SHOULD WE QUESTION AMOXICILLIN DOSES IN THE BNF 1981-2023?

In 2021, it was reported in the Lancet that giving antibiotics was no better than no medicine[1]. In light of this information and for the multiple reasons described below, I consider that the dose of the antibiotic amoxicillin in the BNF March-September 2023[2] for children and adults is too high for the following reasons and for children has been too high since 2010.

Tables 1 and 2 show the doses of amoxicillin from 1981 to 2023, and one can see that the dose for a child up to the age of ten in 1981 had doubled by 2010, and was doubled again in 2015.

However for some reason the dose for adults remained unchanged. If the dose for children was doubled due to antibiotic resistance, why wasn't the dose for adults doubled?

When I asked the current Content Director of the BNF for reasons for the increases, I was given the standard answer discussed further on.

BNF YEAR	AGE	DOSE
1981	Child up to 10yrs	125mg x3pd
Mar 1990	Child up to 10yrs	125mg x3pd
Sept 2000	Child up to 10yrs Adult	125mg x3pd 250mg x3pd
Mar 2005	Child up to 10yrs	125mg x3pd
Sept 2010	Child over 5yrs Adult	250mg x3pd 250mg x3pd

Table 1. BNF Amoxicillin doses 1981 - 2010.

Table 1 shows that in September 2000, the dose for a child up to 10yrs was half that of an adult, but by 2010 the child was receiving the same dose as an adult. Why should the dose for a child over 5yrs suddenly become the same as that for an adult?

Since a child of 5.1yrs weighs approximately18kg and the average weight of an adult aged 30yrs is 85kg, the child weighs 20% that of the adult. So if an adult is prescribed 250mg x3pd as shown for 2010, based on weights, surely the dose for a child of 5.1yrs should be one fifth that for an adult. This would be 50mg x3pd.

Comparing this dose of 50mg x3pd with the dose of 125mg x3pd for a child of 5.1yrs in 1981, this would mean that a child of 5.1yrs would have been overdosed since 1981. I am of the opinion that this comparison using weights is justified, since alternative dosing in the BNF is based on weight i.e. mg/kg.

BNF YEAR	AGE	DOSE
Sept 2010	Child over 5yrs Adult	250mg x3pd 250mg x3pd
Sept 2015 - Mar 2016	Child 5-11yrs Adult	500mg x3pd 500mg x3pd
Mar - Sept 2023	Child 5-11yrs Adult	500mg x3pd 500mg x3pd

Table 2. BNF Amoxicillin doses for 2010 - 2023.

Tables 1 and 2 show that since 2015, a child of 5yrs has been receiving *quadruple* the dose that a child of the same age would have received in 1981. Whereas an adult has only been receiving double the dose that was being prescribed in 2000.

If we compare the dose of 50mg x3pd for a 5.1yr old mentioned above, a dose of 500mg x3pd introduced in 2015 is *ten* times the dose of 50mg x3pd. It is my opinion that this is excessive.

If we look at the dose for another antibiotic cefalexin a cephalosporin, for the years 1981–2023 as shown in table 3, for over forty years it has not been increased despite antibiotic resistance having been reported. In fact the range of 250mg-500mg x4pd given for 1981 was eliminated by 1990, and the lower dose of 250mg x4pd was used for the next 33 years.

BNF YEAR	AGE	DOSE
1981	Adult	250-500mg x4pd
March 1990	Adult	250mg x4pd
Sept 2000	Adult	250mg x4pd
Sept 2010	Adult	250mg x4pd
Sept 2015 - Mar 2016	Adult	250mg x4pd
Mar - Sept 2023	Adult	250mg x4pd

Table 3. BNF Cefalexin dose for 1981-2023

The Summary of Product Characteristics (SPC)[3] for amoxicillin 250mg capsules provided by manufacturers available on the Medicines and Healthcare products Regulatory Agency (MHRA) website, states a starting dose of amoxicillin of 250mg x3pd and 500mg x3pd for *acute* infections. In comparison, the BNF states a starting dose of 500mg x3pd and a *higher* dose of up to 1g x3pd for *severe* infections.

