chadia, MOMBLED Margaux, GUITARIAN Frédéric, AL-GOBARI Muuamar, FALL Mor, **JANIAUD Perrine**, MARCHANT Ivanny, CUCHERAT Michel, BEJAN-ANGOULVANT Théodora, GUEYFFIER François.
Impact of aldosterone antagonists on sudden cardiac death prevention in heart failure and post-myocardial infarction patients: a systematic review and meta-analysis of randomized controlled trials.

*PLoS One*. 2016; 18;11(2):e0145958.
doi: 10.1371/journal.pone.0145958

HUGUES Aurélien, DI MARCO Julie, **JANIAUD Perrine**, BONAN Isabelle, GUEYFFIER François, RODE Gilles.

Efficiency of physical rehabilitation on postural imbalance after stroke: Systematic review and meta-analysis.

*Annals of Physical and Rehabilitation Medicine*. 2016; 59S:e78.

doi: 10.1016/j.rehab.2016.07.183

EYMARD Nathalie, VOLPERT Vitaly, BESSONOV Nikolai, OGUNGBENRO Kayode, **JANIAUD Perrine**, AARONS Leon, BAJARD Agathe, CHABAUD Sylvie, BERTRAND Yves, KASSAI Behrouz, KURBATOVA Polina, CORNU Catherine, NONY Patrice: for the CRESim project group.

Mathematical model of T -cell lymphoblastic lymphoma: disease, treatment, cure or relapse of a virtual cohort of patients.

*Mathematical Medicine and Biology*. Accepted for publication

LAJOINIE Audrey, **JANIAUD Perrine**, HENIN Emilie, GLEIZE Jean-Cédric, BERLION Clémentine, RAJON Kevin, NGUYEN Kim An, NONY Patrice, GUEYFFIER François, MAUCORT-BOULCH Delphine, KASSAI Behrouz

Exploring the effects of solid versus liquid dosage forms of oral medications on adherence and acceptability in children (Protocol).

*Cochrane Database of Systematic Reviews*. Answering reviewers' questions

GAUTIER Isabelle, JANIAUD Perrine, ROLLET Nelly, ANDRE Nicolas, TSIMARATOS Michel, CORNU Catherine, MALIK Salma, GENTILE Stephanie, KASSAI Behrouz

The quality of pediatric trial protocols submitted to a French Institutional Review Board

*PLoS One*. Submitted

### *Poster Communications:*

**JANIAUD Perrine**, LAJOINIE Audrey, COUR-ANDLAUER Fleur, CORNU Catherine, COCHAT Pierre, CUCHERAT Michel, GUEYFFIER François, KASSAI Behrouz

Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children.

*23rd Cochrane Colloquium*, Vienna, Austria, 3-7 October 2015

**JANIAUD Perrine**, CHIGANNE Marie, HERGIBO Fanny, ARAUJO Isabel, CORNU Catherine, KASSAI Behrouz.

Heterogeneity between adults and children for drug efficacy and drug efficacy adjusted for risk.

*23rd Cochrane Colloquium*, Vienna, Austria, 3-7 October 2015

ROLLET Nelly, KASSAI Behrouz, BLANCHARD Pauline, GAUTIER Isabelle, CORNU Catherine, MALIK Salma, **JANIAUD Perrine**.

Quality of pediatric protocols submitted to a French Ethics Committee between 2003 and 2014.

*9th EPICLIN Conference*, Montpellier, France, 20 to 22 May 2015.

ROBIN Audrey, CHAISSAC Elodie, **JANIAUD Perrine**, KASSAI Behrouz.

A checklist to assess the impact of the European Regulation n°1901/2009 on paediatric protocols quality.

*DIA, EuroMeeting*, Amsterdam, Netherlands, 4 to 6 March 2013.

**JANIAUD Perrine** and KASSAI Behrouz.

Is the evolution under placebo different between adults and children?

*8th EPICLIN Conference*, Bordeaux, France, 14-16 May 2014

***Oral Communications***:

**JANIAUD Perrine**, CORNU Catherine, KASSAI Behrouz.

Unnecessary repetitions of pediatric randomized controlled trials: cumulative meta-analyses.

*23rd Cochrane Colloquium*, Vienna, Austria, 3-7 October 2015 (short communication)

**JANIAUD Perrine**, LAJOINIE Audrey, COUR-ANDLAUER Fleur, CORNU Catherine, COCHAT Pierre, CUCHERAT Michel, GUEYFFIER François, KASSAI Behrouz

Similarity of the treatment benefit between children and adults: results of a meta-epidemiological study.

*Congrès des Sociétés de Pédiatrie*, Tours, France, 27-29 May 2015 (short communication)

**JANIAUD Perrine** and KASSAI Behrouz

Is the evolution under placebo different between adults and children?

*Congrès des Sociétés de Pédiatrie*, Lyon, France, 22-24 May 2014.

**JANIAUD Perrine**, COUR-ANDLAEUR Fleur, CORNU Catherine, COCHAT Pierre, CUCHERAT Michel, NEAL Kent, GUEYFFIER François, KASSAI Behrouz.

Similarity of the treatment benefit between children and adults: results of a meta-epidemiological study.

*8th EPICLIN Conference*, Bordeaux, France, 14-16 May 2014

# Abbreviations

AMM: Autorisation de Mise sur le Marché

BPCA: Best Pharmaceuticals for Children Act (U.S.)

CIFRE: Industrial Contract for Training through Research

CONSORT: Consolidated Standards of Reporting Trials

EMA: European Medicines Agency

EMET: Evaluation and Modelling of the Therapeutic Effect

FDA: U.S Food and Drug Administration

FDAMA: Food and Drug Administration Modernization Act (U.S)

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

LBBE: Biometry and Evolutionary Biology Laboratory

MA: Marketing Authorization

METRICS: Meta-Research Innovation Center at Stanford

NEAR: Net Efficacy Adjusted for Risk

OR: Odds ratio

PD: Pharmacodynamics

PIP: Paediatric Investigation Plan (E.U.)

PK: Pharmacokinetics

PREA: Pediatric Research Equity Act (U.S)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSP: Pediatric Study Plan (U.S.)

PUMA: Paediatric Use Marketing Authorization

RCT: Randomized Controlled Trials

ROR: Ratio of Odds Ratios

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

UMR: Mixed Research Unit

# PREFACE

Currently between 50 to 90% of children with serious diseases receive drugs prescribed off-label. This approach is essentially based on the confirmation of the benefit risk ratio of these drugs in adult subjects. Most of the time, the efficacy and safety are directly extrapolated to children without any additional clinical trials apart from an adjustment of the dose according to their weight or body surface area. Such extrapolation often proves to be inaccurate due to obvious differences between adults and children on a pharmacological and physiological level. These differences seem to have a significant impact on the pharmacodynamics (PD) and pharmacokinetic (PK) of the drug, altering its performance and pharmacological activity.

A framework on the concept of extrapolation is being developed at the European Medicines Agency (EMA). In children, the extrapolation of adult data would allow to predict the therapeutic benefit in the pediatric population in order to optimize clinical research, to avoid experimental burden and unnecessary repetitions in this population.

This work explores different top down approaches consistent with the development of the European framework on extrapolation. A meta-epidemiological approach was used to: quantify the similarity of the therapeutic benefit and benefit risk ratio between adults and children; and explore the extrapolation of the perceived placebo effect observed in adults to children. The different treatment effect models built from adult data were also explored to see if they can predict the treatment effect in children and calibrate future pediatric trials for the same drug and indication.

This thesis project was done in the Evaluation and Modeling of the Therapeutic Effect team (EMET) of the UMR CNRS 5558 at the Claude Bernard University, Lyon 1, under the supervision of Professor Behrouz Kassai and Doctor Catherine Cornu. It was funded as part of a three years industrial contract for training through research (CIFRE) by GlaxoSmithKline Laboratory, France, supervised by Roselyne Bidault. The UMR CNRS 5558, Biometry and Evolutionary Biology Laboratory (LBBE), is a mixed research unit regrouping researchers under two common denominators: mathematical and computer modelling methodology in life and medical sciences; and evolutionary perspectives. The Laboratory is organized in 4 departments: Genetics and Evolutionary Genomics; Genetics, Interactions and Evolution of

Genomes; Evolutionary Ecology; and Biostatistics and Modelling for Health and Environment. The EMET team is part of the latter department, regrouping scientists, medical doctors, pharmacy doctors, pharmacologist, mathematicians and statisticians. The team focuses on the evaluation of the therapeutic effect using evidence based medicine approaches such as meta-analyses, and on the construction of explanatory and predictive models to better understand and predict the therapeutic effect on an individual and population level.

In addition during my thesis, I spent 3 month at the University of Stanford, California as a Visiting Student Research. There I had the great opportunity to collaborate with the Meta-Research Innovation Center at Stanford (METRICS) under the supervision of Professor Ioannidis. METRICS focuses on the evaluation of how research is done and interpreted with the need to standardize research practices, reduce biases, enhance reproducibility, increase transparency, and strengthen the evidence base in scientific studies. Professor Ioannidis paper on "Why most published research findings are false" has been the most accessed article in the history of Public Library Science (1). He has also published two papers regarding the extrapolation of the benefit and risk of interventions from adults to children (2, 3).

# SUBSTANTIAL FRENCH SUMMARY

Il a été largement reconnu que pour être en mesure de prescrire un médicament aux enfants avec une balance bénéfice risque acceptable, ils doivent avoir être inclus dans les essais cliniques. Toutefois les enfants sont sous-représentés en recherche clinique ce qui induit un manque de données cliniques chez l'enfant. Entre 1985 et 2005, les essais randomisés ont augmenté de 4,71 essais/an contre seulement 0,4 essais/an en pédiatrie (4).

La recherche clinique en pédiatrie doit faire face à des contraintes éthiques et logistiques plus lourdes que chez l'adulte, ce qui peut expliquer l'inégalité de représentation entre adultes et enfants en recherche clinique. Le marché du médicament pédiatrique étant restreint, par rapport au coût élevé du développement, l'industrie a eu tendance à se désintéresser de cette population. A ceci s'ajoute, les contraintes méthodologiques telles que l'utilisation du placebo qui est difficilement accepté par les parents, la limitation des interventions invasives, et le consentement indispensable des deux parents qui peut s'avérer difficile à obtenir. Il y a un réel dilemme entre l'obligation de réaliser des essais cliniques chez l'enfant pour les protéger des risques liés aux médicaments non testés en pédiatrie et de les protéger des risques potentiels des essais cliniques (5).

La population pédiatrique est une population hétérogène allant de la naissance à la majorité (18 ans). Cela entraine des différences au niveau physiologique et pharmacologique entre les différents groupes d'âge. En effet, on peut difficilement comparer un nourrisson à un adolescent. Cette hétérogénéité, en plus d'influencer l'effet du médicament, peut influencer le choix de la formulation du médicament ainsi que celui du critère de jugement. Par exemple, un critère de jugement donné pourra être rapporté par une tierce personne chez de jeunes enfants et par l'enfant lui-même s'il est plus âgé (5).

Différentes mesures règlementaires ont été mises en place par l'EMA afin d'inciter les industriels et de promouvoir la recherche clinique en pédiatrie (6). Une augmentation de la recherche clinique pédiatrique a pu être observée entre 2007 et 2015, 238 médicaments pour une utilisation chez l'enfant et 39 nouvelles formulations pharmaceutiques adaptées aux enfants ont été autorisées en Europe (7).

Face au manque des données cliniques chez les enfants, il est courant de leur prescrire des médicaments hors de leurs AMM. Cette démarche s'appuie sur l'efficacité de ces produits démontrée chez les sujets adultes. Cette efficacité est directement extrapolée aux enfants sans expérimentation clinique supplémentaire après un simple ajustement de la dose sur le poids ou la surface corporelle des enfants. Une telle extrapolation s'avère souvent inexacte en raison des différences évidentes chez l'enfant aux niveaux pharmacologique et physiologique. Ces différences auraient un impact important aux niveaux pharmacodynamique et pharmacocinétique, influençant la performance et l'activité pharmacologique d'un médicament.

Au niveau du développement du médicament, l'extrapolation a pour but d'éviter les essais inutiles dans la population pédiatrique pour des raisons éthiques et d'efficience afin d'attribuer les ressources aux aires thérapeutiques nécessitant le plus de recherche. L'extrapolation de l'adulte à l'enfant se base sur trois hypothèses fondamentales : histoire naturelle de la maladie similaire, réponse au traitement similaire et relation dose-réponse similaire entre les adultes et les enfants. Selon l'EMA, ces hypothèses sont vérifiées en faisant une revue systématique de la littérature des toutes les données disponibles et par des techniques de modélisation et de simulation. En fonction des données disponibles permettant de vérifier ces hypothèses et de leur certitude, on peut alors définir trois niveau d'extrapolation : pas d'extrapolation (étude de pharmacocinétique (PK) pour déterminer la dose, suivi d'essais d'efficacité et de sécurité du médicament) ; extrapolation partielle (étude de PK et de sécurité du médicament) ; et extrapolation complète (étude de sécurité uniquement) (8). Le processus d'extrapolation doit être continuellement mis à jour et les hypothèses revérifiées en fonction des nouvelles données disponibles (9).

Jusqu'à maintenant les méthodes d'extrapolation mises en avant se basent principalement sur des méthodes de modélisation et simulation qui sont impossibles à mettre en place dans la pratique courante. Nous proposons d'utiliser une approche méta-épidémiologique à partir de données cliniques provenant de méta-analyses d'essais randomisés en double aveugle contre placebo, ayant inclus des adultes et des enfants dans des indications et avec des médicaments identiques, et présentant des données séparées chez l'adulte et l'enfant.

Premièrement nous avons quantifié les similitudes du bénéfice thérapeutique entre adultes et enfants. Le ratio du rapport des cotes par médicament dans une indication a été calculé pour voir si la réponse au traitement était hétérogène entre les adultes et les enfants. Le bénéfice d'un médicament ne pouvant être dissocié de son risque nous nous sommes par la suite intéressé à la balance bénéfice risque chez les adultes et les enfants et si elle était comparable entre les deux populations. Pour cela nous avons calculé l'efficacité nette ajustée sur le risque permettant ainsi une estimation d'un rapport des cotes à partir de la fréquence attendue du nombre de patients répondant en faveur du traitement sans effets indésirables.

Deuxièmement nous avons exploré l'extrapolation de l'évolution sous placebo de l'adulte à l'enfant à l'aide d'une méta-régression. En effet, plusieurs études mettent en avant une évolution sous placebo potentiellement plus importante chez l'enfant par rapport à l'adulte (10, 11). L'évolution sous placebo a l'avantage d'englober tous les facteurs pouvant expliquer une amélioration du critère du jugement sous placebo : l'évolution naturelle et l'amélioration spontanée de la maladie, la régression à la moyenne, l'utilisation de traitements concomitants, la subordination expérimentale, les réponses conditionnées, et l'effet placebo.

Enfin, l'extrapolation a pour but d'utiliser toutes les données disponibles afin d'avoir une meilleure connaissance de l'effet attendu chez l'enfant. Nous proposons d'utiliser le modèle d'effet (12) d'un traitement donné chez l'adulte afin de prédire l'effet du traitement et de mieux calibrer les essais chez l'enfant. Le modèle d'effet est représenté par un Abbé Plot à partir duquel le risque dans le groupe traitement peut être déduit du risque dans le groupe contrôle. Une telle analyse pourrait permettre dans certains cas de réduire le nombre d'enfants à inclure dans les essais toute en assurant une puissance suffisante.

Nos résultats montrent une hétérogénéité significative au niveau de la quantité d'effet mais aussi du fait que l'effet soit bénéfique ou délétère entre adultes et enfants pour 14 de nos 110 méta-analyses évaluées. Des incertitudes importantes ont été observées au niveau des critères de jugement évaluant la sécurité du médicament et sur la balance bénéfice risque ; seulement 13 méta-analyses sur 47 ont une balance bénéfice risque en faveur du traitement chez l'adulte et l'enfant de façon statistiquement significative. Dans certains cas, une différence cliniquement pertinente entre les adultes et les enfants ne peut pas être complètement exclue. De plus les essais adultes ne permettent pas de détecter les évènements indésirables spécifiques à l'enfant.

Nous avons aussi montré une hétérogénéité de l'évolution sous placebo, avec une évolution sous placebo significativement plus importante chez les enfants pour les critères de jugement binaires et qui ne peut pas être exclue pour les critères de jugement continus. Cette différence semble être plus importante lorsque le design de l'étude est en groupes parallèles par rapport aux plans croisés, et lorsque le critère de jugement est objectif par rapport à un critère subjectif. Ignorer une telle différence peut induire des résultats non concluants et ainsi masquer un effet du traitement potentiellement cliniquement pertinent.

Beaucoup de nos méta-analyses ont abouti à un effet non concluant du traitement chez l'adulte et l'enfant. Inclure des enfants dans des essais non-concluants doit être éviter autant que possible, par une utilisation extensive des données disponibles. La calibration des essais dépend de l'estimation a priori de l'effet attendu du traitement sur la base des données publiées. L'utilisation du modèle d'effet semble être une méthode adaptée pour prédire l'effet du traitement chez l'enfant à partir des données adultes et ainsi pouvoir calibrer la taille de l'essai suivant en pédiatrie. Le modèle d'effet a aussi pour avantage de donner une vue d'ensemble de l'évaluation de l'effet du traitement, d'identifier les résultats incohérents, de mettre en évidence les répétitions inutiles des essais cliniques et d'identifier les patients pouvant profiter le plus du traitement.

A travers des travaux connexes nous nous sommes aussi attachés à identifier les répétitions inutiles d'essais cliniques en pédiatrie à l'aide de la méta-analyse cumulative. Sur 32 méta-analyses ayant un effet confirmé du traitement chez l'enfant, 63 essais ayant inclus 6 614 enfants semblent avoir été faits inutilement (l'effet ayant déjà été démontré).

L'extrapolation ne se limite pas au développement d'un nouveau médicament mais est aussi utilisé de façon courante lorsque les pédiatres prescrivent en dehors de son AMM un médicament. Les approches que l'on a utilisées peuvent permettre aux médecins et chercheurs de mieux appréhender les connaissances disponibles et ainsi prendre des décisions mieux informées, l'extrapolation ne pouvant pas se limiter à un simple ajustement de la dose en fonction du poids ou de la surface corporelle.

Nous pensons également que le processus d'extrapolation devrait être accompagné d'au moins un essai randomisé de puissance adéquate chez l'enfant. Les outils exploratoires tels que les études méta-épidémiologiques, méta-analyses cumulatives et le modèle d'effet contribuent de manière importante au processus d'extrapolation de la balance bénéfice risque

de l’adulte à l’enfant et devrait être obligatoire avant tout essai clinique. En effet, plus de 50% des essais sont réalisés sans faire référence aux connaissances déjà acquises ce qui représente un gâchis considérable des ressources (13). Ce phénomène est accentué par le manque de standardisation, malgré l’existence de recommandations claires (14-16), au niveau du rapport des résultats des essais cliniques. Nous insistons sur l'importance d'utiliser et de développer des méthodes de standardisation des essais randomisés et des revues systématiques lorsque les enfants sont impliqués afin de réduire les résultats inutiles et les essais non-concluants.

# GENERAL INTRODUCTION

It has been widely recognized that to be able to give drugs to children with an appropriate benefit risk ratio, we need to include them in clinical trials. Even though regulatory incentives have been implemented to promote pediatric clinical research, data in children compared with adult data are scarce. With not enough data to support their decision, prescribers are often left with the choice to either prescribe a drug with a potential deleterious effect or to deprive children of innovative therapies. The treatment benefit observed in adults is often extrapolated to children after adjustment of the dose according to the body weight or surface with no additional clinical trials in the pediatric population. However, the extrapolation rational should not be solely based on a dose adjustment without justification but should make use of all available evidence. It should not also supplant a well-designed and adequately powered pediatric clinical trial.

## I. Clinical Research in Children

Clinical research in the pediatric population has resulted in major advances. An often cited example would be the trials for the polio vaccine that was quickly put into practice leading to the almost complete eradication of the disease. Clinical trials were also proven of great benefit in childhood lymphoblastic leukemia where the 5 years survival rate improved from 25% in the late 60s to more than 70% in 2005 (17).

### 1. Scarce and incomplete data

Children remain underrepresented in clinical research. Between 1985 and 2005, a systematic review of general medicine journals showed that the number of randomized controlled trials (RCTs) in adults increased by 4.71 RCTs/year versus 0.4 RCTs/year in children (4). In its 10 year report the EMA has noted a slight increase in the proportion of trials that included children, but they remain a minority. It is even more accentuated for neonates. They represent only 26% of the Paediatric Investigation Plans (PIPs) and those are often deferred until more experience is gain in other pediatric age groups (7).

Clinical data in children are also affected by incomplete reporting and/or bias. Low quality trials can result in an overestimation of the treatment benefit by 34% compared with

high quality trials (ratio of odds ratios (ROR) 0.66; 95% CI [0.52; 0.83]) (18). The presence of bias is also true in adult studies but compared with pediatric studies they are more likely to be RCTs, systematic reviews or studies evaluating a therapy (19). RCTs are the gold standard in clinical research and systematic reviews are the highest level of evidence. Such differences in the quality of the evidence between adults and children are baffling. The pediatric population being at higher risk, it seems inacceptable to include children in misleading or bad quality trials.

Guidelines have been developed to help researchers in the reporting of protocols and clinical trials for publication: the CONSORT checklist (Consolidated Standards of Reporting Trials) (14) and the SPIRIT checklist (Standard Protocol Items: Recommendation for Interventional Trials) (15). Despite the existence of these guidelines, there is still room for improvement (20). For example, reviewers have often reported that RCTs are at high risk of bias when it comes to sequence generation and allocation concealment (21, 22). Another shortage in reporting in pediatrics, concerns the reporting of adverse events (AEs). Either they are not reported or it does not follow the CONSORT checklist specific for harms (22, 23). Comparisons between protocols and publication of the trial results have also shown inconsistency in the reporting of outcomes (24), allocation concealment (25) and sample size calculation (26).

None of the checklists mentioned above have been developed specifically for children. The prerequisites in pediatric clinical trials being different from adults, the reporting requirements should differ as well. There is an ongoing project to develop extensions to the CONSORT and SPIRIT specific to children intervention and randomized trials (20). Authors emphasize on the need to clearly state the age-range of the included pediatric subjects, the potential PK-PD differences that may exist between adults and children, the dose given and the long-term safety. All those steps should be made based on a rational justification and if possible supported by a systematic review of all available evidence.

Pediatric trials are also at greater risk of being discontinued and non-published. A review of the pediatric clinical trials on ClinicalTrial.gov between 2008 and 2010 showed that out of 559 identified trials, 19% were discontinued early and 30% were not published. The latter represent 69 165 included pediatric patients for who the benefit risk ratio is unknown because not published (27). Another review of the completed studies for pediatric exclusivity

following the US Food and Drug Administration (FDA) legislation showed that only 45% of the results were published (28). Publication of pediatric trials results in peer-review literature is limited.

## 2. Challenges in conducting pediatric clinical research

The lack of trials in children is often explained by the difficulties of conducting trials due to specific constraints. One predominant constraint is the high cost of drug development compared with the available pediatric market leading to a shortage of funds and often to the disinterest of the pharmaceutical industry.

Regarding ethics, the main pitfall in pediatric clinical research is that children lack the capacity of understanding risks and all decisions regarding their health are taken by a proxy. Parents are often reluctant to agree to the participation of their child due to the potential unknown harms and the uncertainties around the treatment (5). Like *Jospeh et al.* summarized it, "There is a dilemma in finding a balance between the obligation to conduct clinical trials to protect children from the risk of using untested medicines and to protect children against unknown risks and harms which may occur with trial participation" (5).

Trial methodology is often more demanding and complex in children. RCTs are not as well accepted as in adults, especially when the control groups receive a placebo. It seems less acceptable for parents to include their children in a trial where they might not receive the treatment and where this choice is made randomly. The response under placebo was also showed to be more pronounced in children compared with adults (10, 11) making it harder to detect small clinically relevant treatment effect. Such observations have to be taken into account when designing a clinical trial in children using available evidence from adults.

There is also a greater concern in children to reduce the burden of clinical trials procedures. In pediatrics, it is not only one individual involved but the child and his parents. It is important to minimize the stress induced by the participation to a clinical trial but also the burden for parents. Children being a growing population where all interventions could alter their still maturing physiology, procedures are more limited. For example, on average in children blood samples should represent less than 3% of the estimated circulating blood volume over a 2 to 8 week period (5).

When planning for a clinical trial in the pediatric population the challenge remains the sample size. In this population, diseases are often rare and represent a lower burden compare with adults (5, 29). It is therefore harder to include children. Only 38% of the 736 pediatric trials published between 1996 and 2002 had a sample size of more than 100 (30). Such small sample sizes can result in inadequately powered clinical trials, increasing the risk of having inconclusive results and failing to detect small but clinically relevant or rare outcomes (31).

The main complexity of the pediatric population is that it is a heterogeneous population going from birth to 18 years old. A neonate can hardly be compared to an adolescent on the physiological and pharmacological level. Different age cut-offs in the pediatric population have been proposed but no consensus exist. The EMA follows the ICH-E11 recommendation: preterm newborn infants; term newborn infants (0-27 days); infant toddlers (1-23 month); children (2-11 years); and adolescent (12-16 year or 18 years) (32). While, the Standard of Research in Child Health Group proposes to use the subgroups proposed by the Institute of Child Health and Human Development in the US: preterm neonate (33): term neonates (0-27 days); infancy (28 days to 12 months); toddler (13 months to 2 years); early childhood (2-5 years); middle childhood (6-11 years); early adolescent (12-18 years); and late adolescent (19-21 years) (33). When designing a clinical trial, it is important to acknowledge those differences and to gain insight on the efficacy of the drug according to predefined pediatric age-subgroups.

It can also influence the choice of the outcome measures as they may not be suitable for all age groups. The most obvious illustration would be the use of pain scales with the faces scales for younger children versus the numerical scales for older children and adolescents. Some outcomes may also be reported by a proxy for younger children but will be self-reported for older ones. The choice of formulation will also depend on the included age groups with the development of a “child friendly formulation”. The development of child specific formulation represents an even smaller market resulting in the paucity of adapted formulation for younger children (34). Adults formulation are often adapted by crushing tablets or opening capsules to disperse it in liquid. This may compromise the palpability and bioavaibility of the drug and affect its effect.

Inequities between adults, children and between children of different age-subgroups exist. It has been argue that all the hurdles listed above are not insurmountable. Innovative

technologies and methodology have been or are being develop giving more appropriate tools to conduct trials in children (35). Regulatory actions have also been taken in the past 30 years to incentivize research in the pediatric population.

## II. Achievement and Impact of the US and EU Legislation

Children are often referred to as "therapeutic orphans" (36). The European Union (EU) and the United States (US) have taken regulatory action to increase availability of authorized medicines that are appropriate for children use and to produce better informed medicine. A first conjoint effort of harmonization between the founding members (EU, US and Japan) of the International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH) was made in 2000 and resulted in the ICH-E11 guideline. The goal was "to encourage and facilitate timely pediatric medicinal product development" and to provide "approaches to the safe, efficient and ethical study of pediatric medicinal product" (32). However, it only serves as a recommendation. It is the responsibility of each member states to put into practice the objectives defined in the ICH-E11.

### 1. Regulatory Initiatives in the US

As early as 1979, the FDA required that a subsection of the drug label be dedicated to the pediatric use based on adequate well controlled studies. This was reinforced in 1998 to all new therapies and new indications for all drugs and biological products with the Final Pediatric Rule. Pharmaceutical industries retaliated through legal actions against the FDA on the basis that such rule exceeded its statutory authority. In response, the Pediatric Rule was replaced in 2003 by the Pediatric Research Equity Act (PREA) giving the FDA authority to mandate pediatric studies (5).

In parallel, financial incentives were implemented in 1997 through the FDA Modernization Act (FDAMA) which was replaced in 2002 by the Best Pharmaceuticals for Children Act (BPCA). Those acts determine the pharmaceutical products requiring pediatric studies and rewards pharmaceutical companies with six months market exclusivity to existing patent. In conclusion, currently the two regulations applied in the US are the PREA (requirements to study therapeutic products in children under certain circumstance) and the BPCA (incentives to pediatric therapeutic products development) (37) (Figure 1). The FDA can waive studies in children if not pertinent or grant extensions for deferred pediatric studies

(5, 38). The PREA and BPCA have been modified and reinforced over time, resulting in 2012 to the obligation for sponsor to submit a Pediatric Study Plan (PSP) early on in the development process (37).

## 2. Regulatory initiatives in the EU

In Europe the need to include children in drug development, as patients being at an increased risk, was defined in the European Regulation in 1975 (Directive 75/318/EEC) (39). To fill in the gaps in knowledge and practice, the European Pediatric Regulation was implemented in 2007 (Regulation 1901/2006/EU and 1902/2006/EU) (6). The EU regrouped under one regulation the requirement to conduct pediatric clinical research and the incentives. Like the FDA, the EU rewards with a 6 months MA extension all drug development done in children. In addition, the EU implemented another type of MA called a Paediatric Use Marketing Authorization (PUMA). The aim is to encourage the development of a new pediatric indication for off patent medicines. This rewards the PUMA holder with a 10 years data protection.

Since 2008, the EMA requires that the sponsor submits a PIP for all drug development (6). This requirement can be waived off if the indication is not relevant to the pediatric population. The main difference between the PIP and PSP is the time of submission. The FDA requires it at the end of phase 2 while at the EMA, it has to be submitted at the end of phase 1 as soon as the PK studies are done in the adult population.

## 3. Impact of the Regulations

Both in the US and in the EU, the legislations had a favorable impact on the number of clinical trials in children. An increase in the number of drugs with information related to children's use was observed. In 1999 according to the Physicians' Desk Reference in the US, 20% of the drugs relevant to pediatric had information concerning children. This increased to 41% between 2002 and 2008 (40). In its 2015 annual report, the EMA showed that the proportion of pediatric trials has increased to over 18% of all trials (Figure 2) (41). In addition, 238 medicines for use in pediatrics and 39 new pharmaceutical children friendly formulation were authorized in the EU between 2007 and 2015 (7).

Regarding pediatric development plans, in the US between 1998 and 2011, 500 labeling changes were approved of which 453 were related to studies request under the BPCA and PREA regulations (5). In the EU, 100 PIPs have been completed and over 700 are ongoing. By June 30th, 2015, 172 PIPs were to be finished and 60% of which were indeed completed. The major drawback regarding the European regulation concerns the PUMAs. Only two have been granted in the 10 years of the regulation (7).

# III. Extrapolation Framework

The constraints specific to the pediatric population, whether logistic, ethical or methodological, require to better identify pediatric needs, to optimize clinical research and to better allocate resources. All research done upstream pediatric clinical trials represent a major source of information that should not be disregarded.

## 1. Children are not just small adults

Due to the scarcity of clinical data specific to the pediatric population and because they have the right to the same therapeutic standards as adults, off-label use is frequent in children. In hospitals, up to 90% of the neonates in intensive care receive an off-label drug (35, 42). A recent survey in two neonatal intensive care units in Lyon, France, reported that on 8 891 prescriptions to 910 neonates, 5.2% were unlicensed and 59.5% were off-label. Resulting in 95% of the neonates exposed to at least one off-label or unlicensed drug (43). Off-label use in children was also shown to be significantly associated with adverse drug reactions (ADRs) (relative risk (RR) 3.44; 95% confidence interval (CI) [1.26; 9.38]) (44).

Such practice relies on the evaluation and confirmation of the benefit risk ratio in adult trials. It is directly extrapolated to children after adjustment of the dose with no supporting evidence in the pediatric population. Comparison of scaling methods of adult dose for children have shown that the body weight was more appropriate for children between 1 month and 1 year old whereas body surface was better in older children (45). No single suitable dosing algorithm exists for all pediatric age-subgroups.

As the common adage says, “children are not just small adults”(46). Indeed, such extrapolation is often inaccurate due to pharmacological and physiological differences which are not taken into account when adjusting the dose on weight or body surface. Those

differences are explained by obvious anatomical dissimilarities that have an impact on the ADME cycle (absorption, distribution, metabolism and excretion) influencing the PK (i.e. how the organism affects the drug) and PD (i.e. how the drug affects the organism) of the drug. In addition, the pediatric population is a growing heterogeneous group of patient where maturation and development does not happen in a linear fashion (20) and might alter several times the ADME cycle.

The neonates present the most rapid physiological changes occurring compared with other age-subgroups (47). For example, bronchodilators are less effective in younger children due to a variety of etiologic and physiologic reasons (48). There are also differences in AEs. The majority of cases of Reye's syndrome occur in children < 6 years old and nearly all cases appear in children < 12 years old (49). In addition, both ability to report AEs and drug utilizations vary according to the age of the child (33).

Pediatric drug development with adequately designed trials is therefore fundamental in order to provide safe and efficacious drugs to children. When robust similarities exist between adults and children, extrapolation from adult evidence may help reduce the pediatric data requirement by reducing the number and complexity of trials. There is the need to develop a systematic framework for extrapolating all existing evidence from adults to children but also in all aspects of research such as extrapolating preclinical data.

## 2. The extrapolation concept

The following definition has been proposed by the EMA: "Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product. The primary rationale for extrapolation is to avoid unnecessary studies in the target population for ethical reasons, for efficiency, and to allocate resources to areas where studies are the most needed" (50).

Since 1994, the FDA has developed a decision tree (Figure 3) for extrapolating the treatment effect from adults to children (8). It is based on a series of evidence based

assumptions, the three fundamentals being: similar disease progression, similar responses, and similar exposure-response relationship between adults and children. Those assumptions should rely on robust evidence regarding disease pathogenesis, criteria for disease definition, clinical classification, measures of disease progression and pathophysiology, and histopathological and pathobiological characteristics (8). The FDA has defined three levels of extrapolation (Figure 3):

- No extrapolation (Option A): When the fundamental assumptions of similarities of disease progression or of response to intervention are not verified, or when no common PD measurement can be used in adults and children then a full pediatric drug development is required. This includes a PK study to determine the suitable dose in children followed by appropriate efficacy and safety studies.
- Partial extrapolation (Option B): If uncertainties about at least one of the assumption persists a partial pediatric drug development is required. This includes either a single adequate and well controlled trial to confirm efficacy or an exposure-response trial (PK/PD) from which the efficacy can then be predicted if it confirms the assumption of similar exposure-response relationship. PK studies to establish the dose and safety data are also required.
- Full extrapolation (Option C): It relies on preexisting robust data verifying the 3 fundamental assumptions. The effective dose can be identified by matching systemic exposures between adults and children if the necessary data are available, or else PK studies are required to know the appropriate dose. Safety data are required whatever the dose finding method used.

The challenge is in the adequacy of the evidence to support the a priori assumptions made. The rationale for extrapolating the treatment benefit should be based on a body of evidences that takes into account the scientific knowledge of all aspects of the disease and its natural history in adults and children. The developmental changes and their interaction with the disease and response to the drug in children have to also be accounted for and endpoints used to measure efficacy in children have to be valid (8).

The EMA based their extrapolation framework on the same assumptions as the FDA requiring robust evidence to support and verify them. Those evidences are acquired through

systematic reviews of all available evidence in adults and through modeling and simulations approaches (defined as the Extrapolation Concept). Optimal pediatric studies are then planned in accordance with the degree of predicted similarities and their certainty (Extrapolation Plan). The EMA emphasizes on the importance to confirm the extrapolation plan by relevant emerging data in children and to interpret those emerging data in the context of information extrapolated from the adult population (Validation and Confirmation). When not all uncertainties are resolve before the marketing authorization then additional follow-up is required (Further Validation) (Figure 4) (9). The degree of the extrapolation depends on how much of the source data can be used to predict the PK, PD and efficacy. The decision requires timely availability of source data and to find a balance between the uncertainties underlying the extrapolation concept and the additional patient resources required to carry out further studies. The EMA and FDA agree on the fact that safety cannot be extrapolated and that safety studies should always be conducted in order to identify unexpected age-specific safety events (8, 9).

