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Introduction

Since their discovery in the late 1930's, antimicrobial substances (antibiotics) have been efficient for treating infections caused by bacteria and other microbial organisms. Antibiotic treatment has reduced the number of fatalities and the risk of transmitting virulent microbial agents among humans as well as animals. The risks involved in procedures such as transplants, chemotherapy for cancer and even orthopaedic surgery would be substantially higher without the availability of potent antibiotics. In addition, among farm animals, the use of antibiotics as feed-additives has been found to enhance weight gain and growth, thereby increasing productivity.

However, all use of antibiotics carries the side effect of selecting for genetic change in bacteria that may lead to resistance to one or several antimicrobial substances (Ashley and Brindle 1960, Levy et al 1987, Levy 1990, Cohen 1992, Murray 1994, Piddock 1996, Swedish Board of Health and Welfare 2000, Bronswaer et al 2002, WHO 2001 and 2005). In general terms, the risk of resistance increases if antibiotics are prescribed frequently, in low doses over long periods or with the wrong choice of substance. Moreover, when diagnoses are not accurately made, broad-spectrum antibiotics, i.e. antibiotics that target several types of bacteria and not only those causing the disease, are prescribed (ECDC, 2008). Once emerged, bacteria resistant to antibiotics behave like any other contagious disease (OTA 1995, Cohen and Tartasky 1997, Andersson 2006).

The risk of resistance emerging may be larger in veterinary, than in human medicine, since antibiotics often are given as feed-additives in sub-therapeutic doses over longer periods (Cohen 1992). Also, the risk of selecting the wrong substance is higher in veterinary medicine due to lack of diagnostic facilities (WHO 2001). As several bacteria are common to animals and humans, they are treated with substances from the same classes (see, for instance, the lists of substances in SVA 2006, and in Apoteket 2006). Hence, resistance emerging in veterinary medicine may affect humans, and vice versa (Wegener 2003). In addition, increased travel, trade in foodstuffs and movements of animals imply that antimicrobial resistance is rapidly becoming a global threat.

Historically, as resistance developed, new classes of antibiotics were also developed. Today, the flow of new substances has slowed considerably (Cohen and Tartasky 1997, WHO 2001, ECDC 2008). Consequently, we may run out of tools to effectively treat microbial infections. This would result in higher costs of health care in animals and humans, as well as higher costs in animal production. To reduce the rate at which resistance develops, more restrictive policies, primarily relying on voluntary guidelines and legal restrictions, for antibiotic use have emerged.

Voluntary guidelines include guidance for prudent use among veterinarians, as well as information to farmers on prudent use for antibiotics that are sold over the counter. For example, in Sweden it is considered good veterinary practice that drugs should only be prescribed to individual animals after a clinical and laboratory examination identifying the disease causing agent. Another recommendation is that narrow spectrum antibiotics should be preferred to broad spectrum drugs.

Legal restrictions include bans of antibiotics for particular uses (for instance, the US ban on the use of chloramfenikol for food animals and the EU ban on antibiotics as

feed-additives), that only specialists are permitted to issue prescriptions, that the antibiotic is to be used only after prescription and/or only to be sold at pharmacies. Another type of legal restrictions is the withdrawal periods for antibiotics in food animals. These periods will vary according to the type of foodstuff (meat, milk or eggs) to be withdrawn from the food chain, the metabolism of the antibiotic in the treated animal and the maximum residue limits (MRL) of the drug laid down by the Council Regulation (EEC) No 2377/90 in the EU.

On the other hand, it has also been recognised that restrictions on antibiotic use could have negative effects on the development of new antimicrobials since they might reduce the profitability of such efforts to the pharmaceutical industry (c.f. WHO 2001 and the references therein). Quantitative restrictions on the use of existing substances could, therefore, aggravate the problem of securing a steady flow of new substances to replace them when resistance does render them inefficient. Hence, it is of interest to see what economic theory can contribute towards a solution. As it turns out, there are rather few studies on the use of antibiotics by economists (examples are Phelps, 1989; Coast et al 1996, 1998 and 2002; Brown and Gruben, 1997; Laxminarayan and Brown 2001; Laxminarayan 2001 and 2002; Smith and Coast 1998 and 2002; Elbasha, 2003; Horowitz and Moehring, 2004; Smith et al 2005). However, the economic literature provides results from other areas that may be applicable.

Natural resources, public goods, and externalities

Given that microbial sensitivity to antibiotics can be depleted, it may be regarded as a finite natural resource and should be used cautiously in order to maximise utility. Market mechanisms often provide sufficient guidance but *sensitivity* to antibiotics may be characterised as a *public good*, that is, a good for which it is difficult to exclude individuals from consumption. Antibiotic sensitivity is a characteristic incumbent to bacteria, the movement of which is difficult to control. Accordingly, it is virtually impossible to exclude people from benefitting from it. If everyone can benefit from the good, there are no incentives to pay for it, implying that market prices for antibiotic sensitivity will not occur naturally. It has long been recognised that, with no guidance from prices reflecting their values, public goods are likely to be over-utilized in the sense that marginal costs exceed marginal utility of consumption for society as a whole (see for instance Hardin 1968, Varian 1978, Gravelle and Rees 1983, Krebs 1990, or Stiglitz 2000).

Still, *antibiotics* are *private goods* (people who will not pay can be excluded from consuming the good). They, therefore, also have market prices. However, these prices do not include the cost of resistance caused by the use of antibiotics. This is because the cost of resistance is the value of the reduction in antibiotic sensitivity and, since antibiotic sensitivity is a public good, there is no market price that could signal the value of this loss. Accordingly, resistance may be regarded as a *negative externality* (a cost that is not accounted for in the price of the good). This implies that antibiotics consumption may become too high. To complicate matters, there are *positive externalities* (benefits not included in the market price) from the consumption of antibiotics as well. In addition to curing the individual, treatment reduces the risk of the disease being transmitted, and the individual may not accept to pay for this benefit to others that arise from his or her consumption. Positive externalities imply that the

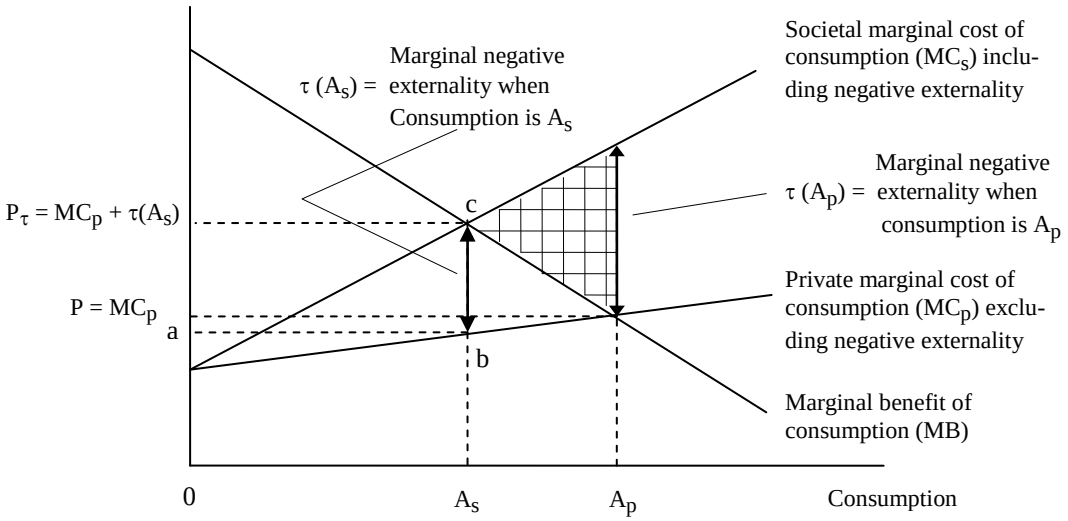
consumption of antibiotics may become too low (the marginal utility of consumption to society – including the beneficial effect on the health of others – exceeds the marginal costs of consumption).

The question then is how to handle the problems caused by externalities. In theory, there are a number of solutions including taxation, subsidies, and the construction of patent rights.

Pigouvian taxes

Negative externalities may be internalised by levying a tax equal to the marginal external cost – a *Pigouvian tax* (Pigou 1932) – on consumption (or production), thereby forcing the individual to also consider the cost of resistance when deciding on antibiotics consumption. The proceeds from the tax could then be used to subsidise pharmaceutical companies for developing new substances, thereby compensating for the reduction in revenues caused by lower sales of antibiotics due to the tax. Figure 1, below, illustrates the principle in a static setting.

Figure 1: Internalisation of a negative external effect by means of taxation.



The individual considers all private costs of antibiotics consumption and maximizes utility by choosing that level of consumption (A_p) where marginal private costs (MC_p) equals marginal benefits (MB). However, at A_p the true marginal costs of consumption to society (including the negative externality) exceed marginal benefits, generating a welfare loss for society (shaded triangle). Levying a tax equal to the value of the *marginal* negative externality (τ which, as can be seen, increases with consumption) on consumption, forces the individual to consider the full societal costs of consumption (MC_s). This results in the socially optimal quantity (A_s), and tax revenues equal to the rectangular area (a-b-c-P_τ).

