



<b>Title</b>	<b>Dosing of oral penicillins in children: is big child=half an adult, small child=half a big child, baby=half a small child still the best we can do?</b>
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## FEATURE

## CHRISTMAS 2011: ORAL TRADITIONS

## Dosing of oral penicillins in children: is big child=half an adult, small child=half a big child, baby=half a small child still the best we can do?

The improving Children's Antibiotic Prescribing UK Research Network thinks it's time to abandon this historical rule of thumb

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The penicillins have been the most important antibiotics used in children for over 50 years. As well as combating the rapid emergence of penicillinase producing bacteria, the development of penicillin derivatives in the 1950s and 1960s allowed oral dosing, removing the need for painful intramuscular injections. Penicillin V, flucloxacillin, and amoxicillin account for nearly 4.5 million of the 6 million prescriptions for oral antibiotics given to children in England each year.<sup>1</sup>

Despite their wide use over many decades, guidance on the correct dose of oral penicillins for children remains confusing. For example, the 2011 summary of product characteristics for Amoxil paediatric suspension in children weighing <40 kg is 40-90 mg/kg/day for all indications,<sup>2</sup> whereas recommendations for amoxicillin, penicillin V, and flucloxacillin in the *British National Formulary for Children* are mostly based on age bands, although weight bands or weight based calculations (mg/kg) are given for some indications. The widely used doses of 62.5 mg or 125 mg are fractions of the adult dose recommended in the *British National Formulary (BNF)* and are still based on the original dosing principle of a big child=half an adult, small child=half a big child, baby=half a small child↓↓↓.

### Limited evidence for dosing regimens

To understand the origins of the age band dosing schedule, we conducted a historical review of the literature and earlier UK prescribing formularies. This comprised an electronic search of PubMed (using a combination of terms including the antibiotic

name, child/paediatric, dose, clinical trial, review, pharmacokinetic) and the summary of product characteristics, a manual search through the archives of the Royal Pharmaceutical Society of Great Britain and British Medical Association, and requests for dosing information submitted under the freedom of information acts to the UK Medicines and Healthcare Products Regulatory Agency and the US Food and Drug Administration. Electronic copies of all the articles recovered from our search are available on request.

The first published studies on oral dosing in children were from 1946 and used penicillin G.<sup>3,4</sup> These and subsequent studies all used child weight to determine dosage (units/lb body weight).<sup>5-7</sup> The results showed that the success of oral administration, particularly in children over 1 year old, was essentially a matter of trial and error because the variation in absorption of the drug was so unpredictable. If 1 mg of penicillin equalled 1667 units,<sup>8</sup> the highest dose of penicillin G that gave consistent bacteriostatic serum levels in these studies was equivalent to about 60 mg every 3 hours, but only in children up to 1 year old. This meant that oral penicillin G was not practical for children older than 1 year with severe illness, and subsequent studies focused on attempts to prolong the therapeutic action of a single injection of penicillin G. Two studies suggested that doses intermediate between those used in infants and adults should be clinically effective in children.<sup>9,10</sup>

By 1958 penicillin V had become available and was clearly the oral antibiotic of choice. A contemporary survey published in

the *BMJ* showed that many UK general practitioners had adopted an age banding dosing system, with children aged under 5 years old receiving 60 mg every 3 hours and older children receiving what was then the recommended adult dose of 125 mg every 3 hours.<sup>11</sup> Prescribing based on age, albeit using a wider range of age bands, had first been suggested in 1953 at an antibiotic conference held in Vienna.<sup>12</sup> Based on the results of oral dosing studies conducted using the scheme for penicillin G described at the conference,<sup>13</sup> a general recommendation to use age banding for all antibiotics in children, irrespective of the type of penicillin or disease indication, was published in the *BMJ* in 1963.<sup>14</sup> Critically, these recommendations have remained unchallenged and unchanged to this day.

## Many children may be underdosed

Recommended dosing regimens for penicillin V (fig 1) in children first appeared in the 1963-66 edition of the *BNF* and have not been changed since. The *BNF* recommends halving the single dose between successive age bands starting from the maximum adult dose of 1000 mg as follows: 12-18 years, 500 mg; 6-12 years, 250 mg; 1-5 years, 125 mg; <1 year, 62.5 mg. The same halving of single doses between age bands from the adult dose has also remained unchanged for flucloxacillin, which first appeared in the 1974-76 edition of the *BNF*, and for amoxicillin, which was first recommended for use in children in the 1976-78 edition. Adult penicillin doses have increased substantially over the years, presumably in response to concerns around increasing antibiotic resistance, but there has been no parallel increase in children's dosing (fig 1).

The 1963 *BNF* included average weight of a child with the age band dosing information: 10 kg (birth to 1 year), 13 kg (2 years), 18 kg (5 years) and 30 kg (10 years). But data used to compile the Health Survey for England 2009 gave the average weights of 5 and 10 year old children as 21 kg and 37 kg, respectively, significantly higher than the 1963 figures.<sup>15</sup> This suggests that the mg/kg doses may be even lower than those set in 1963.

