

Analysis of licensed over-the-counter (OTC) antibiotics in the European Union and Norway, 2012

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Citation style for this article:

Both L, Botgros R, Cavaleri M. Analysis of licensed over-the-counter (OTC) antibiotics in the European Union and Norway, 2012. *Euro Surveill.* 2015;20(34):pii=30002. DOI: <http://dx.doi.org/10.2807/1560-7917.ES.2015.20.34.30002>

Article submitted on 16 September 2014 / accepted on 09 February 2015 / published on 27 August 2015

Antimicrobial resistance is recognised as a growing problem that seriously threatens public health and requires prompt action. Concerns have therefore been raised about the potential harmful effects of making antibiotics available without prescription. Because of the very serious concerns regarding further spread of resistance, the over-the-counter (OTC) availability of antibiotics was analysed here. Topical and systemic OTC antibiotics and their indications were determined across 26 European Union (EU) countries and Norway by means of a European survey. We identified a total of 48 OTC products containing 20 different single antibiotics and three antibiotic combinations as active substances, used mainly as topical preparations in short treatment courses. Given the relevance of these medicines and the increasing risk of antimicrobial resistance, it is important to limit the availability of OTC antibiotics and to monitor their use.

Introduction

The large majority of medicines are restricted to prescription-only-medicines (POM) status across the European Union (EU) Member States, but several medicines are being reassigned to over-the-counter (OTC) status post approval. The latter is done in response to perceived public demand for easier access to medicines and to government policies in some Member States which aim to increase the access of patients to medicines when it is safe to do so. If the safety profile is good and the risk of misuse is low, a previous POM medicine may be reclassified for sale or supply as an OTC medicine, usually under the supervision of a pharmacist [1,2]. The regulatory climate in some European countries appears moderately positive towards down-regulation, but before a medicine can be reclassified from POM to OTC it should meet certain criteria, as listed in the European Commission's guideline on changing the classification for the supply of a medicinal product for human use [3]. This guidance facilitates the harmonisation of POM and OTC status of medicines

throughout the EU; however, there are still considerable differences in Europe due to the different health-care structures and policies (including the extent of pharmacist supervision for OTC medicines), reimbursement policies, and cultural differences of each Member State. Therefore, the availability of OTC medicines varies in the EU and products sold as POM in certain countries can be obtained as OTC medicines in others.

As risk minimisation is an important criterion for some OTC products such as antibiotics, they are usually dispensed under the supervision of a pharmacist, as opposed to buying them 'off the shelf' [4]. Switching to OTC status generally makes a medicine more readily available and is also often associated with a shift of costs from the public purse to the private [1,2]. For pharmaceutical companies, there are potentially attractive aspects to apply for POM to OTC switches, e.g. some advertising restrictions for pharmaceuticals are removed (as European law allows companies to advertise OTC products directly to consumers).

Bacterial infections often present acutely and patients may therefore benefit from easier and quicker access to certain antibacterials. This could potentially shorten the period of illness and reduce both the length of symptoms and infectivity, as opposed to delaying the treatment while waiting to see a physician [5]. However, in light of the current spread of antimicrobial resistance, making antibiotics available as OTC medicines is of concern and might potentially lead to their mis- and overuse [6]. Indeed, the continuous rise of antimicrobial resistance and the concomitant lack of new therapeutic options to fill the gap represent major threats to public health that call for a variety of urgent actions in order to preserve as much as possible the currently available armamentarium. Incorrect use or overuse of antibiotics may not only reduce their benefits for the individual patients but may also lead to treatment failures in the community due to emerging resistance [7,8].

