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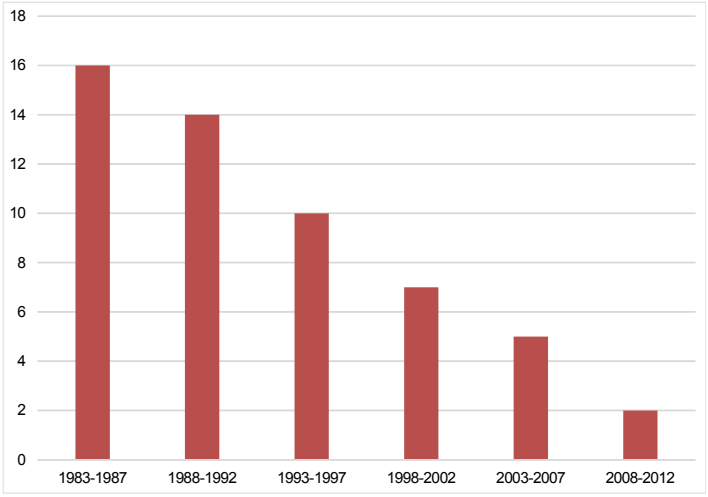
Economic measures to counter antimicrobial resistance

- Human and animal consumption of antibiotics is leading to bacteriological mutations that threaten to make current drugs ineffective in the treatment of certain diseases. In the coming decades, increased antibiotic resistance could cause several million deaths worldwide annually and drive down economic activity by up to 0.8 points of GDP per year in developed countries between now and 2050.
- This health risk requires a global coordinated response, as called for by the G20. Where possible, consumption of existing antibiotics must be reduced and diversified. In addition, research into new antibiotics that are effective against potentially resistant bacteria must be encouraged more strongly. Current R&D spending in this area is insufficient given the risk. In the pharmaceutical industry, intellectual property law provide inventors with returns that depend on the medical service provided, over a specific time-period starting from the date a patent is filed or the marketing authorisation is granted. These rules are less suitable when it comes to new antibiotics as they may be of limited immediate use due to currently available treatments, and the date when they will become needed is unknown.
- To make up for the lack of R&D to combat antimicrobial resistance, , patent rules for this class of drugs need to be harmonized between countries in order to provide protection for new molecules based on their effective marketing date.
- The feasibility of a worldwide reward fund to compensate innovation in the field of antimicrobial resistance should be discussed. Under such a scheme, innovators would transfer their intellectual property rights in exchange for a predetermined reward. This would have the advantage of providing investors with the certainty of a minimal return for discoveries, but would also mean that new drugs could be immediately released in the most effective manner, without the social loss associated with the period of exclusive rights granted by the patent.
- Such a fund could be used to test a reward system for other types of innovation for which the current patent-based incentive system does not in and of itself provide a socially optimal level of R&D investment. This appears to be the case, for example, in the area of efforts to combat the consequences of global warming.

New systemic antibacterial drugs approved by the US Food and Drug Administration



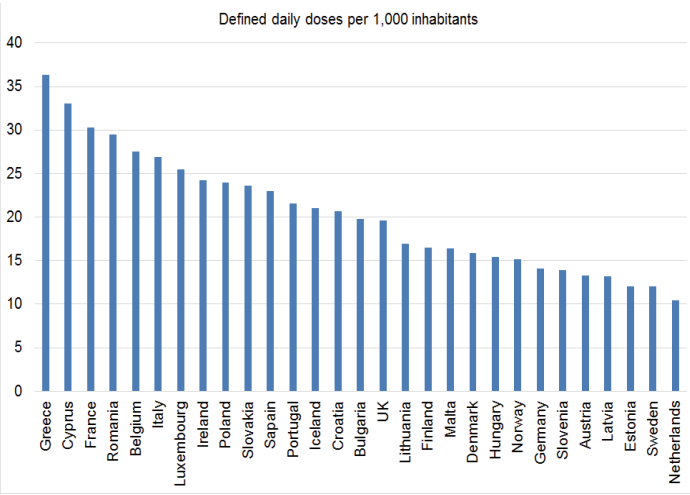
Source: Spellberg et al. (2008), "The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America".