## 3. Extrapolation experiences

Between 1998 and 2008, 370 pediatric studies were submitted to the FDA evaluating 166 products. Overall, 82.5% used adult data for extrapolation among which 14.5% followed a complete extrapolation plan and 68% a partial one. When extrapolation was used, 61% resulted in a new pediatric indication or to an indication extension to a new pediatric age group (8). Out of the 24 products for which a full extrapolation was used, 8% conducted only safety studies. Fifty-seven percent of them fail to achieve pediatric labeling (8). Overall, the use of extrapolation resulted in the reduction in the number of studies and patient needed for pediatric drug development. Failure to obtained pediatric labeling with extrapolation was mostly due to failed or non-interpretable studies; insufficient data generated; high variability in the PK studies; inability to achieve therapeutic concentration in relevant body compartment; or unexpected safety signal.

Up to January 2010, 47 out of 210 positive PIPs opinions made reference to modeling and simulation techniques (51). Modeling and simulation is becoming more common in PIPs and is being recognized as a useful tool to facilitate the extrapolation of efficacy between different age groups. The extrapolation framework in all its aspects (systematic review, modelling and simulation, prediction, and quantification of difference between populations)

should optimize the decision making when resources are scarce, avoid unnecessary studies if prevailing data exist, minimize the number of children to be enrolled in clinical studies and thus reduce the clinical trial burden for the pediatric population.

# OBJECTIVES

The extrapolation of the benefit risk ratio from adults to children occurs during drug development involving simulation and modeling techniques. Those can be difficult to apply in routine practice for pediatricians who routinely extrapolate results of adult studies when prescribing off-label medicines.

Systematic review of the literature is an integral part of the proposed extrapolation frameworks. When well-controlled conclusive studies are available in adults and if the fundamental assumptions of extrapolation are verified (similar disease progression, response to treatment and exposure-response relationship between adults and children) then pediatric trials requirements can be scaled down.

RCTs, double-blinded and placebo-controlled are the gold standard of clinical research. Clinical data from such trials are readily available in published meta-analyses and allows to cover a large scope of indication for which drugs were evaluated in adults and children. We, therefore, proposed to use a meta-epidemiological approach to explore our research objectives.

First, we quantified ***the similarities of the therapeutic benefit between children and adults for a given disease and treatment***. The Ratios of Odds Ratio (ROR) were calculated, for each clinical outcome selected from each included meta-analysis evaluating a drug in an indication, to see if the response to the treatment was clinically heterogeneous between adults and children. The doses administered to children were also explored. The differences in doses used could explain clinical heterogeneity observed between studies.

The benefit of a drug cannot be dissociated from its risks. For most harms, it is unknown if their frequencies are different between adults and children. A previous meta-epidemiological study comparing the safety of medicinal interventions between adults and children had already been done (3). We, therefore, decided to focus on ***the benefit risk ratio of drug interventions between adults and children***. We used the Net Efficacy Adjusted for Risk (NEAR) (52) to illustrate the benefit risk ratio. It allows to estimate an odd ratio (OR) using the expected frequencies of responders to the treatment without harms.

The potential existence of a larger placebo effect in children compared with adults had already been suggested (10, 11). A greater response under placebo in children would reduce the expected effect size increasing the risk of inconclusive treatment effects in children. We explored ***the extrapolation of the perceived placebo effect observed in adults to children*** using a meta-regression analysis. The perceived placebo effect, unlike the placebo effect, covers other factors that may also explain improved clinical outcomes measured in patients receiving placebo. Those factors are: the natural evolution and spontaneous regression of the disease; regression to the mean; the use of concomitant treatment; experimental subordination (the subject says what he thinks the expected response should be); the conditioned response (learning related to a medication and expected effect); and the placebo effect.

The aim of using all available evidence for extrapolation is to have adequately powered pediatric RCTs and to make better informed decision when estimating the expected benefit in children. We proposed ***to use of the effect model for a given treatment and disease in adults to see if they could help predict the treatment effect and calibrate future pediatric clinical trials***. The effect model enables to deduct the risk of presenting an event in the treatment group using the risk in the control group (12). The L'Abbé Plot representation of the effect model allows to visualize the beneficial or deleterious effect of a treatment.

# META-EPIDEMIOLOGICAL APPROACH

A meta-epidemiological study analyses a collection of meta-analysis. The general objective is to compare intervention effect estimates among trials with our without a particular characteristic (53, 54). In our work the deciding characteristic was the population (children versus adults).

## I. Methods

### 1. Search strategy

Three electronic databases (PubMed, EMBASE and the Cochrane Library) were searched for meta-analyses (from 1998 for Cochrane Library and from 1966 for PubMed and from 1947 for EMBASE), with no limitation on diseases or treatments. The advance search tools were used for each database using the following keywords: child, preschool, infant, adolescent adults and placebo. The references were then sorted out according to our inclusion criteria using the EndNote software. The detailed search strategies are described in Appendix 1.

### 2. Meta-analyses selection

Meta-analyses were eligible when they included RCTs that were double-blinded, placebo-controlled and reported separately their results for adults and children. All types of treatments were eligible, except for homeopathic treatments and non-drug interventions. The age limit between children and adults, when necessary, was arbitrarily set at 16 years old. Adult trials may also include a minority of adolescents (>12years). Separate meta-analyses conducted in adults or in children but evaluating the same drug in the same indication with the same outcome, were also included.

It was possible to include more than one drug per review, as long as adults and children data were available for each. A review was considered a duplicate when it included the exactly the same RCTs.

## 3. Data extraction

The following information were extracted from the meta-analyses and entered into the database: i) the conception and design of the study (randomization, parallel group, cross-over, and blinding); ii) patient characteristics (adults or children, disease, number of patients in the placebo and treatment arms); iii) the disease (e.g. asthma); iv) the drug used (some meta-analyses gave information for more than one drug, when possible data were extracted for each drug studied in the meta-analysis); v) the efficacy and safety outcome (number of events and no-events in each arm for binary data or the mean change from baseline to the end of study or the mean at the end of the study for each arm and their corresponding standard deviation for continuous data); v) the dose for adults and the dose adjustment for children when available.

For each included review, trials were grouped by drug and then as pediatric and adult trials according to the cut-off age used in the reviews. The original RCTs were consulted when data regarding the outcome were missing in the meta-analysis report.

## 4. Quality assessment

We reported the quality assessment reported by the authors of the meta-analyses for each included RCT. The Cochrane assessment of risk of bias was reported (54). We also focused on the five-point scoring instrument developed by Jadad (Is the trial randomized and double blinded? Are randomization, blinding, and withdrawals described and adequate?) (55).

## 5. Outcome

For the therapeutic benefit, we extracted the primary outcome defined by the review in both adult and children. When several primary outcomes were reported, we selected the most clinically relevant outcome reported both in adult and children with the most available information. For the NEAR method, the outcomes of interest were the benefit outcome and harm outcomes defined as follow: any AEs, serious adverse event (SAEs), withdrawals due to adverse events and any withdrawals. For the perceived placebo effect, we limited ourselves to primary continuous outcome which illustrated an evolution before and after treatment (i.e. mean change from baseline). An RCT could therefore be extracted more than once if it presented all the required outcomes.

### 6. Unit of analysis and unit of analysis error

The unit of analysis error occurs when dealing with crossover trials and multiple intervention groups. For cross-over trials, data were extracted as presented in meta-analyses. Either data corresponded to the first period or took into account the correlation between treatment periods. For the perceived placebo only data from the first period with placebo were considered. When the effect reported was calculated from the difference between the start and end of the study regardless of the periods (i.e. as if a parallel trial), we extracted the mean change from baseline only for the placebo period.

For multiple intervention groups, when different doses were tested versus placebo the total number of patients in the placebo group was divided by the number of times it was used. This was done to avoid double counting and overrepresentation of the placebo group.

## II. Description of the database

The last literature search was done on October 14th, 2015; 3 749 reviews were identified. Eight hundred and seventeen were assessed from full text among which 219 were excluded because they did not report the same intervention or outcome for both populations and 107 because data were not separated for adults and children. One hundred and eleven reviews were eligible (Figure 5). We extracted binary and/or continuous outcomes depending on the objectives of our work: 72 reviews were included with binary outcomes, 33 with continuous outcomes and 6 with both type of outcomes (Appendix 2).

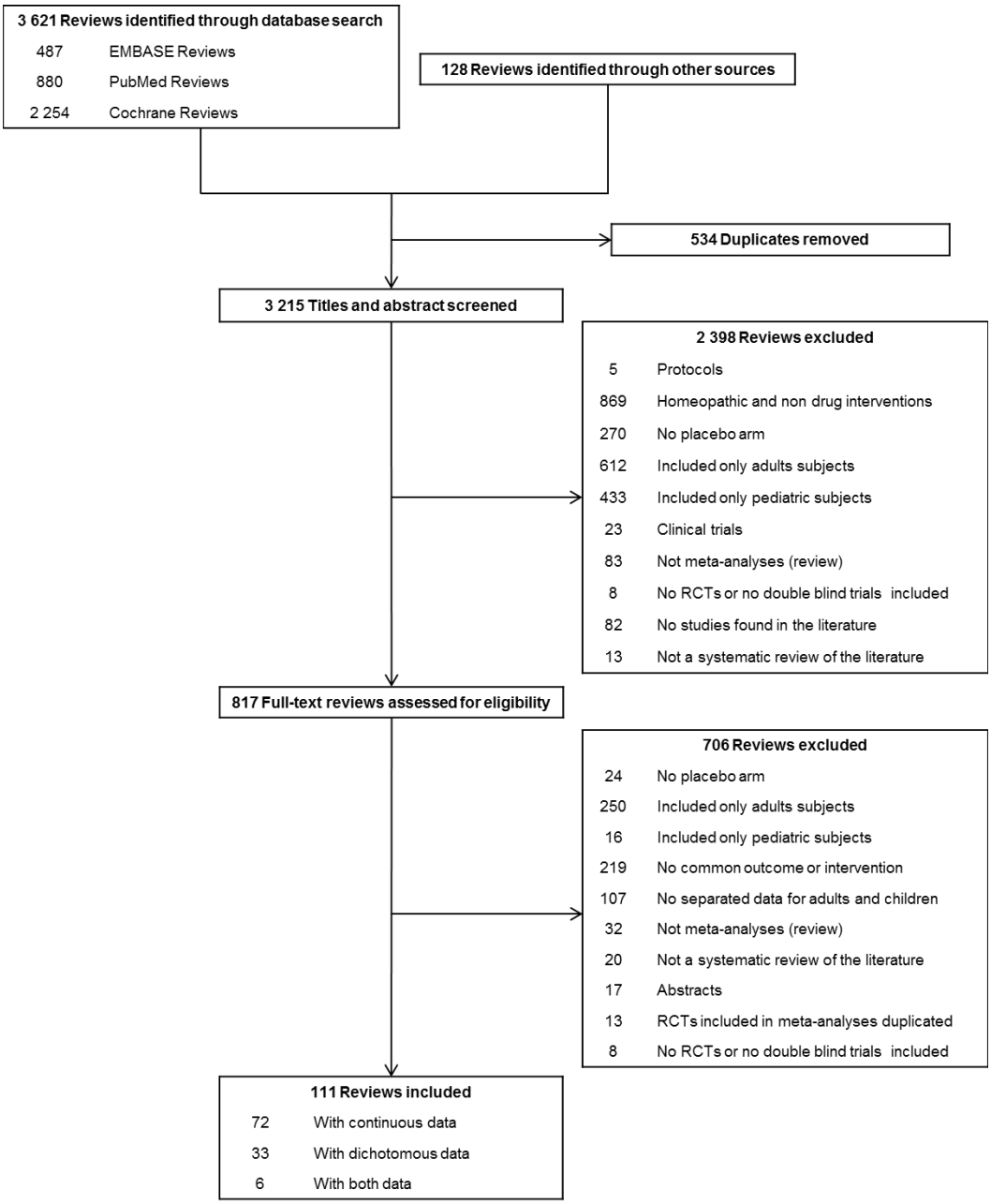



**Figure 5: Flowchart of the literature search**

Ninety-two different drug interventions were included. Some drugs were evaluated by more than one review and/or in different indications. For example, dexamethasone was used for acute bacterial meningitis, postoperative nausea and vomiting, post-tonsillectomy bleeding, post-extubation stridor and sore throat. Overall, we evaluated 150 meta-analyses (i.e. a drug in an indication with an efficacy outcome of interest) (Appendix 2). The 2 most evaluated pharmaceutical categories were: probiotics and antiepileptic (Figure 6). The 3 most studied therapeutic areas were: pulmonary diseases, gastroenterology and postoperative complications (Figure 7).

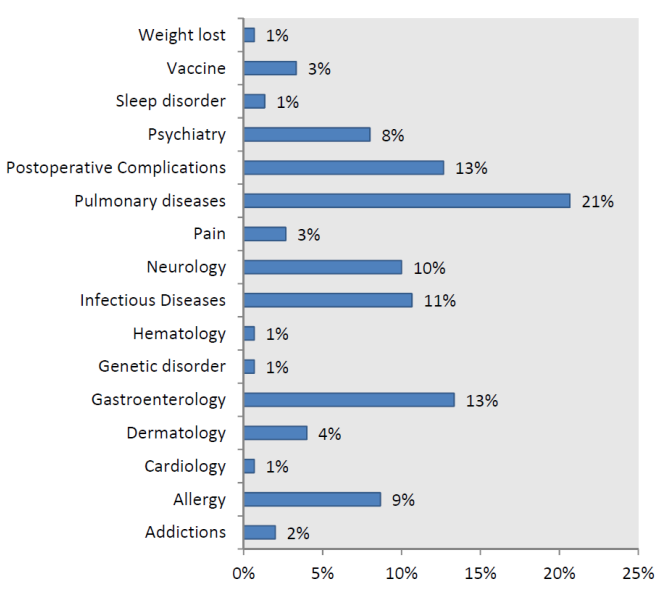



**Figure 6: Proportions of meta-analyses by Therapeutic Area**

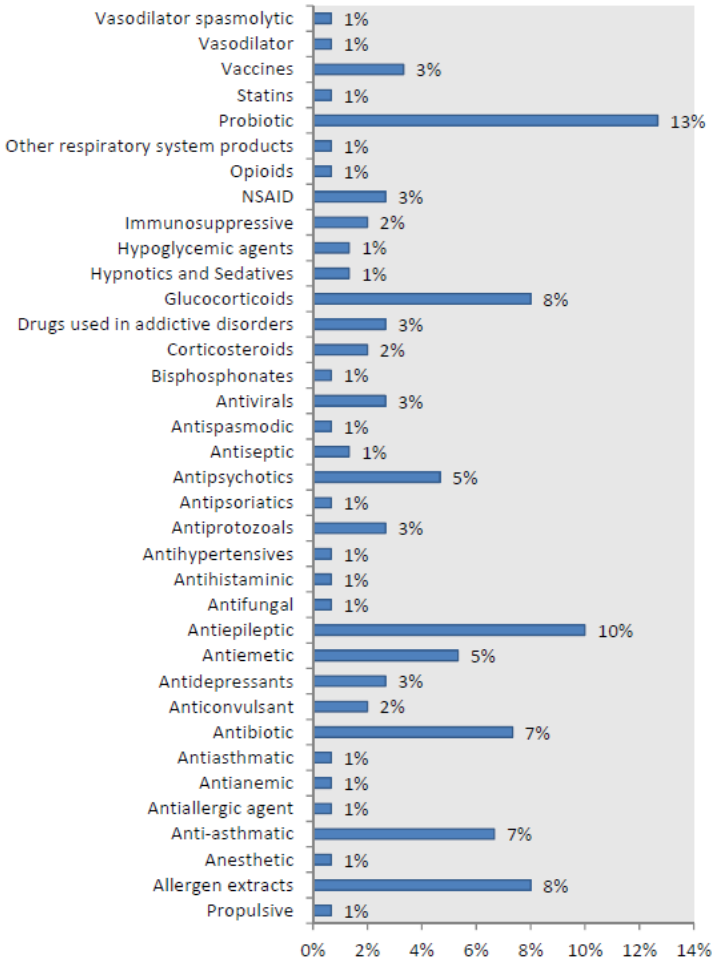



**Figure 7: Proportions of meta-analyses by Pharmacological Categories**

After removal of duplicates, 690 adult (138 030 participants) and 336 pediatric trials (44 239 participants) evaluating 92 different drug interventions were included. More than half of the pediatric trials (192/336) and 50% of the adult trials (343/690) enrolled less than 100 participants. By meta-analyses, the median number of adult trials was 3 with a minimum of 1 and a maximum of 49 trials. The median for pediatric trials was 2 ranging from 1 to 20. The median proportion of pediatric participants out of the total included participants (adults and children) in the meta-analyses was 29% ranging from 3% to 92%.

Concerning quality, all trials were of high quality being randomized double-blinded placebo-controlled trials with a minimum score of 3 on the Jadad scale. For 20% of the reviews (22/111), authors did not report any assessments of the quality. Forty-three percent (49/111) reported quality using the Cochrane quality assessment tool, 5% (5/111) reported in addition the Jadad score and 1% (1/111) only the Jadad score. Authors reported a partial assessment of the quality for 26% of the reviews including a mean of the Jadad score, the overall Jadad score by trials and/or the Cochrane allocation concealment assessment. When the quality assessment was not done or partially done, we checked the quality of the included trials by going back to the original publications.

For pediatric trials, the dose adjustment was recorded. Out of the 150 meta-analyses, 5% (7/111) did not report the dose given to the child and 59% (89/150) reported the dose but no adjustment was done according to the weight or body surface. Only 36% reported a dose adjustment for the pediatric population with one meta-analysis that clearly mentioned that PK studies were done to adjust the dose in adults and children. Regarding the age range of the included pediatric population, 29% (43/150) did not report the age range or mean. Nineteen meta-analyses included neonates, infants and toddlers but along with older children and adolescents. Only one meta-analysis included exclusively children between 9 months and 3 years old evaluating phenobarbitone for treating convulsion due to cerebral malaria.

# Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children

*This article was published as Variance and Dissident with a published commentary by the reviewers. We were invited to answer the commentary.*

ELSEVIER

CrossMark

Journal of Clinical Epidemiology 68 (2015) 1221−1231

Journal of Clinical Epidemiology

REVIEW ARTICLES

# Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children

Perrine Janiaud[a], Audrey Lajoinie[b], Fleur Cour-Andlauer[b], Catherine Cornu[a,b,c], Pierre Cochat[a,d], Michel Cucherat[c], François Gueyffier[a,b], Behrouz Kassai[a,b,c,*]

[a]*UMR 5558 CRNS Lyon, University of Lyon 1, France*
[b]*Clinical Investigation Center, EPICIME, INSERM CIC 1407/UMR 5558 CNRS, Bron, France*
[c]*Department of Clinical Pharmacology, Hospices Civils de Lyon, Lyon, France*
[d]*Department of Pediatric Nephrology, Hopital Femme Mere Enfant, Lyon, France*

Accepted 29 June 2015; Published online 9 July 2015

**Abstract**

**Objective:** Our main objective was to see whether the therapeutic benefit observed in placebo controlled randomized controlled trials (RCTs) is different between adults and children.

**Study Design and Setting:** We searched three electronic databases for meta-analyses that included double-blind, placebo-controlled RCTs with separate results for adults and children. The selected reviews were classified according to disease and drug used. The heterogeneity of treatment response between adults and children was measured using ratio of odds ratios (RORs).

**Results:** We selected 89 meta-analyses and calculated RORs for 124 drugs. Heterogeneity in the direction of the treatment effect was observed in one drug and heterogeneity in the quantity of the treatment effect for 13 drugs, indicating significantly different treatment effect in adults when compared with children. RORs were not significantly different from 1 for 110 drugs. For 36 of these drugs, the treatment effect was confirmed in both populations.

**Conclusion:** We found different treatment benefits estimated by clinical trials performed in adults compared with those performed in children for 14 of 124 drugs. Data on dose adjustment and child age groups from RCTs were not adequately reported to investigate their influence on the treatment benefit dissimilarities. © 2015 Elsevier Inc. All rights reserved.

*Keywords:* Meta-epidemiological study; Extrapolation; Treatment benefit; Pediatrics; Adults; Data reporting

## 1. Introduction

It has been widely recognized that children cannot be provided with safe and efficacious drugs compared with those available for adults without involving them in clinical trials. EU pediatric regulations (Regulation [EC] 1901/2006) now require that clinical trials in minors be planned and conducted for all new products [1]. The main objectives of the pediatric European regulation were to "achieve high-quality ethical pediatric clinical research, increase availability of authorized medicines that are appropriate for children, and produce better information on medicines" [2]. Since 2008, nearly 500 pediatric investigation plans have been approved by the European Medicines Agency, but few of them have been completed [3]. Therefore, many drugs used to treat children in hospitals are either not licensed for use in children or are prescribed outside the terms of their product license (off-label prescribing) because of the lack of clinical trials in this population [4−6]. This may be explained by a lack of knowledge on drug evaluation methodology, the need for large multicenter international trials to evaluate the effectiveness of medicines in children suffering from rare diseases, ethical concerns on treatment randomization, the use of placebos, time consuming or invasive explorations, difficulties for recruiting participants because parents are reluctant to allow their children to participate, and insufficient funding due to the high cost of drug development for a limited market [7,8].

Consequently, care givers are left with the choice to either deprive children from potentially innovative therapies or to prescribe potentially ineffective or harmful drugs.

Conflicts of interest: P.J. is currently receiving a salary from GlaxoSmithKline, France, for her 3 years Ph.D. at the UMR 5558 CNRS. The remaining authors have no conflicts of interest.

* Corresponding author. Hospices Civils de Lyon, Groupement hospitalier Est, Bâtiment Les Tilleuls, 59 boulevard Pinel, 69003 Lyon, France. Tel.: +33(0)4 27 85 77 32; fax: +33(0)4 72 35 73 64.

*E-mail address*: behrouz.kassai-koupai@chu-lyon.fr (B. Kassai).

http://dx.doi.org/10.1016/j.jclinepi.2015.06.021
0895-4356/© 2015 Elsevier Inc. All rights reserved.

**What is new?**

**Key findings**

- Extrapolation of the therapeutic benefit from adults to children is not misleading in some cases, but differences in the direction and amount of the treatment benefit are not uncommon.

**What this adds to what was known?**

- This work emphasizes the importance of reporting data separately for each age groups, and the need to consider all available evidence in adults and children before the extrapolation of the treatment benefit is warranted.

**What is the implication and what should change now?**

- Extrapolation of efficacy from adults to children should be based on all available evidence including RCTs.

In most cases, data are extrapolated from adults to children after adjusting the dose for weight or body surface area. Such extrapolation is often inaccurate due to pharmacological and physiological differences between adults and children of different age groups [9,10]. Because of the complexity of drug action mechanisms and organism responses, it is difficult to predict the treatment benefit in children only based on pathophysiological and pharmacological knowledge.

Adults and children may respond differently to drugs. Randomized controlled trials (RCTs) evaluating drugs versus placebo are the best available evidence to appraise the difference on the therapeutic benefit between adults and children. Our main objective was to explore the available evidence from placebo-controlled RCTs included in meta-analyses to see if the benefit in adults could be extrapolated to children for each drug.

## 2. Methods

### 2.1. Literature search

Three electronic databases (PubMed, EMBASE, and the Cochrane Library) were searched for meta-analyses (from 1998 for Cochrane Library and from 1966 for PubMed and from 1947 for EMBASE), with no limitation on diseases or treatments. The last bibliographic search was performed in February 7, 2014. The following search terms were used: (Child or preschool or infant or adolescent) and (adult*) and placebo. For PubMed, we specified the type of study (“meta-analysis”). For EMBASE, we specified the following filters: “human” and “meta-analysis.”

### 2.2. Meta-analyses selection

Meta-analyses were eligible when they included RCTs in adults and RCTs in children that were double-blinded, placebo-controlled and reported separately their results in adults and children. All types of treatments were eligible, except for homeopathic treatments and nondrug interventions. All age ranges were included. The age limit between adults and children, when necessary, was arbitrarily set at 16 years. Adult trials may also include a few adolescents (>12 years). Meta-analyses conducted in adults or in children but evaluating the same drug in the same indication were also included. Once all the inclusion criteria were met, the RCTs from the included meta-analyses were organized according to the active drug used. A review was considered a duplicate when it included the same RCTs. Two authors (P.J. and B.K.) independently reviewed all citation abstracts and excluded irrelevant studies according to predefined exclusion criteria.

### 2.3. Data extraction

The following information was extracted from the meta-analyses and entered into the database: (1) the conception and design of the study (randomization, parallel group, cross-over, and blinding); (2) patient characteristics (adults or children, disease, number of patients in the placebo and treatment arms, and the number of events and no-events in each arm); (3) the drug used (some meta-analyses gave information for more than one drug, when possible data were extracted for each drug studied in the meta-analysis); (4) the outcome; (5) the dose for adults and the dose adjustment for children when available. When a review studied more than one drug, data for children were extracted for each drug, and the relative benefit for each drug was estimated according to the outcome reported in the meta-analysis.

For each included review, trials were grouped by drug and then as pediatric and adult trials according to the cutoff age used in the reviews. The original RCTs were consulted when data were missing in the meta-analysis report. The doses and dose adjustments were compared to the usual recommendation given in the Theriaque database (http://www.theriaque.org). The pharmacokinetic (PK) parameters (volume of distribution, bioavaibility, half-life, time to peak serum, and clearance) were compared between adults and children using available data in the UpToDate database (http://www.uptodate.com).

The main outcome and the treatment benefit (number of events or effect size in each group) were extracted blindly from the original systematic review by three authors (P.J., A.L., and C.C.). Differences were resolved by consensus.

### 2.4. Quality assessment

We reported the quality assessment reported by the authors of the meta-analyses for each included RCT. For

Cochrane meta-analyses, the Cochrane assessment of risk of bias was reported [11]. For other meta-analyses, we focused on the five-point scoring instrument developed by Jadad and Enkin [12]. (Is the trial randomized and double blinded? Are randomization, blinding, and withdrawals described and adequate?)

### 2.5. Outcome

When one primary outcome was defined in both adult and children, we extracted only the primary outcome. When several primary outcomes were reported, we selected the most clinically relevant outcome reported both in adult and children.

### 2.6. Unit-of-analysis error

For cross-over trials, data were extracted as presented in meta-analyses. Either data corresponded to the first period or took into account the correlation between treatment periods.

When different doses were tested versus placebo, to avoid double counting and overrepresentation of placebo groups, and if it was not done by authors, the total number of patients in the placebo group was divided by the number of times it was used.

### 2.7. Statistical methods

For each drug, separate ORs were calculated for adults and children. An OR $<1$ indicates that the treatment has a beneficial effect and an OR $>1$ a deleterious effect. Stata/IC 12 software (StataCorp, College Station, Texas) was then used to calculate and pool odds ratios (ORs) for dichotomous data. A heterogeneity test (Cochrane Q-test) was performed and a $P$-value of $<0.10$ was considered statistically significant. $I^2$ statistic was also used to measure statistical heterogeneity in the population as a percentage. High heterogeneity is usually characterized by an $I^2$ of 75% or more [13].

For continuous data, Stata/IC 12 software was also used to calculate and pool standardized mean differences (SMDs) using Hedges' method. We then converted the all SMDs into ORs using Hasselblad and Hedges's formula: $\ln OR \approx 1.81 \times SMD$ [14].

To compare the treatment effect in adults and children, we calculated the ratio of odds ratio (ROR) which is assimilated to a paired analysis allowing the estimation of the between-study treatment effect variation [15]. The ROR was defined as the OR in adult divided by the OR in children. To evaluate the heterogeneity of the response proportion between children and adults, the ROR and its confidence interval (CI) were calculated by log-transforming the OR. The $P$-value for the ROR was also calculated to test the statistical significance of the heterogeneity between adults and children. An ROR $>1$ indicates that treatment benefit in children is higher than adults and an ROR $<1$ indicates the reverse. Noninferiority limits were established based on nonconclusive RORs. They correspond to a possible difference in effect between adults and children of at least 25% (ROR $\geq 1.25$ or ROR $\leq 0.8$), 50% (ROR $\geq 1.5$ or ROR $\leq 0.6$), or 100% (ROR $\geq 2$ or ROR $\leq 0.5$).

Differences between treatment effects were identified on forest plots from the differences between the magnitude and the directions of effect sizes observed in children compared with adults.

## 3. Results

The initial search of the electronic databases yielded 3,113 reviews (412 in EMBASE, 734 in PubMed, and 1967 in the Cochrane library), in which 414 reviews were duplicates and were discarded. During the first screening of titles and abstracts, we excluded articles that did not meet inclusion criteria (Fig. 1). When we were not sure, the meta-analyses were read in full. Three hundred meta-analyses were excluded because 195 did not report the same outcomes or interventions for both populations, 95 did not have separate data for adults and children, and 10 meta-analyses with duplicates RCTs. Eighty-nine meta-analyses including 992 RCTs, 294 in children and 698 in adults, were eligible for our study [16–104]. Out of the 89 meta-analyses included, 21 gave no report of the Jadad score or of the risk of bias [25,26,28,38,43–46,49,55–58,74,78,81,84,86,91,96,103]; 12 reported only the Jadad score for each RCTs [23,42,82,88,90,98,100] or an overall score [64,68,75,85,99]; 10 reported the Jadad score and the risk of bias [17,19,31,37,67,70,77,95,101,104]; 31 reported a full assessment of the risk of bias [18,20,21,24,27,29,30,32,34–36,39,47,48,53,54,59–61,65,69,71–73,76,79,87,92–94,102]; and 15 only gave the risk of bias for allocation concealment [16,22,33,40,41,50–52,62,63,66,80,83,89,97].

We evaluated 124 drugs in 26 pharmacology categories. The three most covered pharmacology categories were anti-asthmatics 12.9% (16/24) of the drugs among which 43.7% (9/16) were selective beta-2-adrenoreceptor agonists, 37.5% (6/16) glucocorticoids, and 18.7% (3/16) other type of drugs (see Appendix A at www.jclinepi.com for details); antidiarrheal microorganisms (probiotics) 12.1% (15/124) of the drugs; and antiepileptic 10.5% (13/124) of the drugs. Fifteen reviews studied more than one drug. Eighteen drugs were investigated by more than one review. For example, dexamethasone was investigated in six different reviews, two for its antiemetic action [33,57] and four for its anti-inflammatory action [29,54,66,78] (see Appendix A at www.jclinepi.com).

Five meta-analyses included more than 10 pediatric RCTs [27,29,33,45,95]. For 36% (45/124) drugs, authors gave no precision of the age range or mean of the included children. Most pediatric trials excluded infants and newborns, and only 7% (9/129) drugs were evaluated in those age categories. For example, pimecrolimus 1% in the treatment of atopic

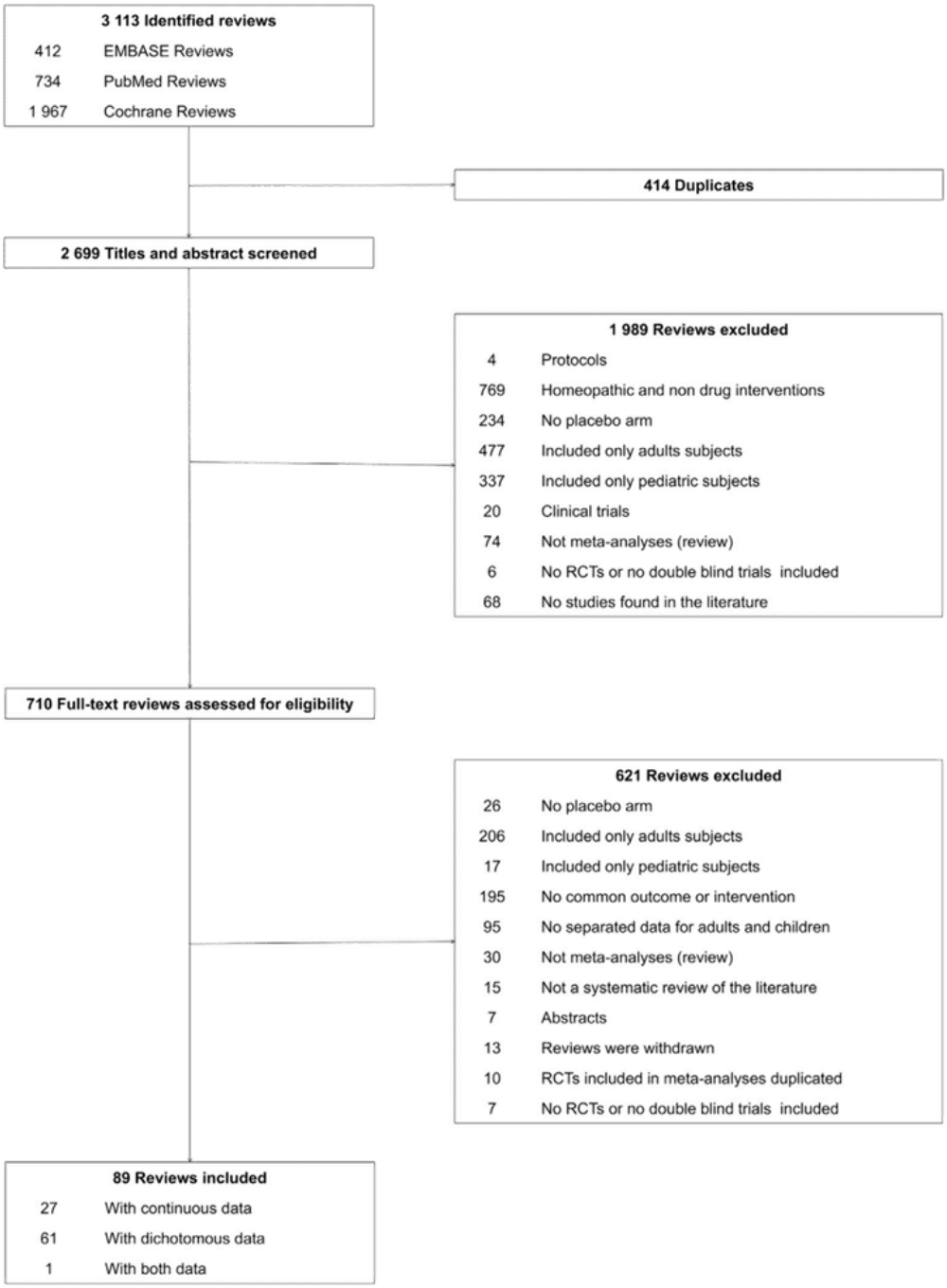



**Fig. 1.** Flowchart of the literature search.

dermatitis (2 months to 16 years old) [23], dexamethasone for treating acute bacterial meningitis (6 weeks to 17 years old) [29], or phenobarbitone for treating cerebral malaria (9 months to 3 years old) [74]. For the dose adjustment according to the weight for children, 57% (71/124) of the drugs were adjusted; 37% (46/124) were not adjusted, and 6% (7/124) no details were provided for the doses administered.

### *3.1. Heterogeneity within adult and pediatric trials*

The pooled OR for trials in adults revealed a significant statistical heterogeneity for 31 drugs, with an $I^2 > 75\%$ for calcipotriol [71], glyceryl trinitrate [76], *Lactobacillus* [64,85], chlorhexidine [92], metformin [26], melatonin [44], fluticasone [18], rybomynyl [28].

In pediatric trials, significant statistical heterogeneity was also detected for 23 drugs with an $I^2 > 75\%$ for salbutamol [27], formoterol [27], budesonide [67], melatonin [99], dexamethasone [66], metronidazole [22], *Saccharomyces* [55], *Lactobacillus* [55], glyceryl trinitrate [76], tacrolimus 0.1% [23], pollen [31], and house dust mite [37,79,103].