TABLE 1

Active substances of single (A) and combination (B) OTC antibiotics and number of EU/EEA countries where OTC antibiotics are available, 2012

| A | |
|---------------------------------------|----------------------|
| Single antibiotics | EU/EEA countries (n) |
| Tyrothricin | 10 |
| Fusafungine | 8 |
| Neomycin | 3 |
| Chloramphenicol | 3 |
| Gentamicin | 2 |
| Oxytetracycline | 2 |
| Nifuroxazide ^a | 2 |
| Bacitracin | 1 |
| Chlortetracycline | 1 |
| Sulfamethizole | 1 |
| Sulfanilamide | 1 |
| Nitrofurazone | 1 |
| Metronidazole | 1 |
| Sulfadimidine | 1 |
| Primycin | 1 |
| Ciprofloxacin | 1 |
| Fusidic acid | 1 |
| Azithromycin ^a | 1 |
| Methenamine ^a | 1 |
| Framycetin | 1 |
| B | |
| Combination products | EU/EEA countries (n) |
| Bacitracin/neomycin combination | 3 |
| Oxytetracycline/polymyxin combination | 1 |
| Neomycin/sulfathiazole combination | 1 |

EU/EEA: European Union/European Economic Area; OTC: over-the-counter.

^a Systemic antibiotics.

Thus, it is no surprise that concerns have been raised about the potential harmful effects of making antibiotics available without prescription [9]. The greatest concern is that the possible risk of societal harm may outweigh the potential benefits to individual patients due to the emergence of antimicrobial resistance.

Importantly, OTC availability generally appears to lead to increases in use: in a Swedish study assessing 16 (non-antibiotic) drugs, OTC availability was associated with a 36% sales increase [10]. Moreover, in a British study, the OTC availability of antibiotic eye drops containing chloramphenicol was associated with a 48% sales increase [11,12]. Further investigation is needed to determine if these increases in consumption will have any effects on antimicrobial resistance.

In the resolution of 11 December 2012 on the Microbial Challenge – Rising threats from Antimicrobial

Resistance, the European Parliament ‘calls on the Member States to raise awareness against over-the-counter and illegal sales of antimicrobials in both the human health and the veterinary sector’ [13]. Based on the above concerns around antibacterials’ use, a survey across the EU Member States to determine the amount of available OTC antibiotics has been conducted. The main objective of this analysis was to get an accurate picture about which antibiotics are available as OTC medicines in the EU and to characterise them in terms of their antibiotics classes, presentation as single/combination products, dosage, pharmaceutical form, and systemic/topical administration. In developing this report, it was decided to concentrate solely on antibiotics while it was recognised at the same time that OTC medicines against fungal, viral and parasitological infections are also available.

Methods

A questionnaire was prepared by the European Medicines Agency (EMA) to investigate the availability of OTC antibiotics across the EU and Norway. The questionnaire was sent by email to the National Competent Authorities (NCAs), i.e. the national regulatory authorities for medicinal products, of the then 27 EU Member States and of Norway, a member of the European Economic Area (EEA). The questionnaire asked for details of the active substance, of the main indication(s), and – if available – of increases in sales/usage and antimicrobial resistance. The replies were edited for length and clarity and antifungals/antivirals/antiseptics were removed from the list where necessary, e.g. products containing (di-)propamidine isetionate were not included. The tables hereafter include topical and systemic antibiotic products (with brand names where available) and main indications for OTC use. Of note, certain antibiotics, including sulfaguandine (*Enteropathyl*, *Sulfadiar*, *Litoxol*) in France or certain framycetin, ofloxacin and rifamycin formulations in Cyprus, are authorised as OTC but are not marketed and were therefore excluded from this analysis. A list of antibiotics was generated and – where possible – preparations were combined to account for different brand names and different presentations (e.g. ointment or cream), resulting in a total of 48 antibiotic pharmaceutical forms. An analysis of the number of active substances, used either alone or in combination, was undertaken. To analyse regional differences in OTC availability across Europe, the countries were grouped into northern/eastern/southern/western European countries according to their classification by the EU Publications Office [14].

