ORIGINAL ARTICLE

Behavioral determinants of antibiotic resistance: The role of social information

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Abstract

The increasing development of resistant pathogens is one of the greatest global health challenges. As antibiotic overuse amplifies antibiotic resistance, antibiotic intake poses a social dilemma in which individuals need to decide whether to prosocially reduce their intake in the collective interest versus to (over)use it even in case of mild diseases. We devise a novel behavioral game paradigm to model the social dilemma of antibiotic intake. Using this new method in an incentivized laboratory experiment ($N = 272$ German participants), we varied whether players had mutual knowledge about their antibiotic intake. The results indicate that there was substantial antibiotic overuse in the absence of social information. Overuse decreased when social information was present. Our postexperimental survey data further suggest that social information impacts people's behavioral motivation, evaluation of the other player, and positive affect. Taken together, providing social information about people's antibiotic intake may help in reducing antibiotic overuse. On a more general level, the novel behavioral game may be adapted to study other aspects of antibiotic intake to promote prudent use of antibiotics.

INTRODUCTION

Antibiotics are one of the greatest medical achievements of the 20th century. Since Fleming's discovery in 1928, penicillin alone has saved millions of lives (Kardos & Demain, 2011). However, researchers warn that even last-resort antibiotics are losing their effectiveness (McKenna, 2013) as bacteria develop growing resistance. For example, 35,000 people die in the United States each year from infections related to resistant pathogens (Cassini et al., 2019; Centers for Disease Control and Prevention, 2019). As a result, the World Health Organization (WHO) classified increasing antimicrobial resistance—"the ability of bacteria, parasites, viruses and fungi to resist [...] medicines"—as one of the 10 threats to global health in the year 2019, threatening to "send us back to a time when we were unable to easily treat infections such as pneumonia, tuberculosis, gonorrhea, and salmonellosis" (WHO, 2019a).

Antibiotics are an effective treatment option for alleviating the worst symptoms of bacterial infections, with few side effects (Colman et al., 2019; Reed et al., 2002). At the same time, however, antibiotic intake has negative externalities as it fosters antibiotic resistance and jeopardizes their long-term effectiveness in society at large (McGowan, 2001). It has been acknowledged that antibiotic resistance has been "accelerated by the misuse and overuse of antibiotics" (WHO, 2019b) in treatment of human diseases and agricultural settings. As a result, antibiotic intake poses a social dilemma (Colman et al., 2019; Laxminarayan & Heymann, 2012), which is accentuated when antibiotics are used in cases of mild disease (such as respiratory tract infections or common colds), threatening its effectiveness when it comes to severe bacterial infections that require antibiotic use.

There have been major contributions to this debate in the literature, either from the doctor's prescription perspective (Linder et al., 2017; Colman et al., 2019; Eilermann et al., 2019; Krockow et al., 2019; Rawson et al., 2020; for a review, see Rose et al., 2019) or in terms of patient factors related to antibiotic intake (Bagnulo et al., 2019; for a review, see Kianmehr et al., 2019). Public awareness of the social dilemma related to antibiotic intake and how to address it is low (Reed et al., 2002; WHO, 2015). It has been shown that patients' preferences are key to understand antibiotic intake, for instance, because strong patient preferences can increase likelihood of antibiotic prescriptions (e.g., Coenen et al., 2006; Macfarlane et al., 1997). The success of delayed prescription, where patients receive the prescription with the advice to wait some days and only to take it when it does not get better or it gets worse (Ryves et al., 2016), could also be affected by strong preferences and the need to get back to work, paired with the belief that antibiotics may shorten the time of sickness (Gaarslev et al., 2016). Moreover, even though many countries have restrictive regulations that antibiotics need to be prescribed, regulations are not always enforced, leading pharmacies to sell antibiotics over the counter, internet pharmacies to sell it with prescriptions from other countries or even without prescription (WHO, 2019b). Yet, understanding individuals' behavioral preferences regarding antibiotic intake is difficult as preference formation and intake decisions take place in people's everyday lives, and there is a complex interplay of a range of determinants.

SOCIAL INFORMATION AND ANTIBIOTIC OVERUSE

As evident from the social dilemma structure of antibiotic intake, one way of conceptualizing antibiotic overuse is that selfishly rational individuals will maximize their personal benefit by taking antibiotics regardless of the severity of a disease, although selective intake in cases of severe disease (but not in cases of mild disease) would maximize the collective benefit (*overuse hypothesis*). One likely explanation in antibiotic overuse is that people do not anticipate that a possible consequence of their behavior is an increase in antibiotic resistance and, therefore, a reduction in social welfare (Tarrant et al., 2019). Even when people know about the underlying social dilemma, there is a lack of feedback regarding their decisions (and those of others) and the corresponding social consequences. For instance, people typically lack information about when others take antibiotics (e.g., whether others only use antibiotics for severe diseases or also for rather mild diseases).

