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MAJOR ARTICLE

Raising aware-ness of antimicrobial stewardship challenges in pediatric emergency care: results from the PERFORM study assessing consistency and appropriateness of antibiotic prescribing across Europe

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Objectives: Optimization of antimicrobial stewardship (AMS) is key to tackling antimicrobial resistance (AMR), which is exacerbated by over-prescription of antibiotics in pediatric Emergency Departments (EDs). We described patterns of empiric antibiotic use in European EDs, and characterized appropriateness and consistency of prescribing.

Methods: Between August 2016 and December 2019 febrile children attending the ED in nine European countries with suspected infection were recruited into the PERFORM (Personalised Risk assessment in Febrile illness to Optimise Real-life Management) study. Empiric systemic

antibiotic use was determined in view of assigned final 'bacterial' or 'viral' phenotype. Antibiotics were classified according to WHO AWaRe.

Results: Of 2130 febrile episodes (excluding children with non-bacterial/non-viral phenotypes), 1549 (72.7%) were assigned a 'bacterial' and 581 (27.3%) a 'viral' phenotype. A total of 1318/1549 (85.1%) episodes with a 'bacterial' and 269/581 (46.3%) with a 'viral' phenotype received empiric systemic antibiotics (first two days of admission). Of those, the majority (87.8% in 'bacterial' and 87.0% in 'viral' group) received parenteral antibiotics. The top three antibiotics prescribed were third-generation cephalosporins, penicillins and penicillin/beta-lactamase inhibitor combinations. Of those treated with empiric systemic antibiotics in the 'viral' group 216/269 (80.3%) received ≥ one *Watch* antibiotic.

Conclusions: Differentiating bacterial from viral etiology in febrile illness on initial ED presentation remains challenging, resulting in a substantial over-prescription of antibiotics. A significant proportion of patients with a 'viral' phenotype received systemic antibiotics, predominantly classified as WHO *Watch*. Rapid and accurate point-of-care tests in the ED differentiating between bacterial and viral etiology, could significantly improve AMS.

Keywords: Antimicrobial Stewardship; paediatric emergency care; antibiotic prescription; AWaRe; Infectious diseases

INTRODUCTION

Febrile illness is one of the most common pediatric presentations at the emergency department (ED), contributing to 14% of attendances. [1] Most febrile children attending the ED likely have a self-limiting or viral infection, with the incidence of serious bacterial infection ranging from 5-15%, [2,3] but approximately 33% receive antibiotics, and frequently broad-spectrum antibiotics. [3,4] Discrepancy between confirmed bacterial infection and antibiotic prescription is partly explained by diagnostic uncertainty; in up to a fifth of presentations, no obvious cause of fever is found on clinical examination. [5,6] This uncertainty gives rise to antimicrobial use for non-bacterial infections and drives antimicrobial resistance (AMR).

Given the ever-increasing threat to public health posed by AMR, [7] judicious use of antimicrobials in the pediatric emergency setting is vital. The World Health Organization (WHO) global action plan encourages identifying patterns of antimicrobial use to optimize AMS programs (ASPs) in pediatric settings. [8]

Recent work has shown that ASPs need to be improved in pediatric primary, secondary, and tertiary care. [3,9,10] Whilst there are significant data on prescribing patterns in primary care and the inpatient setting, there are fewer data on antimicrobial use in EDs. [11-13]

The WHO AWaRe classification, developed as a tool to optimize antimicrobial use [14] classifies antibiotics into three AMS categories. *Access:* narrow spectrum antibiotics considered as first or second-line options for common infections, *Watch:* key targets for AMS initiatives, with higher potential for inducing resistance, and *Reserve:* 'last-resort' options against multi- or extensively drug resistant bacteria. [15]

We aimed to describe patterns of empiric systemic antibiotic use in the context of the WHO AWaRe classification to assess how the use of *Access*, *Watch* and *Reserve* antibiotics varies across European pediatric EDs, microbiological etiology and clinical syndromes. We evaluated appropriateness and consistency of antibiotic prescribing.

