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OFF-LABEL ANTIBIOTIC USE IN CHILDREN IN THREE EUROPEAN COUNTRIES

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OFF-LABEL ANTIBIOTIC USE IN CHILDREN IN THREE EUROPEAN COUNTRIES

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20 21 **ABSTRACT**

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24 *Objective.* Antibiotics are the drugs most frequently prescribed for children, and most of
25 them lack patent protection. The aim of the present study was to evaluate off-label
26 antibiotic use in three European countries.
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33 *Methods.* The data concerning all patients admitted to the neonatal intensive care units
34 (NICUs) and pediatric wards of the centers were collected by the same investigator over a
35 two-week survey period between February and May 2009. Data included age, date of
36 birth, weight, relevant medical history and diagnosis, together with details of all of the
37 antibiotics prescribed (compound, route of administration, dose and indication for use).
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44 *Results.* The study involved 616 children (110 admitted to NICUs: 62 in the UK, 38 in Italy,
45 and 10 in Greece; and 506 admitted to general pediatric wards: 265 in the UK, 94 in Italy
46 and 147 in Greece) and a total of 1244 antibiotic prescriptions were issued (290 in NICUs
47 and 954 in pediatric wards). The results show that off-label antibiotic use is very common
48 in European pediatrics, with only slight but sometimes significant differences between
49 countries. However, this use relates almost exclusively to doses and indications, and
50 rarely to age. The only antibiotics used off-label for age in pediatric clinical practice were
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3 meropenem for neonates and quinolones or linezolid for older children, which represent
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5 priorities for future studies.
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9 *Conclusion.* European-wide educational programmes are urgently needed to meet the
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11 objectives of improving paediatricians' working knowledge of the recommendations
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13 surrounding licensed antibiotics-use in children, and of reducing uncontrolled patterns of
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15 prescribing.
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For Peer Review

INTRODUCTION

A number of hospital- and office-based studies have shown that many of the drugs prescribed to children are used outside their registered doses, age groups, indications and routes of administration [1-12]. This off-label use is related to the practical and ethical difficulties in carrying out clinical trials involving very young subjects. The extensive research required by current standards of drug evaluation in order to register a specific product for paediatric use is often not supported by the profit-driven drug industry because children represent only a small part of the drug market [13]. Furthermore, the limited paediatric drug research that is carried out is often based on small-scale studies that lack the statistical power necessary to draw any firm conclusions concerning the real efficacy of the drugs or their long-term toxic effects [14]. Ethical conflicts are heightened where the toxicity of medicines may be different in children and adults, compounded by issues around informed consent and assent [15].

Off-label drug use can cause significant damage in the developing fetus or child, one of the best examples being the grey baby syndrome due to chloramphenicol [16,17]; but it also gives rise to many minor but not marginal adverse events requiring hospitalisation or additional therapies [18-22]. A number of health authorities have recognised the need to conduct specific studies in children in order to reduce the problem of off-label use. The American Food and Drug Administration (FDA) has prepared the Best Pharmaceutical for Children Act and the Pediatric Research Equity Act, both of which are intended to incentivise drug research in children [23,24]: the first allows companies to qualify for an additional six months' exclusive marketing of a specific molecule provided that they carry out specific paediatric trials [23], and the second, which became law in 2003, states that the FDA can require paediatric studies of a drug for which a new drug application is

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3 submitted if it finds that the product is likely to be used in a substantial number of pediatric
4 patients or would provide a significant benefit over existing treatments [24]. The European
5 Medicines Agency (EMA) has laid down specific rules for marketing authorisations of
6 new medicinal products and for pediatric-use marketing authorisations of off-patent
7 products [25]. It has also agreed a strategy for establishing the European network of
8 pediatric research and providing information concerning pediatric clinical trials. Moreover,
9 in order to encourage studies of drugs that lack patent protection because they have been
10 marketed for many years, it has decided to prepare a list of drugs for which studies in
11 children are urgently needed and can be financed by the European Union [26].
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26 The drugs most frequently prescribed for children are antibiotics [27,28], most of which
27 lack patent protection. The aim of the present study was to evaluate off-label antibiotic use
28 in three European countries.
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38 **METHODS**

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41 Antibiotic prescriptions were evaluated for all inpatients in the neonatal intensive care units
42 (NICUs) and the pediatric medical and surgical wards of two hospitals in UK (St George's
43 Hospital and Evelina Children's Hospital in London), one in Italy (Department of Maternal
44 and Pediatric Sciences of the University of Milan), and one in Greece (Aglaia Kyriakou
45 Children's Hospital, University of Athens). All data on the four sites were collected by the
46 same investigator (AP) during a two-week survey of each hospital between February and
47 May 2009. Data included age, date of birth, weight, relevant medical history and diagnosis,
48 together with details of all of the antibiotics prescribed (compound, route of administration,
49 dose and indication for use). The protocol was approved by the Institutional Review Board
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3 of all centres, and written informed consent was obtained from a parent or legal guardian,
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5 with children aged more than eight years being asked to give their assent.
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9 Off-label antibiotic use was determined on the basis of the information concerning product
10 registration given in the British National Formulary 2009, the Italian Informatore
11 Farmaceutico, and the Greek National Formulary 2006, as well as package insert
12 information and what could be derived from the medical information departments of the
13 pharmaceutical companies concerned. Off-label use was defined as the administration of
14 an antibiotic in situations not covered by the product licence or the summary of product
15 characteristics, or at a different dose or frequency, or to different age groups, or by means
16 of an alternative route. The age groups considered were those defined by EMEA:
17 neonates (0-27 days), infants (28 days to 23 months), children (2-11 years) and
18 adolescents (12-17 years). The prescriptions were then divided into three groups
19 depending on whether the off-label use was related to the patient's age, the drug dose, or
20 the indication. A difference of 10% between the physician's prescription and the reference
21 dose was allowed before considering the administration off-label.
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41 Results were compared using SAS software, version 9.1 (SAS Institute, Cary, North
42 Carolina). In Tables, only antibiotics prescribed at unregistered dose or for an off-label
43 indication in more than 5% of the prescriptions in at least one of the centers are shown.
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45 Categorical variables are reported as numbers and percentages, and analysed by means
46 of contingency tables and the chi-squared or Fisher's test. Continuous variables are given
47 as mean values \pm standard deviation (SD), and analysed using a t test or Wilcoxon's test
48 (for non-normally distributed data). P-values of 0.05 or less were considered to be
49 statistically significant.
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RESULTS

Study population

The study involved a total of 616 children (110 admitted to NICUs: 62 in the UK, 38 in Italy, and 10 in Greece; and 506 admitted to pediatric wards: 265 in the UK, 94 in Italy and 147 in Greece); a total of 1244 antibiotic prescriptions were issued for these patients (290 in NICUs and 954 in pediatric wards). Table 1 shows the demographic characteristics of the study patients. For NICU patients, there were no significant between-country differences in gender or age, or in the presence of underlying chronic conditions, number of antibiotic prescriptions, number of antibiotics used, or clinical indications for the antibiotic prescriptions. On pediatric wards, significantly more children in the neonatal age group were admitted in the UK than in Italy or Greece, and significantly fewer children aged 2-11 years were admitted in the UK than in Greece, while both UK and Italy hospitalised significantly more pediatric patients with underlying chronic diseases than Greece. However, there were no significant between country differences in gender, number of antibiotic prescriptions, number of antibiotics used, or clinical indications for the antibiotic prescriptions on paediatric wards.