The effect of social information/feedback has been studied intensively with regard to doctors' prescribing behavior (for instance, as part of antibiotic stewardship programs; e.g., Eilermann et al., 2019; Welschen et al., 2004), but has been largely ignored when it comes to patients' behavioral preferences of antibiotic intake. For patients, social information may increase the salience of the social welfare consequences of individual behaviors (Chapman et al., 2012). Furthermore, providing social information eliminates the social uncertainty in antibiotic decision-making by (i) informing people about what behavior might be appropriate in a particular situation (e.g., Rönnerstrand & Sundell, 2015; Sniezek et al., 1990) and (ii) reducing the fear of exploitation (Cason & Khan, 1999; De Cremer et al., 2001; Fellner & Lünser, 2014; Yamagishi & Sato, 1986). Social information may also increase trust in the sense that a person will not overuse antibiotics because the information signals other persons' trustworthiness and engagement in cooperation (Tarrant et al., 2019). Therefore, we expected that the presence (vs. absence) of social information would reduce individuals' overuse of antibiotics, that is, individuals would use antibiotics in cases of severe disease but less so in cases of mild disease (*social information hypothesis*).

THE PRESENT RESEARCH

Our contribution is two-fold. First, we devise a novel behavioral game—the Interactive Resistance (I-Resist) game—to open up the "black box" of individuals' behavioral preferences in antibiotic intake when considering the underlying social dilemma. Behavioral games are simplified but precise abstractions of social situations (Camerer, 2003; Murnighan & Wang, 2016; Thielmann et al., 2021). By providing decision-makers with behavior-contingent incentives, behavioral games make decisions truly consequential and, in turn, the behavior less prone to influences of social desirability than, for example, survey responses (Baron, 2001). Behavioral games have been used successfully to model other health behaviors with social-interactive elements, such as vaccine uptake (e.g., Böhm et al., 2016; Chapman et al., 2012). To this end, the I-Resist game models the incentive of the social dilemma in the decision of whether to take antibiotics, capturing both the personal benefit and the collective cost of antibiotic overuse.

As a second contribution, we aimed to answer the following general research question: Do individuals overuse antibiotics when they know about the underlying social dilemma, and how can prudent antibiotic intake be promoted? Utilizing the I-Resist game in a laboratory

experiment with student participants to investigate decisions on antibiotic intake, we examined whether prudent antibiotic intake could be fostered by providing social information about individuals' intake decisions.

METHOD

The I-Resist game

Here, we describe the I-Resist game using the specific parametrization presented to the study participants. The I-Resist game is played by two players over 10 rounds. In each round, every player is endowed with a time budget of 60 s to independently engage in a real-effort task where simple tasks need to be completed (Gill & Prowse, 2012). The task is designed in such a way that there is no intrinsic value in completing the task, but completion aims to assess players' effort to generate payoff. Accordingly, effort is rewarded with a piece rate loan, that is, for each completed task (i.e., piece), players receive 0.20 €. More time is likely to result in more completed tasks and, thus, a higher payoff. Therefore, the payoff models the utility of being healthy (e.g., more work or more leisure time).

In each round, players become ill with either a mild or severe disease.[1] Such differentiation of severity levels aimed to resemble real life situations in which symptom severity might affect the use of antibiotics, such as in some delayed prescription practices (Ryves et al., 2016). For each player, five mild and five severe cases of the disease are randomly distributed over the 10 rounds, and players know about this in advance. A mild disease reduces the time available to work on the real-effort task in the respective round by 50 s, and a severe disease reduces the time by 60 s, resulting in zero working time.

A total of 10 effective units of a medicine are available within each interaction group. After learning about the severity of their disease, each player must independently decide whether to take the medicine. Taking the medicine results in a complete recovery of lost time (irrespective of disease severity) but reduces the number of effective medicine units available. After taking the medicine 10 times within the interaction group (irrespective of which player uses it), the medicine loses its effectiveness such that any further time lost on account of the disease can no longer be recovered.

For simplicity, consider two behavioral strategies that players could adopt in the I-Resist game: cooperation (C), that is, taking the medicine only in cases of severe disease, and defection (D), that is, taking the medicine for both mild and severe diseases. As displayed in Figure 1, the I-Resist game captures the social dilemma of antibiotic intake in a two-player setting by providing individual incentives to consistently take the medicine (D). Specifically, when only considering "pure strategies" (i.e., always taking or not taking the medicine throughout all rounds) defection is the dominant strategy from the individual perspective, because the order of expected payoffs (in terms of time available to work on the real-effort task) resulting from the combination of both players' strategies [own strategy, other player's strategy] is [D, C] > [C, C], and [D, D] > [C, D]. This is at odds with the collectively optimal behavior of taking the medicine only in cases of severe disease, that is, 2 * [C, C] > [D, C] + [C, D]. As such, intake decisions in cases of mild disease are a clear indicator of medicine overuse, which sacrifices social welfare for individual benefit.

