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SAFETY ASSESSMENT IN PAEDIATRIC ANTIBIOTICS CLINICAL TRIALS

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Workshop on development of antibacterial medicinal products for paediatric patients

21-22 June 2018

European Medicines Agency - London

EnprEMA
European network of paediatric research at the European Medicines Agency

PIDRG
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BACKGROUND

- The work plan for the **Committee for Medicinal Products for Human Use** (CHMP) **Infectious Diseases Working Party** (IDWP) for 2016 included the production of a **Paediatric Addendum** to the **guideline on the evaluation of medicinal products** indicated **for treatment of bacterial infections**

- Draft of the **Paediatric Addendum** published for **public consultation** in **March 2018**

- The board of the **European networks for paediatric research at the EMA** (***EnprEMA***) has on parallel agreed to set up a new **Working Group (WG) on paediatric antibiotic (AB) clinical trial (CT) design**, involving **academic**, **regulatory** and **industry** representatives

- **AIM**: to **facilitate the harmonisation** of **neonatal** and **paediatric AB CTs** considering specific aspects of design and conduct. **Complimentary to the Paediatric Addendum** potentially adding value based on **experience from the networks** and **members** involved in the WG.

European Medicines Agency. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements. (EMA/CHMP/187859/2017). Draft 2018.

EnprEMA PAEDIATRIC ANTIBIOTIC WORKING GROUP

- The WG considered **trial design** for **neonates**, **infants**, **children** and **adolescents**
- The WG **focused only on AB**, but considered available guidance on all antimicrobial CT design
- The **role** of the WG is **advisory to elicit and summarise views from a range of key stakeholders**
- The WG had representation from the **Paediatric Committee** (**PDCO**), **CHMP IDWP**, relevant **academic groups/networks**, and **industry**
- The WG has **close liaison with other current European and/or global initiatives** focusing on **paediatric antibiotic CT design**, including the **CTTI Paediatric AB Trials group**
- The WG focused on those aspects not specifically addressed in the Addendum, gathering evidence from both **published literature** and **experience** from the networks and members involved
- The WG **considered** the following **major CIS**:
  - Bloodstream infections (BSI/sepsis)
  - Neonatal sepsis
  - Community-acquired pneumonia (CAP)
  - Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)
  - Complicated urinary tract infections (cUTI)
  - Complicated intra-abdominal infections (cIAI)
  - Acute bacterial skin and soft tissue-infections (cSSTI)

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BUILDING the EVIDENCE

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SR of SAFETY in PAEDIATRIC AB CTs

- The concept of **extrapolation for safety** has been proposed recently to **minimise unnecessary studies in children** and to **maximise** the amount of **information extracted from adults**
- **Safety** information **from the source population** may be used to **predict events in the target population** if mode of **action of the drug and appropriate dose can be extrapolated**
- Considering the **different stages of growth and maturation among different ages**, the collection of safety data to identify **unexpected** (**age-specific**) **adverse events** (AEs) may be **required in the target population**

To **build the evidence to support extrapolation**, and considering the challenges of conducting large-scale RCTs in children, a **systematic review** and **meta-analysis** of **"safety"** AND **"antibiotics"** in **children** was conducted and published

WIDER AIM:

To provide a **summary overview** on the **appropriateness of safety data** reported in **CTs of antibacterial** agents in **children** and **neonates**

SPECIFIC OBJECTIVES:

To evaluate if the **overall quality of safety studies** conducted **in children** allows to **gather a sufficiently robust evidence**

To determine if **age-specific AEs** could be **identified per different AB classes**

Reflection paper on extrapolation of efficacy and safety in paediatric medicine development. EMA 2016

Drugs (2018) 78:231–244
https://doi.org/10.1007/s40265-017-0850-x

Evaluating Safety Reporting in Paediatric Antibiotic Trials, 2000–2016: A Systematic Review and Meta-Analysis

