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Antibiotics Effectiveness Dynamics: Modelling Antibiotic Resistance in the Population and the Use of Rapid Diagnostic Tests

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Abstract

Antibiotic resistance is a global issue. This phenomenon threatens our health care system as well as other sectors, such as our global trade, our agriculture, and our environment. The social and economic costs of this resistance are enormous and will be a huge burden for families, governments and the global economy. Nevertheless, we must consider the efficacy of an antibiotic as a natural renewable resource, precious and scarce, that we must manage optimally and sustainably. The overuse, misuse, and inappropriate prescriptions of antibiotics are considered a major problem in the rise of antimicrobial resistance. Rapid diagnostic tests, as a public good, could greatly reduce inappropriate and unnecessary prescriptions. In order to understand how rapid diagnostic tests are one of the best strategies against the increase of antibiotic resistance, we propose a bio-economic model simulating the infection in population and the level of effectiveness of an antibiotic while introducing the use rapid diagnostic tests and a new susceptible population linked to antibiotic resistance. Our bio-economic model examines the interaction between infection transmissions (antibiotic-resistant and antibiotic sensitive) in population in a pricing policy of a monopolist who is protected by a patent.

Keywords: *Antibiotic resistance, antibiotic effectiveness, rapid diagnostic tests, infection control, dynamic population models, monopolist strategy.*

Resumé

La résistance aux antibiotiques est un enjeu mondial. Cette résistance menace évidemment notre système des soins de santé ainsi que d'autres secteurs, comme le commerce mondial, l'agriculture, et l'environnement. Les coûts sociaux et économiques de cette résistance sont énormes et représenteront un fardeau gigantesque pour les familles, les gouvernements et l'économie mondiale. Malgré tout, nous devons considérer l'efficacité d'un antibiotique comme une ressource naturelle renouvelable, précieuse et peu abondante, qu'il nous faut gérer de façon optimale et durable. La surutilisation et la prescription inappropriée des antibiotiques sont considérées comme un problème majeur dans la montée de la résistance aux antimicrobiens. Les tests de diagnostiques rapides, en tant que bien public, pourraient réduire considérablement les prescriptions inappropriées et inutiles. Afin de comprendre en quoi les tests de diagnostiques rapides sont l'une des meilleures stratégies contre l'augmentation de la résistance aux antibiotiques, nous proposons un modèle bioéconomique simulant l'infection en population et le niveau d'efficacité d'un antibiotique tout en introduisant l'utilisation des tests de diagnostiques rapides et une nouvelle population reliée à la résistance aux antibiotiques. Notre modèle bioéconomique examine l'interaction entre les transmissions d'infections en population (résistant aux antibiotiques et sensible aux antibiotiques) dans une politique de prix d'un monopoleur protégé par un brevet.

Mots clés: *Résistance aux antibiotiques, efficacité des antibiotiques, tests de diagnostic rapides, contrôle des infections, modèles de population dynamiques, stratégie monopolistique.*

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1. Introduction

The discovery of antibiotics has led to a revolution in our approach to healthcare. However, we rely heavily on them today and they are becoming less and less effective. The phenomenon of antimicrobial resistance (AMR) started long before the discovery of antibiotics early in the 20th century. A micro-organism may acquire the ability to resist the effects of an antibiotic by natural selection (the process whereby organisms better adapted to their environment tend to survive and produce more offspring) or by horizontal gene transfer (the process in by which an organism incorporates genetic material from another organism without being the offspring). [1] Bacteria have always developed resistance to survive in nature, but with a very low frequency. In an environment where there is a large presence of antibiotics because of human intervention, natural selection favours the survival of antibiotic-resistant bacteria. Bacteria multiply very fast and, because of genetic mutations (natural event – changes in the genome due to mistakes that enzymes make when copying DNA for its offspring), differences exist in their genetic makeup from one generation to the next. By wiping out most of the bacteria with antibiotics, a small portion would survive – the ones which are usually immune to the effect of an antibiotic. This small number of antibiotic-resistant bacteria are surrounded by all the resources within a body without any competition from the sensitive bacteria strain. These antibiotic-resistant bacteria then multiply and infect other bodies.

As a result, AMR currently threatens our healthcare system, global trade, agriculture, environment, as well as many other health sectors. The social and economic costs of this resistance are gigantic and represent an enormous burden on families, governments, and the global economy. The Review on Antimicrobial Resistance (the Review), was commissioned by the UK Government, who asked economist Jim O'Neill to analyse the global problem of rising drug resistance and propose concrete actions to tackle it internationally (RAR, 2016). The problem is considered one of the major threats to human health just as in the case of climate change. The Review shows that a continuation of the increase in antibiotic resistance would lead to the death of 10 million

[1] The theory of its action was first fully expounded by Charles Darwin in 1859 and is now believed to be the main process that brings about evolution. Contrary to popular belief, people do not become resistant to antibiotics, only the pathogen does.

people annually by 2050, and a reduction of 2 to 3.5 percent in Gross Domestic Product globally (these losses may rise up to USD 100 billion). In the US, for example, bacteria that are resistant to the first line of antibiotic treatments alone are causing around 2 million infections every year. This is costing the US healthcare system around USD 20 billion in excess costs each year (Smith and Coast, 2013). The Review also states that due to the AMR and the birth of multidrug-resistant bacterial strains, common infections are causing around 700,000 deaths every year (this number might be underestimated due to poor surveillance). Tuberculosis (TB) infections alone will cause nearly 200,000 deaths every year from multidrug-resistant bacteria. In India, antibiotic-resistant neonatal infections cause the deaths of nearly 60,000 newborns each year (Laxminarayan, 2013). What is more frightening is that we are down to using our *last line* of defence to treat diseases such as gonorrhoea because of the rapid development of drug-resistant strains and the lack of rapid diagnostic tests (Davies, 2013). If the new antibiotics fail, gonorrhoea-resistant bacteria may not be controlled, and no more treatment options would be available on the shelf.

Fortunately, with all the resources that countries have pooled together and with the addition of new public policies, including improving global surveillance of drug resistance and antimicrobial consumption in humans and animals, cutting unnecessary use of antibiotics, promoting early-stage and non-commercial research, and giving better incentives to promote investment for new drugs and improving existing ones, the combat against AMR seems promising. By transforming the way we use antibiotics, we can reduce unnecessary use, slowing down AMR (eliminating natural selection process for antibiotic resistant-bacteria) which will ultimately making existing drugs last longer. Nevertheless, we should still be very careful and consider the effectiveness of an antibiotic as a renewable natural resource that is both precious and scarce. We will have to manage it optimally and sustainably. With the help of bio-economic models described below, one can refine policy recommendations that account for epidemiological and economic aspects. AMR is a classic problem of an externality, both in terms of health and in the economic sense.

The overuse and misuse of antibiotics are considered a major problem in the rise of AMR. The Review demonstrates that the overuse of antibiotics may compromise modern medicine to such an extent that we would return to medieval-era medicine: many modern procedures, like surgeries, rely on the use of antibiotics to prevent infections. Should we be unable to prevent infections, many standard procedures of today may become out of reach. The team responsible for this study explains that doctors are frequently under pressure to treat patients quickly, leading to the overuse of unnecessary antibiotics. Furthermore, in Southern and Eastern Europe, around twenty to thirty percent of antibiotics are used without a doctor prescription, while in some parts of Africa this figure rises to almost one hundred percent (Laxminarayan et al., 2011). Particularly in those regions, antibiotics are easy to buy, and the lack of regulation certainly promotes overuse. The possibility of buying products online in several countries has also contributed to the increase of antibiotic resistance.

Inappropriate prescriptions have also contributed to the development of such resistance. Studies have shown that the length of antibiotic therapies is incorrect in thirty to fifty percent of cases. Furthermore, antibiotics are also widely used to induce growth and to prevent infections in farm animals and are extensively used in agriculture. An estimated eighty percent of antibiotics sold in the United States are used on animals, which are then ingested by humans. Studies carried out over 35 years ago already have shown that there is a transfer of resistant bacteria of farm animals to humans (Ventola, 2015). Finally, few new antibiotics are being developed in the pharmaceutical industry and obtaining regulatory approval is often an obstacle. This is explained by the fact that, unlike drugs that are used to treat chronic diseases, antibiotics are used for a short period, generate low profits and are often curative.

One of the main findings of the Review is that innovation in rapid diagnostic tests[2] (RDTs) can play an important role in the fight against antimicrobial resistance by reducing unnecessary consumption. In this case, newly developed rapid diagnostic tests would optimise treatment. In this study, Dr. Margaret Chan, Director General of the World Health

[2] They are diagnostic tests that can rapidly determine the type of an infection (viral vs. bacterial) allowing doctors to prescribe correctly for patients.

Organisation, stated that diagnostic tests can show whether an antibiotic is *actually* needed, and which one. Having rapid, low-cost, and readily available diagnostics is an essential part of the solution to solve the AMR problem. Thus, the use and development rapid diagnostic tests are crucial to solve the unnecessary antibiotic utilization problems.

Rapid diagnostic tests would greatly reduce inappropriate and unnecessary prescriptions. For example, in the US, out of 40 million people who received prescriptions for respiratory problems, about 13 million needed those antibiotics (Shapiro et al., 2009). In most cases, infections in the throat are either caused by a virus or bacteria. However, antibiotics do not work on viruses – without a rapid diagnostic test and with the pressure to treat the patient right away *just in case*, antibiotics will also be given to patients who are infected virally. Rapid diagnostic tests are urgently needed by doctors to help patients requiring immediate treatment. Such tests would be able to test for resistance, allowing doctors to give patients the most appropriate available medicine for them. In the case of gonorrhoea, doctors have sometimes stopped prescribing many older drugs due to an increase in antibiotic resistance in the population. However, studies have shown that over 70 percent of gonorrhoea cases in England and Wales were treatable with older drugs (Barry, 2009) such as penicillin.

RDTs represent one of the best strategies against the increase of antibiotic resistance. When treating patients, doctors should be able to test for resistance, allowing them to give patients the most appropriate available medicine and not rush by prescribing the newest antibiotics in treating a certain infection. The use of rapid diagnostic tests will not only improve direct outcomes, but it can also stop transmission rates by shortening the time that people are infectious, thus improving infection control and allowing us to protect our most valuable drugs by only using them when no other drugs would be effective.

The use of diagnostics can be viewed as a *public good* in which society benefits from the conservation of antibiotic effectiveness and the slow development of antibiotic resistance (Laxminarayan, 2010). However, there are near-term costs for physicians and patients being treated. According to the Review, without rapid diagnostic tests, normal tests would simply be too expensive and time consuming compared to the use of an

antimicrobial for doctors *just in case.* Even the use of traditional diagnostic tests, then, could help save costs and reduce waste at a system-wide level and help preserve the usefulness of antibiotics for all. Over the long-term, current related costs are just too high. Meanwhile, many drug companies, including those producing affordable generic antibiotics, have no commercial interest in the advent of rapid diagnostics, which would act to limit the number of antibiotics prescribed. The literature suggests that diagnostic innovation has been very slow, with limited financial incentives to sell or buy these innovative products. This paper will answer whether it is optimal for a firm (the monopolist) to invest in and develop such rapid diagnostic tests as well.

This thesis uses a bio-economic model to examine the interaction between infection transmissions within populations, antibiotic effectiveness (or resistance), and the use of rapid diagnostic tests in the pricing policy of a monopolist who is protected by a patent. More precisely, this study's aim is to develop a dynamic model analyzing the impact of using rapid diagnostic tests with a monopolist that controls fully and endogenously the effectiveness of an antibiotic as well as the market size (infected population) and treatment quantity. This thesis aims at answering the following research question: How does the behavior of a non-myopic monopolist change as a result of the availability of rapid diagnostics tests? We also want to answer how the rapid diagnostic tests benefit the society and what is the mechanism behind to preserve antibiotic effectiveness.

The resolution of our model concluded that an interior solution can be determined for a non-myopic monopolist where its marginal profit equals to the marginal cost plus an external cost which also takes into consideration the effectiveness of the antibiotic and the infected population. However, a smaller portion of the population will be treated for the non-myopic monopolist with rapid diagnostic tests in society. A simulation in continuous time of our models shows that the increased use of rapid diagnostic tests benefits society by maintaining the effectiveness of the antibiotics and by reducing the number of a newly introduced population in our model – healthy individuals who are prone to antibiotic resistance (we will explain this new concept further below and how it is linked to the antibiotic resistance problem). It is also important to notice that our current model

incorporating rapid diagnostic tests do not seem to align with the monopolist incentives. We support novel incentive mechanisms where we introduce a de-linked system and a dual-pricing model to be used as a reward model for the monopolist to ensure a viable market.

2. Literature Review

In this section, we will be conducting a literature review on key issues, concepts, contributions, and results related to the fight against antibiotic resistance and explore the foundations on which to build our bio-economic model in Section 3. First, we will analyze a few epidemiological models on the transmission of infections in populations (epidemiological component). We will then discuss the effectiveness of antibiotics as a natural resource to better understand the phenomenon of antibiotic resistance (the economic component). Finally, we will link the problem of resistance to similar problems in the field of natural resources management. In this case, we will study a bio-economic model that treats the effectiveness of an antibiotic as a scarce natural resource while characterizing the pricing policy of a patent-protected monopolist.

2.1. Epidemiological Component

a) Basic Compartmental Models

The book *Compartmental Models in Epidemiology* (Brauer, 2008) introduces mathematical epidemiology and presents models to study the underlying mechanism for the spread of disease. Brauer formulates the models with the population under study as being divided into compartments and with assumptions about the nature and time rate of transfer from one compartment to another.

For example, the “SIR” model or the Kermack-McKendrick model describes and computes the theoretical number of people infected with a contagious illness in a closed population over time. To model this, the population is being studied into three classes labelled S, I, and R. S(t) denotes the number of individuals who are susceptible to the disease but no infected. I(t) denotes the number of infected individuals, who are assumed to be infectious and able to spread the disease by contact with a susceptible individual. R(t) denotes the number of individuals who have recovered from infection and are then removed from the possibility of being infected again or of spreading infection. The starting point for the study of an epidemic model is (in rate of change):

$$S' = -\beta SI$$

$$I' = \beta SI - \alpha I$$

$$R' = \alpha I$$

Since the probability that a random contact by an infected individual with a susceptible individual who can then transmit infection is $(\frac{S}{N})$, the number of new infections in unit time per infected individual is (βN)$(\frac{S}{N})$, giving a rate of new infections: (βN) $(\frac{S}{N})$ I = βSI. Alternately, it can be said that, for a contact by a susceptible individual, the probability that this contact is with an infected individual is $(\frac{I}{N})$ and thus the rate of new infections per susceptible individual is (βN) $(\frac{I}{N})$, giving a rate of new infections: (βN) $(\frac{I}{N})$ S = βSI.