METHODS

Study population and Study design

The study population consisted of children (aged 0-18 years) enrolled into the Personalised Risk assessment in Febrile illness to Optimise Real-life Management study (PERFORM) between August 2016 and December 2019. PERFORM is a multi-center, prospective, observational cohort study, seeking to improve the diagnosis of febrile illness in children across Europe (https://www.perform2020.org/). Children who attended ED with suspicion of infection and were considered to require blood tests were recruited, independent of the decision for in- or outpatient care. [16] Clinical data was prospectively collected by local study teams. Each patient was assigned final syndrome classification(s) and a phenotype by local study teams, including local principal investigators, based on collected clinical and laboratory data, following clear guidance of the PERFORM phenotyping algorithm (Supplementary Figure 1). [17] To ensure accuracy and consistency of data entry and phenotyping, regular cross-site checks of randomly selected patients were performed. This was complemented by electronic quality control (QC) of all patients in the database.

Written informed consent was obtained from legal guardians of participants or participants themselves as per national guidance. The study was approved by the ethics committees of local recruitment sites and the coordinating site (Imperial College London, 16/LO/1684) (Supplementary Table 1).

Recording of diagnoses and clinical syndrome classifications

Initial and final diagnoses were recorded from pre-specified lists of clinical syndrome classifications within the CRF, by the patient's clinicians (Supplementary Table 2). Presumed etiology was recorded with initial diagnosis, and was categorized into 'Presumed bacterial', 'Presumed viral', 'Presumed non-infectious' (e.g. for inflammatory syndromes) or unspecified.

Phenotyping of participants

Febrile episodes were phenotyped using the PERFORM phenotyping algorithm (Supplementary Figure 1) and then analyzed in one of two groups defined as 'bacterial' or 'viral'. [17] For the 'bacterial' group, we included patients with a 'definite bacterial' phenotype (n=509), and those with a 'probable bacterial' (n=599) or 'bacterial syndrome' (n=441) phenotype (with bacteria detected accounting for all features or clear bacterial diagnosis). Patients who were assigned a final 'definite viral' (n=487) or 'viral syndrome' (with virus detected accounting for all features) (n=94) phenotype were included in the 'viral' group. 'Probable viral' patients were not included, because no definitive causative viral pathogen had been identified. Participants with hospital acquired infections (symptom/fever onset >two days after presentation to hospital) were excluded from the analysis as well as participants with unknown symptom and fever onset, and those for whom research bloods could not be obtained within 2 days after admission (Figure 1).

Antibiotic classes and aware classification

Empiric systemic antibiotics were defined as those prescribed within two days following presentation to hospital. These were categorized by antibiotic classes following the three WHO AWaRe categories (*Access, Watch* and *Reserve*) (Supplementary Table 3).

Outcomes

Primary outcomes were appropriateness and consistency of empiric antibiotic use considering the final phenotype and syndrome classification (Supplementary Table 4). For the 'bacterial' group, withholding antibiotics was defined as inappropriate, unless in certain diagnoses (Supplementary Table 5). This judgment was made by review of final syndrome classification by study clinicians. For the 'viral' group, any antibiotic use was defined as inappropriate (Supplementary Table 4). In addition, for the 'bacterial' group, we described antibiotic use, stratified by both initial and final syndrome classification. Only patients with one main syndrome classification (Supplementary Table 2) were included in the latter analysis, to remove conflicting indications for antibiotic use. We evaluated consistency considering the recorded presumed etiology (bacterial vs viral / non-infectious), where consistency was defined as only using antibiotics when presumed etiology was bacterial. A secondary outcome was describing empiric antibiotic use for the three most common bacterial and viral pathogens.

Statistical analysis

Distribution of variables was described in absolute numbers and percentages. Chi-squared tests were performed to determine if the variables explored were independent of each other, using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). [18]

RESULTS

We included 2130 febrile episodes (from 2090 patients) from nine European countries in the study. 1549 (72.7%) were assigned 'bacterial' and 581 (27.3%) 'viral'. 1156 (54.3%) were male. Median age was 5 years (bacterial) and 3 years (viral). Most patients (714; 33.5%) were from UK sites. (Table 1).

The most common main initial and final syndrome classifications were lower (LRTI) (initial: 421; 19.8%, final: 501; 23.5%) and upper respiratory tract infection (URTI) (initial: 399; 18.7%, final: 435; 20.0%) (Supplementary Table 6).

Overall, 1587 (74.5%) patients received empiric systemic antibiotics with significant variation between countries. The three most frequently prescribed antibiotics in both groups were third-generation cephalosporins (prescribed in 34.6% vs 60.6% respectively of those who received antibiotics), penicillin/beta-lactamase inhibitor combinations (31.1% and 24.5%) and penicillins (26.9% and 23.4%) (Supplementary Table 7 and 8).