### 3.2. Significant relative treatment benefit difference between adults and children

The ROR was significantly different from 1 for 14 drugs [18,27,30,32−34,41,67,90,97,104] (Fig. 2). One drug showed heterogeneity in the direction of the treatment effect. Nonfatal severe adverse events were higher in children taking formoterol [34]. For the other 13 drugs, heterogeneity in the amount of the treatment effect was observed. For five drugs, the treatment benefit was higher in children compared with adults [30,33,90,97]. For nine drugs, the treatment benefit was higher for adults compared with children [18,27,32,34,41,67,104].

The age range of participants in these trials varied from 4 to 19 years. No infants (29 days to 24 months) or newborns (0 to 28 days) were included. For 11 drugs with significant RORs, the doses were not adjusted according to the weight of children [18,27,30,32,34,41,67,90,104]. Children received an adjusted dose for ondansetron (0.10 to 0.15 mg/kg), for dolasetron (1 mg/kg), and for erythropoietin (600 IU/kg) [33,97].

### 3.3. Nonsignificant relative treatment benefit between adults and children

For 110 drugs, RORs were not significantly different from 1. Thirty-two showed a significant benefit in children and adults [23,25−28,32,33,36,38,43,45,55,57,60−62,64,68,71−73,77,80,82,95,96,100], and four showed a significant deleterious effect in children and adults [19,38,44,58]. Twenty-one drugs showed a benefit in adults only [21−23,31,33,37,42,46,48,55,59,63,70,76,79,82,87,101], and 15 only in children [23,24,33,42,51−53,55,69,74,83,85,88,90,98]. Thirty-eight drugs showed no significant benefit both for adults and children [16,17,20,22,24,29,33,35,37,39,40,47−50,54,56,65,66,75,78,81,84,86,89,91−94,98,99,102,103]. Eight of 38 showed a potential benefit in adults but a potential harm in children [16,24,29,33,75,84,89,98,99], and six a potential benefit in children but a potential harm in adults [20,24,37,81,84,86,98] (see Appendix B at www.jclinepi.com, Web only).

Of these 110 drugs, 43 had their doses adjusted according to the weight (see Appendix A at www.jclinepi.com) except for two drugs, dexamethasone for acute bacterial meningitis [29] and trimethoprim/sulfamethoxazole for pneumocystis pneumonia [50], for which the dose was adjusted according to the body surface. For ibuprofen, PK studies determined the dosage [69]. For seven drugs, there were no indications on the doses given. For 60, there were no adjustments according to the weight, but for two drugs, metronidazole for infection after appendicitis (125 mg for 0−3 years old, 250 mg for 3−6 years old, and 500 mg for 7−15 years old) [22] and trimethoprim/sulfamethoxazole for opportunistic infection (240 mg under 5 years old or else 480 mg) [52], doses were given according to the age. When taking into account noninferiority limits for nonstatistically significant RORs, 22 drugs were under the inferiority margin of 25% [17,19,20,23,25,33,35,36,38,42−44,49,55,57,92,102], 27 between 25% and 50% [24−26,29,32,33,38,45,48,51,52,54−56,59−61,70,72−74,77,82,92−94,98,101], 21 between 50% and 100% [21,23,24,28,31,33,39,40,48,63,64,68,71,78,80,82,84,98,103], and 40 above 100% [16,22,23,27,33,37,46,47,50,53,58,62,65,66,69,75,76,79,81−91,95,96,99,100].

## 4. Discussion

The results of systematic reviews assessing 12 therapeutic areas did show heterogeneity in the direction of the treatment effect for formoterol [34] and heterogeneity in the amount of treatment effect for 13 drugs. Pollen used for allergic asthma showed a treatment benefit in adults but a potential harmful effect in children [104], and nicotine patch for smoking abstinence showed a potential benefit in adults but a potential harmful effect in children [41]. The wide CIs of ORs for these two drugs did not allow confirming the heterogeneity in the direction of the treatment effect.

The age range of participants in these trials varied from 4 to 19 years, which indicates that large variations in the treatment benefit may be observed in all age groups. We also explored whether dose adjustment could explain this variation. Surprisingly, no data were available for infants (29 days to 24 months) and newborns (0 to 28 days), and no precision on the doses used was given for five drugs.

For 36 drugs, RORs were not significantly different from 1, and because either the beneficial or the deleterious effects of the treatment were confirmed in both populations, it is reasonable to extrapolate the results observed in adults to children. For example, lamotrigine showed the same benefit on seizure in three reviews [25,80,82], or melatonin used to reduce sleep latency [44] showed no benefit both in adults and children.

For 38 drugs, RORs were not significantly different from 1, and they were inconclusive in adults and children. Twenty-four of 38 had their ORs in adult and children in the same direction. For 20 of them, their pooled ORs were inconclusive indicating the lack of power and the need to conduct more trials [22,33,35,39,40,47,49,50,56,65,66,75,78,91−94,102,103]. For example, ketorolac [84], glycopyrrolate [33], and nitazoxanide [16] included less than 50 patients. In contrast, for dexamethasone for treating sore throat [54], co-trimoxazole for pneumocystis pneumonia

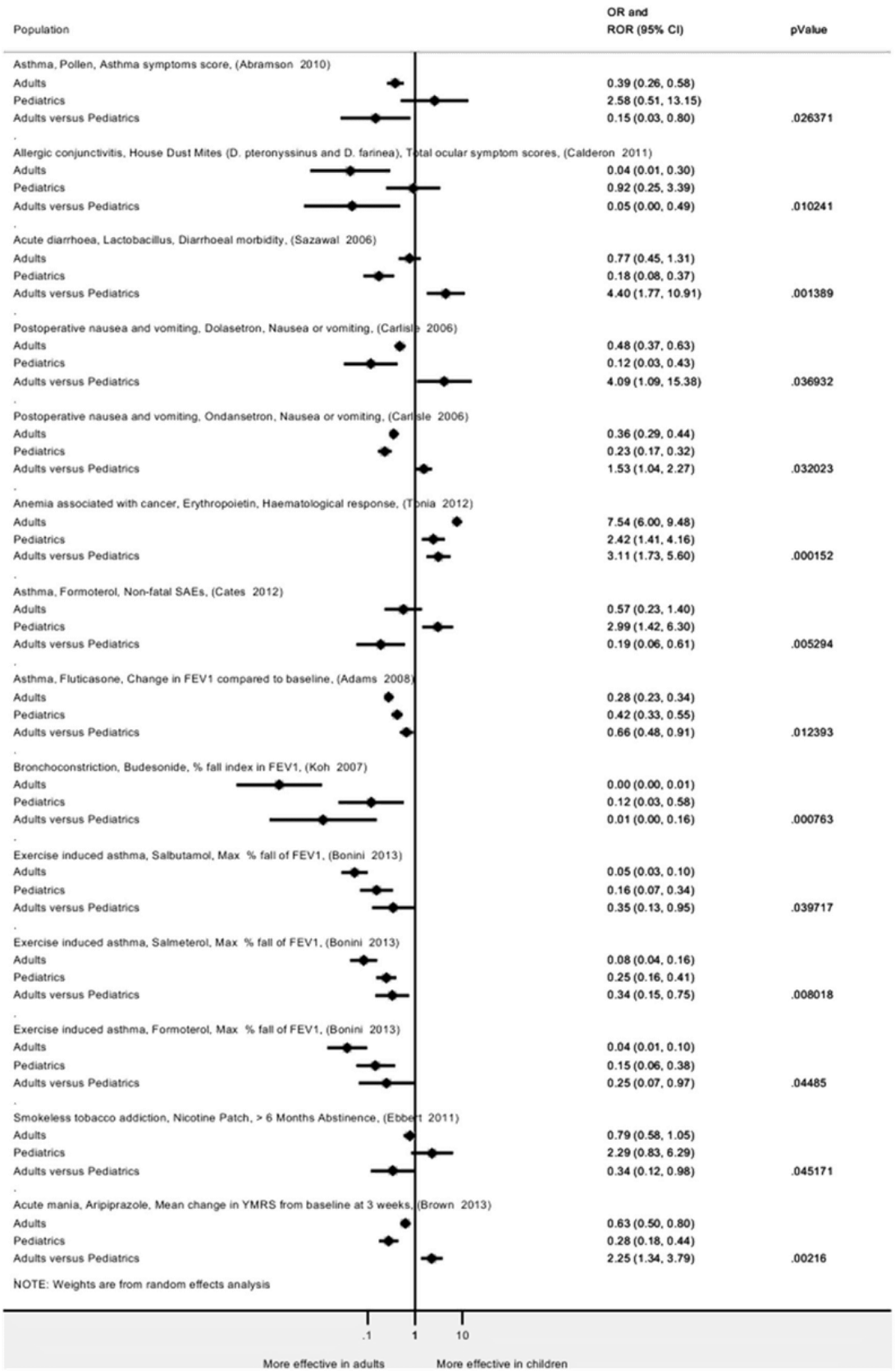



**Fig. 2.** Forest plot of statistically significant RORs with ORs for adults and children: An ROR >1 indicates that treatment benefit in children is higher than adults and an ROR <1 indicates the reverse. An OR <1 indicates a beneficial effect of the treatment and an OR >1 the reverse. OR, odds ratio; ROR, ratio of odds ratio; *P*-value, *P* heterogeneity of ROR; SAEs, serious adverse events; FEV1, forced expository volume in 1 second; YMRS, Young Mania Rating Scale.

[50], *Saccharomyces* for clostridium difficile-associated diarrhea [48], and budesonide for asthma [17], the pooled effect sizes of adults and children studies were statistically significant confirming the treatment benefit. Dose adjustment according to weight was clearly stated for 19 drugs. For the other 19 drugs, the dose adjustment was unclear. For instance for dexamethasone, the dose given to adults according to the usual indication was (20 to 40 mg/day), but children were given 0.6 mg/kg/day while the recommanded dose is 0.1 mg/kg/day [29,54,66,78].

For 15 drugs, RORs were not significantly different from 1, but the results were only significant for children. Twelve showed a benefit in children with a potential benefit in adults [23,24,33,42,51−53,55,85,88,90,98], whereas two showed a potential harmful effect for adults [69,85]. For three drugs, a harmful effect was shown for children with a potential harmful effect in adults [14,83,85], such as for phenobarbitone for treating convulsion in malaria which included infants from 9 months to 3 years old [74]. The small number of adult participants may explain the nonsignificant results of four meta-analyses. Only one systematic review, which was conducted on ibuprofen, had a PK study done to adjust the dose for adults and children [69].

For 21 drugs, RORs were not significantly different from 1, but the results were only statistically significant in adults. Nineteen showed potential benefit in children and a confirmed benefit in adults. For an anti-enterotoxigenic *Escherichia coli* vaccine, the treatment had a significant harmful effect in adults and a potential harmful effect in children [21]. For glyceryl trinitrate ointment for treating anal fissure, the treatment had a beneficial effect on the recurrence and persistence of fissure in adults (OR 95% CI: 0.49 [0.24−0.99]) but a potential deleterious effect in children (OR 95% CI: 1.03 [0.11−9.91]) [76]. The absence of statistical significance did not guarantee the absence of a difference between adults and children. In the case of glyceryl trinitrate ointment, there was a potential treatment effect difference of over 100% (ROR $\geq$ 0.5).

The nonsignificant results reported in children RCTs may be explained by the small number of participants and the lack of adequate dose adjustment. In seven meta-analyses, ORs observed in pediatric trials were quite close to those observed in adults with an upper margin of the CI close to 1 [23,42,63,70,82,87,101]. For example, for topiramate, 86 children were included (OR 95% CI: 0.39 [0.15−1.02]) versus 1,226 adults (OR 95% CI: 0.22 [0.16−0.31]) [63]. The lack of power due to the number of included children could explain the inconclusive ORs. In this case, we had a potential difference of treatment effect of 25 to 50% (ROR $\leq$ 0.6). For metronidazole in the treatment of complicated appendicitis, because there were more children (131) enrolled than adults [75], and assuming the same potential benefit, the dose adjustment (20 mg/kg in children vs. 500 mg to 1 g in adults) and PK parameters may explain the nonsignificant results [22]. For only eight of these drugs, PK data were available. For metoclopramide, the elimination half-life was similar between neonates and adults when adjusted according to weight (5.4 hours in children vs. 5−6 hours in adults). For bupropion, the half-life in children >11 years old was quite similar to adults (16.5 ± 3.9 hours vs. 20 ± 5 hours), at equivalent dose. For metronidazole, the half-life was similar between children, adolescent, and adults (6−10 hours vs. ~8 hours), but doubled in infants (~22.5 hours). For dexamethasone, used as an antiemetic, its half-life was longer in infants (9.3 hours) compared with children (4.3 hours) and with adults (3 hours). Dexamethasone had a beneficial effect for adult and a potential beneficial effect in children for postoperative vomiting [57] but a deleterious effect for preventing death in meningitis [29]. The same type of drugs can be used in different indication, and their effect does not only depend on the patient's PK profile but also on the disease severity. For gabapentin, we found a 20−80%, and for topiramate, a 27−170% increase in the treatment effect that could be explained by PK variabilities [105]. Topiramate and six other drugs that we studied were on the European Medicines Agency (EMA) priority list: fluoxetine, granisetron, clonidine ibuprofen azithromycin, and montelukast [106].

In some meta-analyses, infants and newborns were excluded or the age groups in the pediatric population were not reported. For example, ondansetron for postoperative nausea and vomiting was studied by three different reviews, but none reported the age range of participants [33,45,46]. In the original articles, the pediatric population was reported ranging from 1 to 18 years old. Available data in reviews did not allow us to fully explore the cause of the differences in the treatment response between adults and children and the influence of factors such as age range and dose adjustment on treatment effect and on the PKs and pharmacodynamics profile of the drug.

For example, the clearance of ondansetron in children was found to be higher compared with that in adults but also 20% higher for children aged 3−7 years old compared with 7−12 years old. This can be explained by the large liver compared with the total body weight and an increased metabolism in children [107]. Such example suggests that within the pediatric population, differences in treatment effects can exist. It would be advisable, to better understand the possibility of extrapolating data, to report pediatric clinical data according to the ICH's age group. In our review, only one meta-analysis evaluating ibuprofen for treating asthma did a subgroup analysis according to age groups in the pediatric population [69].

We only explored systematic reviews because they report high-quality, standardized, and user-friendly evidence. However, our results are limited to the studies for which systematic reviews are available and to the reviews that included adults and children RCTs. Our search strategy was designed to identify meta-analyses on both children and adults, evaluating the same drug. Ninety-five meta-analyses studied drugs in adults and children but did not

provide separate information on adults and children. As a result, we only explored the available evidence from 89 of 389 meta-analyses involving both adults and children. It is also likely that we were not able to capture medical interventions for conditions affecting only children.

A recent overview of reviews has investigated the comparative effectiveness of medical interventions of adults and children. They focused on Cochrane reviews with adult and children data without restriction of the comparator, interventions, and blinding [108]. Our conclusions are similar to theirs, but our review has the advantage to cover the entire literature and to focus only on high quality trials.

Our study is restricted to the analyses of trial summary data which may not show important individual patient factors influencing responses. The identification of these factors would be difficult because there is a lack of standardized extraction of those characteristics in the original report of pediatric trials. Our study is also limited by the inadequate standard information on study characteristics such as the quality of RCTs included in systematic reviews or the Jadad score. Summary data from RCTs allow to follow EMA extrapolation framework for the similarity of disease and of clinical endpoint but not for the similarity of drug disposition and effect (PK/PD) [109].

To extrapolate adults' results to children on the basis of the similarity of the clinical benefit, we recommend a separate report of the results for adults and children, including the age group and dose adjustment method, in all studies and meta-analyses. The rational on the dose given to children, such as previous PK or pharmacodynamics studies, should also be reported. Hopefully, the standardized collection and reporting of pediatric clinical trials using the European database created by Article 11 of the Directive 2001/20/EC [110] would avoid unnecessary repetition of trials and a rational approach for extrapolating data from adults to children on the basis of the best available evidence.

A recent report on the experience acquired since the implementation of the pediatric regulation in 2007 shows that this regulatory framework does not guarantee that drugs will swiftly become available in all pediatric indications [3]. Only 29.6% (294/992) of our RCTs included children and they were commonly underpowered. Our results also show the potential influence of PK and PD and the need to better report on the rationale of dose adjustments in RCTs. Modeling approaches were seldom used and reported to define the appropriate dose for RCTs [111].

## 5. Conclusion

The extrapolation of the therapeutic benefit from adults to children is not misleading in some cases. However, heterogeneity in the direction and the amount of the treatment benefit were observed in 14 of 124 drugs assessed by our study. Extrapolation of the treatment effects from adults to children can be delicate and depends on the information reported in publications.

Data on dose adjustment and child age groups from RCTs should be collected, analyzed, and reported to investigate extrapolation from adults to children or before designing new trials. It would also allow us to fully explore possible sources of clinical and statistical heterogeneity, enabling the prediction of situations where there may be differences between adults and children.

## Acknowledgments

The authors thank Hanane Gheit for helping with the literature search and data extraction and Kent Neal for helping with the editing of the article.

Authors' contribution: B.K. and M.C. were responsible for the study concept and design. F.C.-A., B.K., A.L., and P.J. were involved in the literature and data extraction. M.C., B.K., and P.J. were responsible for the data analysis and interpretation. C.C., B.K., and P.J. wrote the article. C.C., P.C., and F.G. critically revised the article. K.N., B.K., and P.J. were responsible for the editing of the article. B.K. supervised the study and is the guarantor.

The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jclinepi.2015.06.021.

## References

[1] Pinxten W, Dierickx K, Nys H. Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials. Eur J Pediatr 2009;168:1225−34.

[2] EMA EMA. 5-year Report to the European Commission. General report on the experience acquired as a result of the application of the paediatric regulation 2012.

[3] European C. General report on experience acquired as a result of the application of the paediatric regulation (Article 50(2) of regulation (EC) No 1901/2006) 2012:Ref Ares(2012)1079926.

[4] Cohen E, Uleryk E, Jasuja M, Parkin PC. An absence of pediatric randomized controlled trials in general medical journals, 1985-2004. J Clin Epidemiol 2007;60:118−23.

[5] Conroy S, McIntyre J, Choonara I, Stephenson T. Drug trials in children: problems and the way forward. Br J Clin Pharmacol 2000;49:93−7.

[6] Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005;164:552−8.

[7] Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. Lancet 2004;364:803−11.

[8] Thomson D, Hartling L, Cohen E, Vandermeer B, Tjosvold L, Klassen TP. Controlled trials in children: quantity, methodological quality and descriptive characteristics of pediatric controlled trials published 1948-2006. PLoS One 2010;5:e13106.

[9] Sammons H, Conroy S. How do we ensure safe prescribing for children? Arch Dis Child 2008;93:98−9.
[10] Shirkey HC. Drugs dosage for infants and children. JAMA 1965; 193:443−6.
[11] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org. Accessed November 10, 2014.
[12] Jadad AR, Enkin M. Randomized controlled trials: questions, answers and musings. USA, UK and Australia: Blackwell; 2008.
[13] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539−58.
[14] Anzures-Cabrera J, Sarpatwari A, Higgins JP. Expressing findings from meta-analyses of continuous outcomes in terms of risks. Stat Med 2011;30:2967−85.
[15] Suzuki S, Moro-oka T, Choudhry NK. The conditional relative odds ratio provided less biased results for comparing diagnostic test accuracy in meta-analyses. J Clin Epidemiol 2004;57:461−9.
[16] Abubakar Ibrahim I, Aliyu Sani H, Arumugam C, Hunter Paul R, Usman N. Prevention and treatment of cryptosporidiosis in immunocompromised patients. Cochrane Database Syst Rev 2007; CD004932.
[17] Adams Nick P, Bestall Janine C, Jones P. Budesonide versus placebo for chronic asthma in children and adults. Cochrane Database Syst Rev 1999;CD002738.
[18] Adams Nick P, Bestall Janine C, Lasserson Toby J, Jones P, Cates Christopher J. Fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database Syst Rev 2008;CD003135.
[19] Adams Nick P, Bestall Janine C, Malouf R, Lasserson Toby J, Jones P. Beclomethasone versus placebo for chronic asthma. Cochrane Database Syst Rev 2005;CD002738.
[20] Afshari A, Brok J, Møller Ann M, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. Cochrane Database Syst Rev 2010; CD002787.
[21] Ahmed T, Bhuiyan Taufiqur R, Zaman K, Sinclair D, Qadri F. Vaccines for preventing enterotoxigenic Escherichia coli (ETEC) diarrhoea. Cochrane Database Syst Rev 2013;CD009029.
[22] Andersen Betina R, Kallehave Finn L, Andersen Henning K. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. Cochrane Database Syst Rev 2005;CD001439.
[23] Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. BMJ 2005;330:516.
[24] Barbui C, Cipriani A, Patel V, Ayuso-Mateos JL, van Ommeren M. Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis. Br J Psychiatry 2011; 198(sup 1):11−6.
[25] Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. Epilepsia 2010;51:7−26.
[26] Bjorkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. J Psychopharmacol 2011; 25:299−305.
[27] Bonini M, Di Mambro C, Calderon Moises A, Compalati E, Schünemann H, Durham S, et al. Beta2-agonists for exercise-induced asthma. Cochrane Database Syst Rev 2013;CD003564.
[28] Boyle P, Bellanti JA, Robertson C. Meta-analysis of published clinical trials of a ribosomal vaccine (Ribomunyl (registered trademark) 1) in prevention of respiratory infections. BioDrugs 2000;14: 389−408.
[29] Brouwer Matthijs C, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2013;CD004405.
[30] Brown R, Taylor Matthew J, Geddes J. Aripiprazole alone or in combination for acute mania. Cochrane Database Syst Rev 2013; CD005000.
[31] Calamita Z, Saconato H, Pelá AB, Atallah ÁN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006;61:1162−72.
[32] Calderon Moises A, Penagos M, Sheikh A, Canonica Giorgio W, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. Cochrane Database Syst Rev 2011;CD007685.
[33] Carlisle J, Stevenson Carl A. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev 2006; CD004125.
[34] Cates Christopher J, Cates Matthew J. Regular treatment with formoterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev 2012;CD006923.
[35] Cates Christopher J, Rowe Brian H. Vaccines for preventing influenza in people with asthma. Cochrane Database Syst Rev 2013; CD000364.
[36] Compalati E, Baena-Cagnani R, Penagos M, Badellino H, Braido F, Gomez RM, et al. Systematic review on the efficacy of fexofenadine in seasonal allergic rhinitis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. Int Arch Allergy Immunol 2011;156:1−15.
[37] Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. Allergy 2009;64: 1570−9.
[38] Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar Disord 2010;12:116−41.
[39] Ducharme Francine M, Ni Chroinin M, Greenstone I, Lasserson Toby J. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database Syst Rev 2010;CD005535.
[40] Dunlop R, Bennett Kyle CLB. Pain management for sickle cell disease in children and adults. Cochrane Database Syst Rev 2006; CD003350.
[41] Ebbert J, Montori Victor M, Erwin Patricia J, Stead Lindsay F. Interventions for smokeless tobacco use cessation. Cochrane Database Syst Rev 2011;CD004306.
[42] Falagas ME, Koletsi PK, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Rello J. Effectiveness and safety of neuraminidase inhibitors in reducing influenza complications: a meta-analysis of randomized controlled trials. J Antimicrob Chemother 2010;65: 1330−46.
[43] Fang Y, Wu X, Xu L, Tang X, Wang J, Zhu G, et al. Randomized-controlled trials of levetiracetam as an adjunctive therapy in epilepsy of multiple seizure types. J Clin Neurosci 2014;21:55−62.
[44] Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One 2013;8: e63773.
[45] Figueredo ED, Canosa LG. Ondansetron in the prophylaxis of postoperative vomiting: a meta-analysis. J Clin Anesth 1998;10: 211−21.
[46] Frost F, Dailler F, Duflo F. [Ondansetron: a meta-analysis on its efficacy to prevent postoperative nausea and vomiting after craniotomy in adults and children]. Ann Fr Anesth Reanim 2010;29: 19−24.
[47] Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie Theresa A, van de Wetering Marianne D, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev 2012;CD004386.
[48] Goldenberg Joshua Z, Ma Stephanie SY, Saxton Jane D, Martzen Mark R, Vandvik Per O, Thorlund K, et al. Probiotics for the

prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev 2013;CD006095.
[49] Graves Patricia M, Gelband H. Vaccines for preventing malaria (blood-stage). Cochrane Database Syst Rev 2006;CD006199.
[50] Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev 2007;CD005590.
[51] Grimwade K, Swingler George H. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. Cochrane Database Syst Rev 2003;CD003108.
[52] Grimwade K, Swingler George H. Cotrimoxazole prophylaxis for opportunistic infections in children with HIV infection. Cochrane Database Syst Rev 2006;CD003508.
[53] Hao Q, Lu Z, Dong Bi R, Huang Chang Q, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev 2011;CD006895.
[54] Hayward G, Thompson Matthew J, Perera R, Glasziou Paul P, Del Mar Chris B, Heneghan Carl J. Corticosteroids as standalone or add-on treatment for sore throat. Cochrane Database Syst Rev 2012;CD008268.
[55] Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA 2012;307:1959−69.
[56] Henzi I, Walder B, Tramer MR. Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies. Br J Anaesth 1999; 83:761−71.
[57] Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000;90:186−94.
[58] Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. J Psychopharmacol 2007;21:864−72.
[59] Hughes John R, Stead Lindsay F, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2014;CD000031.
[60] Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer Ghada A, Al-Ansary Lubna A, Ferroni E. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2010;CD001269.
[61] Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev 2012;CD004879.
[62] Jesner Ora S, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database Syst Rev 2007;CD005040.
[63] Jette N, Hemming K, Hutton Jane L, Marson Anthony G. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database Syst Rev 2008;CD001417.
[64] Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy 2010;30:119−26.
[65] Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database Syst Rev 2013;CD000247.
[66] Khemani Robinder G, Randolph A, Markovitz B. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. Cochrane Database Syst Rev 2009;CD001000.
[67] Koh Mariko S, Tee A, Lasserson Toby J, Irving Louis B. Inhaled corticosteroids compared to placebo for prevention of exercise induced bronchoconstriction. Cochrane Database Syst Rev 2007; CD002739.
[68] Kranke P, Morin AM, Roewer N, Eberhart LH. Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. Acta Anaesthesiol Scand 2002;46: 238−44.
[69] Lands Larry C, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for lung disease in cystic fibrosis. Cochrane Database Syst Rev 2013;CD001505.
[70] Manning P, Gibson Peter G, Lasserson Toby J. Ciclesonide versus placebo for chronic asthma in adults and children. Cochrane Database Syst Rev 2008;CD006217.
[71] Mason Anne R, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. Cochrane Database Syst Rev 2013;CD005028.
[72] Mbizvo Gashirai K, Dixon P, Hutton Jane L, Marson Anthony G. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. Cochrane Database Syst Rev 2012;CD001901.
[73] Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess 2013;17. vi, xi-xiv, 1−322.
[74] Meremikwu Martin M, Marson Anthony G. Routine anticonvulsants for treating cerebral malaria. Cochrane Database Syst Rev 2002; CD002152.
[75] Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emerg Med J 2007;24:823−30.
[76] Nelson Richard L, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. Cochrane Database Syst Rev 2012;CD003431.
[77] Normansell R, Walker S, Milan Stephen J, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014;CD003559.
[78] Plante J, Turgeon AF, Zarychanski R, Lauzier F, Vigneault L, Moore L, et al. Effect of systemic steroids on post-tonsillectomy bleeding and reinterventions: systematic review and meta-analysis of randomised controlled trials. BMJ 2012;345:e5389.
[79] Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). Allergy 2011;66:740−52.
[80] Ramaratnam S, Marson Anthony G, Baker Gus A. Lamotrigine add-on for drug-resistant partial epilepsy. Cochrane Database Syst Rev 2001;CD001909.
[81] Ranji SR, Goldman LE, Simel DL, Shojania KG. Do opiates affect the clinical evaluation of patients with acute abdominal pain? JAMA 2006;296:1764−74.
[82] Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med 2008;5:e166.
[83] Richeldi L, Ferrara G, Fabbri L, Lasserson Toby J, Gibson Peter G. Macrolides for chronic asthma. Cochrane Database Syst Rev 2005; CD002997.
[84] Riggin L, Ramakrishna J, Sommer DD, Koren G. A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of non steroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy. Clin Otolaryngol 2013;38:115−29.
[85] Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One 2012;7:e34938.
[86] Robenshtok E, Gafter-Gvili A, Goldberg E, Weinberger M, Yeshurun M, Leibovici L, et al. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. J Clin Oncol 2007;25: 5471−89.
[87] Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database Syst Rev 2010;CD004332.
[88] Rowe Brian H, Bretzlaff J, Bourdon C, Bota G, Blitz S, Camargo Carlos A. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database Syst Rev 2000;CD001490.
[89] Rowe Brian H, Spooner C, Ducharme F, Bretzlaff J, Bota G. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev 2001;CD002178.
[90] Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis

of masked, randomised, placebo-controlled trials. Lancet Infect Dis 2006;6:374−82.
[91] Shen J, Ran HZ, Yin MH, Zhou TX, Xiao DS. Meta-analysis: the effect and adverse events of Lactobacilli versus placebo in maintenance therapy for Crohn disease. Intern Med J 2009;39: 103−9.
[92] Shi Z, Xie H, Wang P, Zhang Q, Wu Y, Chen E, et al. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. Cochrane Database Syst Rev [Internet] 2013;CD008367.
[93] Singer AJ, Thode HC Jr. Systemic antibiotics after incision and drainage of simple abscesses: a meta-analysis. Emerg Med J 2014; 31:576−8.
[94] Southern Kevin W, Barker Pierre M, Solis-Moya A, Patel L. Macrolide antibiotics for cystic fibrosis. Cochrane Database Syst Rev 2012;CD002203.
[95] Spooner C, Saunders LD, Rowe Brian H. Nedocromil sodium for preventing exercise-induced bronchoconstriction. Cochrane Database Syst Rev 2002;CD001183.
[96] Szajewska H, Mrukowicz J. Meta-analysis: non-pathogenic yeast Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea. Aliment Pharmacol Ther 2005;22:365−72.
[97] Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev 2012;CD003407.
[98] Tsapakis EM, Soldani F, Tondo L, Baldessarini RJ. Efficacy of antidepressants in juvenile depression: meta-analysis. Br J Psychiatry 2008;193:10−7.
[99] van Geijlswijk IM, Korzilius HP, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. Sleep 2010;33:1605−14.
[100] Villar Juan C, Villar Luis A, Marin-Neto Jose A, Ebrahim S, Yusuf S. Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection. Cochrane Database Syst Rev 2002;CD003463.
[101] Walters EH, Gibson Peter G, Lasserson Toby J, Walters Julia AE. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database Syst Rev 2007;CD001385.
[102] Watts K, Chavasse Richard JP. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. Cochrane Database Syst Rev 2012;CD006100.
[103] Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy 2005;60:4−12.
[104] Abramson Michael J, Puy Robert M, Weiner John M. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev 2010;CD001186.
[105] Johannessen Landmark C, Baftiu A, Tysse I, Valso B, Larsson PG, Rytter E, et al. Pharmacokinetic variability of four newer antiepileptic drugs, lamotrigine, levetiracetam, oxcarbazepine, and topiramate: a comparison of the impact of age and comedication. Ther Drug Monit 2012;34:440−5.
[106] EMA. Revised provisional priority list for studies into off-patent paediatric medicinal products EMA/98717/2012. Human Medicines Development and Evaluation; 2013: Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf. Accessed November 10, 2014.
[107] de Alwis DP, Aarons L, Palmer JL. Population pharmacokinetics of ondansetron: a covariate analysis. Br J Clin Pharmacol 1998;46:117−25.
[108] Contopoulos-Ioannidis DG, Baltogianni MS, Ioannidis JP. Comparative effectiveness of medical interventions in adults versus children. J Pediatr 2010;157:322−330.e17.
[109] EMA. Concept paper on extrapolation of efficacy and safety in medicine development EMA/129698/2012. Human Medicines Development and Evaluation; 2012: Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142358.pdf. Accessed November 10, 2014.
[110] Council EPa. Regulation (Ec) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 2006.
[111] Manolis E, Osman Tariq E, Herold R, Koenig F, Tomasi P, Vamvakas S, et al. Role of modeling and simulation in pediatric investigation plans. Pediatr Anesth 2011;21:214−21.

ELSEVIER

Journal of Clinical Epidemiology ■ (2015) ■

Journal of Clinical Epidemiology

VARIANCE AND DISSENT

# Extrapolation will never replace randomized clinical trials

Perrine Janiaud[a,*], Catherine Cornu[a,b,c], Behrouz Kassai[a,b,c]

[a]*UMR 5558 CRNS Lyon, University of Lyon 1, France*
[b]*Clinical Investigation Center, EPICIME, INSERM CIC 1407/UMR 5558 CNRS, Bron, France*
[c]*Department of Clinical Pharmacology, Hospices Civils de Lyon, Lyon, France*

Accepted 17 June 2015; Published online xxxx

**Response to commentary:**

We thank Oostenbring and de Wildt [1] for their comment. In our article [2], we do not challenge the current paradigm that "drugs need to be studied in children." We rather suggest that the extrapolation framework could be improved both for drug development and for routine practice by using all available evidence. Currently, European Medicines Agency and Food and Drug Administration guidelines suggest that when there are robust pharmacokinetic (PK) and pharmacodynamic (PD) data and the disease progression is similar between adults and children, a full extrapolation can be conducted after conducting a safety study and/or a PK study [3,4]. When there are uncertainties on PK−PD, data on efficacy are required and randomized controlled trials (RCTs) become mandatory. The extrapolation process is not limited to drug development because pediatricians routinely extrapolate results of adult studies for treating children without a clear framework. Our contribution shows that we lack data on the dose−effect relationship for different age groups and that the similarities between efficacies of medicines evaluated both in adults and children are commonly unclear, sometimes conflicting or differ quantitatively. With only 36 of 74 treatments effective in both populations, our study illustrates that even for the same disease and same medicines, the clinical efficacy from adults to children cannot be extrapolated systematically.

We believe that the extrapolation process should include at least one RCT in children with a prior mandatory evaluation of all available evidence in adults and children. Fig. 1 demonstrates for ondansetron in preventing postoperative nausea and vomiting, how adult trials could be used before launching studies in children. We constructed an effect model (green line) which is simply the regression line relating the risk in the treated and in the untreated adult population based on the results of RCTs [5]. Such a model allows the prediction of the potential treatment benefit in children before designing a new trial. It improves the calibration of pediatric trial according to the baseline risk, the identification of children who would potentially benefit

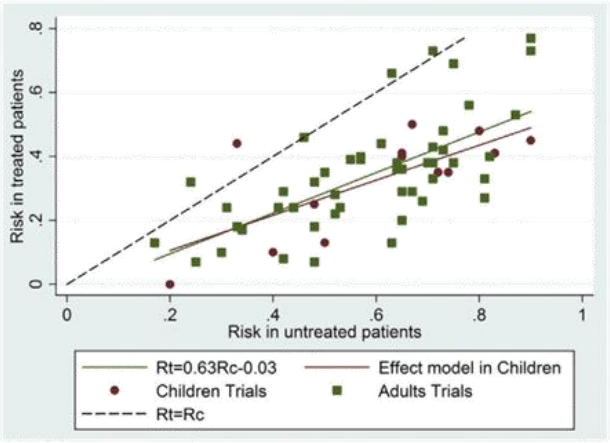



**Fig. 1.** The effect model for ondansetron to prevent postoperative nausea and vomiting using adults randomized controlled trials (RCTs) is illustrated by the green line. Rc corresponds to the risk of presenting the event in the untreated patients or the control group and Rt the risk in the treated patients. The dashed line Rt = Rc is the no effect line, when Rt < Rc, below the dashed line, treatment is effective, and when Rt > Rc, above the dashed line, treatment is harmful. The full line is a linear regression that fits the data in adults. The effect model shows a beneficial effect for ondansetron in the prevention of postoperative nausea and vomiting in adults. The resulting equation of the adult RCTs (green squares) (Rt = 0.63Rc-0.03) can then be used to predict the efficacy in children RCTs (red circles) using the baseline risk. The children trials have also been modeled (red line) on the plot confirming that the effect model in adults gives a good prediction of the treatment benefit in children. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Conflict of interest: None.

