

1 **Psychological and Cultural Factors Influencing Antibiotic**  
2 **Prescription**

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21 **Abstract**

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

32

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

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## **The pandemics of antibiotic resistance**

41 The use of antibiotics may have positive but also negative consequences (see Box 1). Already 50  
42 years ago, some hospitals implemented “programs to control” antibiotic administration. At the  
43 time, the cause of these control programs were the toxic effects (ranging between severe diarrhea  
44 and death from anaphylaxis or aplastic anemia) and the high costs of these drugs to the hospital  
45 [1]. In those golden days of the antibiotic era, medical doctors and bacteriologists were well aware  
46 of antibiotic resistance, considered a problem for individual hospitalized patients, but not a public-  
47 health problem. Nowadays, antibiotic resistance is considered a serious world health challenge. A  
48 recent study by Murray and coworkers has shown that around 1.27 million people died in 2019  
49 due to bacterial resistance to antibiotics worldwide [2]. As noted in a companion commentary  
50 paper, this number of deaths is close to the estimated number of deaths from malaria and AIDS  
51 together in the same year [3]. Not surprisingly, children are also victims of drug resistance. For  
52 example, about two hundred thousand neonatal sepsis deaths are attributable to resistant pathogens  
53 each year [4]. However, efforts should be done to increase the methodologic quality of the  
54 estimations of the correlation between mortality and antibiotic resistance [5].

55 Even when antibiotics target pathogenic bacteria, the antibiotic molecules affect trillions of  
56 bacterial cells comprising hundreds of commensal bacterial species forming the normal microbiota  
57 of human (or animal) bodies. Bactericidal antibiotics kill sensitive cells, and bacteriostatic  
58 antibiotics block bacterial replication. In both cases, sensitive cells leave unused resources, such  
59 as nutrients or colonizable space, so nearby antibiotic-resistant cells thrive even if resistance  
60 mechanisms are biologically costly. This counter-selection of sensitive cells is the basis of

61 Darwinian natural selection occurring every day in patients, livestock, and the environment [6].  
62 As a result, the human usage of these drugs is leaving an indelible antibiotic resistance footprint  
63 [7]. The impact of antibiotic usage on antibiotic resistance is such that there is a positive  
64 relationship between antibiotic use and resistance rate across countries [8–10]. However, we can  
65 learn from the social attitudes and antibiotic-policy measures taken in the countries with lower  
66 resistance rates and act on countries or regions where antibiotic usage is higher. Besides antibiotic  
67 resistance, the extensive use and release of industrial antibiotics might speed microbial evolution  
68 and could have deleterious consequences for the preservation of a healthy ecology of the planet  
69 [11].

70

## 71 **Antibiotic stewardship programs: relevance and impact**

72 **Antibiotic stewardship programs** (see Glossary) are institutional actions to improve antibiotic  
73 prescribing practices, mainly to reduce their use, thus avoiding the selection of antibiotic-resistant  
74 bacterial populations. Their objective is to mitigate the spread of antibiotic resistance by providing  
75 a more individualized (precision) therapy. In particular, they promote (i) the prescription of  
76 antibiotics only when necessary; (ii) a correct choice of antibiotics based on a precise  
77 bacteriological diagnosis (e.g., limiting the use of broad-spectrum antibiotics to specific cases);  
78 and (iii) appropriate doses, length, and route of treatment. These programs are complex, implying  
79 the involvement of medical doctors, nurses, epidemiologists, and pharmacists. This paper argues  
80 that antibiotic stewardship programs should involve other scientists: (i) sociologists, as controlling  
81 the “excess” of antibiotic’s individual use should be considered together with controlling the

82 “access”; and (ii) most importantly, psychologists and, in particular developmental psychologists  
83 [12], as it is discussed in depth in this work.

