

Exploring responses to the need for new antibiotics: How do different incentives compare?

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INTRODUCTION

Each year, an estimated 2 million patients in the EU alone contract hospital-acquired infections, of which 175,000 die due to multidrug resistance¹. We will soon see many more of these cases and eventually resistance to antibiotics will begin to negate the advances achieved in medical care more broadly. For example, advanced surgical procedures and cancer chemotherapy might be impossible to perform without effective antibiotics². Yet few developers are investing in the development of new antibiotics, many having dismantled their infectious disease departments altogether in recent decades. A recent pipeline analysis carried out by the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) warns that there are extremely few novel antibacterialⁱ agents under development, especially those to combat multidrug-resistant Gram-negative bacteria³. Faced with this potential health crisis, it is clear that new incentives to promote R&D in antibiotics are urgently needed and that exploration of strategies to better align R&D priorities with therapeutic needs must take place. Also, in order to ensure that any new antibiotics are better protected in the longer term, it is argued that major adjustments are needed to separate sales from the recouping of R&D costs and that industry should be incentivised towards antibiotic conservation and broader public health goals rather than towards high sales of this precious resource.

In order to kick-start the policy discussions for how to incentivize research and development of new antibiotics, Sweden initiated an expert conference during its Presidency of the European Union in 2009. To keep the momentum of these discussions, build on developments, and bring this arguably desperate situation to the forefront, ReAct arranged a global conference in Uppsala, Sweden in September 2010 on “*The Global Need for Effective Antibiotics – Moving Towards Concerted Action*”. The conference brought together key actors from civil society, academia, industry, government, and supranational organizations to combine efforts and collectively explore ways to prevent an all out health crisis.

The overall goal of immediate action is to pull the early drug candidates through the pipeline, getting at least a handful of new broad-spectrum antibiotics for Gram-Negative infections with different mechanisms of action onto the market in the next 5-10 years - and to promote the reforming of infectious disease departments that have been dismantled within companies and academia in recent decades. Also, in looking ahead, the goal must be to realign overall R&D priorities with clinical need such that the pipeline of effective products does not again dry up.

This report is intended to map and compare a number of so called push and pull incentives (and combinations of them) to further inform decision-making in a direction that makes the most sense given the urgency of the situation, the particularities of the European antibiotics market and different actors’ interests. In particular, this work is intended to update the discussion of the most promising incentives discussed in the “LSE Report⁴” in relation to a number of common criteria and to present potentially important roles for the EU in solving the antibiotics crisis over the short and the longer-term. While considered critical, collaborative efforts such as product development partnerships (PDPs) and open source solutions are not addressed in this report. In addition to the discussion of incentives, possible roles for the EU are briefly discussed at the end of the document, namely regarding the establishment of a European NIH, regulatory reform, action to limit off-label prescription and support for the development and use of rapid point of care diagnostics.

ⁱ Novel antibiotics here refers to those with a new mechanism of action or a new target.

General comparison of incentives by type

Table 1 lists the main advantages and disadvantages of the different types of incentives.

Push mechanisms are research subsidies intended to spark interest in a given scientific area. Push mechanisms will be needed to ensure that expertise can be captured and combined to help develop novel products. However, these mechanisms alone are likely insufficient and need to be combined with a pull mechanism (see below).

A **pull** mechanism offers a reward that is granted only after a product has been fully developed. The success of pull mechanisms in sparking the necessary R&D activity to respond to the urgent need for novel antibiotics is largely a function of the magnitude of the reward on offer. A strong pull incentive has the best chance of luring development beyond the crucial (expensive) Phase III clinical trials. However, major difficulties surround the determination of an appropriate reward size, the political acceptance of a high valued reward, and the public funder's ability to fulfil its commitments given that the political cycle is generally much shorter than the development cycle and certainly shorter than the necessary duration of any proposed commitmentⁱⁱ.

Lego-regulatory mechanisms are pull mechanisms that use the market itself to determine the size of the reward, thereby avoiding the difficulties in calculating a reward size arbitrarily and avoiding problems of credibility and political palatability. **Combination push-pull** mechanisms comprise elements of both push and pull incentives.

Table 1. Merits of incentive type⁵	
Push mechanisms (early research subsidies)	
Advantages	Disadvantages
Require smaller financial outlays	Pose risk funding unsuccessful research
Remove barriers to entry	Principal-Agent problems ⁱⁱⁱ
Attract Small and Medium Enterprises (SMEs)	Risk is borne almost entirely by funder
Useful for encouraging discrete steps in R&D	Risk of dampening entrepreneurial momentum
Simple pull mechanisms (outcome-based, extra-market-determined rewards)	
Advantages	Disadvantages
Reward only successful research	Risk is borne entirely by developer
Minimize developer inefficiencies	Attract only developers with significant funding
More likely to encourage final product development	Promise of large reward may lack credibility due to political and budgeting changes over the duration of product development
	Difficulty in predicting appropriate award size
Lego-regulatory pull mechanisms (outcome-based, market-determined rewards)	
Advantages	Disadvantages
Reward only successful research	Risk is borne entirely by developer
Maintain some link between product use and reward size	Attract only developers with significant funding
Minimize developer inefficiencies	May impede competition
More likely to encourage final product development	

ⁱⁱ US reports of the government renegeing on its commitments to purchase flu vaccineⁱⁱ a few years ago and the attempted renegotiations on flu vaccine purchases in Europe in 2009/2010 are likely to have exacerbated these concerns.

ⁱⁱⁱ Problem in which the principal (here the funder) hires an agent (here the researchers) who has more information than he does and can use this information for purposes not in line with the interests of the principal. In this case the researchers may exaggerate the merits of the investigational product in order to receive funding, which ultimately leads to inefficiency and wasting of resources.

Previous studies have concluded that a push-pull approach is needed⁶. This could mean an incentive with integrated push and pull attributes or it could mean a combination of push and pull incentives.

The following incentive mechanisms were compared using a common set of criteria:

Pull incentives (including lego-regulatory incentives)

- Monetary End Prizes (MEP)
- Buy-Outs (BO)
- Advanced Market Commitments (AMC)
- Health Impact Fund (HIF)
- Pricing and Reimbursement adjustments (P&R)
- Antibiotic Conservation and Effectiveness programme (ACE)

Push-pull incentives

- Orphan Drug incentives (OD)
- Call Options for Antibiotics model (COA)
- Special Designation for priority Antibiotics incentives (SDA)