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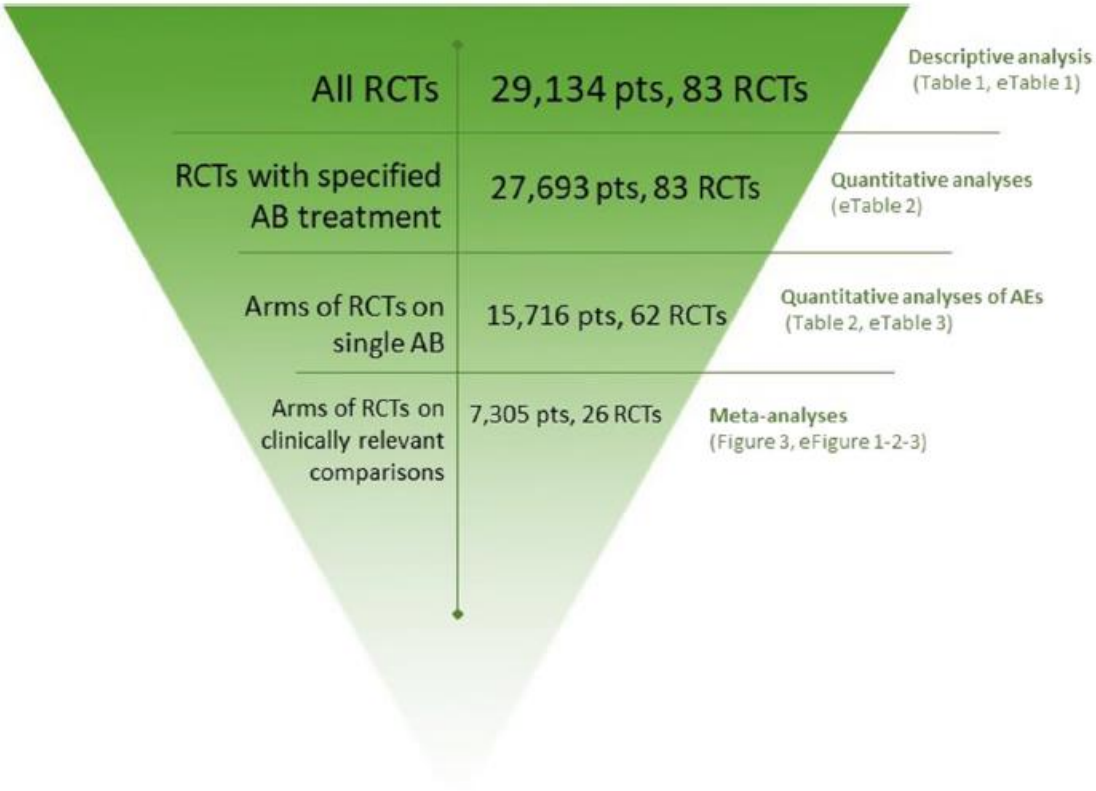

Table 1 Basic characteristics of included trials

	N (%)[a]
Total trials	83
Total patients	29,134
Study design	
Double-blind	28 (34)
Single-blind	10 (12)
Open-label	45 (54)
Sponsor	
Pharmaceutical company	34 (41)
Not for profit	49 (59)
Ongoing trials	13 (16)
Income	
HICs	36 (43)
LMICs	22 (27)
Both	25 (30)
Condition[b]	
Upper respiratory tract infections	25 (30)
Lower respiratory tract infections	17 (21)
Gastrointestinal infections	11 (13)
Unspecified bacterial infections	10 (12)
Sepsis	8 (10)
Other bacterial infections	8 (10)
Urinary tract infections	6 (7)
Skin and soft tissue infections	5 (6)
CNS infections	1 (1)
Safety outcome	
Primary	19 (23)
Secondary	66 (80)
Age groups	
Neonate (0–28 days)	21 (25)
Infant (29 days–24 months)	60 (72)
Child (2–12 years)	67 (81)
Adolescent (12–18 years)	30 (36)
Study drugs	
Single drug	74 (89)
Multiple drugs	12 (15)