84 The concept of antibiotic or antimicrobial stewardship to mitigate drug-resistance levels is  
85 relatively recent. In 1997, the Healthcare Epidemiology Society and the Infectious Diseases  
86 Society of America presented strategies for preventing antimicrobial resistance in hospitals [13].  
87 According to the Scopus database (18/March /2022), no paper mentioned “antibiotic stewardship”  
88 or “antimicrobial stewardship” in the title or abstract in 1998, and just one refers to these words in  
89 1999. However, the number of times these phrases appeared in scientific publications increased  
90 more than a thousand ~~times~~ fold since then. For comparison, the Scopus database size only  
91 increased 3.3-fold in the same period. Nowadays, there are scientific journals dedicated to  
92 stewardship programs, and the role of human educational behavior is increasingly considered in  
93 this field, as is the case of JAC-Antimicrobial Resistance from the British Society for  
94 Antimicrobial Chemotherapy, launched in 2019 and dedicated to “Education and research in  
95 antimicrobial stewardship and resistance”.

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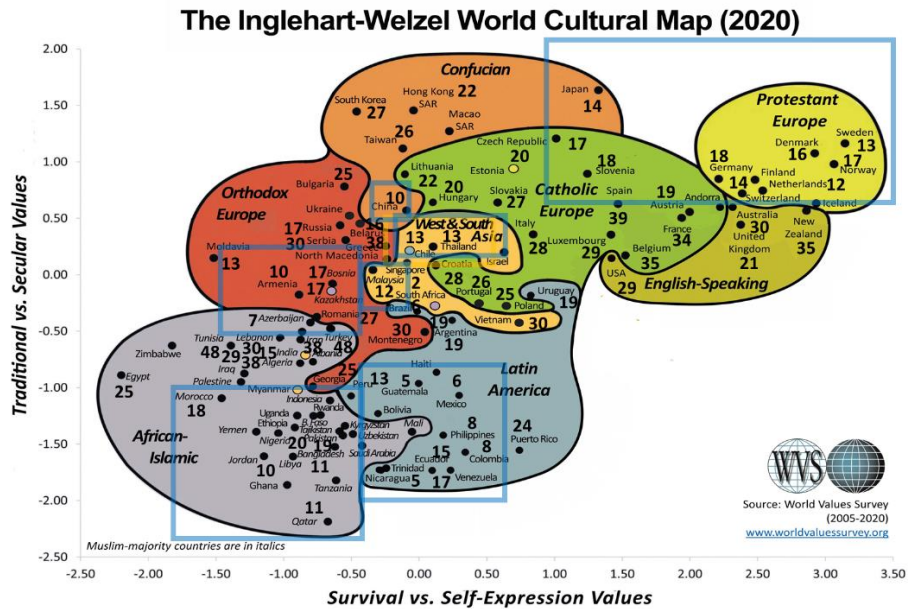
## 97 **Antibiotic stewardship programs require a multidisciplinary approach**

98 Several studies have shown that the total consumption of antibiotics across countries varies  
99 considerably [14,15]. Even within a single country (UK), between and within practices, there is  
100 substantial variability in antibiotic prescription [16]. Epidemiological factors would not be able to  
101 explain these disparities. Other factors must play significant roles, including psychological,  
102 sociological, or cultural differences, and one can find differences among patients or prescribers. In  
103 this work’s line, several researchers have proposed to include other areas of knowledge in these

104 teams, including sociology, anthropology, economics, political sciences, and psychology [17–23].  
105 In particular, behavioral sciences can help deal with the antibiotic-resistance crisis with  
106 quantitative and qualitative methods [24].

107 Qualitative studies focus on answers to “what, how, and why?” questions type, while quantitative  
108 studies focus on “how many, how much, and how often?” questions [25]. We need all question  
109 types. Two recent papers by Borek et al. [26] and Wanat et al. [25] highlighted the opportunities  
110 given by behavioral sciences (health psychology) and their qualitative methods to mitigate  
111 antibiotic resistance (hence, joining efforts to knowledge derived from quantitative methods).  
112 Some studies use both quantitative and qualitative methods. Moreover, hypothesis-driven  
113 strategies may prove highly helpful, and if successful, these hypotheses may end up fruitful beyond  
114 their original scope.