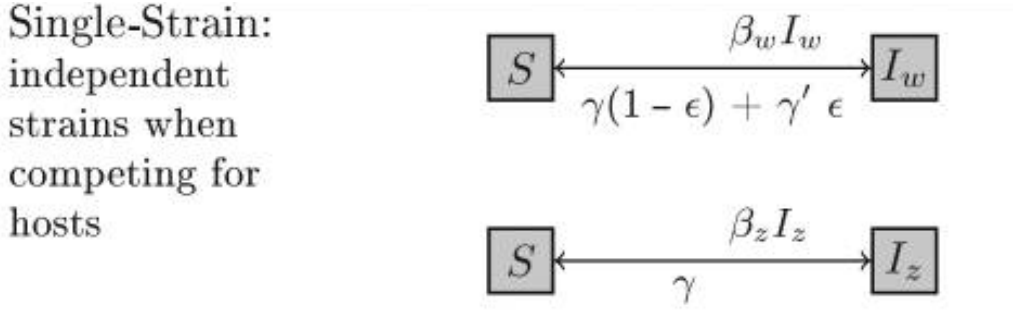
The bio-economic model presented in Section 3 of this paper will borrow from the epidemiological literature the basic compartmental models and their underlying assumptions. In our model, we will assume that the infection takes place with rate βN per unit time and that the infected individuals will leave the infected class when they become healthy. However, infections do not give immunization upon recovery and healthy individual will become susceptible again and might develop a resistance to a treatment.

b) Models with the Evolution and Spread of Antibiotic Resistance

Advanced epidemiological studies were conducted to model the spread of antibiotic-resistant and antibiotic-sensitive bacterial strains from one host to another (Spicknall et al. 2013). The authors show how between-host models are categorized considering the basis of properties of within-host dynamics of antibiotic-resistant and antibiotic-sensitive bacterial strains. Within a host, resistant and sensitive bacteria strains can coexist either at equal levels or where one strain predominates over the other. In contrast, a host may be infected exclusively by a resistant or sensitive strain if coexistence is not permitted. Within-host competition can have differing results; if a host is infected with one strain, there is potential for a novel strain to replace the resident strain. If a host is superinfected with both sensitive and resistant strains, a predominant strain may

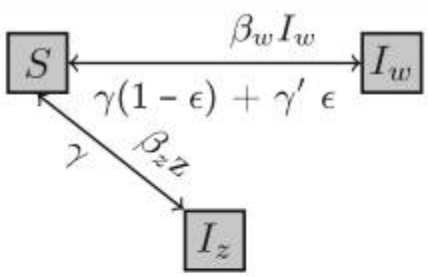
convert from sensitive to resistant or vice versa. The extent of within-host strain coexistence can be characterized in one of three ways described below:

1. In the first case, coexistence will occur within a host with strains of bacteria (resistant or sensitive) at even levels. Both strains of bacteria can infect a host (S) – sensitive or resistant infections. In this case, the presence of one bacterial strain has no effect on the presence of another, indicating no competition of resources at the within-host level or for hosts at the population level. There will be no strain conversion or strain replacement. By referring to the SIS model explained above, coexistence will add a level to the SIS model as presented in the diagram below where I_w and I_z represent infected individuals with antibiotic resistant and sensitive strains of bacterial respectively. We observe both sensitive and resistant infections. γ and γ' represent of the recover rates of for both bacterial strains. ε represents the portion of the population receiving a treatment.
2. In the second case, within-host coexistence will not be allowed. This case does not allow strain conversion. Infected individuals will be infected exclusive by one strain of bacteria, and a novel strain may not infect the strain already present in the host. Sometimes, in a replacement infection model, there is a potential for replacement

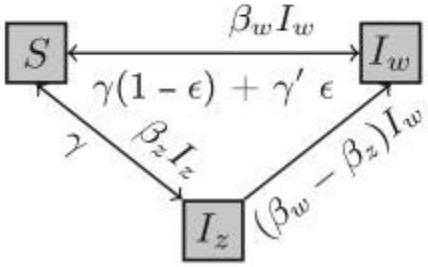


infection when a novel strain challenges a resident strain within a host, while coexistence is still not allowed. The diagram below represents this model when coexistence is not allowed.

Exclusive Infection: hosts can only be infected with either I_W or I_Z

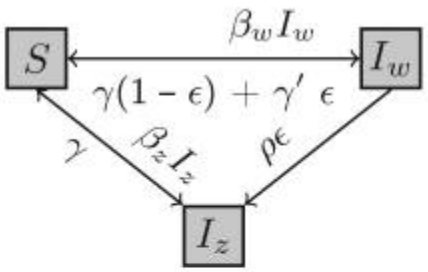


Replacement Infection: I_W may replace I_Z at reinfection

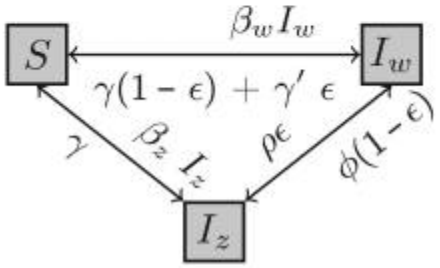


3. In the last case, within-host coexistence can happen for both antibiotic-sensitive and antibiotic-resistant bacterial strains. They occur at uneven levels including both the unidirectional and bidirectional conversion of antibiotic sensitive and resistant strains. In this case, there is an implicit majority-minority relationship between the frequency of coexisting sensitive and resistant strains within a host. Neither of these structures allow for complete replacement infection (dominance of one bacterial strain), while both allow for strain conversion. This conversion can be in one direction (unidirectional), usually conversion of sensitive to resistant, or two directions (bidirectional), where predominantly sensitive infections may convert to resistant and vice versa. The authors propose two models: Sensitive-to-Resistant Conversion and Resistant-to-Sensitive Conversion. The diagram below represents the conversions augmenting the SIS basic model. ρ and φ represents the conversion rates.

Unidirectional Conversion: I_W to I_Z at constant rate



Bidirectional Conversion: I_W-to-I_Z and I_Z-to-I_W, each at constant rates



The models presented in the third case will serve as an important basis for the bio-economic model presented in this paper because of the strain conversion within the host due to competition and coexistence of the two trains. In such a case, the effectiveness of an antibiotic can be restored. This phenomenon is further explored and explained below.

2.2. Economic Component – Effectiveness of an Antibiotic as a Scarce Natural Resource

a) Fitness cost of antibiotic resistance

The foundation of the economic model developed in this paper is based on the phenomenon by which bacteria with antibiotic-resistant genes must also pay a price, or an “opportunity cost”, to survive. Research has shown that, in some cases, the resistant bacteria cannot reproduce very well and tend to have a higher mortality rate in an environment without antibiotics (Bjorkman et al., 1998). Scientists call this phenomenon “the opportunity cost of antibiotic resistance”, or the “fitness cost of resistance”. There is

a cost associated with the gain of resistance, and in the absence of antibiotics, resistant bacteria tend to reproduce more slowly than non-resistant bacteria. Hence, there is competition between antibiotic-resistant bacteria and non-resistant bacteria for resources to survive inside their hosts.

The opportunity cost can be an important factor contributing to the renewal of antibiotic effectiveness (Laxminarayan, 2010). To preserve the effectiveness of an antibiotic, there is a need to study how resistant bacteria and non-resistant bacteria interact. It is important to establish a model that takes the effectiveness of our antibiotics as a scarce natural resource in the same way economists model the extraction of renewable but depletable resources. Just like other natural resources, an optimal management of the effectiveness of our antibiotics is determined by biological dynamics, the evolution of resistant bacteria, the spread of infections, and the demand for treatment in a market.

b) Renewable Natural Resource

The bio-economic model presented in this paper will also consider the effectiveness of antibiotics as a renewable natural resource. This assumption is based on theories developed by Wilen and Msangi (2003). They are the first ones to consider the effectiveness of an antibiotic as a renewable natural resource since some bacteria pay an opportunity cost (fitness cost) to gain resistance which represents an evolutionary disadvantage in an environment without antibiotics. In an environment where the supply of antibiotics, or treatment rate, is low enough, the population of antibiotic-sensitive and antibiotic-resistant bacteria strikes a balance. Researchers show that the effectiveness of an antibiotic can also be regenerated to reach an equilibrium. The objective of Wilen and Msangi's economic theory is to minimize the discounted social costs associated with infections in populations. The researchers demonstrated that the best solution, according to their model, would be to offer an extreme initial treatment followed by an intermediate treatment to the population.

Furthermore, the dynamic model developed in this thesis is based on the foundations laid by Herrmann & Gaudet (2009). Their ideas compare the optimal use of antibiotics when there is an open-access regime. They demonstrated that contrary to the

competitive producers in an open-access regime, the socially optimal solution takes into account the fact that the current treatment decision affects both the future level of efficacy of the antibiotic and the future stock of infected population. Following that, the model developed by Herrmann (2010) demonstrated that a monopolist protected by a patent will behave optimally taking into consideration the future level of antibiotic effectiveness and infected individuals. However, when the patent expires, the monopolist will begin acting more and more myopically leading to an open-access regime. When giving a prolongation of the patent, the monopolist will behave in favour of preserving the effectiveness of an antibiotic, however, it will also favor the spread of infection (market size

2.3. Externality and Optimal Use

In addition, the dynamic model developed in this paper will also compare the social choice of having rapid diagnostic tests being used by a monopolist who is protected by a patent. The model builds on Herrmann and Laxminarayan (2010), in which they state that medical treatment with antibiotics involves benefits and external or non-controllable costs for the person receiving this treatment. By healing the sick suffering from a contagious disease, there will be a positive externality in society: there will be fewer infections in the future and fewer people that can transmit the disease. However, the cost of using an antibiotic is not only the price of the treatment paid by the patient, the government or the insurance provider. There is also a negative externality, or a fictitious cost (shadow price), associated with the reduction in the effectiveness of an antibiotic. Ideally, an antibiotic should be used when the full marginal benefits equal or exceed the full marginal costs.

Our paper also examines the dynamics of infections in two cases: when physicians make use of rapid diagnostic tests, and when they don't. When rapid diagnostic tests are not used, physicians often use the most effective antibiotic. Researchers found that, according to the cost of production and the relative speed in which the efficiency decreases, it is ideal to use a single antibiotic initially (Laxminarayan & Brown 2001). For example, when two drugs have similar production costs, but differ in their level of efficiency, the most effective antibiotic should be used first, since it offers a wider possibility of effective treatments to avoid future infections. This phase continues until the

two antibiotics are equally effective; then, it becomes more efficient to ensure that their use is inversely proportional to the rate at which their effectiveness is reduced.

However, in many cases, powerful antibiotics should ideally be kept in reserve and only be used in a case where the infections cannot be stopped by older medications. For example, as explained earlier, the last line of defence (the most powerful antibiotics) to treat gonorrhoea is prescribed as a precaution for almost all patients, although 70–80% of the older antibiotics could be used. This paper will build a model in which doctors can know if infections are resistant or not and examine the optimal use of antibiotics.

Our dynamic model also explores the market structure in which rapid diagnostic tests are used. Before a patent expires, only one company sells the antibiotic and controls the evolution of its effectiveness. The basic idea came from Mechoulan (2007) and the paper shows that even if it is socially optimal to eradicate an infection, a monopolist will not do so because the spread of the infection represents the market size. The author also shows that the reactivation of a patent after its original expiration can improve the well-being of the population. This occurs when the price given by a monopolist approaches a price that is socially optimal (higher), while the price set by the generic manufacturers is not socially optimal (lower). Therefore, for the development of our dynamic model, it is essential that the monopolist can choose the level of antibiotic effectiveness for a fraction of the population being treated (endogenous).

2.4. The Bio-Economic Model of Herrmann (2010)

a) The Model

To analyse the effect of rapid diagnostic tests in the population and for a monopolist as well as the social benefit derived from them, the dynamic model built in this paper uses a structure developed by Herrmann (2010). In the author's model, the global population is constant and equals N. The healthy population is given by S = N - I, where I is equal to the infected individuals. The infected population I is composed of two sub-populations: the people infected with bacteria susceptible to an antibiotic (I_w) and those infected by bacteria resistant to an antibiotic (I_r). Both versions of bacteria are naturally present in the system (coexistence). β is the rate of transmission of infection within the healthy population and the infected population. The time it takes for one person to infect another is given by terms (2.1) and (2.2) at the change at time *t* (rate of change).

$$\boldsymbol{\beta S(t) I_r(t)} \tag{2.1}$$

$$\boldsymbol{\beta S(t) I_w(t)} \tag{2.2}$$

The problem of antibiotic resistance is determined by a dominant presence of antibiotic-resistant bacteria (I_r) in the system because antibiotic-sensitive bacteria (I_w) are eliminated by antibiotics (phenomenon of natural selection). In this context, the author presents a model (equation 2.3) to measure the effectiveness of an antibiotic (*w*) at time *t* by the proportion of those infected by the antibiotic-sensitive bacteria (I_w) from the infected population overall, or ($I_w + I_r$).

$$\boldsymbol{w = \frac{I_w}{I_w + I_r} = \frac{I_w}{I}} \tag{2.3}$$

The author also states that the infected population can recover naturally. The natural recovery rate when infected with non-resistant bacteria is given by r_w and the natural recovery rate for the population infected with resistant bacteria is given by r_r. If all infected people, I, are treated with an antibiotic, the recovery rate for those infected by resistant bacteria is unchanged, while the recovery rate for those infected by susceptible bacteria becomes $r_w + r_f$ where the variable r_f represents the additional recovery rate when given treatment.

If a fraction $f \in [0, 1]$ of the infected population is treated with the antibiotic (endogenous to the monopolist), the recovery rate for those infected by susceptible bacteria would be $r_w + fr_f$, where the total population infected decreases with a rate of $r_r I_r(t) + (r_w + fr_f) I_w(t)$.

$$\dot{\boldsymbol{I}}_{\boldsymbol{w}} = (\boldsymbol{\beta S} - \boldsymbol{r}_{\boldsymbol{w}} - \boldsymbol{f r}_{\boldsymbol{f}}) \boldsymbol{I}_{\boldsymbol{w}} \tag{2.4}$$

$$\dot{\boldsymbol{I}}_{\boldsymbol{r}} = (\boldsymbol{\beta S} - \boldsymbol{r}_{\boldsymbol{r}}) \boldsymbol{I}_{\boldsymbol{r}} \tag{2.5}$$

$$\dot{\boldsymbol{S}} = -\dot{\boldsymbol{I}} = -\dot{\boldsymbol{I}}_{\boldsymbol{w}} - \dot{\boldsymbol{I}}_{\boldsymbol{r}} \tag{2.6}$$

The differential equations (2.4) to (2.6) represent the dynamics within the population. Equation (2.4) states that the change of people infected with susceptible bacteria is affected by the transmission rate, the natural recovery rate and the recovery of a fraction of the population *f* who is getting the treatment. Equation (2.5), meanwhile, says that changing infected bacteria into resistant bacteria is affected by the transmission rate and the natural rate of recovery. Finally, equation (2.6) indicates the change in the healthy population. Using these equations and a total differential of equation (2.3), the author derived the following differential system:

$$\dot{\boldsymbol{w}} = \boldsymbol{w}(\boldsymbol{1} - \boldsymbol{w})[\boldsymbol{\Delta r} - \boldsymbol{r}_{\boldsymbol{f}} \boldsymbol{f}] \tag{2.7}$$

$$\dot{\boldsymbol{I}} = \boldsymbol{I}\big(\boldsymbol{\beta}(\boldsymbol{N} - \boldsymbol{1}) - \boldsymbol{r}_{\boldsymbol{r}} + \boldsymbol{w}[\boldsymbol{\Delta r} - \boldsymbol{r}_{\boldsymbol{f}} \boldsymbol{f}]\big) \tag{2.8}$$

Equation (2.7) represents the change in the effectiveness of an antibiotic at time *t* and equation (2.8) represents the change in the infected population at time *t*. The author indicates that $\Delta r = r_r - r_w$, which measures the opportunity cost of resistance we mentioned in the previous section. The author shows the two important effects in its dynamic system (Equation 2.7).

The first effect is explained by Δr. If $\Delta r = r_r - r_w$ is positive, this means that resistant bacteria must incur an opportunity cost of the resistance in the absence or low presence of antibiotics. As a result, people infected with resistant bacteria have a natural recovery rate greater than those infected by susceptible bacteria. In other words, the effectiveness of an antibiotic is renewable (because of this opportunity cost) in the system

determined by w (Equation 2.3). The other effect is represented by natural selection (selecting antibiotic resistant bacteria). The additional rate r_f (with antibiotic treatment) in the recovery of infected people by susceptible bacteria potentially leads to the domination of resistant bacteria because antibiotics will remove all non-resistant bacteria in the system (antibiotic-resistant bacteria no longer need to compete against non-resistant bacteria). If a fraction of the infected population ($f = \frac{\Delta r}{rf}$) is treated with an antibiotic, the two effects cancel each other out. For all other values of *f*, a dominant effect, leading to an increase or a decrease of the level of effectiveness of an antibiotic. Assuming that both the fitness cost effect and the natural selection effect are apparent in the system, we must have $f = \frac{\Delta r}{rf} < 1$.

