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Role of Antibiotics and Infection-Host Interactions in the Prevalence of Respiratory Atopy: Experience and Perspective

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Abstract: We have witnessed a dramatic increase in the prevalence of respiratory allergies during the last decades. The role of infections in the prevalence of respiratory allergic diseases is attributed to the antagonism between: a) induction of T helper (Th) 1 immune response by human organism; and b) manipulation of the human immune response toward Th2 profile by common infective agents in order to increase their surviving opportunity. This review proposes an important role of massive antibiotics exposure during neonatal and early childhood on the increasing epidemiological trend. It is believed that the antibiotics exposure during early childhood has also provided better surviving opportunity for atopic individuals with an inadequate immune defense against common infections, deviating therefore the genetic background of general population toward Th2 profile. Taking this into account, we suggest that Th2 profile frequency (and consequently atopic phenotype prevalence) can be increased along an individual lifespan after initial massive antibiotic introduction, until the entire population is exposed to them during childhood. This hypothesis may explain findings on epidemiological surveys, which report a prevalent increase among adults in industrialized countries between 1970s and 2000s, while in recently-developed countries this trend begun only at the end of 1980s. These arguments may lead to the conclusion that infections will manipulate the human immunity along generations, whereas actual antibiotics can increase the prevalence of respiratory allergies among a population only along an individual longevity. These findings may be beneficial in the development of future strategies for management of respiratory allergic or infective pathologies.

Keywords: Antibiotics exposure, common infections, early childhood, prevalence trend, respiratory allergies.

INTRODUCTION – RESPIRATORY ATOPY TREND AND RISK FACTORS

At the beginning of the 20th century, allergies were rare diseases, while the last decades have witnessed a dramatic increase in disease burden and prevalence [1-3]. Allergies represent the most frequent chronic diseases in Europe, affecting more than 60 million people [1]. Data from several sources indicate worldwide increases in bronchial asthma or allergic rhinitis', especially in English-speaking countries [1, 2, 4]. Thus, during the 1990s, the 'prevalence of wheezing or bronchial hyperreactivity in European children aged 13-14 years varied from 32.2% in United Kingdom to only 2.6% in Albania' (Fig. **1**) [1-3, 5-7]. 'Similar variations between European countries are evidenced among adults aged 20-44 years' [2, 8].

There is no more an increasing trend of the prevalence in western countries, while in developing countries the rising trend still continues [9, 10]. Furthermore, the prevalence of allergic pathologies has started to subside in some industrialized countries [10]. While the increasing prevalence is largely explained due to the influence of environmental factors and epigenetic mechanisms, its recent interruption is not fully explained [9]. With respect to increased prevalence, the most important factors comprise improved hygienic conditions, decreased exposure to infections, massive use of antibiotics, exposure to pollution and traffic exhausts, etc. A consistent proportion of these factors are presumed to be components of "hygiene hypothesis", whereas more recently all risk factors are incorporated in "the changing world theory" [10-13].

The identified risk factors for the respiratory atopic pathologies cannot equally account for the global increasing prevalence, international patterns, or recent declines in some western countries [14]. Antibiotic therapy (and its interaction with infections) instead, may be the factor that covers globally the largest human population, compared to other risk factors such as emigration, urban life, improved hygiene, etc. Aim of this review is to explain the possible role of global

