The match between common antibiotics packaging and guidelines for their use in Australia

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In Australia, the greatest tonnage of antibiotics are prescribed in general practice.1,2 Their over-prescription may be contributing to antibiotic resistance.3 This is recognised as a serious threat, putting recovery from serious infection in doubt, and beginning to risk many therapeutic and diagnostic interventions in tertiary care requiring secure antibiotic cover – something now labelled a global threat.4,5 Several guidelines exist in Australia to guide primary care. The Australian (electronic) Therapeutic Guidelines (eTG)6 are widely used; these give evidence-based recommendations on the basis of a diagnosis with a rank order provided for recommended antibiotics, along with dose, frequency, and – importantly – duration. There are other equally evidence-based guides such as the Australian Medicines Handbook,7 these recommend antibiotics to use for different indications (based on the likely infecting organism) and their doses, frequencies, and sometimes duration. Antibiotics are almost universally packaged by manufacturers in packs that heavily influence duration. This had us speculate on the extent packing size matches the guideline recommendations for duration; any mismatch might contribute to unused antibiotics in the community and, if taken by patients on some other occasion, may contribute to unsupervised use and, thereby, resistance.

Methods

A wide range of antibiotics is used in primary care for a large array of different indications. These infections make up 15% of the total number of problems managed in general practice; most are respiratory, urinary and skin.2 We elected to limit the study to a manageable size by identifying the three most common indications for the four most frequently prescribed antibiotics. The numbers of prescriptions for each oral antibiotic derived from the Australian Statistics on Medicines (ASM) 2010 (representing prescriptions dispensed through the Pharmaceutical Benefits Scheme [PBS], the Repatriation Pharmaceutical Benefits Scheme [RPBS], and private prescriptions estimates through community pharmacy surveys)6 were totalled and ranked. Because the ASM does not collect indications for the prescriptions, we identified the most common indications for each antibiotic derived from the Australia 2012–2013 BEACH database.2 Finally, we extracted the data for these antibiotics and indications, recommended by the eTG.6 This information source was chosen from those recommended by the Australian Health Practitioner Regulation Agency (AHPRA)9,10 and routinely used by health professionals, as it makes evidence-based recommendations on the basis of illness diagnosis as specified in the introduction (Table 1).

Abstract

Objectives: To determine the potential for a source of surplus antibiotics in the community to come from the mismatch between the recommended duration of antibiotic treatment for common indications in primary care and that dictated by default pharmaceutical industry packaging.

Methods: Analysis of existing published information of: 1) the most common antibiotics prescribed in primary care in Australia; 2) their most common indications; 3) the guideline recommendations for their duration; and 4) the duration dictated by antibiotic packaging.

Results: Of 32 common antibiotic prescribing scenarios, 10 had doses left over in surplus and 18 had a shortfall, leaving only four in which the packaging size matched the duration recommended by electronic Therapeutic Guidelines. Where there was a shortfall, this was only exactly accommodated by a repeat prescription in two cases.

Conclusions: Mismatch contributes to a shortfall or excess of doses compared to recommended antibiotic treatment protocols and probably exaggerates redundant doses in the community from prescribed antibiotics dispensed and not consumed.

Implications: Prescribers need to be aware that the mismatch between antibiotic pack sizes and guideline recommendations for their duration is contributing to antibiotic resistance in the community.

Key words: infectious diseases, prescribing, pharmacology, antibiotic resistance, drug utilisation
There are differences in definition of diagnostic entities for these data sources. BEACH uses the International Classification of Primary Care, 2nd Edition (ICPC2). The eTG, however, uses different diagnostic entities and we had to map these to each another (Table 2). This is not exact; for example, the second most common acute respiratory infection recorded in the BEACH dataset is ‘Acute Bronchitis/Bronchiolitis’, which probably captures several distinct entities, including acute exacerbations of chronic obstructive pulmonary disease, acute cough associated with undifferentiated respiratory infection, Mycoplasma infection and others. Bronchiolitis is largely confined to the first year of life. Meanwhile, eTG includes influenza, pharyngitis and/or tonsillitis, acute epiglottitis (supraglottitis), otitis externa, otitis media, pertussis, acute bronchiolitis, rhinosinusitis, acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease and croup among “other respiratory tract infections” (Table 2).