Player 1

FIGURE 1 Expected payoff over 10 rounds given that players follow a unique behavioral strategy in the Interactive Resistance (I-Resist) game. Note: Expected payoff is considered as the time (in seconds) available to work on the real-effort task to generate individual payoff (aggregated over 10 rounds). C = Cooperation, that is, taking the medicine only in cases of severe disease; D = Defection, that is, taking the medicine for both mild and severe diseases. The number of rounds in which the medicine is available depends on both players' behavioral strategy. Specifically, the medicine is effectively available for 10 rounds in case of [player 1 strategy: C, player 2 strategy: C]. It is available for $\frac{2}{3}$ * 10 rounds in case of [C, D] and [D, C], respectively, and for $\frac{1}{2}$ * 10 rounds in case of [D, D]. Given a random distribution of mild and severe diseases over the 10 rounds, the expected payoffs (seconds of total working time, given the players' strategies) are calculated as follows: Payoff [C, C] = 10 rounds * probability $\frac{1}{2}$ * 60 s + probability $\frac{1}{2}$ * 10 s = 350 s of total time; Payoff [C, D] = 10 * $\frac{1}{3}$ * 60 + $\frac{1}{3}$ * 10 + $\frac{1}{3}$ * $\frac{0+10}{2}$ = 250; Payoff [D, C] = 10 * $\frac{2}{3}$ * 60 + 10 * $\frac{1}{3}$ * $\frac{0+10}{2}$ = 417; Payoff [D, D] = 10 * $\frac{1}{2}$ * 60 + 10 * $\frac{1}{2}$ * $\frac{0+10}{2}$ = 325

Experimental design

We implemented two experimental between-subjects conditions: *social information absent* and *social information present*. Specifically, we varied the information that the individuals received after each decision in the I-Resist game. In the *social information absent* condition, the individuals did not learn about the other player's decisions until it became apparent as the medicine eventually lost its effectiveness. In the *social information present* condition, individuals received feedback about the severity of the other player's disease and the corresponding decision after each round. Importantly, this means that each player learned about the other player's previous decision but also knew that the other player had learned about their own previous decision.

Sample

We conducted a laboratory experiment with $N = 272$ student participants (39% female) from a German university, aged between 17 and 41 years ($M = 22.70$, $SD = 3.96$), with $n = 138$ participants (69 interaction groups) being assigned to the *social information absent* condition and $n = 134$ participants (64 interaction groups) to the *social information present* condition. The

participants were invited to experimental laboratory sessions comprising 24–30 participants each. Randomization took place on the session level, that is, all participants in one session were assigned to the same experimental condition; participants were not aware of the other condition. The sessions lasted approximately 75 min, and the participants earned €11.80 on average (approx. $13).

The sample size was based on the maximum possible number of participants that could take part during the study period. Considering the participants' repeated intake decisions given severe versus mild diseases and social information being absent or present, a sensitivity power analysis suggested that the acquired sample size was sufficient to detect small-to-medium effects ($f = 0.12$) on the mean intake decisions at the group level in a repeated-measures analysis of variance (ANOVA) with decent power ($1 - \beta = .80$).

Procedure

The participants were recruited through an online recruitment system (Greiner, 2004) in which they had pre-registered. They received information about the study and accepting the invitation to the study served as informed consent. After arrival at the laboratory, they were randomly assigned to one of 30 computer cubicles by drawing an index card. The experiment was programmed using z-Tree (Fischbacher, 2007).

First, the participants completed the incentivized social value orientation (SVO) slider measure, followed by written and read-aloud instructions for the I-Resist game. They had a 60-s practice period to familiarize themselves with the real-effort task (slider positioning task, see supplementary materials; Gill & Prowse, 2012). Three control questions had to be successfully answered to proceed, followed by the generalized trust measure and questions regarding their behavioral motivations. The participants were then randomly paired with another player (who remained their partner throughout all rounds; so-called partner matching protocol) to play the I-Resist game for 10 rounds, with social information after each round being either absent or present. The order of mild and severe diseases was determined at random at the individual level. Once the medicine had been used 10 times, the participants were informed that it was no longer effective and could not be used in the subsequent rounds. Importantly, participants did not learn about the identity of their partner (there were always at least 23 other participants in the same session).

At the very end, participants completed a postexperimental questionnaire, including positive and negative affect, a second assessment of their behavioral motivations, the evaluation of the other player's behavior, and basic demographics. They were eventually informed about their overall payoff resulting from the SVO slider measure and the I-Resist game, and were paid privately.

Secondary measures

In addition to the individual behavior in the I-Resist game as the primary measure of our investigation, we further explored the potential role of and effects on several other variables. As people with a higher propensity to act prosocially may be especially affected by social information, we assessed the interaction effects of the experimental factors with SVO and generalized trust (e.g., Thielmann et al., 2020) on medicine intake. Moreover, we explored the effect of social information on behavioral motivations, the evaluation of the other player's behavior, and positive/negative affect. The respective measures are described below.