115 An interesting example is provided by the superimposition of antibiotic consumption by countries  
116 [14,15,27] and their cultural values, including religion [28] (Figure 1). The **Inglehart-Welzel**  
117 **cultural maps of the world** [29] consider two major dimensions of cross-cultural variation. First,  
118 “traditional versus **secular-rational values**”. **Traditional values** emphasize the importance of  
119 religion (the Latin verb *religare* means “to bind”), and consequently child-parent submission ties,  
120 deference to authority, absolute standards, and traditional family values; secular-rational values  
121 have the opposite preferences to these traditional values. Second, “survival versus **self-expression**  
122 **values**”. **Survival values** emphasize economic and physical (life-death) security; self-expression  
123 values prioritize subjective well-being, self-expression, and quality of life, and a shift in child-  
124 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 [29] and the World Values Survey site <http://www.worldvaluessurvey.org/>, where blue boxes indicate the ensembles of countries with consistently lower values of antibiotic consumption. Most numbers were obtained from Klein et al. [14], and, because of the changing rates over 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. Note that the 2022-version of the Inglehart-Welzel World Cultural Map has already been released. However, here we present the 2020 version because the data about antibiotic consumption in different countries Klein et al (2018) (ref. [14]) are closer to 2020 than 2022.

125

126 Certainly, such a comparison of values and antibiotic consumption indicates that, besides the  
 127 access to antibiotics provided by the national health services, antibiotic policies, including  
 128 antibiotic stewardship programs, should be specifically designed accordingly to socio-cultural  
 129 differences among countries, in a sense, with social psychology. Antibiotic consumption is highly  
 130 dependent on local social norms [30].

131 With few exceptions, Psychology has been outside the scope of antibiotic stewardship programs.  
132 When they do, they often focus on the psychological characteristics of professionals who prescribe  
133 or develop antibiotics. For example, fear of failure or risk-averse may impact the likelihood of  
134 antibiotic prescription by general practitioners (GPs) [31]. Fear of antibiotic toxicity might, in  
135 some cases, inappropriately overcome the fear of death by severe infection, which has negatively  
136 influenced the development of potentially useful antimicrobials, something that has not occurred  
137 in anticancer therapy [32]. Similarly, fear of antibiotic resistance has, in some cases, improperly  
138 replaced fear of infection, either in individual patients or in massive drug administration (MDA),  
139 to decrease children’s morbidity and mortality in low-income countries (see Box 1).

140 Michel-Lepage et al. analyzed antibiotic prescriptions by GPs for tonsillitis in France. Both viruses  
141 and group A *Streptococcus* are causative agents of tonsillitis in children, and a “Rapid Antigen  
142 Diagnostic Test” (RADT) distinguishes the two. GPs unwilling to accept uncertainty and risks  
143 (risk-averse GPs) used RADTs more often; moreover, GPs would be more likely to prescribe  
144 antibiotics when RADTs were not used [31]. Medical doctors may also be concerned about future  
145 complications [33]. Moreover, older general practitioners prescribe antibiotics more often than  
146 younger ones [34]. In a review discussing the missing links of antimicrobial stewardship programs,  
147 Charani et al. remind us that already in the 1970s, antibiotics were characterized as ‘drugs of fear’  
148 because frequently, doctors may choose to prescribe broad-spectrum antibiotics and more  
149 prolonged than the necessary duration of treatment [35].

150 Studies with control groups to learn if there are psychological differences between patients who  
151 leave health appointments with an antibiotic prescription and those who do not are scarce. For  
152 example, a study found that participants with a Catholic background (Catholic Flemish) trusted  
153 and used more antibiotics than those with a Protestant background (Protestant Flemish) and that



154 the former feared more complications than Protestants if no medications were used. This difference  
155 resulted in higher use of antibiotics by the Catholics than by Protestant participants [36]. Such  
156 religious values correlate with the frequency of antibiotic resistance, and consumption differences  
157 were interpreted as “my health and my children’s health should be assured by others, and I should  
158 loudly claim for help” (Catholics) or “I am personally responsible for decisions concerning my  
159 health and the health of my family, and my emotions should be repressed, as I am the responsible  
160 for the action” (Protestants) [28]. Therefore, individual cultural differences impact the likelihood  
161 of antibiotic use [36]. Moreover, the probability of a patient receiving antibiotic treatment  
162 increases with the number of antibiotic prescriptions the patient received in the previous year or  
163 years [16,37]. Some studies indicate that medical doctors tend to overrate patients’ expectations  
164 of antibiotic prescription [38,39]. In this last factor, we have psychological factors of both the  
165 patient and the medical doctor. Furthermore, the odds of patients receiving inappropriate antibiotic  
166 prescriptions (e.g., for acute respiratory tract infection caused by viruses) is higher when the patient  
167 is of working age (e.g., [40,41]. Therefore, time pressure, perhaps linked to uncertainty, also  
168 increases the probability of antibiotic usage.