In both instances the BNF dose is *double* that in the manufacturer's SPC. Since severe means acute, I interpret this to mean that amoxicillin is recommended by the manufacturer to be used *only* when there is a *severe* infection.

The current SPC for amoxicillin 500mg capsules has apart from the heading, recently been removed from the MHRA website. I have been contacting the MHRA about the dose for about two months, asking questions and explaining reasons for my concerns over the dose as I believe from studies of children in England, that amoxicillin causes asthma and diabetes.

The SPC that was available on the MHRA Products website, states that the dose for adults and children >40kg should be 250-500mg x3pd for all of the following *acute* infections: bacterial sinusitis, streptococcal tonsilitis and pharyngitis, exacerbations of chronic bronchitis, otitis media and pyelonephritis.

From that I conclude that 250mg x3pd can be used for *acute* infections and therefore amoxicillin should *not* be used unless there is an *acute* infection. The NHS website now states that antibiotics should not be given for otitis media, and that paracetamol should be given for pain relief as the condition will usually resolve within 1-3 days.

When I asked the current Content Editor of the BNF why amoxicillin doses had been increased back in 2015 and whether the Chair of the Paediatric Formulary Committee in 2015 was aware that the dose for children had already been doubled in 2010, the answer was:

'One of the main sources of information for drug monographs in BNF publications is Summary of Product Characteristics (SPCs), however drug monographs may differ from manufacturer literature...'.

The NICE/BNF website page which describes how the BNF is produced, has also been substantially lengthened since I questioned the current Content Director of the BNF multiple times, about the dose of amoxicillin for children explaining the reasons for my concerns. The information now gives a lot more information about parties that are involved in deciding doses, which would spread the blame for any unsupported increases in dose.

In 2014, a publication[4] which discussed amoxicillin doses stated that doses for children needed to be reconsidered because 30% of children were overweight or obese. Another paper in 2014 also stated that *'more than a third of UK children are overweight or obese*'[5]. This second paper used data for the weights of children from 375 general practices in England provided by the MHRA Clinical Practice Research Datalink (MHRA CPRD).

Living in a deprived area and having visited a few towns in England and Scotland, I didn't believe that 30% of children were either overweight or obese. If the practices were taken from deprived areas, they are likely to have more children who are overweight as children in these areas tend to be more overweight. I informed the MHRA CPRD that I was concerned that the weights of children used in the study were not representative of children in England, and after giving me ridiculous excuses and telling me to contact a professor that had absolutely nothing to do with the study for the data, they still refused to tell me where the practices were from. They did however at one stage direct me to more recent data that admitted that deprived areas in the past had not been as well defined.

For the reasons above and the reasons listed below, I am of the opinion that children and adults have been overdosed since 1981:

1. Sir Ian Fleming who discovered penicillin said that bacteria were clever and would always develop resistance, which is why there have been different generations of penicillins and cephalosporins. So it seems pointless to keep increasing the dose

2. The dose for cefalexin for which antibiotic resistance has also been reported, has for over thirty-five years since 1981 not been increased

3. Antibiotics have been reported as causing hay fever and asthma, so any increase in the dose is likely to increase the incidence of both conditions. As readers are probably aware,

both conditions have increased in the UK and worldwide since penicillins and cephalosporins were introduced

4. Recent research[6] has reported that at higher concentrations bacteria will replicate faster and become *more* resistant. So I am of the opinion that increasing the dose is likely to have adverse effects

5. In an excellent review and meta-analysis of antibiotic exposure and adverse long-term health outcomes in children[7], it was reported that 29/39 (74%) children suffered from atopic dermatitis, 10/25 (40%) children suffered from food allergies and 28/31 (90%) suffered from wheeze after exposure to antibiotics

