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The Early Origins of Oral Penicillin Dosing for Children

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3 Summary
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5 This paper aims to investigate the historical origins of the dosing guidelines for
6 phenoxymethylpenicillin in paediatrics. This dose has remained unchanged for over 50 years
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8 now and it is important to understand the reasoning behind this. As far as it has been
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10 determined there is no definitive explanation for the doses laid out in our current guidelines
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12 and the impact of this still remains unknown.
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The Early Origins of Oral Penicillin Dosing for Children

Optimal dosing of antibiotics maximises efficacy while minimising toxicity and the selection of resistance. Dosing regimens of older off-patent antibiotics are long established clinically but the origins of these doses are often unclear. In 2011, we noted that dosing of the penicillins in paediatrics had remained unchanged for over 50 years and was no longer optimal due to changes in children's weights [1]. The aim of this paper is to explore further the very early origins of the dosing of oral phenoxymethylpenicillin (V), as the first oral penicillin used in children.

History of Oral Penicillin V use in Children

Being able to administer penicillin orally was always a clear goal for children where the original doses given as high-volume intramuscular injections were particularly painful. As far as we have been able to determine, the first reported use of oral penicillin in a child was from 1940 in a 6 month old boy with a *Staphylococcus aureus* urinary tract infection [2]. Further studies in babies and young infants of oral benzylpenicillin (G) demonstrated good oral absorption, but that children over the age of 6-12 months rapidly degraded the drug because of high gastric acidity [3]. The development of phenoxymethylpenicillin (penicillin V) in 1948, capable of withstanding gastric acid, was a clear step forward for paediatric use. The first large series of penicillin V being administered to children, that we can identify, was from Germany in 1953 in 106 children. The dose was based on the weight of the child (<15kg = 15mg given 4hourly, 15-30kg = 30mg 4hourly, >30kg = 30mg 3hourly) [4]. One of the first recorded uses of oral penicillin V in children from the UK was reported in a letter to

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3 the editor in the BMJ by a General Practitioner in 1955 [5]. Although the details provided
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5 are very limited due to the nature of the paper, Dr Bowerbank referenced the doses used in
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7 the German study but decided to simplify the dosing regimen, presumably for a British
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9 primary care setting. He administered 60mg 4hourly to adults and half this dose (30 mg
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11 4hourly) to children of all ages, although the specific age ranges were not stated [5]. He
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13 treated eight children for tonsillitis, five for otitis media and ten for measles prophylaxis and
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15 reported that they all did well on the selected dose [5]. The actual doses used in this small
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17 series were significantly lower than the first paediatric guidelines for penicillin V given in
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19 the 1963 British National Formulary (BNF), but the principle used by Dr. Bowerbank of a
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21 child being dosed as half an adult, rather than based on a weight based calculation,
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23 remained the same in the BNF.
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32 So where did these original doses come from?
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37 There have been a variety of mathematical formulas that have been used historically to
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39 calculate therapeutic drug doses for children extrapolating from an adult dose. It was
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41 considered that derived doses would be most appropriate if proportional to size/weight [6].
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43 This is an important distinction to recognise because, as shown by Bielicki et al, the size of
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45 children of the same age varies considerably making doses based solely on age potentially
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47 subject to error [7]. In order to investigate the origins of the early BNF doses of penicillin V,
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49 we examined a wide range of different methods/rules that have been used for calculating
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51 doses in paediatrics (including Clark's and Young's rules) and found that none of these
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53 standard methods available used for dose scaling matched the recommended BNF
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55 guidelines [6]. These rules may have underpinned the dosing guidance used when
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3 formulating the BNF doses in 1963, yet there is little evidence to support this. It is important
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5 to note that the reported doses of oral penicillin V in paediatrics did vary internationally
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7 through the 1950's with Breese and Disney reporting using doses of 250mg 3 times daily for
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9 children of all sizes and ages in 1956 [8]. Lamb and Maclean published a study in 1957 using
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11 penicillin V doses of 120mg 6 hourly for adults and only 60mg 6 hourly for children, keeping
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13 the principle of a child being half an adult, but doubling the values of those suggested in the
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15 BMJ in 1955 [5,9]. In 1957 a 10 year old boy diagnosed with meningitis in the USA was
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17 treated with penicillin V at a dose of 240mg 6 hourly [10]. This is possibly the first report of
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19 much higher doses being used for specific indications such as meningitis. The concept of a
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21 child being dosed as half an adult was further supported by a 1957 review of penicillin V
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23 which concluded that a child should be administered half an adult dose, and an infant
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25 should be given half a child's dose [10]. See figure 1 for an overview of this timeline.
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35 In 1963 the BNF then published the first national guidelines on using penicillin V for children
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37 in the UK. Infants aged under 1 year were given 62.5mg, children aged 1-5 year olds - 125mg
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39 and 6-12 year olds were given 250mg, with all doses given four times daily. These we
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41 believe to be based on the approximate weights of 10kg, 13-18kg and 30kg respectively,
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43 which were the national averages of a 1 year old, 2-5 year old and 10 year old in the 1960's
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45 [11]. This suggests that the age bands created in the BNF may have been a pragmatic
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47 extension of the general principle of halving adult doses, then halving again. This concept
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49 was potentially more suitable for primary care settings in the UK, where it has never been
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51 routine to weigh older children but to dose medicines based on age. A paper published in
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53 the BMJ in the same year includes a table depicting penicillin V doses of similar values;
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55 birth-6 months = 62.5mg, 1 year-5 years = 125mg and 10 years as 250mg all repeated
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3 6hourly [11]. It is difficult to know if the values published in this paper were influenced by
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5 the recent BNF publication at this time, or if these values represent those already being
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7 utilised in practice prior to the BNF. This paper is the closest identified record of dosing
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9 similar to that in the BNF, but it does not explain the justification of these doses.
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15 The impact of the early Penicillin V dosing regimens on other Penicillins

