

Perspective

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Holistic solution to an old "mystery": the global role of antibiotic consumption patterns in the spread of certain non-contagious diseases in EU countries

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Abstract

The discovery and extensive utilization of antibiotics are highly contributed to the considerable lengthening life expectancy of human beings. Antibiotics, mixed with animal fodder, produced considerable growth promoting effect and hence, extended the indications of antibiotics at a much higher level. The indiscriminate use of antibiotics quickly resulted in the emergence of poly-resistant pathogens and the extensive antibiotic pollution of the environment, particularly of the surface water and rivers through human and animal excreta. Along with extensive and ever increasing antibiotic consumption/pollution, the pandemic-like spreading of certain non-contagious diseases like obesity, diabetes (Type 1-2 T1DM, T2DM), Alzheimer disease (AD), Parkinson disease, multiple sclerosis (MS) etc. started unfolding, which was called as a slow moving disaster, without having any appropriate explanation of the phenomenon. The parallel appearance of those "pandemics", which appeared simultaneously with the extensive antibiotic consumption, might indicate some kind of association. As far as several publications have reported the crucial role of altered gut flora in the development of metabolic disorders (diabetes, obesity) and neurodegenerative diseases alike (PD, AD, MS), it might be suspected that antibiotics, acting through the modification of microbiome, could influence the morbidity (prevalence) of those, non-infectious diseases. This concept, described below, might serve as a unified explanation, not excluding other, contributing causative factors, for the phenomenon, outlined above.

The discovery of penicillin by Fleming in 1937 and later of neomycin and streptomycin by Waksman opened a new chapter of science, discovering the miraculous effect of antibiotics on infectious diseases. After the introduction of penicillin, several broad spectrum antibiotics were discovered also, like aminoglycosides, quinolones, macrolides etc., but their indiscriminate use has led to serious consequences and the rapid development of poly-resistant or panresistant bacterial species, which produced practically incurable infections (1). Out of the approximately 5000 molecules considered as having an antimicrobial effect, one thousand was further investigated, and finally we have about one hundred commercially available antibiotics to treat infections. Most of those drugs are produced by actinomycetes molds and different bacteria. After the „golden age” of antibiotic discovery of '50-ies and '60-ies and the extensive utilization of broad spectrum antibiotics in the late '70-ies and '80-ies, we now face the fact that the production of new classes of antibiotics practically stopped after 1987.

At present, only few antibiotics are in the development, but it is not of certain that they might finally be used as commercially available antibiotics (2). The accidental discovery of the growth promoting potential of antibiotics in the late '40-ies (3) resulted in the large scale utilization of antibiotics mixed to animal fodder which contributed to the extensive environmental pollution and the emergence of multi-resistant bacteria (genes) to the environment along with the development of human infections, practically untreatable with any antibiotics (4). Recently (2013) the yearly consumption of antibiotics in animal husbandry was estimated to be 131,109 tons (5). The “growth promoting effect” of certain broad spectrum antibiotics (than Aureomycin) was observed and documented in premature newborns and school children also (6, 7).

According to ECDC database of antibiotic consumption for 2018 expressed as the number of defined daily dose (DDD)/1000 inhabitants/Day, the average total consumption (community and hospital sector) of antibacterial for systematic use (ATC group J01) in the EU/EEA countries was 20.1 DDD/1000 inhabitants/Day (range: 9.7 – 34.0). During 2013-17, no statistically significant shift in antibiotic consumption was observed in the EU/EEA countries and no significantly increasing trends were reported (8).

Usually, we consider as „epidemic” or “pandemic” the spreading of communicable diseases, but we have to face with the fact that the appearance and spreading of certain non-communicable diseases are similar. In the past few decades the pandemic like spread of several non-infectious diseases are alarming. The reason for the rapidly increasing amount of obesity, particularly childhood obesity, diabetes type 1-2 (T1DM, T2DM), autism, which was hardly heard of 50 years ago, the Alzheimer disease (AD) of which produces more death in the USA, than cardiovascular and certain cancer deaths combined, and the Parkinson disease (PD) doubled its prevalence in the past 25 years. The prevalence of multiple sclerosis (MS) has increased by approximately 10% since 1990. Due to their outstandingly rapid spread, diabetes, obesity, autism, AD, PD and MS can be considered as of major importance. This phenomenon is called as a slow moving disaster (9, 10).