By the same token, positive externalities may be internalised by paying a subsidy equal to the value of the marginal external benefit. Since this "Pigouvian subsidy" lowers the marginal cost of consumption, individuals are compensated for the beneficial effects on others' health that arise from their own consumption.

Though antibiotics consumption does entail positive externalities, there seems to be consensus that negative externalities in the form of resistance prevail. Hence, the further discussion concentrates on the problem of addressing negative externalities. This is complicated by the fact that the magnitude of the negative externality from resistance increases over time as more, or different strains of, bacteria are exposed to antibiotics. Accordingly, a dynamic model is needed to illustrate the issues involved (c.f. Brown and Gruben 1997, Krautkraemer 1998 or Laxminarayan and Brown 2001). For this, the following simplifying assumptions are made:

First, to high-light the general principles, it is assumed that there is only one antibiotic (*A*). Demand for antibiotics, at any point in time, is a function of the price of antibiotics (*P*) and microbial sensitivity to antibiotics (*S*) at that point in time such that a higher price reduces demand and a higher microbial sensitivity increases demand:

$$A_t = A(P_t, S_t), \quad \text{where} \quad \frac{\partial A_t}{\partial P_t} < 0 \quad \text{and} \quad \frac{\partial A_t}{\partial S_t} > 0. \tag{1}$$

Sensitivity to antibiotics is measured as the proportion of bacteria for which antibiotics effectively inhibits growth (c.f. SVA 2006). An increase in accumulated use of antibiotics (*Q*) implies that more bacteria have been exposed to antibiotics and subjected to genetic selection. It is assumed that there are no "fitness costs" associated with resistance (i.e. bacteria that have acquired resistance are no less fit in terms of survival and growth rates than non-resistant bacteria, c.f. Anderson and Levin 1999, Andersson 2003 and 2006, and the references therein). Accordingly, the probability of encountering bacteria that are susceptible to antibiotics decreases with accumulated use. Therefore, sensitivity to antibiotics at a given point in time is assumed to be a decreasing function of the accumulated use of antibiotics at that point in time:

$$S_t = S(Q_t), \quad \text{where} \quad \frac{\partial S_t}{\partial Q_t} < 0. \tag{2}$$

In equilibrium, demand for antibiotics (*A*) equals use of antibiotics. Hence, accumulated use (*Q*) at a given point in time is defined as:

$$Q_t \equiv \int_0^t A_s \, ds, \quad \text{implying that} \quad \frac{\partial Q_t}{\partial t} = A_t, \tag{3}$$

that is, accumulated use increases over time by the amount of present use. Given equations (1) and (2), and the definition in (3), the inverse demand function is:

$$P_t = P\left[A_t, S_t(Q_t)\right], \quad \text{where} \quad \frac{\partial P_t}{\partial A_t} < 0 \quad \text{and} \quad \frac{\partial P_t}{\partial Q_t} = \frac{\partial P_t}{\partial S_t}\frac{\partial S_t}{\partial Q_t} < 0. \tag{4}$$

The inverse demand function indicates how the *marginal value* of antibiotics, as measured by the price (P_t) people are willing to pay for it, evolves as a function of present (A_t) and accumulated (Q_t) use. For a given amount of accumulated use, P_t corresponds

to a point on a given demand curve, such as the *MB*-curve in Figure 1 above. Thus, for a given amount of accumulated use, the marginal value of present use, say A_t equal to A_p, is the vertical distance from the consumption axis to the *MB*-curve at that quantity. An increase in accumulated use (Q_t) reduces microbial sensitivity at any amount of present use, implying that the value of antibiotics is reduced. Hence, an increase in Q_t results in a downward shift of the *MB*-curve.

Finally, the costs of inputs such as capital, labour and raw material associated with the production of antibiotics (*C*), at any point in time, are assumed to be a non-decreasing function of the amount of antibiotics produced (*A*) at that time:

$$C_t = C(A_t), \quad \text{where} \quad \frac{\partial C_t}{\partial A_t} \geq 0. \tag{5}$$

The problem of maximizing the net present value of antibiotics to society can then be formulated as:

$$\begin{aligned} &\max: \int_0^{\infty} e^{-rt} \int_0^{A} \{P[a_t, S_t(Q_t)] - (\partial C_t / \partial a_t)\} da_t \, dt \\ &\text{s.t}: \frac{\partial Q_t}{\partial t} = A_t, \quad S(t=0) = S_0, \quad S(t=\infty) \geq 0 \end{aligned} \tag{6}$$

In terms of Figure 1, the first part of the "inner" integral in eq. (6), i.e. $\int P[a_t, S_t(Q_t)]da_t$, represents the area under the *MB*-curve associated with a given level of accumulated use Q_t (implying a given level of microbial sensitivity to antibiotics, S_t). Similarly, the second part of the inner integral in eq. (6), i.e. $\int (\partial C_t / \partial a_t) da_t$, represents the area under the private marginal cost of consumption curve (MC_p). Thus, the problem in eq. (6) consists of choosing the amount of antibiotics consumption at each point in time (A_t) that maximizes the area between these two curves over time, taking account of the fact that an increase in A_t increases accumulated use (Q_t), which decreases microbial sensitivity, causing the *MB*-curve to shift downwards. Equation (6), therefore, represents a control problem, with Q_t as the state variable and A_t as the control variable. Accordingly, it may be solved by optimal control theory (c.f. Chiang, 1992 or Sydsäter et al, 2005). The current value Hamiltonian (H^c) is (see Appendix):

$$H^c = \int_0^{A} \{P[a_t, S_t(Q_t)] - (\partial C_t / \partial a_t)\} da_t + \lambda(t) A_t, \tag{7}$$

where $\lambda(t)$ is the current value co-state variable for Q_t, which measures the change in the value of the objective function caused by a marginal increase in the control variable, i.e. antibiotics use at time *t*. This implies that $\lambda(t) < 0$ and that $-\lambda(t)$ can be interpreted as representing the *user costs* of antibiotics at time *t*.

The first-order condition for maximization of the societal value of antibiotics is that:

$$\frac{\partial \mathrm{H}^{\mathrm{c}}}{\partial A_t} = 0 \quad \Rightarrow \quad P[A_t, S_t(Q_t)] = (\partial C_t / \partial A_t) - \lambda(t) \,. \tag{8}$$

Thus, at any point in time, the marginal value of antibiotics use $P[A_t, S_t(Q_t)]$ should equal the marginal cost of production ($\partial C_t / \partial A_t$) plus the user costs of antibiotics at that time ($-\lambda(t)$). To calculate the user cost, we first investigate how $\lambda(t)$ develops over time and then solve the resulting differential equation (see Appendix). Differentiating $\lambda(t)$ with respect to time gives:

$$\frac{\partial \lambda}{\partial t} = r\lambda - \int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} da_t \,, \tag{9a}$$

and the solution to this differential equation is:

$$\lambda(t) = \int_t^\infty e^{-r(\theta - t)} \left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} da_t \right] d\theta \,. \tag{9b}$$

Thus, $\lambda(t)$ is the *present value* of the change in microbial sensitivity caused by increased accumulated antibiotics use at time *t*. The increase in accumulated use reduces the share of bacteria that are sensitive to antibiotics, thereby reducing the value of antibiotics (shift the *MB*-curve in Figure 1 downwards), at that point in time. Since there are no fitness costs, the loss (the value of the downward shift in the *MB*-curve) will persist in all future periods. However, rather than shifting the *MB*-curve in Figure 1 downwards, the *MC*-curve is shifted upwards from MC_p to MC_s by a magnitude equal to $-\lambda(t)$ in accordance with the formulation in equation (8).

The result in eq. (9b implies that eq. (9a) can be re-written as:

$$\frac{\partial \lambda}{\partial t} = r \int_t^\infty e^{-r(\theta - t)} \left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} da_t \right] d\theta - \int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} da_t \,. \tag{9c}$$

With the appropriate change of sign, eq. (9c) shows how the user costs develop over time. An intuitive interpretation is as follows. At a given point in time accumulated use increases by the amount of present use. This leads to a reduction in microbial sensitivity and a downward shift in the *MB*-curve. At the next point in time, the costs caused by returns from investment forgone due to the loss of microbial sensitivity at the previous point in time should also be accounted for. Thus, the first term in eq. (9c) measures the returns that would have accrued at the next point in time from investing a sum corresponding to the user costs at the previous point in time. On the other hand, at the next point in time the user costs should be corrected for the value of the loss of microbial sensitivity that already has occurred. This is captured by the second term in eq. (9c). Thus, depending on whether the first term of eq. (9c) is larger or smaller than the second term, the user costs will rise or fall over time.

Finally, substituting (9b) for $\lambda(t)$ in eq. (8), maximizing the societal value of antibiotics requires that:

$$P[A_t, S_t(Q_t)] = (\partial C_t / \partial A_t) - \int_t^{\infty} e^{-r(\theta - t)} \left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} da_t \right] d\theta . \tag{10}$$

Although the user costs are accounted for in the societal maximization problem, they were labelled an "externality" in Figure 1. This would be the case when viewing the problem from the position of an individual pharmaceutical company operating under perfect competition or the position of an individual consumer of antibiotics.