Social value orientation

SVO captures an individual's concern for the welfare of others in relation to their concern for themselves (for a review, see Murphy & Ackermann, 2014), which has been shown to predict prosocial behavior and cooperation (for meta-analyses, see Balliet et al., 2009; Thielmann et al., 2020). To assess the participants' SVO, we used an established measure with excellent measurement properties: the SVO slider measure (Murphy et al., 2011). In this measure, participants make repeated decisions on how to allocate monetary tokens between themselves (sender) and an unknown other (receiver). An example item is (allocation to self/other): [100/50, 94/56, 88/63, 81/69, 75/75, 69/81, 63/88, 56/94, 50/100]. The decisions in the six primary items of the SVO slider measure, as used in the present experiment, revealed a continuous angle score of participants' SVO, ranging from competitiveness ($<-12.04°$), individualism ($-12.04°$ to $22.45°$), and prosociality ($22.45°$ to $57.15°$) to altruism ($>57.15°$).

Using the z-Tree implementation of the SVO slider measure (Crosetto et al., 2019), all the participants completed the measure in the role of the sender. At the end of the experiment, it was randomly determined whether they would be paid in the role of the sender (based on their own allocation decision) or that of the receiver (based on the decision of another sender to which they were randomly matched). One of the allocation items was randomly chosen to become payoff-relevant, with the following conversion rate: 100 tokens = 1.50 €. We used the continuous SVO angle in all the analyses.

Generalized trust

To test the effect of individual-level trust on medicine intake in the I-Resist game, we measured the participants' generalized trust using six items devised by Yamagishi and Yamagishi et al. (1994), for example, "Most people are basically honest" (7-point scale from $1 = I\ don't$ $agree\ at\ all$ to $7 = I\ fully\ agree$). As the scale showed good internal consistency (Cronbach's $\alpha = .84$), we used the (mean-centered) mean value in all the analyses.

Behavioral motivations

We asked the participants about their behavioral motivations in the I-Resist game before and after playing the game. Thus, the measure of ex ante game play assessed the participants' anticipated motivations, whereas the measure of ex post game play assessed the motivations guiding their behavior (in hindsight). The scale comprised 10 items (e.g., Böhm et al., 2013; Wildschut et al., 2002), with two items each assessing the following motivations: maximizing the player's own outcome (max own; e.g., "I want to earn as much money as possible, no matter how much the other person earns."), maximizing the relative outcome (max rel; e.g., "I want to earn more than the other person."), minimizing outcome differences (min diff; e.g., "I want me and the other person to earn about the same."), maximizing the joint outcome (max joint; e.g., "It's important to me that me and the other person make a lot of money."), and distrust (e.g., "I don't trust the other person."). All answers were given on a 7-point scale ($1 = don't\ agree\ at\ all$ to $7 = totally\ agree$). Spearman-Brown coefficients were used as indicators of the internal consistency of the scales (max own: $\rho = .87$; max rel: $\rho = .80$; distrust: $\rho = .68$; max joint: $\rho = .82$; min diff: $\rho = .85$; Eisinga et al., 2013), and their mean values (separately for ex ante and ex post game play) were used in all the analyses.

Evaluation of the other Player's behavior

After playing the game, the participants were asked to evaluate the behavior of the other player in the I-Resist game by means of two items: "I am satisfied with the behavior of the other player" and "I consider the behavior of the other player to be fair." The answers were given on a 7-point scale (1 = *don't agree at all* to 7 = *totally agree*).

Positive/negative affect

The short form of the positive and negative affect schedule (I-PANAS-SF; Thompson, 2007) was used to measure how the participants felt after the game. They answered five items, each measuring positive (e.g., "inspired") and negative (e.g., "afraid") affect. The answers were given on a 7-point scale (1 = *not at all* to 7 = *extremely*). As the items of both positive and negative affect showed acceptable-to-good levels of internal consistency (positive affect: $\alpha = .73$. and negative affect: $\alpha = .57$, respectively), we used their mean values in all the analyses.

Analytical approach

We excluded two interaction groups from the analyses because one person each within these groups failed to follow the instructions for the real-effort task. We restricted all our analyses to rounds in which the medicine was still effective (because the player could no longer defect once the medicine became ineffective), standardizing the relative amount of medicine intake to values from 0 to 1 across all effective decision rounds.

In a first step, we tested our hypotheses on the average intake per interaction group, aggregated across the two players of an interaction group and rounds by means of a repeated measures ANOVA. In a second step, we replicated the analysis on the individual level. To this end, we conducted mixed-effects regressions with a logit link in the R environment (R Core Team, 2020) using the package *lme4* (Bates et al., 2015). We treated the individual decision of taking the medicine per round as the dependent variable (0 = no intake, 1 = intake). Due to the nested structure resulting from the repeated decisions of the participants in the I-Resist game and the joint feedback for participants from the same interaction group in the presence of social information, we treated both the participants (level 2) and the interaction groups (level 3) as random effects, accounting for the interdependent error terms (random intercept model; see Pinheiro & Bates, 2000).[2] Further, given that these models estimate the effect of social information on the decision in the next round, we only included rounds >1 because social information was only available after the first round.