Number of doses of antibiotic required (milligram strength, frequency and duration) was based on the eTG recommendations for each antibiotic and compared with the number of doses provided in a single standard pharmaceutically packaged antibiotic (using three typical patients: an adult; an eight-year-old child (25 kg), and a one-year-old child (10 kg)). We did not use the World Health Organization’s “defined daily dose” (DDD) because this is defined on assumed average maintenance doses rather than reflecting any guideline. We assumed that antibiotics chosen to treat frequent presentations of acute bronchitis would be directed at common causes of the illness.

| Table 2: Mapping different diagnostic categories from BEACH to eTG, and their rank order. |
|-----------------------------------------------|
| **ICPC Respiratory infection terms** | **BEACH ranking of frequency of Respiratory Infection in GP** | **eTG Respiratory infection terms** |
| Upper respiratory infection acute | 1 | Upper respiratory tract infection |
| Acute bronchitis/bronchiolitis | 2 | Acute bronchitis (infections including acute bronchitis) |
| Sinusitis acute/chronic | 3 | Rhinosinusitis/acute bacterial rhinosinusitis |
| Acute otitis media | 4 | Otitis media |
| Tonsillitis acute | 5 | Acute Pharyngitis and/or tonsillitis |
| Strept throat | 5 | Acute Pharyngitis and/or tonsillitis |

| Table 1: Dosing/Duration Information available from AHPRA recommended health practitioner medicines information sources |
|-----------------------------------------------|
| **Source** | **Approach** | **Example Amoxycillin (oral treatment dose)** |
| Australian Medicines Handbook (AMH) | Structured as drug monographs within therapeutic classes providing: | Adult: Oral, 250–500 mg every 8 hours or 1 tablet twice a day. Doses of 1 g every 8 hours may be used in severe infections, e.g. pneumonia. |
|  | • A generic dose range and frequency for the specified antibiotic but not usually a recommended duration | • Gonococcal infection: For confirmed non-beta-lactamase-producing N. gonorrhoeae, Oral, 3 g single dose with probenecid |
|  | • Dose and frequency and duration are listed only for a limited number of indications (e.g. for amoxicillin only two less common indications) | • Eradicaton of H. pylori: With clarithromycin, oral 1 g amoxycillin twice daily for 7 days OR With metronidazole, oral 500 mg amoxycillin 1 times daily for 14 days. |
| Australian Pharmaceutical Formulary and Handbook (APF) | Drug (antibiotic) monographs listed alphabetically provide: | Child: Oral, 15–25 mg/kg (max 500 mg) every 8 hours. For severe infections up to 30 mg/kg (max 1 g) every 8 hours can be used. |
|  | • Only a ‘common dose range’ that includes a generic dose and frequency but for the specified antibiotic no recommended duration | |
|  | • Individual dose and frequency recommendations are not differentiated for common indications | |
| Product Information | Antibiotic monograph usually provides: | Common dosage range |
|  | • Microbiology sensitivity/resistance tables but these are not clearly linked to indication | Adult dose: Oral, 250-500 mg 8-hourly or 1 tablet twice daily |
|  | • A list of indications for the specified antibiotic by broad organ system e.g. upper respiratory tract infections or skin and soft tissue infections: than for specific indications e.g. bronchitis, UTI | Paediatric dose: Oral, 7.5-25 mg/kg 8-hourly |
|  | • Tailored dose and frequencies for a subset of selected indications, however durations are not routinely specified. | |
| eTherapeutic Guidelines (eTG) | Information primarily classified by indication (not as individual drug e.g. antibiotic monographs) | Amoxil brand: Doseage and administration: Normal Renal Function: Upper respiratory tract infections; genito-urinary tract infections; skin and soft tissue infections. |
|  | • Searching by name of drug leads to an index list of indicated uses (diagnoses), selection of an indication leads to information on ranked choice of drug, dose, frequency and duration | Adults – 250 mg every eight hours. |
|  | • Information represents Australian guidelines for recommended therapy for each specified indication including individual antibiotic protocols (drug, dose, frequency and duration). | Children (under 20 kg) – 20 mg/kg/day in equally divided doses every eight hours. |
|  | • Information is based on evidence in literature and consensus expert recommendations on treatments of specific infections | |
|  | | In severe infections or those caused by less susceptible organisms, 500 mg every eight hours for adults and 40mg/kg/day in equally divided doses every eight hours for children may be needed. |
|  | | Lower respiratory tract infections. |
|  | | Adults – 500 mg every eight hours. |
|  | | Children (under 20 kg) – 40 mg/kg/day in equally divided doses every eight hours. |
|  | | Urethritis, gonococcal. Adults – 3 g as single dose. |
|  | | Acute, uncomplicated lower urinary tract infections in non-pregnant adult female. |
|  | | Adults – 3 g as single dose. |
|  | | Alphabetical Index for Amoxycillin by Therapeutic use retrieved > 25 individual indications |
|  | | For example, For Rhinosinusitis: if antibiotics are indicated, use: amoxycillin 500 mg (child: 15 mg/kg up to 500 mg) orally, 8-hourly for 5-7 days |
|  | | For Acute Otitis Media – children with systemic features, use amoxycillin 15 mg/kg up to 500 mg orally, 8-hourly for 5 days |
Table 3: Match between guidelines for the duration of commonly prescribed antibiotics and their pack sizes, antibiotic and indication by order of frequency of use in Australia.