A pharmaceutical firm operating under perfect competition is so small that its production does not affect the price of antibiotics. Thus, although it contributes to the depletion of microbial sensitivity, the effect is so small in relation to that of all other firms' production that the price of antibiotics would be unaffected by a change in the output of the individual firm. Accordingly, from the firm's point of view, the price of antibiotics is exogenously determined (i.e. P_t is not a function of the firm's present and accumulated use as in eq. 4 above). The firm, therefore, receives no signal of the user costs caused by its production of antibiotics and perceives its profits (π), defined as revenues (P_tA_t) minus costs $C(A_t)$ from the production of antibiotics, at a given point in time to be:

$$\pi_t = P_t A_t - C(A_t), \tag{11}$$

and the firm's problem of maximizing the present value of profits over time can be formalized as:

$$\max : \int_0^{\infty} e^{-rt} \left[P_t A_t - C_t(A_t) \right] dt . \tag{12}$$

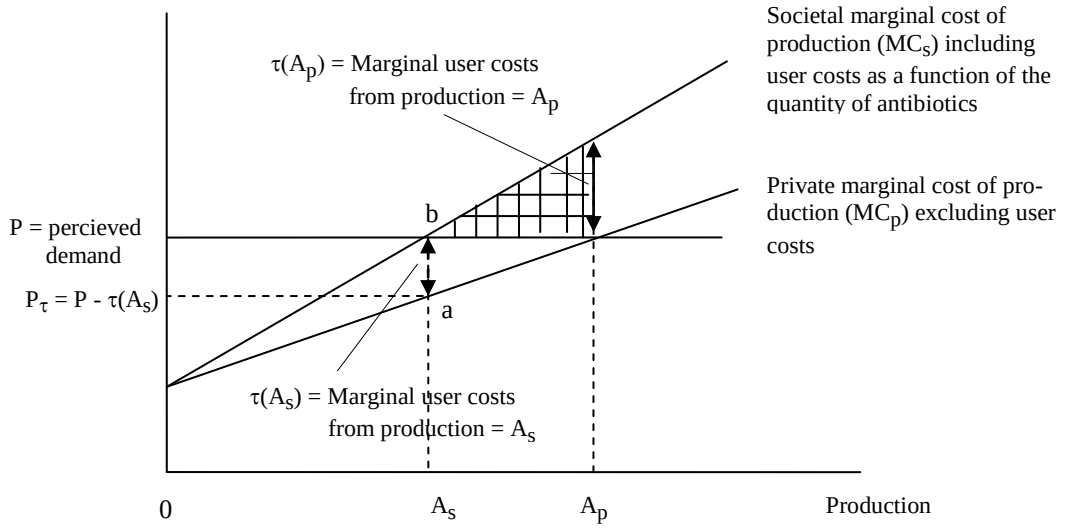
The first-order condition for profit maximization is: $\int_0^{\infty} \frac{\partial e^{-rt} \left[P_t A_t - C_t(A_t) \right] dt}{\partial A_t} = 0$,

implying that: $P_t \int_0^{\infty} e^{-rt} dt = \frac{\partial C_t}{\partial A_t} \int_0^{\infty} e^{-rt} dt \quad \Rightarrow \quad P_t = \frac{\partial C_t}{\partial A_t}$. (13)

As the firm receives no indication of the effect on microbial sensitivity arising from its production, the user costs are external to the firm and not included in the maximization problem. Marginal revenue equals the price of antibiotics and the marginal costs consist only of the costs of capital, labour, and raw material associated with a marginal change in production. The firm, therefore, behaves as if maximizing profits according to a horizontal demand curve corresponding to the straight line P and a

marginal cost curve corresponding to the MC_p-curve in Figure 2 below. As can be seen, maximizing the area between these two curves implies that the firm produces too much antibiotics from the societal perspective and results in a welfare loss corresponding to the shaded triangle.

Figure 2: Welfare effects of antibiotics production when producers do not account for user costs caused by reduced microbial sensitivity.



The externality could be internalised by levying a tax corresponding to the marginal user costs on the firm's production of antibiotics. As the firm perceives demand to be perfectly elastic, raising the price above the given market price P would result in the firm loosing all customers. Hence, levying a tax (τ), equal to $(-\lambda(t))$ as defined in eq. (9b) above, on production implies that the firm will have to bear the entire burden of this tax. This will lower marginal income from antibiotic sales to $P_\tau = (P - \tau)$ and induce the firm to reduce production to the socially optimal quantity A_s. This Pigouvian tax would also result in tax revenues from the firm equal to the rectangle (P_τ-a-b-P), which could be used to subsidize development of new antimicrobial substances.

Similarly, the quantity of antibiotics used by an individual consumer is so small in relation to total use that microbial sensitivity to antibiotics is taken as given at any point in time. In the context of antibiotic consumption in animal health, we may think of an animal-husbandry farmer maximizing profits (π) over time. The revenues and costs of the venture depend on the price and quantity of animal produce and the prices and quantities of a number of inputs, for instance, physical and human capital, the number of animals, the amount and quality of feed and animal health. Animal health, in turn, also depends on physical and human capital, the amount and quality of feed, and antibiotics. To simplify the problem, we assume that all inputs except antibiotics are held constant. The revenues are then a function of quantity (X) and price (P^X) of animal produce. Animal produce is a function of animal health (h) which, in turn, is a function of antibiotics use $h(A)$. Finally, the costs of producing animal health are a function of the quantity (A) and price (P^A) and of antibiotics used. With these assumptions, the animal-husbandry farmer's profit function is:

$$\pi_t = P_t^X X_t\left[h_t(A_t)\right] - P_t^A A_t\,, \tag{14}$$

and the inter-temporal profit maximization problem can be written as:

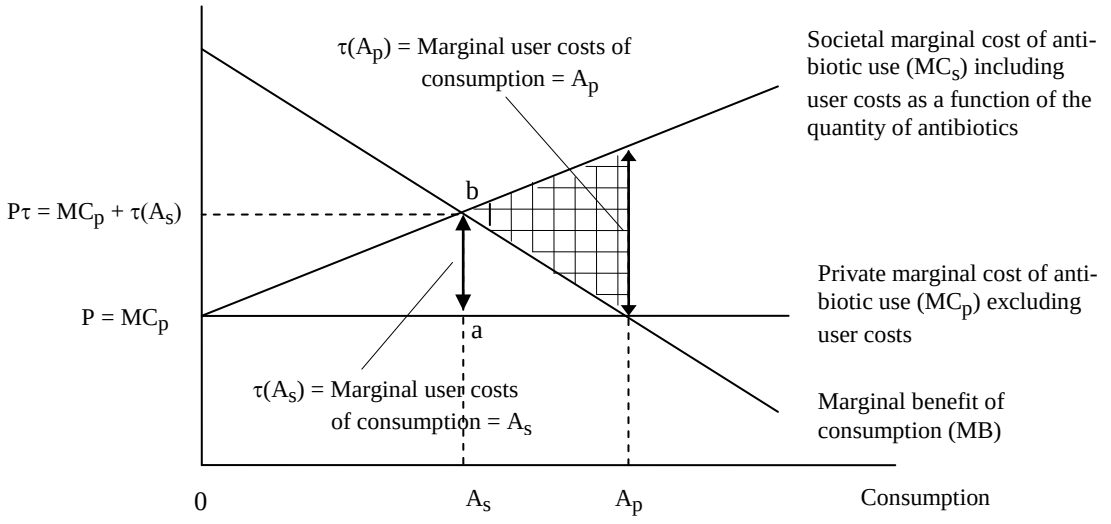
$$\max: \int_0^\infty e^{-rt}\left\{P_t^X X_t\left[h_t(A_t)\right] - P_t^A A_t\right\}dt\,. \tag{15}$$

The first-order condition is: $\int_0^\infty \frac{\partial e^{-rt}\left\{P_t^X X_t\left[h_t(A_t)\right] - P_t^A A_t\right\}dt}{\partial A_t} = 0\,,$ implying that:

$$P_t^X \frac{\partial X_t}{\partial h_t}\frac{\partial h_t}{\partial A_t}\int_0^\infty e^{-rt}dt = P_t^A \int_0^\infty e^{-rt}dt \quad \Rightarrow \quad P_t^X \frac{\partial X_t}{\partial h_t}\frac{\partial h_t}{\partial A_t} = P_t^A\,. \tag{16}$$

Hence, the animal-husbandry farmer does not consider the user costs of antibiotics (they are external to him because of the insignificance of his consumption on microbial sensitivity to antibiotics). He, therefore, behaves as if maximizing profits according to the horizontal MC_p-curve in Figure 3 below and uses too much antibiotics from the societal perspective. The result is a welfare loss corresponding to the shaded triangle in the figure.

Figure 3: Welfare effects of antibiotic consumption when consumers do not account for user costs caused by reduced microbial sensitivity.