Funding: P.J. is currently receiving a salary from GlaxoSmithKline, France, for her 3-year PhD at the UMR 5558 CNRS. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

* Corresponding author. Service de Pharmacologie Clinique et d'Essais Thérapeutiques, UMR 5558 CRNS Lyon, Faculté RTH Laennec, 8 Rue Guillaume Paradin, BP8071, Lyon 69376 cedex 08, France. Tel: +33(0)4 78 78 57 54.

*E-mail address*: perrine.janiaud@etu.univ-lyon1.fr (P. Janiaud).

http://dx.doi.org/10.1016/j.jclinepi.2015.06.019
0895-4356/© 2015 Elsevier Inc. All rights reserved.

more from the treatment, and importantly avoids unnecessary trials in children. In this example, 27 trials have been performed in children! Nineteen were performed after 1995 including 1,662 children, when the treatment benefit has been definitely shown.

Finally, our study shows that the lack of standardized reports limits the feasibility of and the access to a comprehensive synthesis of all available evidence for guiding drug development and clinical practice [6,7].

## References

[1] Oostenbrink R, de Wildt SN. Drug trials: kids are no little adults and not all kids are the same. J Clin Epidemiol 2015. http://dx.doi.org/10.1016/j.jclinepi.2015.06.020. [Epub ahead of print].

[2] Janiaud P, Lajoinie L, Fleur C-A, Cornu C, Cochat P, Cucherat M, et al. Similarity of the treatment benefit between children and adults: results of a meta-epidemiological study. J Clin Epidemiol 2015.

[3] European Medicines Agency. Concept paper on extrapolation of efficacy and safety in medicine development EMA/129698/2012 Human Medicines Development and Evaluation. 2012. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142358.pdf. Accessed April 2015.

[4] Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics 2011;128:e1242–9.

[5] Boissel JP, Cucherat M, Nony P, Chabaud S, Gueyffier F, Wright JM, et al. New insights on the relation between untreated and treated outcomes for a given therapy effect model is not necessarily linear. J Clin Epidemiol 2008;61:301–7.

[6] Clarke M, Brice A, Chalmers I. Accumulating research: a systematic account of how cumulative meta-analyses would have provided knowledge, improved health, reduced harm and saved resources. PLoS One 2014;9:e102670.

[7] Glasziou P. Paul Glasziou: Six proposals for evidence based medicine's future: Available at http://blogs.bmj.com/bmj/2015/03/27/paul-glasziou-six-proposals-for-evidence-based-medicines-future/ Accessed April 14, 2015.

# The benefit risk ratio in adults and children: a meta-epidemiological study

# The benefit risk ratio in adults and children: a meta-epidemiological study

Perrine Janiaud [a], Catherine Cornu[a b c] MD, PhD, Kim-An Nguyen[a b d]; François Gueyffier[a, b] MD, PhD, Behrouz Kassai[a b c §] MD, PhD

[a] UMR 5558, CRNS, Claude Bernard University Lyon , France;

[b] Department of Pharmacotoxicology, CHU Lyon, France;

[c] EPICIME-Clinical Investigation Center, INSERM CIC1407/UMR5558, Bron, France;

[d] Department of neonatal intensive care unit, Hospices Civils de Lyon, Hopital Femme Mere Enfant, Lyon, France

**Abstract**

**Objective:** To explore from available evidence on harms of placebo-controlled RCTs included in meta-analyses whether the benefit risk ratio observed in adult trials is comparable with children.

**Study Design and Setting:** We searched three electronic databases for meta-analyses that included double-blind, placebo-controlled RCTs with separate results for adults and children published up to October 2015. For the quantitative synthesis, only meta-analyses that had an efficacy primary outcome and at least one adverse outcome (adverse events (AEs), serious adverse events (SAEs), any withdrawals and withdrawals due to AEs) were eligible. The net efficacy adjusted for risk odds ratios (NEAR-OR) were calculated for adults and children using the expected frequency of patients responding without harms. The best benefit risk profile corresponds to the greatest number of patients to respond favorably without suffering harms.

**Results:** Only 26 out of 111 included reviews were included, corresponding to 47 meta-analyses evaluating 27 different drugs. Only 2 meta-analyses on harm outcomes were conclusive for children and adults. The NEAR-OR was conclusive in adults and children for 13 out of 47 meta-analyses with a benefit risk ratio in favor of the treatment.

**Conclusion:** Many uncertainties have been observed in the assessment of harms and hence of the benefit risk ratio. There is a need to develop standardized core outcomes of harms and to improve their reporting.

## 1. Introduction

Drug interventions are one of the most common causes of harm in healthcare (1-3). Adverse drug reactions (ADRs) are associated with a substantial increase in morbidity. They lead to additional costs as a result of an increase in the number and duration of hospitalizations and investigations (4).

§ Corresponding author: Prof. Behrouz Kassai, Hospices Civils de Lyon, Groupement hospitalier Est, Bâtiment « Les Tilleuls », 59 boulevard Pinel, 69003 Lyon, France, Telephone: +33(0)4 27 85 77 32, Fax: +33(0)4 72 35 73 64, E-mail address: behrouz.kassai-koupai@chu-lyon.fr

In children, the overall incidence of adverse drug reactions was reported to be 9.53% in hospitalized children, 1.46% in outpatients and represent 2.09% of hospital admissions (5). The pediatric population is vulnerable because all drug exposures may impact their development. Young children aged less than 5 years old are more exposed to the risk of fatal harms due to their renal and hepatic function immaturity compared with older children (6). One of the major factor that contributes to the occurrence of drug related harm in the pediatric population is the use of off-label or unlicensed drugs (7). We systematically reviewed all published

studies evaluating the association between ADRs and off-label or unlicensed drugs. Our results show an increased risk of ADR (OR 1.95; 95%CI [1.39-2.74]) when drugs are unlicensed or used off-label for children. Another systematic review of the literature showed that the percentage of off-label and/or unlicensed drug involved in harms ranged from 23 to 60% (8).

Due to the lack of pediatric randomized controlled trials (RCTs), the treatment benefit or harm is often extrapolated from adult studies when prescribing drugs for children. Such extrapolation is questionable as the treatment benefit and harm might differ between adults and children (9, 10).

The assessment of the benefit risk ratio requires, however, clinically comparable outcomes. The patient's preferences highly influence the choice of clinically relevant outcome. The optimal treatment effect corresponds to the number of patients who respond favorably to the treatment without harms. Such data are rarely reported in publications but can be estimated indirectly by the Net Efficacy Adjusted for Risk (NEAR) as proposed by Boada et al. (11). The aim of our work was to estimate the Net Efficacy Adjusted for Risk in adult and children included in systematic reviews and explore whether it is comparable between those two populations.

## *2.* Methods

### *2.1. Literature Search and Data Extraction*

We identified systematic reviews in PubMed, Embase and Cochrane Library using the following keywords: child, preschool, infant, adolescent, adult and placebo (9). The last update of the literature search was done on October 14th, 2015. Meta-analyses were eligible if they included double-blinded, placebo-controlled RCTs evaluating a drug intervention with separated data for adults and children. Meta-analyses conducted in adults or in children assessing the same drug for the same indication and reporting the same outcomes were also included. A meta-analysis was considered a duplicate when it included exactly the same RCTs.

The data extraction and quality assessment were described in details in the previous report (9). Information on harms was collected (detailed data on harms, summary statistics or descriptive data). When available, data on adverse outcomes were extracted for each intervention group.

### *2.2. Outcome*

For efficacy, we extracted the primary binary outcome defined by the reviews in both adult and children. When several primary outcomes were evaluated, we selected the most clinically relevant outcome. Adverse outcomes retained were: adverse events (AEs), serious adverse events (SAEs), any withdrawals and withdrawals due to AE.

### *2.3. Statistical analyses*

For each included meta-analysis, separated odds ratios (ORs) for efficacy and harms were calculated for adults and children for one drug and one indication. An OR < 1 indicates that the treatment has a beneficial effect and an OR > 1 a deleterious effect. A random effect model was used.

**Table 1: Expected frequencies combining efficacy and harm outcomes**

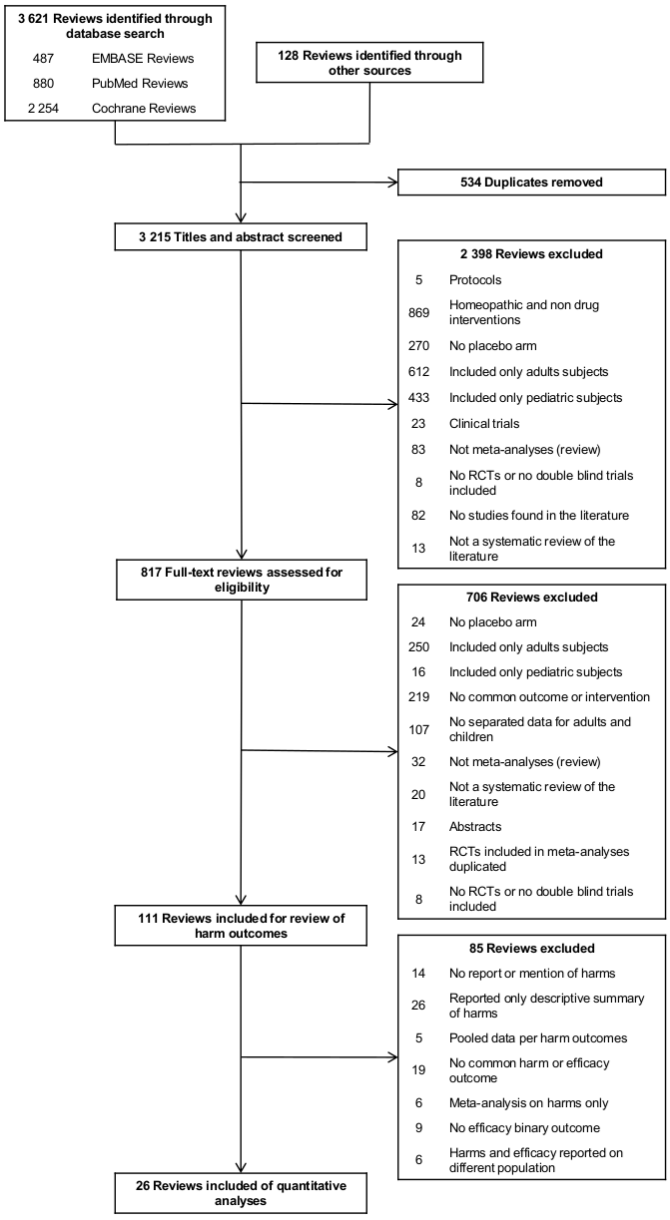
| | **Responders** | **Non-responders** | |
|---|---|---|---|
| **Without ADRs** | A1 | B1 | Total without ADRs |
| **With ADR** | C1 | D1 | Total with ADRs |
| | Total responders | Total non-responders | **Total studied** |

*For example, the expected frequency of responders without harms ($A_1$) in the treatment group is calculated by multiplying the total number of responders by the total number without harms and divided by the total number of participants studied. This is repeated for each cell and for the placebo group ($A_2$, $B_2$, $C_2$, $D_2$).*

*The OR is calculated with the following formula:* $NEAR - OR = A_1 * (C_2 + B_2 + D_2) \Big/ A_2 * (C_1 + B_1 + D_1)$

The expected frequencies of patients responding favorably to the intervention without harms (i.e. responders without harms), responders with harms, non-responders without harms and non-responders with harms were calculated for the treatment and placebo groups (Table 1). The resulting modified 2x2 tables for each included trials were then used to calculate the pooled NEAR odd ratios (NEAR-ORs) for adults and children. A NEAR-OR < 1 indicates a positive benefit risk ratio and a NEAR-OR > 1 a negative benefit risk ratio.

**Figure 1: Flowchart of the literature search and selection**




## 3. Results

We identified 3 749 reviews from which 534 duplicates were discarded. Two hundred and nineteen reviews not reporting the same intervention or outcome for both populations and 107 not reporting data for adults and children separately were excluded. Eighty-five additional reviews were excluded because 14 did not report or mention harms, 26 reported only summary of adverse outcomes and 46 did not report exploitable data for harms (Figure 1). Twenty-six reviews corresponding to 47 meta-analyses were finally included (12-37) assessing 27 different drugs (Supplementary Table 1). Overall 130 adult (28 641 participants) and 48 pediatric trials (7 258 participants) reported outcomes for harms.

### *3.1. Efficacy Outcomes*

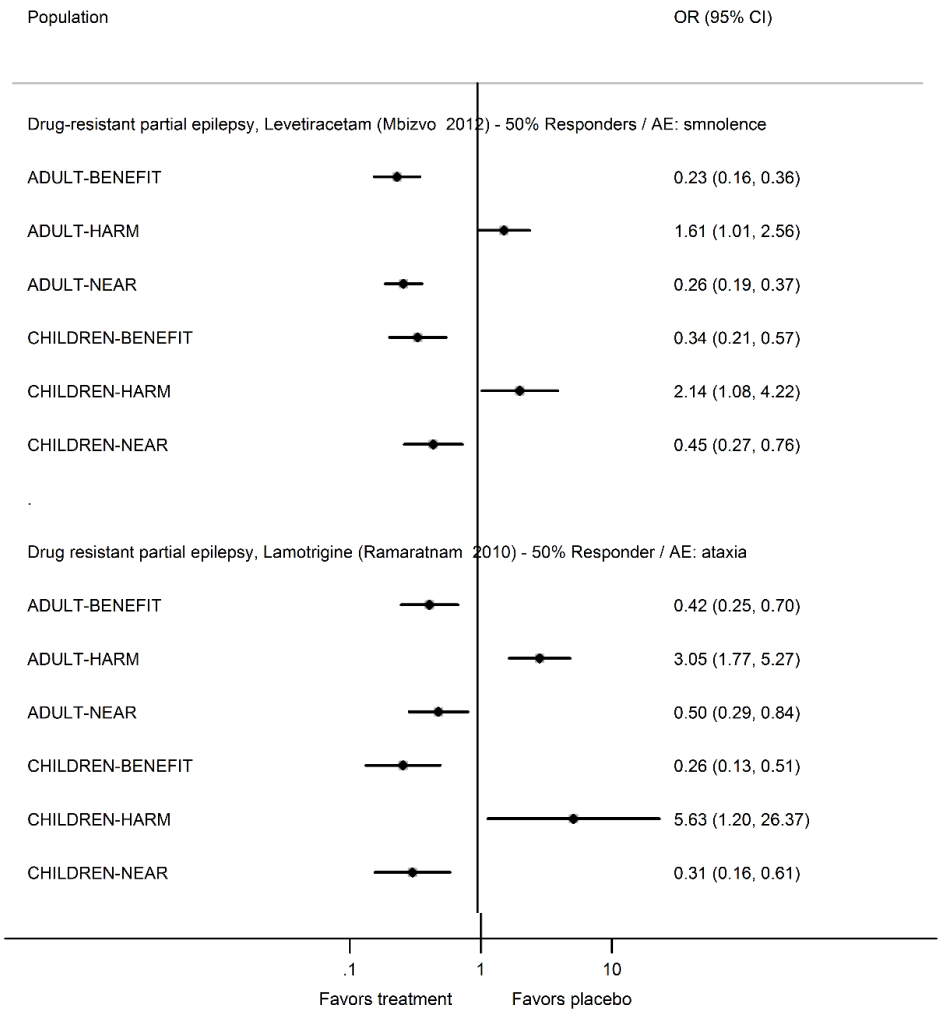
Only 33 efficacy meta-analyses were conducted as some assessed the same drug in the same indication with the same efficacy outcome but with more than one adverse outcome of interest. The treatment was beneficial in adults and children for 9 and inconclusive in adults and children for 10 meta-analyses. For 8 meta-analyses the treatment efficacy was conclusive in adults only, and for 4 the treatment efficacy was conclusive in children only (Supplementary Table 1 and Figure 1).

### *3.2. Adverse Outcomes*

From the 47 meta-analyses: 7 reported occurrences of any AEs, 9 a specific AE, 4 any SAEs, 14 any withdrawals and 13 withdrawals due to AEs. For 7 meta-analyses, the ORs for harms could not be calculated as there were no events in both arms for adults and/or children (Supplementary Figure 1).

Only 2 meta-analyses were conclusive in adults and children. In drug resistant partial epilepsy the odds of adverse events in adults (OR 1.61; 95% CI [1.01; 2.56) and children (OR 2.14; 95% CI [1.08; 4.22]) were higher for levetiracetam (24) and for lamotrigine (adult

**Figure 2: Benefit, harm and efficacy adjusted on harm in adult and pediatric trials with low uncertainties**




OR 3.05 ; 95% CI [1.77; 5.27]; children OR 5.63; 95% CI [1.20; 26.37]) (27) than placebo. For 3 meta-analyses the results were conclusive in children only and 11 in adults only (Figure 2). For 24 meta-analyses the ORs were inconclusive in adults and children.

### *3.3. Net Efficacy Adjusted for Risk*

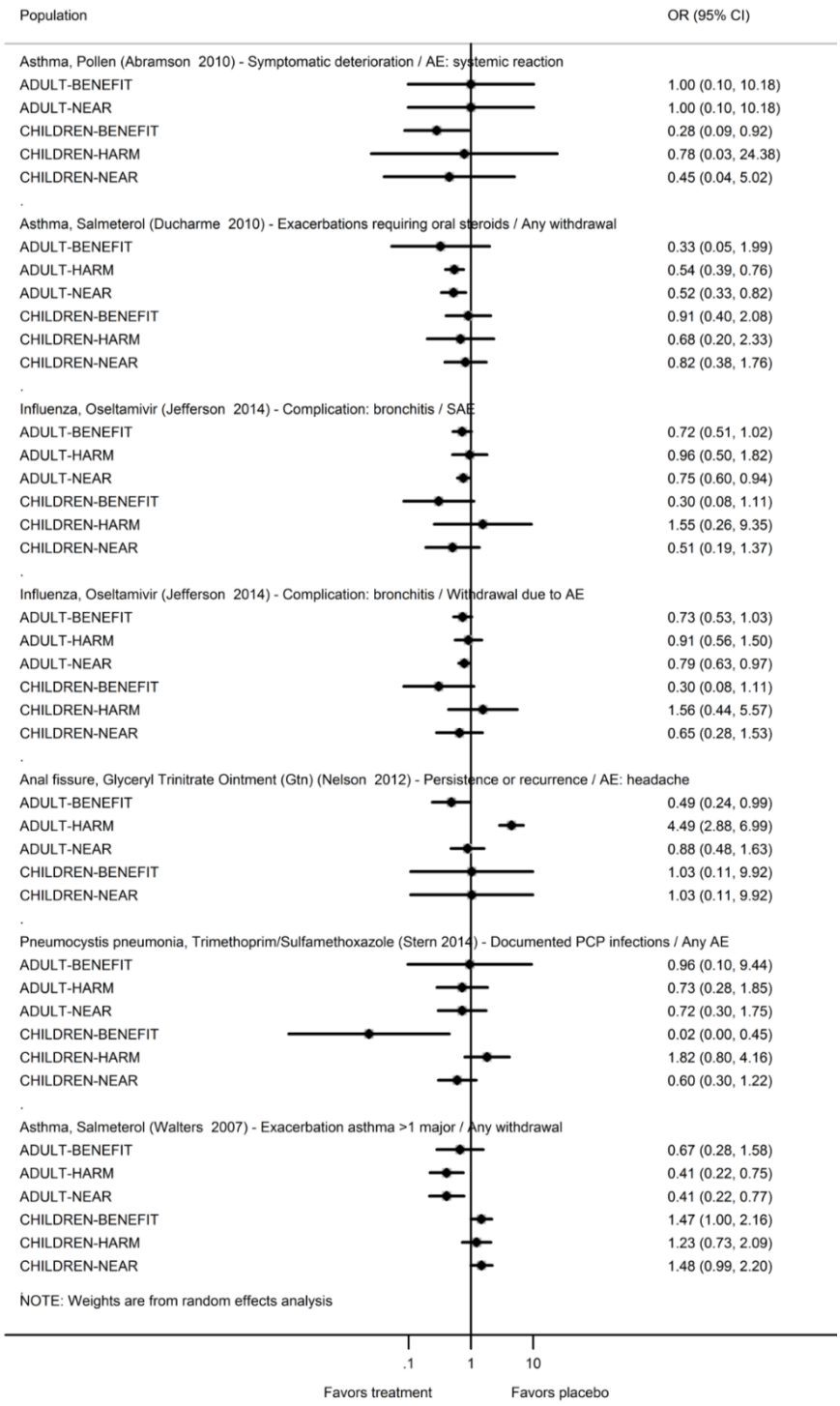
The adjustment on risk resulted in a loss of the benefit the treatment for 2 meta-analyses in children and one in adults while they increased the benefit in favor of the treatment for 4 meta-analyses in adults (Figure 3).

For 13 meta-analyses the NEAR-OR was in favor of the treatment in adults and children. Levetiracetam and lamotrigine had significantly more harms in the treatment group but the NEAR-OR remained in favor of the treatment in both populations (Figure 2). The results were inconclusive for 18 meta-analyses in populations, 11 in children only and 3 in adult only (Supplementary Table 1 and Figure 1).

## 4. Discussion

Only two meta-analyses on lamotrigine and levetiracetam had conclusive results on harm in adults

**Figure 3: Benefit, harm and efficacy adjusted on harm in adult and pediatric trials with high uncertainties**




and children. For 24 meta-analyses the ORs on harms had large uncertainties in adults and children.

Out of 47 meta-analyses, only 13 had a NEAR-OR with a confidence interval < 1 in adults and children in favor of the treatment. The detection of harms in clinical trials in disfavor of the treatment does not necessarily mean that the benefit risk ratio will be turned over. For example, lamotrigine in drug resistant partial epilepsy showed more harms (AE: ataxia) in the treatment group in adults and children but the NEAR remained <1 (27).

We also observed changes in the benefit risk ratio for 7 meta-analyses in disfavor of the treatment. Overall, meta-analyses in adults and children (18/47) showed uncertain NEAR-ORs. Uncertainty in estimating the risk of adverse event was also common (24/47) indicating the probable lack of power to detect harms.

The quality of evidence on harms could also be questioned as randomized trials are designed to estimate the efficacy only. Harms are sometimes collected with no prior definition and standardization, and can be underestimated compared with real life due to a stringent and standardized follow-up of participants.

When extrapolating harms and the benefit risk ratio from adults to children, the major pitfall is the scaling of harms between the two populations. A specific harm can be particularly worrisome in children but of less severity in adults. In addition, exposure to a drug intervention can also lead to harms affecting the growth and maturation of children. Such harms cannot be extrapolated from adults. Only studies identifying age-specific harms in children might estimate the long-term benefit risk ratio of treatments in children (38, 39). Performing these studies is, however, difficult.

Out of our 111 reviews selected initially, only 26 were included in our analysis illustrating the lack of complete reporting of harms. 12.6% reviews did not report or mention harms and 41.4% were non-exploitable because they lacked standardized reporting. Another challenge was to identify common core harm outcomes in adults and children. Children and adults cannot systematically be comparable when it comes to harms. In addition, comparing reported harms maybe misleading when methods of collecting and reporting differ, for instance it has been shown that when patients are assigned to report AEs using a checklist, they reported up to 20-fold more AEs compared to patients assigned to open-ended question reporting (40, 41).

When designing trials, careful thought has to be given to what type of harm outcomes should be collected and how they should be scaled regarding to their severity. An international initiative has been developed to establish a core outcome set for efficacy trials (42) resulting in the identification of the minimal outcomes that should be evaluated (43, 44). The development of such core outcome sets for harms would help to gain in standardization, leading to more reliable evidence based conclusions on the safety of drug interventions.

Evidence of poor reporting of harms in systematic reviews and in RCTs has led to the publication of extensions to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (45) and CONSORT (Consolidated Standards of Reporting Trials) (46) checklist for reporting of harms. There is, however, still room to improve reporting of harms to avoid waste of limited resources available for assessing medicine in children (47-49).

Our conclusions are similar to a previous meta-epidemiological study comparing the risk of harms between adults and children from Cochrane reviews. Authors highlighted the large uncertainties of the estimation of harm outcomes and showed that a twofold difference on harm outcomes between adults and children was suggested by 38% of their meta-analyses (10). Our work has the advantage to cover other literature databases and to include only high quality trials. In addition, we focused our work on the estimation of the benefit risk ratio and not solely on harms.

Our study is restricted to meta-analyses conducted in adults and children reporting efficacy and safety data. Systematic reviews focusing only on harms outcomes were not included and drug interventions for conditions exclusively present in children were not evaluated. Meta-analyses report summary data of RCTs, we were therefore not able to identify individual patient factors (i.e. pediatric age subgroups) that might influence the benefit risk ratio of a drug intervention. We also acknowledge that withdrawals outcomes are biased as

the decision of withdrawing a patient is almost always done unblinded. Patients under placebo are potentially less discontinued compared with patients under treatment.

The NEAR method has some limitations. It cannot be used when efficacy and safety outcomes are reported on different populations. The efficacy outcome may be reported on the intention to treat population while the harm outcome was reported on the per protocol population or vice versa. It also does not take into account the proportional weight of the efficacy versus the safety outcomes (50). The results of the NEAR should always be put in relation to the clinical context at hand. However, NEAR represents a simple tool allowing the combination of efficacy and harms outcomes to give an estimate of the benefit risk ratio without involving complex mathematical models.

## 5. Conclusion

The NEAR was in favor of the treatment in adults and children for 13 out of 47 meta-analyses. The rational for extrapolating the efficacy and harms from adults to children is limited by the uncertainty and lack of evidence. There is a need to standardize core harm outcomes for pediatric trials and report those adequately.

Funds: Perrine Janiaud is receiving a grant from GlaxoSmithKline, France, for her PhD at the UMR 5558 Laboratoire de Biométrie et Biologie Evolutive, CNRS. The funder had no role in study design, data collection and analysis, decision to publish or the preparation of the manuscript

Conflict of interest: The authors have no conflict of interest.

## References

1. Bourgeois FT, Mandl KD, Valim C, Shannon MW. Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. Pediatrics. 2009;124(4):e744-50.
2. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. Jama. 2016;316(20):2115-25.
3. Holdsworth MT, Fichtl RE, Behta M, Raisch DW, Mendez-Rico E, Adams A, et al. Incidence and impact of adverse drug events in pediatric inpatients. Arch Pediatr Adolesc Med. 2003;157(1):60-5.
4. Sultana J, Cutroneo P, Trifiro G. Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother. 2013;4(Suppl 1):S73-7.
5. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol. 2001;52(1):77-83.
6. Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. Arch Dis Child. 2002;87(6):462-6.
7. European Medicines Agency, (EMA). Evidence of harm from off-label or unlicensed medicines in children2004 Date accessed: February, 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004021.pdf.
8. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. Expert Opin Drug Saf. 2006;5(5):703-18.
9. Janiaud P, Lajoinie A, Cour-Andlauer F, Cornu C, Cochat P, Cucherat M, et al. Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children. J Clin Epidemiol. 2015;68(10):1221-31.
10. Lathyris D, Panagiotou OA, Baltogianni M, Ioannidis JP, Contopoulos-Ioannidis DG. Safety of medical interventions in children versus adults. Pediatrics. 2014;133(3):e666-73.

11. Boada JN, Boada C, Garcia-Saiz M, Garcia M, Fernandez E, Gomez E. Net efficacy adjusted for risk (NEAR): a simple procedure for measuring risk:benefit balance. PLoS One. 2008;3(10):e3580.
12. Abramson Michael J, Puy Robert M, Weiner John M. Injection allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews [Internet]. 2010; (8). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001186.pub2/abstract.
13. Brouwer Matthijs C, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database of Systematic Reviews [Internet]. 2015; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004405.pub5/abstract.
14. Brown R, Taylor Matthew J, Geddes J. Aripiprazole alone or in combination for acute mania. Cochrane Database of Systematic Reviews [Internet]. 2013; (12). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005000.pub2/abstract.
15. Carlisle J, Stevenson Carl A. Drugs for preventing postoperative nausea and vomiting. Cochrane Database of Systematic Reviews [Internet]. 2006; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004125.pub2/abstract.
16. Chong J, Haran C, Chauhan Bhupendrasinh F, Asher I. Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. Cochrane Database of Systematic Reviews [Internet]. 2015; (7). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011032.pub2/abstract.
17. Ducharme Francine M, Ni Chroinin M, Greenstone I, Lasserson Toby J. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2010; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005535.pub2/abstract.
18. Goldenberg Joshua Z, Ma Stephanie SY, Saxton Jane D, Martzen Mark R, Vandvik Per O, Thorlund K, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2013; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006095.pub3/abstract.
19. Grimwade K, Swingler George H. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. Cochrane Database of Systematic Reviews [Internet]. 2003; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003108/abstract.
20. Grimwade K, Swingler George H. Cotrimoxazole prophylaxis for opportunistic infections in children with HIV infection. Cochrane Database of Systematic Reviews [Internet]. 2006; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003508.pub2/abstract.
21. Hao Q, Dong Bi R, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database of Systematic Reviews [Internet]. 2015; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006895.pub3/abstract.
22. Jefferson T, Jones Mark A, Doshi P, Del Mar Chris B, Hama R, Thompson Matthew J, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2014; (4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/abstract.
23. Jesner Ora S, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database of

Systematic Reviews [Internet]. 2007; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005040.pub2/abstract.

24. Mbizvo Gashirai K, Dixon P, Hutton Jane L, Marson Anthony G. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. Cochrane Database of Systematic Reviews [Internet]. 2012; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001901.pub2/abstract.
25. Nelson Richard L, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. Cochrane Database of Systematic Reviews [Internet]. 2012; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003431.pub3/abstract.
26. Pulman J, Jette N, Dykeman J, Hemming K, Hutton Jane L, Marson Anthony G. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews [Internet]. 2014; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001417.pub3/abstract.
27. Ramaratnam S, Marson Anthony G, Baker Gus A. Lamotrigine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews [Internet]. 2001; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001909/abstract.
28. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med. 2008;5(8):e166.
29. Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews [Internet]. 2010; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004332.pub2/abstract.
30. Rowe Brian H, Bretzlaff J, Bourdon C, Bota G, Blitz S, Camargo Carlos A. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database of Systematic Reviews [Internet]. 2000; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001490/abstract.
31. Shen J, Ran HZ, Yin MH, Zhou TX, Xiao DS. Meta-analysis: the effect and adverse events of Lactobacilli versus placebo in maintenance therapy for Crohn disease. Intern Med J. 2009;39:103-9.
32. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database of Systematic Reviews [Internet]. 2014; (10). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005590.pub3/abstract.
33. Suttajit S, Srisurapanont M, Maneeton N, Maneeton B. Quetiapine for acute bipolar depression: A systematic review and meta-analysis. Drug Design, Development and Therapy. 2014;8:827-38.
34. Villar Juan C, Perez Juan G, Cortes Olga L, Riarte A, Pepper M, Marin-Neto Jose A, et al. Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection. Cochrane Database of Systematic Reviews [Internet]. 2014; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003463.pub2/abstract.
35. Walters EH, Gibson Peter G, Lasserson Toby J, Walters Julia AE. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database of Systematic Reviews [Internet]. 2007; (1). Available from:

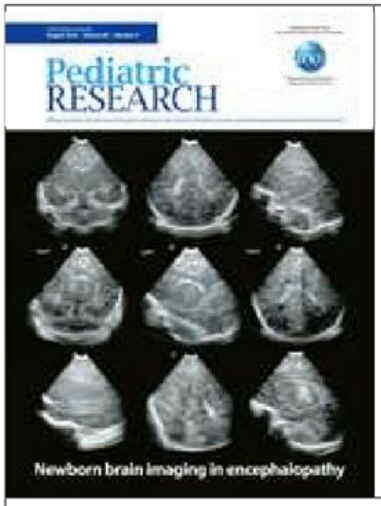
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001385.pub2/abstract.

36. Watts K, Chavasse Richard JPG. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2012; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006100.pub2/abstract.
37. Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2014;18:1-106.
38. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011;128(5):e1242-9.
39. European Medicines Agency, (EMA). Reflection paper on extrapolation of efficacy and safety in paediatric medicine development2016 Date Accessed: February, 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf.
40. Bent S, Padula A, Avins AL. Brief communication: Better ways to question patients about adverse medical events: a randomized, controlled trial. Ann Intern Med. 2006;144(4):257-61.
41. Ioannidis JP, Mulrow CD, Goodman SN. Adverse events: the more you search, the more you find. Ann Intern Med. 144. United States2006. p. 298-300.
42. Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: Its Role in Improving Cochrane Reviews. Cochrane Database Syst Rev. 2012(5):Ed000041.
43. Tong A, Manns B, Hemmelgarn B, Wheeler DC, Evangelidis N, Tugwell P, et al. Establishing Core Outcome Domains in Hemodialysis: Report of the Standardized Outcomes in Nephrology-Hemodialysis (SONG-HD) Consensus Workshop. Am J Kidney Dis. 2017;69(1):97-107.
44. Kelly LE, Jansson LM, Moulsdale W, Pereira J, Simpson S, Guttman A, et al. A core outcome set for neonatal abstinence syndrome: study protocol for a systematic review, parent interviews and a Delphi survey. Trials. 2016;17(1):536.
45. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. Bmj. 2016;352:i157.
46. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004;141(10):781-8.
47. Haidich AB, Birtsou C, Dardavessis T, Tirodimos I, Arvanitidou M. The quality of safety reporting in trials is still suboptimal: survey of major general medical journals. J Clin Epidemiol. 2011;64(2):124-35.
48. Smith SM, Chang RD, Pereira A, Shah N, Gilron I, Katz NP, et al. Adherence to CONSORT harms-reporting recommendations in publications of recent analgesic clinical trials: an ACTTION systematic review. Pain. 2012;153(12):2415-21.
49. Moher D, Glasziou P, Chalmers I, Nasser M, Bossuyt PM, Korevaar DA, et al. Increasing value and reducing waste in biomedical research: who's listening? Lancet. 2016;387(10027):1573-86.
50. Boada J, Boada C, Garcia MM, Rodriguez C, Garcia M, Fernandez E. Net efficacy adjusted for risk: further developments. Expert Opin Drug Saf. 2009;8(6):649-54.

# Is the Perceived Placebo Effect Comparable Between Adults and Children? A Meta-Regression Analysis

ACCEPTED ARTICLE PREVIEW

Accepted Article Preview: Published ahead of advance online publication




# Is The Perceived Placebo Effect Comparable Between Adults and Children? A Meta-regression Analysis

Perrine Janiaud, Catherine Cornu, Audrey Lajoinie, Amina Djemli, Michel Cucherat, Behrouz Kassai

**Cite this article as:** Perrine Janiaud, Catherine Cornu, Audrey Lajoinie, Amina Djemli, Michel Cucherat, Behrouz Kassai, Is The Perceived Placebo Effect Comparable Between Adults and Children? A Meta-regression Analysis, *Pediatric Research* accepted article preview online 20 September 2016; doi:10.1038/pr.2016.181

This is a PDF file of an unedited peer-reviewed manuscript that has been accepted for publication. NPG is providing this early version of the manuscript as a service to our customers. The manuscript will undergo copyediting, typesetting and a proof review before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers apply.