The probability of recovering from infection without antibiotic treatment is defined as $\pi(w) = wr_w + (1-w)r_r$. A higher probability is given to infection with antibiotic treatment:$(\pi(w) + wr_f)$. We will model demand as the same way Herrmann derived demand, by using the following utility function (Equation 2.9). The inverse demand function (Equation 2.10) is derived from the utility of a type of individual who is indifferent between buying the antibiotic or not when infected.

$$u(\theta) = \begin{cases} \theta & \text{if in good health} \\ \pi(w)\theta & \text{if infected and not taking the antibiotic} \\ [\pi(w) + r_f w]\theta & \text{if infected and taking the antibiotic.} \end{cases} \quad (2.9)$$

$$\boldsymbol{P(f,w) = r_f w(1-f)} \quad (2.10)$$

In the case of a monopolist, if a patent exists, assigning exclusive rights to the firm to sell the antibiotic for an exogenously give period of time after which the antibiotic is sold by a generic industry, a non-myopic monopolist will consider the impact of his current decisions on future levels of antibiotic efficacy and infection, and thus on the evolution of the quality of his product and its market size over time. Equation 2.10 is used to derive profit maximization. The objective function of the monopolist is given by equation 2.11 below:

$$\max_{\{0\leq f(t)\leq 1\}} \int_0^T e^{-\rho t}\Pi(t)dt + V^g(T) \tag{2.11}$$

The first order conditions can be derived from the differential systems with equations (2.7) and (2.8) as constraints. The current-value Hamiltonian associated to problem (2.11) is given by (2.12) below:

$$\boldsymbol{H(f,w,I,u,\lambda) = \left[r_f w(1-f) - c\right]fI + uw(1-w)\left[\Delta r - r_f f\right] + \lambda I(\beta(N-I) - r_r + w[\Delta r - r_f f]} \tag{2.12}$$

Its derivative with respect to the control variable is given below with equation 2.13 below:

$$\frac{\partial H}{\partial f} = [r_f w(1-2f) - c]I - r_f w[\mu(1-w) + \lambda I] \tag{2.13}$$

$$\frac{\partial H}{\partial f} \leq 0, \qquad \frac{\partial H}{\partial f} f = 0,\ f \geq 0 \quad \text{or} \quad \frac{\partial H}{\partial f} \geq 0, \quad \frac{\partial H}{\partial f}(1-f) = 0,\ f \leq 1 \tag{2.14}$$

Equation 2.13 is the first-order condition for the maximization of the Hamiltonian with respect to *f(t)* at each instant *t*. The author states that with condition written in equation 2.13, it can never be optimal for the monopolist to sell the antibiotic with a fraction ($f = 1$) of the population. This gives a negative current profit without generating profits in the future. By setting $f = 1$, it inevitably decreases the level of antibiotic efficacy and infection, or at least decelerates the increase in the level of infection, and thus negatively affects the future quality and market size of the antibiotic. It is therefore necessary to have $\partial H/\partial f < 0$. However, it may be optimal to have $f = 0$, thus postponing production and allowing antibiotic efficacy and infection to rise as fast as possible.

There are arbitrage equations that determine the evolution of $u(t)$ and $\lambda(t)$ over time and transversality conditions which states that if there is a strictly positive stock of antibiotic efficacy or of the infected population left at the end of the patent lifetime ($w(t) > 0$, $I(t) > 0$), then that stock must be of no value to the non-myopic monopolist. The same reasoning applies in the limit as *t* tends to infinity in the case of an infinitely long-lasting patent.

In the case of an interior solution, ($0 < f^m < 1$), 2.13 can be written as the following with the condition 2.14 to give 2.15 below:

$$r_f w(1 - 2f^m) = c + \frac{r_f w}{I}[\mu(1 - w) + \lambda I] \tag{2.15}$$

The **Diagram 2.1** below shows the monopolistic interior solution f^m at state (*w, I*) at time *t*:

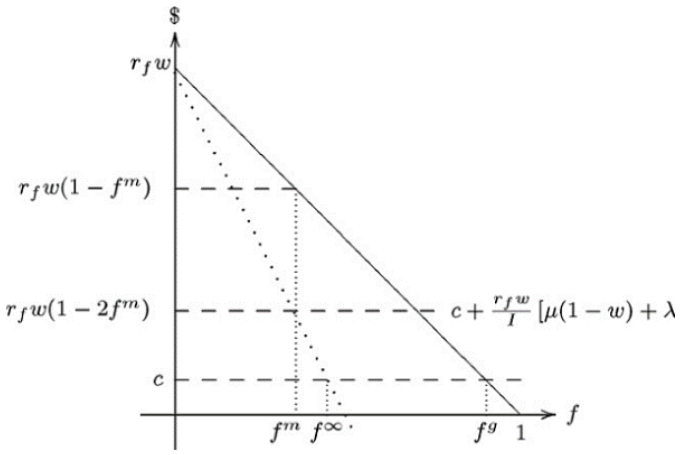


Diagram 2.1: Monopolistic interior solution f^m at state (w, I) at time *t*

The author shows that for an interior solution (f^m), the marginal benefit (($r_f w(1 - 2f^m)$) equals the marginal cost (*c*) plus an external cost that takes into consideration the effectiveness of the antibiotic (*w*) and the infected population (*I*). This reflects the fact that the stock of the infected population can be viewed as an "asset" by the monopolist, since it represents market size when the antibiotic is economically viable. As explained above, whenever $\frac{\Delta r}{rf} \in [1/2, 1]$, the fitness cost effect dominates, i.e. the level of antibiotic efficacy will be increasing over time, as the optimal fraction f served by the monopolist will always be lower than 1 /2 (for c > 0)

Our dynamic model retains the structure developed by Herrmann but contains three additional items. First, there is the addition of a new category of susceptible population. This population is a susceptible and healthy population that is prone to resist

certain antibiotics due to prior use (infected population who was recently treated and became healthy) and due to the presence of antibiotic resistance in the environment. Secondly, the use of rapid diagnostic tests is added to the dynamic model. The model will analyze the impact of using rapid diagnostic tests on a monopolist who controls the market size and derive the social benefit from it. Lastly, the model will provide a more in-depth analysis of the interaction between infected, non-infected populations and the effectiveness of an antibiotic. The different theories will be further examined in the following section.

3. Theoretical Modelling

In this section, we develop a theoretical model that considers the impact of rapid diagnostic tests and model the transmission of antibiotic resistance in a more sophisticated way. The incorporation of a mechanism of infection transmission in the model will allow us to better understand the antibiotic resistance that is generated. The conceptual framework underlying our model is the one developed by Herrmann (2010) where a monopolist is protected by a patent who controls the effectiveness of an antibiotics. However, the transmission mechanism and the population dynamics are specific to this thesis. As mentioned above, our dynamic model will contain three additional items – a new category of susceptible population, the use of rapid diagnostic and an in-depth analysis of the interaction between infected, non-infected populations and the effectiveness of an antibiotic. After presenting the theoretical framework of our model, we will also simulate the social benefit that is generated by rapid diagnostic tests.

3.1. Model

a) The Bio-Economic Model

In our model, we define that the healthy population is given by $S = N - I$, where I is equal to infected individuals. The infected population I is composed of two sub-populations: the people infected with bacteria susceptible to an antibiotic and those infected by bacteria resistant to an antibiotic. Both versions of bacteria are naturally present in the system (with-in hot coexistence). β is the rate of transmission of infection within the healthy population and the infected population.

We present below our assumptions regarding the transmission of infections and antibiotic resistance. We formulate the population dynamics with the following terms and definitions:

$\boldsymbol{S^{NR}}$**:** Susceptible and healthy population that is not prone to infections by antibiotic-resistant bacteria.

$\boldsymbol{S^{R}}$**:** We introduce a new category of healthy population and we will incorporate the "competing bacteria" model. When a patient has been exposed to resistant bacteria,

traces of it remains in the body, so that future infections are more likely to be by antibiotic-resistant bacteria**.** This new population in our model therefore represents susceptible and healthy population that is prone to resist certain antibiotics due to prior use and/or the presence of antibiotic resistance in the environment.

$\boldsymbol{S}$**:** The overall healthy population, which is equal to $S = N - I$.

$\boldsymbol{I^C}$**:** Infected population with a non-resistant bacterial strain or sensitive bacterial strain. Therefore, we assume that this population can be cured with the available antibiotics.

$\boldsymbol{I^{NC}}$**:** Infected population with a resistant bacterial strain. Therefore, we assume that this population cannot be cured.

$\boldsymbol{N}$**:** The overall population, which is assumed to be constant.

$\boldsymbol{I}$**:** The overall infected population, $I = I^C + I^{NC}$.

Moreover, we will also assume different types of infection and recovery relative to different types of infected populations. These are further explained below. Each of the following paragraphs corresponds to an arrow on **Diagram 3.1** on page 36. We explain the each of the type of transmission below based on our understanding of epidemiological models (Spicknall et al. 2013).

1. Susceptible Healthy Population Conversion

The S^R population will not indefinitely carry within them the signs of antibiotic resistance acquired from prior use or misuse of antibiotics. We assume that traces of antibiotics in the body of the S^R population will eventually disappear, so that a fraction δ of this population will become a healthy susceptible population that is not prone to resist to antibiotics again (S^{NR}).

δ**:** Rate at which the resistance in the susceptible population disappears.

2. Curable Infection

We assume that there exists an antibiotic to efficiently treat a case of sensitive bacterial strain infection. In this case, the transmission is from antibiotic-sensitive bacteria (instead of resistance to the one antibiotic used). This results in an interaction between S^{NR} and I^{C}. We will also define the transmission parameter β_c and assume it to be specific to a sensitive bacterial strain.

$\boldsymbol{\beta_c}$: Rate of transmission of non-resistance infection or sensitive infection. These infections are caused by a non-resistant bacterial strain (or sensitive strain) between healthy and infected populations. This term determines the rate of addition at time *t* to the infected population (I^{C}) or the rate at time *t* at which the infected population (I^{C}) grows. The rate of addition is given by $\beta_c S^{NR}(t) I^{C}(t)$.

3. Curable Natural Recovery

The recovery from an infection with the antibiotic-sensitive bacterial strain occurs naturally. This means that our immune system can often take care of this type of infection, or that the bacteria itself will not survive long enough in our body. If there is no antibiotic treatment in a population, this natural recovery occurs at an innate and constant rate r_c. Since a portion *f* of the population will be given treatment, only 1-*f* of the population can naturally recover.

$\boldsymbol{r_c}$**:** Natural recovery rate from non-resistant infection, or the recovery rate without antibiotic treatment for a non-resistant bacterial strain.

$\boldsymbol{f}$**:** Fraction of infected population treated with antibiotics and $f \in [0,1]$. Thus, 1-*f* will be the population that will naturally recover.

4. Non-Curable Natural Recovery

Populations can also be infected with antibiotic-resistant bacteria that are non-curable. We assume that there are no antibiotics to treat this type of infection. However, natural recovery from this infection is possible, thanks to one's immune system or some other conditions that inhibited their survival (i.e., the fitness cost). This occurs at a rate of r_{NC}, which is not modified by antibiotic treatment. Therefore, the population that went through non-curable natural recovery and did not receive treatment is also 1-*f*.

r_{NC}: Natural recovery rate from resistant infection, or the recovery rate without antibiotic treatment of a resistant bacterial strain.

5. Non-Curable Infection

In this case, the infection is transmitted from antibiotic-resistant bacteria. This results in an interaction between S^{NR} and I^{NC} with a rate of transmission denoted by β_{NC}, which we assume to be specific to the resistant strain. In some cases, in order to express the fact that the resistant strain is less "fit" than the sensitive strain, we take β_{NC} to be no greater than β_C.

β_{NC}: Rate of transmission of resistant infection (non-curable infection). These infections are caused by a resistant bacterial strain. This term determines the rate of addition at time *t* to the infected population (I^{NC}) or the rate at time *t* at which the infected population (I^{NC}) grows. The rate of addition at time *t* is given by $\beta_{NC} S^{NR}(t) I^{NC}(t)$.

6. *Curable to Non-Curable Conversion*

In the case of mixed infections, or where both resistant and sensitive bacterial strains coexist in a host body, the resistant strain sometimes becomes the predominant strain. This phenomenon is the consequence of the *natural selection* effect. The use of antibiotics in a population will most likely eliminate all nonresistant or sensitive bacterial strains in our body so that there is no competition left for the resistant strain. This strain conversion, from sensitive to resistant, depends on the antibiotic treatment proportion *f* and the rate ρ at which the resistant strain outcompetes the sensitive strain in the presence of antibiotics. Under the presence of antibiotics, the resistant minority of bacteria within the host takes over at rate ρ as a function of the resistant strain replication rate, the reduced sensitive strain replication rate, and the death rate of sensitive bacteria from antibiotic exposure. The mixed infection could result in either 1) reinfection with one or more strains; 2) initial infection with a heterogeneous bacterial population, some with and some without the resistant trait, rather than a homogeneously sensitive population. In our work, to simplify our model, we assume that this conversion does not occur, or ρ = 0. In the literature, this sort of infection is called a single-strain infection, or exclusive infection.

ρ: The amplification rate of resistant strains under antibiotics. This rate depends on population treatment level f. This is also the failure rate, which can be written as $1 - r_f$.

7. Non-Curable to Curable Conversion

If we assume that there is in-host strain coexistence, then sometimes there is also a conversion from resistant to sensitive strains. This phenomenon is the consequence of the *fitness cost* effect. A rate of amplification for the non-resistant bacteria is determined by φ and the proportion of the population not receiving antibiotic treatment, $(1-f)$. φ is very similar to ρ above. Assuming that there is a mixed infection with predominantly resistant bacteria and some sensitive bacteria, the absence of antibiotic treatment in a host body results in the sensitive bacteria outcompeting the resistant bacteria at rate φ. The underlying *fitness cost* effect could be explained by the mechanism of loss of resistance through backwards mutation or plasmid loss; again, to simplify our model, we assume that this conversion does not occur, or φ = 0.

8. Curable Recovery with Resistance

When the I^C population is receiving a treatment, its recovery will occur at a faster rate defined by r_f. If only a proportion of the population, *f*, is receiving the antibiotic, we assume that the recovery rate from I^C is a function of r_C and r_f. The expected recovery rate from I^C would then be: $r_c(1-f) + r_f f$. The population that will naturally recover will be the $1 - f$ portion. In the other case, the healthy population having recovered from antibiotics is defined as S^R (and not S^{NR}) because we assume that traces of antibiotics will remain inside the host's body for some period of time. Thus, the rate of addition at time *t* for S^R is given by $f r_f I^C(t)$.

$\boldsymbol{r_f}$: Recovery rate with antibiotic treatment. r_f is bigger than r_c.

9. Non-Curable Reinfection

We mentioned above that the S^R population is a healthy population that acquired resistance through prior use or misuse of antibiotics. When S^R is infected again (assuming that S^R will be in contact with both resistant and sensitive bacterial strains, or I^C and I^{NC} populations), this S^R population would then become an infected population that cannot be

cured (I^{NC}). The leftover presence of antibiotics in the host's body will favour the survival of resistant bacteria inside the body when S^R is infected. The rate of addition at time *t* for I^{NC} is given by $\beta_{NC} I^{NC} S^R(t) + \beta_C I^C S^R(t)$ because of the acquired resistance by S^R.

10. *Misuse of Treatment*

We mentioned earlier that the infected population that cannot be cured (I^{NC}) could naturally recover at a rate of r_{NC} to become S^{NR}. In the misuse case, an antibiotic is given to a population infected with a resistant bacterial strain I^{NC}. The population will not recover faster as a response (antibiotic not being effective), and traces of the antibiotic can usually be found in the body. More importantly, a resistance to this antibiotic will be built when the infected population (I^{NC}) recovers naturally because. Therefore, the I^{NC} population would become a healthy population S^R with a rate of addition at time *t*, given by $f r_{NC} I^{NC}(t)$.