RESULTS

Social information and medicine overuse

A repeated-measures ANOVA on the mean medicine intake per interaction group, using disease severity (severe vs. mild), the social information condition (social information absent vs. present), and their interaction as predictors revealed a significant effect for the social information condition, $F(1, 132) = 9.02$, $p = .003$, $\eta_p^2 = 0.06$, as well as for disease severity, $F(1, 132)$

$= 307.18$, $p < .001$, $\eta_p^2 = 0.70$. These effects were qualified by a significant interaction effect, F $(1, 132) = 9.10$, $p = .009$, $\eta_p^2 = 0.06$, indicating that medicine intake in cases of severe disease was high irrespective of social information ($M_{absent} = 0.99$, $SD = 0.05$; $M_{present} = 0.99$, $SD = 0.06$). In contrast, medicine intake was substantial but lower in cases of mild disease, particularly when social information was present ($M_{present} = 0.36$, $SD = 0.38$) compared with being absent ($M_{absent} = 0.54$, $SD = 0.33$). This provides preliminary evidence for both the overuse hypothesis and the social information hypothesis.

To analyze intake decisions on the individual level, we regressed medicine intake on availability of social information (i.e., the experimental factor), disease severity, and their interaction, while controlling for rounds (Table 1, model 1). The analysis revealed a main effect for disease severity, $B = 5.69$, $SE = 0.53$, $p < .001$, $OR = 314.45$, indicating that there was a higher medicine intake in cases of severe disease ($M = 0.99$, $SD = 0.11$) compared with cases of mild disease ($M = 0.39$, $SD = 0.49$). Whereas medicine intake in cases of severe disease maximized

TABLE 1 Mixed-effects models predicting medicine intake in the Interactive Resistance (I-Resist) game by experimental condition

Predictors	Model 1			Model 2			Model 3		
	B	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**
Intercept	0.39	0.34	.257	0.37	0.33	.259	0.37	0.32	.252
Social information (A)	−1.36	0.49	.006	−1.30	0.46	.005	−1.28	0.45	.005
Severity (B)	5.69	0.53	<.001	5.82	0.59	<.001	5.66	0.56	<.001
SVO (C)				−0.02	0.02	.300	−0.01	0.02	.344
Generalized trust (D)				−0.16	0.23	.481	−0.20	0.22	.368
Round	0.22	0.05	<.001	0.21	0.05	.001	0.21	0.05	<.001
A * B	2.22	0.91	.015	2.33	0.94	.014	4.70	2.13	.027
A * C				0.00	0.02	.869	.000	.026	.984
A * D				−0.22	0.31	.492	−.083	.311	.788
B * C				0.00	0.04	.826	−.030	.051	.547
B * D				−0.35	0.43	.417	0.19	.489	.688
A * B * C							0.10	0.08	.207
A * B * D							−2.85	1.42	.046
Observations/individuals/ groups	1722/268/134			1722/268/134			1722/268/134		
Marginal R^2/conditional R^2	0.542/0.859			0.579/0.858			0.683/0.890		
τ00 individual	2.10			2.00			1.81		
τ00 group	5.27			4.50			4.39		
ICC	0.69			0.66			0.65		
AIC/BIC	984.9/1023			984.3/1055.1			980.5/1062.2		

Note: Participants and interaction groups were treated as random effects. Social information: $-0.5 =$ Absent, $+0.5 =$ Present; Severity: $-0.5 =$ Mild, $+0.5 =$ Severe; Round: 2–10. SVO and generalized trust were mean-centered. Bs represent unstandardized regression coefficients. Marginal R^2 refers to the proportion of variance explained by the fixed effects. Conditional R^2 refers to the proportion of variance explained by the fixed effects and the random effect. τ00 Individual $=$ random effect for the individuals. τ00 Group $=$ random effect for the groups. ICC $=$ intraclass correlation for individual decisions nested within groups.

both individual and collective payoffs, medicine intake in cases of mild disease maximized individual payoff but sacrificed collective payoff. The mean number of intakes in cases of mild disease across the rounds was larger than zero, $t(133) = 13.91$, $p < .001$, $d = 1.20$, supporting the overuse hypothesis.

Most interestingly, there was an interaction effect between disease severity and social information, $B = 2.22$, $SE = 0.91$, $p = .015$, $OR = 9.20$. As displayed in Figure 2a, the probability of taking the medicine in cases of mild disease was lower when participants had social information versus when they did not have such information. Information did not matter in cases of severe disease. This pattern provides further support for the social information hypothesis, indicating that medicine overuse decreased when individuals had mutual knowledge about their medicine intake. There was also a main effect for round, $B = 0.22$, $SE = 0.05$ $p < .001$, $OR = 1.24$, indicating that the likelihood of taking the medicine increased over the course of the game, that is, when it became more likely that the medicine would soon lose its effectiveness (similar to the well-known 'endgame effect' in repeated social dilemmas; e.g., Choi & Ahn, 2013).

In the supplementary materials, we report on an exploratory logistic regression predicting medicine intake in cases of mild disease in the first round only, that is, before participants received any feedback about the other player's intake decision. We found that medicine intake was lower when participants anticipated that their own decision and the other player's decision would be mutually shared—even before providing/receiving such information—compared with the condition where no social information was anticipated.