- 62 RCTs for a total of **15,716 patients** were **included in the quantitative analysis**
- **AEs** in paediatric AB CTs **class-specific** and **broadly predictable** compared to adults
- **No children-specific** or **unexpected toxicity** have been pointed out
- Rate of **specific AEs generally low** – Median **SAEs 0.3%**
- **Not possible to stratify safety data by different paediatric age groups**

Drug class	N patients	Overall AEs	Discontinuation due to AEs	Nephro-toxicity	Oto-toxicity	Gastro intestinal	Systemic**	Neurological	Respiratory	Dermatologic	Muscolo-skeletal	Infusional	Lab tot	Overall specific AEs
Penicillins	3,019	12.8 (9.4 – 29.7)	1.1 (0 – 2.7)	0.6*	nr	4.2 (2.3 – 8.3)	0 (0 – 0.8)	0 (0 – 0)	nr	0.7 (0 – 5.3)	nr	0 (0 – 0)	17.7*	9.1 (3.1 – 29.7)
Aminoglycosides	1,308	3.3 (1.1 – 15.8)	0*	1.8 (1.1 – 20)	1 (0 – 1.1)	nr	nr	0 (0 – 0)	nr	nr	nr	nr	nr	2.3 (0.6 – 15.8)
Cephalosporins	2,462	16.5 (4.5 – 42.1)	0.3 (0 – 3)	nr	nr	12.1 (3.6 – 20.5)	0 (0 - 0)	0 (0 – 0)	0 (0 - 0)	0 (0 – 4.2)	nr	nr	0 (0 – 5.2)	14.8 (4.5 – 42.1)
Macrolides	2,931	21.8 (7.7 – 35.9)	0 (0 – 3.3)	nr	nr	8.6 (3.4 – 23.3)	0 (0 – 0)	nr	0 (0 – 0)	0 (0 – 2.2)	nr	nr	9.8*	18.8 (6 – 31.6)
Penicillins+BLI	2,566	46.3 (32.7 – 67.8)	1 (0 – 2.8)	nr	nr	33.9 (23.4 – 43)	0 (0 – 2.3)	nr	0 (0 – 0.3)	7.2 (3.4 – 12.9)	0 (0 – 0)	nr	0 (0 – 0)	43.0 (19.6 – 63.0)
Fluoroquinolones	1,920	35.7 (24.2 – 66.7)	0.8 (0 – 2.2)	nr	nr	17.1 (2.4 – 23.7)	1.1 (0 – 7.5)	nr	0 (0 – 11.4)	0 (0 – 6.25)	3.1 (1.2 – 3.2)	nr	12.5 (3.3 – 19.9)	31.2 (23.4 – 61.1)
Carbapenems	385	32.7*	1.9*	nr	nr	5.8*	nr	nr	nr	nr	nr	10.5*	9.6*	25.9*
Linezolid	683	60.7 (44.5 – 70.4)	2 (0.9 – 7)	nr	nr	9.8 (7.6 – 12.6)	0.5 (0 – 1.3)	0 (0 – 0)	0 (0 – 2.3)	1.3 (0 – 1.4)	nr	0 (0 – 0)	45.6 (5.7 – 52.6)	58.2 (43.7 – 64.3)
Glycopeptides	265	75.4 (37.5 – 90.9)	4.3 (1.7 – 5.7)	8.4*	nr	9.3 (0 – 12.5)	18.6 (5.3 – 27.5)	nr	nr	6.4 (5.3 – 9.1)	nr	nr	41.0 (15.8 – 72.0)	75.4 (27.6 – 87.9)
Sulfonamides + trimethoprim	152	4.6*	2.6*	nr	nr	2.6*	1.3*	nr	nr	0.7*	nr	nr	nr	4.6*
Amphenicols	25	4*	0*	nr	nr	4*	nr	nr	nr	nr	nr	nr	nr	4*
Total	**15,716**	**22.5 (7.7 – 44.6)**	**0.9 (0 – 3)**	**1.8 (0.8 – 15.8)**	**1 (0.2 – 1.1)**	**7.7 (0 – 20.5)**	**0 (0 – 0.5)**	**0 (0 – 0)**	**0 (0 – 0)**	**0 (0 – 4.0)**	**0 (0 – 0)**	**0 (0 – 0)**	**6.8 (0.4 – 21.0)**	**19.2 (4.6 – 42.6)**

Data are expressed as median proportion and IQR range. *Expressed as mean because reported in < 3 studies; **including fever, anaphylaxis and Red Man Syndrome; nr: not reported.