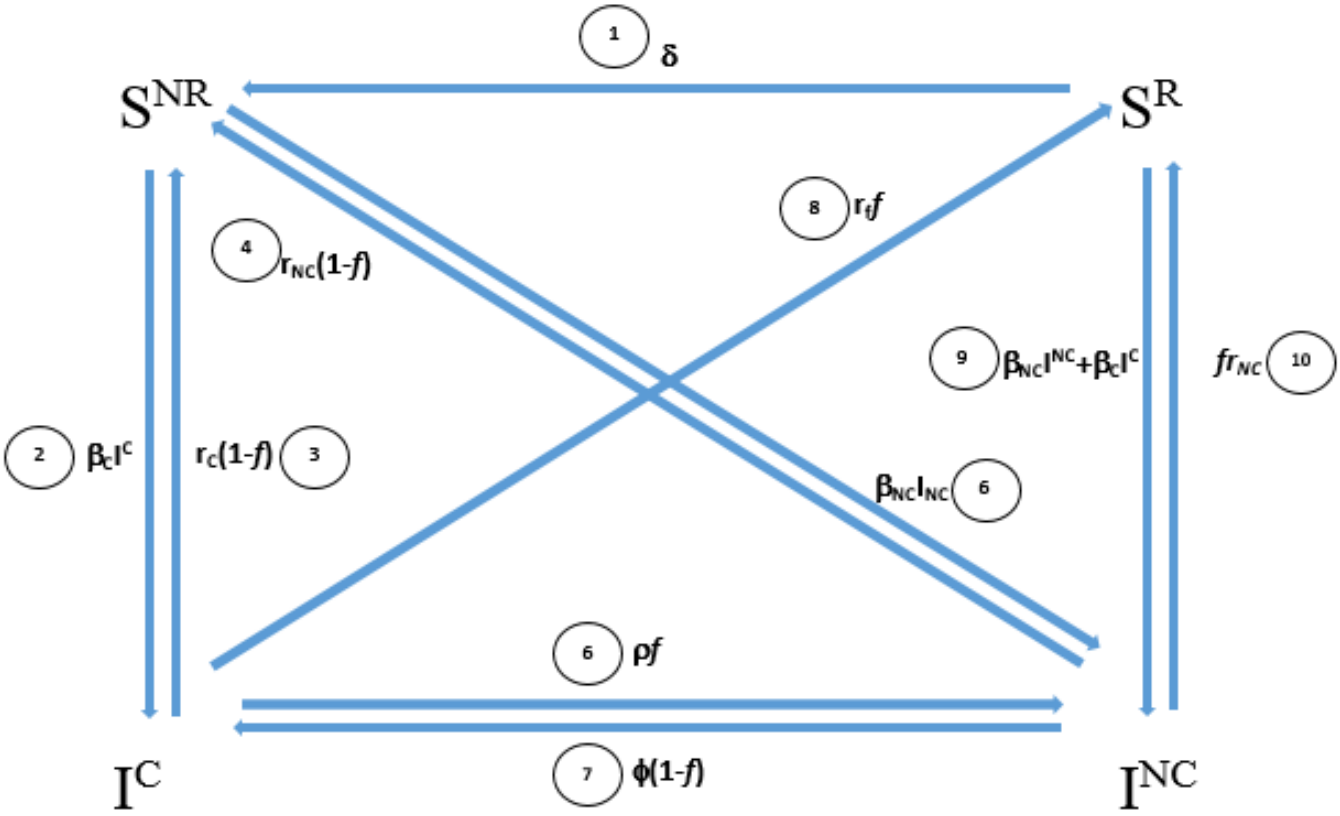


Diagram 3.1: Proposed basic model

b) Population Dynamics

In this section, we will formulate the rate of change for each of the studied populations.

Population S^{NR}

We have identified five phenomena affecting S^{NR}. These five changes are formulated below and numbered according to the different types of cases described above in a):

1. Addition of δ from S^R;

2. Reduction to I^C by $\beta_C I^C$;

3. Addition of $r_C(1-f)$ from I^C;

4. Addition of $r_{NC}(1-f)$ from I^{NC}, and

5. Reduction to I^{NC} by $\beta_{NC} I^{NC}$.

We will also assume that $\beta_C = \beta_{NC} = \beta$; the rate of change S^{NR} is thus given as equation 3.1 below:

$$\dot{S}^{NR} = \delta S^R - \beta(I^C + I^{NC})S^{NR} + (1-f)\,(r_C I^C + r_{NC} I^{NC}) \qquad (3.1)$$

Population I^C

We have identified five phenomena affecting I^C. These five changes are formulated below and numbered according to the different types of cases described above in a):

2. Addition of $\beta_C I^C$ from S^{NR};

3. Reduction to S^{NR} by $r_C(1-f)$;

6. Reduction to I^{NC} by ρf;

7. Addition of $\varphi(1-f)$ from I^{NC}; and

8. Reduction to S^R by $r_f f$.

To make things simple, we will also assume that $\varphi = \rho = 0$ for now. Therefore, the rate of change of I^C is given as equation 3.2 below:

$$\dot{I}^C = (\beta_C S^{NR} - r_C(1-f) - r_f f) I^C \qquad (3.2)$$

Population S^R

We have identified four phenomena affecting S^R. These four changes are formulated below and numbered according to the different types of cases described above in a):

1. Reduction to S^{NR} by δ;

8. Addition of $r_f f$ from I^C;

9. Reduction to I^{NC} by $\beta_{NC}I^{NC} + \beta_C I^C$; and

10. Addition of fr_{NC} from I^{NC}.

Thus, the rate of change of S^R is given as equation 3.3 below:

$$\dot{S}^R = -(\delta + \beta_{NC} I^{NC}) S^R + f(r_f I^C + r_{NC} I^{NC}) \quad (3.3)$$

Population I^{NC}

We have identified six phenomena affecting I^{NC}. These six changes are formulated below and numbered according to the different types of cases described above in a):

4. Reduction to S^{NR} by $(1\text{-}f)r_{NC}$;

5. Addition of $\beta_{NC}I^{NC}$ from S^{NR};

6. Addition of $(1 - r_f)f$ or ρf from I^C;

7. Reduction to I^C by $\varphi(1\text{-}f)$;

9. Addition of $\beta_{NC}I^{NC} + \beta_C I^C$ from S^R; and

10. Reduction to S^R by fr_{NC}.

To keep things simple, we will also assume that $\varphi = \rho = 0$ for now. Therefore, the rate of change of I^{NC} is given as equation 3.4 below (we will also assume that $\beta_{NC} = \beta_C = \beta$):

$$\dot{I}^{NC} = (\beta S - r_{NC}) I^{NC} + \beta S^R I^C \quad (3.4)$$

The Use of Rapid Diagnostic Tests

In current medicine practice, on the one hand, a portion of antibiotic prescriptions are made outside the hospital, by doctors without using a diagnostic tool, by pharmacists or by self-medicating patients buying antibiotics over-the-counter (RAR, 2016). This is part of the overuse of antibiotics problem described above. On the other hand, doctors usually use empirical diagnosis: they will use their expertise, intuition and professional judgement to '*guess*' whether an infection is present and what is likely to be causing it, and thus the most appropriate treatment (RAR, 2016).

In some instances, diagnostic tools (traditional diagnostic tests) are used later to confirm or change that prescription. These traditional diagnostic tests can show whether an antibiotic is needed, and which one is needed. Antibiotics are rarely prescribed based on a definitive diagnosis. Each time a diagnostic test is used, an appropriate option for prescription is followed (e.g.: test for resistance, allowing the most appropriate available medicine for an infection or test for viral infection). The benefits of using traditional diagnostic tests are to preserve antibiotic effectiveness and minimize antibiotic resistance. Thus, the use of ordinary or traditional diagnostic tests can be viewed as a public good. A positive externality is created with the use diagnostic tools because it is socially desirable for antibiotic conservation and slower development of resistance. The cost of using traditional diagnostic tests are longer waiting times and potential complications for patients that are not treated. Tests might represent additional expenses. Bacteria must be cultured for 36 hours or more to confirm the type of infection and the drugs to which it is susceptible (RAR, 2016). An acutely ill patient cannot wait this long for treatment, and even when the health risks are not that high, most doctors' surgeries and pharmacies are under time, patient and financial pressure, and must address patients' needs much faster.

Diagram 3.2 below presents the social benefit and private benefit from the use of traditional diagnostic test.

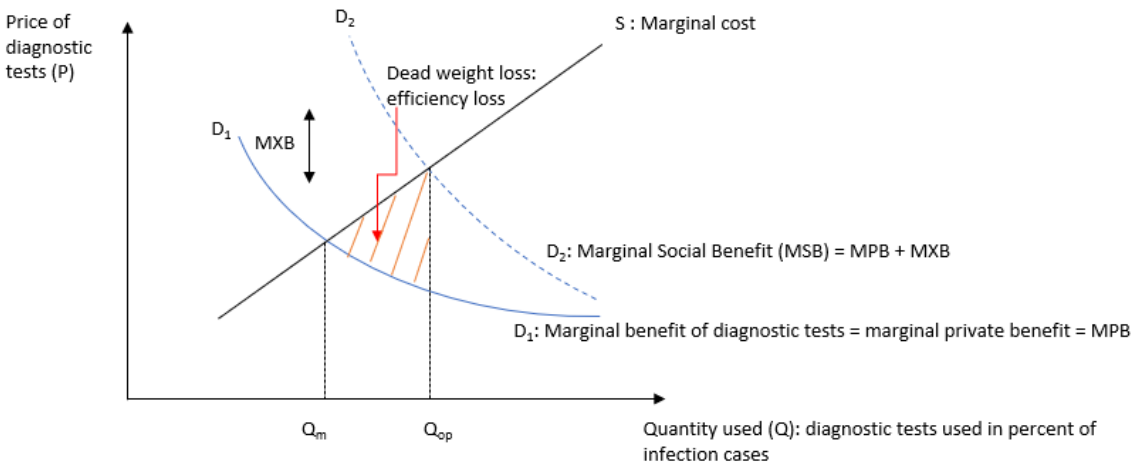


Diagram 3.2: Positive externality with the use of traditional diagnostics

The S curve presented in **Diagram 3.2** represents the marginal cost or the supply curve for the diagnostic tests. S is pointing upward by assuming that each incremental test is going to be a little bit expensive (longer waiting time). D_1 represents the demand curve or the marginal benefit of the diagnostic tests. D_1 is, thus, the marginal private benefit (MPB) for the users of the diagnostic tests. With D_1, we will get at a quantity of diagnostic used ($Q_{m)}$. The social benefit of each diagnostic tests used is represented by D_2. A marginal social benefit (MSB) is added to each MPB which gives us D_2 (the external benefit is presented by MXB and this is presented as the vertical distance between D_1 and D_2). With D_2, we will get at a socially desirable quantity of diagnostic used (Q_{op}). The efficiency loss is where we are leaving behind some social benefit. This is represented by the deadweight loss. One way to reduce this loss is to raise the private demand (D_1). This could be achieved by giving incentives to doctors. However, this method does not help the patient directly or immediately. The cost related to the use traditional diagnostic tests as explained above remains, even if we raise the demand. The alternative way to obtain this surplus is to shift the S curve downward. This can be achieved through rapid diagnostic tests or RDTs. Cheap and rapid diagnostic tests, when developed, can reduce the dead weight loss. Longer waiting times and potential complications for patients can be eliminated. The **Diagram 3.3** below presents this method.

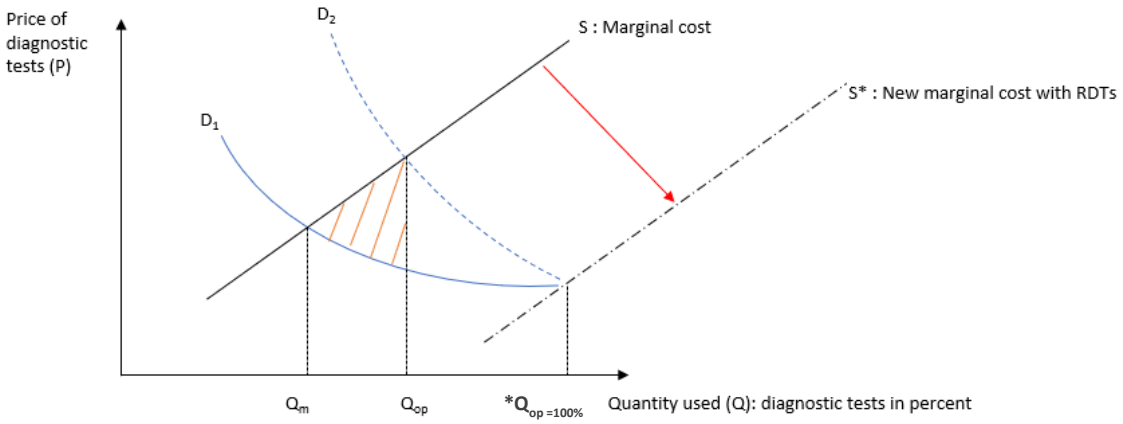


Diagram 3.3: Elimination of the dead weight loss with RDTs

In the diagram, D1 and D2 meet when the percentage of diagnostic tests used reaches 100% (this is in a situation where RDTs are used on all cases or diagnostics because they are rapid and precise). As the treatment percentage increases, the marginal externality decreases. In fact, the distance between D1 and D2 is the positive externality of the rapid diagnostic tests linked to the reduction of antibiotic resistance. Therefore, rapid point-of-care diagnostic tests are a central part of the solution to this demand problem, which results currently in enormous unnecessary antibiotic use.

In the case where rapid diagnostic tests are used, we assume that these tests are extremely efficient and accurate. Consequently, we can detect whether the infection is antibiotic-sensitive or antibiotic-resistant. In this situation, a fraction f_1 and f_2 of the infected population will be treated with antibiotics. With the use of rapid diagnostic tests, f_1 will be associated with the infected population that can be cured (I^C), and f_2 will be associated with the infected population that cannot be cured (I^{NC}). For this section, we assume the test is extremely accurate, and $f_2 = 0$. This means that, with the use of diagnostic tests, there is no misuse of antibiotics (sub-section 10: misuse of treatment). For a non-myopic monopolist to treat the population with its antibiotic in which it takes into consideration the effectiveness of the antibiotic and the infected population in the long run, it is advantageous to develop such rapid diagnostic test since it will reduce the

number of newly healthy population who are prone to antibiotic resistance which, in turn, will preserve the effectiveness of the antibiotics.

Diagram 3.4a below first summarizes the proposed model with the use of rapid diagnostic. **Diagram 3.4b** displays the simplified model where $f_2 = 0$.

