Psychological and Cultural Factors in Children and Societies Influencing Antibiotic Prescription

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Abstract

Humans have been giving a selective advantage to antibiotic-resistant bacteria worldwide by inundating the environment with antimicrobials for about one century. As a result, the efficacy of antibiotics has been impaired. Antibiotic resistance is a public health problem, responsible for increases in mortality and extended stays at hospitals. Hospitals and other clinical settings have implemented stewardship measures to reduce antibiotic administration and prescription. However, these measures demand multifactorial approaches, including multidisciplinary teams in clinical settings and the education of professionals and patients. Individual and social psychologybased research should be considered, as social, cultural, and individual factors impact antibiotic prescription, as shown by recent studies indicating that mother-infant attachment and parenting styles play critical roles in antibiotic use.

Highlights

- 1. Stewardship programs improve antibiotic prescribing practices, mainly to reduce their use, and consequently selection of antibiotic resistance.
- Stewardship programs encompass highly complex healthcare and sociological landscape, requiring the involvement of multidisciplinary teams, namely medical doctors, nurses, and pharmacists. We argue that sociologists and, based on recent studies, psychologists, should get more often involved in these programs.
- 3. Developmental psychology, particularly attachment theory, might help generate the debate around social norms and antibiotic use and, consequently, the acceptance of stewardship.
- 4. There is a possible correlation between the developmental psychological processes and the cultural heritage of the human societies, suggesting precision stewardship programs.

Keywords: Antibiotic resistance; Stewardship programs for antibiotic prescription; Mother-infant attachment; Inglehart-Welzel cultural maps; Psychology of antibiotic use; Sociology of antibiotic use.

The pandemics of antibiotic resistance

The use of antibiotics may have positive but also negative consequences (see Box 1). Already 50 years ago, some hospitals implemented "programs to control" antibiotic administration. At the time, the cause of these control programs were the toxic effects (ranging between severe diarrhea and death from anaphylaxis or aplastic anemia) and the high costs of these drugs to the hospital [1]. In those golden days of the antibiotic era, medical doctors and bacteriologists were well aware of antibiotic resistance, considered a problem for individual hospitalized patients, but not a publichealth problem. Nowadays, antibiotic resistance is considered a serious world health challenge [2]. A recent study by Murray and coworkers has shown that around 1.27 million people died in 2019 due to bacterial resistance to antibiotics worldwide [3]. As noted in a companion commentary paper, this number of deaths is close to the estimated number of deaths from malaria and AIDS together in the same year [4]. Not surprisingly, children are also victims of drug resistance. For example, about two hundred thousand neonatal sepsis deaths are attributable to resistant pathogens each year [5]. However, efforts should be done to increase the methodologic quality of the estimations of the correlation between mortality and antibiotic resistance [6].

Even when antibiotics target pathogenic bacteria, the antibiotic molecules affect trillions of bacterial cells comprising hundreds of commensal bacterial species forming the normal microbiota of human (or animal) bodies. Bactericidal antibiotics kill sensitive cells, and bacteriostatic antibiotics block bacterial replication. In both cases, sensitive cells leave unused resources, such as nutrients or colonizable space, so nearby antibiotic-resistant cells thrive even if resistance mechanisms are biologically costly. This counter-selection of sensitive cells is the basis of Darwinian natural selection occurring every day in patients, livestock, and the environment [7,8]. As a result, the human usage of these drugs is leaving an indelible antibiotic resistance footprint [9]. The impact of antibiotic usage on antibiotic resistance is such that there is a positive relationship between antibiotic use and resistance rate across countries [10–12]. However, we can learn from the social attitudes and antibiotic-policy measures taken in the countries with lower resistance rates and act on countries or regions where antibiotic usage is higher. Besides antibiotic resistance, the extensive use and release of industrial antibiotics might speed microbial evolution

and could have deleterious consequences for the preservation of a healthy ecology of the planet [13].

Antibiotic stewardship programs: relevance and impact

Antibiotic stewardship programs are institutional actions to improve antibiotic prescribing practices, mainly to reduce their use, thus avoiding the selection of antibiotic-resistant bacterial populations. Their objective is to mitigate the spread of antibiotic resistance by providing a more individualized (precision) therapy. In particular, they promote (i) the prescription of antibiotics only when necessary; (ii) a correct choice of antibiotics based on a precise bacteriological diagnosis (e.g., limiting the use of broad-spectrum antibiotics to specific cases); and (iii) appropriate doses, length, and route of treatment. These programs are complex, implying the involvement of medical doctors, nurses, epidemiologists, and pharmacists. This paper argues that antibiotic stewardship programs should involve other scientists: (i) sociologists, as controlling the "excess" of antibiotic's individual use should be considered together with controlling the "access"; and (ii) most importantly, psychologists and, in particular developmental psychologists [14], as it is discussed in depth in this work.

The concept of antibiotic or antimicrobial stewardship to mitigate drug-resistance levels is relatively recent. In 1997, the Healthcare Epidemiology Society and the Infectious Diseases Society of America presented strategies for preventing antimicrobial resistance in hospitals [15,16]. According to the Scopus database (18/March /2022), no paper mentioned "antibiotic stewardship" or "antimicrobial stewardship" in the title or abstract in 1998, and just one refers to these words in 1999. However, the number of times these phrases appeared increased more than a thousand times since then. For comparison, the database size only increased 3.3 fold in the same period. Nowadays, there are scientific journals dedicated to stewardship programs, and the role of human educational behavior is increasingly considered in this field, as is the case of JAC-Antimicrobial Resistance from the British Society for Antimicrobial Chemotherapy, launched in 2019 and dedicated to "Education and research in antimicrobial stewardship and resistance".