We therefore analysed the actual dose that would be received today as both the mg/kg/dose and mg/kg/day for the oral penicillins based on the age bands recommended in the 2010-11 *BNF for Children* and the current weights of children based on the 2009 Health Survey for England data (fig 2). The main problem with age and weight bands is that at older age-weight ranges, substantially lower doses are always recommended. These doses seem strikingly low—for example, a 10 year old child weighing around 40 kg and receiving amoxicillin 250 mg three times a day will receive only around 18 mg/kg/day, much lower than the 40-90 mg/kg/day recommended in the summary of product characteristics for Amoxil.

## Time for an update

The evidence base for many older medicines for children is limited, but we were surprised at the lack of recent evidence to support the *BNF*'s current dosing recommendations for such commonly used drugs as the oral penicillins. The same dosing recommendations seem to have been reused every year for the past 50 years (fig 1). In the 1940s and early 1950s dosing was based on weight, but age bands were introduced from the late 1950s alongside 2.5 ml and 5 ml spoons, which standardised practice and reduced the risk of medication error. The UK's age band dosing recommendations are much lower than the doses recommended by the American Academy of Pediatrics,<sup>16</sup> for example, but does this actually matter, or cause any harm?

Low dosing will lead to subtherapeutic concentrations at the relevant target organ (especially the middle ear), potentially driving antimicrobial resistance,<sup>17, 18</sup> with consequences for both the individual and the community.<sup>19</sup> Underdosing may result in the need for retreatment and increases the risk of severe complications. All the published risk-benefit analyses on the therapeutic balance of antibiotic prescribing for upper respiratory tract infections assume adequate antibiotic dosing.<sup>20</sup> This is a real concern because clinically inadequate dosing would increase the number needed to treat to prevent any severe complications. Studies of paediatric antiretroviral dosing noted that complex schedules using weight bands often led to clinically important underdosing since changes in growth and obesity had not been accounted for.<sup>21</sup> This work led to substantial changes in the dosing recommendations for children receiving antiretrovirals and to standardised treatment guidelines across Europe.<sup>22</sup> A similar programme of work is now required for oral penicillins. Not only do we need to determine the effective doses for children of all ages and weights but we also need to establish more clearly which children really need antibiotics in the era of pneumococcal conjugate (PCV 13), *Haemophilus influenzae* B, and meningitis C vaccines. The rates of prescribing of oral penicillins for children are now rising again in England (primary care trust prescribing data, 2010). Many of the 5 million children in England who receive oral penicillins each year may not need them, but those who do should receive them in an effective dose.

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## Figures



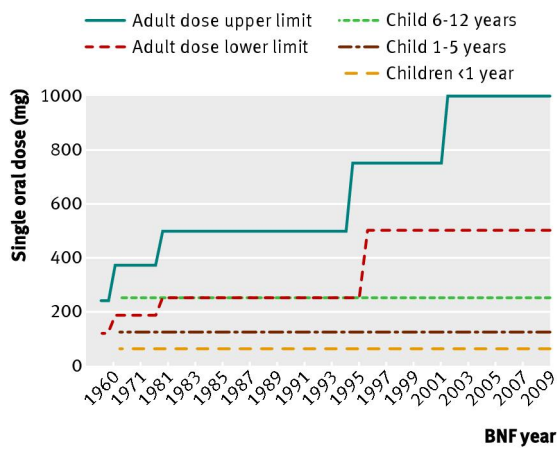
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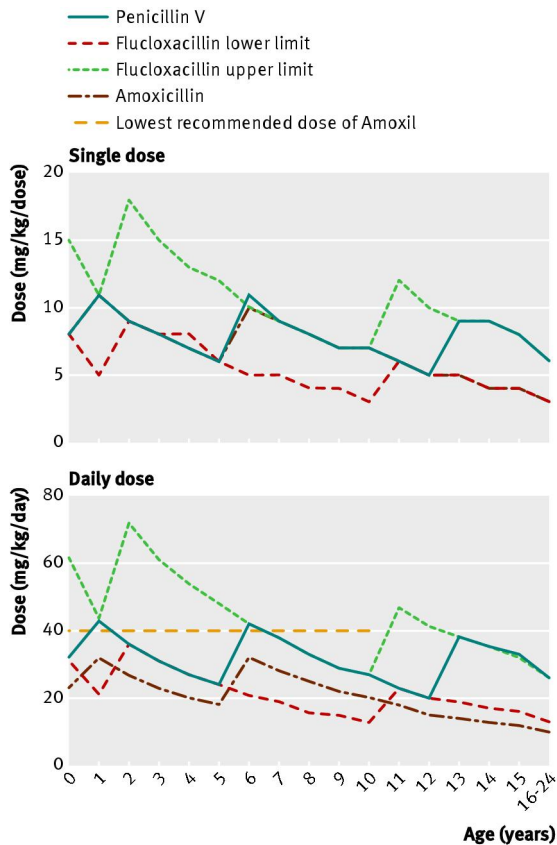
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[Image: Fiona Blair]



**Fig 1** Changes in the single oral dose of penicillin V for children and adults



**Fig 2** Actual dose of oral penicillins received as both mg/kg/dose (top) and mg/kg/day (bottom) based on age bands recommended in the 2010-11 *BNF for Children* and current weights of children from 2009 Health Survey for England. (The lowest dose of Amoxil for children under 40 kg in the summary of product characteristics)