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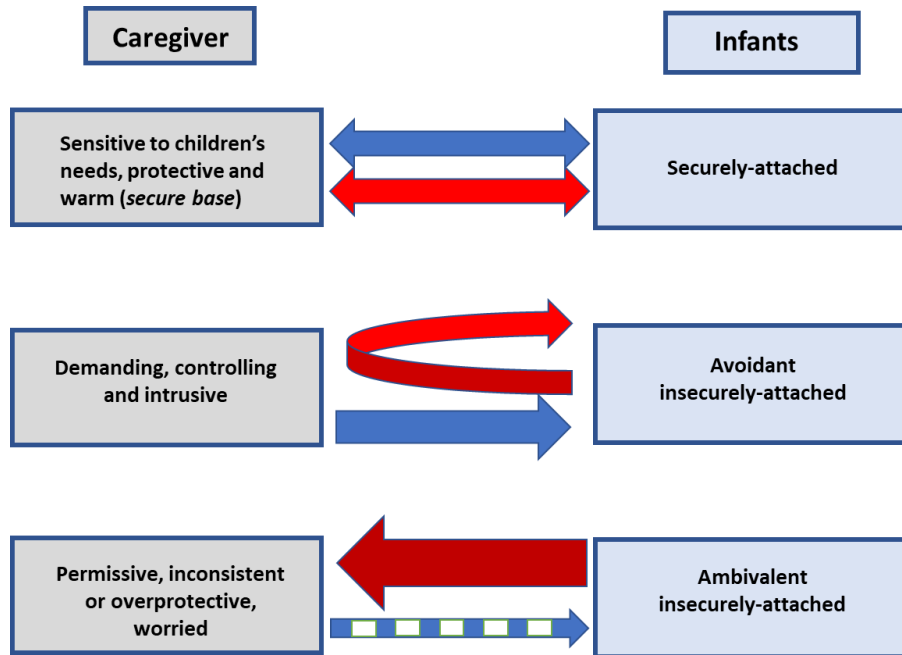
## 170 **The impact of patients’ psychology in drug prescription: the special case of** 171 **pediatric populations**

172 Pediatric appointments can be even more complex because at least a third person is involved, the  
173 patient’s caregiver. An infant, the respective caregiver, and the doctor interact to solve the infant’s  
174 complaints. It is reasonable to assume that the psychological characteristics of all of them may  
175 have a role in the likelihood of antibiotic prescription. Infants are under stress because they are ill

176 and in a strange place (the medical office) and close to a stranger (the doctor). The respective  
177 caregiver (usually the mother or the father) may also be under stress, worried about the child, and  
178 perhaps feeling the obligation to go to work [40,41].

179 Recent studies involving infants and their mothers demonstrated how promising Developmental  
180 Psychology could be for understanding the overprescription of antibiotics and for antibiotic  
181 stewardship programs. For example, Fuertes et al. [42] have shown that antibiotic prescriptions in  
182 the first nine months of life tend to be more likely in a particular group of infants than the other  
183 infants. The odds are impressive: for these children (ambivalent insecurely-attached infants to their  
184 mothers – see below and Boxes 2 and 3), the odds of antibiotic consumption were 25 times higher  
185 (95% confidence interval, 7.01 - 89.40) than in other children. These infants tend to over-  
186 externalize their emotions in the presence of threat or under stress (e.g., when ill, scared, or  
187 frustrated). In this inconsistent behavior, they alternate between a seeking proximity posture and  
188 rejecting their caregiver's affection (Box 2). Also, mothers' behavior may help us anticipate  
189 whether their infants are likely to take (or have taken) antibiotics in the first nine months of life  
190 [42].

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



**Figure 2.** Caregiving and Mother-infant patterns of attachment. The grey boxes on the left correspond to different caregiving styles, and the blue boxes on the right illustrate the infant attachment patterns according to Bowlby [84] and Ainsworth [47]. 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, 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.