As before, it would be possible to induce the animal-husbandry farmer to take account of the user costs by adding a tax (τ), equal to $(-\lambda(t))$ as defined by eq. (9b), on the consumption of antibiotics. Since the animal-husbandry farmer perceives supply to be infinitely elastic at the given market price P, he has to bear the entire burden of the tax himself. This would raise his marginal cost of consumption to $MC_p + \tau$, and reduce consumption to the socially optimal quantity A_s. Again, this Pigouvian tax would raise

revenues from the animal-husbandry farmer equal to the rectangular area (P-a-b-P_τ), which could be used to subsidise development of new antimicrobial substances.

In theory, the solution looks simple enough. All that needs to be done is to levy a tax on the production (consumption) of antibiotics that equals the value of the marginal negative externality arising from producers (consumers) not accounting for the user costs. The decision on how much antibiotics to produce (consume) could then be left to the individual. This approach is likely to result in a more efficient use of antibiotics than quantitative restrictions as it would provide incentives for consumers to reserve the use of antibiotics to cases where the marginal benefit of consumption is sufficiently high to warrant the full marginal costs (including those caused by resistance). It would also provide incentives for producers to develop substances with minimal effects on resistance, thereby reducing the tax levied on their product. As mentioned above, the producers' incentives to develop new substances could be further strengthened by using the tax receipts to subsidize the costs of such efforts.

The catch is, that to construct a tax that equals $\lambda(t)$ in eq. (9b), we need to know by how much a marginal increase in accumulated use of antibiotics reduces microbial sensitivity (increases resistance) over time ($\partial S_t / \partial Q_t$) and by how much this reduces the value of antibiotics $\{\partial P[a_t, S_t(Q_t)]/\partial S_t\}$. There seems to be agreement that resistance increases over time according to a *logistic* function (see for instance Kermack and McKendrik 1927, Bonhofer et al 1997, or Laxminarayan and Brown 2001). For instance, assuming no fitness cost, the model in Bonhofer et al 1997 is:

$$R(t) = \frac{e^{\beta I t} - 1}{e^{\beta I t} - 1 + \frac{1}{\gamma}}\ , \tag{17}$$

where $R(t)$ is resistance (the share of humans and animals infected with bacteria that are insensitive to antibiotics) as a function of time, β is the share of infected (I) that are treated with antibiotics and γ is the share of sensitive bacteria in treated humans and animals that acquire resistance and survive treatment.

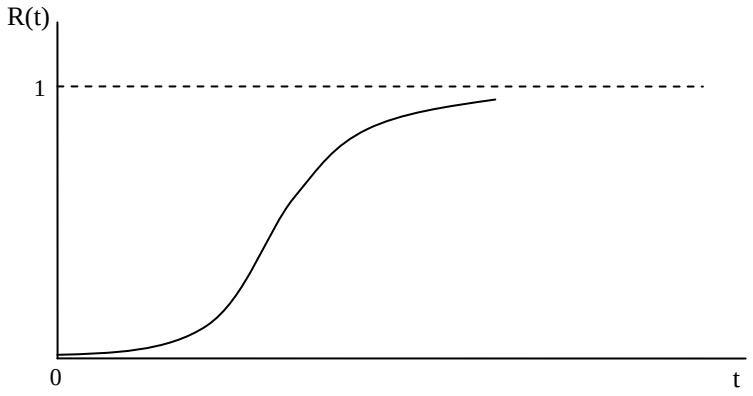
Note that, for $t \geq 0$ and $0 \leq \beta \leq 1$, $e^{\beta I t} \geq 1$. Hence, the numerator of eq. (17) is ≥ 0 and, for $0 \leq \gamma \leq 1$, the denominator is $\geq (1/\gamma)$, implying that resistance is always ≥ 0. Differentiating eq. (17) twice with respect to time, we obtain:

$$\frac{\partial R}{\partial t} = \frac{\frac{\beta I e^{\beta I t}}{\gamma}}{\left(e^{\beta I t} - 1 + \frac{1}{\gamma}\right)^2}\ , \qquad \text{and} \qquad \frac{\partial^2 R}{\partial t^2} = \frac{\frac{(\beta I)^2 e^{\beta I t}}{\gamma}\left[1 + \frac{1}{\gamma^2} - \left(e^{\beta I t}\right)^2\right]}{\left(e^{\beta I t} - 1 + \frac{1}{\gamma}\right)^4}. \tag{18}$$

The first derivative $(\partial R/\partial t)$ in eq. (18) indicates whether resistance will grow or fall over time. Both the numerator and the denominator are > 0, implying that resistance grows over time. The second derivative $(\partial^2 R/\partial t^2)$ shows how the rate of growth of resistance changes over time. The denominator is still > 0. For small values of t, the

numerator is also > 0, indicating that the growth of resistance initially increases when *t* increases. However, at some point the (absolute) value of the last term equals the sum of the two first terms and the numerator equals zero, indicating that the increase in the growth of resistance has stopped. For even larger values of *t*, the (absolute) value of the last term exceeds the sum of the first two terms, implying that the numerator becomes < 0 and that resistance grows at a decreasing rate. Equation (17) also indicates that, when $t = 0$ $R(t) = 0$ and, as t goes towards infinity, $R(t)$ goes towards 1. Hence, resistance develops as illustrated in Figure 4.

Figure 4: Resistance as a logistic function of time



Accumulated use of antibiotics at a given point in time depends on how many of the infected animals and humans that have been treated with antibiotics until that time (Q_t in expression 3 above). In the model by Bohnhofer et al $Q_t = \beta It$. Sensitivity is the opposite of resistance. Hence, we have:

$$S(Q_t) = 1 - R(t) = 1 - \frac{e^{\beta It} - 1}{e^{\beta It} - 1 + \frac{1}{\gamma}}. \tag{19}$$

Implying that:

$$\frac{\partial S}{\partial Q_t} = \frac{\partial(1-R)}{\partial t} = -\frac{\frac{\beta I e^{\beta It}}{\gamma}}{\left(e^{\beta It} - 1 + \frac{1}{\gamma}\right)^2}. \tag{20}$$

Thus, with this simplified model and given information on how long the antibiotic has been in use (t), the number of infected (I), the share of infected that have been treated at each point in time (β) and the share of sensitive bacteria in treated humans and animals that acquire resistance because of treatment (γ), one could calculate $(\partial S_t / \partial Q_t)$ at a given point in time. One could then calculate by how much the reduction in microbial sensitivity would lower the value of antibiotics (i.e. raise the costs in health care and animal production) and compute the value of the integral in eq. (9b).

However, γ and β are not known. Neither are the infection and recovery rates among human and animals, implying that the size of the infected population I is un-known. Moreover, if we drop the simplifying assumption of there being only one antibiotic, it is likely that γ, β and I will differ between classes of antimicrobial substances as well as between strands of bacteria. Thus, the construction of a Pigouvian tax that correctly reflects the costs of reduced microbial sensitivity is not practical.

Of course, any tax that raises the price of antibiotics will reduce consumption, thereby preserving microbial sensitivity. However, if the tax is set higher than the user costs, consumption of antibiotics will fall too much since the marginal benefit of antibiotic treatment will be higher than the costs of the marginal reduction of microbial sensitivity arising from that treatment. The resulting welfare loss may be greater or smaller than the original one depending on how much the tax overshoots the marginal user costs.

Duration and coverage of patents

As an alternative to taxing the consumption of antibiotics, it has been suggested that patents with longer duration should be granted for antibiotics. This rests on the notion that a patent shields the pharmaceutical company from competition, thereby creating a monopoly situation. Hence, longer patent periods for certain antibiotics will provide property rights with longer duration for that particular microbial sensitivity and create incentives for the patent holder to preserve sensitivity for a longer period. However, this solution may not be optimal if the monopoly *cannot discriminate*, which is a reasonable assumption due to the costs of differentiating consumers according to their preferences for antibiotics and prohibiting them from reselling drugs.

A non-discriminating monopoly, facing a demand for antibiotics defined by the assumptions in eq. (1) – (4) and a cost function defined by eq. (5) above, has the profit function:

$$\pi_t^M = P[A_t, S(Q_t)]A_t - C(A_t). \tag{21}$$

Accordingly, the monopoly's problem of maximizing discounted profits over the period from $t = 0$, to $t = T$ (when the patent period ends) can be formulated as:

$$\begin{aligned} &\max: \int_0^T e^{-rt}\{P[A_t, S_t(Q_t)]A_t - C(A_t)\}dt \\ &\text{s.t}: \frac{\partial Q_t}{\partial t} = A_t, \quad S(0) = 0, \quad S(T) \geq 0 \end{aligned} \tag{22}$$