Accepted manuscript

Received 23 May 2016; Accepted 15 July 2016; Accepted article preview online 20 September 2016

© 2016 International Pediatric Research Foundation, Inc. All rights reserved

ACCEPTED ARTICLE PREVIEW

# Is The Perceived Placebo Effect Comparable Between Adults and Children? A Meta-regression Analysis

Running title: The Perceived Placebo Effect in Children

Perrine Janiaud [1], Catherine Cornu [1 2 3], Audrey Lajoinie [1], Amina Djemli [1], Michel Cucherat[2], Behrouz Kassai[1 2 3 *]

[1] UMR 5558, CNRS, Claude Bernard University Lyon 1, Lyon, France;

[2] Department of Clinical Pharmacology, CHU Lyon, Lyon, France;

[3] EPICIME-Clinical Investigation Center, INSERM CIC201/UMR5558, Bron, France;

* Corresponding author: Prof. Behrouz Kassai, MD, PhD Hospices Civils de Lyon, Groupement hospitalier Est, Bâtiment Les Tilleuls, 59 boulevard Pinel, 69003 Lyon, France, Telephone: +33(0)4 27 85 77 32, Fax: +33(0)4 72 35 73 64,

**E-mail address**: behrouz.kassai-koupai@chu-lyon.fr

**Disclosures:** Perrine Janiaud is currently receiving a grant from GlaxoSmithKline, France, for her three years PhD at the UMR 5558 CNRS. The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript

**Conflict of interest:** The authors have no conflict of interest.

**Category of study**: Systematic review

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

**ABSTRACT**

**Background:** A potential larger perceived placebo effect in children compared with adults could influence the detection of the treatment effect and the extrapolation of the treatment benefit from adults to children. This study aims to explore this potential difference, using a meta-epidemiological approach.

**Methods:** A systematic review of the literature was done to identify trials included in meta-analyses evaluating a drug intervention with separate data for adults and children. The standardized mean change and the proportion of responders (binary outcomes) were used to calculate the perceived placebo effect. A meta-regression analysis was conducted to test for the difference between adults and children of the perceived placebo effect.

**Results:** For binary outcomes, the perceived placebo effect was significantly more favorable in children compared with adults ($\beta = 0.13$; $p = 0.001$). Parallel group trials ($\beta = -1.83$; $p < 0.001$), subjective outcomes ($\beta = -0.76$; $p < 0.001$), and the disease type significantly influenced the perceived placebo effect.

**Conclusion:** The perceived placebo effect is different between adults and children for binary outcomes. This difference seems to be influenced by the design, the disease, and outcomes. Calibration of new studies for children should consider cautiously the placebo effect in children.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

**Introduction**

The placebo has been defined as a pharmacological inert substance and the placebo effect as "any effects attributable to a pill, potion or procedure, but not to its pharmacodynamics or specifics properties" (1). Its use in clinical trials became the mean to control for psychological effects associated to the administration of a substance. Researchers soon became aware that the administration of a placebo could result into a relief or an improvement of symptoms. Such effect became known as the placebo effect (2). Placebo effect is usually measured in randomized controlled trials by the nonblinded comparison between placebo and no-treatment groups (3). Consequently, the true effect of placebo interventions is potentially biased by the type of outcomes, co-intervention, selective publication and reporting (4). Placebo research is not limited, however, to the field of clinical trials, and has expanded to the field of neurobiology. Pharmacology, brain imaging techniques, genetics and animal models have shown for instance the capacity of the placebo to mimic active drugs and activate the same brain areas (5), the association of the placebo response with some genotypes in some conditions, and the important role of prefrontal cortex functioning impairment in reducing placebo response (6). The similarity in the mechanism of action between the placebo and the active substance can be explained partly by Pavlovian conditioning or learning by patients of the effect of the active drug (7), and also by expectation, social propagation of expectations, or the Hawthorn effect (5).

Accepted manuscript

Since 1955 with Beecher's statement on the high degree of therapeutic efficacy of placebos (8), the placebo effect, also known as the "true" placebo effect, has been misinterpreted and confounded with the "perceived placebo effect" (9). The perceived placebo effect, the term we will use in this article to avoid any confusion with the placebo effect, equals the "true" placebo effect (10, 11) plus other factors that may explain the improvement or worsening of the

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

patients' outcomes in the placebo arm of clinical trials. Those factors include the natural history with the potential of spontaneous regression of the disease, the regression to the mean, the use of concomitant treatments, the experimental subordination, the conditioned responses, and other unknown factors. Experimental subordination means that the subject learns what the expected effects could be and this conditions his actual response.

As it seems difficult to conduct research in children without direct therapeutic benefits, the placebo effect has been commonly measured from adult trials with a placebo group versus an untreated group. For instance, a meta-analysis focusing on placebo interventions included 202 randomized placebo trials with a no-treatment control group. Authors showed that there was a significant overall effect of placebo and found that placebo interventions can influence patient-reported outcomes. Among the 202 trials, 21 (10.4%) included pediatric subjects, and one included newborns. There were no significant differences between the placebo and no-treatment group for 16 of the pediatric trials, 3 showed a significant difference and 2 had no exploitable outcomes (3). Another narrative review identified 9, 000 citations using the terms "placebo" and "children", among which only 50 (2.5%) studied, but not measured, the perceived placebo effect in children (12).

Accepted manuscript

Because the perceived placebo effect has been mostly studied in adults, its extent is often extrapolated from adults to children. Children and adults, however, differ in terms of physiological development, physiopathology, pharmacokinetics and pharmacodynamics but probably also in terms of perceived placebo effect (13, 14). A recent meta-analysis of antiepileptics suggests that the perceived placebo effect might be higher in children than in adults (15). The authors measured the perceived placebo effect by measuring the difference between the proportion of responders between the start and end of the study in the placebo group. The

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

difference between children and adults could be attributed to a greater regression to the mean in children or to a strong placebo-by-proxy effect. Placebo-by-proxy effect occurs when children are receiving more attention and parents are more eager to report favorable outcomes in the pediatric population (15-17).

In this study we aimed at exploring the differential perceived placebo effect between adults and children in all available published meta-analyses. The main objective of this systematic review of reviews is to confirm a potential more favorable perceived placebo effect in children compared with adults.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

**Results**

We identified 3 484 reviews. After screening of titles and abstracts, and the exclusion of irrelevant and duplicates, 762 reviews were screened (Figure 1). Seventy-five reviews, not reporting the difference between the start and end of the study, were also excluded. Thirty-five reviews, including 179 trials with adult and 117 with pediatric participants, were finally analyzed (15, 18-51) (Supplemental Table S1 online). From these reviews, 19 assessed the risk of bias (18, 20, 22, 25, 26, 28, 29, 32, 35, 37-41, 44, 46, 49-51), 6 reported only the Jadad score (15, 19, 21, 36, 45, 48), 4 assessed only the allocation concealment (34, 42, 43, 47), and 6 did not assess quality (23, 24, 27, 30, 31, 33). Overall, 13 382 adult and 5 417 pediatric participants were enrolled in the placebo groups.

*Results for continuous outcomes*

Two hundred fourteen trials were included, 126 in adults and 88 in children, covering 13 different therapeutic indications. The three most common therapeutic indications were asthma (62 trials), exercise-induced asthma (54 trials), and atopic dermatitis (24 trials) (Table 1). Crossover exercise-induced asthma trials (50 trials) did not report results for each period.

Overall, children's (standardized mean change -0.32; 95% CI (-0.52; -0.12)) and adults' (standardized mean change -0.11; 95% CI (-0.24; 0.02)) outcomes deteriorated with placebo with no significant difference between children and adults ($\beta$ = -0.20; p = 0.30; Figure 2; Supplemental Table S2 and Supplemental Figure S1 online).

*Sensitivity analysis for continuous outcomes*

The sensitivity analyses showed a significant difference between adults' and children's perceived placebo effect when only crossover trials ($\beta$ = 0.5; p = 0.03) and only objective outcomes ($\beta$ = -0.67; p = 0.003) were included. For crossover trials and objective outcomes,

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

children and adults showed an unfavorable effect with placebo. Perceived placebo effect remained unchanged for each stratum of diseases (Supplemental Table S2 and Supplemental Figure S1 online).

*Results for binary outcomes*

Eighty-two trials, 53 in adults and 29 in children, reported binary outcomes in 6 different therapeutic indications. In resistant partial epilepsy, 10 crossover trials reported only the first period. All trials that defined responders as 50% reduction in the number of seizures were in parallel groups.

Binary outcomes improved more with placebo in children (responders proportion 0.32; 95% CI (0.26; 0.39)) than in adults (responders proportion = 0.19; 95%CI (0.15; 0.23), difference between adults and children $\beta = 0.13$; $p = 0.001$; Figure 3; Supplemental Table S3 and Supplemental Figure S2 online).

*Sensitivity analysis for binary outcomes*

For drug resistant partial epilepsy, children (responders proportion 0.18; 95% CI (0.14; 0.22)) improved more with placebo than adults (responders proportion 0.13; 95% CI (0.10; 0.15); difference between adults and children $\beta = 0.06$, $p = 0.02$; Supplemental Table S3 and Supplemental Figure S2 online).

*Other factors than population influencing the perceived placebo effect*

The univariate meta-regression for binary outcomes showed that participants with asthma (($\beta = 0.36$; $p < 0.001$), depression ($\beta = 0.29$; $p < 0.001$), and drug resistant partial epilepsy ($\beta = -0.22$; $p = 0.001$) improved more with placebo compared with other diseases. All the trials were parallel groups and all used subjective outcomes, the univariate and multivariate meta-regression were not feasible (Supplemental Table S3 and Supplemental Figure S2 online).

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

For continuous outcomes, participants with asthma ((β = 0.68; p = 0.001), atopic dermatitis (β = 1.21; p < 0.001), bipolar disorder (β = 1.21; p = 0.001) improved with placebo. Those with exercise-induced asthma (β = -2.23; p < 0.001), however, deteriorated with placebo (Supplemental Table S2 and Supplemental Figure S1 online).

The univariate meta-regression also showed a larger improvement with placebo in parallel group (standardized mean change 0.24; 95% CI (0.14; 0.34)) compared with crossover studies (standardized mean change -1.81; 95% CI (-1.60; -2.01)), and for subjective (standardized mean change 0.75; 95% CI (0.54; 0.95)) compared with objective outcomes (standardized mean change -0.50; 95% CI (-0.61; -0.39))

In the multivariate model, population, design, and outcome, explained 64.03% of the between studies variance. The design (β = -1.83; p < 0.000), the outcome (β = -0.76; p < 0.000) significantly influenced the perceived placebo effect. The difference between children and adults remained non-significant in the multivariate model (β = 0.09; p = 0.526).

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

**Discussion**

In our broad overview we found a significant difference in the perceived placebo effect between adults and children for binary outcomes. Overall, when binary outcomes are used children tend to improve more with placebo compared with adults. The results found for binary outcomes are coherent with Rheims et al. (15) study and the literature (12, 16). The disease, and probably the outcomes and the design seem to influence the perceived placebo effect on binary outcomes and need to be investigated in future studies.

For continuous outcomes, we did not show any difference between adults and children on the perceived placebo effect. The perceived placebo effect seemed to be influenced by the disease, the design of the studies and by type of outcome measures. It increases when the design used was parallel groups compared with crossover as it was shown in a previous report (52). The effect observed with crossover trials for continuous outcomes could be explained by the regression to the mean potentially more important in the first compared with the second period. Patients receiving placebo during the first period may benefit from a favorable natural course of the disease and accentuate the regression to the mean (53). Also, the regression to the mean, as part of the perceived placebo effect, could be diluted by taking the mean effect with placebo regardless of the periods. Patients who receive the drug first and then the placebo may also show a higher placebo response because of a carry-over effect or a conditioning learning effect (54). To be able to investigate further the influence of the design on the perceived placebo effect the outcome measures for the different treatment periods should be analyzed, but they are rarely reported.

The larger improvement with placebo for subjective outcomes might be explained by the measurement bias when these outcomes are used to select patients participating to the trials, and

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

by the regression to the mean (55). The way trials are conducted and patients informed can influence the placebo response (3). Another explanation could be that children show a stronger placebo-by-proxy effect (17). It has also been shown that the mood and belief of the adult caregiver can influence the placebo response in children (56). Conditioning learning plays also an important role in the response of children to the placebo. Children have greater capacity in associative learning (12). This learning process can be emphasized in crossover trials (54).

Our study has some limits. Confounding factors cannot be excluded because of the absence of randomization between compared groups. The difference between the start and end of the study in the placebo arm can also reflect the effect of concomitant treatments and the natural history of the disease. In the absence of no-treatment arm our analysis assumes that the natural history of the disease and the effect of concomitant treatments could be similar in adults and children. Also, for binary outcomes, we were not able to explore the influence of the design and the outcomes measures on the perceived placebo effect. Furthermore, incomplete reports of crossover trials did not allow us to further explore the importance of the regression to the mean in each treatment periods. The major limit on the validity of our study is shared by other recent publications (15, 16, 57, 58) suggesting a higher perceived placebo response in children compared with adults. In summary, our results underline that the difference observed in these reviews should be interpreted cautiously, because they are highly influenced by the disease, the design and the outcomes. It is not clear whether for binary outcomes the difference between adults and children in the perceived placebo effect could disappear when adjusting for these variables.

In order to avoid missing a potential treatment benefit, when performing randomized trials in children, calibration should take account for the design, disease, and type of outcomes.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

## Methods

*Literature search*

The unit of research for our work was the trial and those were identified through a systematic review of meta-analyses in the literature. Three electronic databases (PubMed (US National Library of Medicine, Bethesda, Maryland), Embase (Elsevier, Amsterdam, Netherlands) and the Cochrane Library (John Wiley & Sons, Chichester, UK) ) were searched for meta-analyses, with no limitation, on language, dates, diseases or treatments. The last bibliographic search was done on February 11, 2015. The following search terms were used: (Child OR preschool OR infant OR adolescent) AND adult*) AND placebo. For PubMed, we specified the type of study ("meta-analysis"). For EMBASE, we specified the following filters: "human" and "meta-analysis".

*Meta-analyses selection*

Meta-analyses were eligible when they included randomized controlled trials (RCTs) in adults and children that were double-blinded, placebo-controlled, and reported separately their results for adults and children. All types of pharmacological treatments, except for homeopathic treatments, were eligible. The age limit between adults and children, when necessary, was arbitrarily set at 18 years. The RCTs from the included meta-analyses were classified according to their therapeutic indications. When two reviews reported the same RCTs, the review with the most complete information was considered. When both reported the same information, the most recent review was considered.

Three authors (PJ, BK, AD) reviewed all citation abstracts and excluded irrelevant studies according to pre-specified exclusion criteria.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

*Data extraction*

The following information was extracted for each relevant trial included in the meta-analyses and entered into the database: i) the design of the study (randomization, parallel group, crossover, and blinding); ii) patient characteristics (adults or children, number of patients in the placebo and treatment arms, and the number of events and no-events in each arm for dichotomous data or the mean change from baseline to the end of study for each arms for continuous data ); iii) the disease (e.g. "asthma"); iv) the drug used, when more than one drug was reported, data were extracted for each drug studied in the meta-analysis; v) the drug's therapeutic class ; vi) the outcome; vii) the dose for adults and the dose adjustment methods for children. Duplicated placebo groups, i.e. same RCTs included in different meta-analyses, were excluded.

The main outcome and the treatment benefit (number of events or effect size in each group) were extracted blindly from the original systematic review by three authors (PJ, CC, AL). Differences were resolved by consensus.

*Quality assessment*

We reported the quality assessment reported by the authors of the meta-analyses for each included RCT. We used the assessments reported in meta-analyses, the Cochrane assessment of risk of bias (59), and the five-point scoring instrument developed by Jadad and Enkin (60) or both.

*Outcome*

We extracted the primary outcome measured at the start and end of the study for adults and children. The outcomes were classified as subjective or objective. Subjective outcomes were any outcomes that were reported by the patient or family reported scale, or were subject to

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

measurement bias (Supplemental Table S1 online). When a biological (cholesterol, Hb) or device measurement (spirometer or body weight scale) was used, it was considered as an objective outcome.

*Dealing with missing data*

To fill out missing data, we consulted the original article and contacted authors of meta-analyses. For continuous outcome, we calculated or imputed missing values when the mean change from baseline or the standards deviation were missing (59).

*Unit of analysis error*

The unit of analysis error occurs when dealing with crossover trials and multiple intervention groups. As we were interested in the perceived placebo effect, for crossover trials only data from the first period with placebo were considered. When the effect reported was calculated from the difference between the start and end of the study regardless of the periods (i.e. as if a parallel trial), we extracted the mean change from baseline only for the placebo periods. For multiple intervention groups, i.e. different doses versus placebo, no adjustment was required (59).

*Statistical analysis*

The perceived placebo effect was defined as the change in the outcome experienced by the patient in the placebo arms between the beginning (baseline) and the end of the trial.

For continuous outcomes, we calculated the standardized mean change and for dichotomous data the proportion of responders in the placebo arm. Standardized mean change > 0 indicates improvement and < 0 worsening of the outcomes. To assess a potential difference between children's and adults' perceived placebo effect; univariate random-effect restricted maximum likelihood meta-regression analyses were performed. The meta-regression analyses

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

included the following explanatory variables defined *a priori*: i) population (children under the age of 18 years coded as 1 or adults coded as 0); ii) diseases (dummy variables created, disease of interest coded as 1 and other diseases coded as 0); iii) design of study (crossover coded as 1 or parallel coded as 0); and iv) type of outcome (objective coded as 1 or subjective coded as 0). The multivariate meta-regression included the population, design of the study and outcome variables.

To adjust for multiple testing, the t-test from the Monte-Carlo permutation (with 10 000 replications) was used. When all trials were parallel groups or used only subjective outcomes the multivariate meta-regression was not feasible. The unit of analysis was the trial. All analyses were performed using the Stata/IC12 software (StataCorp LP, College Station Texas).

*Sensitivity analyses*

We conducted sensitivity analyses to test how robust are the potential differences between adults' and children's perceived placebo effect. At each step of the analysis we excluded one of the following categories: crossover trials, parallel trials, trials using an objective outcome, trials using a subjective outcome. We also checked the robustness of our results for each disease separately.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

**Acknowledgements**

Contributors: BK and MC were responsible for the study concept and design. BK, AL, CC, AD and PJ were involved in the literature and data extraction. MC, BK, CC and PJ were responsible for the data analysis and interpretation. BK and PJ wrote the manuscript. All authors critically revised the manuscript. BK and PJ were responsible for the editing of the manuscript. BK supervised the study and is the guarantor

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

**References**


1. Wolf S. The pharmacology of placebos. Pharmacol Rev 1959; 11: 689-704.
2. Boussageon R, Gueyffier F, Moreau A, Boussageon V. [The difficulty of measurement of placebo effect]. Therapie 2006; 61: 185-90.
3. Hrobjartsson A, Gotzsche PC. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev 2010: CD003974. doi: 10.1002/14651858.CD003974.pub3.
4. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008; 336: 999-1003.
5. Benedetti F. Placebo effects: from the neurobiological paradigm to translational implications. Neuron 2014; 84: 623-37.
6. Stein N, Sprenger C, Scholz J, Wiech K, Bingel U. White matter integrity of the descending pain modulatory system is associated with interindividual differences in placebo analgesia. Pain 2012; 153: 2210-7.
7. Ernst E. Placebo: new insights into an old enigma. Drug Discov Today 2007; 12: 413-8.
8. Beecher HK. The powerful placebo. J Am Med Assoc 1955; 159: 1602-6.
9. Ernst E, Resch KL. Concept of true and perceived placebo effects. BMJ 1995; 311: 551-3.
10. Fisher S. Nonspecific factors as determinants of behavioralresponse to drugs. In In: Di Mascio A SR, eds. Clinical Handbook of psychopharmacology. New York: Science House 1971: 17-39.
11. Gotzsche PC. Is there logic in the placebo? Lancet 1994; 344: 925-6.
12. Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. Pediatr Res 2013; 74: 96-102.
13. Klassen TP, Hartling L, Craig JC, Offringa M. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS Med 2008; 5: e172.
14. Janiaud P, Lajoinie A, Cour-Andlauer F, et al. Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children. J Clin Epidemiol 2015; 68: 1221-31.


Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

15. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med 2008; 5: e166.

16. Curie A, Yang K, Kirsch I, et al. Placebo Responses in Genetically Determined Intellectual Disability: A Meta-Analysis. PLoS One 2015; 10: e0133316.

17. Grelotti DJ, Kaptchuk TJ. Placebo by proxy. BMJ 2011; 343:d4345.

18. Adams Nick P, Bestall Janine C, Lasserson Toby J, Jones P, Cates Christopher J. Fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database of Syst Rev 2008: CD003135. doi: 10.1002/14651858.CD003135.pub4.

19. Adams Nick P, Bestall Janine C, Malouf R, Lasserson Toby J, Jones P. Beclomethasone versus placebo for chronic asthma. Cochrane Database of Syst Rev 2005: CD002738. doi: 10.1002/14651858.CD002738.pub2.

20. Adams Stephen P, Sekhon Sarpreet S, Wright James M. Lipid-lowering efficacy of rosuvastatin. Cochrane Database of Syst Rev 2014: CD010254. doi: 10.1002/14651858.CD010254.pub2.

21. Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. BMJ 2005; 330: 516.

22. Barbui C, Cipriani A, Patel V, Ayuso-Mateos JL, van Ommeren M. Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis. Br J Psychiatry 2011; 198: 11-6, sup 1.

23. Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. Epilepsia 2010; 51: 7-26.

24. Bjorkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. J Psychopharmacol 2011; 25: 299-305.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

25. Bonini M, Di Mambro C, Calderon Moises A, et al. Beta2-agonists for exercise-induced asthma. Cochrane Database of Syst Rev 2013: CD003564. doi: 10.1002/14651858.CD003564.pub3.

26. Brown R, Taylor Matthew J, Geddes J. Aripiprazole alone or in combination for acute mania. Cochrane Database of Syst Rev 2013: CD005000. doi: 10.1002/14651858.CD005000.pub2.

27. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar Disord 2010; 12: 116-41.

28. Ducharme Francine M, Ni Chroinin M, Greenstone I, Lasserson Toby J. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database of Syst Rev 2010: CD005535. doi: 10.1002/14651858.CD005535.pub2.

29. Dwan K, Phillipi Carrie A, Steiner Robert D, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database of Syst Rev 2014: CD005088. doi: 10.1002/14651858.CD005088.pub3.

30. Fang Y, Wu X, Xu L, et al. Randomized-controlled trials of levetiracetam as an adjunctive therapy in epilepsy of multiple seizure types. J Clin Neurosci 2014; 21: 55-62.

31. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One 2013; 8: e63773.

32. Hayward G, Thompson Matthew J, Perera R, Glasziou Paul P, Del Mar Chris B, Heneghan Carl J. Corticosteroids as standalone or add-on treatment for sore throat. Cochrane Database of Syst Rev 2012: CD008268. doi: 10.1002/14651858.CD008268.pub2.

33. Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. J Psychopharmacol 2007; 21: 864-72.

34. Jesner Ora S, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database of Syst Rev 2007: CD005040. doi: 10.1002/14651858.CD005040.pub2.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

35. Kim SO, Ah YM, Yu YM, Choi KH, Shin WG, Lee JY. Effects of probiotics for the treatment of atopic dermatitis: A meta-analysis of randomized controlled trials. Ann Allergy Asthma Immunol 2014; 113: 217-26.

36. Koh Mariko S, Tee A, Lasserson Toby J, Irving Louis B. Inhaled corticosteroids compared to placebo for prevention of exercise induced bronchoconstriction. Cochrane Database of Syst Rev 2007: CD002739. doi: 10.1002/14651858.CD002739.pub3.

37. Lands Larry C, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for lung disease in cystic fibrosis. Cochrane Database of Syst Rev 2013: CD001505. doi: 10.1002/14651858.CD001505.pub3.

38. Manning P, Gibson Peter G, Lasserson Toby J. Ciclesonide versus placebo for chronic asthma in adults and children. Cochrane Database of Syst Rev 2008: CD006217. doi: 10.1002/14651858.CD006217.pub2.

39. Mason Anne R, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. Cochrane Database of Syst Rev 2013: CD005028. doi: 10.1002/14651858.CD005028.pub3.

40. Mbizvo Gashirai K, Dixon P, Hutton Jane L, Marson Anthony G. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. Cochrane Database of Syst Rev 2012: CD001901. doi: 10.1002/14651858.CD001901.pub2.

41. Normansell R, Walker S, Milan Stephen J, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database of Syst Rev 2014: CD003559. doi: 10.1002/14651858.CD003559.pub4.

42. Pulman J, Jette N, Dykeman J, Hemming K, Hutton Jane L, Marson Anthony G. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database of Syst Rev 2014: CD001417. doi: 10.1002/14651858.CD001417.pub3.

43. Ramaratnam S, Marson Anthony G, Baker Gus A. Lamotrigine add-on for drug-resistant partial epilepsy. Cochrane Database of Syst Rev 2001: CD001909. doi: 10.1002/14651858.CD001909.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

44. Southern Kevin W, Barker Pierre M, Solis-Moya A, Patel L. Macrolide antibiotics for cystic fibrosis. Cochrane Database of Syst Rev 2012: CD002203. doi: 10.1002/14651858.CD002203.pub4.

45. Spooner C, Saunders LD, Rowe Brian H. Nedocromil sodium for preventing exercise-induced bronchoconstriction. Cochrane Database of Syst Rev 2002: CD001183. doi: 10.1002/14651858.CD001183.

46. Suttajit S, Srisurapanont M, Maneeton N, Maneeton B. Quetiapine for acute bipolar depression: A systematic review and meta-analysis. Drug Des Devel Ther 2014; 8: 827-38.

47. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database of Syst Rev 2012: CD003407. doi: 10.1002/14651858.CD003407.pub5.

48. Tsapakis EM, Soldani F, Tondo L, Baldessarini RJ. Efficacy of antidepressants in juvenile depression: meta-analysis. Br J Psychiatry 2008; 193: 10-7.

49. Walters EH, Gibson Peter G, Lasserson Toby J, Walters Julia AE. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database of Syst Rev 2007: CD001385. doi: 10.1002/14651858.CD001385.pub2.

50. Watts K, Chavasse Richard JPG. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. Cochrane Database of Syst Rev 2012: CD006100. doi: 10.1002/14651858.CD006100.pub2.

51. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technol Assess 2014; 18: 1-106.

52. Evers S, Marziniak M, Frese A, Gralow I. Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies. Cephalalgia 2009; 29: 436-44.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

53. Rutherford BR, Mori S, Sneed JR, Pimontel MA, Roose SP. Contribution of spontaneous improvement to placebo response in depression: a meta-analytic review. J Psychiatr Res 2012; 46: 697-702.

54. Suchman AL, Ader R. Classic conditioning and placebo effects in crossover studies. Clin Pharmacol Ther 1992; 52: 372-7.

55. McDonald CJ, Mazzuca SA, McCabe GP, Jr. How much of the placebo 'effect' is really statistical regression? Stat Med 1983; 2: 417-27.

56. Whalley B, Hyland ME. Placebo by proxy: the effect of parents' beliefs on therapy for children's temper tantrums. J Behav Med 2013; 36: 341-6. .

57. Cohen D, Deniau E, Maturana A, et al. Are child and adolescent responses to placebo higher in major depression than in anxiety disorders? A systematic review of placebo-controlled trials. PLoS One 2008; 3: e2632.

58. Lewis DW, Winner P, Wasiewski W. The placebo responder rate in children and adolescents. Headache 2005; 45: 232-9.

59. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 (updated March 2011) The Cochrane Collaboration, 2011. (http://handbook.cochrane.org/)

60. Jadad AR, Enkin MW. Randomized Controlled Trials: Questions, Answers and Musings. 2nd edn. Oxford, UK: Blackwell Publishing Ltd, 2007: 48-61

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

**Figure and Legends:**

Figure 1: Flowchart of the literature search

Figure 2: Linear regression of the perceived placebo effect in children compared with adults for continuous outcomes

Each circle represents pooled data from pediatric (X axis) and adult (Y axis) studies for the same disease and with the same drug. When the circle is above the diagonal the perceived placebo effect is lower and when it is below, higher, in children compared with adults.

Figure 3: Linear regression of the perceived placebo effect in children compared with adults for binary outcomes Each circle represents pooled data from pediatric (X axis) and adult (Y axis) studies. When the circle is above the diagonal the perceived placebo effect is lower and when it is below, higher, in children compared with adults.

Accepted manuscript

© 2016 International Pediatric Research Foundation, Inc. All rights reserved

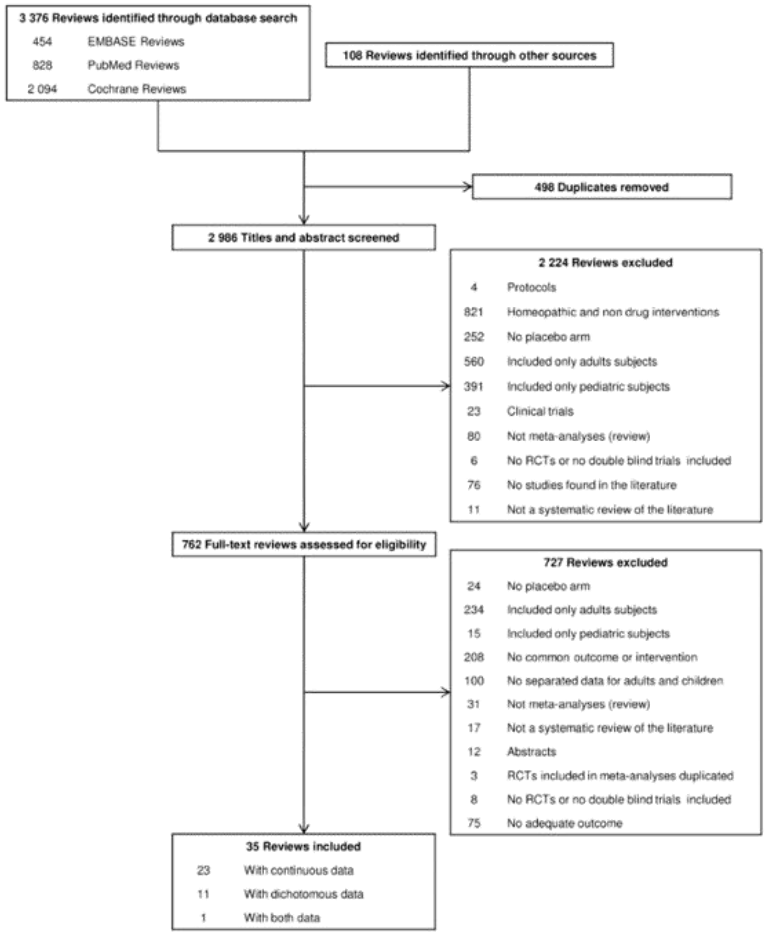
**Table 1: Characteristics of included randomized controlled trials**

| Variable | Continuous Outcomes | | | Binary Outcomes | | |
|---|---|---|---|---|---|---|
| | Total | Adults | Children | Total | Adults | Children |
| **Population:** *n studies (%)* | 214 | 126 (59%) | 88 (41%) | 82 | 53 (65%) | 29 (35%) |
| **Design:** *n studies (%)* | | | | | | |
| Crossover | 50 | 19 (38%) | 31 (62%) | | | |
| Parallel | 164 | 107 (65%) | 57 (35%) | 82 | 53 (65%) | 29 (35%) |
| **Outcome:** *n studies (%)* | | | | | | |
| Objective | 159 | 101 (64%) | 58 (36%) | | | |
| Subjective | 55 | 25 (45%) | 30 (55%) | 82 | 53 (65%) | 29 (35%) |
| **Diseases:** *n studies (%)* | | | | | | |
| Anemia | 10 | 9 (90%) | 1 (10%) | | | |
| Asthma | 62 | 49 (79%) | 13 (21%) | 4 | 3 (75%) | 1 (25%) |
| Atopic dermatitis | 24 | 4 (17%) | 20 (83%) | 5 | 1 (20%) | 4 (80%) |
| Autism spectrum disorder | | | | 3 | 2 (67%) | 1 (33%) |
| Bipolar disorder | 15 | 11 (73%) | 4 (27%) | 7 | 2 (29%) | 5 (71%) |
| Blood lipidic levels | 13 | 12 (92%) | 1 (8%) | | | |
| Chronic plaque psoriasis | 8 | 7 (88%) | 1 (13%) | | | |
| Cystic fibrosis | 9 | 3 (33%) | 6 (67%) | | | |
| Depression | | | | 15 | 10 (67%) | 5 (33%) |
| Drug resistant partial epilepsy | | | | 48 | 10 (21%) | 38 (79%) |
| Exercise induced asthma | 54 | 20 (37%) | 34 (63%) | | | |
| Generalized anxiety disorder | 2 | 1 (50%) | 1 (50%) | | | |
| Osteogenesis imperfecta | 2 | 1 (50%) | 1 (50%) | | | |
| Primary sleep disorder | 5 | 3 (60%) | 2 (40%) | | | |
| Sore throat | 3 | 1 (33%) | 2 (67%) | | | |
| Weight gain due to antipsychotic therapy | 7 | 5 (71%) | 2 (29%) | | | |

Accepted manuscript

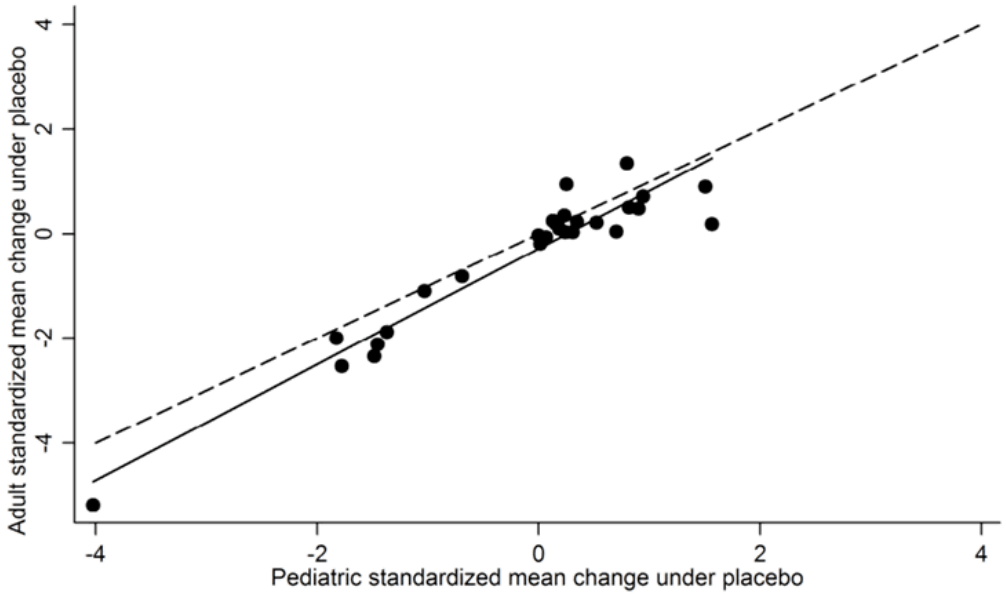
© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

Figure 1



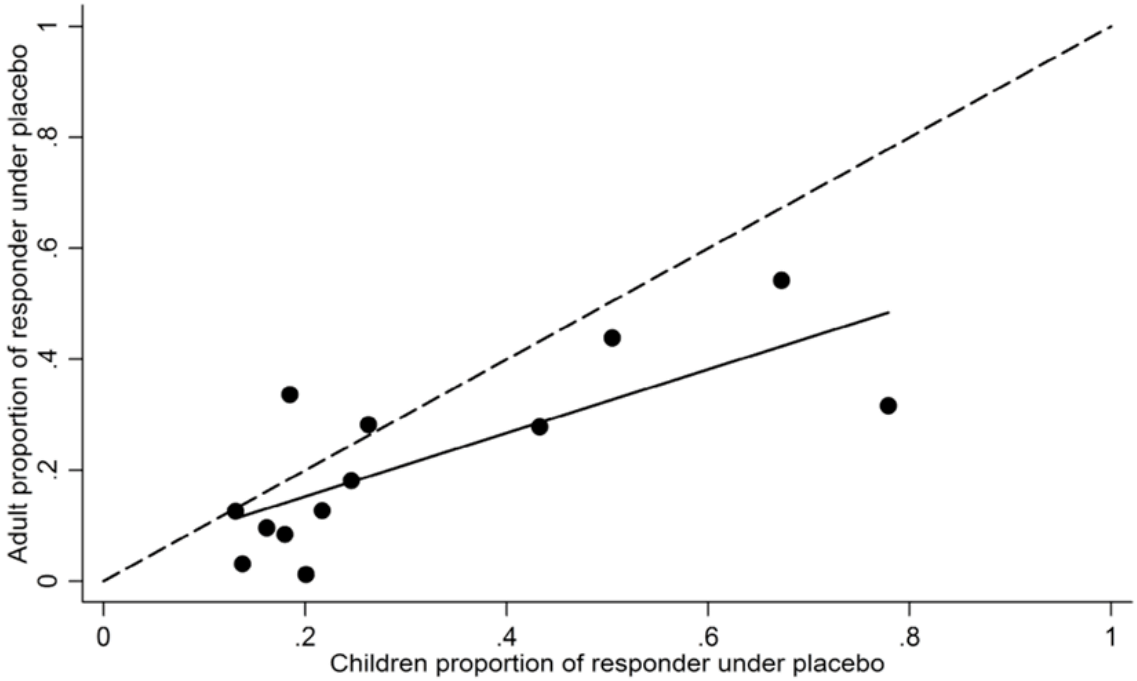

© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

Figure 2




© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

Figure 3




© 2016 International Pediatric Research Foundation, Inc. All rights reserved 

# The Adult Treatment Effect Model for Predicting the Potential Benefit in Children and Calibrating Adequately New Pediatric Clinical Trials

# The Adult Treatment Effect Model for Predicting the Potential Benefit in Children and Calibrating Adequately New Pediatric Clinical Trials

Perrine Janiaud [a], Catherine Cornua [b c] MD, PhD, Patrice Nony [a] MD, PhD, François Gueyffier [a, b] MD, PhD, Behrouz Kassaia [b c §] MD, PhD

a UMR 5558, CRNS, Claude Bernard University Lyon, France;

b Department of Pharmacotoxicology, CHU Lyon, France;

c EPICIME-Clinical Investigation Center, INSERM CIC1407/UMR5558, Bron, France;

**Abstract**

**Objective:** To predict the treatment effect and improve calibration of trials in the pediatric population by modelling the relation between the event rate in the treatment and the placebo group built from adult randomized controlled trials.