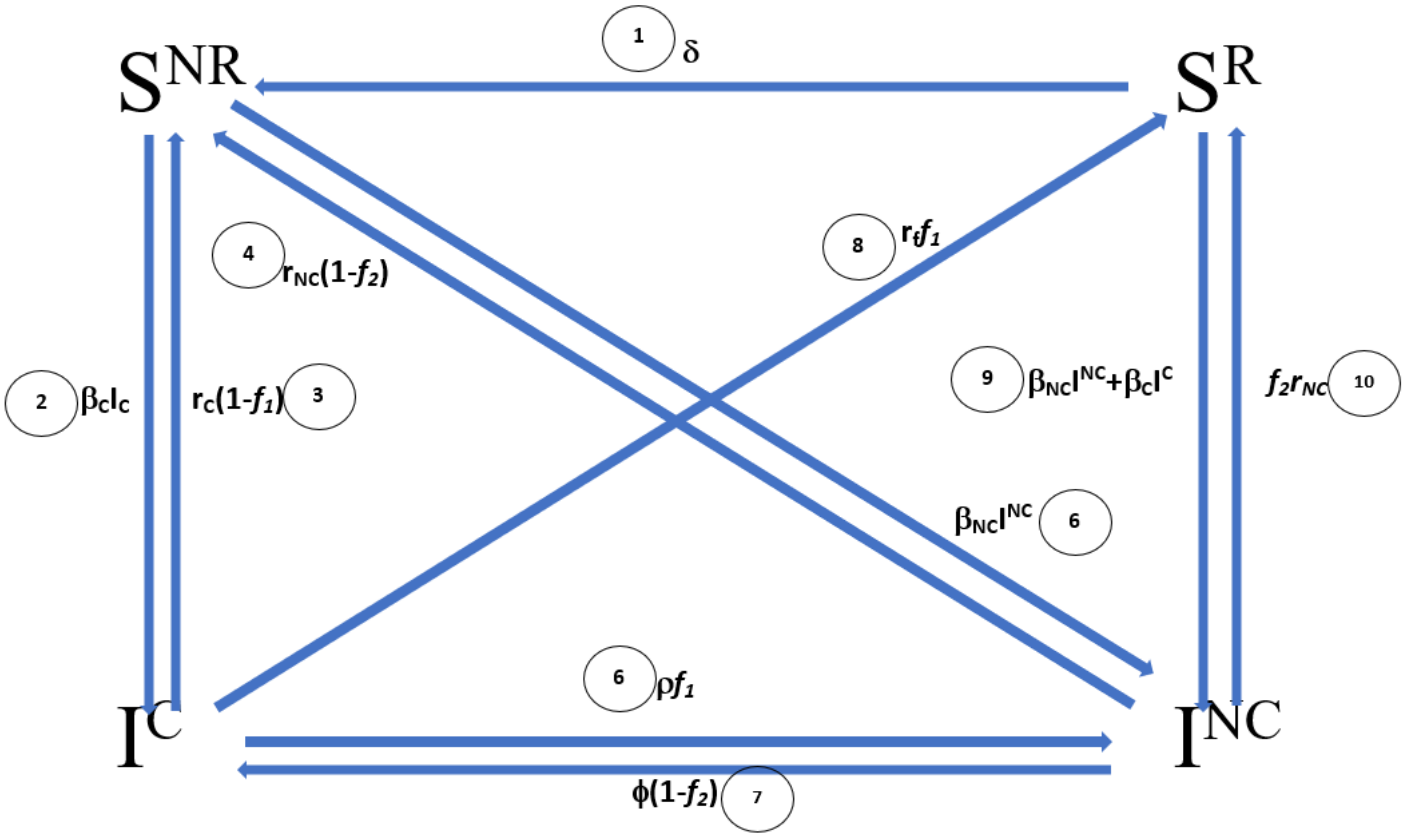


Diagram 3.4a: Proposed model with the use of rapid diagnostic tests

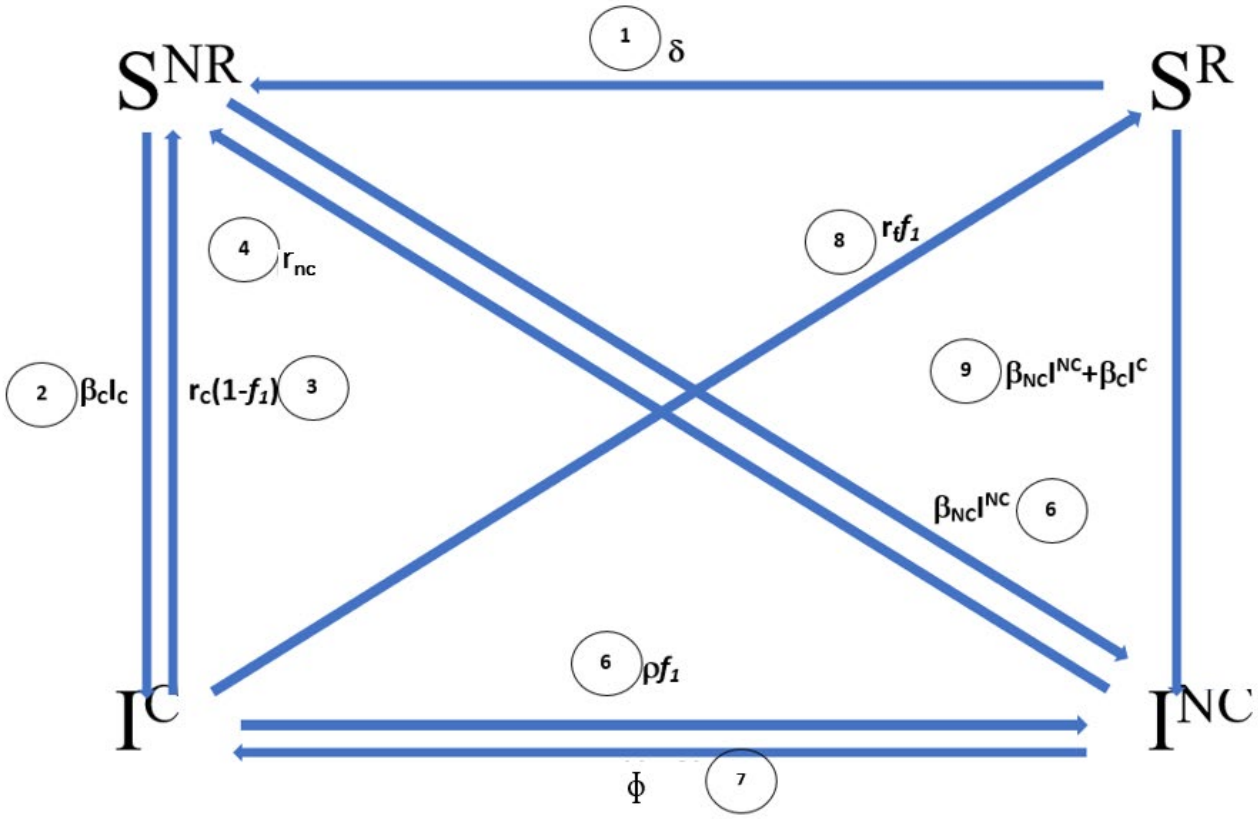


Diagram 3.4b: Proposed model with the use of rapid diagnostic tests ($f_2 = 0$)

c) Demand function

We will use the following assumptions to determine the demand function.

- At first, we will define the effectiveness of an antibiotic (e). This can be measured as the proportion of the curable population over the total infected population. This means that the proportion of the infected population that can be cured is directly proportional to the effectiveness of the antibiotic (the larger the infected population which can be cured within the total population, the more effective is the antibiotic).

$$\boldsymbol{e} = \frac{\boldsymbol{I_C}}{\boldsymbol{I_C + I_{NC}}} \qquad (3.5)$$

- The probability of recovery without the use of antibiotics (i.e., when patients do not know which strains of bacterial they are infected with) is written as the following equation where *e* represents the probability of being infected with the sensitive strains of bacteria (I_C) and (1-e) being the probability of being infected with the resistant strains of bacteria (I_{NC}):

$$\pi(\boldsymbol{e}) = \boldsymbol{e r_C} + (\boldsymbol{1} - \boldsymbol{e}) \boldsymbol{r_{NC}} \qquad (3.6)$$

- The probability of recovery with the use of antibiotics or treatment is written as the following equation:

$$\boldsymbol{P}(\boldsymbol{r}) = \pi(\boldsymbol{e}) + \boldsymbol{e r_f} \qquad (3.7)$$

- The health consideration can be determined with the gross utility of an individual of type θ.
  - $U(\theta) = \theta$, if the individual is in good health (not infected).
  - $U(\theta) = \pi(e)\theta$, if the individual is infected, but is not taking any antibiotics and do not know which strains of bacterial he is being infected with.
  - $U(\theta) = (\pi(e) + er_f)\theta$, if the infected individual is taking antibiotics.
- We introduce **θ'** which is defined as the type of individual who is indifferent whether receiving treatment or not.
- P is defined as the price of the antibiotics. We can therefore determine the value of **θ'** in equation 3.8**:**

$$\pi(\boldsymbol{e})\boldsymbol{\theta'} = \left(\pi(\boldsymbol{e}) + \boldsymbol{e r_f}\right)\boldsymbol{\theta'} - \boldsymbol{P} \qquad (3.8)$$

Which means that:

$$\boldsymbol{\theta'} = \frac{\boldsymbol{P}}{\mathbf{r_f}\boldsymbol{e}} \tag{3.9}$$

With the function associated with θ' (in equation 3.9), the inverse demand function can be derived as equation 3.10 below:

$$\boldsymbol{P(f,e) = r_f e(1-f)} \tag{3.10}$$

1.2 Profit Maximization Problem of the Non-Myopic Monopolist Set-Up

We will assume that a patent exists, assigning exclusive rights to a monopolistic firm to sell the antibiotic for an exogenously given period of time after which the antibiotic is sold by a generic industry. The monopolist will consider the impact of the current decisions on future levels of antibiotic efficacy and infection, and thus, on the evolution of the effectiveness of the antibiotic and its market size over time.

By using the inverse demand function above, we can derive the profit function below:

$$\boldsymbol{\pi(e) = \left[r_f e(t)\left(\left(1-f(t)\right)-\mathbf{c}\right)\right] f(t)\mathbf{I}(t)} \tag{3.11}$$

Endogenous for *e* and *f.*

The effectiveness of an antibiotic can be assumed to be *e*. As previously stated, the proportion of the infected population that can be cured is directly proportional to the effectiveness of the which determine the effectiveness of the antibiotic. Therefore, we assume *e* to be equation 3.5

From the population dynamics derived in part Section 3b, the assumptions for *e* and equations 3.1, 3.2, 3.3. and 3.4, we can derive the following dynamic equations[3]:

$$\boldsymbol{\dot{e} = e\,((1-e)\left(\Delta \mathbf{r} + f\left(r_C - r_f\right) - BS^R\right))} \tag{3.12}$$

$$\boldsymbol{\dot{I} = I[BS - r_{NC} + e(\Delta \mathbf{r} + f\left(r_C - r_f\right)]} \tag{3.13}$$

$$\boldsymbol{\dot{S^R} = fI\left(r_f e + r_{NC}(1-e)\right) - (BI+\delta)S^R} \tag{3.14}$$

[3] The change in the effectiveness ($\dot{e}$) is derived from a total differential of the equation 3.5.

These are the constraints to the profit maximization problem. The two important effects in the biological system are still apparent in Equations 3.12 and 3.13. The term ∆r is represented by $r_{NC} - r_C$. This is the fitness cost effect: if ∆r is positive, then there is renewability of the resource of antibiotic efficacy (resistant strains bacterial will clear faster). The natural selection effect is determined with $r_C - r_f$. This suggests that after a fraction of population *f* receives the antibiotics, the non-resistant bacteria strain will be wiped out giving the dominance of resistant-strain bacteria. Again, if a fraction $f = \frac{\Delta r}{r_f}$ of the infected population is treated with the antibiotic, the fitness cost effect and the natural selection cost effects will cancel out. For all other admissible values of *f*, one effect will dominate giving an increase or decrease in the level of antibiotic efficacy. We must have $(\frac{\Delta r}{r_f}) < 1$, assuming that both the fitness cost effect and the natural selection effect are apparent in the system. The term $-BS^R$ coincides with the increase of resistance in population (decrease of effectiveness of antibiotics).

The maximization problem is described as the following:

$$\boldsymbol{Max\ \pi(t) = \int_0^T e^{-\rho t}\, \pi(t) dt} \qquad (3.15)$$

Equation 3.15 is subject to constraints 3.12, 3.13 and 3.14 since a non-myopic monopolist does consider the long-run effects of his current decisions.

4. Resolution of the Model and Profit Maximization Problem

4.1 Monopolistic (Non-Myopic) Behaviour

In this section, we will explore the optimum of the non-myopic monopolist protected by a patent infinitely and the impact on the effectiveness of the antibiotic. We will set up the Hamiltonian and derive the first order conditions. A non-myopic monopolist considers the effectiveness of the antibiotic, the infected population and the treatment quantities in the long-term. Therefore, the maximization function (3.15) will be subject to the evolution of e, I, and S^R (equations 3.12, 3.13 and 3.14).

a) Model 1 - Without Rapid Diagnostic Tests

In our basic model proposed above (**Diagram 3.1**), we established that without rapid diagnostic tests, we derived the following dynamic/differential equations:

$$\dot{\boldsymbol{S}}^{\boldsymbol{NR}} = \boldsymbol{\delta S^R} - \boldsymbol{\beta}(\boldsymbol{I^C} + \boldsymbol{I^{NC}})\boldsymbol{S^{NR}} + (\mathbf{1} - \boldsymbol{f})\,(\boldsymbol{r_C I^C} + \boldsymbol{r_{NC} I^{NC}}) \quad (3.1)$$

$$\dot{\boldsymbol{I}}^{\boldsymbol{C}} = (\boldsymbol{\beta S^{NR}} - \boldsymbol{r_C}(\mathbf{1} - \boldsymbol{f}) - \boldsymbol{r_f f})\,\boldsymbol{I^C} \quad (3.2)$$

$$\dot{\boldsymbol{S}}^{\boldsymbol{R}} = -(\delta + \boldsymbol{\beta_{NC} I^{NC}})\boldsymbol{S^R} + \boldsymbol{f}(\boldsymbol{r_f I^C} + \boldsymbol{r_{NC} I^{NC}})) \quad (3.3)$$

$$\dot{\boldsymbol{I}}^{\boldsymbol{NC}} = (\boldsymbol{\beta S} - \boldsymbol{r_{NC}})\boldsymbol{I^{NC}} + \boldsymbol{\beta S^R I^C} \quad (3.4)$$

At first, there are steady-state configurations to the epidemiological dynamics described by equations 3.8, 3.9 and 3.10. This gives rise to e^{SS}, I^{SS} and S^{RSS} which denote the steady-state values of e, I and S^R respectively. In order to not have the fitness cost and natural selection effects cancel out on each other, we will have value of any $f \neq (\frac{\Delta r}{r_f})$. Following that, we will then have $\dot{e}$ = 0 (no change in antibiotic effectiveness) for e = 0 or e = 1.

By using the Hamiltonian, we can derive the first order conditions and the shadow prices of the antibiotic effectiveness and the infected individuals. With respect to the non-myopic monopolist, the current-value Hamiltonian associated to the problem is described below:

$$\boldsymbol{H}\,(\boldsymbol{f}, \boldsymbol{e}, \boldsymbol{I}, \boldsymbol{S^R}, \boldsymbol{u}, \lambda, \mathbf{z}) = [\boldsymbol{r_f e}\,(\mathbf{1} - \boldsymbol{f}) - \boldsymbol{c}]\boldsymbol{fI} + \boldsymbol{ue}\,[(\mathbf{1} - \boldsymbol{e})(-\boldsymbol{BS^R} + \Delta\mathbf{r} + \boldsymbol{f}(\mathbf{r_c} - \mathbf{r_f})] +$$
$$\boldsymbol{\lambda}\mathbf{I}[(\boldsymbol{BS} - \mathbf{r_{NC}} + \mathbf{e}(\Delta\mathbf{r} + \boldsymbol{f}(\boldsymbol{r_c} - \boldsymbol{r_f})] + \boldsymbol{z}[\boldsymbol{f}\mathbf{I}(\mathbf{r_f e} + \mathbf{r_{NC}}(\mathbf{1} - \mathbf{e}) - (\boldsymbol{B}\mathbf{I} + \boldsymbol{\delta})\mathbf{S^R}] \quad (4.1)$$

where *u* and λ and *z* measure for the shadow values (prices/costs) associated to the level of antibiotic efficacy and the stock of infected population and the healthy population respectively. The following conditions are necessary for intertemporal profit maximization:

$$\frac{\partial \mathbf{H}}{\partial \mathbf{f}} \leq \mathbf{0}, \frac{\partial \mathbf{H}}{\partial \mathbf{f}}\mathbf{f} = \mathbf{0}, \mathbf{f} \geq \mathbf{0} \ \mathbf{or} \frac{\partial \mathbf{H}}{\partial \mathbf{f}} \geq \mathbf{0}, \frac{\partial \mathbf{H}}{\partial \mathbf{f}} (\mathbf{1} - \mathbf{f}) = \mathbf{0}, \mathbf{f} \leq \mathbf{1} \quad (4.2)$$

$$\dot{\boldsymbol{u}} - \rho \boldsymbol{u} = \partial \mathbf{H} / \partial \mathbf{e} \quad (4.3)$$

$$\dot{\boldsymbol{\lambda}} - \rho \boldsymbol{\lambda} = \partial \mathbf{H} / \partial \mathbf{I} \quad (4.4)$$

$$\dot{\boldsymbol{z}} - \rho \boldsymbol{z} = \partial \mathbf{H} / \partial \boldsymbol{S^R} \quad (4.5)$$

The condition $\frac{\partial H}{\partial f} \leq 0$ in 4.2 is necessary since it will never be optimal for the monopolist to sell the antibiotic to the overall infected population ($f = 1$). This makes current profits negative without generating compensating future profits. Conditions 4.3 to 4.5 are the arbitrage equations to measure the path or evolution over time of the shadow prices associated to the level of antibiotic efficacy and the stock of infected population and the healthy population respectively. These conditions also state that when the monopolist is protected by a patent, the effectiveness of the antibiotics and the infected individuals at the end of patent has no value.