Antibiotic prescribing in neonatal units

There were 12 episodes out of 290 prescriptions in which antibiotics were used outside the registered age range (4.1%). Although there were small number of neonates in the Greek NICU during the study period, there were significantly fewer "outside age range"

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3 prescriptions in the UK (4/172, 4.3%) and Italy (2/91, 2.2%) than in Greece (6/27, 22.2%;
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5 $p < 0.05$ vs UK and Italy). The most frequent of such prescriptions in all centres was for
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7 meropenem (10/12 episodes, 83.3%), which was prescribed because of proven or
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9 suspected sepsis in all cases. The Greek NICU also used imipenem (one case for lower
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11 respiratory tract infection) and ciprofloxacin (one case for urinary tract infection) outside
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13 age range. Moreover, the median gestational and chronological ages of the neonates in
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15 whom antibiotics were used outside the registered age range were significantly lower in
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17 Italy (median gestational age at birth 26 weeks and median age at prescription 24 days)
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19 than in the UK (median gestational age 31.7 weeks, $p < 0.05$ vs Italy; median age 39.5
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21 days, $p < 0.05$ vs Italy) or Greece (median gestational age 33.7 weeks, $p < 0.05$ vs Italy;
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23 median age 64 days, $p < 0.05$ vs Italy). In the UK and Italian NICUs, the off-label use of
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25 antibiotics was related to patients with an underlying chronic disease in all cases, whereas
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27 in Greece this was true of only half of the cases.
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35 Table 2 shows the antibiotics used at an unregistered dose in more than 5% of the
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37 prescriptions in at least one of the centers in patients admitted to NICUs. The number of
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39 such prescriptions was high in all of three countries, but significantly higher in Italy than in
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41 the UK. In all of the NICUs, the antibiotics most frequently prescribed at doses other than
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43 the recommended dose were aminoglycosides (particularly amikacin and gentamicin). Off-
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45 label doses of gentamicin and also amoxicillin-clavulanate were prescribed significantly
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47 more often in the Italian NICU than in the UK units. In most cases, the differences
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49 regarded the administration of a lower than advised total daily dose or different fractioning.
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51 Higher than recommended doses were significantly more common in the Greek than in the
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53 UK NICUs. The most common clinical indication related to the use of off-label doses was
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3 proven or suspected sepsis in all three countries, although significantly more off-label
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5 doses for medical prophylaxis were prescribed in Italy and Greece than in the UK.
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9 Table 3 shows the antibiotics used for an off-label indication in more than 5% of the
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11 prescriptions in at least one of the centers in the patients admitted to the NICUs. The
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13 prevalence of this use was similar in the UK and Greece, but higher in Italy. There were
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15 between-country differences in both the molecules and the individual indications. The
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17 antibiotics most frequently prescribed for an off-label indication were flucloxacillin in the
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19 UK, and ampicillin and gentamicin in Italy and Greece. The most common indications were
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21 suspected or proven sepsis in the UK, and medical prophylaxis in Italy and Greece. More
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23 Italian neonates with underlying chronic disease had off-label indications for the antibiotics
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25 received than UK or Greek neonates in NICUs.
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35 **Antibiotic prescribing on paediatric wards**

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39 Very few children in all centres received an antibiotic that was not licensed for pediatric
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41 use: there were 16 out of 954 (1.7%) prescriptions in which antibiotics were used outside
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43 the registered age range. The antibiotics most frequently used outside the registered age
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45 range were quinolones (11/16, 68.8%) and linezolid (5/16, 31.2%), administered to
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47 children with a severe infection and an underlying chronic disease (mainly cystic fibrosis or
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49 leukemia). The median age of the patients receiving “outside age range” antibiotics was
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51 significantly higher in wards in the UK (median age at prescription 8.19 years) than in Italy
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53 (median age at prescription 4.25 years; $p < 0.05$ vs UK) or Greece (median age at
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55 prescription 0.41 years).
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3 Table 4 shows the antibiotics used at an unregistered dose in more than 5% of the
4 prescriptions in at least one of the centers in patients admitted to pediatric wards. The
5 proportion of prescriptions was quite similar in all of the centres, and the number of
6 antibiotics involved was equally high across countries. In contrast, there were significant
7 between-country differences in antibiotic choice, the most commonly prescribed being
8 amoxicillin-clavulanate in Italy, cefuroxime in Greece, and gentamicin in the UK. The off-
9 label doses were mainly higher than advised in Italy and Greece, and lower than
10 recommended in the UK. The main indications for off-label dosage were sepsis, lower
11 respiratory tract infection and surgical prophylaxis in all three countries, with no difference
12 in prevalence. Doses other than those recommended were used for children aged 28
13 days-23 months significantly more often in Italy than in the UK or Greece, with the median
14 age of children receiving off-label doses being significantly lower in Italy than in the other
15 two countries. Off-label doses were prescribed for children with underlying chronic disease
16 significantly more often in the UK and Italy than in Greece.

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37 Table 5 shows the antibiotics used for off-label indications in more than 5% of the
38 prescriptions in at least one of the centers. The frequency of this use was significantly
39 higher in the UK and Italy than in Greece. Amoxicillin-clavulanate was prescribed
40 significantly more often in Italy than in Greece, and ampicillin-sulbactam significantly more
41 often in Italy than in UK and Greece. The prevalence of use for off-label surgical treatment
42 was significantly higher in the UK and Italy than in Greece. There were no significant
43 between-country differences in the age distribution of the patients or the presence of an
44 underlying chronic disease.

DISCUSSION

Over the last few years, several studies carried out in different settings have clearly demonstrated that the off-label use of drugs is frequent in pediatrics, especially in neonates [1-12]. However, most of them have considered all drugs prescribed to children and provided little details of prescription practice. To the best of our knowledge, this is the first study evaluating off-label antibiotic use in pediatrics that takes into account all of the variables involved in a drug prescription: the age of the patient, the total daily drug dose and its fractioning, and the indication for treatment.

Our findings suggest that pediatric off-label antibiotic use is very common in Europe with only marginal but sometimes significant between-country differences. However, this off-label use almost exclusively relates to doses and indications rather than age as the only antibiotics not registered for specific age groups that neonatologists and pediatricians sometimes deem imperative in very serious clinical situations were meropenem for neonates and quinolones or linezolid for older children.

Sepsis in an NICU is a life-threatening disease that requires prompt and effective antibiotic treatment [29]. Published recommendations suggest that the empirical therapy for newborns should be based on a combination of ampicillin and an aminoglycoside, although the latter can cause severe adverse events and has to be administered cautiously in the first months of life [29]. However, most of the pathogens that cause neonatal bacterial sepsis have become highly resistant to the first-choice combination, especially in the case of a late-onset and probable nosocomial origin [30]. This means that alternative antibiotic therapies are needed, particularly for neonates who remain in NICUs for several days, and justifies the use of meropenem in some cases. Meropenem has a