**Study Design and Setting:** We used systematic reviews of randomized, double-blind placebo-controlled trials evaluating similar drug interventions in adults and children. For each drug and indication, the adult treatment effect model was fitted from the risk in the control and in the treatment groups, assuming a constant relative risk (RR). The model was used to predict the treatment effect in children and calculate the sample size of clinical trials in children. The results were compared to the observed treatment effect and the sample size in the first pediatric trial.

**Results:** Out of 89 reviews, we built effect models for 10 drugs with a conclusive treatment benefit in adults. For 9 drugs the adult effect model predicted the treatment effect in children adequately. For 5 drugs, the pediatric trials were underpowered when compared with the sample size suggested by the model.

**Conclusion:** Effect models based on adult studies helped to predict the treatment effect in children and could improve calibration of new pediatric trials.

## 1. Introduction

In the past decades, regulatory requirements and incentives have promoted pediatric clinical research (1) increasing pediatric information of medicinal products (2). The proportion of pediatric clinical trials conducted in Europe has also increased from 8% in 2006 to 18% in 2015 (3). The EMA has also implemented a Paediatric Use Marketing Authorisation (PUMA) granting a 10-year extension of data protection for pediatric drug development. However, since its implementation 10 years ago, only 2 PUMAs have been granted (4).

Despite new regulation, the availability of evidence-based clinical decision in children remains limited leading to common off-label prescription based on the extrapolation of the observed benefit in adults (5, 6). The ethical and logistic constraints could explain the lack of pediatric evidence. It is still difficult to conduct successful clinical trials in children, because of the lack of research priorities (7), the paucity of institutional

§ Corresponding author: Prof. Behrouz Kassai, Hospices Civils de Lyon, Groupement hospitalier Est, Bâtiment « Les Tilleuls », 59 boulevard Pinel, 69003 Lyon, France, Telephone: +33(0)4 27 85 77 32, Fax: +33(0)4 72 35 73 64, E-mail address: behrouz.kassai-koupai@chu-lyon.fr

funding and the small market size for pediatric medicines (1, 2).

To maximize clinical research and to develop techniques to bridge the gap between adult and pediatric drug development, different frameworks have been proposed for extrapolating the benefit risk ratio observed in adult to children (8, 9). The extrapolation concept is built upon the assumptions of similar disease progression, clinical response to the intervention and exposure-response relationship between adults and children (8). The rationale behind those assumptions is based on the use of all available data without considering formally the quality of the evidence.

Systematic reviews and meta-analyses represent an important source of information when they are based on methodologically sound studies, to estimate the benefit of treatments, confirm efficacy, identify unanswered research questions, design and calibrate adequately new trials in children (10, 11). Yet, available evidence suggests that many new studies are not considering the available evidence provided by systematic reviews (12-14) and involve participants in underpowered and misconducted trials leading to inconclusive, biased or overestimated treatment benefit (15).

The treatment effect model law first defined by Boissel et al. in 1993 (16) stipulates that there is a natural relationship between the frequency of presenting an event in the control and in the treated group (17, 18). The treatment effect is modelled to deduct from the risk in the control group (or baseline risk) the potential risk in the treatment group (Figure 1). We assumed that the effect model fitted from adult studies might help predict the potential treatment effect in children and improve calibration of new trials according to the assumptions on the baseline risk. It also allows to identify outliers, avoid unnecessary repetitions of clinical trials when the effect estimate is precise, and identify patient subgroups that might benefit the most from the treatment. Consequently, the effect model can play an important role for formalizing the extrapolation process from adult to children. This paper focuses on the prediction of the treatment effect in children and the calibration of new pediatric trials when using the treatment effect model built from adult studies. Two illustrative examples show how the effect model could have been used for designing new pediatric trials.

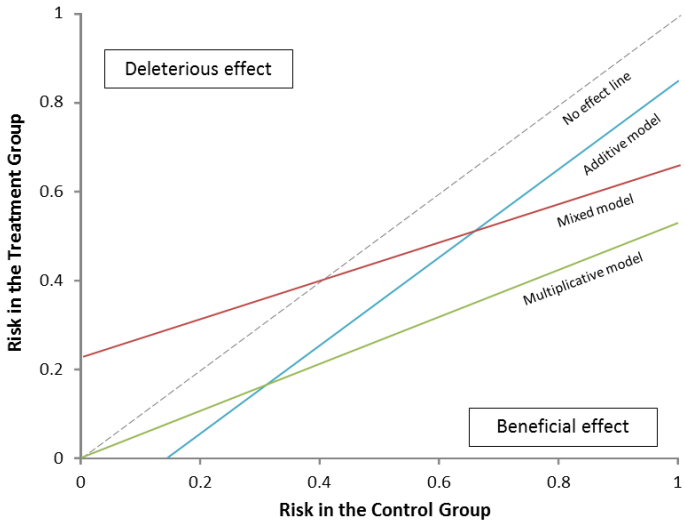



**Figure 1: The Effect Model Law**

*Two models are commonly used, the additive model ($r^T = r^C \times a$; with $a = r^T/r^C$) and the multiplicative model ($r^T = r^C + b$; with $b = r^T - r^C$), $r^T$ being the risk in the treatment group and $r^C$ the risk in the control group. The multiplicative model will often be preferred as it allows proportionality of the effect according to the initial risk. While, for a deleterious outcome the additive model will be preferred as the likelihood of the adverse effect does not depend on an underlying morbid condition. Those two models can be regrouped into one, as the mixed model ($r^E = a\ r^C + b$). With the mixed model, a treatment can have a deleterious effect and a beneficial effect depending on the baseline risk (i.e. the risk in the control group) (18).*

## 2. Methods

We screened PubMed, the Cochrane Library and Embase for meta-analyses that included randomized, double-blind, placebo-controlled trials that evaluated a drug intervention in adults and children. The literature search, selection criteria and data extraction have been described in details in a previous publication (10).

This work focuses only on meta-analyses that had a primary binary outcome. Duplicated RCTs between meta-analyses were removed. Trials from different meta-analyses evaluating the same drug in the same indication and with the same outcome were pooled.

As the purpose of this study was to explore the utility of the treatment effect model when evidence is available in adults, only meta-analyses including pediatric trials published after a minimum of four adult studies, with a range of baseline risk > 0,1, and with conclusive summary estimates were eligible. The number of four trials was chosen in order to have the minimum number of studies to fit an effect model.

### *2.1. Statistical analysis*

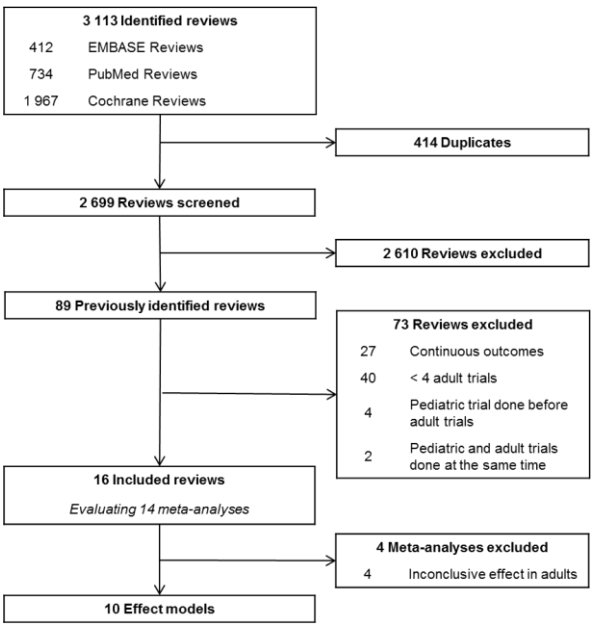
For each drug, separate relative risks (RR) were calculated for adults and children using a random effect model. A RR< 1 indicates a beneficial effect of the treatment and a RR> 1 a deleterious effect of the treatment.

The effect model was plotted using the Abbé plot. Each clinical trial was plotted using the risk in the control group on the X-axis and the risk in the treatment group on the Y-axis. The corresponding effect models were constructed using a linear regression following a RR constant model (18). A weighted regression using the inverse of the variance of the treatment effect in one group was used. The adjusted R-squared was reported to assess the strength of the model. The effect models were reduced to a multiplicative model if the constant term was < 0.03 and to an additive model if the β coefficient was equal to 1. In the cases where the model crossed the no effect line with no evidence of a deleterious effect, the effect model was forced into a multiplicative model. For all effect models when $r^T < r^C$, there was a beneficial effect of the treatment.

The effect models were computed using data from adult clinical trials evaluating a drug for a specific indication. The corresponding RRs in pediatric clinical trials were then plotted with their 95% confidence interval. Using the pediatric observed risk in the control group, the pediatric predicted risk in the treatment group was estimated using the effect model computed in adults. The predicted pediatric RRs were then calculated. The predicted $RR_p$ and observed $RR_o$ were compared using the relative risk ratio (RRR) defined as the predicted $RR_p$ divided by the observed $RR_o$. The corresponding p-values were calculated. A $RRR_{po} < 1$ indicated a larger observed treatment benefit and a $RRR_{po} > 1$ a larger expected treatment benefit.

We screened the original articles of pediatric trials to see whether they report the sample size calculation, and if they cited previous studies or systematic reviews. We calculated the sample size for the first pediatric trial using the adult effect model. This sample size was then

**Figure 2: Flowchart**




*Detailed flowchart for the screening on title, abstract and full text can be found in previous publication (10)*

**Table 1: Comparison of expected and observed RR in children and calibration with 80% power and alpha risk of 5%**

| | | | | | | | | | | According to 1st Pediatric trial | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Therapeutic Area** | **Drug** | **Disease** | **Outcome** | **N adult trials performed before** | **Adj. $R^2$** | **Predicted RR 95%CI** | **Observed RR 95%CI** | **RRR 95% CI** | **p-value** | **Obs. Power** | **N Obs. Per group** | **N Pred. per group** |
| Addictions | Bupropion | Smoking cessation | Abstinence at 6m FU | 6 | 0.997 | 0.89 [0.82; 0.96] | 0.81 [0.32; 2.03] | 0.92 [0.36; 2.30] | 0.85 | 6.27% | TTT=209 PCB=103 | TTT=256 PCB=128 |
| Gastro-enterology | Saccharomyces | Antibiotic associated diarrhea | AAD | 6 | 0.7476 | 0.35 [0.16; 0.75] | 1.58 [0.85; 2.90] | 4.49 [1.69; 1.90] | >0.01 | 36.84% | TTT=388 PCB=391 | 544 |
| Hematology | Erythropoietin | Anemia associated to Cancer | Hematological response | 8 | 0.8778 | 0.53 [0.39; 0.72] | 0.62 [0.46; 0.84] | 1.17 [0.76; 1.81] | 0.47 | 93% | 111 | 38 |
| Neurology | Gabapentin | Drug-resitant epilepsy | 50% responder | 4 | 0.999 | 0.88 [0.80; 0.97] | 0.86 [0.51; 1.42] | 0.97 [0.58; 1.63] | 0.91 | 11.49% | TTT=119 PCB=128 | 266 |
| Neurology | Lamotrigine | Drug-resitant epilepsy | 50% responder | 9 | 0.9926 | 0.90 [0.82; 1.00] | 0.47 [0.27; 0.84] | 0.52 [0.29; 0.94] | 0.03 | 79.56% | TTT=79 PCB=90 | 396 |
| Neurology | Levetiracetam | Drug-resitant epilepsy | 50% responder | 5 | 0.9916 | 0.72 [0.61; 0.83] | 0.44 [0.28; 0.69] | 0.62 [0.38; 1.00] | 0.049 | 97.94% | TTT=101 PCB=97 | 58 |
| Neurology | Topiramate | Drug-resitant epilepsy | 50% responder | 6 | 0.9903 | 0.66 [0.56; 0.78] | 0.51 [0.25; 1.03] | 0.77 [0.38; 1.58] | 0.48 | 52.3% | TTT=46 PCB=50 | 44 |
| Postoperative complications | Dolasetron | Postoperative nausea and vomiting | PONV | 8 | 0.9725 | 0.78 [0.65; 0.94] | 0.41 [0.27; 0.63] | 0.53 [0.33; 0.84] | >0.01 | 99.91% | 50 | 100 |
| Postoperative complications | Droperidol | Postoperative nausea and vomiting | PONV | 5 | 0.8990 | 0.54 [0.31; 0.92] | 0.89 [0.56; 1.41] | 1.66 [0.81; 3.37] | 0.16 | 8.12% | 32 | 52 |
| Postoperative complications | Ondansetron | Postoperative nausea and vomiting | PONV | 10 | 0.912 | 0.86 [0.69; 1.08] | 0.32 [0.16; 0.63] | 0.37 [0.18; 0.75] | > 0.01 | 98.86% | 30 | 284 |

FU: Follow-up; AAD: Antibiotic Associated Diarrhea; PONV: Postoperative Nausea and Vomiting; Obs: Observed; Pred: Predicted; TTT= Treatment group; PCB: Placebo group

A RR< 1 indicates a beneficial effect of the treatment and a RR> 1 a deleterious effect of the treatment. A $RRR_{po}$ < 1 indicated a larger observed treatment benefit and a $RRR_{po}$ > 1 a larger expected treatment benefit

compared with the true sample size of the first pediatric trial and the sample size reported in the method or statistical analysis sections of the original article. The two-independent proportion power analysis with a power of 80% and an alpha risk of 5% available in Stata/IC 12 was used to calculate the sample size. All statistical analyses were done using the Stata/IC 12 software 2012.

## 3. Results

Out of the 89 reviews (10) , 16 including 254 adult (68 407 participants) and 69 pediatric trials (11 327 participants) were considered (19-34). Fourteen drugs and therefore 14 meta-analyses were evaluated. Four meta-analyses with an inconclusive pooled treatment effect in adults were excluded for the effect model analysis. (Supplementary Table 1).

### *3.1. The effect Model and Prediction of the treatment effect in children*

Only 3 out of 10 drugs were assessed on a wide range of risk in the control group: dolasetron, droperidol and ondansetron for postoperative nausea and vomiting (19, 20, 33). For 6 drugs participants were at high risk, with the lowest risk in the control groups being > 0.6 for bupropion for smoking cessation (23), erythropoietin for anemia associated to cancer (26), and gabapentin, lamotrigine and levetiracetam for drug resistance epilepsy (27-29, 31, 32). Saccharomyces for antibiotic associated diarrhea (21, 24) were mostly evaluated in in low risk patients (< 0.4). For all drugs the risks in the control groups in the pediatric trials were in the same range as in adult trials (Supplementary Figures 1) except for saccharomyces.

The effect model was computed for 10 drugs including 191 adult (34 154 participants) and 47 pediatric trials (6 586 participants). Only multiplicative linear model fitted well adult trials with an adjusted R-squared ≥ 0.75 (Table 1).

For ondansetron, dolasetron, lamotrigine and levetiracetam, the treatment effects were underestimated by the adult effect models with a difference of at least 25% between the $RR_p$ and the $RR_o$ ($RRR_{po}$ < 1 and p-value < 0.05). For example, lamotrigine for drug resistant epilepsy, the $RRR_{po}$ was 0.52 (95%CI [0.29; 0.94]) ($RRR_{po}$, p-value= 0.037; $RR_p$ 0.90, 95% CI [0.82; 1.00] versus $RR_o$ 0.47, 95% CI [0.27; 0.84]). The treatment benefit was better for the observed compared with the expected treatment effect ($RR_o$ < $RR_p$) (Table 1). For saccharomyces for antibiotic associated diarrhea, the treatment effect was overestimated with adult effect model with a $RRR_{po}$ of 4.49 (95% CI [1.69; 11.90]) p-value < 0.001). The $RR_o$ was 1.58 (95% CI [0.85; 2.90] and the $RR_p$ was 0.35 (95% CI [0.16; 0.75]).

### *3.2. The effect model and study calibration in children*

Out of the 62 pediatric trials included in the different effect models, 49% percent (23/47) of articles did not report their sample size calculation. Fifty-one percent (24/47) reported their a priori sample size calculation among which 63% (15/24) reported the expected number of events in the control or the baseline risk for the outcome measured (Table 2). Only 6 out of 24 articles reported the use of previous trial results for their sample size calculation. In the rationale of the articles, 93% (44/47) cited previous studies of which only 9% (4/44) were a systematic review (Table 2).

**Table 2: Sample size calculation and prior evidence reported in the original pediatric trials (N=47)**

| **Sample size calculation:** | **% (n/N)** |
|---|---|
| Not reported: | 49% (23/47) |
| Reported elements of calculation: | 51% (24/47) |
| Number of events given by group: | 63% (15/24) |
| Only expected difference between groups: | 29% (7/24) |
| Calculation done on a different outcome compared to meta-analysis: | 8% (2/24) |
| **Prior evidence citation:** | |
| No citation of prior evidence: | 6% (3/47) |
| Citation of adult trials only: | 8% (4/47) |
| Citation of adult and pediatric trials: | 85% (40/47) |
| Citation of systematic reviews: | 8% (4/44) |

**Table 3: Comparison of the sample size using the effect model, reported a priori in the articles and enrolled finally in the study**

| Drug | Disease | Outcome | A priori power | N A priori per group | Obs. Power | N Obs. Per group | Pred. Power | N Pred. per group |
|---|---|---|---|---|---|---|---|---|
| Bupropion | Smoking cessation | Abstinence at 6m FU | | TTT=650 PCB=325 | 6.27% | TTT=209 PCB=103 | 80% | TTT=256 PCB=128 |
| Dolasetron | Postoperative nausea and vomiting | PONV | 80% | 113 | 99.91% | 50 | 80% | 100 |

The a pirori sample size calculation for the first pediatric trial was reported for 4 drugs out of 10. For levetiractam and topiramate, the sample size was calculated on an outcome that differed from the outcome selected for the meta-analyses and were therefore excluded. For bupropion, authors estimated an a priori baseline risk of 0.85 which corresponded to a risk predicted by the adult effect model of 0.77 with treatment. Using a power of 90% and a ratio 2:1, as reported by authors, resulted in 650 participants in the treatment and 325 in the control group (35). For dolasetron, the a priori reported baseline risk was 0.75, the risk predicted by the model in the treatment group of 0.59, and a sample size of 113 in each group (36) (Table 3).

For 7 drugs the sample size calculated with the adult effect model was bigger than the sample size enrolled in the studies. For 3 drugs, the samples enrolled were bigger compared with the sample calculated from the model (Table 1).

*3.3. Illustrative examples*

Ondansetron for postoperative nausea and vomiting was assessed by 10 trials in adults before the first trial in children in 1994. The pooled RR was 0.71, (95%CI [0.6, 0.83]) in adults while the RR for the first pediatric trial was 0.32 (95% CI [0.16; 0.63]). A multiplicative linear treatment effect model in adults was fitted (adjusted R-squared=0.96) (Figure 3). The response to the treatment was heterogeneous in adults ($I^2$= 85%) with some outliers. The predicted RR in children was $RR_p$ 0.86 (95% CI [0.69; 1.08]) versus the observed $RR_o$ 0.32 (95% CI [0.16; 0.63]), and the $RRR_{po}$ was 0.37 (95% CI [0.18; 0.75]) (p-value < 0.001). None of the pediatric trials reported the sample size calculation details but they all cited previously conducted adult trials in postoperative nausea and vomiting and one previous pediatric trial in post chemotherapy nausea and vomiting (37). As the effect size was finally higher than predicted, the sample size calculated from the model overestimated the number of patients required (284 patients per group) while the sample enrolled in the trial was 30 per group with a 98.86% power.

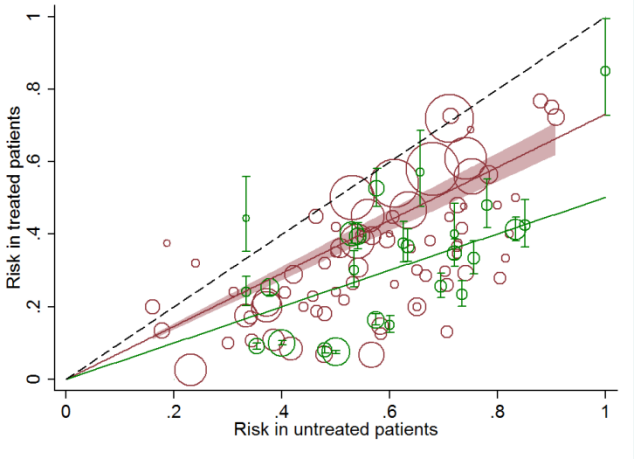
The second example is gabapentin in drug resistant epilepsy. The effect model in adults fitted with a multiplicative linear model (adjusted R-squared=0.999) presented in Figure 4. Four adult trials (RR 0.47 (95% CI [0.32; 0.71]) were conducted before the first published pediatric trial. The $RR_p$ was 0.88, 95% CI [0.80; 0.97] versus $RR_o$ 0.86, 95%CI [0.51; 1.42], and $RRR_{po}$ 0.97, 95% CI [0.58; 1.63] (p-value =0.91). No a priori sample size calculation was reported for the pediatric trial, the power of the trial with 119 participants in the treatment and 128 in the control group was 11.49%. According to the effect model in adults, 266 participants should have been enrolled per group to obtain an 80% power.

## 4. Discussion

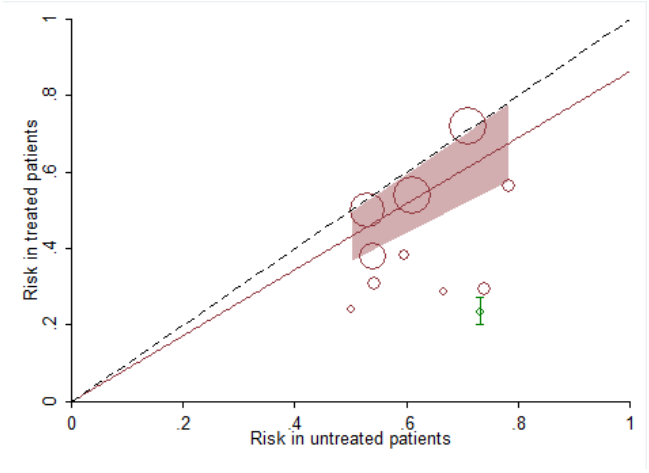
The effect model fitted with adult trials could have helped predict the treatment effect in children for 9 out 10 drugs assessed by systematic reviews and improve calibration of new trials for 6 drugs. Underestimations of the treatment effect using the adult effect model were

**Figure 3: Effect Model for Ondansetron for Postoperative Nausea and Vomiting**

*Red circles and red line correspond to the effect model in adults, in green the effect model in children. Each point represents a trial, the size of the circle represents the weight of each trials (i.e. the inverse of the variance).*



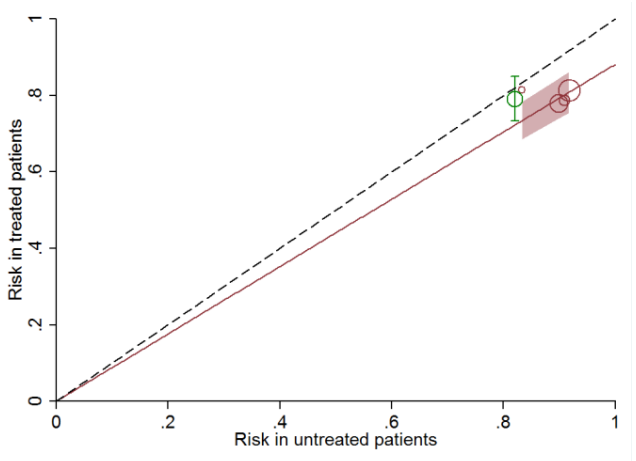

*(A) Effect model with all trials*
*The effect model in adults was riskT =0.7315302*riskC (adjusted R-squared= 0.9120) and in children riskT= riskT= 0.4977433* riskC (adjusted R-squared= 0.8176)*



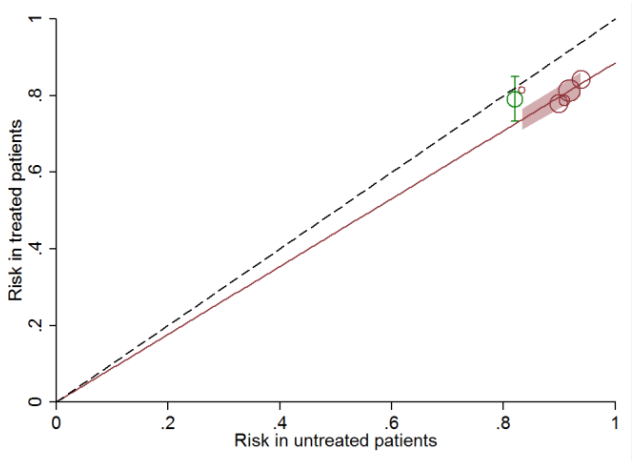

*(B) Effect model before the first pediatric trials*
*Ten adult trials were published beforehand and 5 pediatric trials were published the same year.*
*The effect mode in adults was riskT =0.8630062riskC (adjusted R-squared= 0.9578)*

**Figure 4: Effect Model for Gabapentin for Drug Resistant Epilepsy**

*Red circles and red line correspond to the effect model in adults, in green the effect model in children. Each point represents a trial, the size of the circle represents the weight of each trials (i.e. the inverse of the variance).*




*(A) Effect model with all trials*
*The effect model in adults was riskT= 0.8855016*riskC (adjusted R-squared= 0.9992).*




*(B) Effect model before the first pediatric trials*
*Four adult trials were published beforehand. The effect mode in adults was riskT=0.881275 *5riskC (adjusted R-squared=0.9990)*

observed. For ondansetron in postoperative nausea 50 patients were enrolled per group with a power of 99.91% while sample size calculated by the model with a power of 80% was 284 per group. The treatment effect was better $RR_o$ 0.54 (95% CI [0.46; 0.63]) than the effect predicted by the model ($RR_p$ 0.73, 95%CI [0.71; 0.75]). The examples of ondansetron, dolasetron and lamotrigine illustrate a possible greater effect in

favor of the treatment in children compared with adults. There was one example of overestimation of the treatment effect for saccharomyces. The risk in the control group for the first pediatric group was < 0.1 with no prior evidence of adults in that range of risks.

Pediatric clinical trials for 5 drugs were underpowered and led to inconclusive results in children. For example, gabapentin for drug resistant epilepsy, the power was 11.84% with 266 participants in each group detecting a treatment effect of $RR_o$= 0.47, (95% CI [0.13; 1.68]). According to the effect model in adults, the required sample size was 266 patients per group and 80% power to detect a treatment effect $RR_p$= 0.88 (95% CI [0.80; 0.97]). For ondansetron, previous pediatric trials had been also conducted for chemotherapy induced emesis (37). Using adult and data reported by Litman for a different indication to model the treatment effect would have helped to better calibrate the following pediatric trial (38).

Interestingly, for erythropoietin, levetiracetam and topiramate, the effect model could have avoided the unnecessary enrolment of participants. For example, erythropoietin enrolled 111 patients per groups for a power of 93% detecting a treatment effect $RR_o$= of 0.62 (95% CI [0.46; 0.84]) while 38 per group was estimated using the effect model in adults with a power of 80% to detect a treatment effect RRp= 0.53 (95% CI [0.39; 0.72]).

Our results show that 49% of our trials did not report the sample size calculation. And when reported, only 6 out of 24 clearly cited a previous study. Evidence of lack and incompleteness of reporting the sample size calculation are common (15, 39). In addition, Vickers et al. showed that one quarter of trials required five times as many patients as specified in the sample size calculation (39, 40). Inadequate powered trials and with up to 50% of trials design not referring to previous evidence are two identified reasons contributing to the waste in research (41, 42).

The main limitation of the effect model tool is the use of the proportion of events in the control group as a measure of the underlying risk. The proportion of events in the control group is measured with error and does not reflect the true underlying risk, (43, 44), which can result in an underestimation of the regression slope due to the regression to the mean. The use of the adult effect model requires to have a conclusive treatment effect and a large range of possible baseline risk in adults. Four drugs were excluded because, the adult treatment effects were inconclusive. Thus, overall 4 741 pediatric patients have been included in clinical trials without prior conclusive evidence in adults. However, the effect model uses summarized data from clinical trials which when published are readily available, requires little statistical implementation, identifies outliers and subgroups who might benefit more from the treatment. We based our rationale on the date of the trials publications but a trial can be published several years after the end of the study. Our results are also limited to the studies for which systematic reviews are available, not capturing all RCTs. We limited our study to situations where we had at least 4 adult trials before the first pediatric trial. It does not take into account adult or pediatric trials done afterwards or whether the effect models using all available pediatric trials would influence the adult effect model.

## 5. Conclusion

The effect model is a useful tool for formalizing the extrapolation of the treatment benefit from adults to children when evidence is available from adult trials. It also improves calibration of new clinical trials maximizing pediatric clinical research by reducing the number of underpowered trials.

Funds: Perrine Janiaud is currently receiving a grant from GlaxoSmithKline, France, for her three years PhD at the UMR 5558 CNRS. The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript

Conflict of interest: The authors have no conflict of interest

**References**

1. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. Br J Clin Pharmacol. 2015;79(3):357-69.
2. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014;73:2-13.
3. European Medicines Agency, (EMA). Report to the European Commission on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation1 and on the companies that have failed to comply with any of the obligations in this regulation - Year 2015 2106 Date Accessed: February 2017. Available from: http://ec.europa.eu/health//sites/health/files/files/paediatrics/2015_annual_report.pdf.
4. European Medicines Agency, (EMA). 10-year Report to the European Commission, General report on the experience acquired as a result of the application of the Paediatric Regulation 2016 Date Accessed: February 2017. Available from: http://ec.europa.eu/health//sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf.
5. Conroy S, McIntyre J, Choonara I, Stephenson T. Drug trials in children: problems and the way forward. Br J Clin Pharmacol. 2000;49(2):93-7.
6. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr. 2005;164(9):552-8.
7. Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gulmezoglu AM, et al. How to increase value and reduce waste when research priorities are set. Lancet. 2014;383(9912):156-65.
8. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011;128(5):e1242-9.
9. European Medicines Agency, (EMA). Reflection paper on extrapolation of efficacy and safety in paediatric medicine development2016 Date Accessed: February, 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf.
10. Janiaud P, Lajoinie A, Cour-Andlauer F, Cornu C, Cochat P, Cucherat M, et al. Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children. J Clin Epidemiol. 2015;68(10):1221-31.
11. Janiaud P, Cornu C, Lajoinie A, Djemli A, Cucherat M, Kassai B. Is the perceived placebo effect comparable between adults and children? A meta-regression analysis. Pediatr Res. 2016.
12. Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S, et al. Reducing waste from incomplete or unusable reports of biomedical research. Lancet. 2014;383(9913):267-76.
13. Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. J R Soc Med. 2007;100(4):187-90.
14. Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. Lancet. 376. England2010. p. 20-1.
15. Abdulatif M, Mukhtar A, Obayah G. Pitfalls in reporting sample size calculation in randomized controlled trials published in leading anaesthesia

journals: a systematic review. Br J Anaesth. 2015;115(5):699-707.

16. Boissel JP, Collet JP, Lievre M, Girard P. An effect model for the assessment of drug benefit: example of antiarrhythmic drugs in postmyocardial infarction patients. J Cardiovasc Pharmacol. 1993;22(3):356-63.
17. Boissel JP, Cucherat M, Nony P, Chabaud S, Gueyffier F, Wright JM, et al. New insights on the relation between untreated and treated outcomes for a given therapy effect model is not necessarily linear. J Clin Epidemiol. 2008;61(3):301-7.
18. Cucherat M, Boissel JP. [Effect models and meta-analysis]. Therapie. 1997;52(1):13-7.
19. Carlisle J, Stevenson Carl A. Drugs for preventing postoperative nausea and vomiting. Cochrane Database of Systematic Reviews [Internet]. 2006; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004125.pub2/abstract.
20. Figueredo ED, Canosa LG. Ondansetron in the prophylaxis of postoperative vomiting: a meta-analysis. J Clin Anesth. 1998;10:211-21.
21. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JNV, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: A systematic review and meta-analysis. JAMA - Journal of the American Medical Association. 2012;307:1959-69.
22. Henzi I, Walder B, Tramer MR. Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies. Br J Anaesth. 2000;83:761-71.
23. Hughes John R, Stead Lindsay F, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. Cochrane Database of Systematic Reviews [Internet]. 2014; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000031.pub4/abstract.
24. Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS ONE. 2012;7.
25. Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. Lancet Infect Dis. 2006;6:374-82.
26. Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews [Internet]. 2012; (12). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003407.pub5/abstract.
27. Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. Epilepsia. 2009;51:7-26.
28. Fang Y, Wu X, Xu L, Tang X, Wang J, Zhu G, et al. Randomized-controlled trials of levetiracetam as an adjunctive therapy in epilepsy of multiple seizure types. Journal of Clinical Neuroscience. 2014;21:55-62.
29. Mbizvo Gashirai K, Dixon P, Hutton Jane L, Marson Anthony G. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. Cochrane Database of Systematic Reviews [Internet]. 2012; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001901.pub2/abstract.
30. Pulman J, Jette N, Dykeman J, Hemming K, Hutton Jane L, Marson Anthony G. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews [Internet]. 2014; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001417.pub3/abstract.