1. Antibiotic resistance is a major public health issue that needs to be addressed at international level

1.1 The effectiveness of antibiotics, which decreases with use, is a public health issue

Antibiotic consumption is associated with a negative externality. In response to the therapies used against them — antibiotics and therapies involving antibiotics[1] — bacteria can become resistant via mutation or acquire a resistance gene from another bacterium. Prolonged and massive use of the same antibiotics therefore leads to increased bacterial resistance and decreases the effectiveness of the therapy. This can become a serious problem, particularly in hospitals where resistant bacteria can lead to medical complications and incur additional therapy costs.

Chart 1: Total volume of antibiotics prescribed in 2016



Source: European Centre for Disease Prevention and Control.

Growth in antimicrobial resistance (AMR) is partly the result of over-consumption of antibiotics in the areas of human and animal health. France is a large consumer of antibiotics: in 2015, some 1,300 tons were consumed, including around 800 tons for human use (see Chart 1). The country is in third place in Europe with respect to antibiotics consumed outside hospitals[2], with per capita and per-day consumption rates having risen slightly over the past decade (+3%). Rates of antibiotic consumption in the hospital sector and for animal use are lower (7th and 10th place, respectively) and are declining (see Chart 2).

AMR is a global public health issue. KPMG (2014) estimates that a 40% increase in AMR could result in 10 million deaths worldwide annually by 2050, including 330,000 in Europe. Although the reliability of these figures remains open to question[3], everyone agrees on the scale of the problem, as evidenced by the string of resolutions that the WHO General Assembly has adopted since 1998. In OECD countries, it is thought that the economic impact of increased resistance will be significant: a drop of between 0.1 and 0.8 points of GDP per year by 2050, depending on the extent of the increase.[4]

Chart 2: Antibiotics consumption in France, 2005-2015 (Index 1 in 2005)

Source: ANSM, Anses, DG Trésor calculations.

Health authorities are monitoring antimicrobial resistance. They have observed the appearance of highly-resistant bacteria (HRB) that have developed transmissible resistances to colistin[5], thereby threatening the overall effectiveness of healthcare systems. AMR is already having an impact on healthcare in France: *Santé Publique France* has estimated that in 2012 there were 158,000 cases of multi-drug resistant infections that led to 12,000 deaths. Bacterial infections, which today account for 2% of deaths, could thus again become a significant cause of mortality.

(1) For example therapies affecting the immune system, such as cancer treatments, depend on effective antibiotics to limit the likelihood of complications.
(2) As opposed to antibiotics used in the hospital sector. Some 90% of antibiotics for human use are consumed in the community.
(3) See, for example, de Kraker et al. (2016).
(4) Taylor J., Hafner M., Yerushalmi E., Smith R., Bellasio J., Vardavas R., Bienkowska-Gibbs T., & Rubin J. (2014), "Estimating the economic cost of antimicrobial resistance: Model and Results", *RAND Europe*, Cambridge.
(5) In 2013, the French National Agency for Medicines and Health Products Safety (ANSM) classified colistin as a drug of last resort (DoLR).

1.2 Antibiotic resistance requires a coordinated international response

The ability to resist bacteria is a global public good, and the market for antibiotics is highly globalised. For these two reasons, the issue of AMR needs to be addressed at international level. It requires coordinated implementation of three types of policies to reduce and streamline consumption of existing antibiotics, and to encourage the development of new drugs to treat resistant bacteria, such as HRBs, against which there is currently no effective therapy.

We must first seek to reduce consumption of existing antibiotics where possible, via prevention efforts in human and animal health, innovative diagnostic methods and incentives for both prescribers and consumers. To this end, taxing antibiotics for human use is not the best solution, as public health objectives and social protection schemes generally make using them price-insensitive.

We must then streamline use of existing antibiotics in order to avoid exposing pathogens to the same therapeutic treatment. This could involve improved diagnostic methods[6], which would mean that narrow-spectrum antibiotics could be used instead of broad-spectrum ones. A wider range of molecules could be employed, based on providing practitioners with better information about existing drugs, and through extensions of therapeutic indications when existing antibiotics are proven effective against bacteria for which they were not initially approved.

Lastly, we need to boost innovation efforts to bring out new antibiotics that are effective against resistant bacteria (see Box 1). Although it is difficult to be prescriptive in terms of optimal levels of R&D on AMR, the extent of the potential public health issue and the inadequacy of the current means for rewarding innovation (see below) suggest that current levels are insufficient.