193

194 Given the tendency of insecurely-ambivalent infants to inflate emotions near their caregivers and  
 195 health professionals (see Box 3), Fuertes et al. [42] hypothesized that that behavior pattern could  
 196 lead to antibiotic use in the first nine months. Indeed, 89.7% (26 out of 29) of ambivalent  
 197 insecurely-attached infants, contrasting with 25.7% (27 out of 105) of the other infants, i.e., of  
 198 **securely-attached** and **avoidant insecurely-attached infants** (Figure 3A) [42].

199 Another study, this time with infants with low gestational weight (lower than 1599 g) ranging  
 200 between 23 to 34 gestational weeks, also shows that antibiotic prescription in the first nine months

201 of corrected age (because some infants of this study were preterms) is three times more likely  
202 among ambivalent-attached infants (95% confidence interval, 1.02 - 8.99) than among the other  
203 infants [43]. This proportion is impressive given that we know that children with low birth weight  
204 have more comorbidities and are more likely to take antibiotics than others (60.0% against 39.6%)  
205 [42,43]. In fact, many very low-birth children are prone to infections, which could weaken the  
206 impact of attachment patterns on antibiotic prescription.

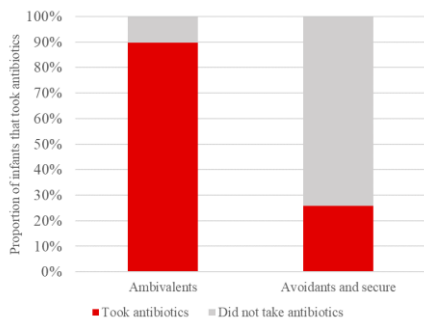
207 The attachment relationship between infants and their caregivers starts as soon as birth. Therefore,  
208 an insecure-ambivalent mother-infant attachment originates early and results from daily  
209 interactions with caregivers. For example, mothers of insecure-ambivalent infants are more  
210 unresponsive in free play than other mothers, and mothers of securely attached infants are more  
211 sensitive to their infants during free play [44–46]. Developmental psychologists define maternal  
212 sensitivity as the mother’s ability to read and interpret an infant’s solicitations and stressful signals  
213 and her ability to comfort the infant [47–50]. Of course, many factors play a critical role in  
214 maternal sensitivity, namely family socioeconomic status (SES), maternal education, parents’  
215 mental health, number of family risk factors, or parental stress. A binary logistic regression  
216 analysis has shown that maternal sensitivity predicts antibiotic uptake in the first nine months of  
217 the infant’s life [42] (Figure 3B).

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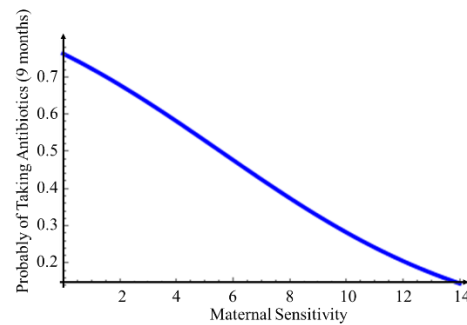
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220

(a)



(b)



**Figure 3.** The 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. [42]. (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 [42].

221

222 In another study, Stern et al. (2020) found that the odds of antibiotic use in the first 12 months of  
223 the infant’s life also decrease with maternal sensitivity, defined as the extent to which the mother  
224 promptly and appropriately responds to the infant’s signals and needs [51]. The size effect of this  
225 relation was low, and there are at least two explanations for that. The proportion of the three  
226 attachment patterns among infants in this study is unknown. However, maternal sensitivity is  
227 higher for both insecurely-attached infants (avoidants and ambivalents) patterns [49], whereas the  
228 odds for antibiotic use are higher only for ambivalent infants [42]. Therefore, if the proportion in  
229 the sample of insecure-avoidant infants is high or the proportion of insecure-ambivalent infants is  
230 low, the impact of maternal sensitivity on antibiotic use should become less clear. An alternative

231 explanation is related to the fact that Stern et al. (2020) performed their study in the Netherlands  
232 and Fuertes et al. (2020) in Portugal [42,51]. The antibiotic prescription rate in the Netherlands  
233 has been one of the lowest in the European region, with 12 defined daily doses (DDDs) per 1000  
234 inhabitants per day [14]. In contrast, Portugal consumed more than the double, 26 DDDs per 1000  
235 inhabitants per day [14] (Figure 1). With a lower number of prescriptions in the Netherlands, the  
236 impact of maternal sensitivity on antibiotic prescription may fade away.