Antibiotic stewardship programs require a multidisciplinary approach

According to WHO [17], the total consumption of antibiotics among 45 European and Asian countries and Kosovo varied considerably (data from 2015). The median value of antibiotic consumption was 17.9 (IQR: 14.5–24.3) defined daily doses (DDD) per 1000 inhabitants per day, ranging from 7.7 DDD per 1000 inhabitants per day in Azerbaijan to 38.2 DDD per 1000 inhabitants per day in Turkey [17]. A recent study in the UK has revealed significant variability in antibiotic prescription even within a single country, both between and within practices [18]. Epidemiological factors would not be able to explain the disparities in antibiotic consumption across countries, between regions within countries [19], or across prescribers [20]. Other factors must play significant roles, including psychological, sociological, or cultural differences, and one can find differences among patients or prescribers. In the line that is proposed in this work, several researchers have proposed to include other areas of knowledge in these teams, including sociology, anthropology, economics, political sciences, and psychology [21–26]. In particular, behavioral sciences can help deal with the antibiotic-resistance crisis with quantitative and qualitative methods.

Qualitative studies focus on answers to "what, how, and why?" questions type, while quantitative studies focus on "how many, how much, and how often?" questions [27]. We need all question types. Two recent papers by Borek et al. [28] and Wanat et al. [27] highlighted the opportunities given by behavioral sciences (health psychology) and their qualitative methods to mitigate antibiotic resistance (hence, joining efforts to knowledge derived from quantitative methods). Some studies use both quantitative and qualitative methods. Moreover, hypothesis-driven strategies may prove highly helpful, and if successful, these hypotheses may end up fruitful beyond their original scope.

An interesting example is provided by the superimposition of antibiotic consumption by countries [17,29,30] and their cultural values, including religion [31] (Figure 1). The Inglehart-Welzel cultural maps of the world [32] consider two major dimensions of cross-cultural variation. First, "traditional versus secular-rational values". Traditional values emphasize the importance of religion (the Latin verb *religare* means "to bind"), and consequently child-parent submission ties, deference to authority, absolute standards, and traditional family values; secular-rational values have the opposite preferences to these traditional values. Second, "survival versus self-expression

values". Survival values emphasize economic and physical (life-death) security; self-expression values prioritize subjective well-being, self-expression, and quality of life, and a shift in child-rearing values from an emphasis on hard work towards freedom, imagination and tolerance.

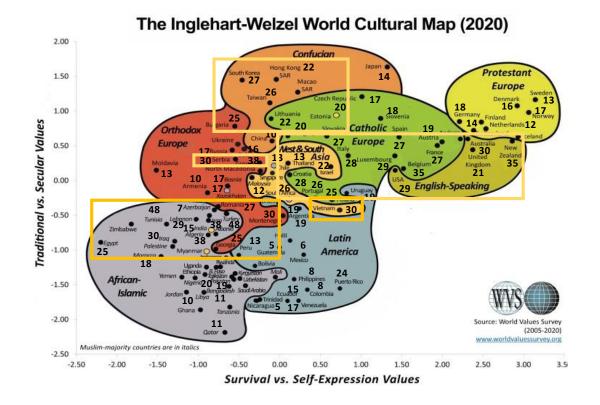


Figure 1. Antibiotic consumption (DDDs/1000 inhabitants/day) per country (numbers in black) during the last 10-15 years versus human values in the different cultural-geographical regions of the world. Figure adapted from [33], where yellow boxes indicate the ensembles of countries with consistently higher values of antibiotic consumption. Most numbers were obtained from Klein et al. [30], and, because of the changing rates along the last decade (to less consumption, particularly in Europe), some of them might somewhat differ in some cases from other sources, but the differences between countries (more or less consumption) are essentially maintained among culturally separated countries.

Certainly, such a comparison of values and antibiotic consumption indicates that antibiotic policies, including antibiotic stewardship, should be specifically designed accordingly to sociocultural differences among countries, in a sense, with social psychology. Antibiotic consumption is highly dependent on local social norms [34].

With few exceptions, Psychology has been outside the scope of antibiotic stewardship programs. When they do, they often focus on the psychological characteristics of professionals who prescribe or develop antibiotics. For example, fear of failure or risk-averse may impact the likelihood of antibiotic prescription by general practitioners (GPs) [35]. Fear of antibiotic toxicity might, in some cases, inappropriately overcome the fear of death by severe infection, which has negatively influenced the development of potentially useful antimicrobials, something that has not occurred in anticancer therapy [36].

Michel-Lepage et al. analyzed antibiotic prescriptions by GPs for tonsillitis in France. Both viruses and group A *Streptococcus* are causative agents of tonsillitis in children, and a "Rapid Antigen Diagnostic Test" (RADT) distinguishes the two. GPs unwilling to accept uncertainty and risks (risk-averse GPs) used RADTs more often; moreover, GPs would be more likely to prescribe antibiotics when RADTs were not used [35]. Medical doctors may also be concerned about future complications [37]. Moreover, older general practitioners prescribe antibiotics more often than younger ones [38]. In a review discussing the missing links of antimicrobial stewardship programs, Charani et al. remind us that already in the 1970s, antibiotics were characterized as 'drugs of fear' because frequently, doctors may choose to prescribe broad-spectrum antibiotics and more prolonged than the necessary duration of treatment [39].

Studies with control groups to learn if there are psychological differences between patients who leave health appointments with an antibiotic prescription and those who do not are scarce. For example, a study found that participants with a Catholic background (Catholic Flemish) trusted and used more antibiotics than those with a Protestant background (Protestant Flemish) and that the former feared more complications than Protestants if no medications were used. This difference resulted in higher use of antibiotics by the Catholics than by Protestant participants [40]. Such

religious values correlate with the frequency of antibiotic resistance, and differences in consumption were interpreted as "my health and my children's health should be assured by others, and I should loudly claim for help" (Catholics) or "I am personally responsible for decisions concerning my health and the health of my family, and my emotions should be repressed, as I am the responsible for the action" (Protestants) [31]. Therefore, individual cultural differences impact the likelihood of antibiotic use [40]. Moreover, the probability of a patient receiving antibiotic treatment increases with the number of antibiotic prescriptions the patient received in the previous year or years [18,41]. Some studies indicate that medical doctors tend to overrate patients' expectations of antibiotic prescription [42–44]. In this last factor, we have psychological factors of both the patient and the medical doctor. Furthermore, the odds of patients receiving inappropriate antibiotic prescriptions (e.g., for acute respiratory tract infection caused by viruses) is higher when the patient is of working age (e.g., [45–47]. Therefore, time pressure, perhaps linked to uncertainty, also increases the probability of antibiotic usage.