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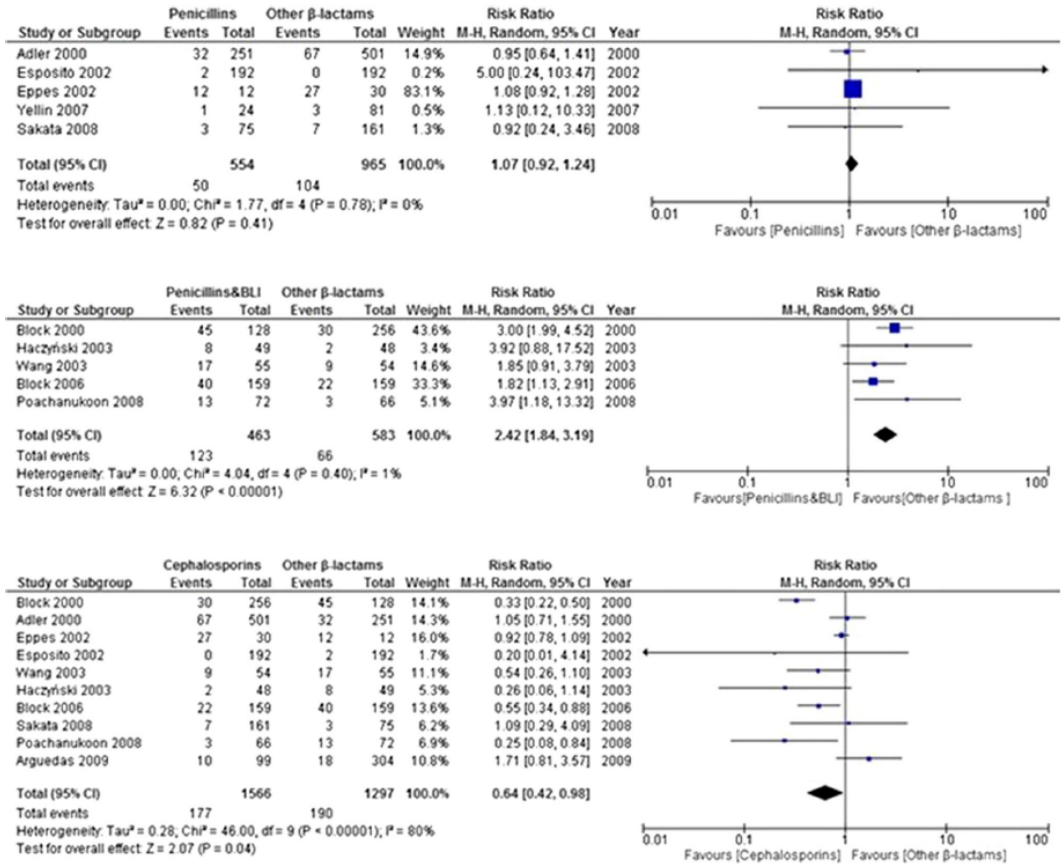
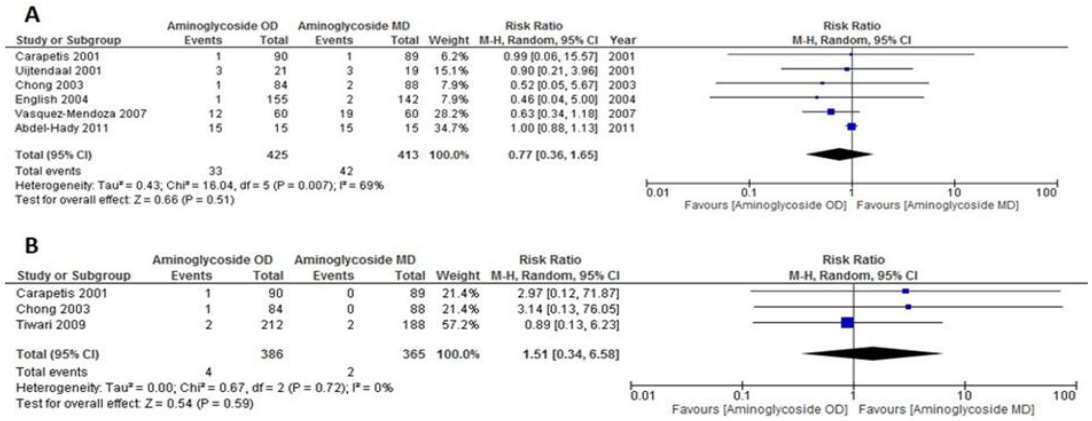