Results

In October 2012, a questionnaire was circulated to the EU Member States and Norway. Twenty-six of 28 targeted countries responded and Excel tables listing OTC antibiotics and indications were received by EMA in January 2013. The 48 identified antibiotic pharmaceutical forms (averaging ~1.2 OTC pharmaceutical forms per country) contained 20 different active substances

TABLE 2A

Topical OTC antibiotics and indications in the EU Member States and Norway, 2012

| EU/EEA country | OTC antibiotics | Indications |
|-----------------|--|---|
| Northern Europe | | |
| Denmark | NA | NA |
| Estonia | Fusafungine (<i>Bioparox</i>), nasal/oral aerodispersion | Topical treatment of upper respiratory tract infections caused by microorganisms susceptible to fusafungine. |
| Finland | NA | NA |
| Latvia | 1. Chloramphenicol, ointment 2. Chloramphenicol combination (including methyluracil), ointment | 1. Topical treatment of infected wounds in the reparative (tissue regeneration) phase, long indelible trophic ulcers, II-III degree burns and bedsores. 2. Topical treatment of infected wounds in the purulent-necrotic phase. |
| | Nitrofurazone, solution for local use | Topical treatment of bacterial infections of the skin and mucosa. |
| | Tyrothricin combination (including lidocaine hydrochloride, chlorhexidine digluconate), lozenges | Recommended for short-term relief of symptoms of oral and throat inflammation. Prevention of infections before/during mouth and throat operations (tooth extractions, gum surgical treatment). |
| Lithuania | Tyrothricin combination (including lidocaine hydrochloride, chlorhexidine digluconate), lozenges | Short-term relief of symptoms of oral and throat inflammation. Prevention of infections before/during mouth and throat operations. |
| Norway | Bacitracin combination (including chlorhexidine) (<i>Bacimycin</i>), ointment (500E/g/5mg/g) | Local treatment of superficial skin infections caused by Gram-positive and Gram-negative pathogenic bacteria. Impetigo, paronychia, furunculosis, infected wounds and eczema. Prophylactic use for superficial burns. |
| Sweden | Metronidazole (topical) | Treatment of rosacea. |
| Eastern Europe | | |
| Bulgaria | Fusafungine (<i>Bioparox</i>), nasal/oral aerodispersion | Treatment of infections and inflammatory diseases of the respiratory tract (rhinitis, rhinopharyngitis, tracheitis, laryngitis, tonsillitis, post-tonsillectomy and sinusitis) in adults and children aged over 30 months. |
| | Tyrothricin (<i>Trachisan</i>) combination (including lidocaine hydrochloride, chlorhexidine digluconate), lozenges | Local treatment of oral cavity and throat inflammations, such as stomatitis, gingivitis, periodontitis, glossitis, tonsillitis, pharyngitis, dysphagia. Prophylaxis of pre- and post- surgery infections of oral cavity and throat (tooth extraction, surgical treatment of gums, tonsillectomy). |