As the monopoly has to take account of the fact that an increase in antibiotics use at time t increases accumulated use at that time, which decreases microbial sensitivity and shifts the demand curve downwards, the problem is similar to that in eq. (6) above. However, since the monopoly's profit function differs from the societal value

function in eq. (6) above, so does the monopoly's current value Hamiltonian, which is:

$$\mathrm{H}_m^c = P[A_t, S_t(Q_t)]A_t - C(A_t) + \lambda(t)A_t . \tag{23}$$

The first-order condition for profit maximization is then:

$$\frac{\partial \mathrm{H}_m^c}{\partial A_t} = 0 \qquad \Rightarrow \quad P[A_t, S_t(Q_t)] + \frac{\partial P[A_t, S_t(Q_t)]}{\partial A_t} A_t = \frac{\partial C}{\partial A_t} - \lambda , \tag{24}$$

i.e., marginal revenue, $P[A_t, S_t(Q_t)] + \{\partial P[A_t, S_t(Q_t)] / \partial A_t\} A_t$ shall equal marginal costs $(\partial C / \partial A_t)$ plus the monopoly's user costs, which are found by proceeding in the same way as before. Hence, if the time horizon is infinite:

$$\lambda(t) = \int_t^\infty e^{-r(\theta - t)} \left\{ \frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} A_t \right\} d\theta , \tag{25a}$$

and develops over time according to:

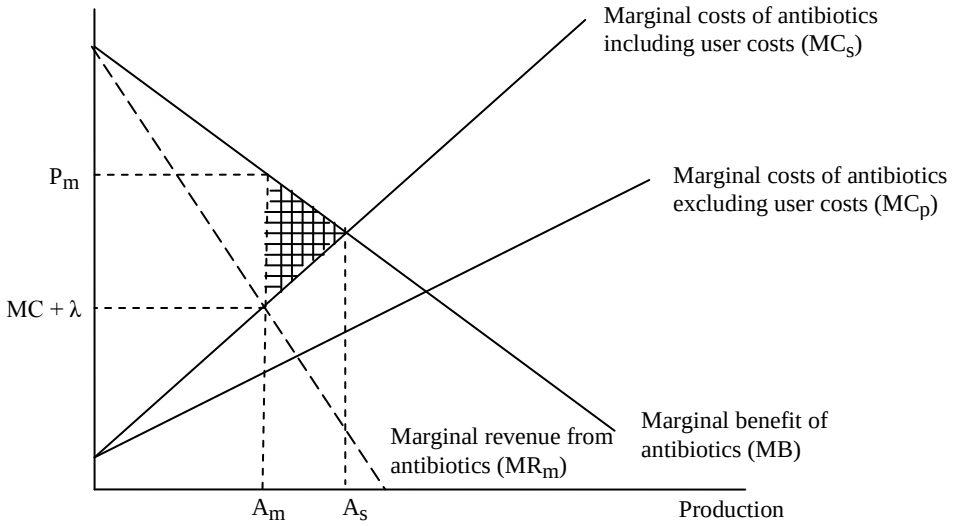
$$\frac{\partial \lambda}{\partial t} = r \int_t^\infty e^{-r(\theta - t)} \left\{ \frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} A_t \right\} d\theta - \frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} A_t . \tag{25b}$$

Thus, substituting the expression in (25a) for $\lambda(t)$ in eq. (24), maximizing the monopoly's profits from antibiotics requires that:

$$P[A_t, S_t(Q_t)] + \frac{\partial P[A_t, S_t(Q_t)]}{\partial A_t} A_t = \frac{\partial C}{\partial A_t} - \int_t^\infty e^{-r(\theta - t)} \left\{ \frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t} \frac{\partial S_t}{\partial Q_t} A_t \right\} d\theta . \tag{26}$$

Hence, the monopoly does account for user costs. However, in the absence of user costs, a non-discriminating monopoly will produce a smaller quantity than the societal optimum since marginal revenues decrease at a faster rate than societal marginal benefits. Adding the user costs shifts the marginal cost function upwards. This results in a solution such as in Figure 5 where the quantity of antibiotics produced by the monopoly (A_m) is too small, implying a welfare loss equal to the shaded triangle. The only exception would be if the MC_s-function should become vertical at the point of interception with the MR_m-function, in which case the quantity chosen by the monopoly would coincide with the socially optimal quantity.

Figure 5: Welfare effects of monopoly production



There are also other problems with the "prolongation of patent duration strategy". For instance, it has been shown that bacteria that acquire resistance to one particular antibiotic substance may also become resistant to other substances belonging to the same class or having the same mode of action. One concern is the multidrug efflux pumps that could confer resistance for several antibiotics (Walsch and Fanning, 2008; and Van Bambeke et al., 2006, Mahamoud et al, 2007). Cross-resistance has been an issue for many years for bacterial species such as coagulase negative staphylococci (John and Harvin, 2007). Thus, to induce the patent holder to account for user costs it may be necessary to extend the patent coverage to all substances belonging to a particular class or that could confer cross resistance. This would have the side effect of substantially reducing competition between pharmaceutical companies. If competition is an important driver for the development of new and more effective solutions to existing problems, i.e. antibiotic substances to which bacteria are less likely to develop resistance, this should not be taken lightly.

Another argument against prolonged patent periods (and extended patent coverage) is the excess profits for drug companies to the detriment of consumers of drugs and the society i.e., the tax payer. Hall (2001) suggested that the trade off between longer patent periods and global welfare gains were not obvious and Gore (1982) suggested other means for supporting drug research such as investment tax credits for research expenses. In a review by Scherer (2007) it was noted that patent protection appeared to be relatively unimportant for pharmaceutical companies' research and development decisions.

A tax based on the replacement costs

Though resistance starts to develop as soon as a substance is used, the available evidence suggests that a new antibiotic substance will last for some years before resistance becomes problematic. The duration of this period depends on the amount of antibiotics used and the type of use. For example Bager et al., 1997 found that the zoo

technical use of antibiotics such as avoparcin was seen as contributing to the emergence of vancomycin resistant enterococci (VRE) in poultry and pigs. The use of broad spectrum antibiotics for metaphylactic and prophylactic purposes, often at sub therapeutic doses, is another example of antibiotic use seen to contribute to the emergence of resistance (EMEA, 1998).

Thus, another solution to the problem of how to best contain resistance would be to stick to the tax on antibiotics, but calculate it using the costs of developing a new substance (*C*), the time until which resistance renders the present substances inefficient (*T*), and the annual number of doses sold during this time (*N*) as parameters. That is, the tax would be calculated as:

$$\Psi = \frac{C}{N \times T}. \tag{27}$$

Similar to the Pigouvian tax, a tax based on the costs of developing a new substance would serve to contain the consumption of antibiotics, thereby slowing down the development of resistance, and the proceeds from the tax could be used to subsidise the development of new substances, thereby increasing the probability of them being available when present substances have been rendered inefficient. Although there is no presumption that this "replacement cost tax" would be *optimal* (i.e. reflect the true marginal cost of resistance), it may be the best available approximation and, therefore, minimize the risk of excess taxation.

To calculate the replacement cost based tax (Ψ) one needs information on the costs of developing new drugs, the expected annual amount of antibiotics used, and the expected time until the drug becomes inefficient. While such data are difficult to obtain some information could be found in the literature.

Cost of developing new drugs

Information on drug development costs are the private property of pharmaceutical companies and, therefore, not readily observable. Nevertheless, estimates of the expected development costs for a drug successfully brought to the market have been made by, for instance, Hansen, 1979; DiMasi et al, 1991; OTA, 1993; Myers and Howe, 1997; Kettler, 1999; DiMasi et al, 2003; Gilbert et al 2003; Adams and Brantner, 2006; Vernon et al, 2009 and Adams and Brantner, 2010.

To assure that only drugs with new modes of action were considered all studies concern new chemical entities (NCE). All studies also utilise firm-level, as opposed to industry level data. Another common feature is that the costs are calculated as the sum of the expected out-of-pocket and opportunity costs of capital incurred during each of the three phases of the development process. The expected *out-of-pocket* costs depend on how many drug candidates that enter phase 1 of the development process and the costs they incur during this phase, how many of the candidates that have entered phase 1 that also enter phase 2 and the cost they incur during phase 2, how many of the candidates in phase 2 that enter phase 3 and the costs they incur during phase 3, and, finally, on how many of the candidates in phase 3 that enter the market. The expected *opportunity costs* of capital are obtained by multiplying the expected out-of-

pocket costs in each phase with the real rate of return on capital assets since this is what the out-of-pocket costs could have earned had they been invested otherwise.

However, the studies use data from different sources and periods. Hence, the expected costs differ even when calculated at fixed prices. The cost estimates from the respective studies are shown in Table 1 below.

Table 1: Estimates of expected development costs (including opportunity costs of capital) for new drugs (2008 prices obtained by using the U.S. GDP deflator and then converting to € using the exchange rate 1€ = 1.48 $US)

Study	Data period	Real rate of return	Success rate	Expected cost (Million $US)	Expected cost (Million €)
Hansen 1979	1963-1975	8 %		175	118
DiMasi et al 1991	1970-1982	9 %	23 %	401	271
OTA 1993	1970-1982	10 %	23 %	554	374
Myers and Howe 1997	1970-1982	11 %	23 %	590	399
Kettler 1999	1970-1982	9 – 10 %	20 – 23 %	401-790	271-534
DiMasi et al 2003	1980-1999	11 %	21.5 %	978	661
Gilbert et al 2003	1995-2002		8 – 14 %	1701	1149
Adams and Brantner 2006	1989-2002	11 %	23.9 %	1059	716
Vernon et al 2009	1980-1999	14 %	23 %	1210	818
Adams and Brantner 2010	1989-2001	11 %	25.5 %	1481	1001

The obvious observation is that the estimated costs increase over time. There are several reasons for this. One is that stricter regulations (for instance the 1992 Prescription Drug Act) may have prolonged the periods of clinical testing and also the approval period after clinical testing. Other things equal, this will increase both the out-of-pocket and the opportunity costs of capital.