The impact of patients' psychology in drug prescription: the special case of pediatric populations

Pediatric appointments can be even more complex because at least a third person is involved, the patient's caregiver. An infant, the respective caregiver, and the doctor interact to solve the infant's complaints. It is reasonable to assume that the psychological characteristics of all of them may have a role in the likelihood of antibiotic prescription. Infants are under stress because they are ill and in a strange place (the medical office) and close to a stranger (the doctor). The respective caregiver (usually the mother or the father) may also be under stress, worried about the child, and perhaps feeling the obligation to go to work ([45–47]).

Recent studies involving infants and their mothers demonstrated how promising Developmental Psychology could be for antibiotic stewardship programs. For example, Fuertes et al. [48] have shown that antibiotic prescriptions in the first nine months of life tend to be more likely in a particular group of infants than the other infants. The odds are impressive: for these children (ambivalent insecurely-attached infants to their mothers – see below and Boxes 2 and 3), the odds of antibiotic consumption were 25 times higher (95% confidence interval, 7.01–89.40) than in

other children. These infants tend to over externalize their emotions in the presence of threat or under stress (e.g., when ill, scared, or frustrated). In this inconsistent behavior, they alternate between a seeking proximity posture and rejecting their caregiver's affection (Box 2). Additionally, mothers' behavior may also help anticipate whether their infants are likely to take or to have taken antibiotics in the first nine months of life [48].

But how can parenting and human attachment (Boxes 2 and 3, and Figure 2) be associated with antibiotic uptake?

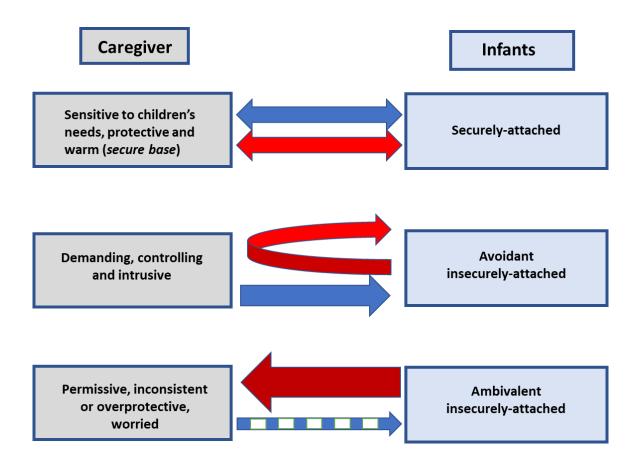


Figure 2. Caregiving and Mother-infant patterns of attachment. The grey boxes on the left side correspond to different caregiving styles, and the blue boxes on the right side illustrate the infant attachment patterns according to Bowlby [49] and Ainsworth [50]. Blue arrows represent the strength and direction of caregiving. In the case of secure attachment, the arrow is bidirectional because relationships are reciprocal and mutually engaged. The intermittent arrow of ambivalent attachment represents the caregiver's inconsistent response. Red arrows represent the infant attachment behavior, which is a behavioral strategy to cope with adults' caregiving. Infants with an ambivalent attachment communicate their needs intensively when facing the inconsistent response from their caregivers – this is represented with a robust red arrow. Avoidants turn to themselves to find means to solve their needs.

Given the tendency of insecurely-ambivalent infants to inflate emotions near their caregivers and health professionals (see Box 3), Fuertes et al. [48] hypothesized that that behavior pattern could lead to antibiotic use in the first nine months. Indeed, 89.7% (26 out of 29) of ambivalent insecurely-attached infants, contrasting with 25.7% (27 out of 105) of the other infants, i.e., of insecurely-attached avoidant and securely-attached infants (Figure 3A) [48].

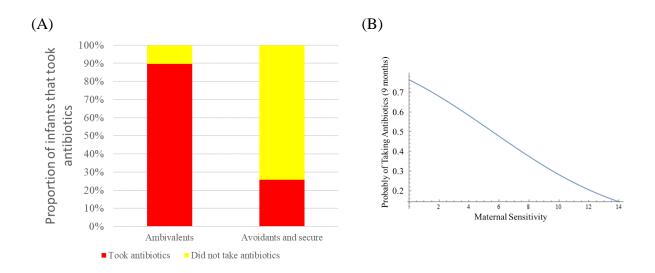


Figure 3. Likelihood of taking antibiotics depends on the mother-infant relationship. (a) In the first nine months of life, the odds of consuming antibiotics among insecurely-ambivalent attached infants were 25 times higher (95% confidence interval, 7.01–89.40) than among infants with the other two attachment patterns combined (secure and insecure-avoidant). See the text for definitions. Data from Fuertes et al. [48]. (b) Relationship between maternal sensitivity and antibiotic consumption in the first nine months of the infant. Fuertes et al. (2020) performed a binary logistic regression analysis showing that maternal sensitivity (scored between 0 and 14) predicts antibiotic uptake in the nine months of the baby's life with $\beta = -0.21$ and the constant C = 1.167. The line represents $\frac{1}{1+e^{-(C+\beta.m)}}$, which is the probability that the infant takes antibiotics in the first nine months of life, and *m* is maternal sensitivity [48]. In this research, the CARE-Index protocol was used to assess maternal sensitivity by observing the mother-infant interaction when infants are 9-months [51]. This method defines maternal sensitivity as any behavior that satisfies the infant by reducing distress and disengagement and increasing the infant's comfort and attentiveness [51].