Furthermore, the derivative with respect to the control variable f of the Hamiltonian is derived as the following:

$$\frac{\partial \mathbf{H}}{\partial \mathbf{f}} = (\mathbf{r_f e}(\mathbf{1} - \mathbf{2}\boldsymbol{f}) - \mathbf{c})\mathbf{I} + \mathbf{e}(\mathbf{r_c} - \mathbf{r_f})(\boldsymbol{u}(\mathbf{1} - \mathbf{e}) + \boldsymbol{\lambda}\mathbf{I}) + \mathbf{zI}(\mathbf{r_f e} + \mathbf{r_{nc}}(\mathbf{1} - \mathbf{e})) \quad (4.6)$$

When $\frac{\partial H}{\partial f}$ = 0, we have the following monopolistic interior solution f^m at state (*e, I*) at time *t*:

$$\mathbf{r_f}\boldsymbol{e}(\mathbf{1} - \mathbf{2}\boldsymbol{f^m}) = \boldsymbol{c} + \left(\frac{\boldsymbol{e}}{\boldsymbol{I}}\right)(\boldsymbol{r_f} - \boldsymbol{r_c})[(\boldsymbol{u}(\boldsymbol{e} - \mathbf{1}) - \boldsymbol{\lambda}\mathbf{I}) - \boldsymbol{z}\left(\boldsymbol{r_f e} + \boldsymbol{r_{nc}}(\mathbf{1} - \boldsymbol{e})\right)] \quad (4.7)$$

The solution at time *t* can be demonstrated with the following graph:

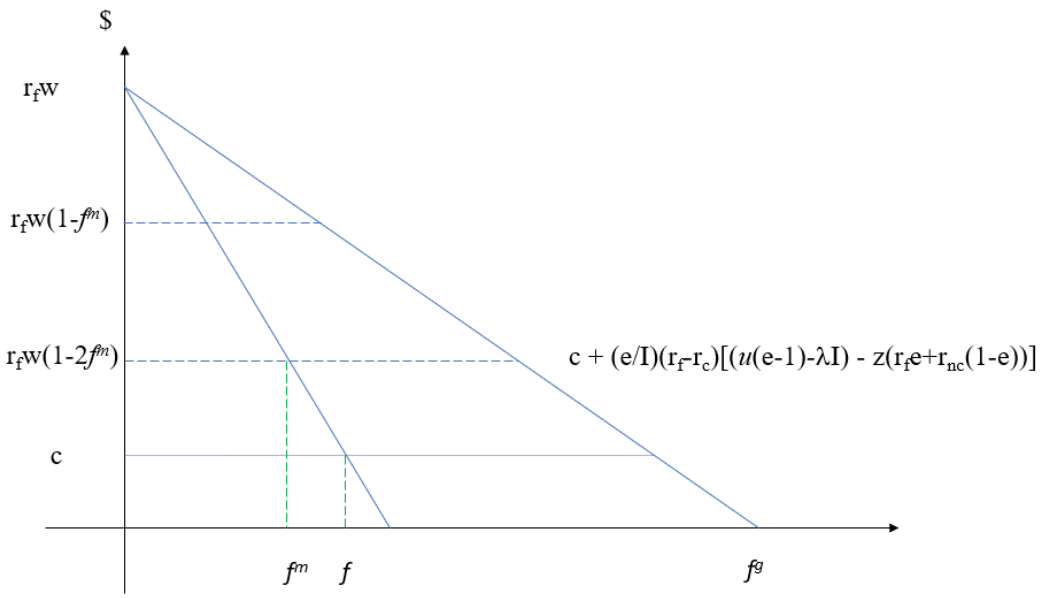


Diagram 4.1: Interior solution for the monopolist – without rapid diagnostic tests

It is optimal for the non-myopic monopolist to treat the population at f^m. In **Diagram 4.1**, the interior solution (f^m) is shown. The marginal benefit ($(r_f e(1-2f^m))$) equals the marginal cost (c) plus an external cost which also takes into consideration the effectiveness of the antibiotic (e) and the infected population (I). This result is consistent with the literature as demonstrated in Herrmann's paper. As for the myopic monopolist, the marginal benefit equals only to the marginal cost for a solution at *f* since it does not consider the effectiveness of the antibiotic (e) and the infected population (I). Therefore, the non-myopic monopolist will treat a smaller portion of the population given the constraints derived for e and I.

On the other hand, we will depict the dynamics in time of the variables under study[4] in a simulation. We will be looking particularly at the evolution of the effectiveness of the antibiotics (*e*) and the susceptible healthy population who are prone to resistance (S^R) in our model.

The **Diagram 4.2** below shows the dynamics in time of the effectiveness of the antibiotics[5].

[4] Python (programming language) is used and codes are available in the annexe.
[5] In our simulation, the time horizon is fixed, and we assume that our population size is fixed as well. The values for other parameters used in the dynamic equations are based on epidemiological studies (Spicknall et al. 2013).

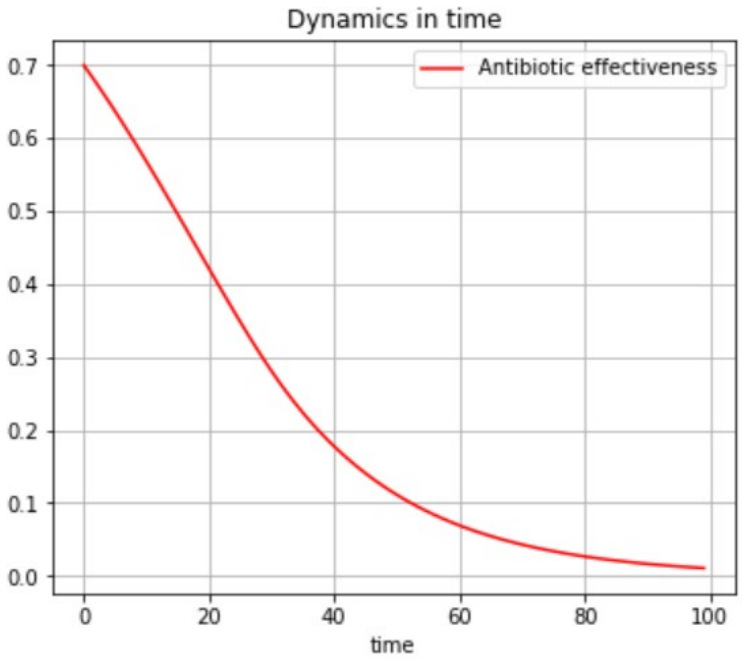


Diagram 4.2: Antibiotic effectiveness – dynamics in time

We assume that the effectiveness of the antibiotic is not at 100% initially since there might be resistance already existing in nature. As time goes by, we observe that, in our simulation, the effectiveness diminishes since the antibiotic is being used in population for all infected individuals (without knowing what type of infections). In the simulation, the effectiveness of the antibiotic asymptotically approaches 0 for the non-myopic monopolist as the effectiveness of an antibiotic has no value for the monopolist at the end of the patent. The fitness cost of the resistant strain of bacteria (opportunity cost) could contribute to the renewal of antibiotic effectiveness. However, we observe that this was not enough to increase the effectiveness of the antibiotic in our first model (without RDTs).

Moreover, the **Diagram 4.3a** below shows the dynamics in time of the healthy population who are prone to resistance (S^R) in our simulation. In **Diagram 4.3b**, we added the antibiotic effectiveness dynamic as well. **Diagram 4.3c** presents the phase diagram.

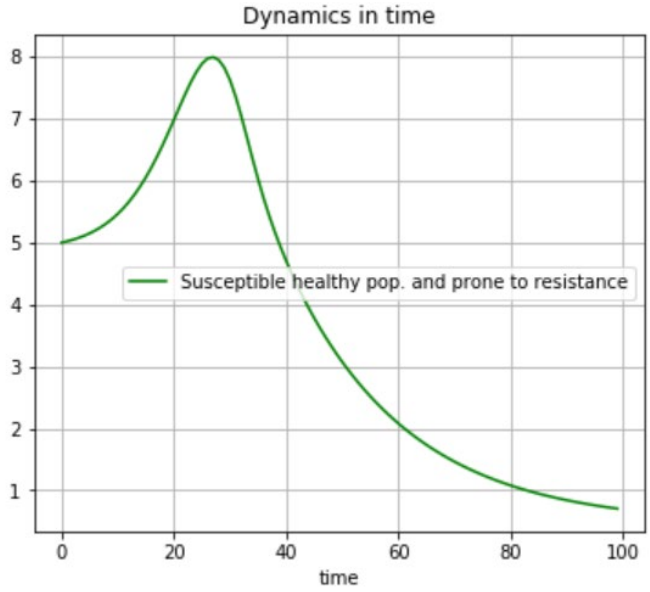


Diagram 4.3a: Healthy population prone to resistance – dynamics in time

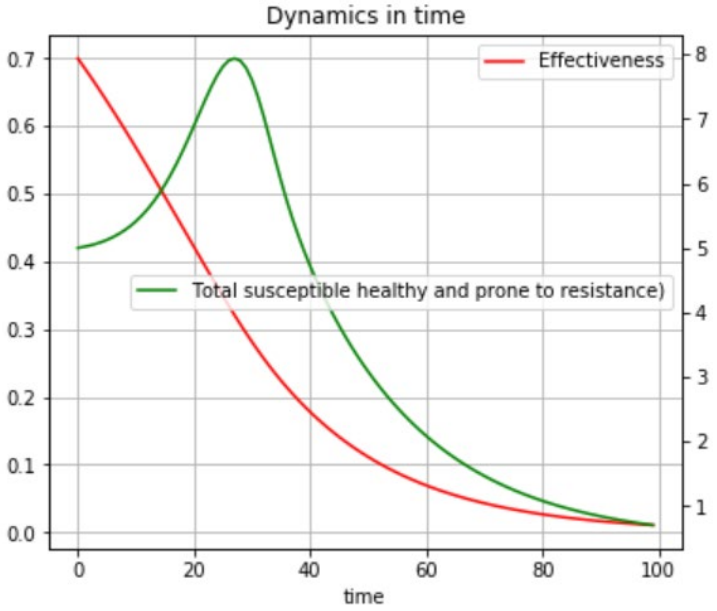


Diagram 4.3b: Effectiveness and Healthy population prone to resistance – dynamics in time

Diagram 4.3c: Effectiveness and Healthy population prone to resistance – Phase Diagram

In our proposed model, we suggested that the crucial component leading to antibiotic resistance is the population prone to infections by bacteria that are resistant to antibiotics (S^R). This population will increase as infected individuals will be mistreated giving rise to antibiotic resistance. As the effectiveness of the antibiotics decrease with time as shown above, we observe that the S^R population will then decrease with time. This is consistent with our model since this population will eventually all be infected with antibiotic resistant bacteria.

b) Model 2 - With Rapid Diagnostic Tests

Our proposed second model (**Diagram 3.3**) incorporate the use of rapid diagnostic tests where we assume f_2 = 0, since the diagnostics tests are extremely efficient, and we do not mistreat infected individuals.

The following dynamic equations are derived (by repeating steps in section 3.1b):

$$\dot{S}^{NR} = \delta S^R - \beta(I^C + I^{NC})S^{NR} + (1-f)\,(r_C I^C) + r_{NC} I^{NC} \quad (4.8)$$

$$\dot{I}^C = (\beta S^{NR} - r_c(1-f) - r_f f)I^C \quad (4.9)$$

$$\dot{S}^R = -(\delta + \beta I)S^R + I^C r_f f \quad (4.10)$$

$$\dot{I}^{NC} = -(\beta S - r_{NC})I^{NC} + \beta S^R I^C \quad (4.11)$$

We observe that only the differential equations $\dot{S}^{NR}$ and $\dot{S}^{R}$ are different in our second model.

With the use of the equations derived above and the assumption of *e* proposed (total differential), we can also derive the following epidemiological dynamic equations:

$$\dot{\boldsymbol{e}} = \boldsymbol{e}\,((\,\mathbf{1}-\boldsymbol{e})\big(\,\boldsymbol{r_{NC}} - \,\boldsymbol{r_C} + \boldsymbol{f}\big(\boldsymbol{r_C}-\boldsymbol{r_f}\big) - \boldsymbol{BS^R}\big)) \tag{4.12}$$

$$\dot{\boldsymbol{I}} = \boldsymbol{I}[\boldsymbol{BS} - \boldsymbol{r_{NC}} + \boldsymbol{e}(\boldsymbol{r_{NC}} - \,\boldsymbol{r_C} + \,\boldsymbol{f}\big(\boldsymbol{r_C}-\boldsymbol{r_f}\big)] \tag{4.13}$$

$$\dot{\boldsymbol{S^R}} = \boldsymbol{fI}\big(\boldsymbol{er_f}\big) - (\boldsymbol{BI}+\boldsymbol{\delta})\boldsymbol{S^R} \tag{4.14}$$

As there are no changes regarding the equations involving $\dot{I}^{NR}$ and $\dot{I}^{C}$, only the equation for $\dot{S}^{R}$ is different from the constraints derived in equations 4.12, 4.13 and 4.14.

The Hamiltonian associated to the problem is described below with our second case using rapid diagnostic tests:

$$\boldsymbol{H}(\boldsymbol{f},\boldsymbol{e},\boldsymbol{I},\mathbf{S^R},\boldsymbol{u},\boldsymbol{\lambda},\boldsymbol{z}) \;=\; [\mathbf{r_f}\boldsymbol{e}(\mathbf{1}-\boldsymbol{f})-\mathbf{c}]\boldsymbol{f}\mathbf{I} \;+\; \boldsymbol{ue}[(\mathbf{1}-\boldsymbol{e})(-\boldsymbol{B}\mathbf{S^R}+\boldsymbol{\Delta}\mathbf{r}+\boldsymbol{f}(\mathbf{r_c}-\mathbf{r_f})] +$$
$$\boldsymbol{\lambda}\mathbf{I}[(\boldsymbol{BS}-\mathbf{r_{NC}}+\mathbf{e}(\boldsymbol{\Delta}\mathbf{r}+\boldsymbol{f}(\boldsymbol{r_c}-\boldsymbol{r_f})] \;+\; \boldsymbol{z}[\boldsymbol{f}\mathbf{I}(\mathbf{er_f}\;(\boldsymbol{B}\mathbf{I}+\;\boldsymbol{\delta})\mathbf{S^R}] \tag{4.13}$$

The condition $\frac{\partial H}{\partial f} \leq 0$ is again necessary since it will never be optimal for the monopolist to sell the antibiotic to the overall infected population (*f* = 1). This makes current profits negative without generating compensating future profits.

The derivative with respect to the control variable *f* of the Hamiltonian is derived as the following:

$$\frac{\partial \mathbf{H}}{\partial \mathbf{f}} = \big(\boldsymbol{r_f}\boldsymbol{e}(\mathbf{1}-\mathbf{2}\boldsymbol{f})-\boldsymbol{c}\big)\boldsymbol{I} + \boldsymbol{e}\big(\boldsymbol{r_c}-\boldsymbol{r_f}\big)(\boldsymbol{u}(\mathbf{1}-\boldsymbol{e})+\boldsymbol{\lambda}\mathbf{I}) + \boldsymbol{zIer_f} \tag{4.14}$$

When $\frac{\partial H}{\partial f}$ = 0, we have the monopolistic interior solution f^{m*} at state (*e, I*) at time *t*:

$$\boldsymbol{r_f}\boldsymbol{e}(\mathbf{1}-\mathbf{2}\boldsymbol{f^{m*}}) = \boldsymbol{c} + (\tfrac{\boldsymbol{e}}{\boldsymbol{I}})(\boldsymbol{r_f}-\boldsymbol{r_c})[(\boldsymbol{u}(\boldsymbol{e}-\mathbf{1})-\boldsymbol{\lambda}\mathbf{I}) - \boldsymbol{z}\big(\boldsymbol{r_f}\boldsymbol{e}\big)] \tag{4.15}$$

The solution at time *t* is demonstrated in **Diagram 4.4** below:

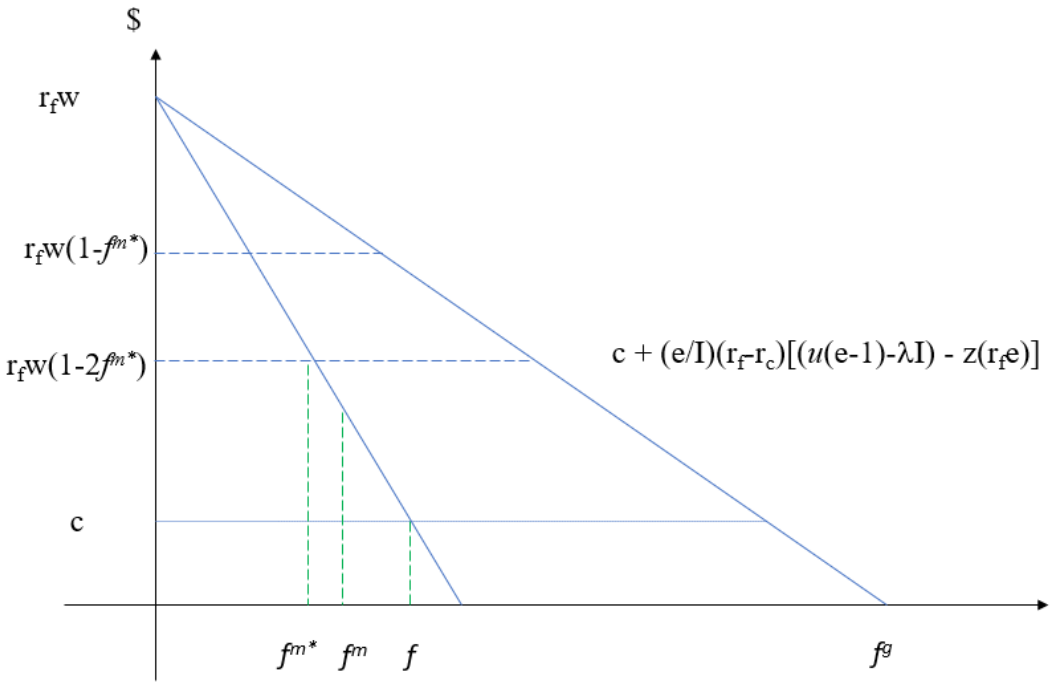


Diagram 4.4: Interior solution for the monopolist – with rapid diagnostic tests

As discussed above, it is optimal for the non-myopic monopolist to treat the population at f^m (in the first case). In our second model with rapid diagnostic tests, the marginal benefit $(r_f e(1-2f^m)$ also equals the marginal cost (*c*) plus an external cost which also takes into consideration the effectiveness of the antibiotic (e) and the infected population (*I*). In **Diagram 3.6**, the interior solution (f^{m*}) is shown to the left of f^m from the solution in the first model, since the external cost (which takes into consideration *e* and *I)* is smaller (the term $\boldsymbol{z(r_f e)}$ in equation 4.15 is smaller than the term $\boldsymbol{z\left(r_f e + r_{nc}(1-e)\right)}$] presented in equation 4.7). With the rapid diagnostic tests, there are less infected population that the monopolist can treat since we eliminated mistreatment and overuse. To maximize profit, the monopolist choses to treat a smaller portion of the population given the constraints derived for *e* and I.