In two further models reported in Table 1, we added the participants' SVO and generalized trust as predictors as well as their two-way (model 2) and three-way (model 3) interactions with social information and disease severity. In addition to the effects found in the previous model, there was a significant three-way interaction between the presence of social information, disease severity, and generalized trust, model 3: $B = -2.85$, $SE = 1.43$, $p = .046$, $OR = 0.06$, but this effect was mainly driven by a two-way interaction between social information and disease severity. As shown in Figure 2b, in cases of mild disease, the probability of taking the medicine decreased with increasing levels of trust, regardless of the social information condition. Trust was less important in cases of severe disease, but it decreased medicine intake somewhat more in the presence of social information (vs. absent).

To better understand how the individuals processed the feedback from the other player in the presence of social information, we regressed medicine intake in this experimental condition on the severity of the player's disease, the severity of the other player's disease, and the other player's decision in the previous round. We also included the participants' SVO and generalized trust as well as the measures' interactions with disease severity (Table 2, model 4). In addition to the effects shown earlier, there was also a main effect for the other player's decision in the previous round, $B = 1.42$, $SE = 0.56$, $p = .011$, $OR = 4.13$, indicating that the participants were more likely to take the medicine when the other player used it in the previous round.

Psychological effects of social information

To better understand the psychological effects of social information, we explored the participants' motivations, perceptions of the other player, and affect when information was absent versus when it was present. First, we conducted mixed-effects regressions to test the effect of social information and time (before vs. after playing the I-Resist game; treating participants and interaction groups as random effects) on each behavioral motivation, as reported by the participants.
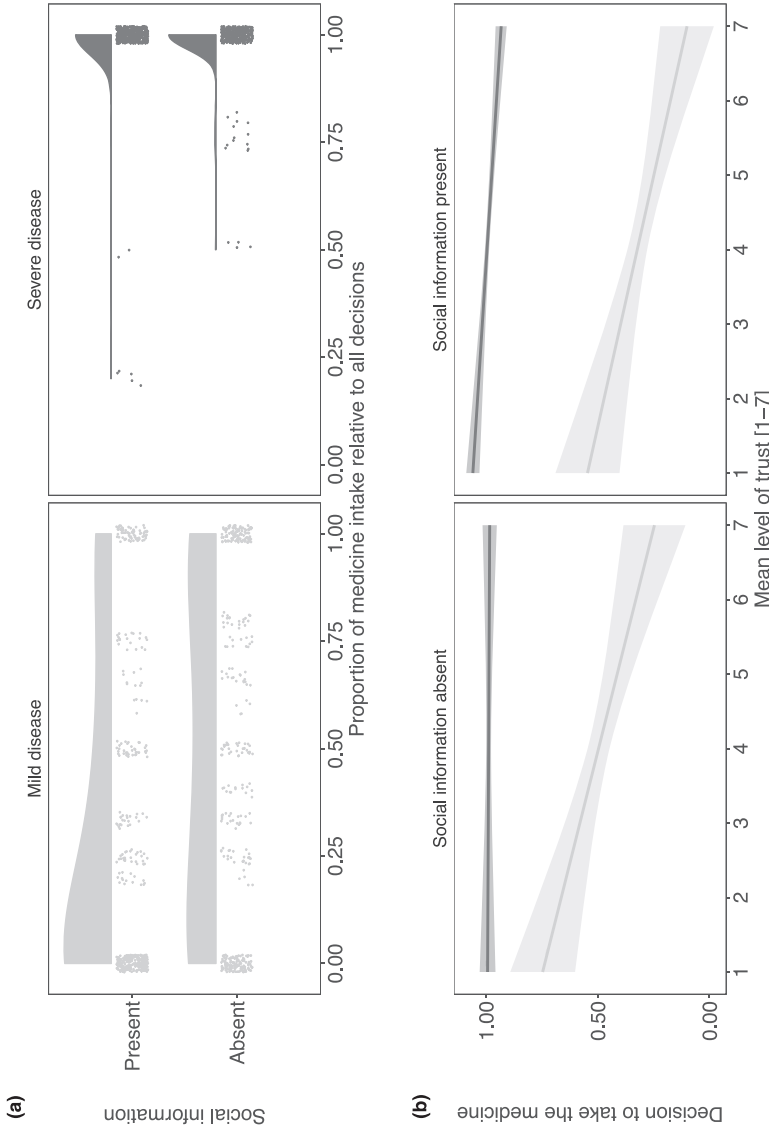
FIGURE 2 Proportion of medicine intake relative to all possible decisions as a function of disease severity and social information (panel a). Probability of taking the medicine as a function of disease severity, social information, and generalized trust (panel b). Note: Light gray: mild disease, dark gray: severe disease. (a) Dots represent single participants and display the proportion of medicine used relative to all possible decisions in which the medicine was effective. For example, if a participant took the medicine in three out of three cases (alternatively: four out of five), he/she received a value of 1 (0.8). Areas represent the density distribution across all participants. For the severe disease (right), the proportion of participants who took the medicine was high, irrespective of social information. In contrast, for the mild disease (left), the proportion of participants who took the medicine was low and lowest when social information was present. (b) Lines represent the proportion of participants taking the medicine across all rounds where the medicine was effective, depending on disease severity, social information, and generalized trust. Areas represent 95% confidence intervals. High-trusting individuals were particularly willing to cooperate by reducing medicine overuse