6. Children treated with amoxycillin for earaches suffered 2-6 times more recurrent infections, and children treated with antibiotics for streptococcal tonsillitis suffered 2-8 time more recurrence[8]

7. Rare side-effects of amoxicillin include breathing problems and wheezing. Therefore, higher doses are likely to increase the number of individuals suffering from such symptoms, with the result that they might be misdiagnosed as being asthmatic, when it is a condition that will resolve once the offending agent has been removed

8. There are no clinical studies which have looked at the effects of repeated doses

9. The SPC states a starting dose of 250mg for *acute* infections which is half the BNF dose

10. The maximum dose stated in the SPC for severe infections is 500mg x3pd. In comparison, the maximum dose in the BNF is 1,000mg, double that stated in the SPC

11. Antibiotics have been linked to hay fever and food allergies and we now have epidemics of these. So a higher dose is likely to result in more casualties, especially since children in the UK over the age of 5yrs have since 2010 been receiving an adult dose.

Prior to 1870, there was very little awareness of allergic disease[9]. Drug taking really began in the Victorian era from 1837[10] with pills being rolled out by hand and only small manufacturers existing until the 20th century. During the 20th century many more drugs were isolated or synthesized with increasing frequency after 1950[11].

Fig.1 Victorian pill making machine in an apothecary circa 1860.

Penicillin became available to the public in 1946 and asthma did not increase until 1960 when many more drugs became available. The establishment of the NHS in 1948 meant that visits to the doctors and prescriptions were free, so more people were likely to take medicines and suffer from its side effects.

The first clinical use of penicillin was a trial consisting of only five patients who were suffering from severe sepsis and multiple abscesses[12]. They conveniently referred to reactions to penicillin as 'allergies'. To have noticed 'allergies' in a sample size of just five patients supports the results shown in point 5 above. I believe that the side effects of penicillin were conveniently blamed on the constitution of the patient as it was a wonder drug, and doctors didn't want to acknowledge that it had side effects.

Penicillin was then used in soldiers from 1943 during World War II, as many were dying from infected wounds. Since it was used for very serious infections in the clinical trial, I think it possible that the dose was of a high level designed to treat very severe infections. The syringe shown in figure 2 gives an indication of how primitive medicine was in the 1940s.

Fig. 2 Penicillin syringe used during the war

Since there were no real clinical trials and high doses were probably used to combat the serious infections when penicillin was first used, can we be sure that the early dose was appropriate for minor conditions that are most frequently treated today? It also seems logical to conclude that the dose of later penicillins, was probably based on the early dose, although perhaps adjusted down.

When the drug company Beechams (now part of GlaxoSmithKline, GSK) launched Amoxil in the UK in 1972, I wonder whether it took into account the fact that amoxicillin reaches 2–3 times higher a level in blood than ampicillin in animals[13]?

In the UK studies have shown that 20% of antibiotics prescribed in primary care in England are inappropriate[14]. In the USA, the Centres for Disease Control and Prevention reported in 2016 that 30% of antibiotics prescribed are unnecessary[15].

So why do doctors prescribe when they themselves have sometimes admitted to prescribing without good reason? Figure 3 shows how the BNF for 1971 is dwarfed by that for 2023, which should convey to any reader that doctors today are faced with ever increasing demands.