Box 1 : The current state of investment in R&D on antimicrobial resistance

Innovation in the area of antibiotics may appear lacklustre, but could produce new molecules in the near future. According to Cecchini *et al.* (2015), most of the large pharmaceutical firms have moved away from antibiotic research, and the last major innovation was in 1987[a]. Since the mid-1980s, the average number of new molecules approved each year by the US Food and Drug Administration has fallen eightfold (from 16 for the period 1983-1987 to only 2 between 2008 and 2012). Innovative efforts have, however, picked up slightly in the last few years, with five new marketing authorisations for the period 2013-2016. This low level of innovation could be the result of declining returns from pharmaceutical research (DiMasi, 2014), combined with antibiotic market failures and an ill-suited intellectual property rights system.

R&D is not completely lacking, however. In December 2017, Pew Charitable Trust listed 48 new antibiotics in clinical trials in the US, including 15 that had reached Phase 3 (the most advanced). One was awaiting marketing authorisation and two had just been approved. In the Pew list, US companies are over-represented (14 out of 40[b]), no French companies appear and only three of the world's top ten firms are present. R&D appears to be conducted almost exclusively by mid-sized companies. This does not prevent R&D from being more or less directly managed by major firms (that may sub-contract the work), and innovative companies from being ultimately taken over. Assuming that only one in five infectious disease products will be approved for patients (Hay *et al.*, 2014), and that the clinical trials period lasts approximately eight years (DiMasi, 2014), the pipeline in its current state will produce one new drug per year in the years to come.

a. Bayer's ciprofloxacin, marketed as Ciflox in France.
b. Compared with 15 out of 32 in late 2016. US firms account for 19 of the 48 molecules registered for clinical trials.

2. The current patent system for pharmaceutical innovation is not appropriate for R&D on AMR

2.1 Pharmaceutical companies are structurally underinvesting in R&D on antimicrobial resistance

If a drug therapy is effective, neither users nor prescribers will question it. They will not spontaneously consume an innovative (and more expensive) drug, even if it reduces the risk of resistant bacteria developing. This limits the demand for new antibiotics as long as the old ones are effective. In the case of narrow-spectrum antibiotics, demand is further undercut by the cost of diagnostics; this makes the use of broad-spectrum antibiotics more economical, but brings with it a greater risk of developing resistance. The consumption of these drugs therefore generates a social

(6) Antibiotic susceptibility testing (AST), which gives a precise understanding of the infection, is currently a lengthy and expensive process.

cost that is not taken into account by private stakeholders (a negative externality).

Moreover, the date when there could be a market for new antibiotics — due to older and hitherto widely-used ones becoming ineffective — is unknown.

2.2 The current framework for rewarding innovation does not create sufficient impetus for R&D in the field of antibiotics

Generally speaking , patents provide 20 years of protection for innovations. In the pharmaceutical sector, the time interval between patent filing and marketing authorisation (MA) can be very long, sometimes more than a decade. To maintain a sufficient monopoly period, many countries, including EU Member States, the US and Japan, extend patent protection. In Europe, the supplementary protection certificate (SPC) extends protection for a period corresponding to the period between the date of filing of the patent and the issuance of the MA, with a maximum extension of five years.

For several reasons, this system is insufficient for R&D on AMR. On one hand, patent protection is not harmonised at global level, and it does not exist in some emerging economies where the issue of antibiotic resistance is particularly pressing. On the other, by taking the date of the MA as a reference, countries do not factor in uncertainty regarding the actual emergence of a market for the new antibiotic, which depends on the appearance of a bacterium that is resistant to standard therapies.

In addition, the regulatory framework for clinical trials is not conducive to R&D on AMR, since the process requires clinical trials to assess the efficacy of treatment in relation to existing drugs. In France, for example, this is used as the basis for determining the therapeutic benefit and the improvements to the medical service provided, which are used to set the rate of reimbursement and the price of the drug, respectively.[7] In the absence of bacteria that is already resistant to other antibiotics, there is no reason why the therapeutic benefit should be greater than with existing drugs, and there appears to be zero improvement in the medical service provided. The price set for a new antibiotic will therefore be at most the same as the reference molecule, which is often old, marketed as a generic and sold at a price that is unsustainable for a new drug. In addition, innovations in antibiotic resistance have a preventive role, so that the therapeutic benefit and the improvement to the medical service provided can be adjusted significantly over time, even though there is currently no scheme to update these parameters.