TABLE 2   Mixed-effects models predicting medicine intake in the Interactive Resistance (I-Resist) game in the social information condition

Predictors	Model 4		
	B	SE	p
Intercept	−1.47	0.47	0.001
Severity (A)	14.12	3.13	<.001
SVO angle (B)	−0.02	0.01	.207
Generalized trust (C)	−0.23	0.20	.234
Severity other player previous round (D)	3.36	3.16	.287
Decision other player previous round (E)	1.41	0.55	.011
Round	0.35	0.08	<.001
A * B	0.12	0.07	.107
A * C	−3.29	1.55	.033
D * E	−4.17	3.22	.196
A * D	−6.29	71.77	.930
A * E	2.40	71.76	.973
Observations/individuals/groups	914/132/66		
Marginal R^2/conditional R^2	0.802/0.944		
τ00 individual	0.64		
τ00 group	7.75		
ICC	0.72		
AIC/BIC	424.4/491.9		

Note: Participants and interaction groups were treated as random effects. Social information: −0.5 = Absent, +0.5 = Present; Severity: −0.5 = Mild, +0.5 = Severe. Decision of the other person in the previous round: −0.5 = No, +0.5 = Yes; Severity of the other person's disease in the previous round: −0.5 = Mild, +0.5 = Severe; Round: 2–10. SVO and generalized trust were mean-centered. *B*s represent unstandardized regression coefficients. Marginal R^2 refers to the proportion of variance explained by the fixed effects. Conditional R^2 refers to the proportion of variance explained by the fixed effects and the random effect. τ00 Individual = random effect for the individuals. τ00 Group = random effect for the groups. ICC = intraclass correlation for individual decisions nested within groups.

Here, we focused on the interaction effect of social information and time as this was an indicator of motivation change due to the participants' experiences in the different experimental conditions (for the complete list of regression models, including the main effects and the visualization of effects, see supplementary materials). The results suggest a significant interaction effect of social information and time on distrust, $B = −0.44$, $SE = 0.18$, $p = .016$, indicating that distrust toward the other player decreased when social information was present but not when it was absent. Further, there was also an interaction effect on the motivation to maximize joint outcomes, $B = 0.34$, $SE = 0.15$, $p = .022$, indicating that this motivation decreased when social information was absent but remained constantly high when social information was present.

In a second step, we investigated how the participants perceived the other player's behavior after they had played the I-Resist game with versus without social information. A MANOVA showed that social information significantly affected the evaluation of the other person's behavior, Wilks' $\Lambda = .906$, $F(2, 131) = 6.757$, $p < .001$, $\eta_p^2 = 0.09$. Therefore, and as indicated in subsequent univariate ANOVAs, the participants were more satisfied with the behavior of the other

player, $F(1, 132) = 13.39$, $p < .001$, $\eta_p^2 = 0.09$, and rated the other player's behavior as fairer, $F(1, 132) = 9.788$, $p = .002$, $\eta_p^2 = 0.07$, when social information was present than when it was not.

Finally, a MANOVA showed a marginally significant effect of the social information condition on the participants' affect, Wilks' $\Lambda = .95$, $F(2, 132) = 2.991$, $p = .053$, $\eta_p^2 = 0.04$. Subsequent univariate ANOVAs predicting both positive and negative affect separately revealed that the participants perceived more positive affect when social information was present than when it was absent, $F(1, 132) = 4.485$, $p < .036$, $\eta_p^2 = 0.03$. There was no significant effect on the participants' negative affect, $F(1, 132) = 1.924$, $p = .16$, $\eta_p^2 = 0.01$.

DISCUSSION

Reducing the speed at which bacteria develop resistance to antibiotics is a pressing issue for global health (Laxminarayan & Heymann, 2012). Although antibiotic resistance is a natural phenomenon, it is accelerated by inappropriate and excessive intake of antibiotics, and therefore, it is partly a behavioral problem in nature (Centers for Disease Control and Prevention, 2019).

Summary and implications

By using a novel behavioral game paradigm to model the underlying social dilemma of antibiotic intake, this study helps to better understand the behavioral determinants of antibiotic resistance and the potential levers in fostering prudent use of antibiotics. Our results indicate that even when people are exposed to this social dilemma—requiring cooperative efforts to reduce antibiotic resistance—they are prone to selfishly overuse the medicine, thus sacrificing social welfare. This is remarkable because it indicates that merely communicating the interdependent incentive structure of antibiotic intake may not be sufficient in avoiding antibiotic overuse.