| Czech Republic | Fusafungine (<i>Bioparox</i>), nasal/oral aerodispersion | Local treatment of inflammations and infections of pharyngeal and respiratory mucosa – in rhinitis, sinusitis, rhinopharyngitis, laryngitis, pharyngitis, tonsillitis, tracheitis, bronchitis and after tonsillectomy; for children over 30 months of age and adults. |
| Hungary | Fusafungine (<i>Bioparox</i>), nasal/oral aerodispersion (50mg/10 ml) | Treatment of infections and inflammations of upper airways (rhinitis, rhinopharyngitis, tracheitis, laryngitis, tonsillitis, condition following tonsillectomy, sinusitis) for adults or children aged over 30 months. |
| | Gentamicin (<i>Gentamicin-Wagner</i>), ointment (1mg/g) | Skin infections caused by gentamicin sensitive bacteria. |
| | 1. Oxytetracycline (<i>Tetran</i>), ointment (10mg/g) 2. Oxytetracycline (<i>Tetran</i>), powder for external use | 1. Skin infections caused by oxytetracycline sensitive bacteria 2. Shallow wound infections caused by oxytetracycline sensitive bacteria. |
| | Primycin (plus lidocaine) (<i>Ebrimycin</i>), gel | Prevention of bacterial infection of fresh, shallow lesions, burns, lacerations, local treatment of lesions infected by primycin-sensitive bacteria, lacerations, post-operational wounds, trophic ulcers (e.g.: ulcuc cruris, decubitus), necrotic open suppurations (e.g.: gangraena, fistula, chronic osteomyelitis, abscess), superficial and deep suppurations (e.g.: folliculitis, acne vulgaris, impetigo contagiosa, ecthyma, furuncle, carbuncle, panaritium). |
| Romania | Tyrothricin (<i>Dorithricin</i>) combination (including benzalkonium chloride), lozenges | Symptomatic treatment of infections of the mouth and pharynx accompanied by swallowing difficulties and sore throat. |
| | Bacitracin and neomycin combination (<i>Baneocin</i>), cutaneous powder and ointment | Infections caused by neomycin and/or bacitracin-susceptible organisms. |
| | Fusafungine (<i>Bioparox</i>), nasal/oral aerodispersion (50mg/10ml) | Treatment of infections and inflammatory diseases of the upper respiratory tract (rhinitis, rhinopharyngitis, tonsillitis, tracheitis, post-tonsillectomy, laryngitis, tracheitis, sinusitis) for adults and children aged over 30 months. |
| Slovakia | Tyrothricin (<i>Trachisan</i>) combination (including lidocaine hydrochloride, chlorhexidine digluconate), lozenges | Local treatment of oral cavity and throat inflammations (stomatitis, gingivitis, tonsillitis) pharyngitis, dysphagia. Infection of upper respiratory tract (pharyngitis, dysphagia). For prophylaxis of post-surgery infections of oral cavity and throat (tooth extraction, tonsillectomy). |
| | Fusafungine (<i>Bioparox</i>), nasal/oral aerodispersion | Local treatment of inflammations and infections of oropharyngeal and respiratory mucosa in rhinitis, sinusitis, rhinopharyngitis, laryngitis, pharyngitis, tonsillitis, post tonsillectomy, tracheitis, bronchitis. |
| Slovenia | NA | NA |