The attachment relationship between infants and their caregivers starts as soon as birth. Therefore, an insecure-ambivalent mother-infant attachment originates pretty early and results from daily interactions with caregivers. For example, mothers of insecure-ambivalent infants are more unresponsive in free play than the other mothers, and mothers of securely attached infants are more sensitive to their infants during free play [52–54]. Developmental psychologists define maternal sensitivity as the mother's ability to read and interpret an infant's solicitations and stressful signals and her ability to comfort the infant [55–58]. Of course, many factors play a critical role in maternal sensitivity, namely family socioeconomic status (SES), maternal education, parents' mental health, number of family risk factors, or parental stress. A binary logistic regression analysis has shown that maternal sensitivity predicts antibiotic uptake in the first nine months of the infant's life [48] (Figure 3B).

In another study, Stern et al. found that the odds of antibiotic use in the first 12 months of the infant's life also decrease with maternal sensitivity, defined as the extent to which the mother promptly and appropriately responds to the infant's signals and needs [59]. The size effect of this relation was low, and there are at least two explanations for that. The proportion of the three attachment patterns among infants in this study is unknown. However, maternal sensitivity is higher for both insecurely-attached infants (avoidants and ambivalents) patterns [57], whereas the odds for antibiotic use are higher only for ambivalent infants [48]. Therefore, if the proportion in the sample of insecure-avoidant infants is high or the proportion of insecure-ambivalent infants is low, the impact of maternal sensitivity on antibiotic use should become less clear. An alternative explanation is related to the fact that Stern et al. performed their study in the Netherlands and Fuertes et al. in Portugal. The antibiotic prescription rate in 2015 in the Netherlands was one of the lowest in the European region, with 9.78 defined daily doses (DDDs) per 1000 inhabitants per day, whereas Portugal consumed almost the double, 17.72 DDDs per 1000 inhabitants per day [17]; in Figure 1, the estimated consumptions were 12 and 26 DDDs, respectively, showing that differences are proportional in most studies. With lower number of prescriptions in the Netherlands, the impact of maternal sensitivity on antibiotic prescription may fade away.

The formerly presented (Figure 1) Inglehart-Wenzel World Cultural Map reflects such differences. Indeed, four studies in the Netherlands found that only 3.7% to 10.8% of infants were ambivalentattached [60], against 19.5% (25/108) or 21.6% (29/134) in two recent Portuguese studies performed with independent samples [48,61]. These results suggest that ambivalent attachment behavior should be more frequent in countries with more antibiotic consumption, mainly when antimicrobials are easily available by public health services. Although many factors affect attachment organization (since the reasons for children's stress are multiple, not only being sick), it would be interesting to study the association between antibiotic consumption and the prevalence of attachment patterns across cultures. For example, studies performed in Sweden and Germany ("European Protestant" countries that stand together in Figure 1) with low antibiotic consumption (Figure 1) also indicated low proportions of ambivalent-attached infants, 3.9% (2 ambivalentattached out of 51 infants) and 9.8% (7/71), respectively [62,63]. In contrast, ambivalent attachment in Israel is overrated in both Arabic (13%) and Jewish (26%) samples [64,65]. Yet, the effect of religion is not clear-cut; family socioeconomic status and parents' educations have large contributions to the attachment patterns prevalence [65]. Moreover, unfortunately, most studies indicating the proportion of attachment patterns across countries were published many years ago, show a high heterogeneity between samples within countries, and/or were performed with small samples that may not mirror the whole country [60,64–66]. Studies comprising large and representative samples in each country could unveil the relationship between cultural factors, religion and traditional factors, parenting, and health practices. However, the "ambivalentattached" behavior of children might reflect the "ambivalent" cultural attitudes of the societies, particularly those where the secular-rational values of "modernity" and self-expression coexist with the traditional, secular values that assure survival under extreme circumstances. These ambivalent societies occupy the central part of the Inglehart-Wenzel World Cultural Map (figure 1), and are associated with a consistent over-use of antibiotics. Children are crying for an antibiotic, but society is responsive to this demand.

Conclusion

Antibiotics are the most frequent medications prescribed in the pediatric population [67–71], which is unfortunate because antibiotic usage contributes to drug resistance and may have individual adverse effects. On the other hand, pediatric antimicrobial stewardship programs have

successfully decreased antibiotic use, healthcare costs, and antibacterial resistance in both inpatient and outpatient settings.

Many studies have shown that several factors impact the likelihood of antibiotic prescription, rather than only health factors or medical indicators. For example, the quality of attachment to the caregivers in the first year of life correlates with antibiotics prescription. The mechanisms involved in these associations are still unclear, but perhaps there is a complex interaction between children's strategies to obtain care and relief when ill and the parents' ability (or difficulty) to meet their needs and support children in self-regulating during sickness. Such behaviors may trigger infants' and parents' distress and children's overreactions, leading to miscommunication of symptoms to health professionals. These processes are far from being understood, creating the need for new longitudinal research lines that include new dimensions, namely infants' and caregivers' psychology.

Antibiotic stewardship programs already involve multidisciplinary teams, mainly composed of medical doctors, nurses, and pharmacists, but the battle against the pandemics of antibiotic resistance could improve significantly by including other areas of knowledge, as several previous studies have already demonstrated [24,72–75]. The works discussed here indicate that, beyond physical factors, individual psychological differences between patients or between patients' caregivers impact antibiotic prescription. We suggest that these "attachment psychological dynamics" reflect the societies' cultural attitudes, and those countries where rational-modernity behaviors coexist with traditional values are expected to have an ambivalent behavior leading to higher antibiotic consumption. Further studies in Psychology should clarify the role of caregivers and infants, including their relationship types and their behavior in the diagnosis during visits to medical offices.