DESCRIPTION OF CRITERIA TO COMPARE INCENTIVE MECHANISMS

1. Brief description of incentive mechanism.
2. Support conservation efforts. An incentive that places relatively less pressure on developers to mass-market their product or supports the internalization of resistance-related costs are considered to support conservation efforts.
3. Decoupling of profits and the recouping of R&D costs from sales/prices. Rewarding the development of antibiotics through mechanisms other than sales revenues (achieving partial decoupling through, for example, financial rewards) may help reduce pressure on developers to aggressively market their products (thereby supporting antibiotic conservation efforts). Full decoupling (e.g. through patent buyouts) eliminates developer monopolies, granting the funder control of marketing, pricing, and product availability.
4. Likely beneficiaries. SMEs and larger developers stand to benefit differently from incentives depending on their design. SMEs are unlikely to be able to participate in incentive schemes that fail to provide research subsidies unless they have access to venture capital or other 'push' funding.
5. Share risk between funder and developer. Given the lack of activity in this area when developers are forced to bear the full risk in R&D, risk-sharing arrangements are considered important elements in optimal incentive design.
6. Achieve political support. In general incentives that require overt calculation of award size are likely to face more opposition than those that use the market itself to establish it. Diverting costs onto other patient groups is also considered to be less politically manoeuvrable than maintaining the distorting nature of the market intervention within the antibiotics market itself. Proposals requiring major shifts in the traditional business model may take longer to achieve political support. (Likely/Reasonably achievable/Challenging/Highly challenging).
7. Encourage purchase of best drug available on market. In committing early to purchase products with defined characteristics, incentives can provide more assurance to developers, however, better products may also reach the market. The purchasing of the originally agreed product would then be sub-optimal.
8. Use market to determine optimal reward size or need for external financing of the incentive. While stating a reward size ex ante (before product development) provides a good opportunity for public health authorities to communicate their therapeutic priorities as well as the price they are willing to pay for products responding to those priorities, given the inherent difficulties in calculating the appropriate award size externally from the market and the uncertainty surrounding a product's resistance profile (the timeframe over which it will remain effective), incentives based on independent calculation of award size may be more challenging to implement.
9. Offer rewards solely for successful research. This criterion relates to the potential for wasting of resources and to product quality.
10. Avoid principal-agentⁱⁱⁱ problems. The more developers are forced to make a case for the merits of the investigational product in order to get funding the more it risks posing problems of overstating the potential and decreasing the effectiveness of the incentive.
11. Promote clear communication between funder and developer regarding willingness to pay for specified product. Clear signals of prioritization and the price the payer/funder is willing to pay lowers the risk to the developer, facilitates participation, and reduces the chance of wasted effort.

12. Help overcome Tragedy of the Commons^{iv} through internalization of costs of resistance.
When the developer is forced to have a stake in the long-term effectiveness of the product the incentive to over-sell and over-market are removed and conservation efforts are enhanced.
13. Encourage competition. The encouragement of new market entrees by brand and/or generic competitors.
14. Encourage follow-on innovation. While follow-on products are not generally novel enough to avoid cross-resistance with the earlier generation products over the long-term, they can slow resistance in the short term. In this regard, the complete removal of the incentive to produce follow-on products is considered sub-optimal.
15. Estimated relative transaction costs associated with implementation of the incentive. (Low/Modest/Medium/High).
16. Expected timeframe to implement the incentive. (Short/Medium/Long).
17. Amount of new legislation or institutional infrastructure required. (Minor/Medium/Major).
18. Issues surrounding the incentive's potential to spur desired R&D in the short-term.
19. Clear hurdles and barriers.
20. Experiences with mechanism to date.

^{iv} Tragedy of the Commons occurs when private companies have no incentive to take into account how their sales impact on future antibiotic effectiveness. Due to existence of cross-resistance across different antibiotics produced by various companies in the market they can each aggressively market their product to gain market share with complete disregard for the growth of resistance.

PULL MECHANISMS

Monetary End Prizes	
1.	Brief description of incentive mechanism. End prizes promise a large financial reward after a technology has been developed.
2.	Support conservation efforts. No.
3.	Decoupling of profits and the recouping of R&D costs from sales/prices. No. Despite the massive subsidy that the prize can represent—in the basic prize model—there is no control over prices of the eventual drug. Alternate designs could however include conditions over price or arrangements such as for licensing that would influence price.
4.	Likely beneficiaries. In some ways prizes could be well suited to SMEs. For example, the single product portfolio approach can be very appealing to smaller companies. For those with a few in their portfolio, a prize could be seen as a good opportunity to validate their technologies. Also, the lower revenue requirements of SMEs suggest that the reward size could be smaller than for large companies. However, like most pull incentives the post-development granting of prizes generally presents difficulties in terms of encouraging smaller developers to participate. Prizes will only attract SMEs that already benefit from early stage funding in the form of venture capital or other very significant push funding. Milestones payments (smaller prizes paid for achieving specified stages in R&D) could be used to provide funding to developers earlier in the process. Also, as the most expensive stage of clinical trials occurs with Phase III testing, providing a milestone payment after Phase II could help SMEs find the additional funds to conduct Phase III trials.
5.	Share risk between funder and developer. If the prize is sufficiently large to have a strong pull effect it can be assumed that there could not be multiple winners. In this case, the fact that a prize mechanism only awards a prize to the company that first reaches a specific pharmaceutical goal adds significant risk and uncertainty to developers considering the specified R&D. The usual uncertainties that developers have about whether or not their basic research will pan out and whether or not the various stages of clinical trials will be successful are therefore compounded by the risk that they may not win the race to the finish line. All risk borne by developer. In order to reduce the risk to the developer and maintain forward momentum in the earlier stages, milestone payments for the achievement of key steps in the R&D process, such as the completing of Phase I and Phase II trials, have been proposed. In revealing the initial strategies chosen for the development of the new product, milestone prizes may also help reduce the chances of exploration within a common resistance group (so could reduce some risk for the public funder). A disadvantage of milestone rewards is that the funding body would be rewarding some research on products that would never reach the market: a product might make it through Phase I and receive an award for reaching that milestone, but it may fail during Phase II trials. However, as significant proportion of molecules fail during Phase I, setting the first milestone for successful Phase I trials eliminates part of this weakness.
6.	Achieve political support. Challenging.
7.	Encourage purchase of best drug available on market. Pose the risk of rewarding development of sub-optimal drug.
8.	Use market to determine optimal reward size or need for external financing of the incentive. External financing required.
9.	Offer rewards solely for successful research. Yes.
10.	Avoid principal-agent problems. Yes
11.	Promote clear communication between funder and developer regarding willingness to pay for specified product. Yes.
12.	Help overcome Tragedy of the Commons through internalization of costs of resistance. No
13.	Encourage competition. No.