However, when individuals had mutual knowledge about their medicine intake, overuse decreased substantially. This means that individuals were more likely to create a social contract (Korn et al., 2020) of appropriate antibiotic intake when they shared their intake decisions with each other. On a conceptual level, this finding suggests that individuals indeed represent antibiotic intake as a social dilemma that can partly be solved by increasing trust. Moreover, there was some indication that high-trusting individuals showed less antibiotic overuse. Although this result should be interpreted with caution and should be replicated with more test power, it is in line with previous research showing that higher levels of country-level distrust in 19 European countries were associated with higher amounts of antibiotics consumed in these countries (Blommaert et al., 2014) and that participants with high levels of generalized trust were more willing to wait for antibiotic treatment (Rönnerstrand & Sundell, 2015).

The results suggest that providing social information on antibiotic intake is beneficial as several motivational processes were affected by the presence of social information. That is, the presence (vs. absence) of social information helped to decrease distrust, maintain the motivation to increase joint benefits, and increase perceptions of fairness. Thus, a possible implication is that policymakers and health campaigns should provide information about the detrimental societal effects of (over)using antibiotics (if not clearly indicated on the basis of medical grounds) as well as feedback about people's intake decisions (e.g., via digitalized feedback platforms). Indeed, social feedback, for example in the form of social comparisons, achievement of

collective goals, or mere visibility of own and others' behaviors, has been shown to positively affect several health decisions, such as vaccination (Korn et al., 2018), handwashing (Lapinski et al., 2013), or exercise and healthy diet behavior (Yun & Silk, 2011). Further, once a majority complies and foregoes antibiotics in the treatment of minor diseases, this descriptive norm should also be communicated.

Limitations

It should be noted that providing feedback about individual health behaviors raises ethical questions, for instance, regarding participant anonymity (both when assessing and sharing health-related data). Future research should therefore aim to show the effectiveness of providing social information when feedback is given in a more impersonal or anonymous way (e.g., by aggregating the decisions of several people).

Relatedly, the present manipulation of social information did not distinguish between the potential independent behavioral consequences of providing feedback about one's own behavior and receiving feedback about the behavior of others. For instance, the fact that the participants were aware of the other person's knowledge of their behavior—even though the pairing of participants was anonymous, and they did not know whom their partner was—could have increased their prosocial behavior (A. Bradley et al., 2018). One of the potential mechanisms underlying such an effect could be people's reputational concerns (e.g., Wu et al., 2016). Future research should aim to disentangle these effects and their underlying processes.

Finally, the behavioral-game setting relied on a social-dilemma perspective of antibiotic intake. Yet, not all people may be aware of this dilemma. In fact, how people decide about antibiotic intake may partly be driven by how they represent the decision-making situation in the first place; thus, more knowledge in this regard is needed.

Outlook

Our novel behavioral game may be used in future research to further illuminate individual factors related to antibiotic intake as well as to test policy interventions aimed at reducing antibiotic overuse (Rau et al., 2020). The I-Resist game provides a complementary method (in addition to survey studies or randomized controlled trials) to investigate factors related to individuals' antibiotic intake. In addition, the method provides a compromise between the high internal validity and controllability (but lower external validity) of survey studies and the high external validity (but lower internal validity and more complex implementation) of field studies. Further, the I-Resist game could be easily adapted, for instance, in terms of the number of players and behavioral incentives (e.g., costs of mild and severe illness). It would also be possible to model the diagnostic uncertainty (e.g., revealing whether the antibiotic helps to cure the illness only after a few rounds of illness), which is linked to the misuse of antibiotics (Teixeira Rodrigues et al., 2013). Additionally, to model the doctor's perspective (C. P. Bradley, 1992; Colman et al., 2019), one could include a third player to decide for (some of the) players. This would allow to investigate the interplay of patients' preferences and doctors' prescribing behavior. It is also possible to vary the way in which the participants communicate within the game or the interdependence of players' outcomes. In any case—and despite the advantages of our behavioral-game approach—we believe that it would be important to replicate the results

obtained in such an artificial environment with other methods (e.g., survey studies, randomized controlled trials).

Overall, our results should be seen as a starting point for researchers to provide policymakers with evidence-based interventions aimed at reducing antibiotic overuse. We propose that causal and comparably easy-to-conduct intervention studies using tools like the I-Resist game are advisable before implementing more costly randomized controlled trials. As such, social and behavioral scientists can help to better understand how to reduce antimicrobial resistance and, consequently, save lives.

CONFLICT OF INTEREST
None of the authors has to declare a conflict of interest.

ETHICS STATEMENT
Approval by an institutional review board was not mandatory for behavioral studies without invasive procedures or pharmaceutical treatments at the university where the study was conducted. The study was otherwise conducted in accordance with the guidelines by the World Medical Association's Declaration of Helsinki.

DATA AVAILABILITY STATEMENT
The supplementary materials, including the study instructions, supplementary results, data, and analysis code, are available via the Open Science Framework: https://osf.io/782gy/.

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ENDNOTES
[1] Note that we decided not to include rounds in which players would stay healthy as such rounds would yield no meaningful information about the social dilemma of antibiotic intake because there would be no value in taking antibiotics.

[2] Considering both random intercepts and slopes does not qualitatively change the results. Therefore, we decided to report results from the simpler model specification.

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