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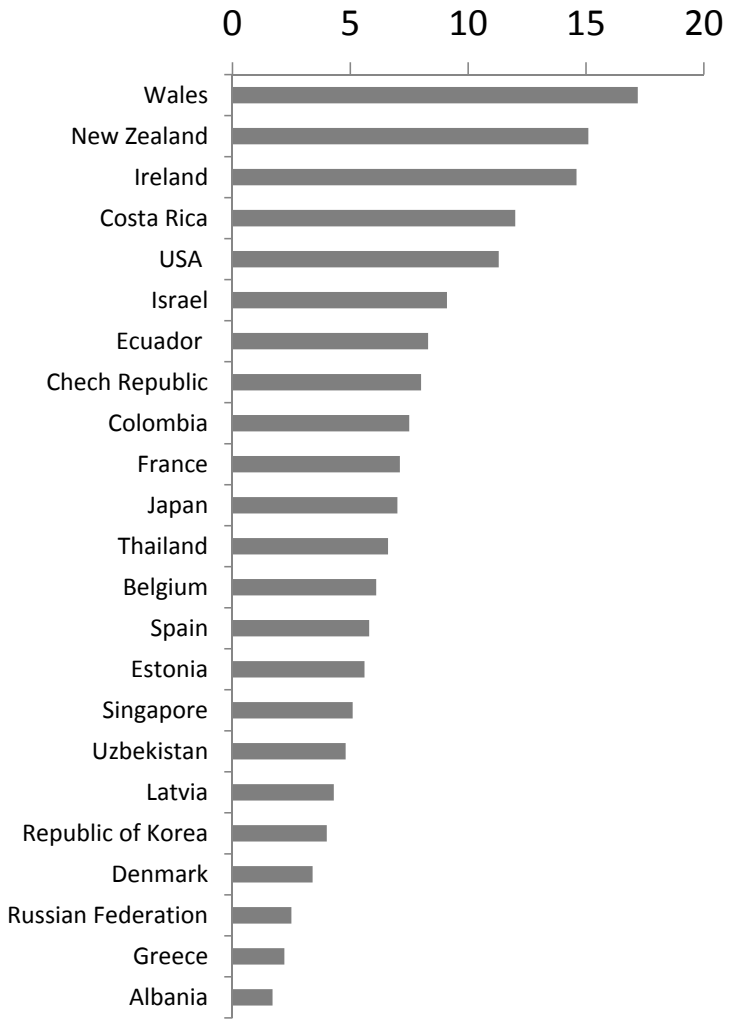

Fig. (1). Prevalence of asthma during the end of 20th century:

Asthma prevalence has varied from 0.5-5% in developing countries to 20-25% in English-speaking countries such as Australia and New Zealand (Bull World Health Organ, vol. 83, no. 7, Genebra Jul. 2005, http://www.who.int/bulletin) [7, 8].

exposure to antibiotics and its interaction with infections on the prevalent trends of respiratory allergies.

THE ROLE OF INFECTIONS IN THE RESPIRATORY ATOPY

According to worldwide knowledge, the role of infections in the prevalence of respiratory allergies consists in the antagonism between: a) induction of human T helper (Th) 1 immune response as consequence of infection; and b) manipulation of this immune response toward Th2 profile by common infective agents in order to increase the invaders' surviving opportunity [2, 15]. On the first hand, it is postulated that 'antibiotic-induced growth inhibition of enteric flora can suppress the "education" of Th1 profile immune response in children, leading to the induction of a Th2 allergic inflammatory predisposition' without changes of genome even after exposure to one course of antibiotics in the first year of life [2, 12, 13, 16-20]. On the other hand, different infectious agents can manipulate the host immunity through induction of Th2/Immunoglobulin (Ig) E response, in order to increase their surviving chances [2, 15, 21, 22]. Thus, development of hyperreactive respiratory symptoms during common bacterial and viral infections after a "silent" incubatory period suggests that microorganisms may manipulate host immunity, allowing themselves a "safe escape" for a few days to do that, before the production of eradicative IgA or IgG antibodies [22]. While common microorganisms induce hyperreactive/allergic respiratory symptoms after their reproduction, massive infestation with various geohelminths in equatorial regions is associated with suppression of respiratory symptoms and a lower prevalence of atopic pathologies despite the potent IgE induction [1, 21, 23-29]. The negative correlation of infective agent survival to the concentration of specific IgG1 and IgA suggests that in vivo, Th2 profile may not simply be a host-chosen reaction only, but also the most efficient and beneficial humoral response during host-infection interaction [30-33]. Taken into account

that a vast proportion of infections cannot be eradicated by traditional antibiotics and that actual human populations show more frequently Th2/IgE profile in association with antibiotics' use, it could be concluded once more that the development of bronchial and nasal hyperreactivity after early respiratory infections could be considered a predictor for a future allergic "career" as well as a consequence of the invaders' manipulatory abilities in order to reassure their own reproduction/survivorship [34-36].

RELATIONSHIP ANTIBIOTICS EXPOSURE – ATOPY TREND

From the discovery of penicillin by Alexander Fleming in 1928, Australia was the first country to make the drug available for civilian use after World War II, followed by USA and Western European countries [37]. Massive exposure to antibiotics in the rest of the world followed stepwise within few decades, and nowadays antibiotics are largely used for the treatment and prevention of common bacterial infections.