Appropriateness of antibiotic use

1318/1549 (85.1%) patients in the 'bacterial' group received empiric systemic antibiotics with 1157/1318 (87.8%) of those administered parenterally (IV/IM). 231 (14.9%) patients in the 'bacterial' group did not receive empiric antibiotics, of which 120 (7.7%) were considered inappropriate (Supplementary Table 5). 269/581 (46.3%) of patients in the 'viral' group received inappropriate empiric antibiotics (87.0% of those IV/IM).

Of patients receiving antibiotics in the 'bacterial' group, 70.0% received at least one *Access* antibiotic and 61.0% at least one *Watch* antibiotic. Of patients receiving antibiotics in the 'viral' group, 50.2% received at least one *Access* antibiotic and 80.3% at least one *Watch* antibiotic (Figure 2A and B, Supplementary Table 7 and 8). There was a significant variation in proportion of AWaRe antibiotics used, in different countries, with Slovenia having the highest (89.2%) and Germany the lowest (39.3%) proportion of *Access* antibiotic use. We identified an *Access* use of 49.1% across all countries. (Figure 2C)

Most patients with one initial main syndrome classification were attributed the same main final syndrome classification 1326/1520 (87.2%) (Supplementary Figure 2). In patients in the 'bacterial' group with one initial syndrome classification, the most common antibiotic classes prescribed varied by syndrome – however, penicillins, penicillin/beta-lactamase inhibitor combinations and second- and third-generation cephalosporins accounted for the majority of antibiotics (Figure 3A, C). Central nervous system (CNS) showed the highest proportion of *Watch* antibiotic use. In patients with one final syndrome classification, antibiotic choice and use of *Watch* antibiotics followed a similar pattern (Figure 3B, D).

Consistency of antibiotic use

Of 251 episodes with a presumed viral or non-infectious etiology, 41 (16.3%) were subsequently phenotyped as 'bacterial' and 30 (73.2%) of those received antibiotics; the remaining 210/251 (83.7%) were assigned a 'viral' phenotype, of which 65 (31.0%) received antibiotics (Figure 4A). 95/251 (37.8%) episodes in this group received antibiotics inconsistent with the presumed etiology. An age-stratified overview of antibiotic prescribing patterns for patients with an initial viral or non-infectious initial syndrome classification is shown in Supplementary Table 9.

Of 887 episodes with a presumed bacterial etiology, 825 (93.0%) were assigned a final 'bacterial' phenotype, of which 741 (89.8%) received antibiotics. 62 (7.0%) of these episodes were assigned a final 'viral' phenotype, 48 (77.4%) received antibiotics (Figure 4B). 98/887 (11.0%) of episodes in this group, did not receive antibiotics – which is inconsistent with the presumed etiology.

For episodes in whom the initial syndrome classification included both presumed bacterial and viral etiologies, unspecified infection, or undifferentiated fever (n=992), 683 (68.9%) were attributed a final 'bacterial' phenotype of which 550 (80.5%) received antibiotics. 309 (31.1%) were attributed a final 'viral' phenotype, of whom 157 (50.8%) received antibiotics (Figure 4C).

Most common pathogens in the 'bacterial' group were *Escherichia coli*, *Streptococcus pyogenes* (GAS) and *Staphylococcus aureus* (Supplementary Table 10). Many patients with infections caused by these pathogens received systemic *Watch* antibiotics (63.3%, 47.8% and 49.0% respectively) (Supplementary Table 11). The most common viral pathogens in the 'viral' group were Influenza A/B, Rhino/Enterovirus and Respiratory Syncytial Virus (RSV) (Supplementary Table 10). In patients with these pathogens, many received antibiotics (35.3%, 64.0%, 66.7%. respectively). 79.7% of all the patients who received systemic antibiotics with Influenza A and B (73.8%), Rhino/Enterovirus (84.2%) and RSV (81.0%). received at least 1 *Watch* antibiotic (Supplementary Table 12).

DISCUSSION

We assessed appropriateness and consistency of empiric antibiotic use in European EDs using data from the PERFORM study, for children attending ED with suspected infection and considered to require blood tests, and describe antibiotic use as per the AWaRe classification.