14. Encourage follow-on innovation.	In general no, however, to promote follow-on innovation, one idea developed in the Sanders bill in the US is to have payments for a new product reflect the incremental value of the therapeutic improvements and the degree to which the new product builds on or benefits from the innovation of the originator product, with the developer of the originator continuing to receive payments even if their market share falls to nil.
15. Estimated relative transaction costs associated with implementation of the incentive.	Modest.
16. Expected timeframe to implement and stimulate development.	Short.
17. Amount of new legislation or institutional infrastructure required.	Minor.
18. Issues surrounding the incentive's potential to spur desired R&D in the short-term	May suffer from lack of familiarity in the short-term but likely to gain attention from developers as they search for new business models in the medium-to-long term.
19. Clear hurdles and barriers	While prize mechanism offers very strong incentives to meet a specific target profile it may offer a weaker incentive to develop a drug that exceeds the target profile or a useful drug that doesn't quite have the required profile. Also, if the incentive relies only on the promise of rewards (as opposed to fully earmarked existing sum), they are at the mercy of the changing political and economic (and associated budgetary) tide.
20. Experiences with mechanism to date.	So far no large end prize has been used for the purpose of stimulating pharmaceutical R&D. However, a number of targeted, milestone-type prizes have been offered in recent years such as the 1996 CASP prize for protein structure prediction, the 2006 X-Prize Foundation prizes for genomics. Several PPPs have also offered prizes to solve through the InnoCentive website. Generally these prizes have been relatively small and aimed at achieving the solution to very specific scientific problems, not product development. For example, the International AIDS Vaccine Initiative offered a \$150,000 prize for the protein to help in furthering HIV vaccine design and development. So far, despite more than 300 responses to the challenge, no submissions met the prize requirements. However, in 2008 there were two winners of the \$20,000 prize offered by the TB Alliance (in collaboration with the Rockefeller Foundation and InnoCentive) for the development of simpler and safer ways for making the Phase II tuberculosis (TB) drug PA-824. The size of the prize was small and the potential of the winning ideas still needs to be explored but it is believed that in getting rid of an explosive starting material, reducing the number of synthesis steps, and eliminating a reactant known to be skin and eye irritants, the proposed solutions could reduce production costs and ultimately allow patients to be treated for less. MSF and the Gates Foundation are also reported to be exploring the use of prizes to promote the development of new biomarkers for TB diagnostics.

Buy-out	
1.	Brief description of incentive mechanism The use of a large end prize to purchase the full rights to a product by the funder.
2.	Support conservation efforts. Conservation likely to be improved given that pressure to over-market or sell will be reduced (or even eliminated).
3.	Decoupling of profits and the recouping of R&D costs from sales/prices. Full decoupling.
4.	Likely beneficiaries. Companies with sufficient capital (large companies or small companies with good access to early funding sources such as venture capital); Milestones payments could be used to provide funding to developers earlier in the process.
5.	Share risk between funder and developer. All risk borne by developer.
6.	Chances of achieving political support. Challenging given that sum needed will likely be high
7.	Encourage purchase of best drug available on market. Risk of purchasing sub-optimal drug. The very high price that must be offered to encourage development and sale of the rights to a product (at least in the traditional private business model) would be much higher than a normal prize and would imply that the donor/buyer may be 'putting all the eggs in one basket', likely leaving little or nothing to invest in purchasing any eventual better drug that comes on the market. A buy-out from a more publically-driven model would likely achieve a lower buy-out price.
8.	Use market to determine optimal reward size or need for external financing of the incentive. External financing required.
9.	Offer rewards solely for successful research. Yes.
10.	Avoid principal-agent problems. Yes
11.	Promote clear communication between funder and developer regarding willingness to pay for specified product. Yes.
12.	Help overcome Tragedy of the Commons through internalization of costs of resistance. Funder (in this case the buyer of rights) may internalize costs of resistance if is a public body playing role of direct party to implications of resistance.
13.	Encourage competition. No.
14.	Encourage follow-on innovation. No.
15.	Estimated relative transaction costs associated with implementation of the incentive. Medium (due to need for management).
16.	Expected timeframe to implement and stimulate development. Short-to-medium.
17.	Amount of new legislation or institutional infrastructure required. While a prize-based mechanism could be relatively easily established within an existing EU body (e.g. DG Research & Innovation), a buyout would likely require a new legal entity to handle all the arrangements.
18.	Issues surrounding the incentive's potential to spur desired R&D in the short-term. May be limited by lack of familiarity.
19.	Clear hurdles and barriers. The forgoing of IP rights may be especially concerning to what has been an IP-driven industry. Private developers will be particularly reluctant to give up rights to a product that could achieve substantial sales over a significant amount of time such as with a broad-spectrum novel product that can be freely priced in many national markets. The calculation of the buyout would have to account for this. It is not immediately clear who the owner of the rights should be.
20.	Experiences with mechanism to date. None.

Advanced Markets Commitments (AMC)	
1. Brief description of incentive mechanism.	An AMC consists of one or more donors making a legally binding commitment to heavily subsidise the future purchase of a given volume of a drug once it is developed, presuming that it meets specified standards and that there is demand for the drug in the market.
2. Support conservation efforts.	Generally, conservation may be somewhat improved given that pressure to over-market or sell will be reduced, however, the effect is unlikely to be substantial. While pre-purchase of antibiotics can help guarantee a minimum revenue stream to developers, it can also create pressures on MS ministers and health systems to consume the amount of the purchase. As seen in the case of the recent H1N1 pandemic, there is little slack in political sphere and public opinion given to health planners who over-purchase a product—even in the case of a pandemic. However, there is a key difference here between the risks of over-purchasing a vaccine and over-purchasing an antibiotic: if the over-purchase results in pressures on the health system to absorb the excess (for example, to cover up or to mitigate political or public criticism) this would work directly against conservation efforts.
3. Decoupling of profits and the recouping of R&D costs from sales/prices.	The price of units included in the contract are negotiated, the larger the volume commitment the lower the expected negotiated price. Although there is less control over long-term prices than a buy-out, AMCs could help achieve tiered global pricing (e.g. prices established according to relative income) if the EU is willing to subsidize and negotiate on the part of these countries. For units sold outside of contract (for example to payers not included in the contract or beyond the time limits of the contract) the developer retains full control of pricing. Overall, the developer still has the incentive to sell as many units as possible and to charge the maximum price possible outside contract sales. Conditions over longer-term "tail price" could be included (with the expectation of sticking points) to help control prices but the incentive to achieve high sales volumes will remain.
4. Likely beneficiaries.	Companies with sufficient capital (large companies or small companies with good access to early funding sources such as venture capital); Milestones payments could be used to provide funding to developers earlier in the process.
5. Share risk between funder and developer.	In specifying the number of doses to be purchased as well as their price, AMCs have the benefit of aligning incentives for the funder, developer and user early in the development process. Specified volume and price increase the perceived level of funder commitment (compared to prizes) and conversely reduces the risk to developers. It can also increase the size of the market for the eventual product. Pricing structure and IP arrangements also affect developer reward and hence risk. Pricing structure and the terms dictating how a developer is able to exploit it's monopoly protection will likely have the greatest impact on developer reward and hence risk. AMCs applied to antibiotics would likely raise challenges with product specification and quantity guarantee given the changes in the market and the unpredictability of resistance. There may be substantial risks in committing to purchase large quantities of the developed product before its resistance profile is properly understood – cross-drug resistance with the novel product could render it largely obsolete before the product is even fully on the market. One suggestion is to avoid establishing a contractual minimum threshold quantity thereby leaving the funder free to choose amongst all the products qualifying for the price guarantee ⁷ . This more closely mimics an actual market. However, it substantially increases the risk to the developer.
6. Chances of achieving political support.	Reasonably achievable.
7. Encourage purchase of best drug available on market.	Poses risk of purchasing sub-optimal drug. This can be mitigated against by making the ultimate purchase of the product optional, however, optionality greatly increases the risk to the developer and hence may deter participation.
8. Use market to determine optimal reward size or need for external financing of the incentive.	External determination of reward size but done by product price which is negotiated.