Box 1: Individual benefits and disadvantages of antibiotic use

Benefits

Antibiotics have transformed modern medical and veterinary sciences since the second half of the 20th century [76]. Firstly, antibiotics have been precious in treating bacterial infections. For example, in early times, with penicillin only, the mortality rate associated with pneumococcal pneumonia decreased by about four to eightfold [77,78]. In our days, the mass distribution of a broad-spectrum antibiotic agent to preschool children has reduced mortality in areas of sub-Saharan Africa [79]. Secondly, antibiotics have not only decreased the infective morbidity, but helped perform medical procedures like complicated surgeries, organ transplantation, intensive care, and anticancer chemotherapy [80]. Finally, a formerly unexpected benefit (in this case for human nutrition) beyond these two health-related: antimicrobials are suitable growth promoters in livestock [81,82]. The individual feeling about benefits is based on the prestige of antibiotics as the *only* curing agents, preventing severe illnesses, blocking transmissible diseases and mitigating the symptoms of the infection without major risks of toxicity.

Disadvantages

The negative consequences of overuse of antibiotics on human health of human communities have been extensively published, being mostly focused on toxicity and the selection of antibiotic-resistant bacteria, but environmental damage of the microbiosphere cannot be discarded. The risks-versus-benefits for the individual have been scarcely treated, and should include the cumulative effect of antibiotic exposure along life, increasing the risk of carrying multiresistant opportunistic bacteria, eventually lethal in elderly pathological events [83]. The consequences of multi-exposure to antibiotics could resemble chronic hypercholesterolemia, high blood pressure or diabetes. Antibiotic abuse in children is particularly frequent, critically involving social norms and mother-child behavioral cultures. but might have negative consequences. A study involving a large children cohort from the USA has revealed a positive association between antibiotic prescription in the first six months of infants' life and the development of asthma and allergy when they are six years old [84]. A study involving several thousands of dyads of infants with their mothers found a positive association between antibiotic prescription in the first six months of life and an increased probability of overweight at seven years old among children whose mothers had an average healthy weight, indicating the role of early damage of individual microbiota [85] [86] [87]. Bile acid metabolism influenced by altered microbiota composition is likely associated with this body mass increase [87,88], recalling the effect of antibiotics to increase weight in farm animals [89]. Moreover, antibiotic uptake increases pathogens' susceptibility and is related to several health conditions such as inflammatory bowel disease, rheumatoid arthritis, type 1 diabetes, and atopy [90–95]. At individual level, negative beliefs about antibiotics include fear of toxicity, frailty, and general weakness.

Box 2 – Patterns of infant attachment to caregivers

Human beings are prone to become attached to caregivers (primarily mothers/fathers) during their first year of life [49]. Across human cultures, the quality of attachment affects all areas of individual development, from socialization and close relationships to language or cognitive development. A body of research has shown that infants' quality of early care becomes internalized, forming maps of representation of their own self, others' behavior, and relationships, and shaping infants' social functioning from early ages to adulthood [96,97]. Children can function in the world with confidence if they can develop trust in the accessibility and reliability of their attachment figures. This confidence results from secure relationships between the infant and their main caregivers [49].

However, infants must use different behavioral strategies to maintain a close proximity with caregivers. Children learn to adapt their behavior according to their caregivers' responses during infancy. Accordingly, Bowlby found that some infants are **securely attached** to their caregivers, while others are insecurely attached [49]. Securely attached infants tend to exhibit their emotions and intentions openly by spontaneous communication of their needs or seeking closer contact with caregivers. By using their caregiver as a secure base for exploration, securely attached infants are easily comforted. In contrast, **insecurely-attached** stressed infants do not rely on a secure base. Securely-attached children and adolescents have better academic outcomes, more friends at school, and positive relationships with their loved ones [98].

In the late sixties and seventies, Mary Ainsworth developed an experimental protocol denominated Strange Situation to study attachment behavior [50]. The Strange Situation paradigm consists of an experimental protocol that takes 21 minutes and is composed of eight episodes where the central idea is to observe the reaction under mild but increasing levels of stress on the infant. In this protocol, the infant is introduced to a strange playroom, interacts with an unfamiliar adult (the stranger), and is submitted to brief separations from and reunions with the parent [50,97].

Using this experimental paradigm, Ainsworth found two main patterns among insecurely attached infants, and they are somewhat opposite to each other [50,55]. **Insecurely-attached**

avoidant (or simply avoidant) infants likely avoid proximity with their attachment figures by over-activating the exploratory system (e.g., playing with toys). In contrast, **ambivalent insecurely-attached** infants (or simply ambivalent infants) tend to show contradictory behaviors, trying to attract the attention of their caregivers, but simultaneously showing their angriness for presumed lack of response, including some resistance to physical contact [53,54]. For a review, see Cassidy and Shaver [97].

Box 3: Ambivalent insecurely-attached infants: crying for antibiotics!

The experience of illness and pain trigger attachment behavior because, in these circumstances, individuals are under stress and threat and claim help from caregivers [49]. Caregivers frequently respond by providing means to lessen infants' pain. However, some caregivers respond to infants' needs with the conviction of children's potential for endurance and self-healing and inconsistency, anxiety, or simply no interaction [57,97]. In response to this caregiver's behavior, these infants tend to **amplify emotional displays**, a typical behavior pattern of ambivalent insecurely-attached infants, expressing anxiety responses with heavy crying, inability to self-soothe, or strong motor reactions [99]. They oscillate with behaviors of proximity seeking, contact, and desire for comfort, aiming at getting responses and attention from caregivers [55,100].

Patients' insecurity and anxiety impact patient-doctor interaction. A study involving infants aging between 6 and 32-months found no differences between the prevalence of otitis in securely and insecurely attached infants [101]. However, mothers of insecurely-attached infants become more anxious and have more negative perceptions of their infants' health conditions [101]. Furthermore, insecure-ambivalent individuals have higher symptom-reporting and request more health visits [102–104]. However, this can be mitigated by alternative supporting attitudes of caregivers and doctors.