We demonstrate that a significant proportion of children within this cohort receive systemic antibiotics including substantial use of *Watch* antibiotics, with some variation between European countries. Across the cohort, the proportion of empiric antibiotics prescribed from the *Access* category (49.1%) fell below the WHO target of 60%, illustrating an excessive use of *Watch* antibiotics. [14] A recent national AWaRe-based analysis of prescription data from pediatric outpatient and EDs in 16 secondary and tertiary care hospitals in China reported similar results.

Watch antibiotics were most frequently prescribed (82.2%) with third-generation cephalosporins (43.3%) being the most commonly prescribed. [19] Variation in antibiotic use is not limited to EDs and continuous monitoring of *Watch* antibiotic use in pediatric hospitals will be important for AMS interventions.

We show that many patients with viral illness receive empiric antibiotics at presentation to the ED. Of particular note, the proportion of patients receiving *Watch* antibiotics was higher in the 'viral' compared to the 'bacterial' group (Figure 2).

In a small proportion (7.7%) of patients with a 'bacterial' phenotype, empiric antibiotics were withheld, for conditions where this would be considered inappropriate. However, a small proportion (32%) of those received antibiotics in the last 7 days prior to attending ED. In general, this lack of consistency in antibiotic prescribing highlights the critical need for improved diagnostics and AMS.

Our data suggest that diagnostic uncertainty contributes to inappropriate antibiotic use in viral diseases. While most often the presumed etiology was correct and treated appropriately (Figures 4A, B) when bacterial or viral etiologies were not clearly identified (Figure 4C), >50% of cases in the 'viral' group received empiric antibiotics. Since molecular testing often detects both bacterial and viral pathogens in febrile children, it seems difficult for clinicians to withhold antibiotics when a viral cause is identified with the remaining possibility of an additional bacterial infection, whilst slow diagnostic tools such as cultures are still pending. [20] Over a third of children for whom only viral or non-infectious etiology was recorded as the initial syndrome classification, received antibiotics, suggesting that diagnostic uncertainty is not the only driver of inappropriate antibiotic initiation. This effect was particularly seen in the very young: clinicians were more likely to start empiric antibiotics in patients <5 years of age ($p=0.01$) (Supplementary Table 9), suggesting that clinicians may be less confident withholding antibiotics in very young febrile children. It was not possible to retrospectively determine if other factors influenced the decision, such as time of day, social circumstances, parental concerns or overcrowding.

The *Watch* antibiotic use for patients within each given final syndrome classification was similar to those with that same initial syndrome classification (Figure 3A, C versus 3B, D) – suggesting that in these groups it is not only uncertainty but perhaps other factors such as age and severity of disease, influencing clinicians to act cautiously, thus driving excess *Watch* use. The role of sepsis mandates [21,22] or fear of missing sepsis, and potential litigation, may also contribute, at the expense of optimal AMS. The high proportion of *Watch* antibiotics in some groups appear appropriate, such as CNS infections where third-generation cephalosporins are recommended as first-line, or in UTI and intra-abdominal infections caused by Gram-negative bacteria with varying resistance profiles.

The most common causative bacteria were *Escherichia coli*, *Streptococcus pyogenes* (GAS) and *Staphylococcus aureus*, were all associated with considerable empiric *Watch* antibiotics use. Whilst the resistance pattern of *E. coli* is variable, warranting broader spectrum antibiotics, this finding is particularly striking for *S. pyogenes*, where often penicillin is a suitable choice. [23] This may reflect the wide variety of syndromes and severity of syndrome associated with this pathogen, ranging from URTI or soft tissue infections to severe pneumonia or (toxin-mediated) septic shock.

The most common causative viruses were Influenza A/B, Rhino/Enterovirus and RSV. More than 60% of patients with RSV and Rhino/Enterovirus received antibiotics, and overall, 79.7% received *Watch* antibiotics. Since most of these common viruses can cause sepsis-like systemic disease, this may trigger sepsis screening and empiric use of *Watch* antibiotics. [24] The COVID-19 pandemic has highlighted how sepsis-like presentations of viral illness in adult patients can lead to increased use of inappropriate antibiotics, [25,26] showing the pertinence of this phenomenon in the adult setting too.