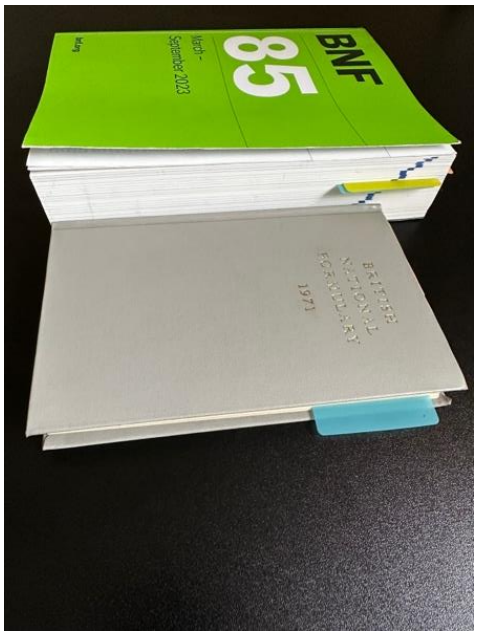


Fig. 3 Comparing the BNF 2023 AND 1971

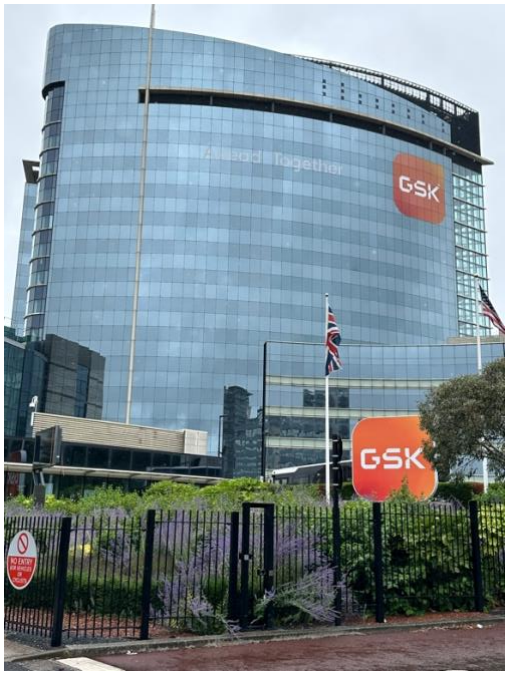
It has been reported that doctors may prescribe because they are faced with time constraints, want to provide patient satisfaction, succumb to pressure from themselves possibly thinking that there is an expectation of a prescription, and also because they have concerns that the symptoms are due to bacterial infections which can be similar to viral infections[16].

It is my opinion that patients need educating about the side effects of drugs because with the marvels of modern surgery and many attractive new hospitals in the UK and Australia, they might be unwittingly led to believe that modern medicines are a panacea for all ills. Education that advises them that many conditions will resolve of their own accord might also be beneficial. Even the Victorians have been reported as taking strong potions for conditions such as coughs and colds. Perhaps sometimes patients simply want a few days off work. Many of the unsuspecting public today are probably entranced by media reports of successful

trials of the latest drugs, not realising that such studies such as a trial for teplizumab to prevent insulin dependent diabetes, is flawed.

Drug companies invest a lot of money in making connections with key opinion leaders, such as professors in universities and hospitals and fund medical practices and charitable organizations so that they can promote their drugs. From my experience they don't like questions about their drugs being asked.

When I repeatedly asked GSK in west London over about six weeks, five questions about the number of clinical trials of amoxicillin in children, how the original dose was determined and whether there had ever been any long-term follow-up studies of children who had taken repeated courses of amoxicillin, GSK contacted the police. And the Emergency Response Team of the Metropolitan Police emailed me late on the night of 10 August 2023 about *'unwanted correspondence and visits*'.



I had been in contact with two Directors, Global Corporate Media Relations, who had responded to my emails only asking me each time what my was article about, which media outlet I was writing for and if I was available for a phone call. I suspect that they knew from searching the internet that I blamed antibiotics for causing asthma and diabetes and don't want the public to learn of any link.

Any reduction in the number of asthmatics is likely to affect their sales of Ventolin and Advair used by asthmatics. At one point GSK turned over $8B a year from the sales of Advair[17]. GSK had lied to the police, so I explained exactly what had occurred, after which I said that I wouldn't contact GSK again and the police closed the case.

In 2012, GSK was fined $3Billion the largest health care fraud settlement in US history and the largest payment ever by a drug company. In 2014 GSK was fined $490Million, this time for bribing health officials in China.

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