3. R&D on AMR could be fostered by modifying the means for rewarding innovation

3.1 The intellectual property rights system could be adapted to the specifics of AMR

Adjusting the intellectual property rights system could provide more incentives for R&D on AMR. Within the current framework of innovation protection, a two-step approach has emerged and is the subject of discussions within the G20 under the German Presidency. The first step involves broadening and harmonising the principle of the SPC at global level. This would cover all potential markets for AMR innovations.

Subsequently, SPCs granted for new molecules discovered as part of R&D on AMR could cover not only the period between patent filing and marketing authorisation, but could extend this period up to when the product is first marketed. This would bring the patent protection more into line with the period of demand for the new innovative drug.

Both of these measures would increase incentives for R&D on AMR. They would, of course, alter the intellectual property protection system for pharmaceutical innovation in the area of antimicrobial resistance, but without calling into question the fact that this protection is a source of incentives for R&D and innovation in this area. Given the potential impact of AMR on the economy and on healthcare, however, it is legitimate to investigate the possibility of using other types of R&D incentives to address it (see Box 2).

(7) For example, a drug that offers no improvement to the medical service provided cannot be marketed and reimbursed at a higher rate than comparator drugs.

Box 2 : Other systems to encourage R&D

Patents create incentives for innovation — they allow successful inventors to benefit from their discoveries for a limited period while at the same time ensuring that the innovation will eventually be given wider distribution. The period of protection offered by a patent is a transitional phase during which the total surplus is not maximised: by limiting the distribution of the innovation, the monopoly that it grants results in a net loss for society. The use of patents is justified, however, where the transition pre-invention situation to the situation after the patent enters the public domain cannot take place spontaneously without resorting to a transitional monopoly phase.

Alternatives to patent protection for innovations are possible. These seek to avoid the net loss created by the monopoly that the patent confers, but also to limit the problems associated with the sharp rise in the number of active patents. The advantages and disadvantages of these systems are a subject of discussion amongst economists, particularly as regards the pharmaceutical industry, which is characterised by very high research costs, low marginal production costs and the fact that copying drugs is relatively easy.

The alternative systems described in Table 1 take as their starting point Samuelson (1954) who, in the presence of pure collective goods, recommended a prize or subsidy system that would allow free access to innovation, thus maximising the total surplus without a transition period. In such a system, unlike an intellectual property rights system, R&D funding is provided by the public authority and not by the private sector.

This public support could take the form of actions that would reduce invention costs (a "push" scenario), such as direct subsidies for R&D, whether selective or not.

Selective support leads to the issue of decision-making, since the social value of an innovation cannot be observed ex-ante by the public authorities. It also creates a delegation problem - how can the most efficient company for development be identified? This can be overcome by setting up an auction system for companies wishing to develop an innovation (Gandal & Scotchmer, 1993).

In the case of non-selective support, the distortion linked to the financing of the scheme is theoretically greater, since the absence of a decision leads to financing for all innovations, whether or not they have a significant social value, and for all companies, whether or not they are efficient, i.e. at a higher total cost.

Such support may also include actions to shift the demand curve (a "pull" scenario), such as a government commitment to purchase a minimum quantity of products or the payment of bonuses in return for the company's commitment to either make the new product available at marginal cost or transfer it to the public domain. Like patents, this system could be used to select the most efficient company, depending on the scheme selected (a single prize, for example, only rewards the company that developed the innovation first).

In France during the 18th and 19th centuries, the *Académie des Sciences* awarded bonuses for innovations, although this was later abandoned due to numerous conflicts between jury members over which innovations should be rewarded. In 1988, the British Parliament chose to reintroduce a prize system to reward the inventor of a chickenpox vaccine. In the United States, the Medical Innovation Prize Act, a failed 2005 legislative initiative, aimed to replace the patent system with a public bonus system for medical and biomedical innovations.

Taken all together, attempts to introduce a prize system for innovation remain marginal.