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3 broad antibacterial spectrum, a very good safety profile, and good pharmacokinetic and
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5 pharmacodynamic characteristics [31]. However, although it has been widely successfully
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7 used to treat severe infections, including bacterial sepsis and meningitis in children and
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9 infants aged ≥ 3 months [32], it has not yet been registered for neonates and infants aged
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11 < 3 months. Our data show that comprehensive clinical research into its use for severe
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13 infections in this age group is a clinical priority for neonatologists.
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19 Quinolones and linezolid are not licensed for use during the first 18 years of life but studies
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21 of quinolones have clearly demonstrated that ciprofloxacin and levofloxacin (the molecules
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23 used in the centres involved in this study) can be administered to pediatric patients with
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25 good results and without any significant adverse events [33,34]. Nevertheless, the use of
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27 quinolones should be limited to diseases caused by pathogens resistant to all of the other
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29 licensed drugs because they may rapidly select antimicrobial resistance in the case their
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31 widespread and uncontrolled administration. The situation of linezolid is similar as it is a
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33 relatively new drug for which pediatric experience is limited to complicated infections in
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35 patients with underlying chronic disease [35-37]. We found that quinolones and linezolid
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37 were mainly used in children with cystic fibrosis or oncohematological diseases in which
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39 complicated infections due to bacterial resistance to commonly used antibiotics is very
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41 frequent.
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3 The high prevalence of antibiotic prescriptions for off-label indications or at unregistered
4 doses in our NICUs and pediatric wards is in line with previously published data
5 concerning the pediatric use of antibiotics [1-12]. It may be that pediatricians have a poor
6 understanding of the properties and characteristics of antibiotics nor how they should be
7 prescribed to treat bacterial diseases at different pediatric ages, but our findings raise
8 some interesting afterthoughts.
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18 First of all, certain antibiotics, especially aminoglycosides, were prescribed at below than
19 recommended doses, mainly in the UK and Italian NICUs, which may reflect
20 neonatologists' fear of known adverse effects [2] and a preference to reduce the risk by
21 limiting dosage rather than respecting published recommendations. The higher than
22 recommended dosage of aminoglycosides observed for the NICU in Greece is difficult to
23 explain, but it highlights the need for a comprehensive review of the dosing of potentially
24 toxic antibiotics in such setting.
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36 Secondly, the main off-label indications for which antibiotics were used in NICUs were
37 proven or suspected sepsis in the UK, and medical prophylaxis in Italy and Greece. The
38 rational approach to antibiotics in neonates involves using narrow-spectrum drugs
39 whenever possible, treating infection and not colonisation, and limiting the duration of
40 therapy [30], which makes it difficult to explain their use for off-label indications. It is
41 possible that many of the antibiotics approved for use in neonates have been licensed for
42 so long that the emergence of bacterial resistance is being observed or suspected,
43 underpinning the tendency to move to off-license alternatives.
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56 Thirdly, for the pediatric inpatient populations, the number of prescriptions made at
57 unregistered doses could be due to clinicians translating the findings of well-conducted
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3 post-marketing studies into their clinical practice. Aminoglycosides serve as a good
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5 example of this: having been licensed with the recommendation to divide the total daily
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7 dose into two or three administrations depending on the patients' age and renal function,
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9 subsequent clinical trials have shown equivalent or superior clinical outcome from once
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11 daily dosing of the total daily dose, with a reduced lower risk of toxicity [38,39]. Similarly,
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13 amoxicillin, licensed in children at a recommended dose of 40-50 mg/kg/day, proved to be
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15 effective against *Streptococcus pneumoniae* strains with relative resistance to penicillin
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17 when used at higher dose (80-90 mg/kg/day) without concomitant increase in the
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19 incidence of adverse events [40,41].
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26 Evidence of the clinical effectiveness of other antimicrobials when used for off-label
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28 indications may also be influencing practice: for example, the use of macrolides for
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30 bronchitis or acute infectious wheezing was not considered appropriate until that the role
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32 of atypical bacteria was demonstrated in these diseases [42-44]. It may be, therefore that
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34 some of the off-label prescribing described in this study constituted active rational
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36 decision-making by clinicians based on the emerging evidence. However, how much off-
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38 label prescribing is merely 'personal practice' error or experimentation without an
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40 appropriate clinical trial setting cannot be evaluated from this study.
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46 In conclusion, although only four centres have been evaluated in our study and this limits
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48 the speculation on the possible causes of differences between countries as well as it does
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50 not really represent the entire European Union, our data confirm that the off-label use of
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52 antibiotics in newborns, infants and children is widespread and that the bulk of this cannot
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54 be justified on the grounds of optimizing clinical care. As suggested by the FDA and EMEA
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56 [23-26], studies of the antibiotics that are not licensed for specific pediatric age groups are
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58 urgently needed in order to evaluate how they should be administered in order to optimize
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3 clinical results while minimising the risk of adverse events. In the case of already licensed
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5 antibiotics, the studies performed after their licensing should be carefully reviewed and the
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7 recommendations modified when new knowledge acquired. Finally, national and
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9 European-wide educational programmes should meet the dual objectives of improving
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11 paediatricians' working knowledge of the recommendations surrounding licensed
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13 antibiotics-use in children, and of reducing uncontrolled patterns of prescribing that may
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15 increase the risk of antimicrobial resistance.
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Table 1. Demographic characteristics of the study population.

	NICUs			Pediatric wards		
	UK (n=62)	Italy (n=38)	Greece (n=10)	UK (n=265)	Italy (n=94)	Greece (n=147)
Males (%)	33 (53.2)	25 (65.8)	6 (60.0)	144 (54.3)	56 (59.6)	89 (60.5)
Age						
0-27 days, No. (%)	48 (77.4)	30 (78.9)	5 (50.0)	24 (9.0) ^a	2 (2.1)	4 (2.7)
28 days-23 months, No. (%)	14 (22.6)	8 (21.1)	5 (50.0)	100 (37.7)	38 (40.4)	51 (34.8)
2 years-11 years, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	102 (38.5) ^b	47 (50.0)	80 (54.4)
12 years-17 years, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	39 (14.7)	7 (7.4)	12 (8.1)
Patients with underlying chronic disease, No. (%)	50 (80.6)	32 (84.2)	8 (80.0)	150 (56.6) ^c	49 (52.1) ^d	51 (34.7)
Total number of antibiotic prescriptions (mean per patient)	172 (2.77)	91 (2.39)	27 (2.70)	545 (2.05)	160 (1.70)	249 (1.69)
Total number of antibiotics used (mean per patient)	13 (0.20)	10 (0.26)	15 (1.5)	32 (0.12)	29 (0.30)	29 (0.19)
Total number of indications (mean per patient)	77 (1.24)	45 (1.18)	12 (1.2)	300 (1.13)	105 (1.11)	153 (1.04)

NICUs: neonatal intensive care units; UK: United Kingdom. ^ap<0.05 vs Italy and Greece; ^bp<0.05 vs Greece; ^cp<0.0001 vs Greece; no other significant between-country difference.

Table 2. Antibiotics used at an unregistered dose in more than 5% of the prescriptions in at least one of the centers in patients admitted to NICUs.