9. Offer rewards solely for successful research. Yes.
10. Avoid principal-agent problems. Largely yes.
11. Promote clear communication between funder and developer regarding willingness to pay for specified product. Yes.
12. Help overcome Tragedy of the Commons through internalization of costs of resistance. No.
13. Encourage competition. No.
14. Encourage follow-on innovation. No.
15. Estimated relative transaction costs associated with implementation of the incentive. Modest.
16. Expected timeframe to implement. Short-term.
17. Amount of new legislation or institutional infrastructure required. Minor.
18. Issues surrounding the incentive's potential to spur desired R&D in the short-term. As regards AMCs, several academics ^{8,9,10} as well as the large companies themselves, via IFPMA, have in the past suggested that they are likely to be most relevant 'in areas where most needs can be met through adaptive research [incremental innovation]' ¹¹ rather than as major promoters of innovation as suggested by the CGD. This suggests they would not be suitable for achieving a novel antibiotic in the short-to-medium term. This may reflect the idea that they are not seen to sufficiently lower the risks associated with undertaking innovative research. However, it may reflect the more traditional thinking of companies previously. There does appear to be more positive view of such proposals today.
19. Clear hurdles and barriers. In applying AMCs to antibiotics, challenges are likely to arise, particularly regarding product specification and quantity guarantees in view of the changes in the market and the unpredictability of resistance. Another challenge concerns the determination of the purchase volume given changes in the epidemiological environment (compounded in the case of epidemic susceptibility or biothreat). One option would be for the government to commit to purchasing a certain amount and stockpile the product if too much is purchased ^v .
20. Experiences with mechanism to date. The idea of the AMC was first introduced by Michael Kremer and in 2005, the Center for Global Development built on the idea with detailed design specifications. In 2007 the first AMC was established when the GAVI Alliance received US \$1.5 billion in pledges from 5 countries (Canada, Italy, Norway, Russia, and the United Kingdom) and the Bill & Melinda Gates Foundation to adapt a pneumococcal vaccine to include target strains found in the developing world ¹² . The GAVI Alliance promised \$1.3 billion through 2015. Implementing countries are meant to provide a small co-payment to contribute towards the cost of the vaccines. The rollout of pneumococcal vaccines began in December 2010 and is now underway in Nicaragua, Honduras, Guyana, Sierra Leone, Yemen, Kenya, Democratic Republic of the Congo and Mali ¹³ and Rwanda has just become the first developing nation to include the pneumococcal vaccine within routine immunisation programmes ¹⁴ . These are clearly very important steps forward. However, this specific AMC model has been criticised because of the pre-existence of developed world demand (and hence market size with considerable pull effect) and because two candidate vaccines were already nearing regulatory approval when the AMC was announced ^{15,16} . Effectively the AMC served more as a procurement contract to encourage companies to meet demand in poor countries at subsidised prices rather than stimulating the development of a vaccine that otherwise would not have been developed ¹⁷ . In this sense, the only AMC that the world has any experience with is not actually a pull mechanism to promote innovation.

^v To qualify for stockpiling, antibiotics may have to be formulated for simple consumption to ensure that they can be disseminated widely to the public in the case of an epidemic. Indeed anecdotal evidence from the US suggests that antibiotics in their originally marketed parenteral formulations are generally not considered for stockpiling. This may have substantial cost implications for developers and must be accounted for in AMC designs with high volume commitments.

PUSH-PULL INCENTIVE MECHANISMS

Orphan drug incentives	
1. Brief description of incentive mechanism.	Drugs to treat rare conditions can qualify as orphan drugs and receive orphan drug designation are granted access to the EMA's centralised approval procedure, fee reductions for regulatory procedures, free scientific advice, and ultimately 10 year market exclusivity over the indication if they make it to market. Also, while not standardized across Europe, orphan drugs also receive tax incentives from the Member State (MS) level ^{vi} .
2. Support conservation efforts.	No (off-label prescribing allows for prescription beyond the indication for which product is intended).
3. Decoupling of profits and the recouping of R&D costs from sales/prices.	No.
4. Likely beneficiaries.	SMEs (and increasingly larger companies) are benefiting from orphan drug incentives.
5. Share risk between funder and developer.	Yes.
6. Chances of achieving political support.	Increasingly challenging due to the perceived abuse of orphan legislation (see description of experience with orphan legislation below).
7. Encourage purchase of best drug available on market.	Does not inhibit.
8. Use market to determine optimal reward size or need for external financing of the incentive.	Market determines reward but extended IP protection may affect market price.
9. Offer rewards solely for successful research.	Early benefits such as fee waivers and tax incentives lost if product does not reach the market.
10. Avoid principal-agent problems.	Largely yes
11. Promote clear communication between funder and developer regarding willingness to pay for specified product.	States a clear priority on the part of the regulator but doesn't associate the priority with a clear price.
12. Help overcome Tragedy of the Commons through internalization of costs of resistance.	No.
13. Encourage competition.	No.
14. Encourage follow-on innovation.	No.
15. Estimated relative transaction costs associated with implementation of the incentive.	Low
16. Expected timeframe to implement.	Short.
17. Amount of new legislation or institutional infrastructure required.	None.
18. Issues surrounding the incentive's potential to spur desired R&D in the short-term.	Incentive has been unsuccessful in driving antibiotic R&D thus far and unlikely to do so in future.
19. Clear hurdles and barriers.	Antibiotics can already qualify for orphan status under the current legislation—indeed a handful of products with antibiotic properties have already received orphan designation and reached the market ¹⁸ . However, in order to do so developers must prove that the prognosis or expression of the disease for which the product is intended is different from the general condition. This is generally not easy to do and overall current legislation also is not designed for acute, short-term conditions in the way it sets out eligibility criteria-which lies at the base of the Regulation ^{vii} . Also, the rarity criterion is a barrier to investment if the spectrum of activity is initially unclear. Overall, given the pre-existence of orphan legislation and the lack of effect on spurring investment in the antibiotics market (and its success in spurring investment in other markets) suggest that the incentive is ill-suited to antibiotics.

^{vi} Lessons from the US, suggest that the primary attraction of this type of legislation for the pharmaceutical industry is the market exclusivity component.

20. Experiences with mechanism to date. Implemented in the EU in 2000 orphan drug legislation has proven to be successful in promoting R&D in drugs for rare diseases. However, the legislation has also proved problematic in several ways. Market exclusivity over the indication decreases competition and in many cases leads to high prices faced by public payers. A ‘take it or leave it’ scenario ensues, possibly compounded by public pressure to fund emotively termed ‘orphan’ products, with payers being left with little choice but to pay the high prices. High prices have also led to varying levels of access to orphan drugs across the EU Member States.

While high prices are arguably necessary to recoup R&D costs when patient populations are small, the manner in which the market exclusivity provisions are applied are also seen to be problematic. Critics point to the exclusivity application over the indication as extremely anti-competitive^{viii}. Another problem concerns the accumulation of indications over which market exclusivity applies. Developers are currently able to apply for orphan status under numerous indications as long as each is considered ‘rare’. The EMA accepts the definition of rarity independently, without adding up the number of intended patients overall. The accumulation of 5 indications by Glivec (imatinib), a cancer drug developed by Novartis, is demonstrating the potential for what can be seen as abuse of the orphan legislation.