We will again depict the dynamics in time of the variables under study in our second model: the effectiveness of the antibiotics (*e*) and the susceptible healthy population who are prone to resistance (S^R).

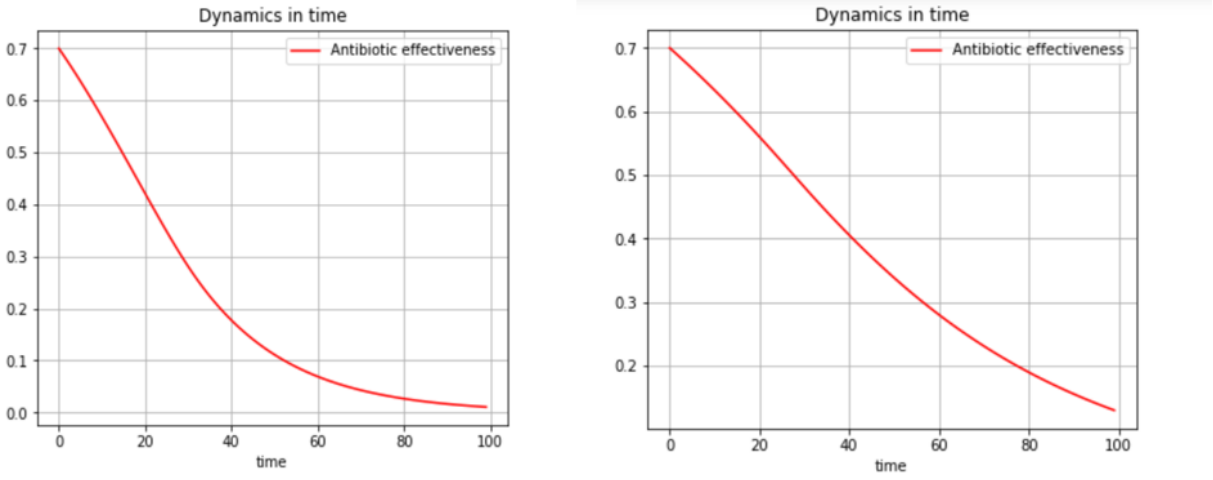
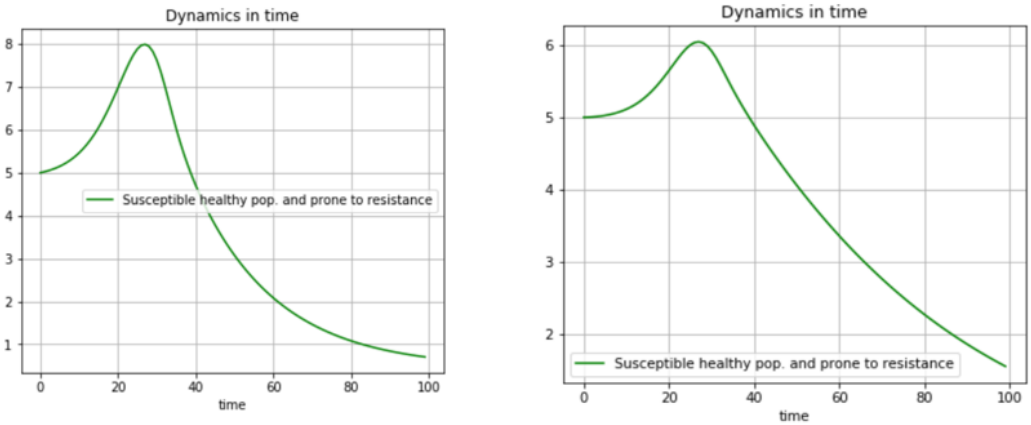


Diagram 4.5: Antibiotic effectiveness – dynamics in time comparison

In **Diagram 4.5**, we present the dynamics of the effectiveness of the antibiotics for both models. As the time goes by, we observe that the effectiveness diminishes slower in our second model. For example, at t = 40, we have the effectiveness of the antibiotic at 40% whereas in our first model with the misuse of antibiotics, the effectiveness of the antibiotic dropped to roughly 18% already. Since we eliminated misuse and overuse of antibiotics in our second model, social benefit can be expected from the increase of rapid diagnostic tests as predicted. We can therefore preserve the effectiveness of the antibiotics for a longer period.

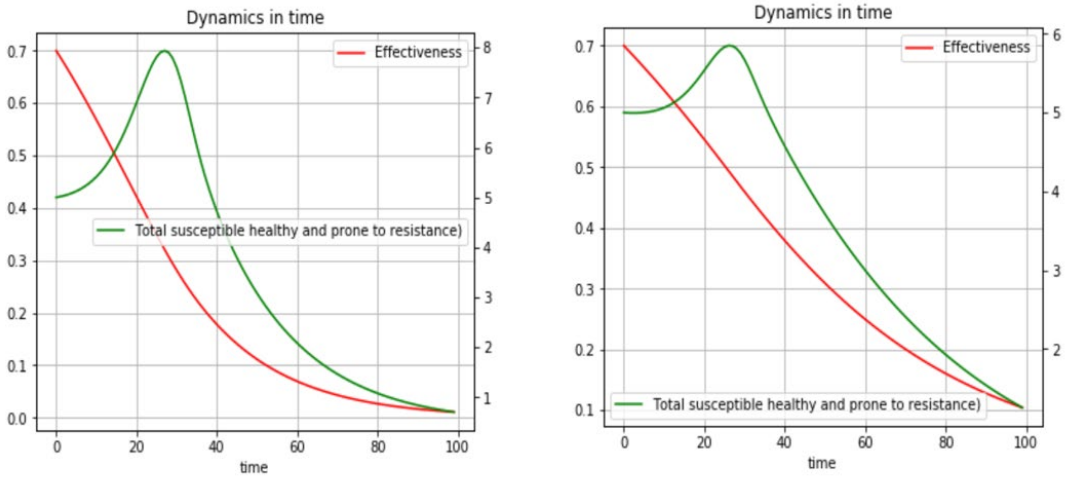
If we look at the evaluation of the decisive health population (S^R) who are prone to resistance in **Diagram 4.6a** and **Diagram 4.6b** below, we also observe benefit from the

use of rapid diagnostic tests. **Diagram 4.6c** presents the phase diagram.



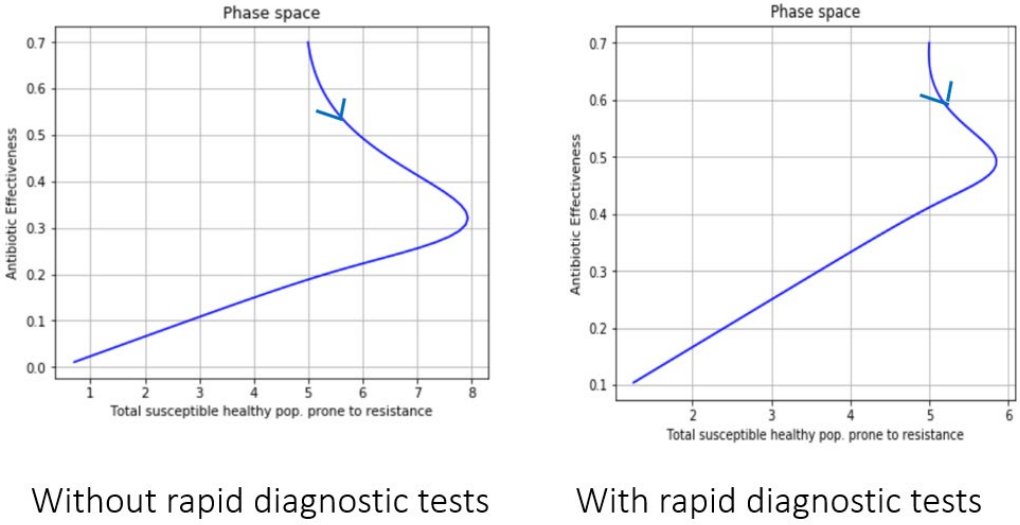
Without rapid diagnostic tests With rapid diagnostic tests

Diagram 4.6a: Healthy population prone to resistance – dynamics in time comparison



Without rapid diagnostic tests With rapid diagnostic tests

Diagram 4.6b: Effectiveness and Healthy population prone to resistance – dynamics in time comparison



Without rapid diagnostic tests With rapid diagnostic tests

Diagram 4.6c: Effectiveness and Healthy population prone to resistance – Phase diagram comparison

When the misuse and the overuse of antibiotics are eliminated in our second model, the S^R population is reduced as observed in **Diagram 4.6a**. In the simulation of the first model, the S^R population peaked at 8 individuals whereas in the second model, the peak is at 6 individuals. Consequently, there will be less infected individuals who will developed resistant infections because of a reduced number of the S^R population.

4.2 Welfare Implications

Social welfare function is the sum of the surplus of all individuals (whether infected or not and whether being treated or not) and the surplus of the manufacturers of the antibiotics. Recall from Section 3c), the probability of recovery without the use of antibiotics (i.e., when patients do not know which strains of bacterial they are infected with) is written as the following equation, where *e* represents the probability of being infected with the sensitive strains of bacteria (I^C) and $(1 - e)$ being the probability of being infected with the resistant strains of bacteria (I^{NC}):

$$\pi(\boldsymbol{e}) = \boldsymbol{e}\boldsymbol{r_C} + (\mathbf{1} - \boldsymbol{e})\boldsymbol{r_{NC}} \qquad (3.6)$$

The probability of recovery with the use of antibiotics or treatment is written as the following equation (augmented from $\pi(\boldsymbol{e})$):

$$\boldsymbol{P}(\boldsymbol{r}) = \pi(\boldsymbol{e}) + \boldsymbol{e}\boldsymbol{r_f} \qquad (3.7)$$

The health consideration can be determined with the gross utility of an individual of type θ[6].

- $U(\theta)$ = θ, if the individual is in good health (not infected).
- $U(\theta)$ = $\pi(e)\theta$, if the individual is infected, but is not taking any antibiotics and do not know which strains of bacterial he is being infected with.
- $U(\theta)$ = $(\pi(e) + er_f)\,\theta$, if the infected individual is taking antibiotics for treatment.

We also introduced **θ'** which is defined as the type of individual who is indifferent whether receiving treatment or not. P is defined as the price of the antibiotics. Therefore, we can derive equation 3.8

$$\pi(e)\theta' = \left(\pi(e) + er_f\right)\theta' - P \qquad (3.8)$$

The inverse demand function can be derived as the following:

$$P(f, e) = r_f e(1 - f) \qquad (3.10)$$

Given the determination of the demand function from the above, the social welfare can be written as:

$$W(f, e, I) = N\int_0^1 U(\theta)\, d\theta - cfI \qquad (4.17)$$

$$= (N - I)\int_0^1 U(\theta)\, d\theta + \quad (I)\int_0^{\theta'(p)} \pi(e)\,\theta\, d\theta \;+\; (I)\int_{\theta'(p)}^1 (\pi(e) + r_f w)\,\theta - p)\, d\theta + (p - c)fI$$

$$W(f, e, I) = \frac{1}{2}(N - 1) + \frac{1}{2}\pi(e)I + \frac{1}{2}r_f eIf^2 + \left[r_f e(1 - f) - c\right]fI \qquad (4.18)$$

In Equation 4.18:

- The term $\frac{1}{2}(N - I)$ can be defined as the surplus derived by the portion of the population which is healthy. θ = ½ represents the mean valuation of the good health.

[6] We assume that θ is equally distributed on the interval 0-1.

- The term $\frac{1}{2}\pi(e)I$ can be understood as the surplus of portion of the infected population which values good health at less than θ'(p), therefore this portion of population chooses to not buy the antibiotic. They recover at the natural recovery $\pi(e)$.
- The term $\frac{1}{2}r_f eIf^2$ can be interpreted as is the surplus to the individuals who choose to buy the treatment at price P, since they have a valuation of good health higher than θ'(p). They recover at an increased probability: $P(r) = \pi(e) + er_f$
- Consistent with the monopolist maximization problem, the last term $[r_f e(1-f) - c]fI$ is the surplus of the producers of an antibiotic against the sensitive infection.

The social optimum problem is to determine $f(t)$ to maximize the welfare function[7]:

$$Max\ \pi(w) = \int_0^T e^{-\rho t} w(f(t), e(t), I(t)) dt$$

Subject to the following constraints demonstrated in our second model (with the use of rapid diagnostics):

$$\dot{e} = e\,((1-e)(r_{NC} - r_C + f(r_C - r_f) - BS^R)) \quad (4.12)$$

$$\dot{I} = I[BS - r_{NC} + e(r_{NC} - r_C + f(r_C - r_f)] \quad (4.13)$$

$$\dot{S^R} = fI(er_f) - (BI + \delta)S^R \quad (4.14)$$

The Hamiltonian associated to the problem is described below:

$$H(f, e, I, S^R, u, \lambda, z) = \frac{1}{2}(N-1) + \frac{1}{2}\pi(e)I + \frac{1}{2}r_f eIf^2 + [r_f e(1-f) - c]fI + ue[(1-e)(-BS^R + \Delta r + f(r_c - r_f)] + \lambda I[(BS - r_{NC} + e(\Delta r + f(r_c - r_f)] + z[fI(er_f\ (BI + \delta)S^R] \quad (4.19)$$

The derivative with respect to *f* is:

$$\frac{\partial H}{\partial f} = r_f eIf + (r_f e(1-2f) - c)I + e(r_c - r_f)(u(1-e) + \lambda I) + zIer_f$$

[7] We assume a finite time T.

$$= (\boldsymbol{r_f e(1-f)-c)I + e\left(r_c - r_f\right)(u(1-e)+\lambda I) + zIer_f} \quad (4.20)$$

As explained above, where *u*, λ and *z* stand for the shadow values associated to the level of antibiotic efficacy and the stock of infected population and the healthy population respectively.

The following conditions are necessary for intertemporal profit maximization:

$$\boldsymbol{\frac{\partial H}{\partial f} \leq 0, \frac{\partial H}{\partial f} f = 0, f \geq 0 \text{ or } \frac{\partial H}{\partial f} \geq 0, \frac{\partial H}{\partial f}(1-f) = 0, f \leq 1} \quad (4.2)$$

$$\boldsymbol{\dot{u} - \rho u = \partial H / \partial e} \quad (4.3)$$

$$\boldsymbol{\dot{\lambda} - \rho\lambda = \partial H / \partial I} \quad (4.4)$$

$$\boldsymbol{\dot{z} - \rho z = \partial H / \partial S^R} \quad (4.5)$$

Condition in 4.2 is the first-order condition for the Hamiltonian maximization for $f(t)$.