	UK (No. of prescriptions=172)	Italy (No. of prescriptions=91)	Greece (No. of prescriptions=27)
Antibiotics used at an unregistered dose, No. (%)	65 (37.8) ^a	47 (51.7)	12 (44.4)
Main molecules			
Amikacin, No. (%)	27 (15.7)	12 (13.2)	3 (11.1)
Amoxicillin-clavulanate, No. (%)	0 (0.0) ^a	6 (6.6)	0 (0.0)
Gentamicin, No. (%)	11 (6.4) ^a	17 (18.7)	1 (3.7)
Metronidazole, No. (%)	6 (3.5)	6 (6.6)	1 (3.7)
Trimethoprim, No. (%)	9 (5.2)	0 (0.0)	0 (0.0)
Vancomycin, No. (%)	4 (2.3)	4 (4.4)	3 (11.1)
Others, No. (%)	8 (4.6)	3 (2.2)	4 (14.8)
Higher than advised doses, No. (%)	5 (2.9) ^b	8 (8.8)	6 (22.2)
Lower than advised doses, No. (%)	32 (18.7)	22 (24.2)	4 (14.8)
Incorrect frequency, No. (%)	28 (16.3)	17 (18.7)	2 (7.4)
Main indications			
Medical prophylaxis, No. (%)	1 (0.6) ^{b, c}	13 (14.3)	3 (11.1)
Sepsis, No. (%)	45 (26.2)	18 (19.8)	6 (22.2)
Surgical prophylaxis, No. (%)	9 (5.2)	4 (4.4)	0 (0.0)
Surgical treatment, No. (%)	9 (5.2)	9 (9.9)	0 (0.0)
Urinary tract infection, No. (%)	0 (0.0)	0 (0.0)	2 (7.4)
Others, No. (%)	1 (0.6)	3 (3.3)	1 (3.7)
Median gestational age at birth, weeks (range)	31.2 (23 – 41)	32.6 (24 – 41)	32.9 (24 – 39)
Median age at prescription (range), days	29 (1-205)	24 (1-176)	37 (4-104)
Patients with underlying chronic disease, No. (%)	59 (34.3)	39 (42.8)	9 (33.4)

NICU: neonatal intensive care unit; UK: United Kingdom. ^ap<0.05 vs Italy; ^bp<0.05 vs Greece; ^cp<0.0001 vs Italy; no other significant between-country difference.

Table 3. Antibiotics used for an off-label indication in more than 5% of the prescriptions in at least one of the centers in patients admitted to NICUs.

	UK (No. of prescriptions =172)	Italy (No. of prescriptions=91)	Greece (No. of prescriptions =27)
Antibiotics used for an off-label indication, No. (%)	40 (23.3) ^a	35 (38.5)	7 (25.9)
Main molecules			
Amoxicillin-clavulanate, No. (%)	1 (0.6) ^a	7 (7.7)	0 (0.0)
Ampicillin, No. (%)	0 (0.0) ^a	13 (14.3)	1 (3.7)
Cefaclor, No. (%)	0 (0.0) ^b	0 (0.0) ^b	2 (7.4)
Flucloxacillin, No. (%)	27 (15.7) ^{a, b}	0 (0.0)	0 (0.0)
Gentamicin, No. (%)	0 (0.0) ^a	12 (13.2)	1 (3.7)
Others, No. (%)	12 (7.0) ^a	3 (3.3) ^b	3 (11.1)
Main indications			
Medical prophylaxis, No. (%)	0 (0.0) ^c	28 (30.8)	5 (18.5)
Sepsis, No. (%)	29 (16.9) ^a	4 (4.4)	1 (3.7)
Others, No. (%)	11 (6.4)	3 (3.3)	1 (3.7)
Mean gestational age at birth, weeks (range)	28.4 (23- 41)	33.5 (24-41)	33.2 (25-38)
Median age at prescription, days (range)	30 (1-192)	22 (1-176)	35 (4-104)
Patients with underlying chronic disease, No. (%)	40 (23.3) ^a	34 (37.3)	6 (22.2)

NICU: neonatal intensive care unit; UK: United Kingdom. ^ap<0.05 vs Italy; ^bp<0.05 vs Greece; ^cp<0.0001 vs Italy and Greece; no other significant between-country difference.

Table 4. Off-label antibiotics used at an unregistered dose in more than 5% of the prescriptions in at least one of the centers in patients admitted to pediatric wards.

	UK	Italy	Greece
	(No. of prescriptions=545)	(No. of prescriptions=160)	(No. of prescriptions =249)
Antibiotics used at an unregistered dose, No. (%)	163 (29.9)	44 (27.5)	63 (25.3)
Main molecules			
Amoxicillin-clavulanate, No. (%)	17 (3.1) ^a	13 (8.1)	5 (2.0) ^a
Cefuroxime, No. (%)	5 (0.9) ^b	0 (0.0) ^b	5 (6.0)
Gentamicin, No. (%)	64 (11.7) ^{a, c}	2 (1.2)	2 (0.8)
Others, No. (%)	77 (14.1)	29 (18.1)	51 (20.5)
Higher than advised dose, No. (%)	62 (11.4)	26 (16.3)	38 (15.3)
Lower than advised dose, No. (%)	83 (15.2) ^b	16 (10.0)	19 (7.6)
Incorrect frequency, No. (%)	18 (3.3)	2 (1.3)	6 (2.4)
Main indications			
Lower respiratory tract infection, No. (%)	19 (3.5)	9 (5.6)	14 (5.6)
Sepsis, No. (%)	30 (5.5)	8 (5.0)	3 (1.2)
Surgical prophylaxis, No. (%)	50 (9.2)	9 (5.6)	13 (5.2)
Others, No. (%)	64 (11.7)	18 (11.3)	33 (13.3)
Age			
0-27 days, No. (%)	20 (3.7)	1 (0.6)	2 (0.8)
28 days-23 months, No. (%)	47 (8.6) ^a	25 (15.6)	17 (6.8) ^a
2-11 years, no. (%)	69 (12.7)	16 (10.0)	42 (16.9)
12-17 years, no. (%)	27 (4.9)	2 (1.3)	2 (0.8)
Median age (range), years	5.34 (0.01-17.30) ^a	3.80 (0.04-14.49)	4.43 (0.03-13.27) ^a
Patients with underlying chronic disease, no. (%)	122 (22.4) ^c	30 (18.8) ^b	26 (10.4)

UK: United Kingdom. ^ap<0.05 vs Italy; ^bp<0.05 vs Greece; ^cp<0.0001 vs Greece; no other significant between-country difference.

Table 5. Antibiotics used for an off-label indication in in more than 5% of the prescriptions in at least one of the centers in patients admitted to pediatric wards.

	UK (No. of prescriptions=545)	Italy (No. of prescriptions=160)	Greece (No. of prescriptions=249)
Antibiotics used for an off-label indication, No. (%)	155 (28.4) ^a	48 (30.0) ^a	49 (19.7)
Main molecules			
Amoxicillin-clavulanate, No. (%)	45 (8.3) ^a	11 (6.9) ^a	4 (1.6)
Ampicillin-sulbactam, No. (%)	0 (0.0) ^b	16 (10.0)	0 (0.0) ^b
Gentamicin, No. (%)	27 (5.0) ^{a, c}	0 (0.0)	0 (0.0)
Others, No. (%)	83 (15.2)	21 (13.1)	45 (18.1)
Main indications			
Surgical prophylaxis, No. (%)	52 (7.9)	21 (13.1)	31 (12.4)
Surgical treatment, No. (%)	37 (4.8) ^a	8 (5.0) ^a	3 (1.2)
Others, No. (%)	66 (12.1) ^a	19 (11.9)	15 (6.0)
Age			
0-27 days, No. (%)	11 (2.0)	1 (0.6)	0 (0.0)
28 days-23 months, No. (%)	44 (8.1)	17 (10.6)	17 (6.8)
2-11 years, No. (%)	71 (13.0)	23 (14.4)	23 (9.3)
12-17 years, No. (%)	29 (5.3)	7 (4.4)	9 (3.6)
Median age, years (range)	5.61 (0.01-16.88)	5.74 (0.04-16.29)	5.85 (0.13-15.09)
Patients with underlying chronic disease, No. (%)	101 (18.6)	28 (17.5)	38 (15.3)

UK: United Kingdom. ^ap<0.05 vs Greece; ^bp<0.0001 vs Italy; ^cp<0.05 vs Italy; no other significant between-country difference.