Worldwide it is believed that 'the affluent life and especially the exposure to antibiotics have provided supplemental survival possibilities especially among atopic individuals, declining the mortality rate after common respiratory or gastroenteric infections in the early life' [38]. This is because 'the use of broad-spectrum antibiotics may increase surviving rates during serious infections in children who fail to provide adequate natural immune responses' similarly to IgA or IgG antibodies [39, 40]. In effect, 'prior to the antibiotic era, subjects showing a deficit of this response did have less opportunities to survive, and consequently to have their own offspring'. In contrast, 'the massive introduction of broad-spectrum antibiotics has promoted relative surviving parity against these infections' [2]. The effect of exposure to antibiotics among young subjects who inhered predominantly Th2/IgE profile has possibly enabled the partial deviation of immune-genetic thesaurus for successive adult population within a few decades to a more frequent allergy-predisposing genotype. Despite the lack of identified changes, it is not excluded that the frequency of hereditary markers corresponding to genotype of IgE antibodies or Th2 profile may be also more frequently shown among respective populations [15]. The missed antibiotic-related surviving effect has accounted for increased rates of fatal respiratory infections among South-American children of low socioeconomic status, whereas children coming from affluent societies experienced more frequently the respiratory allergies or used more frequently antibiotics [41]. These findings demonstrate that a large exposure to antibiotics during early life may provide much higher surviving chances for children who experience 'serious respiratory and gastrointestinal infections, even if they possess inappropriate natural immune response' [15].

Furthermore, the massive use of antibiotics together with better living conditions in western countries could have been the initial factor on the discrepancy of allergy prevalence between industrialized and non-industrialized world [2]. It is likely that epidemiological difference first corresponds with time-point that begins about 20-25 years after initial massive exposure to antibiotics [11, 23]. This time-point, in turn, corresponds to the start of increasing prevalence trend for respiratory allergies that is predominantly observed in 'industrialized countries, particularly over the last 35-40 years of 20th century' [3, 42]. Thus, von Mutius et al. have demonstrated that 'in genetically similar individuals, the prevalence of respiratory allergies was significantly higher among school children living in the former West (Munich) as compared with children in the former East Germany (Leipzig and Halle)' [3, 23, 43]. 'An interesting fact was the finding that the mentioned east-west differences are observed only among children and younger adults but not among Germans born before 1960s, suggesting that a "cohort effect" has been operating with the lifetime allergy risk being influenced by living conditions in early childhood' [10, 11, 23]. In parallel to Western Europe, 'significant increases in asthma morbidity in the USA have occurred since 1970s, particularly among immigrants or African-Americans subjects [2, 44]. Compared to western countries, the prevalence's increase of atopic pathologies in the rest of the world is observed at a subsequent time [10, 45]. Several studies performed in the tropical regions have provided further evidence that atopic disorders occur more commonly among individuals living in urban, more affluent and westernized areas compared with those living in rural areas with traditional lifestyle [21, 23].

The genetic heterogeneity of populations in English-speaking countries indicates for far higher immigration rates (compared to other industrialized countries), whereas the highest prevalence of asthma symptoms among immigrants can be explained by "fireside/fireplace hypothesis" [23, 46]. According to this hypothesis, 'the use of fire as means of coping with harsh temperature variation since the migration in the northern regions of the world, would have led to more time spent in close proximity to smoke – a known air polluter' [2, 46]. While 'subjects who experienced during generations a more permanent and continuous exposure to smoke are better protected against airways pathologies, the African-American subjects (who originate from equatorial regions) experience more frequently respiratory diseases after exposure toward tobacco, trafficor industrial polluters' [2, 46]. This is because their exposure toward fire and smoke during generations was nearly occasional for climatic reasons and therefore, the adaptation toward this pollution actually is inadequate. Atopic predisposition among immigrant populations of West-European countriesis reflected in the increased rate of IgE-mediated asthma, whereas a delayed atopy rising prevalence is happening in developing countries [9, 10, 47]. Nevertheless, the increase was more evident 'in the older age-group, suggesting that environmental influences on the development of allergy may not be limited to early childhood' [9].