Fig. 3 Diarrhoea in β-lactams: meta-analysis. *M–H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

META-ANALYSES

- Drug **classes most represented** (i.e. involving the great majority of children)
- Comparison of the **AEs most frequently reported**



eFig. 2 Toxicity in Aminoglycosides: one daily dose (OD) versus multiple daily doses (MD) Meta-analysis (A: nephrotoxicity, B: ototoxicity)

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CONCLUSIONS

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Key Points
Data reported for the antibiotic classes most commonly used in children showed that adverse events (AEs) in paediatric patients were class-specific and broadly predictable.
Within the limitations of the lack of neonatal data, no age-specific or unexpected toxicity has been identified.
For common antibiotic classes, with well-established safety profiles in adults, it is potentially possible to simplify the safety assessments if combined with enhanced postmarketing approval pharmacovigilance for monitoring emerging AEs in routine clinical practice.

1. **For certain AB classes**, it is possible to **simplify the safety assessments** in **parallel paediatric trials**
2. **Bridging** safety data **from adults** **feasible for some AB classes** but specific **age-groups data still necessary**
3. **Low quality** and **high heterogeneity** (*study design, population, data reporting*) **reduce the strength of conclusions**

Pansa P et al. Drugs 2018

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RECOMMENDATIONS

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KEY COMPONENTS of SAFETY

SAFETY REPORTING

- Specific section on **safety reporting** in every paediatric AB CT
- Studies should provide:
  - Justification for **sample size** for safety and definition of **safety population** in studies having safety as **primary endpoint**
  - Definition for:
    - How harms-related **information was collected** *(mode of data collection, timing, attribution methods, harms-related monitoring and stopping rules)*
    - **Pre-definition** of each specific **clinical/laboratory/imaging addressed AEs**
    - **Grading** *(mild, moderate, severe)*
    - **Relationship with study drug** *(expected vs unexpected)*
    - Reference for **Coding System** *(taking into account that most groups are now using the DAIDS grading system)*
  - **Overall analysis** presented first, followed by **stratification** by different **age groups**
  - Data on any **modification to randomised treatment** OR **withdrawals because of AEs**
  - All the **denominators** and all **absolute risks per arms** and **per AE** **type, grade,** and **seriousness**

Haidich AB, J Clin Epidemiol 2011; 64(2): 124-35
Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.0

STANDARDISING SAMPLE SIZES for REGULATORY PAEDIATRIC AB CTs

KEY UNDERPINNING CONCEPTS:

- **Rates of AEs/serious AEs** (SAEs) in **children** are **generally low**, often lower than in adults, and **class predictable**
- **AEs/SAEs specific to children** occur **extremely rarely**, but are important to detect
- **Blinded (placebo-controlled) or unblinded comparative trials** aim to estimate the difference between AE rates with the new antibiotic *vs* a comparator: **sample sizes are typically large** if designed to exclude differences outside a non-inferiority margin, or **powered only to detect very large reductions in AEs which may not be realistic**