When $\frac{\partial H}{\partial f}$ = 0, we have the social optimum interior solution f^s at state (*e, I*) at time *t* and condition 4.2 can be derived as:

$$\boldsymbol{r_f e(1-f^s) = c + (\frac{e}{I})(r_f - r_c)[(u(e-1)-\lambda I) - z\left(r_f e\right)]} \quad (4.21)$$

- The left side of equation 4.21 can be defined as the social optimum price of the antibiotic.
- The social optimum price of the antibiotic is equal to the marginal cost (c) plus an opportunity cost which also takes into consideration the effectiveness of the antibiotic (e) and the infected population (I). Similar to the monopolist problem, we observe that in the socially optimal solution with the use of rapid diagnostics, the future level of effectiveness of an antibiotic and the future number of infected individuals will be impacted by the current level of treatment. The monopolist problem and the social optimum problem both introduce an implicit social benefit to preserve the effectiveness of the antibiotics and an implicit the social cost related to the infection level in population (the respective shadow prices). A simulation for the effectiveness of the antibiotic and the S^R population should match the monopolist in the model 2 with the use of rapid diagnostic tests.

4.3 Discussion

As discussed earlier, the overuse and misuse of antibiotics are the main cause of antibiotic resistance. To further understand this problem, we assume that when a patient has been exposed to antibiotic-resistant bacteria, traces of it remains in the body, so that future infections are more likely to be by antibiotic-resistant bacteria. We also assume that even after a successful treatment, the infected population (I^C) will become a susceptible and healthy population that is prone to resist to an antibiotic due to prior use or the presence of antibiotic resistance in the environment. We build on Herrmann's model to integrate a crucial factor in the development of antibiotic resistance. Consequently, we introduce a newly healthy population (S^R) and a mechanism in our bio-economic model to link this population to antibiotic resistance.

Considering the fact that rapid diagnostic tests represent one of the best strategies and by construct in our model, rapid diagnostic tests alleviate the externality problem linked to the overuse and misuse of antibiotics. However, we still need to identify the impact of these tests on the S^R population since this population is a key factor to antibiotic resistance. Therefore, we introduced rapid diagnostic tests in our model to simulate situations where antibiotics are used in an efficient way (when $f_2 = 0$ or no misuse/overuse of antibiotics). As observed in our simulation, when an antibiotic is overused or misused (without rapid diagnostic tests), the S^R population peaked at a higher level. When there is a higher level of S^R population among healthy individuals, the effectiveness of an antibiotic decreases more rapidly as the S^R population will eventually all turn into I^{NC} (where the infected individuals are untreatable). When the infected population is mostly composed of the I^{NC} population, the effectiveness of an antibiotic will be extremely low (recall that $\boldsymbol{e} = \frac{\boldsymbol{I_C}}{\boldsymbol{I_C}+\boldsymbol{I_{NC}}}$). We therefore observe an important relationship between the use rapid diagnostic tests and the S^R population. In fact, the rapid diagnostic tests do not affect the effectiveness of antibiotic directly, it instead controls the spread S^R population which will eventually preserve antibiotic effectiveness.

From the in-depth analysis of our model and from the results shown, it is socially desirable to have rapid diagnostic being carried out and to preserve the effectiveness of

the antibiotic. Moreover, we realized that in order to have a better fighting chance against antibiotic resistance, it is indispensable to control the spread of the S^R population and rapid diagnostic tests can strongly help. However, from the monopolist point of view, efficient rapid diagnostic tests can limit their potential market (the monopolist will be limited to treat sensitive infections). If the monopolist were to invest to develop such efficient rapid diagnostic tests, the return on investment for the new technologies will not be directly proportional to the volume of tests used since we showed above that a smaller portion of population will be treated.

Nonetheless, our analysis and results demonstrated the important relationship between the S^R population and antibiotic resistance. While investment in the development of efficient rapid diagnostic test is important, it is imperative to monitor the change in the S^R population or to minimize this population as a preventive measure. In our model, we also suggested the susceptible healthy population conversion where a fraction δ of the S^R population will become again a healthy susceptible population that is not prone to resist to antibiotics (we assume this occurs also naturally). In the absence of efficient rapid diagnostic tests, a deeper understanding of this conversion might provide us other ammunitions to tackle the problem of antibiotic resistance. Policies should be centered to reduce traces of antibiotics in our environment. This might increase the rate of δ which will decrease the S^R population and preserve antibiotic effectiveness.

4.4 Incentive Models

In this section, we will explore incentives for the monopolist to develop such rapid diagnostic tests. Most of the current reward systems adopted in our society to advance for devolvement of antibiotics are called “push incentives” (Aral, 2017). Government agencies and private companies have essentially only provided push incentives for antibiotic development. We observe that this is typically in the form of grants and public-private partnerships, as well as regulatory disincentives. However, in the context of rapid diagnostic tests, the push incentives can only reduce the overall cost of research and development at best. Therefore, this will not solve the problem that the rapid diagnostic tests will limit the potential market (infected people) for the monopolist. We will present two additions to our proposed model which are based on new mechanisms of action.

a) « Fully-Delinked » Reward System

We learned the antibiotic market is unique as the effectiveness of a drug decreases with its use. Therefore, the market model for antibiotics is usually not aligned with public health objectives. In the book “Superbugs: An Arms Race against Bacteria”, there are currently proposals for a reward system against sales volumes to ensure a viable market. These systems are called “pull incentives” and the basic idea behind this model is to reward successful development by increasing or ensuring future revenue. Pull incentives provide known return on investment (i.e., periodic payments or market-entry rewards).

We can incorporate pull incentives in our model to reward the use of rapid diagnostic tests used and to ensure known return on the investment for the monopolist. Payments will be made to reward efficient rapid diagnostic tests used that align with the current public health priorities. These payments can also provide a predictable return on investment for the monopolist if it was developing such tests.

We previously set the profit function of the monopolist as the following in our proposed model:

$$\boldsymbol{\pi(e) = \left[r_f e(t)\left(\left(1 - f(t)\right) - \mathrm{c}\right)\right] f(t)\mathrm{I}(t)}$$

The alternative with the addition of pull incentive would give rise to the following profit function:

$$\boldsymbol{\pi(e) = \left[r_f e(t)\left(\left(1 - f(t)\right) - \mathrm{c}\right)\right] f(t)\mathrm{I}(t) + lumpsum\ periodic\ payment}$$

These payments can be in form of reimbursement or market entry reward.

However, lumpsum payments or transfers are poor choices of incentives because of the costs maintaining them. A tax would ideally need to be introduced and other mechanism to obtain fund are needed to ensure sustainability.

b) Dual pricing strategy and value-based model

When an infected individual is being treated initially, a doctor might use the new antibiotic developed by the monopolist because of the patient’s needs. The price of the antibiotic for the first few days would be set to a base price that would be lower than the

full price charged by the monopolist. When rapid diagnostic tests are ordered by physicians and when clinicians would confirm the right use the new antibiotic empirically, a premium higher price would be charged to the hospital. If no diagnostic tests are ordered by clinicians, any longer treatment duration with this antibiotic would also be charged the higher price.

This model compensates the value of the antibiotic developed by the monopolist in the presence of rapid diagnostic tests. In our proposed model, we understand that if an individual is infected with drug-resistance infection or other types of infection, the value of the monopolist antibiotic is low, and a treatment with this antibiotic is not socially desirable. However, after a rapid diagnostic test, the type infection can be confirmed. The antibiotic developed by the monopolist might become significantly more valuable if no other antibiotics can treat the infection. The second higher price captures the value of the monopolist's antibiotic. The model compensates for the loss of market size of the monopolist with the use of rapid diagnostic tests by physicians. While the rapid diagnostic tests give the precision on the treatment choices, it also confirms when an antibiotic is more valuable than others. Therefore, a premium price would be charged by the monopolist after infections are confirmed by the rapid diagnostic tests.

5. Conclusion and future directions

Antibiotic resistance could lead us back into the dark ages where minor infections or surgeries can claim human lives. One of the main causes of antibiotic resistance is the misuses and overuse of antibiotics. Rapid diagnostic tests would greatly reduce inappropriate and unnecessary prescriptions and represent one of the best strategies against the increase of antibiotic resistance. The use of rapid diagnostic tests will not only improve direct outcomes, but it can also preserve the effectiveness of an antibiotic. We have built a bio-economic model to examine the interaction between infection transmissions within populations, antibiotic effectiveness (or resistance), and the use of rapid diagnostic tests in the pricing policy of a monopolist who is protected by a patent. In order to better understand antibiotic resistance and the impact of rapid diagnostic tests, we build on Herrmann's model to add a susceptible and healthy population that is prone to resist certain antibiotics due to prior use and due to the presence of antibiotic resistance in the environment and how rapid diagnostic tests impact this new population. Our first model concluded that a non-myopic monopolist (without the use of rapid diagnostic tests) will find an interior solution where its marginal benefit equals the marginal cost plus an external cost which also takes into consideration the effectiveness of the antibiotic and the infected population. A smaller portion of the population will be treated compared to the interior solution of a myopic monopolist who does not care about future impact on the effectiveness of the antibiotics. In our second model (with the use of rapid diagnostics tests), we showed that an even smaller portion of population will be treated by the non-myopic monopolist. Nonetheless, the simulation of our models show that in fact the increased use of rapid diagnostic tests benefited the society by reducing the number of newly healthy population who are prone to antibiotic resistance which, in turn, will preserve the effectiveness of the antibiotics. Although we demonstrated the benefit of the rapid diagnostic tests, the current model incorporating rapid diagnostic tests do not seem to align with the monopolist incentives. We present novel mechanism of incentives for the monopolist in our model to increase the development and the use of rapid diagnostic tests. A mixture of a de-linked system and a dual-pricing model can be used as a reward model for the monopolist to ensure a viable market. These incentives could be sustained through a tax on generic antibiotic use while providing a disincentive for inappropriate use of

antibiotic. We also proposed a better monitoring and the development of new policies to control the newly introduced healthy population which we believe is a key factor in the development of antibiotic resistance.

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Annexe 1 – Python Code

Model 1 - Without rapid diagnostic:

```
import numpy as np
import matplotlib.pyplot as plt
from scipy import integrate
# define system in terms of a Numpy array
def Sys(X, t=0):
    # here X[0] = x and x[1] = y and x[2] = z
    return np.array([(X[0]*(1-X[0]))*(rnc - rc + f*(rc-rf) - b*X[2]),
                     X[1]*((b*s - rnc) + (X[0]*(rnc-rc + f*(rc-rf)))),
                     f*X[1]*(rf*X[0]+rnc*(1-X[0]))- (b*X[1]+q)*X[2]])

# generate 1000 linearly spaced numbers for x-axes
t = np.linspace(0,5,100)
# initial values:
Sys0 = np.array([0.7, 10, 20])

# type "help(integrate.odeint)" if you want more information about integrate.odeint inputs and outputs.
X, infodict = integrate.odeint(Sys, Sys0, t, full_output=True)
# infodict['message']                    # integration successful
```

```
x,y,z = X.T


#plot
fig = plt.figure(figsize=(15,5))
fig.subplots_adjust(wspace = 0.5, hspace = 0.3)
ax1 = fig.add_subplot(1,2,1)
ax2 = fig.add_subplot(1,2,2)


ax1.plot(x, 'r-', label='Antibiotic effectiveness')
ax1.set_title("Dynamics in time")
ax1.set_xlabel("time")
ax1.grid()
ax1.legend(loc='best')


ax2.plot(x, y, color="blue")
ax2.set_xlabel("x")
ax2.set_ylabel("y")
ax2.set_title("Phase space")
ax2.grid()


#2
```

```
fig = plt.figure(figsize=(15,5))
fig.subplots_adjust(wspace = 0.5, hspace = 0.3)
ax1 = fig.add_subplot(1,2,1)
ax2 = fig.add_subplot(1,2,2)

ax1.plot(y, 'b-', label='Total infected people')
ax1.set_title("Dynamics in time")
ax1.set_xlabel("time")
ax1.grid()
ax1.legend(loc='best')

ax2.plot(x, y, color="blue")
ax2.set_xlabel("x")
ax2.set_ylabel("y")
ax2.set_title("Phase space")
ax2.grid()

#3
fig = plt.figure(figsize=(15,5))
fig.subplots_adjust(wspace = 0.5, hspace = 0.3)
ax1 = fig.add_subplot(1,2,1)
ax2 = fig.add_subplot(1,2,2)
```

```
ax1.plot(z, 'g-', label='Susceptible healthy pop. and prone to resistance')

ax1.set_title("Dynamics in time")

ax1.set_xlabel("time")

ax1.grid()

ax1.legend(loc='best')


ax2.plot(x, z, color="blue")

ax2.set_xlabel("x")

ax2.set_ylabel("z")

ax2.set_title("Phase space")

ax2.grid()
```

Model 2 - With Rapid Diagnostic:

```
import numpy as np

import matplotlib.pyplot as plt

from scipy import integrate

# define system in terms of a Numpy array

def Sys(X, t=0):

    # here X[0] = x and x[1] = y and x[2] = z

    return np.array([(X[0]*(1-X[0]))*(rnc - rc + f*(rc-rf) - b*X[2]),

                     X[1]*(b*s - rnc + X[0]*(rnc-rc+f*(rc-rf))),

                     f*X[1]*(rf*X[0]) - (b*X[1]+q)*X[2]])


# generate 1000 linearly spaced numbers for x-axes
```

```
t = np.linspace(0,2,100)

# initial values:

Sys0 = np.array([0.7, 10, 20])


# type "help(integrate.odeint)" if you want more information about integrate.odeint inputs and outputs.

X, infodict = integrate.odeint(Sys, Sys0, t, full_output=True)

# infodict['message']                    # integration successful


x,y,z = X.T


#plot

fig = plt.figure(figsize=(15,5))

fig.subplots_adjust(wspace = 0.5, hspace = 0.3)

ax1 = fig.add_subplot(1,2,1)

ax2 = fig.add_subplot(1,2,2)


ax1.plot(x, 'r-', label='Antibiotic effectiveness')

ax1.set_title("Dynamics in time")

ax1.set_xlabel("time")

ax1.grid()

ax1.legend(loc='best')
```

```
ax2.plot(x, y, color="blue")
ax2.set_xlabel("x")
ax2.set_ylabel("y")
ax2.set_title("Phase space")
ax2.grid()

#2

fig = plt.figure(figsize=(15,5))
fig.subplots_adjust(wspace = 0.5, hspace = 0.3)
ax1 = fig.add_subplot(1,2,1)
ax2 = fig.add_subplot(1,2,2)

ax1.plot(y, 'b-', label='Total infected people')
ax1.set_title("Dynamics in time")
ax1.set_xlabel("time")
ax1.grid()
ax1.legend(loc='best')

ax2.plot(x, y, color="blue")
ax2.set_xlabel("x")
ax2.set_ylabel("y")
ax2.set_title("Phase space")
```

```
ax2.grid()


#3
fig = plt.figure(figsize=(15,5))
fig.subplots_adjust(wspace = 0.5, hspace = 0.3)
ax1 = fig.add_subplot(1,2,1)
ax2 = fig.add_subplot(1,2,2)

ax1.plot(z, 'g-', label='Total susceptible healthy pop. and prone to resistance')
ax1.set_title("Dynamics in time")
ax1.set_xlabel("time")
ax1.grid()
ax1.legend(loc='best')

ax2.plot(x, z, color="blue")
ax2.set_xlabel("x")
ax2.set_ylabel("z")
ax2.set_title("Phase space")
ax2.grid()

#all together

fig = plt.figure(figsize=(15,5))
```

```
fig.subplots_adjust(wspace = 0.5, hspace = 0.3)

ax1 = fig.add_subplot(1,2,1)

ax2 = fig.add_subplot(1,2,2)


ax1.plot(z, 'g-', label='Effectiveness')

ax1.plot(y, 'b-', label='Total infected')

ax1.plot(x, 'r-', label='Total susceptible healthy')

ax1.set_title("Dynamics in time")

ax1.set_xlabel("time")

ax1.grid()

ax1.legend(loc='best')
```