The strengths of our study are a large prospectively collected multi-center, international cohort over four years, stratified by AWaRe classification to characterize antibiotic use. Data from nine European countries were included, although the largest proportion was recruited from UK centers. Limitations are that children recruited in PERFORM are not representative of all febrile children as only those needing blood tests were recruited in the study, however diagnostic uncertainty and antibiotic prescribing are likely more relevant in these more severe presentations of illness. In addition, we only used a clearly defined subset of the PERFORM cohort. We did not include patients with a final phenotype of, 'other infection' (n=27), 'uncertain infection or inflammation' (n=198), 'inflammatory' (n=143) or 'trivial' and 'other causes of illness' (n=263) –nor did we include patients with 'unknown bacterial or viral' (n=758), 'probable viral' (n=627) or 'viral syndrome' where there was no viral pathogen identified (n=193). [17] (Figure 1) – as it would not be possible to consider appropriateness of antibiotic use in these phenotypes. This skewed our population towards those with a 'bacterial' phenotype, but on the other hand made the analysis and respective results much clearer. This dataset includes patients with a range of co-morbidities, some of whom were deemed high risk for infection, and our analysis did not stratify by co-morbidity, or by severity of disease. Data on bacterial antibiotic resistance profiles were unavailable, so retrospectively commenting on the appropriateness of using AWaRe antibiotics in view of the actual resistance profile of the detected pathogens was not possible. Data were not available on penicillin allergy status, so antibiotic choices could therefore not be corrected for that.

In conclusion, the differentiation of bacterial or viral etiology of febrile illness on presentation to the ED is challenging. A significant proportion of patients with a final 'viral' phenotype received antibiotics during admission, predominantly classified as *Watch*. Even where the clinician's judgment suggests a syndrome not requiring antibiotics, clinical uncertainty or concern about a bacterial co-/superinfection can result in high *Watch* antibiotic use until a bacterial cause can be

excluded, or a specific pathogen is identified. A recent report from the PERFORM study concluded that it is not always possible to distinguish between bacterial and viral infections, as both pathogens are often jointly detected, leading to broad-spectrum antibiotic use. [20] The tension between AMS and urgent treatment for presumed sepsis is well recognized. However recent guidelines suggest that unless there is septic shock, there is time to wait up to 3 hours for further assessment to decide on appropriateness of antibiotics [24]. It is here where novel rapid diagnostics could improve AMS, whilst ensuring that those who need urgent antibiotics receive them.

Future research into improved diagnostic tools is critical for AMS, such as the development of rapid discriminatory point-of-care tests (POCTs). Current POCTs which aid clinicians in differentiating between bacterial and viral infection have limited clinical utility and are not ubiquitously available or favored by clinicians. [27] In some instances, such rapid tools could be useful for improving *Access* antibiotic use, such as the correct use of rapid antigen testing for *S. pyogenes*, strictly following recommended McIsaac Score assessment. [28] A positive rapid antigen test may give clinicians confidence to use phenoxymethylpenicillin over broader-spectrum alternatives for children presenting with URTI but would not be as useful for other syndromes caused by this pathogen. Future studies are needed to understand current variability in use and integration of these tests into ED workflow.

Host-response based blood biomarkers can provide reliable prediction of etiology. [29] Clinical trials evaluating the impact of implementing novel host response POCTs on antibiotic prescribing decisions for febrile children in the ED will be crucial. Clinicians worldwide should develop ASPs that incorporate the AWaRe classification into their strategies, using WHO defined targets for *Access* use as a pragmatic framework for monitoring and optimizing antibiotic use. Ultimately, this will enable clinicians worldwide to be more AWaRe of the importance of shifting from *Watch* to *Access* antibiotic use.

Conflict of interest

AP reports consulting fees from Shionogi outside the submitted work; grants or contracts paid to institution from Gates, Wellcome, Cepi, MRC, NIHR; royalties or licenses from AstraZeneca (Oxford University has entered into a partnership with AZ for development of COVI19 vaccines); and unpaid roles as Chair of DHSC's Joint Committee on Vaccination and Immunisation and as Member of WHOs SAGE until 2022. FM-T reports financial support for educational activities from Sanofi, MSD, Moderna, GSK, Biofabri, Astrazeneka, Novavax, Janssen and Pfizer outside the submitted work; travel expenses and meeting fees covered by Pfizer, MSD, GSK, Sanofi; participation on Data Safety Monitoring Board or Advisory Board for Pfizer and Biofabri; roles as Wellcome Trust (Grant 203928/Z/16/Z), Coordianator of Spanish Pediatric Critical Trials Network, Coordinator of WHO collaborating centre for vaccine Safety of Santiago de Compostela; principal investigator in randomized controlled trials of Ablynx, Abbot, Seqirus, Sanofi ,MSD, Merck, Pfizer, Roche, Regeneron, Jansen, Medimmune,