EU/EEA: European Union/European Economic Area; NA: not available (no OTC antibiotics available); OTC: over-the-counter.

TABLE 2B

Topical OTC antibiotics and indications in the EU Member States and Norway, 2012

| EU/EEA country | OTC antibiotics | Indications |
|-----------------|--|---|
| Southern Europe | | |
| Cyprus | Neomycin | Dermatological and ophthalmological use. |
| Greece | Neomycin (<i>Pulvo-47</i>), aerosol for topical application | Local use for prophylaxis in post-surgical and other injuries. |
| Italy | Bacitracin and neomycin antibiotic combination (<i>Cicatrene</i>), cream and cutaneous powder | Superficial skin infections (folliculitis, furunculosis, small burns and infected wounds). |
| Malta | NA | NA |
| Portugal | Fusafungine (<i>Locabiosol</i>), oral/nasal aerosol (125µg) | Local treatment of diseases of the upper respiratory tract (rhinopharyngitis). |
| | 1. Tyrothricin (<i>Hydrotricine</i>) 2. Tyrothricin (4mg) combination (including cetylpyridinium chloride 1mg, oxybuprocaine 0.2mg) (<i>Mebocaina Forte</i>) | 1. Local treatment of topical infections localised and limited to the buccal mucosa and oropharyngeal. 2. Local treatment of sore throat and infections of mouth and pharynx. |
| Spain | Gentamicin (<i>Oculos Epitelizante</i>), ointment | Treatment of ocular infections. |
| | Neomycin (<i>Blastoestimulina</i> ointment, <i>Edifaringén</i> tablets, <i>Phonal</i> tablets for solution, <i>Rinobanedif</i> ointment, and <i>Synalar nasal</i>) | E.g. wound healing. |
| | Tyrothricin (<i>Anginovag</i> solution for spraying, <i>Bucometasana</i> tablets, <i>Cicatral</i> ointment, <i>Cohortán Rectal</i> ointment, <i>Denticelso</i> solution, <i>Miozets</i> tablets, <i>Koki</i> tablets, <i>Piorlis</i> skin solution, <i>Roberfarín</i> spray, and <i>Viberol</i> mouth solution) | Treatment of topical infections. |
| Western Europe | | |
| Austria | NA | NA |
| Belgium | Bacitracin and neomycin antibiotic combination (<i>Neobacitracine Nouvelle Formule</i>) | Local antibiotic treatment of infections caused by sensitive germs. Treatment of skin infection. |
| | Chloramphenicol (<i>Erfa chloramphenicol</i>) | Local antibiotic treatment of infections caused by sensitive germs. Should not be used for minor infections or for prophylaxis. |
| | Chlortetracycline (<i>Aureomycin</i>), (1%), ointment | Ocular infections caused by tetracycline-sensitive microorganisms |
| | Framycetin (<i>Septomixine Nouvelle Formule</i>) | Minimisation of pain and canal disinfection. |
| | <i>Fusidic acid</i> : 1. <i>Fucidin crème</i> (2%), cream/ <i>Fucidin zalf</i> (2%), ointment 2. <i>Fucidin Intertulle</i> (2%), impregnated fabric 3. <i>Fucithalmic</i> (10mg/g), eye drops 4. <i>Affusine</i> (20mg/g), cream | 1. Infections caused by <i>Staphylococcus aureus</i> , <i>Streptococcus spp.</i> Infection prophylaxis. 2. Infected wounds and superficial skin infections. Traumatic and surgical wounds. Deep or superficial burns. 3. Anterior segment eye infections caused by sensitive microorganisms. 4. Treatment of non-severe, superficial, non-extensive, primary skin infections caused by microorganisms sensitive to fusidic acid, especially infections caused by <i>Staphylococcus</i> . |
| | Oxytetracycline (<i>Terra-cortril</i>) | Skin infections with severe inflammatory reaction, infected atopic dermatitis, infected contact dermatitis. |
| | 1. Oxytetracycline (<i>Terramycine</i>) + polymyxine B antibiotic combination, ointment 2. Oxytetracycline (<i>Terramycine</i>) + polymyxine B antibiotic combination, eye ointment | 1. Prophylaxis and treatment of local skin infections. 2. Treatment of superficial ophthalmic infections. |
| | 1. Tyrothricin combinations (<i>Tyrothricine Lidocaine Citroen/Munt Melisana</i>) 2. Tyrothricin (<i>Lemocin</i>) combination (incl. cetrimoniumbromide, lidocaine) | 1. Local or adjuvant symptomatic treatment of painful mouth and throat infections. 2. Symptomatic treatment of inflammatory and painful infection of buccopharyngeal crossroad. |
| France | NA | NA |
| Germany | Fusafungine (<i>Locabiosol</i>), oral/nasal aerodispersion (0,5mg/0,125mg) | Rhinosinusitis, Laryngitis, Rhinopharyngitis, Streptococci infections. |
| | 1. Tyrothricin (<i>Dorithricin</i>) combination (including benzocaine, benzalkonium chloride), lozenges 2. Tyrothricin (<i>Lemocin</i>) combination (including cetrimoniumbromide, lidocaine), lozenges/oral solution 3. Tyrothricin (<i>Tyrosur</i>), gel and powder (<i>Micasal</i>) | 1. Infections of mouth and throat. 2. Inflammations of mouth and throat. 3. Wounds with bacterial superinfection. |
| | Ireland | NA |
| The Netherlands | NA | NA |
| United Kingdom | Chloramphenicol, eye drops and eye ointment | Treatment of acute bacterial conjunctivitis in adults and children aged 2 years and over. |
| | Tyrothricin, throat pastilles/lozenges | Treatment of infections of the mouth and pharynx. |

EU/EEA: European Union/European Economic Area; NA: not available (no OTC antibiotics available); OTC: over-the-counter.