Another is that the real rate of return on capital assets used to calculate the opportunity cost of capital differs between studies. A higher real rate of return implies a higher opportunity cost of capital and, hence, raises the expected development costs.

Yet another reason concerns the estimated transition probabilities (the share of drug candidates that moves from one phase of the development process to the next). Higher transition probabilities increase the number of drug candidates entering the next development phase, thereby raising the development costs. On the other hand, a larger share of drug candidates making it through *all* phases reduce the cost per drug brought to the market. Thus, high transition probabilities in early phases in combination with low transition probabilities at the final stage results in higher expected development costs for a drug successfully brought to the market. While not all studies report transition probabilities for each phase, the estimated share of candidates making it all

the way to approval (success rate) differ between studies. Other things equal, a lower success rate increases the expected development costs

In addition, the studies by Hansen 1979, DiMasi et al (1991 and 2003), OTA 1993, Myers and Howe 1997 and Vernon et al 2009 only included self originated drug candidates while the studies by Adams and Brantner (2006 and 2010) and Gilbert et al 2003 also included drug candidates that were licensed in. It is suggested that the firm's expected development costs will be lower for licensed in drugs since part of the costs have been covered by the firm of origin (or the government if the compound originated in governmental or academic laboratories).

A final caveat is that the estimated expected costs are for the average drug, not the average antibiotic. The studies by Adams and Brantner 2006 and 2010, and a study by DiMasi et al 2004 do report estimates broken down by therapeutic categories. Adams and Brantner estimate the expected costs for "anti-infectives" which are lower than for the average drug. However, due to the limited number of observations on anti-infective drugs, the variation is large and the estimate is not statistically significantly different from 0 at conventional levels. Contrary, DiMasi et al find the expected development costs for anti-infectives to be significantly higher that for the average drug. However, they note that this is driven by very high development costs for *AIDS* and *anti-viral drugs*.

Accordingly, since there are no statistically significant indications that the development costs of antibiotics are different from those of the average drug, the latter may be the best available estimate to base the replacement cost tax on. Still, we need to address the fact that the estimated development costs have increased over time partly because of real changes in development costs and partly because of refinements in the methodology of estimation. This suggests that we should choose as recent an estimate as possible as the basis for the tax (for instance the Adams and Brantner estimate from 2010).

Amounts of antibiotics consumed

As to information on the amount of antibiotics consumed, measured as active substance, we utilise the report from the European Commissions' Scientific Steering Committee on antibiotic uses. The data are shown in Tables 2 and 3. The consumption of antibiotics in the EU 15 was close to 10 493 tonnes in 1997. The veterinary and zootechnical use constitutes approximately half of the consumption, while the veterinary use constitute one third of the total consumption within the EU.

Table 2: Consumption of antibiotics in the EU - Scientific Steering Committee (SSC) report 1999, Annex 2)

Domain of use	**Quantity used** (tonnes active substance)
Human medicine	5400
Veterinary medicine	3494
Zootechnical use (antimicrobial feed additives or growth promoters)	1599
Sum	10493

Table 3: Estimated antimicrobial sales volumes veterinary clinical use (SSC report 1999) for the year 1997.

Type of antibiotic	Tonnes of active substance	% of total sales
Penicillin	322	9.2
Tetracyclines	2294	65.7
Macrolides	424	12.1
Amino glycosides	154	4.4
Fluroquinolones	43	1.2
Trimetroprim Sulphas	75	2.1
Other therapeutics	182	5.2
Sum	3494	

Time to resistance

The time until resistance emerges appears to be brief though the antibiotic will remain useful for a longer period if the use is managed with a view to maintaining the efficacy of the drug. Based on different sources such as Wikipedia accessed 2009, the European Commission's Scientific Steering Committee (SSC) report from 1999, the report and qualitative risk assessment from the Committee of Veterinary Medicinal Products (CVMP) of the European Medicines Agency (EMEA), 1999; a somewhat coherent picture emerges that is illustrated in Tables 4-6.

From Table 4 it appears that once antibiotics is introduced for use in human and veterinary medicine, the first signs of resistance appears after only a few years. Nevertheless, avoparcin (a growth promoter for use in pig and poultry production) was introduced in the late 1970's, and was not linked to resistance until approximately 10 years later (Bager et al, 1997). The period between introduction and before serious problems emerge appears to be between 10-40 years.

Table 4: Time from introduction to resistance based on Wikipedia accessed Feb 19, 2009 http://en.wikipedia.org/wiki/Antibiotic_resistance)

Antibiotic	Introduction in clinical use	Resistance detected	Serious problem
Penicillin	1943	1947	1950ties
Methicillin	1959	1961	2000 (CDC)[1]
Fluroquinolone	1982	1985	1990 ties
Vancomycine	1958 (approved) 1978 (avoparcin introduced)	1987	1990ties (VRE) 2002 (Vancomycin resistant staphylococcus aureus, VRSA)
Cephalosporins	1964 (1st generation)	1983	ESBL (1994)[2]

[1] http://www.cdc.gov/Features/MRSA/ accessed November 24, 2008.

[2] Quinn JP, 1994. Clinical significance of extended-spectrum beta-lactamases. Eur J Clin Microbiol Infect Dis. 13 Suppl 1:S39-42

Table 5 presents the results from EMEA's review (1999) of the emergence of resistance. It appears that the time from introduction to clinical use or zootechnical growth

promotion in the case of avoparcin until resistance emerges ranges from 0 to 9 years with an average of 3 years. In this table the time to emergence of resistance was measured from the introduction into clinical use.

Table 5: Time to resistance based on the EMEA report of July 14, 1999

Antibiotic	**Discovered**	**Introduced in clinical use**	**Resistance identified**	**Years from introduction to emergence of resistance**
Penicillin (classes)	1940	1943	1940	0
Streptomycin	1944	1947	1947	0
Tetracycline	1948	1952	1956	4
Erythromycin	1952	1955	1956	1
Vancomycine	1956	1972 (avoparcine 1978)	1987	15 (9 for avoparcine)
Methicillin	1959	1961	1965	4
Nalidixic acid	1960	1962	1966	4
Gentamicin	1963	1967	1970	3
Fluroquinolone	1978	1982	1985	3
3rd generation Cephalosporins	1964 (1st generation)	1983	1985	2

Looking at the veterinary side in particular, the European Commission's Scientific Steering Committee (SSC) report (1999) noted the period it takes from introduction of an antibiotic into an animal compartment or production system until resistance was detected. It appeared to be a period ranging from 3-6 years before resistance emerged in the production system or compartment (Table 6). Hence, it seems that the period, for which bacteria remains sensitive to an antibiotic is between 2 and 10 years.

Table 6: Time from introduction to emergence of resistance in animal compartments based on SSC report, May 28, 1999

Antibiotic, bacterium, compartment or production system, country (ref)	**Introduced**	**Resistance emerged**	**Time from introduction to resistance**
Enrofloxacin, Campylobacter jejuni, Poultry production, UK (Gaunt 1996)	1993	1997 (10 % prevalence of enrofloxacin resistance)	4 years
Enrofloxacin, Campylobacter jejuni, Poultry production, Netherlands (Gaunt 1996)	1987	1993 (14 % prevalence of enrofloxacin resistance)	6 years
Olaquindox, Pig production, UK (Linton 1988)	1982	1985 (6% prevalence)	3 years

Prices of antibiotics

The prices of antibiotics in € per kg active substance are not transparent within the EU. For illustrative purposes, we use the official catalogue for veterinary drugs in Sweden (FASS) and the prices for antibiotics therein. We estimate the average price per kilogram active substance based on the prices of the following drugs benzyl penicillin, doxycycline, oxytetracycline, tylosine and tiamuline, intended for use as feed additives apart from penicillin. The price per kg active substance ranged from 263 to 415 €, with an average of 303 € (using the exchange rate of 11 SEK = 1 €).

Results

The results appear in Table 7. The estimates are based on (1) the expected costs for developing a new antibiotic, (2) the expected amount of active substance consumed, and (3) the expected time beween the development and introduction of a new antibiotic. In the third column, the tax is related to the average price of veterinary antibiotics in Sweden (333 € per kg active substance). As a comparison, the additional costs due to a tax based on expected development costs as estimated by Adams and Brantner (2010) would be 96 € (29%) or 57 € (17%) per kilogram active substance, if the objective was to bring a new antibiotic drug to the market every 3rd or 5th year for registration, respectively.

Table 7: Estimates of the replacement cost based tax.