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20 It is important to understand not only where the oral dose of penicillin V in children
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22 originated, but also the potential influence this dosing regimen has likely had on the
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24 regimens of other subsequent oral penicillins. At present, the doses given for penicillin V
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26 and flucloxacillin are exactly the same in the UK, although flucloxacillin was licenced many
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28 years later. The dosing regimens for amoxicillin were also originally the same as penicillin V
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30 until the dose was recently doubled in older children after we demonstrated a mismatch in
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32 prescribing against the guidance [12]. In a follow up paper we modelled this phenomenon
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34 and found very little likelihood now of significant under dosing [13]. In the review already
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36 discussed published in the BMJ in 1963, penicillin V, ampicillin, cloxacillin and phenethicillin
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38 were all given to children at the same doses, which are also the doses still recommended in
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40 the BNF-C today over 50 years later with very few studies conducted on clinical efficacy
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42 since [11].
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52 In conclusion we have found that early dosing of penicillin V in paediatrics was founded on
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54 limited expert-based recommendations. The exact basis for the dosing of penicillin V in the
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56 1963 BNF cannot now be identified. The most probable first use in the UK was by a GP in
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58 1955 who treated a child with half the usual adult dose and this fundamental principle of
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3 dosing penicillins in children appears to have remained unchanged ever since. Further
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5 clinical and pharmacokinetic studies are required to determine the optimal clinically
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8 effective dosing regimen.
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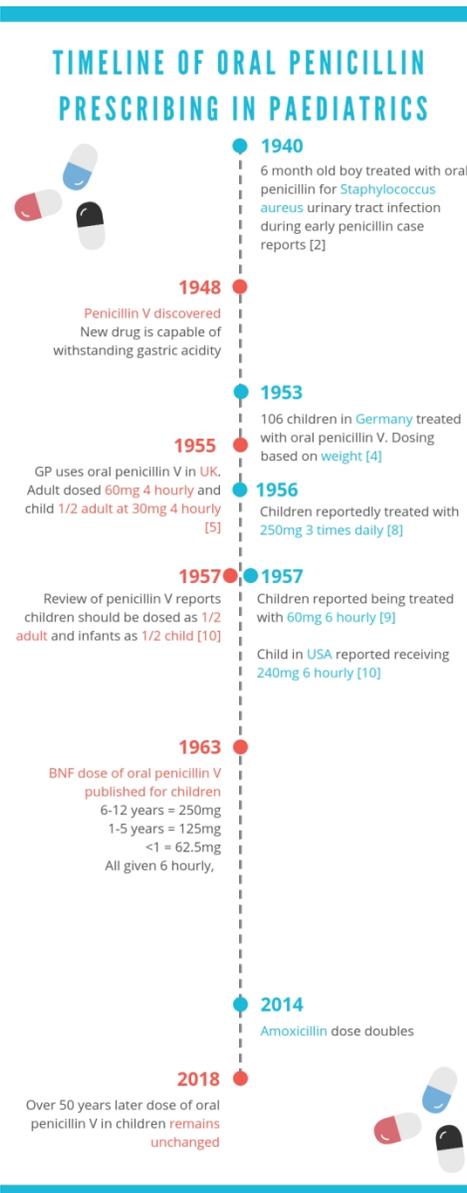
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14 Figure Legend

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16 Figure 1. Timeline of Oral Penicillin Prescribing in Paediatrics. BNF = British National
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18 Formulary.
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Timeline of Oral Penicillin Prescribing in Paediatrics. BNF = British National Formulary.