TABLE 3

Synthetic OTC antibiotics (sulfonamide and quinolone) for topical application and their indications in European Union countries, 2012

| EU country | OTC antibiotics | Indications |
|------------|--|---|
| Estonia | Sulfamethizole (<i>Sulfametizol Nycomed</i>), eye drops (4%) | Short-term treatment of bacterial eye infections. |
| Latvia | Sulfanilamide, ointment and cutaneous powder | Topical treatment of skin infections caused by Gram-positive or Gram-negative bacteria. |
| Hungary | Sulfadimidine (<i>Septosyl</i>), eye ointment | Acute and chronic conjunctivitis of bacterial origin, cornea infiltration and ulcer, several types of blepharitis (acute, chronic, ulcerative) blepharo-conjunctivitis, hordeolum, infected eyelid eczema, inflammation of the tear duct, removal of foreign body from conjunctive or from cornea, prevention of infection following other superficial eye interventions. |
| Romania | Ciprofloxacin (plus fluocinolone acetonide), (<i>Ototis</i>), auricular drops, solution | Acute and chronic external otitis of bacterial origin, with intact tympanic membrane in adults and children in particular, infected eczema of the ear canal. |
| Italy | Neomycin and sulfathiazole antibiotic combination (<i>Streptosil neomicina</i>), ointment and cutaneous powder | Superficial skin infections (folliculitis, furunculosis, small burns and infected wounds). |

EU: European Union; OTC: over-the-counter.

(single antibiotics) and three mixtures containing multiple antibiotics (Table 1). Of these 20 active substances, eight were available in more than one Member State.

All OTC antibiotics are listed in Table 2 together with their country of availability. A total of 20 EU/EEA Member States have OTC antibiotics: 16 of these have only topical antibiotics, two have only systemic antibiotics, and another two have both topical and systemic antibiotics available on the market. The number of OTC antibiotics available in each Member State varied widely across the EU, ranging from zero to eight OTC antibiotics. No OTC antibiotics are available in Austria, Finland, Ireland, Malta, the Netherlands and Slovenia, whereas countries like Belgium and Hungary offer a relatively wide range of different OTC antibiotics (eight and five, respectively) (Table 2).

It has recently been reported that non-prescription antibiotics use (including non-legal use) varies between European regions, e.g. the lowest levels of non-prescription antibiotics use were observed in northern Europe (weighted non-prescription use was 3%) while the highest levels were observed in eastern Europe (weighted non-prescription use was 30%) [15]. To investigate whether this geographical distribution is preserved for the licensed OTC antibiotics listed here (Table 2), the EU/EEA Member States were grouped into northern/eastern/southern/western European countries. This revealed that northern European countries have the least amount of OTC antibiotics (n=7). Both eastern and western Europe have a relatively high amount of OTC antibiotics (n=12 in both cases) but it should be mentioned that the high numbers in western Europe were mainly due to Belgium which accounted for eight of 12 OTC antibiotics available in western European countries.

It was observed that certain antibiotics are frequently assigned to OTC status across the EU, in particular a large number of tyrothricin and fusafungine products (available in 10 and eight countries, respectively) (Table 2). Fusafungine products are available as OTC medicines in eight of the 26 EU/EEA Member States analysed here, especially in the eastern European countries (five out of six Member States). Likewise, chloramphenicol and neomycin products are more frequently available without prescription. In contrast, certain products like methenamine, metronidazole, azithromycin and nitrofurazone are rarely available as OTC medicines across the EU/EEA Member States.

The OTC antibiotics available in the EU belong to various antibiotic classes, e.g. tetracyclines and sulphonamides. Table 3 shows all synthetic OTC antibiotics of the sulphonamide and quinolone classes. Overall, the vast majority (20 of 23) of OTC single antibiotics/antibiotic mixtures identified here are solely used for topical application, with a few exceptions including oral methenamine (ATC code J01XX05), nifuroxazide (ATC code A07AX03) and azithromycin (ATC code J01FA10) (Table 4). Of the 23 single antibiotics and antibiotic mixtures, 19 are used for infections of the skin, eyes, and oral/pharyngeal/respiratory mucosa, one is used for ear infections (ciprofloxacin), one is used for diarrhoea (nifuroxazide), one is used for genital infections (azithromycin), and one is used for urinary tract infections (methenamine).