OFF-LABEL ANTIBIOTIC USE IN CHILDREN IN THREE EUROPEAN COUNTRIES

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ABSTRACT

Objective. Antibiotics are the drugs most frequently prescribed for children, and most of them lack patent protection. The aim of the present study was to evaluate off-label antibiotic use in three European countries.

Methods. The data concerning all patients admitted to the neonatal intensive care units (NICUs) and pediatric wards of the **centers** were collected by the same investigator over a two-week survey period between February and May 2009. Data included age, date of birth, weight, relevant medical history and diagnosis, together with details of all of the antibiotics prescribed (compound, route of administration, dose and indication for use).

Results. The study involved 616 children (110 admitted to NICUs: 62 in the UK, 38 in Italy, and 10 in Greece; and 506 admitted to general pediatric wards: 265 in the UK, 94 in Italy and 147 in Greece) and a total of 1244 antibiotic prescriptions were issued (290 in NICUs and 954 in pediatric wards). The results show that off-label antibiotic use is very common in European pediatrics, with only slight but sometimes significant differences between countries. However, this use relates almost exclusively to doses and indications, and rarely to age. The only antibiotics used off-label for age in pediatric clinical practice were meropenem for neonates and quinolones or linezolid for older children, which represent priorities for future studies.

Conclusion. European-wide educational programmes are urgently needed to meet the objectives of improving paediatricians' working knowledge of the recommendations surrounding licensed antibiotics-use in children, and of reducing uncontrolled patterns of prescribing.

INTRODUCTION

A number of hospital- and office-based studies have shown that many of the drugs prescribed to children are used outside their registered doses, age groups, indications and routes of administration [1-12]. This off-label use is related to the practical and ethical difficulties in carrying out clinical trials involving very young subjects. The extensive research required by current standards of drug evaluation in order to register a specific product for paediatric use is often not supported by the profit-driven drug industry because children represent only a small part of the drug market [13]. Furthermore, the limited pediatric drug research that is carried out is often based on small-scale studies that lack the statistical power necessary to draw any firm conclusions concerning the real efficacy of the drugs or their long-term toxic effects [14]. Ethical conflicts are heightened where the toxicity of medicines may be different in children and adults, compounded by issues around informed consent and assent [15].

Off-label drug use can cause significant damage in the developing fetus or child, one of the best examples being the grey baby syndrome due to chloramphenicol [16,17]; but it also gives rise to many minor but not marginal adverse events requiring hospitalisation or additional therapies [18-22]. A number of health authorities have recognised the need to conduct specific studies in children in order to reduce the problem of off-label use. The American Food and Drug Administration (FDA) has prepared the Best Pharmaceutical for Children Act and the Pediatric Research Equity Act, both of which are intended to incentivise drug research in children [23,24]: the first allows companies to qualify for an additional six months' exclusive marketing of a specific molecule provided that they carry out specific paediatric trials [23], and the second, which became law in 2003, states that the FDA can require pediatric studies of a drug for which a new drug application is submitted if it finds that the product is likely to be used in a substantial number of pediatric

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3 patients or would provide a significant benefit over existing treatments [24]. The European
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5 Medicines Agency (EMA) has laid down specific rules for marketing authorisations of
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7 new medicinal products and for pediatric-use marketing authorisations of off-patent
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9 products [25]. It has also agreed a strategy for establishing the European network of
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11 pediatric research and providing information concerning pediatric clinical trials. Moreover,
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13 in order to encourage studies of drugs that lack patent protection because they have been
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15 marketed for many years, it has decided to prepare a list of drugs for which studies in
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17 children are urgently needed and can be financed by the European Union [26].
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21 The drugs most frequently prescribed for children are antibiotics [27,28], most of which
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23 lack patent protection. The aim of the present study was to evaluate off-label antibiotic use
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25 in three European countries.
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28 29 30 31 **METHODS**

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33 Antibiotic prescriptions were evaluated for all inpatients in the neonatal intensive care units
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35 (NICUs) and the pediatric medical and surgical wards of two hospitals in UK (St George's
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37 Hospital and Evelina Children's Hospital in London), one in Italy (Department of Maternal
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39 and Pediatric Sciences of the University of Milan), and one in Greece (Aglaia Kyriakou
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41 Children's Hospital, University of Athens). All data on the four sites were collected by the
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43 same investigator (AP) during a two-week survey of each hospital between February and
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45 May 2009. Data included age, date of birth, weight, relevant medical history and diagnosis,
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47 together with details of all of the antibiotics prescribed (compound, route of administration,
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49 dose and indication for use). The protocol was approved by the Institutional Review Board
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51 of all centres, and written informed consent was obtained from a parent or legal guardian,
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53 with children aged more than eight years being asked to give their assent.
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3 Off-label antibiotic use was determined on the basis of the information concerning product
4 registration given in the British National Formulary 2009, the Italian Informatore
5 Farmaceutico, and the Greek National Formulary 2006, as well as package insert
6 information and what could be derived from the medical information departments of the
7 pharmaceutical companies concerned. Off-label use was defined as the administration of
8 an antibiotic in situations not covered by the product licence or the summary of product
9 characteristics, or at a different dose or frequency, or to different age groups, or by means
10 of an alternative route. The age groups considered were those defined by EMEA:
11 neonates (0-27 days), infants (28 days to 23 months), children (2-11 years) and
12 adolescents (12-17 years). The prescriptions were then divided into three groups
13 depending on whether the off-label use was related to the patient's age, the drug dose, or
14 the indication. A difference of 10% between the physician's prescription and the reference
15 dose was allowed before considering the administration off-label.
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34 Results were compared using SAS software, version 9.1 (SAS Institute, Cary, North
35 Carolina). **In Tables, only antibiotics prescribed at unregistered dose or for an off-label
36 indication in more than 5% of the prescriptions in at least one of the centers are shown.**
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41 Categorical variables are reported as numbers and percentages, and analysed by means
42 of contingency tables and the chi-squared or Fisher's test. Continuous variables are given
43 as mean values \pm standard deviation (SD), and analysed using a t test or Wilcoxon's test
44 (for non-normally distributed data). P-values of 0.05 or less were considered to be
45 statistically significant.
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55 RESULTS

56 Study population

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3 The study involved a total of 616 children (110 admitted to NICUs: 62 in the UK, 38 in Italy,
4 and 10 in Greece; and 506 admitted to pediatric wards: 265 in the UK, 94 in Italy and 147
5 in Greece); a total of 1244 antibiotic prescriptions were issued for these patients (290 in
6 NICUs and 954 in pediatric wards). Table 1 shows the demographic characteristics of the
7 study patients. For NICU patients, there were no significant between-country differences in
8 gender or age, or in the presence of underlying chronic conditions, number of antibiotic
9 prescriptions, number of antibiotics used, or clinical indications for the antibiotic
10 prescriptions. On pediatric wards, significantly more children in the neonatal age group
11 were admitted in the UK than in Italy or Greece, and significantly fewer children aged 2-11
12 years were admitted in the UK than in Greece, while both UK and Italy hospitalised
13 significantly more pediatric patients with underlying chronic diseases than Greece.
14 However, there were no significant between country differences in gender, number of
15 antibiotic prescriptions, number of antibiotics used, or clinical indications for the antibiotic
16 prescriptions on paediatric wards.