Scientists working on the explanation of this phenomenon, keep on digging deep to identify the molecular background, discovered several possible pathways and mechanisms leading to the development of those ailments and all of them emphasised the crucial role of the intestinal microbiome alteration (dysbiosis), but some external factors are suspected triggering the development of dysbiosis (11.). Several sequencing efforts were made to elucidate the complete composition of gut flora. Till now, 1952 uncultured bacterial species were verified by reconstructing 92,143 metagenome assembled-genomes from 11,850 human gut microbiota, which is considered 281% increase in phylogenetic diversity (12). Antibiotics are powerful

agents influencing the composition of the intestinal flora and producing dysbiosis, by reducing the diversity of the bacterial taxa in the gut. An extensive meta-analyses of articles dealing with the effect of antibiotics on the microbiome since the very first publication summarizes the observations. Penicillin has not much effect on the gut flora, but amoxicillin, amoxicillin/clavulanic acid, cephalosporins, macrolide, quinolone, lipopolysaccharide, ketolide, fosfomycin; tigecycline has increased the dominance of non *E. coli* (mostly *Citrobacter*, *Enterobacter* and *Klebsiella* spp.) Enterobacteriaceae.

In contrary, most of the above antibiotics (amoxicillin, macrolide, clindamycin, quinolone, and sulfonamide) reduce the presence of *E. coli* in the gut flora, but the combination of amoxicillin/clavulanate has increased its abundance. Macrolide, doxycycline reduced the rate of *Enterococcus* spp. In the gut flora, while amoxicillin, piperacillin, ticarcillin, cephalosporin (1-4th generations), lipoglycopeptides, carbapenem has enhanced their presence (13). Antibiotics reach our body as either therapeutic agents or from the environment, particularly from the heavily polluted rivers, because of the antibiotic enriched animal fodder, industrial waste and human excreta entering the surface water and ending up in the rivers and are present in the potable water also (14-16).

The decisive role of dysbiosis in the process of developing certain chronic diseases might raise the theory that the quality and quantity of antibiotic insult on human microbiome might trigger the development of different diseases and antibiotic consumption preferences in different countries might be related to the different, emerging, non-contagious diseases, showing pandemic-like spread. The issue that growth-promoting effect of antibiotics added to animal fodder of food animals might similarly affect humans as well, was first raised in 2005 (17).

Further research by the author has led to the discovery of the significant selective correlation between childhood obesity and certain antibiotic consumption in EU countries (18). The significant association was found between the consumption of narrow spectrum penicillin and the prevalence increase of PD. Simultaneously, we observed the inhibitory effect of broad spectrum penicillin and the prevalence in PD as well (19). Further comparisons of large databases derived from ECDC (20) yearly reports of antibiotic consumption by EU countries (1997-2018) and the prevalence of diabetes (21) AD (22), and MS (23) derived from different resources (publications are in progress) demonstrated the promoting and inhibitory effect of different classes of antimicrobial agents on the development of those diseases.

As a conclusion, I have detected two different, very distinctive patterns of antibiotic consumption, what I have called “Scandinavian type” with dominant consumption of narrow spectrum penicillin and tetracycline and higher

prevalence of PD (24), MS (23) and T1DM (21), and the “Mediterranean type” with dominant consumption of broad spectrum antibiotics, including broad spectrum penicillins, and higher prevalence of childhood obesity (25, 26), T2DM (21), and AD (22). Cross-association was observed with childhood obesity and AD. We found similar antibiotic consumption patterns in MS, and T1DM. This observation is being supported by the reported three fold higher prevalence of MS among patients with T1DM (27) and indicating the possible inhibitory effect of clavulanic acid in T1DM and

MS. The holistic approach permitted us to consider the similarities of the parallel appearance and spreading of certain non-contagious pandemics, which appeared roughly at the same time as the widespread consumption of antibiotics. Those findings clearly pointing to the possible common origin of the developing and spreading of certain non-contagious diseases included in the study and serve as an explanation for the “mystery” of the large scale spreading of obesity, diabetes, PD, AD and MS.

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