Although each potential scheme has been thoroughly assessed, there are few comparative analyses of these various systems. Gallini & Scotchmer (2002) point out that the choice depends in part on the nature of the economic sector, but that — given the impossibility of linking subsidies to the overall net surplus of innovation — patents make it possible to be discriminative and to select projects with high potential value added. Scotchmer (1999) confirms that an intellectual property rights system appears to be the most appropriate if the government is unable to identify *ex-ante* the cost and the social value of innovation.

However, these analyses do not factor in the recent spike in the number of patents in circulation and the resulting legal uncertainty. If the costs of litigation and of managing the patent system become higher than the inefficiency costs associated with public R&D subsidies, alternative solutions should be tested. Halfway between the patent system and public subsidies, we might imagine, like Jaffe & Lerner (2006), intermediate solutions, such as the introduction of restrictions on intellectual property rights (mandatory licencing, the obligation to licence on reasonable and non-discriminatory terms, limitation of injunction procedures, etc.), which would reduce the costs associated with the sharp rise in the number of patents in circulation.

Table 1:

	Benefits	Inefficiences
Patent system	- Decision-making is devolved onto companies - Protection for innovation is awarded only to the most efficient company	- Net loss associated with a temporary monopoly - Duplication of investments
Non-selective "push" scenario	- Removal of the net loss associated with a temporary monopoly - No decision-making or delegation problems for the public authorities	- No selection of either innovation or company - Distortion connected to the financing of the scheme - Duplication of investments
Selective "push" scenario	- Removal of the net loss associated with a temporary monopoly	- Decision-making problem - Delegation problem - Distortion connected to the financing of the R&D efforts
"Pull" scenario	- Removal of the net loss associated with a temporary monopoly - Reward of the innovation is awarded only to the most efficient company	- Decision-making problem - Distortion connected to the financing of the R&D efforts - Duplication of investments

3.2 Setting up a reward fund for innovation in the area of AMR should be considered

Several reports recommend that the current system for protecting pharmaceutical innovation should be supplemented by a fund that would reward companies for introducing a new antibiotic onto the market. In exchange for a reward, the company would transfer the intellectual property rights, allowing the drug to be marketed at an affordable price. This would free up the drug after its discovery, thereby limiting the net loss associated with the exclusive rights granted by the patent, as well as offsetting the failure linked to uncertainty about the date the drug will actually be marketed. Moreover, from a dynamic point of view, this would make the innovator's income less dependent on sales of the new antibiotic, which in turn limits incentives for over-consumption and the resulting negative externalities.

The value of a reward system, however, depends on how it is applied, and this must be carefully assessed. The public authorities must step in at various levels: setting the amount of the reward, managing the award process and the intellectual property rights, financing the reward, etc. Each of these interventions must be tailored to avoid distortions and inefficiencies.

Determining the appropriate level of reward is critical for avoiding both under- and over-investment in R&D. It presupposes that the public authorities are able to anticipate the market value of the innovation patent at the time of its appearance, as well as the externalities generated by it. In the case of AMR, this is particularly difficult to estimate for two reasons:

- Antibiotics are used throughout the world. They are used to complement a number of therapies and are sometimes substituted for other antibiotics
- The need and effectiveness of the future treatment depend both on the emergence of new resistant bacteria, the absolute effectiveness of the drug itself and its relative effectiveness compared to other drugs that may have been discovered to treat the same illness

Both the Boston Consulting Group[8] and the O' Neill report in the Review on Antimicrobial Resistance[9] estimate that the ideal amount of the reward should be about $1bn per molecule, based on development costs and the estimated market size.

The fund should reward innovations that meet needs and objectives which have been previously defined by a panel of experts. However, the process and the type of solution required to achieve these objectives should not be determined in advance, so as not to steer R&D initiatives in one direction or another, or cause duplication. It is therefore necessary to avoid prior selection, on the basis of a dossier, of projects involved in the process.

So that research can be conducted by the most effective entity, the system should provide a reward for each stage of development, from the pre-clinical trials phase through to marketing authorisation. In this way, the initial patent holder can, if desired, transfer the intellectual property rights in exchange for a reward and let others continue the research and in turn receive rewards should they develop the product. The reward amounts across the various stages of development should factor in uncertainty[10] about the safety and effectiveness of the therapy. In addition, each reward should be paid in instalments, to take into account possible ex-post findings of non-compliance with certain clauses (such as pharmacovigilance) or health authorities' reassessments of treatment effectiveness.[11]

If the innovator agrees to accept the reward, he or she surrenders the patent, which then enters the public domain. This allows the inventor to be distinguished from the manufacturer[12], ensures fair competition between manufacturers[13], including in terms of productivity[14], and encourages wider distribution of the innovation and its use in related fields.