237 The formerly presented (Figure 1) Inglehart-Wenzel World Cultural Map reflects such differences.  
238 Indeed, four studies in the Netherlands found that only 3.7% to 10.8% of infants were ambivalent-  
239 attached, against 19.5% (25/108), 19.5% (16/82), or 21.6% (29/134) in three recent Portuguese  
240 studies performed with independent samples [42,52–54]. These results suggest that ambivalent  
241 attachment behavior should be more frequent in countries with more antibiotic consumption,  
242 mainly when antimicrobials are easily available by public health services. Although many factors  
243 affect attachment organization (since the reasons for children’s stress are multiple, not only being  
244 sick), it would be interesting to study the association between antibiotic consumption and the  
245 prevalence of attachment patterns across cultures. For example, studies performed in Sweden and  
246 Germany (“European Protestant” countries that stand together in Figure 1) with low antibiotic  
247 consumption (Figure 1) also indicated low proportions of ambivalent-attached infants, 3.9% (2  
248 ambivalent-attached out of 51 infants) and 9.8% (7/71), respectively [55,56]. In contrast,  
249 ambivalent attachment in Israel is overrated in both Arabic (13%) and Jewish (26%) samples  
250 [54,57]. Yet, the effect of religion is not clear-cut; family socioeconomic status and parents’  
251 educations have large contributions to the attachment patterns prevalence [57]. Moreover,  
252 unfortunately, most studies indicating the proportion of attachment patterns across countries were  
253 published many years ago, show a high heterogeneity between samples within countries, and/or

254 were performed with small samples that may not mirror the whole country [54,57,58]. Studies  
255 comprising large and representative samples in each country could unveil the relationship between  
256 cultural factors, religion and traditional factors, parenting, and health practices. However, the  
257 “ambivalent-attached” behavior of children might reflect the “ambivalent” cultural attitudes of the  
258 societies, particularly those where the secular-rational values of “modernity” and self-expression  
259 coexist with the traditional, secular values that assure survival under extreme circumstances. These  
260 ambivalent societies occupy the central part of the Inglehart-Wenzel World Cultural Map (figure  
261 1), and are associated with a consistent over-use of antibiotics. Children are crying for an antibiotic,  
262 but society is responsive to this demand.

263

## 264 **Concluding remarks**

265 Antibiotics are the most frequent medications prescribed in the pediatric population [59–63],  
266 which is unfortunate because antibiotic usage contributes to drug resistance and may have  
267 individual adverse effects (Box 1). On the other hand, pediatric antimicrobial stewardship  
268 programs have successfully decreased antibiotic use, healthcare costs, and antibacterial resistance  
269 in both inpatient and outpatient settings.

270 Many studies have shown that several factors impact the likelihood of antibiotic prescription,  
271 rather than only health factors or medical indicators. For example, the quality of attachment to the  
272 caregivers in the first year of life correlates with antibiotics prescription. The mechanisms involved  
273 in these associations are still unclear, but perhaps there is a complex interaction between children’s  
274 strategies to obtain care and relief when ill and the parents’ ability (or difficulty) to meet their  
275 needs and support children in self-regulating during sickness. Such behaviors may trigger infants’

276 and parents' distress and children's overreactions, leading to miscommunication of symptoms to  
277 health professionals. These processes are far from being understood, creating the need for new  
278 longitudinal research lines that include new dimensions, namely infants' and caregivers'  
279 psychology.

280 Antibiotic stewardship programs already involve multidisciplinary teams, mainly composed of  
281 medical doctors, nurses, and pharmacists, but the battle against the pandemics of antibiotic  
282 resistance could improve significantly by including other areas of knowledge, as several previous  
283 studies have already demonstrated [20,24,64–67]. The works discussed here indicate that, beyond  
284 physical factors, individual psychological differences between patients or between patients'  
285 caregivers impact antibiotic prescription. We suggest that these “attachment psychological  
286 dynamics” reflect the societies' cultural attitudes, and those countries where rational-modernity  
287 behaviors coexist with traditional values are expected to have an ambivalent behavior leading to  
288 higher antibiotic consumption (see Outstanding Questions box).