Discussion

The contribution of OTC antibiotics' use to the development and spread of antimicrobial resistance genes and bacteria is not known. However, all antibiotic use – whether it is prescription or non-prescription – exerts

TABLE 4

Systemic OTC antibiotics and their indications in European Union countries, 2012

| EU country | OTC antibiotics | Indications |
|----------------|--|---|
| Denmark | Methenamine (Hiprex), tablets | Prophylaxis of urinary tract infections, especially for patients with a catheter. |
| Slovakia | Nifuroxazide (Endiex), oral administration | Acute diarrhoea of bacterial origin without signs of invasion; diarrhoea related to the bowel dysmicrobia. |
| France | Nifuroxazide (Ercefuryl and generics) | Treatment of acute diarrhoea presumed to be of bacterial origin, in the absence of suspected invasive phenomena. |
| United Kingdom | Azithromycin (1g) | Treatment of confirmed asymptomatic <i>Chlamydia trachomatis</i> genital infection in individuals aged 16 years and over, and for the epidemiological treatment of their sexual partners. |

EU: European Union; OTC: over-the-counter.

antimicrobial selection pressure [16,17]. A first step in trying to assess the contribution of OTC antibiotics to emerging resistance is to investigate which and how many antibiotics are affected and whether they are administered topically or systemically. Our analysis of OTC antibiotics in the EU and Norway demonstrates that (i) only few antibiotics with OTC status are currently available across the EU and Norway (on average one-two OTC antibiotic pharmaceutical forms/country); (ii) the large majority (20 of 23 single/combination active substances) of the OTC antibiotics identified here are solely used for topical application, except methenamine, nifuroxazide and azithromycin; (iii) overall, it is not apparent that the current situation for OTC antibiotics in the EU and Norway poses substantial risks, but further monitoring would still be warranted.

Among the critically important antibiotics defined by the World Health Organization (WHO) [18] only azithromycin, a macrolide antibiotic for the treatment of laboratory-confirmed asymptomatic genital chlamydial infections, is available in the EU as a systemic OTC medicine, and only in the United Kingdom (UK). However, it has to be recognised that appropriate safeguards are in place in this case: to avoid OTC antibiotic misuse or overuse, patients with suspected *Chlamydia* infection buy an approved testing kit in a UK pharmacy or online and post a urine sample to an approved laboratory [19]. If the test is positive, the patient can request azithromycin from a pharmacy. The pharmacist will ask the patient about symptoms, advice the patient on the use of azithromycin, and provide a notification slip (bearing the unique index patient identifier) for the sexual partner(s) who will be able to purchase azithromycin tablets from the pharmacy [19]. The approved testing laboratory performing the urine test must collect data on tests performed which are available for monitoring at quarterly intervals by regulatory authorities. One drawback would be that if any co-infection (e.g. gonococcal infection) is occurring, this could be missed by avoidance of general practitioner (GP) consultation with potential deleterious consequences.

Several antibiotics have been assigned from POM to OTC status fairly recently and it is currently not clear whether their OTC availability might lead to increased resistance. However, it should be noted that antimicrobial resistance has been reported for the POM counterparts of several OTC antibiotics listed in this report, e.g. widespread resistance against fusidic acid (as POM) has recently been reported in Malta [20]. It cannot be ruled out that making fusidic acid widely available as an OTC medicine could increase the risk of emerging resistance and thereby reduce its activity in other applications such as a valuable anti-staphylococcal agent to treat osteomyelitis. Despite a lack of hard evidence regarding emerging resistance resulting from the usage of OTC antibiotics – most of which are used topically – we believe it would be important that antibiotics are not made available as OTC medicines particularly if they belong to classes of agents frequently used to treat serious infections. This would possibly not preclude the option to retain a limited number of available OTC antibiotics, constituted only by well-characterised agents with no or limited prescription indications and with no cross-resistance potential to other important antimicrobials. Moreover, the use of oral OTC antibiotics (e.g. methenamine) should be limited and monitored closely.