One possible explanation is that medical consultations are often stressful situations. In the case of pediatric appointments, infants are ill, their parents are often stressed, and someone unknown

to the infant (health professional(s)) provides intrusive care. Unfortunately, this stress might impact pediatric consultations and infant evaluation, mainly in the case of insecurely-attached infants. To prevent this effect, pediatric teams often adopt personal and friendly postures when in contact with children [105].

References

- 1 Kunin, C.M. et al. (1973) Use of Antibiotics. Ann Intern Med 79, 555–560
- 2 Neu, H.C. (1992) The crisis in antibiotic resistance. *Science* 257, 1064–1073
- 3 Murray, C.J. *et al.* (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 399, 629–655
- 4 Laxminarayan, R. (2022) The overlooked pandemic of antimicrobial resistance. *The Lancet* 399, 606–607
- 5 Laxminarayan, R. *et al.* (2016) Access to effective antimicrobials: a worldwide challenge. *The Lancet* 387, 168–175
- 6 Pezzani, M.D. *et al.* (2021) Methodological quality of studies evaluating the burden of drug-resistant infections in humans due to the WHO Global Antimicrobial Resistance Surveillance System target bacteria. *Clinical Microbiology and Infection* 27, 687–696
- 7 Andersson, D.I. and Hughes, D. (2014) Microbiological effects of sublethal levels of antibiotics. *Nature reviews. Microbiology* 12, 465–478
- 8 Andersson, D.I. and Hughes, D. (2017) Selection and Transmission of Antibiotic-Resistant Bacteria. *Microbiol Spectr* 5,
- 9 Patrick, D.M. and Hutchinson, J. (2009) Antibiotic use and population ecology: How you can reduce your "resistance footprint." *CMAJ* 180, 416–421
- 10 Goossens, H. *et al.* (2005) Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *The Lancet* 365, 579–587
- 11 Davies, J. and Davies, D. (2010) Origins and Evolution of Antibiotic Resistance. *Microbiol Mol Biol Rev* 74, 417–433
- 12 Megraud, F. *et al.* (2021) Helicobacter pylori resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. *Gut* 70, 1815–1822
- 13 Baquero, F. (2021) Threats of antibiotic resistance: an obliged reappraisal. *Int Microbiol* 24, 499–506
- 14 Goff, D. (2022) BSAC Vanguard Series: The future of antibiotic stewardship-managing access and excess. *J Antimicrob Chemother* 77, 863–864
- 15 Shlaes, D.M. *et al.* (1997) Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. *Clin Infect Dis* 25, 584–599
- 16 Shlaes, D.M. *et al.* (1997) Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: Guidelines for the Prevention of Antimicrobial Resistance in Hospitals. *Infection Control and Hospital Epidemiology* 18, 275–291
- 17 WHO (2018) WHO report on surveillance of antibiotic consumption: 2016-2018 early implementation.,
- 18 Palin, V. *et al.* (2019) Antibiotic prescribing for common infections in UK general practice: variability and drivers. *J Antimicrob Chemother* 74, 2440–2450
- 19 Cars, O. *et al.* (2001) Variation in antibiotic use in the European Union. *Lancet* 357, 1851–1853
- 20 Cordoba, G. *et al.* (2015) Prescribing style and variation in antibiotic prescriptions for sore throat: cross-sectional study across six countries. *BMC Fam Pract* 16, 7
- 21 Furuya, E.Y. and Lowy, F.D. (2006) Antimicrobial-resistant bacteria in the community setting. *Nat Rev Microbiol* 4, 36–45

- 22 Charani, E. *et al.* (2014) The Role of Behavior Change in Antimicrobial Stewardship. *Infectious Disease Clinics* 28, 169–175
- 23 Tonkin-Crine, S. *et al.* (2015) Contribution of behavioural science to antibiotic stewardship. *BMJ* 350, h3413
- 24 Lorencatto, F. *et al.* (2018) Driving sustainable change in antimicrobial prescribing practice: how can social and behavioural sciences help? *J Antimicrob Chemother* 73, 2613–2624
- 25 Bassetti, M. *et al.* (2019) Challenges and research priorities to progress the impact of antimicrobial stewardship. *Drugs Context* 8, 212600
- 26 Cuevas, C. *et al.* (2021) Improving antibiotic use through behaviour change: a systematic review of interventions evaluated in low- and middle-income countries. *Health Policy and Planning* 36, 754–773
- 27 Wanat, M. *et al.* (2022) The value, challenges and practical considerations of conducting qualitative research on antimicrobial stewardship in primary care. *JAC-Antimicrobial Resistance* 4, dlac026
- 28 Borek, A.J. *et al.* (2022) How can behavioural science contribute to qualitative research on antimicrobial stewardship in primary care? *JAC-Antimicrobial Resistance* 4, dlac007
- 29 Browne, A.J. *et al.* (2021) Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study. *The Lancet Planetary Health* 5, e893–e904
- 30 Klein, E.Y. *et al.* (2018) Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences* 115, E3463–E3470
- 31 Baquero, F. *et al.* (2002) Antibiotic consumption and resistance selection in Streptococcus pneumoniae. *J Antimicrob Chemother* 50 Suppl S2, 27–37
- 32 Inglehart, R.F. (2022) The Inglehart-Welzel World Cultural Map. at http://www.worldvaluessurvey.org/
- Inglehart, R.F. *et al.*, eds. World Values Survey: 7th round- Country-Pooled Datafile. .
 (2022), Madrid: JD Systems Institute.
- 34 Hernando-Amado, S. *et al.* (2020) Antibiotic Resistance: Moving From Individual Health Norms to Social Norms in One Health and Global Health. *Front Microbiol* 11, 1914
- 35 Michel-Lepage, A. *et al.* (2013) Cross-sectional survey: risk-averse French GPs use more rapid-antigen diagnostic tests in tonsillitis in children. *BMJ Open* 3, e003540
- 36 Rolain, J.M. and Baquero, F. (2016) The refusal of the Society to accept antibiotic toxicity: missing opportunities for therapy of severe infections. *Clin Microbiol Infect* 22, 423–427
- Little, P. *et al.* (1997) Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *Brit Med J* 315, 350–352
- 38 Wang, K.Y. *et al.* (2009) Which practices are high antibiotic prescribers? A cross-sectional analysis. *Br J Gen Pract* 59, e315–e320
- 39 Charani, E. *et al.* (2010) Antibiotic stewardship programmes—what's missing? *Journal of Antimicrobial Chemotherapy* 65, 2275–2277
- 40 Deschepper, R. *et al.* (2002) Cross-cultural differences in lay attitudes and utilisation of antibiotics in a Belgian and a Dutch city. *Patient Educ Couns* 48, 161–169
- 41 Shallcross, L. *et al.* (2017) Antibiotic prescribing frequency amongst patients in primary care: a cohort study using electronic health records. *Journal of Antimicrobial Chemotherapy* 72, 1818–1824