Permitting the accumulation of indications—while clearly not accidental and intended to promote the exploration of new indications—directly contravenes the spirit of the orphan legislation—to build markets where none naturally exist due to small patient numbers (based on the principles of equity). Finally, the eligibility criterion of being to demonstrate lack of natural profitability in a market—an inherent part of both US and EU orphan policies—has been put by the way side. Increasingly common off-label use of these products further amplifies the perception of abuse.

^{viii} However, the ambiguity in the wording of the derogations which allow the breaking of the exclusivity (to allow competitors onto the market) may be less stringent than at first glance. Namely the derogation based on superiority is ill defined and thus allows for entry of competitors with potentially only minor comparative advantages such as those pertaining to formulation. In the case of orphan drugs for pulmonary hypertension, derogations permitted entry to not one but four competitors within the indication.

The Call Options for Antibiotics (COA) Model	
1. Brief description of incentive mechanism.	The COA is a push-pull mechanism based on both the principles of call options in equity markets and a flexible AMC. It allows investors to purchase the right to buy a drug at a later time, in this case the right to purchase a specified amount of an antibiotic at a later date for a specified price. If the product does not reach the market, the purchaser has no further obligation and has only paid the price of the initial option contract. If the project is terminated at any stage—for example following problems during clinical trials--the purchaser retains access and joint ownership of the early findings of the research conducted using the funds from the option. This grants the purchaser joint rights to any later antibiotic developed from that initial research.
2. Support conservation efforts.	No.
3. Decoupling of profits and the recouping of R&D costs from sales/prices.	The price of units included in the options contract are negotiated; the earlier in the R&D process, the cheaper the price of the product. As under AMCs, for units sold outside of contract (for example to payers not included in the contract or beyond the time limits of the contract) the developer retains full control of pricing. Overall, the developer still has the incentive to sell as many units as possible and to charge the maximum price possible outside contract sales.
4. Likely beneficiaries.	Sale of options early in development process provide funding that could help smaller developers participate but they would likely still require sources of capital up to the point at which their investigational product can be presented as a viable one. Familiarity with shareholders may help spark interest in the larger or publically owned firms.
5. Share risk between funder and developer	The COA model provides only the option, rather than a commitment, to buy the product. This places substantial risk on the developer. However, the premium paid by the purchaser early in the development phase compensates the developer for some of this demand-side risk.
6. Chances of achieving political support.	Reasonably achievable.
7. Encourage purchase of best drug available on market.	The presence of sunk costs (investments already made) in certain projects may unduly influence organizations to purchase sub-par drugs when other better options may have become available in the interim.
8. Use market to determine optimal reward size or need for external financing of the incentive.	External determination of reward size but done by product price which is negotiated.
9. Offer rewards solely for successful research.	Option premium lost to developer if product is unsuccessful.
10. Avoid principal-agent problems.	In order to sell options and attain early funding developers must make the case for their investigational product. This presents an opportunity for principal-agent problems to arise.
11. Promote clear communication between funder and developer regarding willingness to pay for specified product.	Yes.
12. Help overcome Tragedy of the Commons through internalization of costs of resistance.	No
13. Encourage competition.	Yes.
14. Encourage follow-on innovation.	No.
15. Estimated relative transaction costs associated with implementation of the incentive.	Low-to-modest.
16. Expected timeframe to implement.	Short-term.
17. Amount of new legislation or institutional infrastructure required.	Minor.

18. Issues surrounding the incentive's potential to spur desired R&D in the short-term. By spreading the cost of drug purchase over time it may also be more fiscally feasible than other pull mechanisms. This can improve the chances of compliance and help to increase the credibility of the scheme. The quality marker within the model crucially allows for the size of the reward to be determined as a function of the type of product developed – more for innovative therapies and less for me-too drugs. Overall, with regards to its potential success in resolving the urgent needs for new antibiotics, the COA may be limited by a lack of familiarity.

19. Clear hurdles and barriers. The COA hinges on thorough evaluation of the potential drugs and therefore asymmetry of information may hinder efficient allocation of resources to different projects. The model allows potential gaming as developers could take early seed money and then prematurely terminate a project that became more expensive or less viable than expected. Reputational concerns are likely to be important in preventing such offences. Also, when the purchased number of call options has been used the antibiotics return to full price rather than the marginal cost of production. This could have a negative effect on antibiotic prices in developing countries that would only be part of the option scheme if developed and developing country markets were segmented appropriately. However, it could be argued that the higher prices in developed countries could help prevent over-diffusion and consumption of the product. Also, arrangements for joint ownership of early research findings in the event of product failure are likely to be difficult.

20. Experiences with mechanism to date. None.

Special designation for priority antibiotics	
1. Brief description of incentive mechanism.	A Special designation (SD) granted by EMA could provide access to EMA's centralised approval procedure, fee reductions for regulatory procedures, and free scientific advice, along with a period of extended data exclusivity on a sliding scale with product quality, namely with regard to resistance. In exchange for increased IP protection, developers would be completely prohibited from marketing their products. While allowances would be made for academic and association-organized conferences to share data and information on product qualities with the medical community, sales representation and all other activities would be prohibited. Also in exchange for the exclusivity provisions, the developer would have to commit to a (national income-driven) tiered pricing scheme for sales to poorer countries. Failure to comply would result in removal of the exclusivity provision within the European market. Early research-related tax incentives could also be granted (at the MS level).
2. Support conservation efforts.	Bans marketing of product which may affect consumption.
3. Decoupling of profits and the recouping of R&D costs from sales/prices.	No decoupling but includes element to help control pricing. While the EMA has no legal authority over pricing, verification of tiered pricing could take place based on a dossier with independent validation by, for example, DG Trade. The general regulatory approach to tiered pricing could be relatively 'light touch', using media (including new technologies that foster greater pricing transparency) and public relations for further enforcement.
4. Likely beneficiaries.	SMEs and larger companies.
5. Share risk between funder and developer.	Yes.
6. Chances of achieving political support.	Reasonably achievable. Familiarity with orphan legislation and structures help decision-makers perceive how such a mechanism would work, while the proposed IP provisions should prove more politically palatable than that which is causing much criticism of orphan legislation.
7. Encourage purchase of best drug available on market.	Does not inhibit.
8. Use market to determine optimal reward size or need for external financing of the incentive.	Market determines reward but extended IP protection may affect market price.
9. Offer rewards solely for successful research.	Early benefits such as fee waivers, tax incentives, and early scientific advice is lost if product does not reach the market.
10. Avoid principal-agent problems.	Principal-agent problems may arise in terms of laying the eligibility of the product for designation (e.g. regarding known spectrum of activity). These must be mitigated against in the evidence dossier requirements.
11. Promote clear communication between funder and developer regarding willingness to pay for specified product.	States a clear priority on the part of the regulator but doesn't associate the priority with a clear price.
12. Help overcome Tragedy of the Commons through internalization of costs of resistance.	No.
13. Encourage competition.	Competition within the delineated priority therapeutic area could increase due to lure of the incentives package but generic competition would be impeded through the expanded data exclusivity provision.
14. Encourage follow-on innovation.	Follow-on innovation requiring access to data would be impeded by the extended data exclusivity.
15. Estimated relative transaction costs associated with implementation of the incentive.	Low.
16. Expected timeframe to implement.	Short-term.
17. Amount of new legislation or institutional infrastructure required.	Minor.