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FIGURE LEGENDS

Figure 1: Febrile episodes selected for analysis

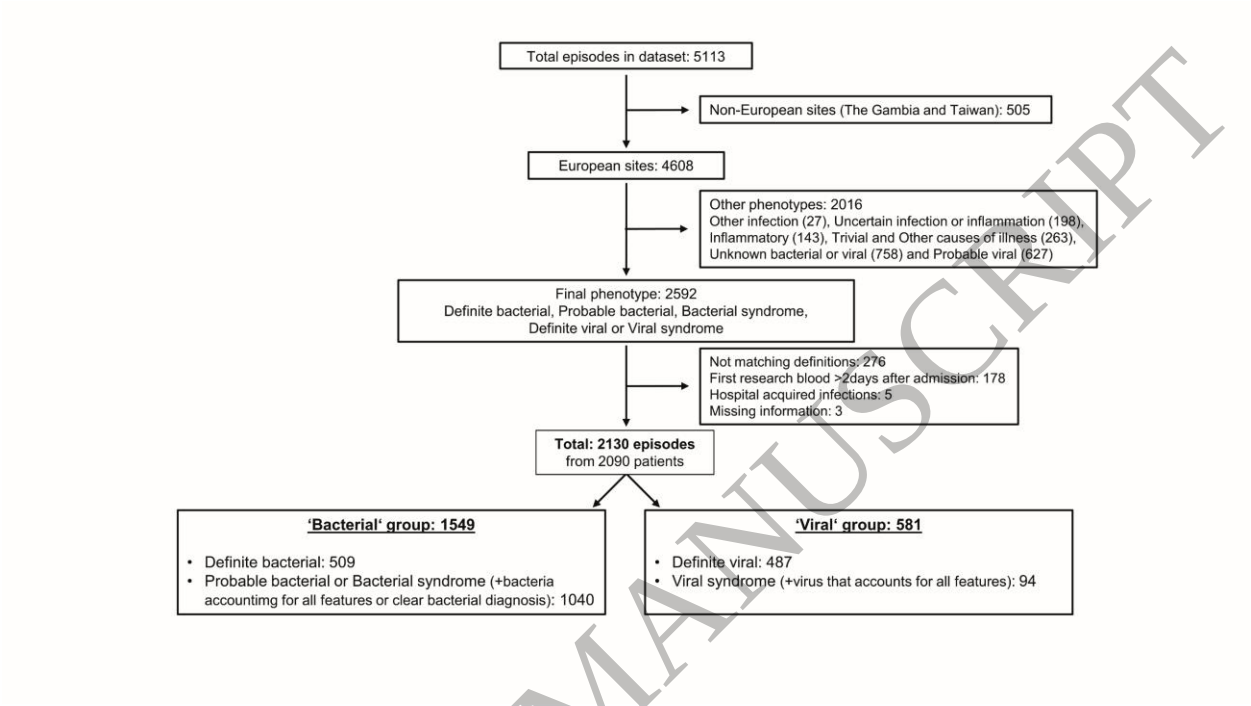
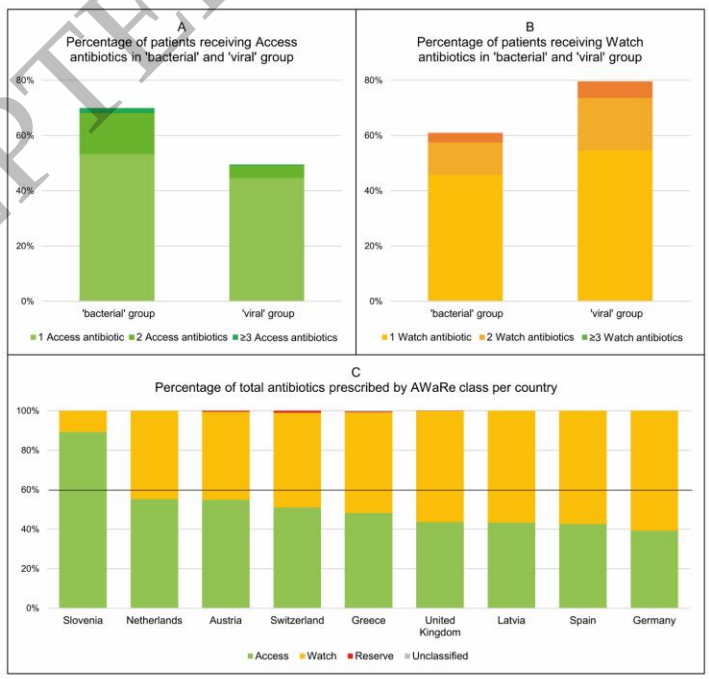
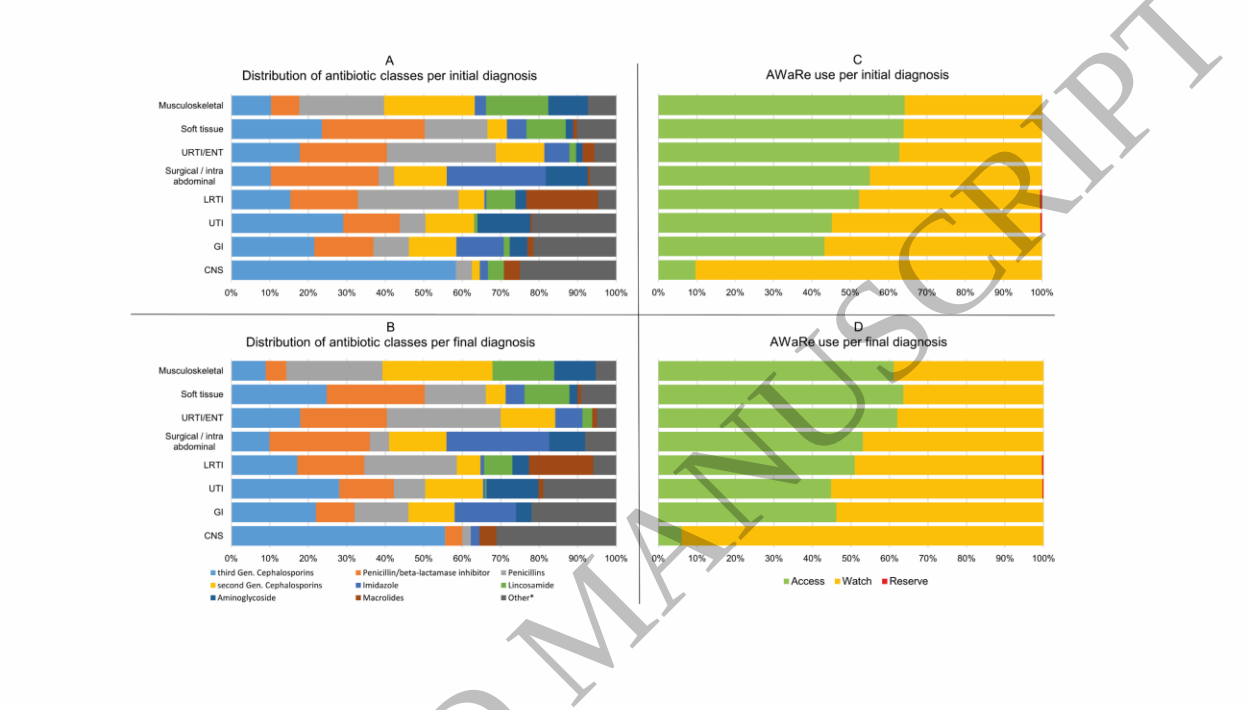