It is important to note that there are certain conditions for OTC supply and products may be limited to specific indications with appropriate restrictions on strength, dose and pack size. Additional considerations might apply to certain OTC antibiotics, e.g. in the case of OTC azithromycin: the national usage of the product should be monitored and Periodic Safety Update Reports (PSURs) should be submitted by the Marketing Authorization (MA) holder at six monthly intervals including usage data and any available information on resistance in *Chlamydia trachomatis*, *Neisseria gonorrhoea* and other pathogens [21].

It should be mentioned that, in addition to OTC antibiotics, patients may receive antibiotics without a prescription, even if these are not legally classified as OTC medicines: antibiotics could be obtained without

prescription illegally from pharmacies (or through the Internet), which occurs in various degrees across Europe as discussed elsewhere [15,22,23]. Moreover, patients sometimes take antibiotics from previous treatment courses prescribed for themselves or their family members, as described in a recent Eurobarometer [24].

Two surveys of the general population from eastern Europe were recently reported [23,25]. Data from Lithuania, Poland, and Romania [23] suggested that frequency of antibiotic use varied from 23% to 51%. Of antibacterials used, weighted non-prescription use was 30%. Of the non-prescription antibiotics, 68% were purchased at a pharmacy and 32% were from friends, family, or home. Given these high numbers, it is important to reduce the availability of non-prescription antibiotics. This is in line with the European Parliament's resolution to raise awareness against OTC and illegal sales of antimicrobials [13]. Non-prescription use has been speculated to play a role in selecting and maintaining high levels of community antimicrobial resistance [25-28]. Although self-medication antibiotics are usually associated with short treatment courses [29-30] community antimicrobial resistance was nevertheless common in various studies that examined communities with frequent use of non-prescription antimicrobials [31-33].

Because the OTC status of individual antibiotics has so far been decided at the national and not the European level, it is no surprise that there is not much overlap between countries concerning the type and number of OTC antibiotics. Reasons for these differences might include national healthcare policies, reimbursement policies, and the different roles of pharmacists in dispensing OTC antibiotics to patients. As shown by the data generated by the European Surveillance for Antimicrobial Consumption Network (ESAC-Net), the use of systemic antimicrobials varies greatly between EU Member States [34]. As such, it is expected that a similar national variation in use would apply to OTC antibiotics. While the use of systemic antibiotics is regularly monitored across Europe by ESAC-Net, there is no European network in place for monitoring the use of the various OTC antibiotics licensed across the EU, which seems justified based on the very limited number of OTC antibiotics currently available in the EU. Although installing such a network for OTC antibiotics might perhaps be considered useful in the future, a more effective approach would be to limit the number of OTC antibiotics as much as possible in the first place.

The efficacy of antibiotics needs to be preserved – by all means necessary – and it could therefore be argued that antibiotics (in particular oral antibiotics) should not be made available as OTC medicines as a matter of principle. In cases where antibiotics are assigned to OTC status, this should be done with great caution and following appropriate consideration of the potential risk of triggering cross-resistance to any other

antibiotic with prescription indications. Moreover, measures should be in place to ensure patient safety and adequate monitoring of usage and antimicrobial resistance.

Acknowledgements

Funding sources had no role in the writing of this manuscript. The views in this article are the personal views of the authors. Those views may not be understood or quoted as being made on behalf, or reflecting the position, of the European Medicines Agency (EMA) or one of its committees or working parties.

Conflict of interest

None declared.

Authors' contributions

All authors contributed equally in the writing of the manuscript.

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