18. Issues surrounding the incentive's potential to spur desired R&D in the short-term. Familiarity and previous success with of existing incentive mechanism with similar structure and design would suggest possibility for efficient implementation and impact.
19. Clear hurdles and barriers. The condition tying incentive rewards to long-term pricing strategies will be the most difficult mechanism to implement within this package of incentives.
20. Experiences with mechanism to date. None.

Adjustments to current national pricing and reimbursement (P&R) regimes	
1. Brief description of incentive mechanism.	Pricing and reimbursement adjustments that more explicitly link prices offered by the public payer to therapeutic value. Higher prices with reasonable volume measures can lure investment in R&D using the market.
2. Support conservation efforts.	Prices and reimbursement have a direct influence on prescribers' and patients' decision-making, which in turn would provide support to conservation efforts.
3. Decoupling of profits and the recouping of R&D costs from sales/prices.	No.
4. Likely beneficiaries.	The profit lure of more favourable prices would appeal to larger companies and smaller companies capable of attracting venture capital or other early and mid research investment.
5. Share risk between funder and developer.	All risk borne by the developer. However, in contrast to patent-term extensions, P&R incentives would allow developers to recoup R&D costs early on ¹⁹ and reduce the amount of risk faced by developers.
6. Chances of achieving political support.	Reasonable-to-likely (on Member State level); Very challenging (on EU level).
7. Encourage purchase of best drug available on market.	Yes.
8. Use market to determine optimal reward size or need for external financing of the incentive.	Market (demand) determines reward.
9. Offer rewards solely for successful research.	Yes.
10. Avoid principal-agent problems.	Largely yes, however, opportunities for principal-agent problems do arise in, for example, the submission of cost-effectiveness evidence.
11. Promote clear communication between funder and developer regarding willingness to pay for specified product.	Depends on clarity and explicitness of pricing and reimbursement schemes.
12. Help overcome Tragedy of the Commons through internalization of costs of resistance.	No.
13. Encourage competition.	Yes.
14. Encourage follow-on innovation.	Yes although dependent on reimbursement scheme.
15. Estimated relative transaction costs associated with implementation of the incentive.	Low.
16. Expected timeframe to implement.	Medium term (on Member State level), long term for minimal coordination amongst Member States.
17. Amount of new legislation or institutional infrastructure required.	None-to-low.
18. Issues surrounding the incentive's potential to spur desired R&D in the short-term.	In the current climate, standardization across Member States seems unlikely.
19. Clear hurdles and barriers.	Given the small size of Member States, they are incapable of significantly influencing R&D investment priorities on their own. The success of this type of reform as an incentive would depend largely on the number of Member States adopting such an approach. A few Member States explicitly offering high prices and favourable reimbursement policies does not make for a sufficiently appealing offer. A standardised, long-term European approach to assessment would make the prioritization of antibiotics more credible and in turn greatly contribute to the strength of such an incentive.

20. Experiences with mechanism to date. Several Member States have sought to support innovation and a full R&D pipeline for pharmaceuticals overall by limiting the use of their power as monopsonist (single payer) in bargaining down prices of new technologies. Pricing strategies in the UK and Germany are largely based on free pricing and, as such, could offer a relatively higher price to innovative or highly therapeutic products. One problem has been in the reimbursement policies. Uniqueness of a drug's resistance profile is under-valued in the current system of pricing & reimbursement as well as within the structure and eligibility requirement of existing incentive mechanisms. For example, in the UK, the current system of drug comparisons and ensuing selection or de-selection from reimbursement does not adequately take into account the need for new drugs that are different from the existing drugs on the market to help dampen the growth rate of resistance and improve the longevity of our drugs arsenal. Reimbursement decisions involving cost-effectiveness make broad reimbursement difficult for new antibiotics. In the case of several types of antibiotics, there are already drugs on the market and they are inexpensive, some available in generic form. If they are still sufficiently effective then the case for allowing a high price to achieve only a moderate incremental benefit above the existing drug is difficult. Also, if the new drug is only as effective as the existing drug but not superior then a higher price will by definition lead to it appearing less cost-effective than the existing drug and therefore likely not reimbursed. It should be emphasized that even with the use of economic evaluation, a truly superior product—for example against MDR Gram-Negative infections—should be able to command a reasonably high price. The problem is the relative price. As long as drugs in therapeutic categories such as cancer receive prices on such a different scale to antibiotics, the chances of directing private investment in this direction are limited.

Antibiotic Conservation and Effectiveness (ACE) programme	
1. Brief description of incentive mechanism.	The ACE Programme proposal ²⁰ has three main components: <ul style="list-style-type: none"> a. ACE reward payments to developers for new antibiotics would be based on the success achieved in meeting public health and conservation goals, the magnitude being tied to the therapeutic benefit of the drug that developer brought to market. Developers could then pay providers to support stewardship and surveillance activities. The "pay for performance" incentives would encourage companies to maximize effective access (low prices) while also eliminating wasteful antibiotic uses. b. Market exclusivity provisions would be tied to the continuing effectiveness of the drug. The regulatory agency, accompanied by a panel of experts, would set targets, e.g. requiring resistance to remain below an established level. c. Limited waivers of antitrust and fraud & abuse laws would be used to enable coordination of market activities where cross-resistance could occur. Specifically, the authors propose that for identified drug-bug pairings where cross-resistance is a problem the regulatory agency would coordinate with the enforcement agencies to issue certificates or waivers authorizing limited joint coordination of conservation activities that would not result in prosecution. Without these waivers, it is difficult to coordinate conservation within a germ shed or across drug-bug pairs.
2. Support conservation efforts.	Yes, developer incentive to oppose conservation efforts is removed.
3. Decoupling of profits and the recouping of R&D costs from sales/prices.	The magnitude of ACE payments would be based on the achievement of public health gains through antibiotic stewardship and infection control. Duration of payments is linked to the efficacy of the drug.
4. Likely beneficiaries.	The profit lure of more favourable prices would appeal to larger companies and smaller companies capable of attracting venture capital or other early and mid research investment.
5. Share risk between funder and developer.	Development risk is borne by the developer, but the public payer bears the financial risk (increased reimbursement) if the antibiotic yields outstanding health benefits.
6. Chances of achieving political support.	Antitrust reform and paying through the reimbursement mechanism are likely to be challenging, however, developers have demonstrated preliminary openness to the proposal.
7. Encourage purchase of best drug available on market.	Yes.
8. Use market to determine optimal reward size or need for external financing of the incentive.	Reward determined by health outcomes.
9. Offer rewards solely for successful research.	Yes.
10. Avoid principal-agent problems.	Developer provided evidence for the calculation of ACE payments may run the risk of manipulation.
11. Promote clear communication between funder and developer regarding willingness to pay for specified product.	Depends on clarity and explicitness of pricing and reimbursement schemes.
12. Help overcome Tragedy of the Commons through internalization of costs of resistance.	Yes.
13. Encourage competition.	Moderately inhibiting.
14. Encourage follow-on innovation.	Moderately inhibiting.
15. Estimated relative transaction costs associated with implementation of the incentive.	Medium-to-high.
16. Expected timeframe to implement.	Medium-to-long term.
17. Amount of new legislation or institutional infrastructure required.	Significant.