Years	**tax € per kg of active substance**	**% tax imposed of antibiotic drug cost based on a price of 333€ per kg active substance**
1	286.5	85.9%
2	143.2	43%
3	95.5	28.6%
4	71.6	21.5%
5	57.3	17.2%
6	47.7	14.3%
7	40.9	12.3%
8	35.8	10.7%
9	31.8	9.5%
10	28.6	8.6%

Discussion

In this paper we have developed an analytical framework for assessing the economics of antibiotic resistance in veterinary medicine. There are three externalities to keep in mind when discussing the use of antibiotics; two negative - the risk of resistance development in the pathogenic microorganisms causing disease in animals and humans and the presence of antibiotic residues in foods, and one positive - the limiting of the spread of bacterial animal diseases curable by antibiotics.

By using preventive measures (e.g. bio security, vaccination, good surveillance, rapid detection and treatment) the transmission of bacterial diseases could be contained without using antibiotics. It may be noted that incentives to apply these measures increase with the price of antibiotics. The risk of antibiotic residues in food can be managed by using compulsory withdrawal times for eggs, milk and when sending animals to slaughter after treatment. This leaves the risk of emerging resistance for which the farmer and the veterinarian do not face the full marginal societal cost and therefore have an incentive to use too much antibiotics. Moreover without compensatory interventions, the pharmaceutical industry also seems to have inadequate incentives for developing new antibiotics and for the sustainable use of current ones. As the use of new antibiotics should be restricted in order to sustain antibiotic sensitivity, the net present value of a new antibiotic drug will be lower compared with developing a drug aimed at lifelong treatment (e.g., hypertension drugs) for wealthy human patients. If a new antibiotic is developed, the pharmaceutical firm needs to maximize sales during the few years (around 10) of patent protection to recoup its investment, before facing competition from generic substances. As a consequence, the finite resource of antibiotic sensitivity among pathogenic bacteria is depleted. There are therefore, some important questions when discussing the economics of sustainable use of antibiotics; (1) what is the best way to align the externalities of veterinary drug use and development with the incentives for farmers, veterinarians and pharmaceutical industry, and (2) how should the revenues from this tax be used? The aim should be to maximize long-run net socio-economic and medical benefits.

Possible measures for aligning the incentives and externalities include legislation, taxation such as Pigouvian taxes, extended patent rights or establishing property rights for antibiotic sensitivity. Whilst there is no perfect solution, a tax based on the expected development costs offer one practical option for aligning the incentives and externalities for antibiotic use and development. It is a second best solution as a Pigouvian tax would be more efficient. However due to lack of knowledge regarding the costs of resistance and the speed at which different antibiotics induce resistance, the first best solution is not possible. To maximize efficiency the tax should be collected, and the funds disbursed, globally reflecting the global public good element of the antibiotic sensitivity, e.g. a task for FAO/WHO. However, the legal, administrative and political issues involved could present considerable obstacles to this solution. A practical option could be to develop a European Union strategy by collecting the tax within the EU and give the EU institutions the mission of distributing the funds for research. We therefore chose to illustrate the tax based on EU data. However, the information in Tables 1-6 was not easily accessible, and should be updated before any policy decisions are made.

The revenue from the tax should be invested in the research and development of new antibiotics, preferably new classes of antibiotics. This preference is because the lower probability of already established resistance mechanisms conferring resistance to new classes of antibiotics. A reasonable ambition could be to develop a new class of antibiotics every 5^{th} year, implying a tax of around 17% (Table 7) on the price of antibiotics for veterinary use. Whether this tax should be extended to human use of antibiotics is beyond the scope of this paper, but is clearly a subject for further study. A complementing strategy for the use of revenue from the tax is to fund research and development for alternatives to antibiotics for treating and preventing animal diseases and their transmission. Examples include development of vaccines, pre- and probiot-

ics, and development of efficient bio security measures pre-harvest. Thus, a portfolio approach devoting resources to the development of antibiotics and their alternatives might be the best strategy.

The answer to the question of when an antibiotic is considered useless due to resistance is at the end of the day practical. Thus, we have used broad intervals (1 to 10 years) for the duration of antibiotic sensitivity when estimating the tax based on development costs (Table 7). We believe the findings in Tables 4-6 should be used as a broad guidance for policy makers when implementing the development cost based tax rather than interpreted as scientific truths. It is obvious that the emergence of resistance will differ between specific combinations of bacteria species and different types of antibiotics. Accordingly, it would be a major improvement if the tax could be differentiated according to the type of antibiotics, the different kind of bacterial infections and the different uses of antibiotics e.g. therapeutic versus zoo-technical. However, a practical approach is needed to fund the research and development of new antibiotic drugs and to balance the marginal social costs with the marginal benefits of antibiotic use, and the approach used in this paper should be seen as a rough approximation.

One critical issue is whether or not resistance is reversible. Traditionally the view has been that the development of antimicrobial resistance in bacterial populations imposes a fitness cost on the resistant bacteria's metabolism. Accordingly, once the antibiotic is removed from an environment, other bacteria not being hampered by the fitness cost will multiply quicker and dominate. Therefore, the bacterial populations would become dominated by sensitive bacteria, and the efficacy of antibiotics would be restored.

However, Zhang et al (2006) suggested that this view should be balanced because, while there are many resistance-conferring mutations entailing a biological fitness cost, others (e.g. fluoroquinolone resistance in Campylobacter) have no cost or even enhanced fitness. Moreover, for e.g. Salmonella, the fitness disadvantage due to antimicrobial resistance can be restored by acquired compensatory mutations. The compensated or even enhanced fitness associated with antibiotic resistance may facilitate the spread and persistence of antimicrobial-resistant Salmonella and Campylobacter in the absence of selection pressure, creating a significant barrier for controlling antibiotic-resistant pathogens. Andersson (2003) noted that though many drug resistances confer a fitness cost, suggesting that they might disappear by reducing the volume of antibiotic use, increasing evidence from laboratory and epidemiological studies indicate that several processes will act to cause long-term persistence of resistant bacteria. Resistance can be natural or acquired. Some bacterial species, such as Pseudomonas aeruginosa, show a high intrinsic resistance to a number of antibiotics whereas others are normally highly antibiotic susceptible such as group A streptococci. Acquired resistance usually has a biological cost for the microorganism, but compensatory mutations accumulate that abolish this fitness cost, explaining why many types of resistances may never disappear in a bacterial population. The WHO review (2003) of the termination of antimicrobial growth promoters in Denmark noted that there was a marked decrease in the food animal reservoir of resistant enterococci, while no effects where observed on the gram negative bacteria. In reviewing the natural experiment of the ban of avoparcin as growth promoter in Danish and Norwegian poultry farms Johnsen et al (2009) concluded that complete eradication of antimicro-

bial resistance in bacterial populations following decreased drug use is not straightforward. Resistance determinants may persist at low, but detectable, levels (1-2% prevalence) for many years in the absence of the corresponding drugs. In the special case of TB, Gagneux (2009) pointed out that the future of the multidrug resistant and the extensively drug resistant tuberculosis epidemics depends in part on the competitive fitness of drug-resistant strains. Borrell and Gagneux (2009) concluded that compensatory evolution, which has been shown to mitigate the fitness defects associated with drug resistance in other bacteria, could be an important factor in the emergence and spread of drug-resistant M. tuberculosis.

Hence on the balance of current evidence it seems like antibiotic resistance may become less reversible as time goes and the fitness costs decline. Compensatory evolution that ameliorates the costs of resistance, the occurrence of cost-free resistances and genetic linkage between non-selected and selected resistances will confer a stabilization of the resistant bacteria. Normark and Normark (2002) concluded that antibiotic resistance is a clinical and socioeconomic problem that is here to stay. Thus, it is important to implement strategies that reduce the rate of appearance and spread of resistant bacteria to allow new drug discovery to catch up with bacterial resistance development.

Conclusion

The sensitivity of bacteria to antibiotics should be managed as a finite natural resource. A tax based on the expected costs of development new antibiotic substances may offer a practical option for balancing the incentives and externalities of antibiotic use and development.

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Appendix

The condition for optimal consumption of antibiotics

Inter-temporal maximization of societal net present value of antibiotics consumption requires that we:

$$\max: \int_0^{\infty} e^{-rt} \int_0^{A} \{P[a_t, S_t(Q_t) - (\partial C_t / \partial a_t)]\} da_t \, dt$$
$$\text{st}: \quad \frac{\partial Q_t}{\partial t} = A_t, \quad \frac{\partial S(Q_t)}{\partial Q_t} < 0, \quad S(t=0) = S_0, \quad S(t=T) \geq 0 \tag{A1}$$

The Hamiltonian for this problem is: $\mathrm{H} = e^{-rt} \int_0^{A} \{P_t[a_t, S_t(Q_t)] - (\partial C_t / \partial a_t)\} da_t + \mu(t) A_t$.