Notably, recent findings demonstrate that the epidemiological differences in respiratory allergic pathologies between industrialized and recently-developed countries in European subjects born after 1960s are diminished during 1990s like in the reunified Germany [11, 48]. Moreover, general

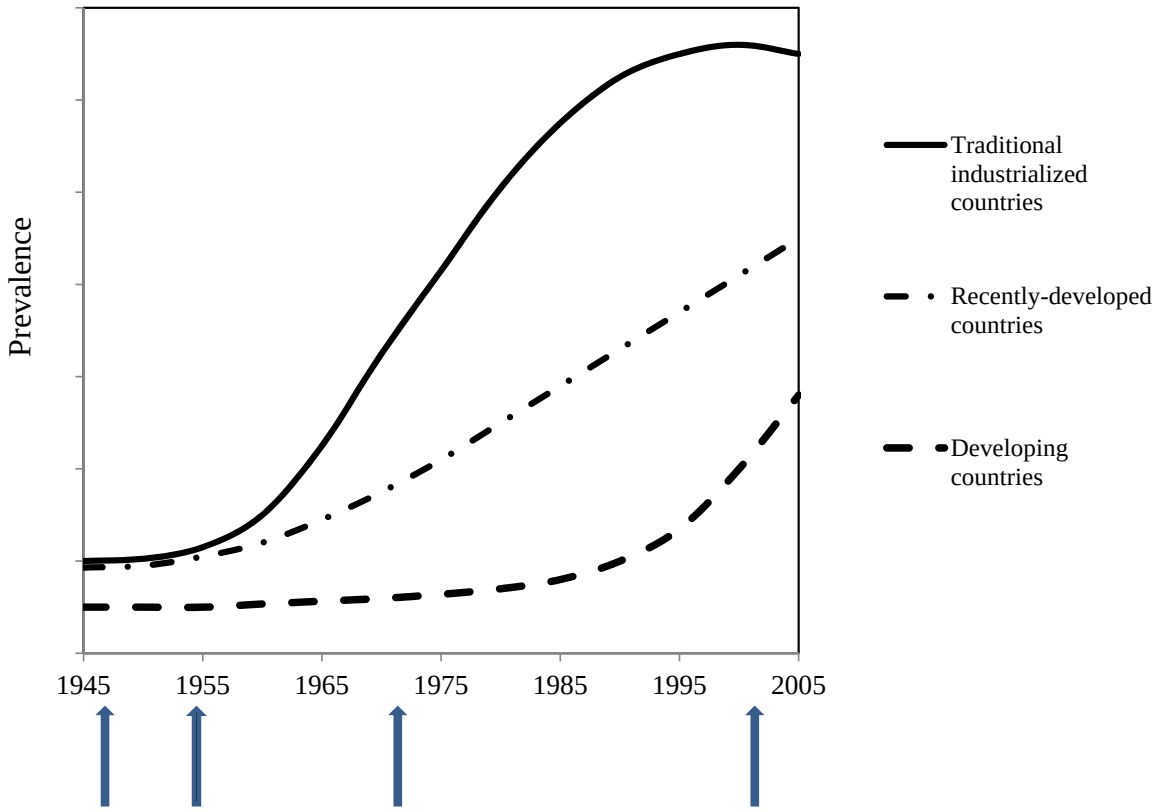

Fig. (2). Asthma prevalence trend and introduction to antibiotics:

Three different asthma prevalence trends (high, intermediate and low) are distinguishable, which are developed under interaction of several risk and protecting factors (Bull World Health Organ, vol. 83, N 7, Genebra Jul. 2005, http://www.who.int/bulletin) [7]. Initial exposure to antibiotics is shown via three arrows (respectively beginning from the left). The beginning of prevalence discrepancies in adults correspond with a time-point of about 20 years after their exposure to antibiotics (first arrow from the left). This could be explained by the fact, that in industrialized countries, antibiotics' surviving role for the Th2-born populations during early childhood is reflected in the population's genome of adults during 1960s-1970s. This effect is shown later in recently-industrialized countries (second arrow from the left) and much later in developing countries (third arrow from the left), that reflects the time-point of the antibiotics exposure in population's early childhood. The arrow on the right represents the time-point when all adults in industrialized countries are exposed to antibiotics during their early childhood and have own offspring until early 2000. This time-point corresponds to the end of influence for the factor antibiotics exposure and possibly for the "hygiene hypothesis". The analogue time-point for the rest of world should on the next decades, but the highest asthma prevalence will be not necessarily equally to developed countries because of actual strategies on the limitation of antibiotics use.