<p>18. Issues surrounding the incentive’s potential to spur desired R&D in the short-term. Competition agencies in the United States and the EU have indicated provisional openness to such a suggestion, however, implementation requires reforms in several sectors.</p>
<p>19. Clear hurdles and barriers. The proposal to create umbrella-like patents/collusion over resistance classes (forcing developers to internalize the cost of resistance, thereby increasing individual developer stake in maintaining product efficacy) raise questions of acceptability and practicality.</p>
<p>20. Experiences with mechanism to date. None, although movements towards greater value-based pricing have been made in some European countries and in Australia.</p>

Health Impact Fund (HIF)	
1.	Brief description of incentive mechanism. HIF ²¹ is a utility-based mechanism that consists of a fund that would reward developers retrospectively, based on the estimated health benefits achieved through the consumption of their products the previous year. Developers agree to sell their products at or near cost in exchange for payment through the reward mechanism. The HIF would have no involvement in funding research but would simply issue rewards for fully developed products according to their assessed impact. HIF has recently been shortlisted by the WHO Consultative Expert Working Group on Research and Development ²² in its search for sustainable ways of stimulating R&D of essential medicines.
2.	Support conservation efforts. Some would argue that the removal of the price barrier could lead to overuse of the novel product, especially as it would be seen as the best product available (having established high therapeutic value). Also, HIF designs include financial encouragement to market products which could work directly against conservation efforts. However, HIF uses randomized surveys and other information to gather information on how products are being used. Where they are found to be inappropriately prescribed the reward would be reduced proportionately.
3.	Decoupling of profits and the recouping of R&D costs from sales/prices. No decoupling of revenue from sales volume in the basic HIF proposal although alternate designs to remove the link to sales are being proposed. Full decoupling of prices from the recouping of R&D costs.
4.	Likely beneficiaries. Developers of products sold at high volume, with high therapeutic benefit.
5.	Share risk between funder and developer. All risk borne by the developer.
6.	Chances of achieving political support. Challenging to highly challenging.
7.	Encourage purchase of best drug available on market. Does not inhibit.
8.	Use market to determine optimal reward size or need for external financing of the incentive. Governments and other donors would finance the HIF but it uses market forces to establish the relative size of the reward. For example, if all registered products were estimated to have saved 20 million Quality-Adjusted Life Years (QALYs), a product that had saved 2 million of these would receive 10% of the money in the fund. Optionality allows for self-adjustment in the establishment of reward size: if payments are too high, more products will be registered with the HIF (individual product payments will then fall as the funds will be spread over more products) and vice versa.
9.	Offer rewards solely for successful research. Yes.
10.	Avoid principal-agent problems. The provision of sales data by the developer gives an opportunity for principal-agent problems to arise.
11.	Promote clear communication between funder and developer regarding willingness to pay for specified product. Prior to product development the developer has little indication of the magnitude of the reward given that the reward is determined only later, after health gains achieved, and in relation to the number of other products in the scheme.
12.	Help overcome Tragedy of the Commons through internalization of costs of resistance. No
13.	Encourage competition. If technical (and biological) barriers to producing novel antibiotics are sufficiently low, high volume sales of a new product lead to a greater number of new products entering the market. If the barriers are high, there will be no or few competitors (and the use of a highly precious resource could be over-facilitated, requiring stringent guidelines and prescription controls). Also, the retention of IP rights in HIF has been argued to inhibit generic competition ²³ .
14.	Encourage follow-on innovation. Does not inhibit.
15.	Estimated relative transaction costs associated with implementation of the incentive. High (due to calculation of health impact and monitoring of sales).
16.	Expected timeframe to implement. Long term.

<p>17. Amount of new legislation or institutional infrastructure required. Major. Public bodies would have to be highly involved in administering the scheme. Within Europe individual Member States could take on this responsibility within existing HTA bodies. However, as with any incentive to motivate a global industry, the investment prioritization signals would be much stronger if done at the European level. Administration at EU level would however require some amendments to distribution of authority and much opposition should be anticipated on the basis of subsidiarity.</p>
<p>18. Issues surrounding the incentive’s potential to spur desired R&D in the short-term. In paying developers retrospectively according to the estimated health benefits derived from the use of their products, the HIF would initially likely promote the production of much needed medicines for diseases that are concentrated amongst the poor given population and relative health gains to be achieved. The curing of resistant bacterial infection would likely be associated with high QALY values (much health gain) but the existence of generic antibiotics that treat the majority of bacterial infections and the risk of spreading resistance would not make antibiotics an obvious choice for early HIF registration. However, over time increasing obsolescence of older antibiotics will make utility-based approaches more relevant for rewarding the development of broad-spectrum antibiotics.</p>
<p>19. Clear hurdles and barriers. An HIF system could be subject to gaming, especially in countries with health systems with limited capacity in data collection and management. Burden of disease figures are in many countries are still only vague estimates. However, one could argue that if an entire reward structure to industry were to depend on accurate burden estimates far more investment would be made towards achieving this. These investments must be accounted for. Also, for an HIF to function correctly and be seen as fair system for rewarding the development of novel antibiotics, the emergence of resistance and the therapeutic benefit of newer and older products would need to be tracked very regularly. Trials and monitoring would have to become routine—far more routine than current practice—and could prove burdensome over time.</p>
<p>20. Experiences with mechanism to date. None.</p>

ADDITIONAL ROLES FOR THE EU IN STEMMING THE ANTIBIOTICS CRISIS

New public institutions

It is increasingly clear that there is a much greater role for public institutions in driving appropriate R&D efforts and coordinating conservation policies across sectors (see LSE Report) if we are to avert a health crisis in future. This may mean expanding the role of existing institutions, but more likely it will require the establishment of new structures. For example, the EU may benefit greatly from having its own National Institutes of Health (NIH). **A European NIH** could serve or improve the following functions:

- a. Watchdog role to make predictions of therapeutic need alongside ongoing analyses of pharmaceutical pipelines to see if needs are likely to be met
- b. Fund translational research amongst academic laboratories: Funding for multidisciplinary collaboration to help tie basic research with drug development and medical practice—“from bench to bedside”.
- c. Support for open-access research: Funding for publically-accessible data repositories such as molecule libraries
- d. Offer grants & fellowships: Funding for capacity building and training of both new and experienced researchers
- e. Coordinate a patent pool to explore fixed-dose combinations of existing drugs to slow the growth of resistance.
- f. Fund and facilitate major collaborative efforts such as product development partnerships or other innovative institutional schemes to steer research in differing directions with regards to resistance (to avoid producing drugs that confer cross-resistance), to overcome key research bottlenecks, and to accelerate development.
- g. Partner in drug development with the new National Center for Advancing Translational Sciences (the new body currently under creation within US NIH that will undertake drug development directly in priority areas rather than just support development by other entities)

EU as global leader in regulatory reform

Due to a difficult political environment in the United States, the FDA could be described as an agency with less manoeuvrability than its European counterpart, the EMA. Safety scandals such as the Ketek^{ix} case have resulted in a more cautious and risk-averse approach being taken by Congress. This has impeded the FDA and has led them to be less supportive of innovative research and altering of regulation barriers which otherwise may have facilitated development of much needed technologies.