| Antibiotic | Infection indication | doses/day | Duration suggested by guideline (Days) | Duration dictated by pack size (Days) | Shortfall of doses | Pack/bottle size (no. of doses) | Extra doses (left over) |
|------------|----------------------|-----------|--------------------------------------|--------------------------------------|-------------------|---------------------------------|------------------------|
| **Amoxicillin** | | | | | | | |
| | | 500mg x 20 | 50mg/ml x 100ml | 25mg/ml x 100ml | | | |
| Bronchitis<sup>4,6</sup> | | | | | | | |
| | | 3 | 5 | 6.7 | | | |
| | | 3 | 5 | 2.7 | | | |
| Sinusitis<sup>1</sup> | | | | | | | |
| | | 3 | 5 | 6.7 | | | |
| | | 3 | 5 | 4.4 | | | |
| Otitis media<sup>2</sup> | | | | | | | |
| | | 3 | 5 | 5.5 | | | |
| | | 3 | 5 | 5.5 | | | |
| Cephalixin | | | | | | | |
| | | 500mg x 20 | 50mg/ml x 100ml | 25mg/ml x 100ml | | | |
| Urinary tract infection<sup>3</sup> | | | | | | | |
| | | 2 | 5 (female) | 10 | | | |
| | | 2 | 14 (male) | 10 | | | |
| | | 4 | 5 | 4 | | | |
| | | 4 | 5 | 5 | | | |
| Skin infection<sup>1,2</sup> | | | | | | | |
| | | 2 | 5 | 5 | | | |
| | | 2 | 5 | 4 | | | |
| | | 2 | 5 | 5 | | | |
| Bronchitis | | | | | | | |
| | | N/I | N/I | N/I | N/I | | |
| Amoxycillin + Clavulanate (A+C) | | See notes<sup>1,4,5</sup> | | | | | |
| | | | 80+11.4mg/ml x 60ml | 80+11.4mg/ml x 60ml | | | |
| Sinusitis<sup>1</sup> | | | | | | | |
| | | 3 | 7 | 3.3(k) | | | |
| | | 3 | 7 | 2.8 | | | |
| | | 3 | 7 | 7.1 | | | |
| Urinary tract infection<sup>1</sup> | | | | | | | |
| | | 2 | 5 (female) | S(m) | | | |
| | | 2 | 14 (male) | S(m) | | | |
| | | 2 | 5 | 4.3 | | | |
| | | 2 | 5 | 10.7 | | | |
| Otitis media<sup>1</sup> | | | | | | | |
| | | 3 | 5 | 3.3(k) | | | |
| | | 3 | 5 | 2.8 | | | |
| | | 3 | 5 | 7.1 | | | |
| Roxithromycin | | 300mg x 5 | 50mg x 10 | 50mg x 10 | | | |
| Bronchitis | | | | | | | |
| | | 1 | N/I | N/I | N/I | N/I | |
| Streptococcal throat<sup>6,8</sup> | | | | | | | |
| | | 1 | 10 | 5 | | | |
| | | 2 | 10 | 2.5 | | | |
| | | 2 | 10 | 5<sup>p</sup> | | | |
| Skin infection<sup>1,2,6</sup> | | | | | | | |
| | | 1 | 10 | 5 | | | |
| | | 2 | 10 | 2.5 | | | |
| | | 2 | 10 | 5<sup>p</sup> | | | |