Antibiotic prescribing in neonatal units

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There were 12 episodes out of 290 prescriptions in which antibiotics were used outside the registered age range (4.1%). Although there were small number of neonates in the Greek NICU during the study period, there were significantly fewer "outside age range" prescriptions in the UK (4/172, 4.3%) and Italy (2/91, 2.2%) than in Greece (6/27, 22.2%; $p < 0.05$ vs UK and Italy). The most frequent of such prescriptions in all centres was for meropenem (10/12 episodes, 83.3%), which was prescribed because of proven or suspected sepsis in all cases. The Greek NICU also used imipenem (one case for lower respiratory tract infection) and ciprofloxacin (one case for urinary tract infection) outside age range. Moreover, the median gestational and chronological ages of the neonates in

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3 whom antibiotics were used outside the registered age range were significantly lower in
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5 Italy (median gestational age at birth 26 weeks and median age at prescription 24 days)
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7 than in the UK (median gestational age 31.7 weeks, $p < 0.05$ vs Italy; median age 39.5
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9 days, $p < 0.05$ vs Italy) or Greece (median gestational age 33.7 weeks, $p < 0.05$ vs Italy;
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11 median age 64 days, $p < 0.05$ vs Italy). In the UK and Italian NICUs, the off-label use of
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13 antibiotics was related to patients with an underlying chronic disease in all cases, whereas
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15 in Greece this was true of only half of the cases.
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19 Table 2 shows the antibiotics used at an unregistered dose in more than 5% of the
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21 prescriptions **in at least one of the centers** in patients admitted to NICUs. The number of
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23 such prescriptions was high in all of three countries, but significantly higher in Italy than in
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25 the UK. In all of the NICUs, the antibiotics most frequently prescribed at doses other than
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27 the recommended dose were aminoglycosides (particularly amikacin and gentamicin). Off-
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29 label doses of gentamicin and also amoxicillin-clavulanate were prescribed significantly
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31 more often in the Italian NICU than in the UK units. In most cases, the differences
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33 regarded the administration of a lower than advised total daily dose or different fractioning.
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35 Higher than recommended doses were significantly more common in the Greek than in the
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37 UK NICUs. The **most common** clinical indication related to the use of off-label doses was
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39 proven or suspected sepsis in all three countries, although significantly more off-label
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41 doses for medical prophylaxis were prescribed in Italy and Greece than in the UK.
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48 Table 3 shows the antibiotics used for an off-label indication in more than 5% of the
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50 prescriptions **in at least one of the centers** in the patients admitted to the NICUs. The
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52 prevalence of this use was similar in the UK and Greece, but higher in Italy. There were
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54 between-country differences in both the molecules and the individual indications. The
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56 antibiotics most frequently prescribed for an off-label indication were flucloxacillin in the
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58 UK, and ampicillin and gentamicin in Italy and Greece. The **most common** indications were
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3 suspected or proven sepsis in the UK, and medical prophylaxis in Italy and Greece. More
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5 Italian neonates with underlying chronic disease had off-label indications for the antibiotics
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7 received than UK or Greek neonates in NICUs.
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10 11 12 **Antibiotic prescribing on paediatric wards** 13

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15 Very few children in all centres received an antibiotic that was not licensed for pediatric
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17 use: there were 16 out of 954 (1.7%) prescriptions in which antibiotics were used outside
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19 the registered age range. The antibiotics most frequently used outside the registered age
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21 range were quinolones (11/16, 68.8%) and linezolid (5/16, 31.2%), administered to
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23 children with a severe infection and an underlying chronic disease (mainly cystic fibrosis or
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25 leukemia). The median age of the patients receiving “outside age range” antibiotics was
26
27 significantly higher in wards in the UK (median age at prescription 8.19 years) than in Italy
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29 (median age at prescription 4.25 years; $p < 0.05$ vs UK) or Greece (median age at
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31 prescription 0.41 years).
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36 Table 4 shows the antibiotics used at an unregistered dose in more than 5% of the
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38 prescriptions in at least one of the centers in patients admitted to pediatric wards. The
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40 proportion of prescriptions was quite similar in all of the centres, and the number of
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42 antibiotics involved was equally high across countries. In contrast, there were significant
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44 between-country differences in antibiotic choice, the most commonly prescribed being
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46 amoxicillin-clavulanate in Italy, cefuroxime in Greece, and gentamicin in the UK. The off-
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48 label doses were mainly higher than advised in Italy and Greece, and lower than
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50 recommended in the UK. The main indications for off-label dosage were sepsis, lower
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52 respiratory tract infection and surgical prophylaxis in all three countries, with no difference
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54 in prevalence. Doses other than those recommended were used for children aged 28
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56 days-23 months significantly more often in Italy than in the UK or Greece, with the median
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3 age of children receiving off-label doses being significantly lower in Italy than in the other
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5 two countries. Off-label doses were prescribed for children with underlying chronic disease
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7 significantly more often in the UK and Italy than in Greece.
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10 Table 5 shows the antibiotics used for off-label indications in more than 5% of the
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12 prescriptions **in at least one of the centers**. The frequency of this use was significantly
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14 higher in the UK and Italy than in Greece. Amoxicillin-clavulanate was prescribed
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16 significantly more often in Italy than in Greece, and ampicillin-sulbactam significantly more
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18 often in Italy than in UK and Greece. The prevalence of use for off-label surgical treatment
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20 was significantly higher in the UK and Italy than in Greece. There were no significant
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22 between-country differences in the age distribution of the patients or the presence of an
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24 underlying chronic disease.
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31 **DISCUSSION**

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33 Over the last few years, several studies carried out in different settings have clearly
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35 demonstrated that the off-label use of drugs is frequent in pediatrics, especially in
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37 neonates [1-12]. However, most of them have considered all drugs prescribed to children
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39 and provided little details of prescription practice. To the best of our knowledge, this is the
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41 first study evaluating off-label antibiotic use in pediatrics that takes into account all of the
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43 variables involved in a drug prescription: the age of the patient, the total daily drug dose
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45 and its fractioning, and the indication for treatment.
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50 Our findings suggest that pediatric off-label antibiotic use is very common in Europe with
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52 only marginal but sometimes significant between-country differences. However, this off-
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54 label use almost exclusively relates to doses and indications rather than age as the only
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56 antibiotics not registered for specific age groups that neonatologists and pediatricians
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3 sometimes deem imperative in very serious clinical situations were meropenem for
4 neonates and quinolones or linezolid for older children.
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8 Sepsis in an NICU is a life-threatening disease that requires prompt and effective antibiotic
9 treatment [29]. Published recommendations suggest that the empirical therapy for
10 newborns should be based on a combination of ampicillin and an aminoglycoside,
11 although the latter can cause severe adverse events and has to be administered
12 cautiously in the first months of life [29]. However, most of the pathogens that cause
13 neonatal bacterial sepsis have become highly resistant to the first-choice combination,
14 especially in the case of a late-onset and probable nosocomial origin [30]. This means that
15 alternative antibiotic therapies are needed, particularly for neonates who remain in NICUs
16 for several days, and justifies the use of meropenem in some cases. Meropenem has a
17 broad antibacterial spectrum, a very good safety profile, and good pharmacokinetic and
18 pharmacodynamic characteristics [31]. However, although it has been widely successfully
19 used to treat severe infections, including bacterial sepsis and meningitis in children and
20 infants aged ≥ 3 months [32], it has not yet been registered for neonates and infants aged
21 < 3 months. Our data show that comprehensive clinical research into its use for severe
22 infections in this age group is a clinical priority for neonatologists.
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43 Quinolones and linezolid are not licensed for use during the first 18 years of life but studies
44 of quinolones have clearly demonstrated that ciprofloxacin and levofloxacin (the molecules
45 used in the centres involved in this study) can be administered to pediatric patients with
46 good results and without any significant adverse events [33,34]. Nevertheless, the use of
47 quinolones should be limited to diseases caused by pathogens resistant to all of the other
48 licensed drugs because they may rapidly select antimicrobial resistance in the case their
49 widespread and uncontrolled administration. The situation of linezolid is similar as it is a
50 relatively new drug for which pediatric experience is limited to complicated infections in
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3 patients with underlying chronic disease [35-37]. We found that quinolones and linezolid
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5 were mainly used in children with cystic fibrosis or oncohematological diseases in which
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7 complicated infections due to bacterial resistance to commonly used antibiotics is very
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9 frequent.