At this point in time, Europe may be better placed to take the lead on key issues such as antibiotics and move forward a fruitful discussion on further use of pharmacokinetic and pharmacodynamic modelling, conditional approval, trial design, etc. This in turn may lead to a much-needed boost to developers eager to work in this area but who feel inhibited by high and seemingly unpredictable regulatory barriers.

European action to limit off-label prescription

A key component in stemming overuse of antibiotics, that also has direct bearing on some of the incentives discussed earlier, is stricter limitations on off-label prescription^x. While in areas such as paediatrics off-label prescription may be necessary, the numerous trials in the US and the Mediator case in France, show that off-label prescription is often not well justified. Within Europe, Member

^{ix} Involved FDA acceptance of a drug based on fraudulent data.

^x Prescription of a drug outside of the indication for which it received marketing approval.

States currently deal with off-label prescribing on an entirely independent basis. However, as resistance to antibiotics extends far beyond the Member State level, the Europe Union should take concise action to protect priority antibiotics. Strict monitoring of appropriate use of priority drugs should become a European priority with naming and shaming (along with legal recourse) to counter abuses. Stricter regulations over antibiotic use should accompany any new overall piece of European legislation on antibiotics. Limiting off-label prescription would also have important knock-on effects in terms of preventing the abuse of regulatory incentives that can cause further market distortions rather than rectifications (see discussion of orphan incentives) .

European support for the development and use of rapid point of care diagnostics

Currently, the high growth of resistance stems in part from over-prescription of antibiotics resulting in inappropriate diagnosis. As culture and sensitivity tests can require 48 hours to provide results even for the most rapidly growing bacteria²⁴, few infections are microbiologically confirmed sufficiently quickly to guide treatment decisions²⁵. This presumptive treatment of patients means that viral infections are often misdiagnosed as bacterial infections and antibiotics are inappropriately prescribed or broad-spectrum antibiotics are used where narrow spectrum antibiotics are available. Physician risk aversion (which is compounded by mounting tendency for litigation in some countries) and the ensuing over-prescription of antibiotics will continue to amplify the growth of resistance until doctors have more sophisticated and effective, rapid, easy-to-use, point-of-care diagnostics. Far more needs to be done to support for the necessary basic research to produce these devices as well as increase access to and appropriate use of them.

CONCLUSIONS

The impending global health crisis of antibiotic obsolescence underlines the need for deliberate action to spur R&D of new antibiotics, alongside coordinated conservation initiatives. Numerous proposals have been put forward by several groups, each scoring differently against the chosen criteria, many of which pose important trade-offs. In determining the optimal way forward the weight given to each of the respective criteria will of course be different for different stakeholders. However, a few important points should be made. Any incentive or incentive package should be designed such that they strike a balance between the traditional entrepreneurial model of reasonably high risk to the developer compensated by high rewards and some early risk-mitigating funding²⁶. The timeframe should also be borne in mind: the implementation of any new legislation is likely to take a minimum of 5 years and new drug development generally takes more than 10 years. The more an incentive can fit into the existing regulatory infrastructure and the greater the familiarity with the mechanism amongst all parties, the faster one can expect the incentive to be fully implemented and bear fruits.

Also, in considering the incentives we should also be aware of the uncertainties we are dealing with. If we have already or are about to hit major scientific roadblocks then the approach to antibiotics may need to focus on finding ways of solving those problems. One way may be to focus on promoting the development of more narrow-spectrum antibiotics, over broad-spectrum drugs. Used in combinations and along with complimentary diagnostic tests, narrow spectrum antibiotics could help curb the growth of resistance over time. Also, assuming that we can drive the desired level of innovation by fuelling our traditional business model could be short-sighted given these uncertainties. The necessary innovative approaches may be more likely constructed as part of partnerships rather than in information silos. Therefore, in parallel to a push-pull incentive to reignite R&D for antibiotics - public funding should be used to support partnerships and other collaborative approaches. The discussion of these options is, as already stated, outside of the scope of this overview but should not be forgotten.

When it comes to incentives primarily targeted towards the private business, a number of conclusions can be made: Strategies that help decouple the recouping of R&D costs and profits from sales would lead to far less (if any) marketing, which in turn would lower over-consumption of

priority drugs such as antibiotics. Strategies that decouple the recouping of R&D costs and profits from prices would also give the funder much more control over affordability both within and outside of Europe. So through a bold choice of incentive strategy Europe can have a major impact on the level of access to medicines in poorer countries.

On a technical front, it should be noted that with any pull mechanisms it is extremely difficult to determine beforehand the appropriate contract terms without knowing the costs of production or regulatory reactions (which have been fickle in recent times) in advance. These difficulties also hinder the ability of developers to assess whether the promised reward is worthwhile and may limit participation. This suggests that the value of the incentive will have to be high. However, the EU should not shy away from using its combined market size to direct the pharmaceutical market. Prior to the H1N1 pandemic, Member States may have been fiercely independent in their desire for negotiate on their own, however, once the challenges (e.g. perceived dominance by some Member States, political risks associated with over-purchase, etc.), came to light, the desire to have the EC put out common calls grew considerably. This move towards common negotiation and purchase could be harnessed and used to drive an incentive mechanism.

Also, longer-term action to appropriately re-align R&D investment priorities with therapeutic needs should begin now. This requires taking a holistic view of pharmaceutical market rewards and how they influence investment decisions. This requires looking at the relative attractiveness of antibiotics to other therapeutic areas in the current system. Namely it requires looking at how attractive other therapeutic areas are due to prevalence/incidence, frequency of use, and the price levels achieved/granted. Reconsideration of current regulatory incentives (EU and Member State level) as well as the overall pricing and reimbursement framework (Member State level) should take place. Given the small size of Member States individually, they are incapable of significantly influencing R&D investment priorities. European systems are too fragmented and individually too small to provide the scale of demand to have much influence. If, however, the basic priorities could be agreed upon at the EU level (for example through a loose banding system^{xi}), the larger scale could help dictate the direction of investment. The size of the EU market as a whole is greater than the size of the US market and thus could influence investment priorities to an equal or greater extent through both prices & reimbursement and targeted incentives where key markets fail to sufficiently pull needed supply.

An ideal incentive scheme would be implemented on a global level in view of the global nature of antibiotic resistance. But, unfortunately, the difficulty in garnering global support is likely to prevent global solutions from resolving our urgent innovation needs for antibiotics in the near future. In the immediate future, the EU alone, or in conjunction with the US, should make a concrete move to implement a targeted incentive mechanism to promote R&D for antibiotics. At the same time, longer-term reforms to the current system should be initiated now and be much bolder in order to adequately realign investment priorities with public health needs and ensure that the areas of greatest therapeutic need can attract the best scientific minds from all sectors.

^{xi} Segmentation by broad priority levels.

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