Reasonable approach would be to ensure **sufficient children receive a new antibiotic** to enable:

- *A high probability of determining that the overall AE/SAE rate is estimated reasonably precisely*
- *A reasonable probability of observing an adverse event which occurs in 1/20 children*

Pansa P et al. Drugs 2017
Flahault A et al. J Clin Epidemiol 2005

- This could be done within a **single-arm interventional paediatric AB CTs** having **safety** as a **primary endpoint**, according to the **rates of AEs per single drug class** from the safety systematic review

- A standard **single-arm proportion test** can be used (Flahault et al, 2005)

- Given an **expected proportion** of **children experiencing** one or more **AEs**, and a **maximum acceptable value** for this proportion, the **sample sizes provide a 0.95, 0.90 and 0.80 probability** that **the upper 95% CI around the proportion of children experiencing AEs in the new trial is below the maximum acceptable value**

- The fourth, sixth and eighth columns provide **the upper 97.5% confidence limit around an observation of zero AEs** of a particular type **from this number of children** (i.e. the **degree of certainty that an AE that was not observed in the trial genuinely had a low frequency**)

Drug class	Overall percentage experiencing AEs*	Sample size to provide >0.80 probability that final 95% CI around estimated AE rate is no more than 10% above this	Upper 97.5% confidence limit around an observation of 0/N	Sample size to provide >0.90 probability that final 95% CI around estimated AE rate is no more than 10% above this	Upper 97.5% confidence limit around an observation of 0/N	Sample size to provide >0.95 probability that final 95% CI around estimated AE rate is no more than 10% above this	Upper 97.5% confidence limit around an observation of 0/N
Penicillins	13	106	3.4%	139	2.6%	172	2.1%
Aminoglycosides	3	51	7.0%	70	5.1%	79	4.6%
Cephalosporins	16	114	3.2%	152	2.4%	190	1.9%
Macrolides	22	135	2.7%	180	2.0%	229	1.6%
Penicillins+BLI	46	165	2.2%	226	1.6%	283	1.3%
Fluoroquinolones	36	161	2.3%	225	1.6%	277	1.3%
Carbapenems	33	158	2.3%	214	1.7%	270	1.4%
Linezolid	61	153	2.4%	205	1.8%	258	1.4%
Glycopeptides	75	117	3.1%	153	2.4%	185	2.0%
Sulfonamides + trimethoprim	5	59	6.1%	85	4.2%	102	3.6%
Amphenicols	4	55	6.5%	73	4.9%	91	4.0%

IMPROVING POST MARKETING APPROVAL PHARMACOVIGILANCE

- Reporting of **pharmacovigilance data** on **antibiotics** in neonates and children currently **limited**
- **Pharma companies** conduct a comprehensive **assessment of drug safety following marketing approval**, and then **submit** this data to the local **drug regulatory authority** → significant amount of **resources** for both **investigators** and **industries**