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12 The high prevalence of antibiotic prescriptions for off-label indications or at unregistered
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14 doses in our NICUs and pediatric wards is in line with previously published data
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16 concerning the pediatric use of antibiotics [1-12]. It may be that pediatricians have a poor
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18 understanding of the properties and characteristics of antibiotics nor how they should be
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20 prescribed to treat bacterial diseases at different pediatric ages, but our findings raise
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22 some interesting afterthoughts.
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27 First of all, certain antibiotics, especially aminoglycosides, were prescribed at below than
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29 recommended doses, mainly in the UK and Italian NICUs, which may reflect
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31 neonatologists' fear of known adverse effects [2] and a preference to reduce the risk by
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33 limiting dosage rather than respecting published recommendations. The higher than
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35 recommended dosage of aminoglycosides observed for the NICU in Greece is difficult to
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37 explain, but it highlights the need for a comprehensive review of the dosing of potentially
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39 toxic antibiotics in such setting.
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44 Secondly, the main off-label indications for which antibiotics were used in NICUs were
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46 proven or suspected sepsis in the UK, and medical prophylaxis in Italy and Greece. The
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48 rational approach to antibiotics in neonates involves using narrow-spectrum drugs
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50 whenever possible, treating infection and not colonisation, and limiting the duration of
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52 therapy [30], which makes it difficult to explain their use for off-label indications. It is
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54 possible that many of the antibiotics approved for use in neonates have been licensed for
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56 so long that the emergence of bacterial resistance is being observed or suspected,
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58 underpinning the tendency to move to off-license alternatives.
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3 Thirdly, for the pediatric inpatient populations, the number of prescriptions made at
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5 unregistered doses could be due to clinicians translating the findings of well-conducted
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7 post-marketing studies into their clinical practice. Aminoglycosides serve as a good
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9 example of this: having been licensed with the recommendation to divide the total daily
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11 dose into two or three administrations depending on the patients' age and renal function,
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13 subsequent clinical trials have shown equivalent or superior clinical outcome from once
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15 daily dosing of the total daily dose, with a reduced lower risk of toxicity [38,39]. Similarly,
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17 amoxicillin, licensed in children at a recommended dose of 40-50 mg/kg/day, proved to be
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19 effective against *Streptococcus pneumoniae* strains with relative resistance to penicillin
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21 when used at higher dose (80-90 mg/kg/day) without concomitant increase in the
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23 incidence of adverse events [40,41].
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29 Evidence of the clinical effectiveness of other antimicrobials when used for off-label
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31 indications may also be influencing practice: for example, the use of macrolides for
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33 bronchitis or acute infectious wheezing was not considered appropriate until that the role
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35 of atypical bacteria was demonstrated in these diseases [42-44]. It may be, therefore that
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37 some of the off-label prescribing described in this study constituted active **rational**
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39 decision-making by clinicians based on the emerging evidence. However, how much off-
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41 label prescribing is merely 'personal practice' error or experimentation **without** an
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43 appropriate clinical trial setting cannot be evaluated from this study.
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48 In conclusion, although only four centres have been evaluated in our study and this limits
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50 the speculation on the possible causes of differences between countries as well as it does
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52 not really represent the entire European Union, our data confirm that the off-label use of
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54 antibiotics in newborns, infants and children is widespread and that the bulk of this cannot
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56 be justified on the grounds of optimizing clinical care. As suggested by the FDA and EMEA
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58 [23-26], studies of the antibiotics that are not licensed for specific pediatric age groups are
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3 urgently needed in order to evaluate how they should be administered in order to optimize
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5 clinical results while minimising the risk of adverse events. In the case of already licensed
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7 antibiotics, the studies performed after their licensing should be carefully reviewed and the
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9 recommendations modified when new knowledge acquired. Finally, national and
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11 European-wide educational programmes should meet the dual objectives of improving
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13 paediatricians' working knowledge of the recommendations surrounding licensed
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15 antibiotics-use in children, and of reducing uncontrolled patterns of prescribing that may
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17 increase the risk of antimicrobial resistance.
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Table 1. Demographic characteristics of the study population.

	NICUs			Pediatric wards		
	UK (n=62)	Italy (n=38)	Greece (n=10)	UK (n=265)	Italy (n=94)	Greece (n=147)
Males (%)	33 (53.2)	25 (65.8)	6 (60.0)	144 (54.3)	56 (59.6)	89 (60.5)
Age						
0-27 days, No. (%)	48 (77.4)	30 (78.9)	5 (50.0)	24 (9.0) ^a	2 (2.1)	4 (2.7)
28 days-23 months, No. (%)	14 (22.6)	8 (21.1)	5 (50.0)	100 (37.7)	38 (40.4)	51 (34.8)
2 years-11 years, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	102 (38.5) ^b	47 (50.0)	80 (54.4)
12 years-17 years, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	39 (14.7)	7 (7.4)	12 (8.1)
Patients with underlying chronic disease, No. (%)	50 (80.6)	32 (84.2)	8 (80.0)	150 (56.6) ^c	49 (52.1) ^d	51 (34.7)
Total number of antibiotic prescriptions (mean per patient)	172 (2.77)	91 (2.39)	27 (2.70)	545 (2.05)	160 (1.70)	249 (1.69)
Total number of antibiotics used (mean per patient)	13 (0.20)	10 (0.26)	15 (1.5)	32 (0.12)	29 (0.30)	29 (0.19)
Total number of indications (mean per patient)	77 (1.24)	45 (1.18)	12 (1.2)	300 (1.13)	105 (1.11)	153 (1.04)

NICUs: neonatal intensive care units; UK: United Kingdom. ^ap<0.05 vs Italy and Greece; ^bp<0.05 vs Greece; ^cp<0.0001 vs Greece; no other significant between-country difference.

Table 2. Antibiotics used at an unregistered dose in more than 5% of the prescriptions in at least one of the centers in patients admitted to NICUs.