Figure 2 A, B, C Proportion of *Access*, *Watch* (and *Reserve*) antibiotics prescribed in the 'bacterial' and 'viral' group



FOOTNOTE Figure 2
Black line indicates the WHO target for *Access* use (60%)

Figure 3 A, B, C, D Distribution of antibiotics (classes and AWaRe classification) per one main initial and final syndrome classification in the 'bacterial' group



FOOTNOTE Figure 3
LRTI: lower respiratory tract infection
URTI/ENT: upper respiratory tract infection, ear nose throat
Musculoskeletal: musculoskeletal infection
CNS: central nervous system infection
GI: gastrointestinal infection
Surgical / intra-abdominal: surgical / intra-abdominal infection
Soft tissue: soft tissue infection
UTI: urinary tract infection
Other: First Generation Cephalosporins, Glycopeptide, Fluoroquinolones, Carbapenems, DHFR inhibitor, Other, Fourth Generation Cephalosporins, Nitrofurantoin, Oxazolidinones, Rifamycins, Tetracyclins, Amphenicols and Unknowns

Figure 4 A, B, C Number of febrile episodes with 'bacterial' and 'viral' phenotype receiving antibiotics in relation to the presumed etiology of the initial syndrome classification

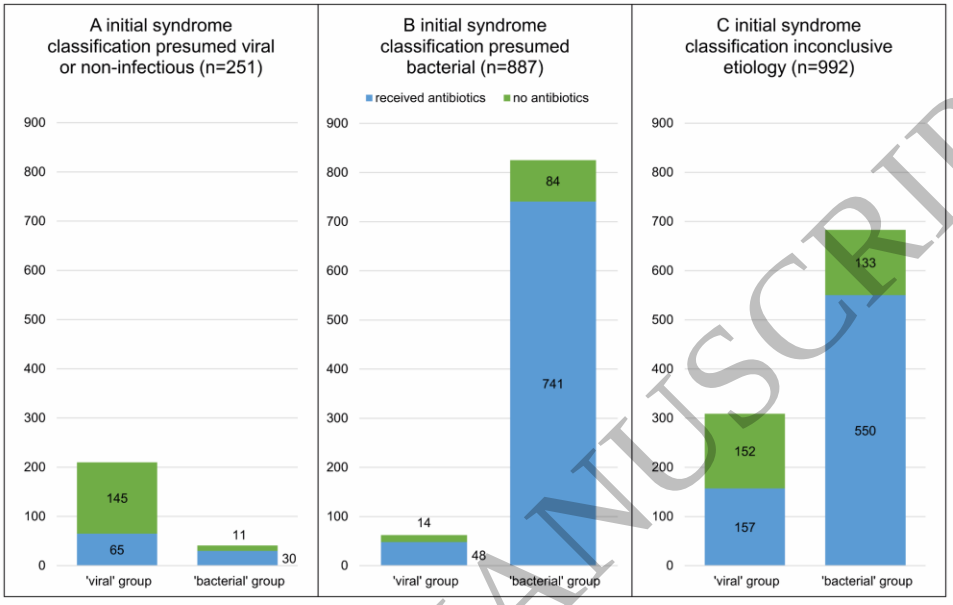


Table 1: Descriptive Data of febrile episodes included in the analysis (n = 2130)

	Bacterial (n=1549)		Viral (n=581)		Total (n=2130)		p-value
	(n; %)		(n; %)		(n; %)		(chi-square)
Sex							0.570
Male	847	54.7	309	53.2	1156	54.3	
Female	702	45.3	272	46.8	974	45.7	
Age (years)							<0.001
<1	220	14.2	160	27.5	380	17.8	
1-5	640	41.3	240	41.3	880	41.3	
6-14	553	35.7	150	25.8	703	33.0	
15-17	136	8.8	31	5.3	167	7.8	
Country							<0.001
Austria	148	9.6	46	7.9	194	9.1	
Germany	21	1.4	10	1.7	31	1.5	
Greece	149	9.6	107	18.4	256	12.0	
Latvia	194	12.5	46	7.9	240	11.3	
Netherlands	186	12.0	55	9.5	241	11.3	
Slovenia	127	8.2	24	4.1	151	7.1	
Spain	152	9.8	64	11.0	216	10.1	
Switzerland	79	5.1	8	1.4	87	4.1	
United Kingdom	493	31.8	221	38.0	714	33.5	
Ethnicity*							<0.001
European	1316	85.0	447	77.0	1763	82.8	
(North) African	35	2.3	22	3.8	57	2.7	
Asian	58	3.7	49	8.4	107	5.0	
Middle Eastern	36	2.3	26	4.5	62	2.9	
South America	3	0.2	0	0.0	3	0.1	
Other	10	0.6	7	1.2	17	0.4	
Mixed	26	1.7	14	2.4	40	1.9	
Antibiotic use last seven days before presentation							0.128
Yes	370	23.9	120	20.7	490	23.0	
No	1179	76.1	461	79.3	1640	77.0	
Patients after presentation to Emergency Department							0.356
admitted	1305	84.2	477	82.1	1782	83.7	
discharged	210	13.6	86	14.8	296	13.9	
transferred	30	1.9	14	2.4	44	2.1	
unknown	4	0.3	4	0.7	8	0.4	

*81 (3.8%) missing/unknown