"Westernization" is associated with increased prevalence of atopic diseases mostly in previously low and mid-income countries, whereas in the western countries are already reported no increase or even decrease in asthma prevalence over the last 10-15 years has been reported [6-10, 12-14, 45].

The divergent trends in prevalence of allergic diseases needs more research into finding the real causes [1, 6]. Reference to our proposal regarding the significant role of the massive exposure to antibiotics, differences in respiratory allergy prevalence may reflect timing of the first massive exposure to antibiotics: a higher prevalence could correspond to an earlier initial exposure to antibiotics (Fig. **2**) [2, 7, 11, 15, 23]. In our opinion, the diminishing prevalence trend for respiratory allergies in the industrialized countries indicates that impact of antibiotics use on the rising trend of allergy prevalence may continue for a period of active individual longevity (which includes period of childhood and fertile adulthood). This period in industrialized countries begins with initial antibiotic exposure after World War II with respective consequences first observed after 1960s, and ends actually during years 2000s (about 60 years after initial use of antibiotics) with interruption of the atopy rising trend [2, 11, 15, 23]. In contrast, the epidemiological trend in the recently-developed countries (where antibiotic use begun later) is leading to the reduction of epidemiological differences with western ones [9-11, 14, 15, 48]. Nevertheless, the intensity and mosaic of risk factors for the respiratory allergies vary between various countries, while the actual strategy on the antibiotics' use among children is quite different to the previous century. It is expectable that actual epidemiological trend of allergies would be a reality in recently-developed countries, with variable and lower trends compared to western countries during the last century, as long as actual antibiotics' application is not so massive as compared to

antecedent decades [15]. Maybe in a few decades, antibiotics exposure will no longer be a risk factor for asthma and atopy among populations of recently-developed countries, 'including the important period between 0 and 1 year of age' [13]. This concept (in concert with other established risk factors) can explain the increased allergy prevalence in industrialized countries among autochthonous populations, as well as the actual divergent trends in prevalence of respiratory allergies between them and populations of recently-developed countries. In addition, our suggestion may explain why subside of prevalence increase in industrialized countries occurred just about 10 years ago, which nearly corresponds to the above-mentioned human life cycle (childhood + fertile lifespan) since respective antibiotics exposure. The influence of antibiotics for the lifelong period since first exposure, especially during first life year, agrees with the fact that antibiotics are considered risk factor for asthma in children in precedent decades, while actually this concept is likely to be considered as false in studies originating from industrialized countries [12, 13, 15, 16, 45]. If correct, this epidemiological pattern will occur in every (recently-developed) country at a certain time. Considering the above, "hygiene hypothesis" should play a role on rising prevalence trend until the entire population would be exposed to antibiotics during early childhood and not necessarily until the reaching of such increased prevalence for respiratory allergies like in western countries.

CONCLUSION

- Exposure to antibiotics and the reduction of intestinal microbioma are both considered synergistic factors for the induction of the atopic response, and it affects the largest populations, as the major component of "hygiene hypothesis" and "the changing world theory".
- In this context, antibiotics behave not only as suppressors of immune "education" but also as "lucky devils" for relative "immuno-deficient" Th2-born subjects during their early life, leading also to a possible deviation of populations' genetic background toward the Th2/IgE profile.
- This work tried to explain the discrepancy between the actual increase of respiratory allergy prevalence in recently-developed countries and its deceleration in western countries (where this trend has lowed down or interrupted) through the argument that antibiotics exposure could be involved in the allergy prevalence increase only for a period of individual life longevity. The end of this period corresponds to the time-point when all population has experienced antibiotics exposure and has survived common childhood infections.
- Finally, the knowledge of above-mentioned interactions may help us to develop better etiological theories about respiratory allergic diseases that can replace the actual theory, or to incorporate it as an additional possible scenario.

CONFLICTS OF INTEREST

The author confirms that this article content has no conflicts of interest.

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