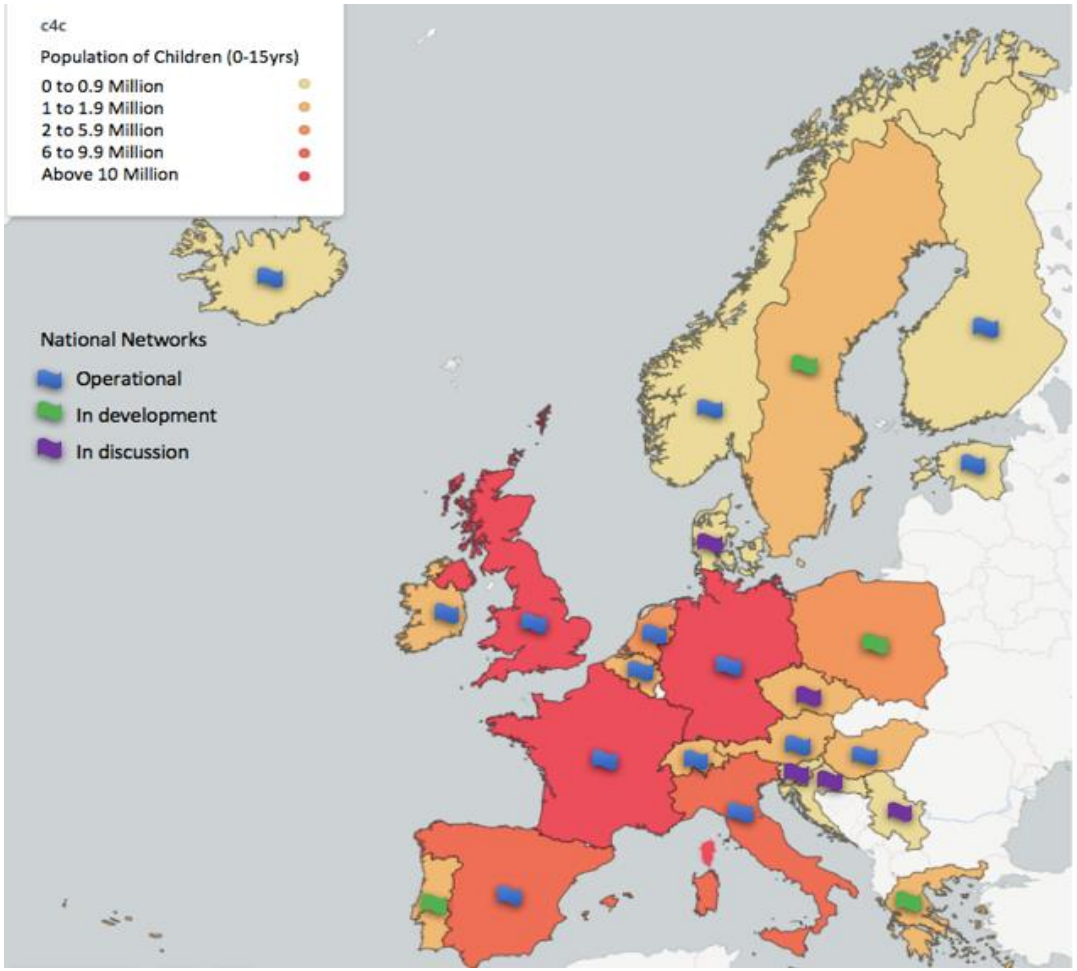
POSSIBLE SOLUTIONS:

- The establishment of a **network of different stakeholders** (academics, physicians, regulators and governments) who share **common interests in paediatric pharmacovigilance**
- A "**sentinel sites approach**" involving **centres in all regions across the world :** prospective cohort studies **using electronic data records**
  - **GAIA project** : voluntary network to improve the quality of safety data in a specific population
  - **web-based disease-specific drug registries** put in place in Europe to enhance the exchange of information and expertise between centres → **prospectively collect toxicity data** in children, generally **open access** and **cheap** to maintain
- The institution of a **European electronic registry** using the well-established **PENTA network** (www.pentatrials.org) potentially functional option to collect **safety and outcome data** on both **new and old off-patent key antibiotics** in children and neonates
- Creation of a **pan-European paediatric clinical trial network** (www.conect4children.org)

conect 4children
COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

PENTA - ID
www.penta-id.org

c4c consortium members



- 10 EFPIA companies
- 18 pediatric national networks
- 2 large patient advocacy groups
- 8 EU Multinational sub-specialty Networks
- 2 large children's hospitals

CONCLUSION

- The **role of the WG** was meant to be **advisory to elicit and summarise views** from a **range of key stakeholders**
- The **sample sizes provided** are **intended to inform investigators** on the number of **children to be enrolled to adequately power single-arm studies** on these antibiotic classes **having safety as a primary endpoint**
- An improved used of **bridging of safety** could allow potentially more **simplified design** of CTs, **improving** their **conduct** and **efficiency**
- **Report** on the **EnprEMA paediatric antibiotic working group** currently in circulation between WG members

QUESTIONS ?