## **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. 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 [68,69]. In our days, the mass distribution of a broad-spectrum antibiotic agent to preschool children has reduced mortality in areas of sub-Saharan Africa [70]. Secondly, antibiotics have not only decreased the infective morbidity, but helped perform medical procedures like complicated surgeries, organ transplantation, intensive care, and anticancer chemotherapy [71]. Finally, a formerly unexpected benefit (in this case for human nutrition) beyond these two health-related: antimicrobials are suitable growth promoters in livestock [72]. 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 throughout life, increasing the risk of carrying multiresistant opportunistic bacteria, eventually lethal in elderly pathological events [73]. 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 [74]. Another 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 being overweight at seven years old among children whose mothers had an average healthy weight, indicating the role of early damage of individual microbiota [75–77]. Bile acid metabolism influenced by altered microbiota composition is likely associated with this body mass increase [77,78], recalling the effect of antibiotics on increasing weight in farm animals [79]. 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 [80–83]. At the individual level, negative beliefs about antibiotics include fear of toxicity, frailty, and general weakness.

289

### **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 [84]. 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 [84,85]. 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 [84].

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 [84]. 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 [86].

In the late sixties and seventies, Mary Ainsworth developed an experimental protocol denominated Strange Situation to study attachment behavior [47]. 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 [47,85].

Using this experimental paradigm, Ainsworth found two main patterns among insecurely attached infants, and they are somewhat opposite to each other [47]. 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 anger for presumed lack of response, including some resistance to physical contact [45,46]. For a review, see Cassidy and Shaver [85].

290

**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 [84]. 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 [49,85]. 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 [87]. They oscillate with behaviors of proximity seeking, contact, and desire for comfort, aiming at getting responses and attention from caregivers [47].

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 [88]. However, mothers of insecurely-attached infants become

more anxious and have more negative perceptions of their infants' health conditions [88]. Furthermore, insecure-ambivalent teenagers and adults have higher symptom-reporting and request more health visits [89–91]. 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 [92].

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298 **Glossary**

299 **Ambivalent insecurely-attached infants:** one of the two main attachment patterns among  
300 insecurely attached infants. These infants tend to show contradictory behaviors, trying to attract  
301 the attention of their caregivers, but simultaneously showing their anger for presumed lack of  
302 response, including some resistance to physical contact. Moreover, these infants communicate  
303 their needs intensively when facing inconsistent responses from their caregivers and tend to  
304 exacerbate emotions.

305 **Antibiotic Stewardship Programs:** these institutional actions aim to improve antibiotic  
306 prescribing practices, mainly to diminish their use.

307 **Avoidant insecurely-attached infants:** these infants turn to themselves to find means to solve  
308 their needs. One of the two patterns of insecurely attached infants.

309 **Human Attachment:** during their first year of life, human beings are prone to become attached  
310 to caregivers (primarily mothers and fathers). Infants adopt a behavioral strategy to maintain  
311 proximity with caregivers and to obtain care and comfort from them.

312 **Inglehart-Welzel cultural maps of the world:** according to the political scientists Ronald  
313 Inglehart and Christian Welzel, there are two major dimensions (created by running factor  
314 analysis over a set of ten indicators) of cross-cultural variation in the world. The two dimensions  
315 are traditional values versus secular-rational values and survival values versus self-expression  
316 values.

317 **Secular-rational values:** have the opposite preferences to these traditional values.

318 **Securely-attached infants:** these infants are reciprocal and mutually with caregivers (mostly  
319 mothers and fathers). These infants display their emotions and intentions openly by spontaneous  
320 communication of their needs or seeking closer contact with caregivers.

321 **Self-expression values:** these values prioritize subjective well-being, self-expression, and  
322 quality of life, and a shift in child-rearing values from an emphasis on hard work towards  
323 freedom, imagination, and tolerance. The opposite of survival values.

324 **Survival values:** these values emphasize economic and physical (life-death) security. The  
325 opposite of self-expression values.

326 **Traditional values:** these values emphasize the importance of religion, and consequently child-  
327 parent submission ties, deference to authority, absolute standards, and traditional family values.  
328 The opposite of secular-rational values.

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