The current value Hamiltonian ($\mathrm{H}^{\mathrm{c}} = e^{rt}\mathrm{H}$) is therefore:

$$\mathrm{H}^{\mathrm{c}} = \int_0^{A} \{P_t[a_t, S_t(Q_t)] - (\partial C_t / \partial a_t)\} da_t + \lambda(t) A_t, \quad \text{where} \quad \lambda(t) = e^{rt}\mu(t). \tag{A2}$$

The first-order condition is that:

$$\frac{\partial \mathrm{H}^{\mathrm{c}}}{\partial A_t} = 0 \quad \Rightarrow \quad P[A_t, S_t(Q_t)] = (\partial C_t / \partial A_t) - \lambda(t). \tag{A3}$$

The time derivative of $\lambda(t)$ using the expression in (A2) is:

$$\frac{\partial \lambda}{\partial t} = re^{rt}\mu + e^{rt}\frac{\partial \mu}{\partial t} \quad \Rightarrow \quad \frac{\partial \lambda}{\partial t} = r\lambda + e^{rt}\frac{\partial \mu}{\partial t} \quad \Rightarrow \quad \frac{\partial \mu}{\partial t} = e^{-rt}\left(\frac{\partial \lambda}{\partial t} - r\lambda\right).$$

But according to the maximum principle (c.f. Chiang, 1992 or Sydsäter et al, 2005):

$$\frac{\partial \mu}{\partial t} = -\frac{\partial \mathrm{H}}{\partial Q_t}, \quad \text{hence, we have:} \quad -\frac{\partial \mathrm{H}}{\partial Q_t} = e^{-rt}\left(\frac{\partial \lambda}{\partial t} - r\lambda\right) \quad \text{or, after re-arranging:}$$

$$\frac{\partial \lambda}{\partial t} = -e^{rt}\frac{\partial \mathrm{H}}{\partial Q_t} + r\lambda.$$

Since: $-e^{rt}\frac{\partial \mathrm{H}}{\partial Q_t} = -\frac{\partial \mathrm{H}^{\mathrm{c}}}{\partial Q_t}$, or equivalently: $\frac{\partial \lambda}{\partial t} = r\lambda - \frac{\partial \mathrm{H}^{\mathrm{c}}}{\partial Q_t}$,

we have: $\frac{\partial \lambda}{\partial t} = r\lambda - \int_0^{A} \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t} da_t$, (A4)

where the last equality is eq. (9a) in the main text. To obtain the expression for $\lambda(t)$ in eq. (9b), start by re-arranging (A4) and multiply both sides with the integrating factor e^{-rt} to get:

$$e^{-rt}\frac{\partial \lambda}{\partial t} - e^{-rt} r\lambda = -e^{-rt}\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t} da_t \ . \tag{A5}$$

As the left-hand side of (A5) equals $\dfrac{\partial e^{-rt}\lambda}{\partial t}$ we have:

$$e^{-rt}\lambda = -\int e^{-rt}\left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t} da_t\right] dt + K \quad \text{implying that:}$$

$$\lambda(t) = e^{rt}K - e^{rt}\int e^{-rt}\left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t} da_t\right] dt \ .$$

$$\text{Defining: } F(t) = \int e^{-rt}\left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t} da_t\right] dt, \quad \Rightarrow \quad \lambda(t) = e^{rt}\left[K - F(t)\right]. \tag{A6}$$

To determine the constant *K* in (A6) the value of $\lambda(t)$ must be given at some *t*. Here, we utilize the terminal condition and the corresponding transversality conditions. The terminal condition is that $S(T) \geq 0$, i.e. that microbial sensitivity should not have been exhausted before the end of the period, implying that $Q(T) \leq Q_T$. This results in the transversality conditions:

$$\lambda(T) = \lambda_T = 0 \ \textit{iff} \ \ S(T) > 0$$

$$\lambda(T) = \lambda_T > 0 \ \textit{iff} \ \ S(T) = 0$$

$$\text{Accordingly: } \lambda(T) = \lambda_T = e^{rT}\left[K - F(T)\right] \quad \Rightarrow \quad K = e^{-rT}\lambda_T + F(T) \ . \tag{A7}$$

Substituting $K = e^{-rT}\lambda_T + F(T)$ for *K* in (A6), we get:

$$\lambda(t) = e^{rt}\left\{\left[e^{-rT}\lambda_T + F(T)\right] - F(t)\right\} \quad \Rightarrow \quad \lambda(t) = e^{-r(T-t)}\lambda_T + e^{rt}\left[F(T) - F(t)\right]. \tag{A8}$$

Using the definition of $F(t)$ in (A6), the last term in eq. (A8) becomes:

$$F(T) - F(t) = \int_t^T e^{-r\theta}\left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t} da_t\right] d\theta \text{, and substituting this in eq. (A8) we get:}$$

$$\lambda(t) = e^{-r(T-t)}\lambda_T + e^{rt}\int_t^T e^{-r\theta}\left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t} da_t\right] d\theta \ . \tag{A9}$$

Since the integration in eq. (A9) is with respect to θ, the term e^{rt} can be included as a constant under the integral, implying that:

$$\lambda(t) = e^{-r(T-t)}\lambda_T + \int_t^T e^{-r(\theta-t)}\left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t}da_t\right]d\theta,$$

and if the time horizon is infinite, we have:

$$\lambda(t) = \lim_{T\to\infty} e^{-r(T-t)}\lambda_T + \int_t^\infty e^{-r(\theta-t)}\left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t}da_t\right]d\theta,$$

implying that the first term goes to 0 and:

$$\lambda(t) = \int_t^\infty e^{-r(\theta-t)}\left[\int_0^A \frac{\partial P[a_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t}da_t\right]d\theta, \qquad \text{(A10)}$$

which is equation (9b) in the main text.

The condition for maximizing the patent holder's profit:

For the duration of the patent, the patent holder's problem is to maximize the present value of monopoly profit:

$$\begin{aligned}&\max: \int_0^T e^{-rt}\left[P[A_t, S_t(Q_t)]A_t - C(A_t)\right]dt\\ &\text{Subject to}: \frac{\partial Q_t}{\partial t} = A_t, \quad \frac{\partial S(Q_t)}{\partial Q_t} < 0, \quad S(t=0) = S_0, \quad S(t=T) \geq 0\end{aligned} \qquad \text{(A11)}$$

Since: $\mathrm{H} = e^{-rt}\left\{P[A_t, S_t(Q_t)]A_t - C(A_t)\right\} - \mu(t)A_t \quad \Rightarrow \quad \mathrm{H}^c = P[A_t, S_t(Q_t)]A_t - C(A_t) - \lambda(t)A_t$.

The first-order condition for profit maximization is:

$$\frac{\partial \mathrm{H}^c}{\partial A_t} = 0 \quad \Rightarrow\Rightarrow \quad P[A_t, S_t(Q_t)] + \frac{\partial P[A_t, S_t(Q_t)]}{\partial A_t}A_t = \frac{\partial C}{\partial A_t} + \lambda. \qquad \text{(A12)}$$

The time derivative of $\lambda(t)$ using the definition in (A2) is:

$$\frac{\partial \lambda}{\partial t} = r\lambda - \frac{\partial H^c}{\partial Q_t} \quad \Rightarrow \quad \frac{\partial \lambda}{\partial t} = r\lambda - \frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t}\frac{\partial S_t}{\partial Q_t}A_t, \qquad \text{(A13)}$$

which is eq. (25b) in the main text.

Re-arranging and multiplying both sides with the integrating factor e^{-rt}, we obtain:

$$e^{-rt}\frac{\partial \lambda}{\partial t} - e^{-rt}r\lambda = -e^{-rt}\frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t}\frac{\partial \mathrm{S_t}}{\partial \mathrm{Q_t}}\mathrm{A_t} \quad \Rightarrow \quad e^{-rt}\lambda = -\int e^{-rt}\left\{\frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t}\frac{\partial \mathrm{S_t}}{\partial \mathrm{Q_t}}\mathrm{A_t}\right\}dt + K$$

.

Hence: $\lambda(t) = -e^{rt}\left[K - \int e^{-rt}\left\{\frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t}\frac{\partial \mathrm{S_t}}{\partial \mathrm{Q_t}}\mathrm{A_t}\right\}dt\right]$,

and defining: $F(t) = \int e^{-rt}\,\frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t}\frac{\partial \mathrm{S_t}}{\partial \mathrm{Q_t}}\mathrm{A_t}\,dt$, $\quad\Rightarrow\quad \lambda(t) = -e^{rt}\left[K - F(t)\right]$. (A14)

Determine *K* by utilizing the terminal and transversality conditions:

$\lambda(T) = \lambda_T = 0$ *iff* $S(T) > 0$

$\lambda(T) = \lambda_T > 0$ *iff* $S(T) = 0$

Thus: $\lambda(T) = \lambda_T = e^{rT}\left[K - F(T)\right] \quad\Rightarrow\quad K = e^{-rT}\lambda_T + F(T)$.

Therefore: $\lambda(t) = e^{rt}\left[e^{-rT}\lambda_T + F(T) - F(t)\right] \quad\Rightarrow\quad \lambda(t) = e^{-r(T-t)}\lambda_T + e^{rt}\left[F(T) - F(t)\right]$,

and using the definition of $F(t)$ in (A14):

$$\lambda(t) = e^{-r(T-t)}\lambda_T + \int_t^T e^{-r(\theta-t)}\left\{\frac{\partial P[A_t, S_t(Q_t)]}{\partial S_t}\frac{\partial \mathrm{S_t}}{\partial \mathrm{Q_t}}\mathrm{A_t}\right\}d\theta, \qquad \text{(A15)}$$

which is eq. (25a) in the main text.