**Notes:**
- a: The most appropriate form and strength of antibiotic was chosen for age according to recommendations in Therapeutic Guidelines for treatment of specified infection.
- b: The shortest course of the recommended treatment was chosen, when open to choice.
- c: Doses rounded to nearest whole dose.
- d: The most common subgroup taken as “non-severe suspected bacterial pneumonia, or exacerbations of prior COPD; e: Amoxicillin per dose: Bronchitis (d) 500mg (child amoxicillin 25 mg/kg orally up to 1g); f: Amoxicillin per dose: sinusitis & otitis media 500mg (child 15mg/kg to max of 500mg); g: Cephalexin per dose: OTI 500mg (child 12.5mg/kg up to 500mg); h: Both and carbuncles/ Staphylococcus; i: Cephalexin per dose (h): Both & carbuncles 1 g (child: 25 mg/kg up to 1g) orally, 12-hourly for 5 days; j: Amoxicillin + clavulanate per dose: amoxycillin resistant suspected/pneumonia, OTI 750mg (child 22.5+3.2 mg/kg up to 750mg); k: Amoxicillin + clavulanate 875+125mg; l: Amoxicillin + clavulanate per dose: UTI 500mg+125 (child 22.5+3.2 mg/kg up to 625mg); m: Amoxicillin + clavulanate 500+125mg; n: If there is penicillin allergy; o: Roxithromycin per dose: 300mg (child 8-16mg/kg up to 30mg); p: As dose for one year old is 0.8 tablet, 0.2 is wasted; q: Staphylococcal or streptococcal infection; N/I = Not indicated.
community acquired pneumonia such as Streptococcus pneumoniae and Haemophilus influenzae; urinary tract infection in non-pregnant women and men was directed at Escherichia coli; and skin infections (boils/carbuncles, and “other skin infections”) directed at Staphylococcus and Streptococcus species.

Results

We consistently found a mismatch between the number of doses and the duration mandated by standard packaging sizes and recommended by guidelines for the most commonly prescribed antibiotics and their indications in primary care (see Table 3). The four most commonly prescribed antibiotics are specified in the Table. For each one, the top three ranked indications are listed in an individual column. There are three rows for each indication, showing the doses and duration recommended by the guideline versus the duration dictated by the pack size, calculated for an adult, 25 kg child and 10 kg child. The number of doses available in a single proprietary pack of the specified antibiotic at the recommended ranged from five to 20 (represented by filled circles) with any shortfall or extra doses left in the pack represented by unfilled circles. Out of 32 most common antibiotic-prescribing scenarios, 10 had doses left over in surplus and 18 had a shortfall, leaving only four in which the packaging size resulted in the exact duration recommended by eTG guidelines. Where there was a shortfall, this was only exactly accommodated by a repeat prescription in two cases (Table 3).

Discussion

This mismatch in duration between guidelines and that dictated by packaging may mean that a considerable quantity of antibiotics are dispensed and not consumed for the prescribed acute illness, contributing to redundant antibiotic doses in the community. Since the mismatch is the rule rather than the exception, we can speculate that this is a large quantity.

Weaknesses in this study include the use of just one set of guidelines. However, this commonly used resource proved the most robust across the AHPRA recommended information sources. The difficulty we encountered in mapping the eTG diagnostic categories, and those set by the BEACH data-collection classification, mean that some diagnoses may be inaccurate – with implications for both the most common rubric as well as the best guidelines to fit the diagnosis. Nevertheless, we have seen no other studies that have considered this issue. There are, of course, other contributions to unused antibiotics in the community, including repeat prescriptions (sometimes inadvertently delivered by default settings in general practice prescribing software) and the failure by patients to complete the prescribed course.

Nonetheless, our finding represents a problem that is probably more extensive than most prescribers realise. It is unlikely that all primary care clinicians follow optimal guidelines in their antibiotic prescribing – this is one of the causes of antibiotic resistance. Yet evidence-based guidelines are seen as an important means of changing over-prescribing. Even if general practitioners attempt to follow guidelines, difficulties in matching diagnoses and trying to match pack size with recommendations is an important obstacle to their doing so effectively.

Solutions are not obvious. One would be changes to legislation so that the Therapeutic Goods Administration (TGA) requires manufacturers to package antibiotics in accordance with guideline recommendations. However, this would be difficult as the same antibiotic is prescribed for several indications and for different durations; and resistance is likely from the pharmaceutical industry. Another solution would be to educate general practitioners in specifying the guideline recommended duration for antibiotics when prescribing them, thereby overriding the default pack quantity in their prescribing software and instead incorporating an algorithm derived from guidelines to calculate the associated required quantity. However, even if general practitioners were persuaded to change their usual behaviour, pharmacists would need corresponding dispensing software to calculate and pass on the costs to the PBS, RPBS or private health funds for the extra time and stock loss, and the implementation of safety strategies to prevent the reuse of part-packs with varying expiry dates associated with removing doses from their packages. Nonetheless, some solution needs to be trialled to close off what may be another threat to antibiotic resistance in the community.

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