- 42 Macfarlane, J. *et al.* (1997) Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *BMJ* 315, 1211–1214
- 43 Butler, C.C. *et al.* (1998) Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 317, 637–642
- 44 Sirota, M. *et al.* (2017) Expectations for Antibiotics Increase Their Prescribing: Causal Evidence About Localized Impact. *Health Psychol* 36, 402–409
- 45 Dekker, A.R.J. *et al.* (2015) Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. *Fam Pract* 32, 401–407
- 46 Denny, K.J. *et al.* (2019) Appropriateness of antibiotic prescribing in the Emergency Department. *Journal of Antimicrobial Chemotherapy* 74, 515–520
- 47 Kimura, Y. *et al.* (2019) Longitudinal trends of and factors associated with inappropriate antibiotic prescribing for non-bacterial acute respiratory tract infection in Japan: A retrospective claims database study, 2012–2017. *PLOS ONE* 14, e0223835
- 48 Fuertes, M. *et al.* (2020) Maternal sensitivity and mother-infant attachment are associated with antibiotic uptake in infancy. *J Health Psychol* DOI: 10.1177/1359105320941245
- 49 Bowlby, J. (1969) Attachment and loss., IPenguin Book.
- 50 Ainsworth, M.D.S. *et al.* (1978) *Patterns of attachment A Psychological Study of the Strange Situation.*, Lawerence Erlbaum Associates.
- 51 Crittenden, P.M. (2003) CARE-Index Manual, Family Relations Institute.
- 52 Belsky, J. (1999) Interactional and contextual determinants of attachment security. In *Handbook of attachment: Theory, research, and clinical implications*. (Cassidy, J. and Shaver, P. R., eds), pp. 249–264, The Guilford Press
- 53 DeWolff, M.S. and van Ijzendoorn, M.H. (1997) Sensitivity and attachment: A metaanalysis on parental antecedents of infant attachment. *Child Dev* 68, 571–591
- 54 Lucassen, N. *et al.* (2011) The Association Between Paternal Sensitivity and Infant-Father Attachment Security: A Meta-Analysis of Three Decades of Research. *J Fam Psychol* 25, 986–992
- 55 Ainsworth, M.D.S. *et al.* (1974) Infant-mother attachment and social development: Socialization' as product of reciprocal responsiveness to signals. In *The integration of a child into a social world* (Richards, M., ed), pp. 9–135, Cambridge University Press
- 56 Braungart-Rieker, J.M. *et al.* (2001) Parental sensitivity, infant affect, and affect regulation: Predictors of later attachment. *Child Dev* 72, 252–270
- 57 Beeghly, M. *et al.* (2011) Maternal sensitivity in dyadic context: Mutual regulation, meaning-making, and reparation. In *Maternal sensitivity: A scientific foundation for practice.* (Davis, D. W. and Logsdon, M. C., eds), pp. 59–83, Nova Science Publishers
- 58 Mesman, J. *et al.* (2012) Parental sensitivity to infant distress: what do discrete negative emotions have to do with it? *Attach Hum Dev* 14, 337–348
- 59 Stern, J.A. *et al.* (2020) Beyond Early Adversity: The Role of Parenting in Infant Physical Health. *J Dev Behav Pediatr* 41, 452–460
- 60 Van IJzendoorn, M.H. and Kroonenberg, P.M. (1988) Cross-cultural patterns of attachment: A meta-analysis of the strange situation. *Child Development* 59, 147–156
- 61 Barbosa, M. *et al.* (2021) Emerging patterns of infant regulatory behavior in the Still-Face paradigm at 3 and 9 months predict mother-infant attachment at 12 months. *Attachment & Human Development* 23, 814–830