Lastly, in a bid to limit distortions and facilitate its introduction, financing for the reward fund should come from the general budgets of the contributing countries. To boost incentives, various mechanisms have been considered, including a tax on sales of antibiotics combined with a so-called "pay or play" regime, in which companies could deduct R&D expenditure on AMR from their taxes. This has the disadvantage of directing R&D incentives towards companies that already produce antibiotics, which is not an optimal solution, particularly since the major part of antibiotics is currently generic and generally produced by manufacturers and companies that are not specialised in medical research, and that are far removed from the inventors. Another, more certain option is one in which the inventors receive the reward, after which the profits from the marketing of the drug are partly returned to the fund up to the amount of the reward. Theoretically, this would create an incentive for pharmaceutical companies while limiting the budgetary cost. However, since the company would retain the intellectual property rights, it would have the power to pass on part or all of its mandatory contribution to the drug price — all the more so as it meets a real need.

Since spending on drugs is largely covered by national health insurance schemes, an additional argument in favour of a budgetary funded reward fund is that the impact of a tax on the sale of antibiotics or higher drug prices and the way in which this ultimately affects society would depend on each country's social welfare systems. Given the global nature of the problem and the need to address it through multilateral fora such as the G20, these country-specific impacts are neither economically desirable nor likely to foster global consensus. This budgetary funding does not, however, address the issue of how contributions to the fund should be broken down among the various countries. Consideration could also be given to seeking innovative financing for such a fund, as part of an internationally-accepted framework, along the lines of those established or proposed as part of efforts to combat climate change and global health initiatives. In the past, such funding has taken the form of taxes on goods or services linked to globalisation, such as the solidarity tax on airline tickets.

(8) Boston Consulting Group (2017), "Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development", Report for the German Guard Initiative.
(9) *The Review on Antimicrobial Resistance* (2016), "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations".
(10) It is estimated that only about 10% of therapies tested in humans reach the market. For example, see Hay *et al.*, 2014.
(11) This type of mechanism is similar to the "bounty" mechanisms sometimes proposed for pharmaceutical innovation (cf. Grinols & Lin, 2011, or Lin, 2016) as an alternative to the patent system, which consists in offering in exchange for the intellectual property of the innovation a premium paid over several periods according to the volume of sales of the treatment. In the specific case of antibiotics, however, the link between premium amount and sales volume is not desirable, as the effectiveness of the drug decreases with its intensity of use.
(12) For innovators who do not have the appropriate facilities, the search for a manufacturer can lead to uncertainties and transaction costs, which can be reflected in R&D costs.
(13) If there is market failure and no manufacturer spontaneously produces the drug despite global demand, the public authorities always have the possibility of contracting with a manufacturer and commissioning a specific volume at a negotiated price.
(14) If the innovative company only agreed to market a treatment at a price close to marginal cost but retained the monopoly on production, it would have no incentive to reduce its production costs.

3.3 Testing the effectiveness of a reward fund scheme could lead to its use in other areas

Although the reward fund is currently little-used to encourage innovation, the standard model of patent-protected intellectual property has its limitations. This is especially true in areas where there is a high degree of uncertainty as to when demand will manifest itself, which can lead to (socially inefficient) underinvestment in R&D. AMR is one such case, but there are others.

Global warming issues seem to be one such case. Although there is growing certainty about the magnitude of the global challenge for populations, there is still, if not more, uncertainty about the timing and the conditions under which private investment in research in these areas could provide a return. This is due to uncertainty about when problems that today's R&D could attempt to solve will emerge, as well as to their interconnectedness, which is far more complex than in the case of AMR, since determining the profitability of an innovation depends on how present and future markets, energies and means for adaptation will interact with public policies that have largely yet to be defined. These characteristics weaken the incentive nature of the intellectual property rights system, and we should examine any and all instruments that could complement and bolster it.

In addition to its intrinsic benefits, an international reward fund to stimulate AMR innovation could serve as a trial run for the use of such initiatives to foster R&D in other areas. Mainstreaming such a system, however, would make the issue of financing even more pressing.

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