31. Ramaratnam S, Marson Anthony G, Baker Gus A. Lamotrigine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews [Internet]. 2001; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001909/abstract.
32. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med. 2008;5(8):e166.
33. Frost F, Dailler F, Duflo F. [Ondansetron: a meta-analysis on its efficacy to prevent postoperative nausea and vomiting after craniotomy in adults and children]. Ann Fr Anesth Reanim. 2010;29:19-24.
34. Cates Christopher J, Cates Matthew J. Regular treatment with formoterol for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews [Internet]. 2012; (4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006923.pub3/abstract.
35. Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. Arch Pediatr Adolesc Med. 2007;161(11):1068-74.
36. Karamanlioglu B, Turan A, Memis D, Sut N. Comparison of oral dolasetron and ondansetron in the prophylaxis of postoperative nausea and vomiting in children. Eur J Anaesthesiol. 2003;20(10):831-5.
37. Litman RS, Wu CL, Catanzaro FA. Ondansetron decreases emesis after tonsillectomy in children. Anesth Analg. 1994;78(3):478-81.
38. Janiaud P, Cornu C, Kassai B. Extrapolation will never replace randomized clinical trials. J Clin Epidemiol. 2016;71:109-10.
39. Charles P, Giraudeau B, Dechartres A, Baron G, Ravaud P. Reporting of sample size calculation in randomised controlled trials: review. Bmj. 2009;338:b1732.
40. Vickers AJ. Underpowering in randomized trials reporting a sample size calculation. J Clin Epidemiol. 2003;56(8):717-20.
41. Moher D, Glasziou P, Chalmers I, Nasser M, Bossuyt PM, Korevaar DA, et al. Increasing value and reducing waste in biomedical research: who's listening? Lancet. 2016;387(10027):1573-86.
42. Ioannidis JP, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet. 2014;383(9912):166-75.
43. Schmid CH, Lau J, McIntosh MW, Cappelleri JC. An empirical study of the effect of the control rate as a predictor of treatment efficacy in meta-analysis of clinical trials. Stat Med. 1998;17(17):1923-42.
44. Sharp SJ, Thompson SG, Altman DG. The relation between treatment benefit and underlying risk in meta-analysis. Bmj. 1996;313(7059):735-8

# DISCUSSION

Our research focuses on the rationale use of all available evidence before extrapolating the benefit risk ratio from adults to children. The extrapolation, as proposed by the EMA, relies on the following assumptions: similar disease progression, similar responses, and similar exposure-response relationship between adults and children. Through this meta-epidemiological study, we emphasize that extrapolation might not replace a well-designed and adequately powered RCT in children. Assessment of all available evidence by using meta-analyses assessing a drug intervention in an indication in adults and children is a valuable complement before extrapolating from adults to children.

## *EXPLORING THE EVIDENCE FROM RCTs IN ADULTS FOR EXTRAPOLATION PROCESS*

Our results showed that significant heterogeneity, in the amount but also in the direction of the treatment effect, can be observed when comparing the treatment benefit between adults and children. When looking at inconclusive RORs for the treatment benefit, 45% of the meta-analyses showed a potential two-fold or greater difference between adults and children. Regarding the benefit risk ratio of drug interventions, large uncertainties were observed on the assessment of harm outcomes and hence of the benefit risk ratio, with only 13 out of 47 meta-analyses with a confirmed benefit risk ratio in favor of the treatment in adults and children. In some cases, clinically relevant differences between adults and children cannot be completely excluded. Adult trials cannot detect adverse events when they are specific to children. However, data from adult RCTs represent a valuable source of information that cannot be ignored.

We also showed heterogeneity between adults and children in the perceived placebo effect. The difference was statistically significant for binary outcomes while it could not be excluded for continuous outcomes. Such differences can be influenced by the design of the trial, parallel versus crossover, and the type of outcome, objective versus subjective. To ignore such differences can result into inconclusive results in children masking a potentially clinically relevant treatment effect. When a systematic review is conducted prior to a future

trial, we should explore the potential existence of a larger perceived placebo effect in children.

### *PREDICTION OF THE TREATMENT BENEFIT AND CALIBRATION OF NEW TRIALS*

The need to include children in RCTs without exposing them to unnecessary risks is the basis of the extrapolation concept. Thirty-eight out 120 meta-analyses had an inconclusive treatment effect on the benefit and 27 out 47 on harmful effects in adults and children. It seems inacceptable to include children in inconclusive trials even more so when adequate calibration from data in adults is possible. The calibration of the trial relies on the estimation of the expected treatment benefit using prior data or expertise. However, discrepancies between observed and expected benefit are common (56, 57). In addition to the systematic review and meta-analysis process, we used the effect model using adult data to predict the treatment effect in children studies and calibrate new trials according to the baseline risk. The effect model predicted well the treatment effect in children. For 5 drugs, the pediatric trials were underpowered and the treatment effects were inconclusive. The use of the effect adult effect model and of the observed risk in the control group in children could have helped to better calibrate those pediatric clinical trials. The effect model has also the advantage to give an overview of the assessment of the treatment effect, to identify incoherent results (i.e. outliers), highlight unnecessary repetitions of clinical trials and identify patients who might benefit the most from the treatment.

Efficiency also involves the identification of unmet needs and situation where additional research is unnecessary and thus increasing clinical utility of trials. Using a cumulative meta-analysis approach, we searched for trials iterated unnecessarily. For 37 meta-analyses with a conclusive treatment effect in children, our results showed that 63 trials including 6 164 children appeared to be unnecessary. The most striking example was for ondansetron for postoperative nausea and vomiting. Twenty-six placebo-controlled RCTs were conducted in children between 1994 and 2007. The cumulative treatment benefit was statistically significant as soon as the first trial in 1994. By 1995, the cumulative treatment benefit was confirmed and seemed to stabilize with a cumulative number of 825 included patients. For ondansetron, 19 trials including 1 662 were unnecessarily exposed to constraints and risks of a clinical trial (Appendix 3). As early as 1992, Lau et al. proposed to use the cumulative meta-analysis as a tracking tool of trials to help planned future ones (58). This is

supported by a systematic review of cumulative meta-analysis emphasizing that beneficial and harmful effects could have been detected earlier (59). It would have allowed an earlier availability of innovative beneficial drugs to patients and avoid exposing them to unnecessary harms (59) and thus avoid a waste of resources. We believe that the cumulative meta-analysis and the effect model can greatly contribute to the body of knowledge and help summarized available evidence to make better informed decision in the drug development and extrapolation framework.

### *QUALITY AND REPORTING OF TRIALS*

The uncertainties around the extrapolation concept are highly correlated to the availability, quality and comparability of the data. Evidences of poor reporting and of low quality are common in the literature (20). Our work was also limited to the lack of standardized reporting of pediatric age-groups and dose adjustment. Data were never reported according to the different pediatric age-ranges and the dose-adjustments were reported in only 36% of our meta-analyses. We acknowledge that the absence of such information limits our interpretation and that we were not able to identify potential existing differences across the different age groups. We would like also to reiterate the importance of using available reporting checklists such as the CONSORT (14), SPIRIT (15) and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (16). More importantly, those checklists are currently being adapted specifically to pediatric research which will help to work towards increasing the value of research (20).

Our study was also limited by the unavailability of similar outcomes or interventions between adults and children resulting in the exclusion of 219 reviews. For harmful events, the comparability between adults and children was also limited due to how they were collected and scaled according to their severity. Initiatives to develop core outcome sets specific to these populations (60, 61), and core outcomes sets common to adults and children should increase the number of usable reports. In addition, over 50% of research is designed without reference to existing evidence and they are not interpreted in the context of systematic assessments of other relevant evidence (13). The lack of transparency and completeness of research reports contribute to the waste of time and resources invested in clinical research (13, 62). It also poses a major ethical issue towards patients. Lack of reporting could either deprive patients from innovative drug intervention or expose them to avoidable harms.

## *PERSPECTIVES*

We acknowledge that using summarized data cannot permit to identify individual factors that could influence the response to the treatment. Using individual patient data to identify individual factors of interests could improve our approach. The extrapolation framework in all its aspects (systematic review, modeling and simulation, prediction, and quantification of difference between populations) should optimize the decision making when resources are scarce, avoid unnecessary studies if prevailing data exist, minimize the number of children to be enrolled in clinical studies and thus reduce the clinical trial burden for the pediatric population. More generally, systematic review of available evidence should be mandatory prior to any new research.

# CONCLUSION

The extrapolation process is not limited to drug development. Pediatricians routinely extrapolate results of adult studies when prescribing off-label medicine. Although regulatory agencies have developed extrapolation frameworks when it comes to drug development, those are difficult to apply in routine practice. Meta-epidemiological approaches can help researchers and physicians gain insight on the knowledge available to make better informed decisions.

The work conducted during this PhD has contributed to better acknowledge that extrapolation in pediatrics cannot solely be based on the adjustment of the dose according the weight or body surface or on PK-PD similarities. The extrapolation justification might benefit from systematic synthesis of all available data regardless of the source population or indication. We also suggest that the extrapolation process needs at least one adequately informed and powered RCT in children. However, pediatric studies are to be conducted when they address unmet needs.

Meta-epidemiological studies, cumulative meta-analysis and the effect model contribute efficiently to the extrapolation process and are useful before conducting any new research. We also emphasize the importance of using and developing methods of standardization of reporting RCTs and systematic reviews when children are involved in order reduce useless results and underpowered trials. This would help to work towards reducing waste of research resources and to improve research utility.

# REFERENCES


1. Ioannidis JP. Why most published research findings are false. PLoS Med. 2005;2(8):e124.

2. Contopoulos-Ioannidis DG, Baltogianni MS, Ioannidis JP. Comparative effectiveness of medical interventions in adults versus children. J Pediatr. 2010;157(2):322-30.e17.

3. Lathyris D, Panagiotou OA, Baltogianni M, Ioannidis JP, Contopoulos-Ioannidis DG. Safety of medical interventions in children versus adults. Pediatrics. 2014;133(3):e666-73.

4. Cohen E, Uleryk E, Jasuja M, Parkin PC. An absence of pediatric randomized controlled trials in general medical journals, 1985-2004. J Clin Epidemiol. 2007;60(2):118-23.

5. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. Br J Clin Pharmacol. 2015;79(3):357-69.

6. European Medicines Agency, (EMA). Paediatric RegulationDate Accessed: February 2017. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp.

7. European Medicines Agency, (EMA). 10-year Report to the European Commission, General report on the experience acquired as a result of the application of the Paediatric Regulation 2016 Date Accessed: February 2017. Available from: http://ec.europa.eu/health//sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf.

8. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011;128(5):e1242-9.

9. European Medicines Agency, (EMA). Reflection paper on extrapolation of efficacy and safety in paediatric medicine development2016 Date Accessed: February, 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf.

10. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med. 2008;5(8):e166.

11. Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. Pediatr Res. 2013;74(1):96-102.

12. Boissel JP, Collet JP, Lievre M, Girard P. An effect model for the assessment of drug benefit: example of antiarrhythmic drugs in postmyocardial infarction patients. J Cardiovasc Pharmacol. 1993;22(3):356-63.

13. Moher D, Glasziou P, Chalmers I, Nasser M, Bossuyt PM, Korevaar DA, et al. Increasing value and reducing waste in biomedical research: who's listening? Lancet. 2016;387(10027):1573-86.

14. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.

15. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-7.

16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41.

17. Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. Lancet. 2004;364(9436):803-11.

18. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998;352(9128):609-13.

19. Martinez-Castaldi C, Silverstein M, Bauchner H. Child versus adult research: the gap in high-quality study design. Pediatrics. 2008;122(1):52-7.

20. Clyburne-Sherin AV, Thurairajah P, Kapadia MZ, Sampson M, Chan WW, Offringa M. Recommendations and evidence for reporting items in pediatric clinical trial protocols and reports: two systematic reviews. Trials. 2015;16:417.

21. Crocetti MT, Amin DD, Scherer R. Assessment of risk of bias among pediatric randomized controlled trials. Pediatrics. 2010;126(2):298-305.

22. Moher D, Soeken K, Sampson M, Ben-Porat L, Berman B. Assessing the quality of reports of systematic reviews in pediatric complementary and alternative medicine. BMC Pediatr. 2002;2:3.

23. de Vries TW, van Roon EN. Low quality of reporting adverse drug reactions in paediatric randomised controlled trials. Arch Dis Child. 2010;95(12):1023-6.

24. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. Jama. 2004;291(20):2457-65.

25. Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. Bmj. 2005;330(7499):1049.

26. Chan AW, Hrobjartsson A, Jorgensen KJ, Gotzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. Bmj. 2008;337:a2299.

27. Pica N, Bourgeois F. Discontinuation and Nonpublication of Randomized Clinical Trials Conducted in Children. Pediatrics. 2016;138(3).

28. Benjamin DK, Jr., Smith PB, Murphy MD, Roberts R, Mathis L, Avant D, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. Jama. 2006;296(10):1266-73.

29. Thomson D, Hartling L, Cohen E, Vandermeer B, Tjosvold L, Klassen TP. Controlled trials in children: quantity, methodological quality and descriptive characteristics of pediatric controlled trials published 1948-2006. PLoS One. 2010;5(9).

30. Sammons HM, Choonara I. Clinical trials of medication in children, 1996-2002. Eur J Clin Pharmacol. 2005;61(2):165-7.

31. Cramer K, Wiebe N, Moyer V, Hartling L, Williams K, Swingler G, et al. Children in reviews: methodological issues in child-relevant evidence syntheses. BMC Pediatr. 2005;5:38.

32. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for Human use, (ICH). Clinical Investigation of Medicinal Products in the Pediatric Population, ICH-E112004 Date Accessed: February 2017. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf.

33. Williams K, Thomson D, Seto I, Contopoulos-Ioannidis DG, Ioannidis JP, Curtis S, et al. Standard 6: age groups for pediatric trials. Pediatrics. 2012;129 Suppl 3:S153-60.

34. Abdel-Rahman SM, Reed MD, Wells TG, Kearns GL. Considerations in the rational design and conduct of phase I/II pediatric clinical trials: avoiding the problems and pitfalls. Clin Pharmacol Ther. 2007;81(4):483-94.

35. Conroy S, McIntyre J, Choonara I, Stephenson T. Drug trials in children: problems and the way forward. Br J Clin Pharmacol. 2000;49(2):93-7.

36. Shirkey H. Therapeutic orphans. Pediatrics. 1999;104(3 Pt 2):583-4.

37. U.S Food and Drug Administration, (FDA). Pediatric Product DevelopmentDate Accessed: February 2017. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

38. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014;73:2-13.

39. Autret E. European regulatory authorities and pediatric labeling. Pediatrics. 1999;104(3 Pt 2):614-8.

40. Sachs AN, Avant D, Lee CS, Rodriguez W, Murphy MD. Pediatric information in drug product labeling. Jama. 2012;307(18):1914-5.

41. European Medicines Agency, (EMA). Report to the European Commission on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation1 and on the companies that have failed to comply with any of the obligations in this regulation - Year 2015 2106 Date Accessed: February 2017. Available from: http://ec.europa.eu/health//sites/health/files/files/paediatrics/2015_annual_report.pdf.

42. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr. 2005;164(9):552-8.

43. Riou S, Plaisant F, Maucort Boulch D, Kassai B, Claris O, Nguyen KA. Unlicensed and off-label drug use: a prospective study in French NICU. Acta Paediatr. 2015;104(5):e228-31.

44. European Medicines Agency, (EMA). Evidence of harm from off-label or unlicensed medicines in children2004 Date accessed: February, 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004021.pdf.

45. Johnson TN. The problems in scaling adult drug doses to children. Arch Dis Child. 2008;93(3):207-11.

46. Klassen TP, Hartling L, Craig JC, Offringa M. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS Med. 2008;5(8):e172.

47. Coppini R, Simons SH, Mugelli A, Allegaert K. Clinical research in neonates and infants: Challenges and perspectives. Pharmacol Res. 2016;108:80-7.

48. Frey U, von Mutius E. The challenge of managing wheezing in infants. N Engl J Med. 360. United States2009. p. 2130-3.

49. Waldman RJ, Hall WN, McGee H, Van Amburg G. Aspirin as a risk factor in Reye's syndrome. Jama. 1982;247(22):3089-94.

50. European Medicines Agnecy, (EMA). Concept paper on extrapolation of efficacy and safety in

medicine development2012 Date Accessed: February 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129285.pdf.

51. Manolis E, Osman TE, Herold R, Koenig F, Tomasi P, Vamvakas S, et al. Role of modeling and simulation in pediatric investigation plans. Paediatr Anaesth. 2011;21(3):214-21.

52. Boada JN, Boada C, Garcia-Saiz M, Garcia M, Fernandez E, Gomez E. Net efficacy adjusted for risk (NEAR): a simple procedure for measuring risk:benefit balance. PLoS One. 2008;3(10):e3580.

53. Trinquart L, Dechartres A, Ravaud P. Commentary: Meta-epidemiology, meta-meta-epidemiology or network meta-epidemiology? Int J Epidemiol. 2013;42(4):1131-3.

54. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions 2011. Available from: http://handbook.cochrane.org/.

55. Jadad AR, Enkin MW. Randomized Controlled Trials: Questions, Answers and Musings: Wiley; 2008.

56. Charles P, Giraudeau B, Dechartres A, Baron G, Ravaud P. Reporting of sample size calculation in randomised controlled trials: review. Bmj. 2009;338:b1732.

57. Vickers AJ. Underpowering in randomized trials reporting a sample size calculation. J Clin Epidemiol. 2003;56(8):717-20.

58. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med. 1992;327(4):248-54.

59. Clarke M, Brice A, Chalmers I. Accumulating research: a systematic account of how cumulative meta-analyses would have provided knowledge, improved health, reduced harm and saved resources. PLoS One. 2014;9(7):e102670.

60. Prinsen CA, Vohra S, Rose MR, King-Jones S, Ishaque S, Bhaloo Z, et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. Trials. 2014;15:247.

61. Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: Its Role in Improving Cochrane Reviews. Cochrane Database Syst Rev. 2012(5):Ed000041.

62. Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S, et al. Reducing waste from incomplete or unusable reports of biomedical research. Lancet. 2014;383(9913):267-76.

# Appendix 1: Research strategy for the literature database

Research strategy Cochrane library: (from 1998 to February 2014) the search was conducted from "The Cochrane Database of Systematic Reviews" in "all fields" and the review limit was added.

#1 child*

#2 preschool

#3 infants

#4 adolescent

#5 (#1 OR #2 OR #3 OR #4)

#6 adult*

#7 (#5 AND #6)

#8 placebo*

#9 (#7 AND #8)

Research strategy in PubMed: (from 1966 to February 2014) the following search limit was added: meta-analysis

(child* OR preschool OR infant OR adolescent) AND adult*) AND placebo

Research strategy in EMBASE: (from 1947 to February 2014) the following search filters were used: EMBASE AND humans AND meta-analysis.

((child* OR preschool OR infant OR adolescent) AND adult*) AND placebo

# Appendix 2: Included meta-analysis characteristics and references

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Allergy | Asthma | Abramson 2010 | Allergen extracts | Pollen | Asthma symptoms score | 13 | 447 | 3 | 96 | 5-15y | No adjustment according to weight |
| Infectious diseases | Cryptosporidiosis | Abubakar 2007 | Antiprotozoals | Nitazoxanide | Resolution Of Diarrhoea | 1 | 54 | 1 | 49 | 1-7y (1.8) | No adjustment according to weight but 5 times lower compared to adults |
| Pneumology | Asthma | Adams 1999 | Glucocorticoids | Budesonide | % FEV1 predicted | 6 | 117 | 4 | 119 | 6-17y | No adjustement according to weight |
| Pneumology | Asthma | Adams 2005 | Glucocorticoids | HFA-BDP | Change in FEV1 compared to baseline | 1 | 178 | 1 | 236 | 5-12y | No adjustement according to weight |
| Pneumology | Asthma | Adams 2008 | Glucocorticoids | Fluticasone | FEV1 % predicted change from baseline | 33 | 7224 | 5 | 899 | 4-11y | No adjustment according to weight, same as adults |
| Cardiology | Blood lipidic levels | Adams 2014 | Statins | Rosuvastatin | % change in total cholesterol | 12 | 1901 | 1 | 176 | 10-17y | No adjustment |
| Pneumology | ARDS (acute respiratory distress syndrome) | Afshari 2010 | Vasodilator | Nitric Oxide | Mortality | 3 | 712 | 1 | 108 | NA | No adjustment according to weight |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vaccines | Enterotoxigenic E. coli diarrhoea | Ahmed 2013 | Vaccines | Etec Wc-Rctb | AEs any symptoms | 3 | 230 | 4 | 529 | 6m-12y | No adjustment according to weight |
| Postoperative Complication | Postoperative infection after appendicitis | Andersen 2005 | Antiprotozoals | Metronidazole | Wound infection | 3 | 480 | 1 | 133 | 16m-15y | 0-3 yrs, 125mg; 3-6 yrs, 250 mg; 7-15 yrs, 500 mg |
| Postoperative Complication | Postoperative infection after complicated appendicitis | Andersen 2005 | Antiprotozoals | Metronidazole | Wound infection | 2 | 75 | 2 | 131 | NA | 20 mg/kg |
| Dermatology | Atopic Dermatitis | Ashcroft 2005 | Immuno-suppressive | Pimecrolimus 1% | Clinical Improvement | 1 | 88 | 4 | 695 | 2m-18Y | NA |
| Dermatology | Atopic Dermatitis | Ashcroft 2005 | Immuno-suppressive | Tacrolimus 0,03% | Clinical Improvement | 2 | 423 | 2 | 320 | 2-16y | NA |
| Dermatology | Atopic Dermatitis | Ashcroft 2005 | Immuno-suppressive | Tacrolimus 0,1% | Clinical Improvement | 2 | 421 | 2 | 327 | 2-16y | NA |
| Psychiatry | Depression | Barbui/Tsapakis 2011/2008 | Antidepressants | Paroxetine | ≥ 50% Responder | 3 | 239 | 3 | 654 | 7-18y | No adjustment according to weight and same dose as adults |
| Psychiatry | Depression | Barbui/Tsapakis 2011/2008 | Antidepressants | Fluoxetine | ≥ 50% Responder | 1 | 157 | 4 | 565 | 7-18y | No adjustment according to weight and same dose as adults |
| Psychiatry | Depression | Barbui/Tsapakis 2011/2008 | Antidepressants | Amitriptyline | ≥ 50% Responder | 1 | 38 | 3 | 78 | 12-18y | 5 mg/kg maximum of 300 mg |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pneumology | Acute cough | Becker 2015 | Anti-asthmatic | Salbutamol | Cough after 7 days | 1 | 101 | 1 | 59 | 1-10y | 0.10 mg/kg |
| Neurology | Refractory Epilepsy | Beyenburg 2010 | Antiepileptic | Lamotrigine | Responder Rate= 50% Seizure Reduction | 3 | 515 | 3 | 413 | 2-25y (10.6) | adjustment according to age with maximal dose determine |
| Neurology | Refractory Epilepsy | Beyenburg 2010 | Antiepileptic | Levetiracetam | Responder Rate= 50% Seizure Reduction | 8 | 1740 | 1 | 198 | (10) | 30 mg/kg |
| Neurology | Refractory Epilepsy | Beyenburg 2010 | Antiepileptic | Topiramate | Responder Rate= 50% Seizure Reduction | 8 | 832 | 2 | 182 | (10.1) | 6 mg/kg |
| Weight lost | Weight gain as a side effect of antipsychotic drug therapy | Bjorkmen-Bergman 2011 | Hypoglycemic agents | Metformin | % in body weight change | 5 | 264 | 2 | 70 | (11.6) | No adjustment according to weight |
| Pneumology | Exercise induced asthma | Bonini 2013 | Anti-asthmatic | Formoterol | Max % fall of FEV1 | 3 | 47 | 7 | 142 | 4-17y | No adjustment according to weight |
| Pneumology | Exercise induced asthma | Bonini 2013 | Anti-asthmatic | Salbutamol | Max % fall of FEV1 | 10 | 199 | 12 | 262 | 4-15y | No adjustment according to weight |
| Pneumology | Exercise induced asthma | Bonini 2013 | Anti-asthmatic | Salmeterol | Max % fall of FEV1 | 3 | 82 | 9 | 181 | 4-16y | No adjustment according to weight |
| Pneumology | Exercise induced asthma | Bonini 2013 | Anti-asthmatic | Terbutaline | Max % fall of FEV1 | 3 | 53 | 3 | 51 | 6-17y | No adjustment according to weight |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vaccine | Respiratory infections | Boyle 2000 | Vaccines | Ribomynyl | Number of infections per person (3m) | 4 | 1057 | 4 | 360 | NA | NA |
| Infectious diseases | Acute bacterial meningitis | Brouwer 2013 | Glucocorticoids | Dexamethasone | Mortality | 4 | 1255 | 13 | 1904 | 0-17y | 0.6 to 1.2 mg/m² or 0.6 to 0.9 mg/kg |
| Psychiatry | Acute mania | Brown 2013 | Antipsychotics | Aripiprazole | Mean change in YMRS from baseline at 3 weeks | 6 | 1570 | 2 | 295 | 10-17y (13.4) | No adjustment according to weight |
| Allergy | Asthma | Calamita 2006 | Allergen extracts | Pollen | Asthma symptoms score | 1 | 30 | 4 | 144 | NA | No adjustment according to weight |
| Allergy | Allergic conjunctivitis | Calderon 2011 | Allergen extracts | House Dust Mites | Total ocular symptom scores | 1 | 20 | 3 | 114 | NA | No adjustment according to weight |
| Allergy | Allergic conjunctivitis | Calderon 2011 | Allergen extracts | Pollen | Total ocular symptom scores | 18 | 1862 | 6 | 743 | 3-17y | No adjustment according to weight |
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Antihypertensive | Clonidine | Nausea or vomiting | 4 | 175 | 1 | 72 | NA | 3 mcg/kg |
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Glucocorticoids | Dexamethasone | Nausea or vomiting | 23 | 1812 | 3 | 143 | NA | 0.5 mg/kg |
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Antiemetic | Dixyrazine | Nausea or vomiting | 1 | 51 | 1 | 60 | NA | 0.25 mg/kg |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Antiemetic | Dolasetron | Nausea or vomiting | 8 | 1622 | 1 | 50 | NA | 1 mg/kg with maximal dose established |
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Antipsychotics | Droperidol | Nausea or vomiting | 38 | 3295 | 8 | 363 | NA | 0.08 to 0.75 mg/kg |
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Antispasmodic | Glycopyrrolate | Nausea or vomiting | 1 | 53 | 1 | 40 | NA | 7.5 mcg/kg |
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Antiemetic | Hyoscine | Nausea or vomiting | 5 | 513 | 1 | 40 | NA | No adjustment according to weight |
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Antiemetic | Metoclopramide | Nausea or vomiting | 38 | 1884 | 4 | 146 | NA | 0.12 to 0.25 mg/kg |
| Postoperative Complication | Postoperative nausea and vomiting | Carlisle 2006 | Antiemetic | Ondansetron | Nausea or vomiting | 49 | 4060 | 13 | 880 | NA | 0.10 to 0.15 mg/kg (not adjusted for all trials) |
| Pneumology | Asthma | Cates 2012 | Anti-asthmatic | Formoterol | Non-fatal SAEs | 6 | 1274 | 3 | 1700 | 5-19y (9.7) | No adjustment according to weight |
| Vaccine | Influenza in asthma | Cates 2013 | Vaccines | Im Trivalent Inactivated Type A And B | Asthma exacerbation within 2 weeks (Aes) | 2 | 1526 | 1 | 712 | (9.4 ±13.8) | No adjustment according to weight |
| Pneumology | Asthma | Chong 2016 | Corticosteroids | Beclomethasone | Exacerbations requiring oral corticosteroids | 1 | 240 | 2 | 311 | 1-18y | no |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Allergy | Asthma | Compalati 2009 | Allergen extracts | House Dust Mites | 12 hour reflective total symptom score (TSS) | 1 | 50 | 3 | 131 | 6-18y | No adjustment according to weight |
| Allergy | Allergic Rhinitis | Compalati 2009 | Allergen extracts | House Dust Mites | Effect on total asthma symptom score | 1 | 19 | 3 | 181 | 5-18y | No adjustment according to weight |
| Allergy | Seasonal Allergic Rhinitis (SAR) | Compalati 2011 | Antihistaminic | Fexofenadine | Effect on total rhinitis symptom score | 4 | 1166 | 1 | 932 | 5-12y (8.8) | No adjustement according to weight |
| Psychiatry | Bipolar disorder | Correll 2010 | Antipsychotics | Aripiprazole | Response Rate | 3 | 854 | 2 | 296 | 10-17y | No adjustment according to weight |
| Psychiatry | Bipolar disorder | Correll 2010 | Antipsychotics | Olanzapine | Response Rate | 2 | 254 | 1 | 161 | 13-17y (15.3) | No adjustment according to weight |
| Psychiatry | Bipolar Disorder | Correll 2010 | Antipsychotics | Risperidone | Diminution YMRS score | 1 | 259 | 2 | 169 | 10-17y (13) | No adjustment according to weight |
| Vaccine | Influenza | Demicheli/ Jefferson 2014/2012 | Vaccines | Inactivated Tri or Bivalent Vaccines | Influenza | 14 | 21450 | 5 | 1628 | 6m-19y | No adjustment according to weight |
| Allergy | Rhinoconjunctivitis | Devillier 2014 | Allergen extracts | Grass pollen | Symptoms score | 8 | 2975 | 3 | 844 | 5-17y | No adjustment according to weight |
| Pneumology | Asthma | Ducharme 2010 | Anti-asthmatic | Salmeterol | Exacerbations requiring oral steroids | 6 | 1034 | 5 | 409 | (12.1y) | No adjustment according to weight, same as adults |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pain | Pain Management | Dunlop 2006 | NSAID | Ketorolac | Total dose of strong opioid in 4h | 1 | 24 | 1 | 22 | NA | 0.9 mg/kg |
| Genetic disorder | Osteogenesis imperfecta | Dwan 2014 | Bis-phosphonates | Alendronate | Mean % change in spine BMD | 1 | 64 | 1 | 112 | 4-19y (11y) | No adjustment according to weight, if <40 kg: 5 mg |
| Addictions | Smokeless tobacco addiction | Ebbert 2011 | Drugs used in addictive disorders | Nicotine Patch | ≥ 6 Months Abstinence | 3 | 833 | 1 | 198 | 14-19y | No adjustment according to weight and same dose as adults |
| Infectious diseases | Influenza | Falagas 2010 | Antivirals | Oseltamivir | Influenza complications | 3 | 905 | 1 | 452 | 1-12y | 4 mg/kg maximum of 200 mg |
| Infectious diseases | Influenza | Falagas 2010 | Antivirals | Zanamivir | Influenza complications | 5 | 1363 | 1 | 346 | 5-12y | No adjustment according to weight, same as adults |
| Neurology | Partial Seizure Epilepsy | Fang 2013 | Antiepileptic | Levetiracetam | ≥ 50% Reduction In Seizure Frequency | 8 | 1980 | 2 | 314 | NA | NA |
| Sleep disorder | Primary Sleep Disorder | Ferracioli-Oda 2013 | Hypnotics and Sedatives | Melatonin | Reduction of sleep latency | 10 | 549 | 2 | 95 | NA | No adjustment according to weight |
| Postoperative Complication | Postoperative nausea and vomiting | Figueredo 1997 | Antiemetic | Ondansetron | PONV | 37 | 10344 | 13 | 1734 | NA | No adjustment according to weight, lower dose compared to adults |
| Postoperative Complication | Postoperative nausea and vomiting | Frost 2010 | Antiemetic | Ondansetron | Vomitting | 6 | 408 | 3 | 149 | NA | 0.15 mg/kg |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Infectious diseases | Bacterial infection in afebrile neutropenic chemotherapy patients | Gafter-Gvili 2012 | Antibiotic | Trimethroprim/ Sulfamethoxazole | All-cause mortality | 3 | 150 | 2 | 151 | NA | 3.0 mg/kg (not adjusted for all trials) |
| Gastroenterology | Clostridium difficile-associated diarrhea | Goldenberg 2013 | Probiotic | Lactobacillus | Incidence of CDAD | 9 | 1819 | 2 | 359 | (4.6y) | No adjustment according to weight |
| Gastroenterology | Clostridium difficile-associated diarrhea | Goldenberg 2013 | Probiotic | Saccharomyces | Incidence of CDAD | 6 | 938 | 1 | 246 | 6m-15y (4.9y) | No adjustment according to weight |
| Vaccine | Malaria | Graves 2006 | Vaccines | Msp1/Msp2/Resa Vaccine in Adjuvant Montanide | Firmness at injection site | 1 | 33 | 1 | 240 | 5-9y | No adjustment according to weight, same as adults |
| Infectious diseases | Opportunistic infections in HIV patients | Grimwade 2003/2006 | Antibiotic | Trimethroprim/ Sulfamethoxazole | Mortality | 3 | 1384 | 1 | 534 | 1-15y (4.2) | If <5yrs, 240mg; if >5yrs, 480mg |
| Pneumology | Acute upper respiratory tract infections | Hao 2015 | Probiotic | Lactobacillus | Patients with URTI episodes | 2 | 470 | 5 | 1457 | < 12y | No adjustment according to weight |
| Pain | Sore throat | Hayward 2012 | Glucocorticoid | Dexamethasone | Complete resolution of pain at 24h | 1 | 77 | 3 | 366 | 4-18y (10.8y) | 0.6 mg/kg |
| Gastroenterology | Antibiotic associated diarrhea | Hempel 2012 | Probiotic | Bacillus | Antibiotic-associated diarrhea | 1 | 247 | 1 | 120 | (6.6y) | No adjustment according to weight |
| Gastroenterology | Antibiotic associated diarrhea | Hempel 2012 | Probiotic | Genera blends | Antibiotic-associated diarrhea | 18 | 2532 | 6 | 533 | (5.1y) | No adjustment according to weight |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gastroenterology | Antibiotic associated diarrhea | Hempel 2012 | Probiotic | Lactobacillus | Antibiotic-associated diarrhea | 12 | 1818 | 5 | 716 | (8.5y) | No adjustment according to weight |
| Gastroenterology | Antibiotic associated diarrhea | Hempel 2012 | Probiotic | Saccharomyces | Antibiotic-associated diarrhea | 8 | 1083 | 4 | 1514 | NA | No adjustment according to weight |
| Postoperative Complications | Postoperative nausea and vomiting | Henzi 1998 | Propulsive | Metoclopramide | Late vomiting (0-24h) | 4 | 339 | 5 | 323 | NA | 0.1 to 0.25 mg/kg |
| Postoperative Complications | Postoperative nausea and vomiting | Henzi 2000 | Glucocorticoid | Dexamethasone | Vomiting Free | 3 | 159 | 5 | 471 | NA | NA |
| Psychiatry | Generalized Anxiety Disorder | Hidalgo 2007 | Antidepressant | Sertraline | HAM-A Hamilton Anxiety Scale | 1 | 370 | 1 | 22 | NA | No adjustment according to weight |
| Pneumology | Non-cystic Fibrosis Bronchiectasis | Hnin 2015 | Antibiotic | Azithromycin | Exacerbations | 2 | 224 | 1 | 89 | | 30 mg/kg |
| Addictions | Smoking addiction | Hughes 2014 | Drugs used in addictive disorders | Bupropion | Abstinence At 6 Months Follow-Up | 9 | 3323 | 2 | 312 | 14-16y (16y) | No adjustment according to weight and same dose as adults |
| Infectious diseases | Influenza | Jefferson 2014 | Antivirals | Oseltamivir | Complication: bronchitis | 8 | 4452 | 3 | 1359 | NA | 2 mg/kg |
| Infectious diseases | Influenza | Jefferson 2014 | Antivirals | Zanamivir | Complication: bronchitis | 12 | 6072 | 2 | 337 | 5-12y | No adjustment according to weight and same dose as adults |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Psychiatry | Autism spectrum disorder | Jesner 2007 | Antipsychotics | Risperidone | Improvement Of The Clinical Global Impression Score | 1 | 30 | 2 | 178 | 5-17y (8.2y) | 2.5 mg if 20-40 kg and 3.3 mg if >45 kg |
| Gastroenterology | Antibiotic associated diarrhea | Kale-Phradhan 2010 | Probiotic | Lactobacillus | Occurrence of Diarrhea | 6 | 1279 | 4 | 585 | NA | No adjustment according to weight, lower dose compared to adults |
| Infectious diseases | Acute purulent rhinitis | Kenealy 2013 | Antibiotic | Amoxicillin | Persistent rhinitis | 1 | 384 | 1 | 113 | 2-10y | No adjustment according to weight, 5 times lower compared to adults |
| Pneumology | Asthma | Kew 2015 | Antibiotic | Troleandomycin | Steroid reduction | 1 | 56 | 1 | 11 | 6-17y (13.8) | No adjustment according to weight, same as adults |
| Pneumology | Post-extubation stridor | Khemani 2011 | Glucocorticoids | Dexamethasone | Re-intubation rate | 2 | 774 | 3 | 266 | NA | 0.25 to 0.5 mg/kg |
| Dermatology | Atopic Dermatitis | Kim 2014 | Probiotic | Lactobacillus | Change in total SCORAD | 4 | 120 | 20 | 1421 | 1m-13y | No adjustment according to weight |
| Pneumology | Common acute respiratory infections | King 2014 | Probiotic | Lactobacillus | Mean duration of illness | 6 | 1581 | 2 | 1409 | (2.5y) | No adjustment according to weight |
| Pneumology | Bronchoconstriction | Koh 2007 | Corticosteroids | Budesonide | % fall index in FEV1 | 1 | 34 | 4 | 117 | 6-18y (10.3y) | No adjustement according to weight but lower dose compared to adults |
| Postoperative Complications | Postoperative nausea and vomiting | Kranke 2001 | Antiemetic | Dimenhydrinate | Ponv Free | 3 | 1579 | 4 | 325 | NA | 0.5 to 2.2 mg/kg IV |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pneumology | Cystic Fibrosis | Lands 2013 | NSAID | Ibuprofen | Annual rate change in % predicted FEV1 | 1 | 35 | 3 | 191 | 5-18y | 20 to 30 mg/kg, maximum of 1600mg |
| Infectious diseases | Cholera | Leibovici-Weissman 2014 | Antibiotic | Tetracycline | Bacteriological failure | 2 | 103 | 1 | 91 | 1-5y | 6.5 mg/kg |
| Pneumology | Asthma | Manning 2008 | Glucocorticoid | Ciclesonide | Change in FEV1 predicted | 2 | 1322 | 1 | 891 | 4-11y (8.2y) | No adjustment according to weight |
| Dermatology | Chronic plaque psoriais | Mason 2013 | Antipsoriatics | Calcipotriol | Investigators' Assessment of Overall Global Improvement | 7 | 2032 | 1 | 77 | 2-14y (10y) | No adjustment according to weight |
| Neurology | Drug-resistant partial epilepsy | Mbizvo 2012 | Antiepileptic | Levetiracetam | 50% Responders | 8 | 1446 | 2 | 296 | 3-17y | 60 mg/kg |
| Allergy | Seasonal Allergic Rhinitis (SAR) | Meadows 2013 | Allergen extracts | Pollen | Symptoms score | 28 | 3248 | 9 | 1343 | 4-18y | No adjustment according to weight |
| Neurology | Convulsions in cerebral malaria | Meremikwu 2002 | Antiepileptic | Phenobarbitone | Death within 6 months | 1 | 48 | 1 | 340 | 9m-3y | 20 mg/kg |
| Pneumology | Acute Asthma | Mohammed 2007 | Anticonvulsant | Magnesium sulphate IV | Hospital admission | 6 | 625 | 3 | 115 | 1-18y | Adjustment according to weight with maximal dose determine |
| Pneumology | Acute Asthma | Mohammed 2007 | Anticonvulsant | Magnesium sulphate nebulised | Hospital admission | 4 | 297 | 1 | 62 | 5-17y | No adjustment according to weight |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gastroenterology | Eosinophilic esophagitis | Murali 2015 | Glucocorticoid | Budesonide | Clinical response | 1 | 23 | 1 | 36 | NA | No adjustment according to weight |
| Gastroenterology | Eosinophilic esophagitis | Murali 2015 | Glucocorticoid | Fluticasone | Histological response | 2 | 70 | 1 | 31 | NA | No adjustment according to weight |
| Gastroenterology | Anal fissure | Nelson 2012 | Vasodilator spasmolytic | Glyceryl Trinitrate Ointment (Gtn) | Persistence or recurrence | 9 | 936 | 3 | 118 | NA | 0.2% cream |
| Pneumology | Asthma | Normansell 2014 | Antiasthmatic | Omalizumab | Serious AE | 3 | 1317 | 1 | 317 | 6-12y | 0.02 mg/kg/IgE |
| Allergy | Asthma | Normansell 2015 | Allergen extracts | Grass pollen | Serious AE | 3 | 195 | 1 | 35 | 6-17y | No adjustment according to weight |
| Allergy | Asthma | Normansell 2015 | Allergen extracts | HDM | 50% Reduction In Inhaled Steroid Usage | 5 | 1346 | 4 | 213 | 5-15y | No adjustment according to weight |
| Psychiatry | Obsessive Compulsive Disorder | Ori 2015 | Antibiotic | d-cycloserine | Treatment responders | 1 | 24 | 3 | 74 | (13.4y) | No adjustment according to weight |
| Psychiatry | Post-traumatic Stress Disorder | Ori 2015 | Antibiotic | d-cycloserine | Treatment responders | 3 | 149 | 1 | 47 | (12.5y) | No adjustment according to weight |
| Postoperative Complications | Post-tonsillectomy bleeding | Plante 2012 | Glucocorticoids | Dexamethasone | Post-tonsillectomy bleeding | 5 | 258 | 11 | 957 | 0-18y | Adjustment according to weight with maximal dose determine |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neurology | Drug-resistant partial epilepsy | Pulman 2014 | Antiepileptic | Topiramate | 50% Reduction In Seizure Frequency | 10 | 1312 | 1 | 86 | 2-16y | 6 mg/kg |
| Allergy | Allergic Rhinitis | Radulovic 2011 | Allergen extracts | House Dust Mites (D. pteronyssinus and D. farinea | Symptoms score | 1 | 19 | 3 | 97 | 4-18y | No adjustment according to weight |
| Neurology | Drug resistant partial epilepsy | Ramaratnam 2010 | Antiepileptic | Lamotrigine | 50% Responder | 10 | 841 | 1 | 199 | 2-16y | 2.7 to 12.9 mg/kg depending on use of other AEDs |
| Pain | Acute abdominal pain | Ranji 2006 | Opioids | Morphine sulfate IV | Changes in abdominal examination results | 3 | 192 | 1 | 108 | 5-16y | Adjustment according to weight |
| Neurology | Drug resistant partial epilepsy | Rheims 2008 | Antiepileptic | Gabapentin | 50% Responder Rate | 5 | 959 | 1 | 247 | 3-12y (9) | 23 to 35 mg/kg, 57% higher compared to adults |
| Neurology | Drug resistant partial epilepsy | Rheims 2008 | Antiepileptic | Lamotrigine | 50% Responder Rate | 9 | 598 | 1 | 199 | 2-16y | 3 to 15 mg/kg, similar dose to adults |
| Neurology | Drug resistant partial epilepsy | Rheims 2008 | Antiepileptic | Levetiracetam | 50% Responder Rate | 4 | 998 | 1 | 198 | 4-17y (10y) | 60 mg/kg, 100% higher compared to adults |
| Neurology | Drug resistant partial epilepsy | Rheims 2008 | Antiepileptic | Oxcarbazepine | 50% Responder Rate | 1 | 694 | 1 | 267 | 3-17 (11y) | 30 to 36 mg/kg, 60% higher compared to adults |
| Neurology | Drug resistant partial epilepsy | Rheims 2008 | Antiepileptic | Topiramate | 50% Responder Rate | 8 | 966 | 1 | 86 | 2-16y (9y) | 6 mg/kg, 50% lower compared to adults |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Postoperative Complications | Bleeding after tonsillectomy | Riggin 2013 | NSAID | Ketoprofen | Most severe post-tonsillectomy bleeding | 3 | 222 | 2 | 139 | NA | 2 to 3 mg/kg |
| Postoperative Complications | Bleeding after tonsillectomy | Riggin 2013 | NSAID | Ketorolac | Most severe post-tonsillectomy bleeding | 1 | 40 | 1 | 105 | NA | 1 mg/kg |
| Gastroenterology | Antibiotic associated diarrhea | Ritchie 2012 | Probiotic | Lactobacillus | Diarrhea | 3 | 354 | 3 | 388 | NA | No adjustment according to weight |
| Gastroenterology | Helicobacter pylori infection | Ritchie 2012 | Probiotic | Lactobacillus | Improvement of erradication rate | 3 | 200 | 1 | 86 | NA | NA |
| Gastroenterology | Antibiotic associated diarrhea | Ritchie 2012 | Probiotic | Saccharomyces | Diarrhea | 3 | 650 | 1 | 246 | NA | No adjustment according to weight |
| Infectious diseases | Fungal infection in Cancer patients | Robenshtok 2007 | Antifungal | Ketoconazole | Invasive fungal infection | 2 | 145 | 1 | 125 | (7y) | No adjustment according to weight |
| Addictions | Alcohol dependence | Rosner 2010 | Drugs used in addictive disorders | Acamprosate | Return to any drinking | 19 | 4837 | 1 | 26 | 16-19y (17.1y) | No adjustment according to weight |
| Pneumology | Asthma | Rowe 2000 | Anticonvulsant | Magnesium Sulfate | Hospital admission | 2 | 171 | 2 | 62 | 1-18y | 25 mg/kg or 0.2 ml/kg |
| Pneumology | Acute asthma | Rowe 2001 | Corticosteroids | Methylprednisolone | Admitted to hospital | 5 | 343 | 2 | 118 | 2-18y | 2 to 4 mg/kg |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gastroenterology | Acute diarrhoea | Sazawal 2006 | Probiotic | Lactobacillus | Diarrhoeal morbidity | 9 | 1055 | 6 | 2502 | NA | No adjustment according to weight |
| Gastroenterology | Acute diarrhoea | Sazawal 2006 | Probiotic | Saccharomyces | Diarrhoeal morbidity | 4 | 484 | 1 | 246 | NA | No adjustment according to weight |
| Gastroenterology | Crohn's disease | Segal 2014 | Drugs used in addictive disorders | Naltrexone | Withdrawal due to AE | 1 | 34 | 1 | 12 | 6-17y | 0.1 mg/kg |
| Pain | Vaccin injection pain | Shah 2015 | Anesthetic | Lidocain-prilocain | Pain scale | 1 | 60 | 1 | 161 | 4-6y | No adjustment according to weight |
| Gastroenterology | Crohn's disease | Shen 2009 | Probiotic | Lactobacillus | Rate of clinical relapse | 4 | 209 | 1 | 75 | 13-18y (14.8) | No adjustment according to weight |
| Infectious diseases | Ventilator-associated pneumonia | Shi 2013 | Antiseptic | Chlorhexidine (Gel) | Incidence of ventilator-associated pneumonia (VAP) | 2 | 268 | 1 | 86 | 3m-15y | No adjustment according to weight |
| Infectious diseases | Ventilator-associated pneumonia | Shi 2013 | Antiseptic | Chlorhexidine (Solution) | Incidence of ventilator-associated pneumonia (VAP) | 3 | 547 | 1 | 160 | 0-17y (11.5) | No adjustment according to weight |
| Infectious diseases | Cutaneous abscesses | Singer 2013 | Antibiotic | Trimethroprim/Sulfamethoxazole | % Without Abscesses Recurrence | 1 | 190 | 1 | 149 | 1-12y (4) | 10 to 12 mg/kg of TMP |
| Pneumology | Cystic Fibrosis | Southern 2012 | Antibiotic | Azithromycin | Change in FEV1 % predicted (at 2months) | 1 | 41 | 2 | 123 | 6-18y | No adjustment according to weight, 250mg but if >40kg 500 mg |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pneumology | Bronchoconstriction | Spooner 2002 | Antiallergic agent | Nedocromil sodium (NCS) | Max % fall of FEV1 | 5 | 62 | 11 | 162 | 6.5-19y (11.4y) | No adjustement according to weight |
| Infectious diseases | Pneumocystis pneumonia | Stern 2014 | Antibiotic | Trimethroprim/Sulfamethoxazole | Documented PCP infections | 2 | 174 | 2 | 220 | 4.5-6.5y | 910 to 950 mg/m² adjustment according to body surface |
| Psychiatry | Bipolar disorder | Suttajit 2014 | Antipsychotics | Quetiapine | 50% responder | 5 | 2451 | 2 | 224 | 10-18y | No adjustmenet according to weight |
| Gastroenterology | Antibiotic associated diarrhea | Szajewska 2015 | Probiotic | Lactobacillus | Risk of diarrhoea | 5 | 743 | 4 | 386 | NA | No adjustment according to weight |
| Gastroenterology | Antibiotic associated diarrhea | Szajewska 2015 | Probiotic | Saccharomyces | Incidence of diarrhoea | 4 | 830 | 1 | 246 | 6m-14y | No adjustment according to weight |
| Neurology | Epilepsy following traumatic head injury | Thompson 2015 | Antiepileptic | phenytoin | early seizures | 1 | 404 | 1 | 102 | < 10y | 18 mg/kg |
| Gastroenterology | Irritable bowel disease | Tiequn 2015 | Probiotic | Lactobacillus | Response to treatment | 3 | 273 | 2 | 130 | (9.2y) | No adjustment according to weight |
| Hematology | Anemia associated with cancer | Tonia 2012 | Antianemic | Erythropoietin | Haematological response | 11 | 1931 | 1 | 222 | NA | 600 IU/kg, higher dosage compared to adults |
| Sleep disorder | Delayed Sleep Phase Disorder | van Geijlswijk 2010 | Hypnotics and Sedatives | Melatonin | Dim light melatonin onset | 1 | 11 | 3 | 200 | NA | No adjustment according to weight |