	UK (No. of prescriptions=172)	Italy (No. of prescriptions=91)	Greece (No. of prescriptions=27)
Antibiotics used at an unregistered dose, No. (%)	65 (37.8) ^a	47 (51.7)	12 (44.4)
Main molecules			
Amikacin, No. (%)	27 (15.7)	12 (13.2)	3 (11.1)
Amoxicillin-clavulanate, No. (%)	0 (0.0) ^a	6 (6.6)	0 (0.0)
Gentamicin, No. (%)	11 (6.4) ^a	17 (18.7)	1 (3.7)
Metronidazole, No. (%)	6 (3.5)	6 (6.6)	1 (3.7)
Trimethoprim, No. (%)	9 (5.2)	0 (0.0)	0 (0.0)
Vancomycin, No. (%)	4 (2.3)	4 (4.4)	3 (11.1)
Others, No. (%)	8 (4.6)	3 (2.2)	4 (14.8)
Higher than advised doses, No. (%)	5 (2.9) ^b	8 (8.8)	6 (22.2)
Lower than advised doses, No. (%)	32 (18.7)	22 (24.2)	4 (14.8)
Incorrect frequency, No. (%)	28 (16.3)	17 (18.7)	2 (7.4)
Main indications			
Medical prophylaxis, No. (%)	1 (0.6) ^{b, c}	13 (14.3)	3 (11.1)
Sepsis, No. (%)	45 (26.2)	18 (19.8)	6 (22.2)
Surgical prophylaxis, No. (%)	9 (5.2)	4 (4.4)	0 (0.0)
Surgical treatment, No. (%)	9 (5.2)	9 (9.9)	0 (0.0)
Urinary tract infection, No. (%)	0 (0.0)	0 (0.0)	2 (7.4)
Others, No. (%)	1 (0.6)	3 (3.3)	1 (3.7)
Median gestational age at birth, weeks (range)	31.2 (23 – 41)	32.6 (24 – 41)	32.9 (24 – 39)
Median age at prescription (range), days	29 (1-205)	24 (1-176)	37 (4-104)
Patients with underlying chronic disease, No. (%)	59 (34.3)	39 (42.8)	9 (33.4)

NICU: neonatal intensive care unit; UK: United Kingdom. ^ap<0.05 vs Italy; ^bp<0.05 vs Greece; ^cp<0.0001 vs Italy; no other significant between-country difference.

Table 3. Antibiotics used for an off-label indication in more than 5% of the prescriptions in at least one of the centers in patients admitted to NICUs.

	UK (No. of prescriptions =172)	Italy (No. of prescriptions=91)	Greece (No. of prescriptions =27)
Antibiotics used for an off-label indication, No. (%)	40 (23.3) ^a	35 (38.5)	7 (25.9)
Main molecules			
Amoxicillin-clavulanate, No. (%)	1 (0.6) ^a	7 (7.7)	0 (0.0)
Ampicillin, No. (%)	0 (0.0) ^a	13 (14.3)	1 (3.7)
Cefaclor, No. (%)	0 (0.0) ^b	0 (0.0) ^b	2 (7.4)
Flucloxacillin, No. (%)	27 (15.7) ^{a, b}	0 (0.0)	0 (0.0)
Gentamicin, No. (%)	0 (0.0) ^a	12 (13.2)	1 (3.7)
Others, No. (%)	12 (7.0) ^a	3 (3.3) ^b	3 (11.1)
Main indications			
Medical prophylaxis, No. (%)	0 (0.0) ^c	28 (30.8)	5 (18.5)
Sepsis, No. (%)	29 (16.9) ^a	4 (4.4)	1 (3.7)
Others, No. (%)	11 (6.4)	3 (3.3)	1 (3.7)
Mean gestational age at birth, weeks (range)	28.4 (23- 41)	33.5 (24-41)	33.2 (25-38)
Median age at prescription, days (range)	30 (1-192)	22 (1-176)	35 (4-104)
Patients with underlying chronic disease, No. (%)	40 (23.3) ^a	34 (37.3)	6 (22.2)

NICU: neonatal intensive care unit; UK: United Kingdom. ^ap<0.05 vs Italy; ^bp<0.05 vs Greece; ^cp<0.0001 vs Italy and Greece; no other significant between-country difference.

Table 4. Off-label antibiotics used at an unregistered dose in more than 5% of the prescriptions in at least one of the centers in patients admitted to pediatric wards.

	UK (No. of prescriptions=545)	Italy (No. of prescriptions=160)	Greece (No. of prescriptions =249)
Antibiotics used at an unregistered dose, No. (%)	163 (29.9)	44 (27.5)	63 (25.3)
Main molecules			
Amoxicillin-clavulanate, No. (%)	17 (3.1) ^a	13 (8.1)	5 (2.0) ^a
Cefuroxime, No. (%)	5 (0.9) ^b	0 (0.0) ^b	5 (6.0)
Gentamicin, No. (%)	64 (11.7) ^{a, c}	2 (1.2)	2 (0.8)
Others, No. (%)	77 (14.1)	29 (18.1)	51 (20.5)
Higher than advised dose, No. (%)	62 (11.4)	26 (16.3)	38 (15.3)
Lower than advised dose, No. (%)	83 (15.2) ^b	16 (10.0)	19 (7.6)
Incorrect frequency, No. (%)	18 (3.3)	2 (1.3)	6 (2.4)
Main indications			
Lower respiratory tract infection, No. (%)	19 (3.5)	9 (5.6)	14 (5.6)
Sepsis, No. (%)	30 (5.5)	8 (5.0)	3 (1.2)
Surgical prophylaxis, No. (%)	50 (9.2)	9 (5.6)	13 (5.2)
Others, No. (%)	64 (11.7)	18 (11.3)	33 (13.3)
Age			
0-27 days, No. (%)	20 (3.7)	1 (0.6)	2 (0.8)
28 days-23 months, No. (%)	47 (8.6) ^a	25 (15.6)	17 (6.8) ^a
2-11 years, no. (%)	69 (12.7)	16 (10.0)	42 (16.9)
12-17 years, no. (%)	27 (4.9)	2 (1.3)	2 (0.8)
Median age (range), years	5.34 (0.01-17.30) ^a	3.80 (0.04-14.49)	4.43 (0.03-13.27) ^a
Patients with underlying chronic disease, no. (%)	122 (22.4) ^c	30 (18.8) ^b	26 (10.4)

UK: United Kingdom. ^ap<0.05 vs Italy; ^bp<0.05 vs Greece; ^cp<0.0001 vs Greece; no other significant between-country difference.

Table 5. Antibiotics used for an off-label indication in more than 5% of the prescriptions in at least one of the centers in patients admitted to pediatric wards.

	UK (No. of prescriptions=545)	Italy (No. of prescriptions=160)	Greece (No. of prescriptions=249)
Antibiotics used for an off-label indication, No. (%)	155 (28.4) ^a	48 (30.0) ^a	49 (19.7)
Main molecules			
Amoxicillin-clavulanate, No. (%)	45 (8.3) ^a	11 (6.9) ^a	4 (1.6)
Ampicillin-sulbactam, No. (%)	0 (0.0) ^b	16 (10.0)	0 (0.0) ^b
Gentamicin, No. (%)	27 (5.0) ^{a, c}	0 (0.0)	0 (0.0)
Others, No. (%)	83 (15.2)	21 (13.1)	45 (18.1)
Main indications			
Surgical prophylaxis, No. (%)	52 (7.9)	21 (13.1)	31 (12.4)
Surgical treatment, No. (%)	37 (4.8) ^a	8 (5.0) ^a	3 (1.2)
Others, No. (%)	66 (12.1) ^a	19 (11.9)	15 (6.0)
Age			
0-27 days, No. (%)	11 (2.0)	1 (0.6)	0 (0.0)
28 days-23 months, No. (%)	44 (8.1)	17 (10.6)	17 (6.8)
2-11 years, No. (%)	71 (13.0)	23 (14.4)	23 (9.3)
12-17 years, No. (%)	29 (5.3)	7 (4.4)	9 (3.6)
Median age, years (range)	5.61 (0.01-16.88)	5.74 (0.04-16.29)	5.85 (0.13-15.09)
Patients with underlying chronic disease, No. (%)	101 (18.6)	28 (17.5)	38 (15.3)

UK: United Kingdom. ^ap<0.05 vs Greece; ^bp<0.0001 vs Italy; ^cp<0.05 vs Italy; no other significant between-country difference.