- 62 Lamb, M.E. *et al.* (1982) Security of mother- and father-infant attachment and its relation to sociability with strangers in traditional and nontraditional Swedish families. *Infant Behavior and Development* 5, 355–367
- 63 Rauh, H. *et al.* (2000) Stability and change in infant-mother attachment in the second year of life: Relations to parenting quality and varying degrees of day care experience. In *The Organization of Attachment Relationships: Maturation, Culture, and Context* (Crittenden, P. M. and Claussen, A. H., eds),
- 64 van Ijzendoorn, M.H. and Sagi-Schwartz, A. (2008) Cross-cultural patterns of attachment: Universal and contextual dimensions. In *Handbook of attachment: Theory, research, and clinical applications*. (Cassidy, J. and Shaver, P. R., eds), pp. 880–905, The Guilford Press
- 65 Mesman, J. *et al.* (2016) Cross-cultural patterns of attachment. *Handbook of attachment: Theory, research, and clinical applications*
- Gloger-Tippelt, G. *et al.* (2000) "Strange-Situation"-Studies in German Speaking Countries: An Overview. In *Psychologie in Erziehung und Unterricht (PEU)* 47 (Crittenden, P. M. and Claussen, A. H., eds), pp. 87–98
- 67 Sturkenboom, M.C.J.M. *et al.* (2008) Drug use in children: cohort study in three European countries. *BMJ* 337, a2245
- 68 Hersh, A.L. *et al.* (2011) Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics* 128, 1053–1061
- 69 Chai, G. *et al.* (2012) Trends of outpatient prescription drug utilization in US children, 2002-2010. *Pediatrics* 130, 23–31
- 70 Stam, J. *et al.* (2012) Antibiotic use in infants in the first year of life in five European countries. *Acta Paediatrica, International Journal of Paediatrics* 101, 929–934
- 71 Holstiege, J. and Garbe, E. (2013) Systemic antibiotic use among children and adolescents in Germany: A population-based study. *European Journal of Pediatrics* 172, 787–795
- 72 Deschepper, R. *et al.* (2008) Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? *BMC Health Serv Res* 8, 123
- 73 Grigoryan, L. *et al.* (2008) Determinants of self-medication with antibiotics in Europe: The impact of beliefs, country wealth and the healthcare system. *Journal of Antimicrobial Chemotherapy* 61, 1172–1179
- 74 Hulscher, M.E. *et al.* (2010) Antibiotic prescribing in hospitals: a social and behavioural scientific approach. *The Lancet Infectious Diseases* 10, 167–175
- 75 Krockow, E.M. *et al.* (2022) Prosociality in the social dilemma of antibiotic prescribing. *Current Opinion in Psychology* 44, 164–169
- Hutchings, M.I. *et al.* (2019) Antibiotics: past, present and future. *Current Opinion in Microbiology* 51, 72–80
- 77 Tomasz, A. (1997) Antibiotic Resistance in Streptococcus pneumoniae. *Clinical Infectious Diseases* 24, S85–S88
- 78 Singer, M. et al. (2008) Historical and Regulatory Perspectives on the Treatment Effect of Antibacterial Drugs for Community-Acquired Pneumonia. CLIN INFECT DIS 47, S216– S224
- 79 Keenan, J.D. *et al.* (2018) Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa. *New England Journal of Medicine* 378, 1583–1592
- 80 Laxminarayan, R. *et al.* (2013) Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases* 13, 1057–1098
- 81 Cully, M. (2014) Public health: The politics of antibiotics. *Nature* 509, S16–S17

- 82 Rushton, J. (2015) Anti-microbial Use in Animals: How to Assess the Trade-offs. *Zoonoses and Public Health* 62, 10–21
- 83 Baquero, F. (2007) Evaluation of risks and benefits of consumption of antibiotics: from individual to public health. In *Encyclopedia of Infectious Diseases: Modern Methodologies* (Tibayrenc, M., ed), John Wiley and Sons, Hoboken, New Jersey.
- Risnes, K.R. *et al.* (2011) Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. *American journal of epidemiology* 173, 310–8
- 85 Ajslev, T.A. *et al.* (2011) Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *International journal of obesity* 35, 522–9
- 86 Saari, A. *et al.* (2015) Antibiotic Exposure in Infancy and Risk of Being Overweight in the First 24 Months of Life. *Pediatrics* 135, 617–626
- 87 Korpela, K. *et al.* (2016) Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nat Commun* 7, 10410
- 88 Vrieze, A. *et al.* (2014) Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity. *Journal of Hepatology* 60, 824–831
- 89 Cox, L.M. (2016) Antibiotics shape microbiota and weight gain across the animal kingdom. Animal Frontiers 6, 8–14
- 90 Russell, S.L. *et al.* (2012) Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep* 13, 440–447
- 91 Giorgio, V. *et al.* (2013) Pediatric non alcoholic fatty liver disease: Old and new concepts on development, progression, metabolic insight and potential treatment targets. *BMC Pediatrics* 13,
- 92 Francino, M.P. (2016) Antibiotics and the Human Gut Microbiome: Dysbiose sand Accumulation of Resistances. *Front Microbiol* 6,
- 93 Gensollen, T. *et al.* (2016) How colonization by microbiota in early life shapes the immune system. *Science* 352, 539–544
- 94 Livanos, A.E. *et al.* (2016) Antibiotic-mediated gut microbiome perturbation accelerates development of type 1 diabetes in mice. *Nat Microbiol* 1, 1–13
- 95 Jian, C. *et al.* (2021) Early-life gut microbiota and its connection to metabolic health in children: Perspective on ecological drivers and need for quantitative approach. *eBioMedicine* 69,
- 96 Bowlby, J. (1973) Attachment and loss: Separation, 3rd Printing edição., 2Basic Books.
- 97 Cassidy, J. and Shaver, P.R. (2018) *Handbook of Attachment Theory, Research, and Clinical Applications*, (3rd edn) Guilford Press.
- 98 Sroufe, L.A. (2005) Attachment and development: A prospective, longitudinal study from birth to adulthood. *Attachment & Human Development* 7, 349–367
- 99 Barbosa, M. et al. (2018) Robust Stability and Physiological Correlates of Infants' Patterns of Regulatory Behavior in the Still-Face Paradigm at 3 and 9 Months. *Dev Psychol* 54, 2032–2042
- 100 Bretherton, I. (1992) The Origins of Attachment Theory Bowlby, John and Ainsworth, Mary. *Dev Psychol* 28, 759–775
- 101 McCallum, M.S. and McKim, M.K. (1999) Recurrent Otitis Media and Attachment Security: A Path Model. *Early Education and Development* 10, 517–534
- 102 Andrews, N.E. *et al.* (2011) Adult attachment and reports of pain in experimentally-induced pain. *Eur J Pain* 15, 523–530

- 103 Feeney, J.A. (2000) Implications of attachment style for patterns of health and illness. *Child Care Hlth Dev* 26, 277–288
- 104 Meredith, P. *et al.* (2008) A review of the evidence linking adult attachment theory and chronic pain: Presenting a conceptual model. *Clin Psychol Rev* 28, 407–429
- 105 Levetown, M. and and the Committee on Bioethics (2008) Communicating With Children and Families: From Everyday Interactions to Skill in Conveying Distressing Information. *Pediatrics* 121, e1441–e1460