| Therapeutic Area | Disease | Authors | Pharmacology Categoryt | Drug | Outcome | N Adult trials | N Adults included | N Children trials | N Children included | Age range (Mean) | Dose adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dermatology | Hirsutism | van Zuuren 2015 | Hypoglycemic agents | Metformin | Mean change from baseline in Ferriman-Gallwey score | 3 | 74 | 1 | 16 | 12-18y | No adjustment according to weight |
| Neurology | Epilepsies | Verrotti 2015 | Antiepileptic | Levetiracetam | Adverse events | 21 | 2448 | 2 | 296 | 4-17y | 60mg/kg |
| Infectious diseases | Trypanosoma cruzi infection | Villar 2014 | Antiprotozoals | Benznidazole | Negative Xenodiagnosis | 1 | 50 | 1 | 106 | NA | 5 mg/kg same dosage as adults |
| Pneumology | Asthma | Walters 2007 | Anti-asthmatic | Formoterol | exacerbation asthma >1 major | 3 | 1495 | 1 | 249 | (9.4y) | No adjustment according to weight, same as adults |
| Pneumology | Asthma | Walters 2007 | Anti-asthmatic | Salmeterol | Change of FEV | 13 | 2778 | 2 | 505 | 6-17y (9.6) | No adjustment according to weight, same as adults |
| Pneumology | Asthma | Watts 2012 | Anti-asthmatic | Montelukast | Hospital admission | 2 | 772 | 1 | 276 | (9.0y) | No adjustment according to weight |
| Pneumology | Cystic Fibrosis | Whiting 2014 | Other respiratory system products | Ivacaftor | Absolute change in % predicted FEV1 | 1 | 161 | 1 | 52 | 6-11y (9.0y) | No adjustment according to weight |
| Allergy | Allergic Rhinitis | Wilson 2005 | Allergen extracts | House Dust Mites (D. pteronyssinus and D. farinea | Symptoms score | 2 | 45 | 2 | 81 | NA | No adjustment according to weight |

1. Abramson Michael J, Puy Robert M, Weiner John M. Injection allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews [Internet]. 2010; (8). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001186.pub2/abstract.

2. Abubakar Ibrahim I, Aliyu Sani H, Arumugam C, Hunter Paul R, Usman N. Prevention and treatment of cryptosporidiosis in immunocompromised patients. Cochrane Database of Systematic Reviews [Internet]. 2007; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004932.pub2/abstract.

3. Adams Nick P, Bestall Janine C, Jones P. Budesonide versus placebo for chronic asthma in children and adults. Cochrane Database of Systematic Reviews [Internet]. 1999; (4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003274/abstract.

4. Adams Nick P, Bestall Janine C, Lasserson Toby J, Jones P, Cates Christopher J. Fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2008; (4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003135.pub4/abstract.

5. Adams Nick P, Bestall Janine C, Malouf R, Lasserson Toby J, Jones P. Beclomethasone versus placebo for chronic asthma. Cochrane Database of Systematic Reviews [Internet]. 2005; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002738.pub2/abstract.

6. Adams Stephen P, Sekhon Sarpreet S, Wright James M. Lipid-lowering efficacy of rosuvastatin. Cochrane Database of Systematic Reviews [Internet]. 2014; (11). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010254.pub2/abstract.

7. Afshari A, Brok J, Møller Ann M, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. Cochrane Database of Systematic Reviews [Internet]. 2010; (7). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002787.pub2/abstract.

8. Ahmed T, Bhuiyan Taufiqur R, Zaman K, Sinclair D, Qadri F. Vaccines for preventing enterotoxigenic Escherichia coli (ETEC) diarrhoea. Cochrane Database of Systematic Reviews [Internet]. 2013; (7). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009029.pub2/abstract.

9. Andersen Betina R, Kallehave Finn L, Andersen Henning K. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. Cochrane Database of Systematic Reviews [Internet]. 2005; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001439.pub2/abstract.

10. Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. BMJ (Clinical research ed). 2005;330(7490):516.

11. Barbui C, Cipriani A, Patel V, Ayuso-Mateos JL, van Ommeren M. Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis. The British journal of psychiatry : the journal of mental science. 2011;198(1):11-6, sup 1.

12. Becker Lorne A, Hom J, Villasis-Keever M, van der Wouden Johannes C. Beta2-agonists for acute cough or a clinical diagnosis of acute bronchitis. Cochrane Database of Systematic Reviews [Internet]. 2015; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001726.pub5/abstract.

13. Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. Epilepsia. 2010;51(1):7-26.

14. Bjorkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. Journal of psychopharmacology (Oxford, England). 2011;25(3):299-305.

15. Bonini M, Di Mambro C, Calderon Moises A, Compalati E, Schünemann H, Durham S, et al. Beta2-agonists for exercise-induced asthma. Cochrane Database of Systematic Reviews [Internet]. 2013; (10). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003564.pub3/abstract.

16. Boyle P, Bellanti JA, Robertson C. Meta-analysis of published clinical trials of a ribosomal vaccine (Ribomunyl(registered trademark)1) in prevention of respiratory infections. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy. 2000;14(6):389-408.

17. Brouwer Matthijs C, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database of Systematic Reviews [Internet]. 2015; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004405.pub5/abstract.

18. Brown R, Taylor Matthew J, Geddes J. Aripiprazole alone or in combination for acute mania. Cochrane Database of Systematic Reviews [Internet]. 2013; (12). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005000.pub2/abstract.

19. Calamita Z, Saconato H, Pelá AB, Atallah ÁN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. 2006.

20. Calderon Moises A, Penagos M, Sheikh A, Canonica Giorgio W, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. Cochrane Database of Systematic Reviews [Internet]. 2011; (7). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007685.pub2/abstract.

21. Carlisle J, Stevenson Carl A. Drugs for preventing postoperative nausea and vomiting. Cochrane Database of Systematic Reviews [Internet]. 2006; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004125.pub2/abstract.

22. Cates Christopher J, Cates Matthew J. Regular treatment with formoterol for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews [Internet]. 2012; (4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006923.pub3/abstract.

23. Cates Christopher J, Rowe Brian H. Vaccines for preventing influenza in people with asthma. Cochrane Database of Systematic Reviews [Internet]. 2013; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000364.pub4/abstract.

24. Chong J, Haran C, Chauhan Bhupendrasinh F, Asher I. Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. Cochrane Database of Systematic Reviews [Internet]. 2015; (7). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011032.pub2/abstract.

25. Compalati E, Baena-Cagnani R, Penagos M, Badellino H, Braido F, Gomez RM, et al. Systematic review on the efficacy of fexofenadine in seasonal allergic rhinitis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. Int Arch Allergy Immunol. 2011;156(1):1-15.

26. Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. Allergy. 2009;64(11):1570-9.

27. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar disorders. 2010;12(2):116-41.

28. Demicheli V, Jefferson T, Al-Ansary Lubna A, Ferroni E, Rivetti A, Di Pietrantonj C. Vaccines for preventing influenza in healthy adults. Cochrane Database of Systematic Reviews [Internet]. 2014; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001269.pub5/abstract.

29. Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Medicine. 2014;12(1).

30. Ducharme Francine M, Ni Chroinin M, Greenstone I, Lasserson Toby J. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2010; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005535.pub2/abstract.

31. Dunlop R, Bennett Kyle CLB. Pain management for sickle cell disease in children and adults. Cochrane Database of Systematic Reviews [Internet]. 2006; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003350.pub2/abstract.

32. Dwan K, Phillipi Carrie A, Steiner Robert D, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database of Systematic Reviews [Internet]. 2014; (7). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005088.pub3/abstract.

33. Ebbert J, Montori Victor M, Erwin Patricia J, Stead Lindsay F. Interventions for smokeless tobacco use cessation. Cochrane Database of Systematic Reviews [Internet]. 2011; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004306.pub4/abstract.

34. Falagas ME, Koletsi PK, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Rello J. Effectiveness and safety of neuraminidase inhibitors in reducing influenza complications: a meta-analysis of randomized controlled trials. The Journal of antimicrobial chemotherapy. 2010;65(7):1330-46.

35. Fang Y, Wu X, Xu L, Tang X, Wang J, Zhu G, et al. Randomized-controlled trials of levetiracetam as an adjunctive therapy in epilepsy of multiple seizure types. Journal of Clinical Neuroscience. 2014;21(1):55-62.

36. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One. 2013;8(5):e63773.

37. Figueredo ED, Canosa LG. Ondansetron in the prophylaxis of postoperative vomiting: a meta-analysis. J Clin Anesth. 1998;10(3):211-21.

38. Frost F, Dailler F, Duflo F. [Ondansetron: a meta-analysis on its efficacy to prevent postoperative nausea and vomiting after craniotomy in adults and children]. Ann Fr Anesth Reanim. 2010;29(1):19-24.

39. Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie Theresa A, van de Wetering Marianne D, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database of Systematic Reviews [Internet]. 2012; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004386.pub3/abstract.

40. Goldenberg Joshua Z, Ma Stephanie SY, Saxton Jane D, Martzen Mark R, Vandvik Per O, Thorlund K, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2013; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006095.pub3/abstract.

41. Graves Patricia M, Gelband H. Vaccines for preventing malaria (blood-stage). Cochrane Database of Systematic Reviews [Internet]. 2006; (4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006199/abstract.

42. Grimwade K, Swingler George H. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. Cochrane Database of Systematic Reviews [Internet]. 2003; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003108/abstract.

43. Grimwade K, Swingler George H. Cotrimoxazole prophylaxis for opportunistic infections in children with HIV infection. Cochrane Database of Systematic Reviews [Internet]. 2006; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003508.pub2/abstract.

44. Hao Q, Dong Bi R, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database of Systematic Reviews [Internet]. 2015; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006895.pub3/abstract.

45. Hayward G, Thompson Matthew J, Perera R, Glasziou Paul P, Del Mar Chris B, Heneghan Carl J. Corticosteroids as standalone or add-on treatment for sore throat. Cochrane Database of Systematic Reviews [Internet]. 2012; (10). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008268.pub2/abstract.

46. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JNV, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: A systematic review and meta-analysis. JAMA - Journal of the American Medical Association. 2012;307(18):1959-69.

47. Henzi I, Walder B, Tramer MR. Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies. Br J Anaesth. 1999;83(5):761-71.

48. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesthesia and analgesia. 2000;90(1):186-94.

49. Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. Journal of psychopharmacology (Oxford, England). 2007;21(8):864-72.

50. Hnin K, Nguyen C, Carson Kristin V, Evans David J, Greenstone M, Smith Brian J. Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. Cochrane Database of Systematic Reviews [Internet]. 2015; (8). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001392.pub3/abstract.

51. Hughes John R, Stead Lindsay F, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. Cochrane Database of Systematic Reviews [Internet]. 2014; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000031.pub4/abstract.

52. Jefferson T, Jones Mark A, Doshi P, Del Mar Chris B, Hama R, Thompson Matthew J, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2014; (4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/abstract.

53. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. Vaccines for preventing influenza in healthy children. Cochrane Database of Systematic Reviews [Internet]. 2012; (8). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004879.pub4/abstract.

54. Jesner Ora S, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database of Systematic Reviews [Internet]. 2007; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005040.pub2/abstract.

55. Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy. 2010;30(2):119-26.

56. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database of Systematic Reviews [Internet]. 2013; (6). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000247.pub3/abstract.

57. Kew Kayleigh M, Undela K, Kotortsi I, Ferrara G. Macrolides for chronic asthma. Cochrane Database of Systematic Reviews [Internet]. 2015; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002997.pub4/abstract.

58. Khemani Robinder G, Randolph A, Markovitz B. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. Cochrane Database of Systematic Reviews [Internet]. 2009; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001000.pub3/abstract.

59. Kim SO, Ah YM, Yu YM, Choi KH, Shin WG, Lee JY. Effects of probiotics for the treatment of atopic dermatitis: A meta-analysis of randomized controlled trials. Annals of Allergy, Asthma and Immunology. 2014;113(2):217-26.

60. King S, Glanville J, Sanders ME, Fitzgerald A, Varley D. Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: A systematic review and meta-analysis. British Journal of Nutrition. 2014;112(1):41-54.

61. Koh Mariko S, Tee A, Lasserson Toby J, Irving Louis B. Inhaled corticosteroids compared to placebo for prevention of exercise induced bronchoconstriction. Cochrane Database of Systematic Reviews [Internet]. 2007; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002739.pub3/abstract.

62. Kranke P, Morin AM, Roewer N, Eberhart LH. Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. Acta Anaesthesiol Scand. 2002;46(3):238-44.

63. Lands Larry C, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for lung disease in cystic fibrosis. Cochrane Database of Systematic Reviews [Internet]. 2013; (6). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001505.pub3/abstract.

64. Leibovici-Weissman Ya, Neuberger A, Bitterman R, Sinclair D, Salam Mohammed A, Paul M. Antimicrobial drugs for treating cholera. Cochrane Database of Systematic Reviews [Internet]. 2014; (6). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008625.pub2/abstract.

65. Manning P, Gibson Peter G, Lasserson Toby J. Ciclesonide versus placebo for chronic asthma in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2008; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006217.pub2/abstract.

66. Mason Anne R, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. Cochrane Database of Systematic Reviews [Internet]. 2013; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005028.pub3/abstract.

67. Mbizvo Gashirai K, Dixon P, Hutton Jane L, Marson Anthony G. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. Cochrane Database of Systematic Reviews [Internet]. 2012; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001901.pub2/abstract.

68. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health technology assessment (Winchester, England). 2013;17(27):vi, xi-xiv, 1-322.

69. Meremikwu Martin M, Marson Anthony G. Routine anticonvulsants for treating cerebral malaria. Cochrane Database of Systematic Reviews [Internet]. 2002; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002152/abstract.

70. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: Systematic review and meta-analysis. Emergency Medicine Journal. 2007;24(12):823-30.

71. Murali AR, Gupta A, Attar BM, Ravi V, Koduru P. Topical steroids in Eosinophilic Esophagitis: Systematic Review and Meta-analysis of Placebo Controlled Randomized Clinical Trials. Journal of gastroenterology and hepatology. 2015.

72. Nelson Richard L, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. Cochrane Database of Systematic Reviews [Internet]. 2012; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003431.pub3/abstract.

73. Normansell R, Kew Kayleigh M, Bridgman A-L. Sublingual immunotherapy for asthma. Cochrane Database of Systematic Reviews [Internet]. 2015; (8). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011293.pub2/abstract.

74. Normansell R, Walker S, Milan Stephen J, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2014; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003559.pub4/abstract.

75. Ori R, Amos T, Bergman H, Soares-Weiser K, Ipser Jonathan C, Stein Dan J. Augmentation of cognitive and behavioural therapies (CBT) with d-cycloserine for anxiety and related disorders. Cochrane Database of Systematic Reviews [Internet]. 2015; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007803.pub2/abstract.

76. Plante J, Turgeon AF, Zarychanski R, Lauzier F, Vigneault L, Moore L, et al. Effect of systemic steroids on post-tonsillectomy bleeding and reinterventions: Systematic review and meta-analysis of randomised controlled trials. BMJ (Online). 2012;345(7873).

77. Pulman J, Jette N, Dykeman J, Hemming K, Hutton Jane L, Marson Anthony G. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews [Internet]. 2014; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001417.pub3/abstract.

78. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). Allergy. 2011;66(6):740-52.

79. Ramaratnam S, Marson Anthony G, Baker Gus A. Lamotrigine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews [Internet]. 2001; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001909/abstract.

80. Ranji SR, Goldman LE, Simel DL, Shojania KG. Do opiates affect the clinical evaluation of patients with acute abdominal pain? Journal of the American Medical Association. 2006;296(14):1764-74.

81. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med. 2008;5(8):e166.

82. Riggin L, Ramakrishna J, Sommer DD, Koren G. A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of non steroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2013;38(2):115-29.

83. Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS ONE. 2012;7(4).

84. Robenshtok E, Gafter-Gvili A, Goldberg E, Weinberger M, Yeshurun M, Leibovici L, et al. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(34):5471-89.

85. Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews [Internet]. 2010; (9). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004332.pub2/abstract.

86. Rowe Brian H, Bretzlaff J, Bourdon C, Bota G, Blitz S, Camargo Carlos A. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database of Systematic Reviews [Internet]. 2000; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001490/abstract.

87. Rowe Brian H, Spooner C, Ducharme F, Bretzlaff J, Bota G. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database of Systematic Reviews [Internet]. 2001; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002178/abstract.

88. Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. The Lancet infectious diseases. 2006;6(6):374-82.

89. Segal D, MacDonald John K, Chande N. Low dose naltrexone for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews [Internet]. 2014; (2). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010410.pub2/abstract.

90. Shah V, Taddio A, McMurtry CM, Halperin SA, Noel M, Pillai Riddell R, et al. Pharmacological and Combined Interventions to Reduce Vaccine Injection Pain in Children and Adults: Systematic Review and Meta-Analysis. The Clinical journal of pain. 2015;31(10 Suppl):S38-63.

91. Shen J, Ran HZ, Yin MH, Zhou TX, Xiao DS. Meta-analysis: the effect and adverse events of Lactobacilli versus placebo in maintenance therapy for Crohn disease. Intern Med J. 2009;39(2):103-9.

92. Shi Z, Xie H, Wang P, Zhang Q, Wu Y, Chen E, et al. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. Cochrane Database of Systematic Reviews [Internet]. 2013; (8). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008367.pub2/abstract.

93. Singer AJ, Thode Jr HC. Systemic antibiotics after incision and drainage of simple abscesses: A meta-analysis. Emergency Medicine Journal. 2014;31(7):576-8.

94. Southern Kevin W, Barker Pierre M, Solis-Moya A, Patel L. Macrolide antibiotics for cystic fibrosis. Cochrane Database of Systematic Reviews [Internet]. 2012; (11). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002203.pub4/abstract.

95. Spooner C, Saunders LD, Rowe Brian H. Nedocromil sodium for preventing exercise-induced bronchoconstriction. Cochrane Database of Systematic Reviews [Internet]. 2002; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001183/abstract.

96. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database of

Systematic Reviews [Internet]. 2014; (10). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005590.pub3/abstract.

97. Suttajit S, Srisurapanont M, Maneeton N, Maneeton B. Quetiapine for acute bipolar depression: A systematic review and meta-analysis. Drug Design, Development and Therapy. 2014;8:827-38.

98. Szajewska H, Kolodziej M. Systematic review with meta-analysis: Lactobacillus rhamnosus GG in the prevention of antibiotic-associated diarrhoea in children and adults. Alimentary pharmacology & therapeutics. 2015;42(10):1149-57.

99. Szajewska H, Kolodziej M. Systematic review with meta-analysis: Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea. Alimentary pharmacology & therapeutics. 2015;42(7):793-801.

100. Thompson K, Pohlmann-Eden B, Campbell Leslie A, Abel H. Pharmacological treatments for preventing epilepsy following traumatic head injury. Cochrane Database of Systematic Reviews [Internet]. 2015; (8). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009900.pub2/abstract.

101. Tiequn B, Guanqun C, Shuo Z. Therapeutic effects of lactobacillus in treating irritable bowel syndrome: A meta-analysis. Internal Medicine. 2015;54(3):243-9.

102. Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database of Systematic Reviews [Internet]. 2012; (12). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003407.pub5/abstract.

103. Tsapakis EM, Soldani F, Tondo L, Baldessarini RJ. Efficacy of antidepressants in juvenile depression: meta-analysis. The British journal of psychiatry : the journal of mental science. 2008;193(1):10-7.

104. van Geijlswijk IM, Korzilius HP, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. Sleep. 2010;33(12):1605-14.

105. van Zuuren Esther J, Fedorowicz Z, Carter B, Pandis N. Interventions for hirsutism (excluding laser and photoepilation therapy alone). Cochrane Database of Systematic Reviews [Internet]. 2015; (4). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010334.pub2/abstract.

106. Verrotti A, Prezioso G, Di Sabatino F, Franco V, Chiarelli F, Zaccara G. The adverse event profile of levetiracetam: A meta-analysis on children and adults. Seizure. 2015;31:49-55.

107. Villar Juan C, Perez Juan G, Cortes Olga L, Riarte A, Pepper M, Marin-Neto Jose A, et al. Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection. Cochrane Database of Systematic Reviews [Internet]. 2014; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003463.pub2/abstract.

108. Walters EH, Gibson Peter G, Lasserson Toby J, Walters Julia AE. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database of Systematic Reviews [Internet]. 2007; (1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001385.pub2/abstract.

109. Watts K, Chavasse Richard JPG. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. Cochrane Database of Systematic Reviews [Internet]. 2012; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006100.pub2/abstract.

110. Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health technology assessment (Winchester, England). 2014;18(18):1-106.

111. Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis*. 2005.

# Appendix 3: Unnecessary repetitions of pediatric clinical trials: cumulative meta-analyses

**Background**: Because children are a vulnerable population, it is essential to avoid unnecessary trials when enough evidence is available.

**Objective:** Our objective was to identify unnecessary repetitions of randomized clinical trials (RCTs) in the pediatric population, using cumulative meta-analyses, when either the beneficial or deleterious effect of the treatment had been confirmed.

**Methods:** We searched three electronic databases for meta-analyses. Double-blind, placebo–controlled RCTs including adults and children were eligible. The random effect model was used to pool effect over time by including studies according to their year of publication. We performed cumulative meta-analysis to identify significant benefit or risk when multiple RCTs were available for children.

**Results:** Eighty-nine meta-analyses were preliminarily identified, including 992 RCTs among which only 294 pediatric trials evaluating 124 drugs. Only 33 drugs had more than one pediatric trial and had a confirmed treatment effect. Ondansetron for postoperative nausea and vomiting was assessed by 26 pediatric RCTs. The treatment benefit was confirmed as of 1995 (Figure 1). Cumulative meta-analysis showed that 19 trials, including 1 662 children were unnecessary. Overall, 63 trials including 6 164 children were unnecessary.

**Conclusion:** Our preliminary results suggest the presence in the literature of reports of unnecessary RCTs in children. Clinical research in children should focus on unmet needs and avoid exposing children to unnecessary trials.

*This work was carried out by Amina Djemli Master 2 Master in Evaluation of therapeutics, biostatistics and clinical epidemiology, University Paris Descartes during her internship at the LBBE supervised by Pr Kassai's and I.*

**Figure: Cumulative meta-analysis for ondansetron for postoperative nausea and vomiting**

