Work Package 2, Task 3: Identified risks and bottlenecks to antibiotics innovation

Introduction

This document is first and foremost a deliverable to Task 7, whose team requested a list of risks and bottlenecks that could be transformed into a set of criteria to evaluate and assess different proposed reward models and other incentives and solutions. This output is based upon a literature review, stakeholder interviews, and input from multiple WP2 team members. The list will also be transformed by the Task 11 team into a narrative to set the stage for the final DRIVE-AB recommendations.

A bottleneck is a situation in which the process of bringing a candidate drug further down the R&D pipeline is delayed or stopped by non-scientific factors. Risks are uncertain circumstances that can lead to a bottleneck or to a no-go decision. The consistency of these definitions can be open to discussion; for instance, the first definition paradoxically implies that, by the definition itself, there is no such thing as a scientific bottleneck. Yet, they have been helpful in identifying and searching for risks and bottlenecks. However, we do not really see the need for placing too much emphasis on distinguishing between risks and bottlenecks in the following, so below they are treated as one single category or phenomenon, sometimes abbreviated as R&B.

Both conservation and global access are key features of any global response to antibiotic resistance (ABR). They are not barriers to be removed, but essential design features of the global response to ABR. For our purposes in WP2, they increase expenses or decrease revenues and therefore impact profitability. So any innovation solutions must be even more robust (addressing financial challenges for both manufacturers and purchasers) in order to overcome the drag from these essential initiatives. Therefore, we included a section on access issues in the list below.

Methodology

The list of risks and bottlenecks below is a result of a process consisting of the following stages:

1. Olof and Carl prepared two documents: 'Drive AB Task 3 Literature Review' and 'Drive AB Task 3 Review of Additional Literature' (see details of literature review below).
2. Kellie prepared a list of R&B based on the literature survey, included as Appendix 2 in this document. The appendix also contains comments from Nicole and Kevin.
3. Jens prepared a revised list, to which Nicole, Ka and Ross added comments and content. That version was presented at the Task 3 team meeting 12 August.
4. The Task 3 team meeting resolved that a revised list (i.e. more granular, based on 'root' causes) be presented to the entire WP2 team prior to a designated teleconference. Additional input from the Task 3 team was requested, but none received as of 28 August.
5. Jens selected relevant R&Bs from the preceding documents and compiled a new, detailed draft list.

6. Jens uploaded the Task 3.5 interview transcripts and the interview summaries[1] submitted from Tasks 3.2, 3.3, 3.4, and 3.7 into the Nvivo qualitative data analysis software, coded the material, and determined the level of support for each R&B from the different stakeholder groups. New R&Bs were added to the list as appropriate.
7. Similarly, Jens then uploaded the two literature review reports (see activity 1 above) into the Nvivo software, coded the material, and determined the level of support for each R&B in the reviewed literature. New R&Bs were added to the list as appropriate.
8. The list of R&B was continuously revised in parallel with activities 6 and 7, and subsequently critically reviewed against the points made in previous discussions.
9. Ross quality controlled the entire process, by reviewing the interview transcripts (where available for review), the interview summaries, the Nvivo coding (by reviewing an extracted report document), and the present draft list of risks and bottlenecks (see separate document).
10. A revised draft list was circulated to the entire WP2 team.
11. The draft was discussed in teleconferences on September 8 and September 11, and based on that feedback, as well as emails from some participants, Ross, Rik and Jens finalized the list.

The details of the methodology of the literature survey are as follows: The aim was to provide a comprehensive account of bottlenecks and risks in AB development as discussed in the reviewed literature. The review was fulfilled by means of a 'review of reviews' based on key literature as contributed by the wider WP2 Team as well as by experts such as John Rex, Adrian Towse, Donald Light and James Love. After the relevant articles were identified, they were abstracted by two Team 3 members. The review summarized bottlenecks and risks by the established categories of:

1. Financial Bottlenecks & Risks,
2. Regulatory Bottlenecks & Risks,
3. Scientific Bottlenecks & Risks,
4. Other Bottlenecks & Risks.

The review refrained from analyzing or categorizing the findings further but instead present, point by point, lists of bottlenecks and risks drawn straight from literature.

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[1] See separate fortcoming document on economic models and business models for the interview survey methodology.

Preliminary output to Task 4

A preliminary assessment concluded that the following tentative list of risk and bottlenecks categories should be submitted to the Task 4 Team:

1. Insufficient general scientific or methodological progress in the field
2. High R&D costs for developers, and lack of R&D funding
3. Low revenues from antibiotics
4. High levels of risk and uncertainty
5. Regulatory issues

About the list of risks and bottlenecks

We distinguish between 'root' and 'secondary' causes, with a high degree of granularity. 'Secondary' means that the point is an effect of one or several 'root' causes (or of causes not mentioned in the list). It does not imply that the points in question are secondary in importance. The high level of granularity has resulted in some overlap and potentially some redundancies between the different points. We included risks and bottlenecks that are not unique to antibiotics.

We also developed a metric for indicating the level of support for each R&B point made. Please see the following table.

Table 4. Legend for metric applied in list of risks and bottlenecks

	Legend, Survey column (i.e. interview surveys, Tasks 3.2, 3.3, 3.4, 3.5, 3.7)
○	Risk/bottleneck has not been mentioned
◗	Risk/bottleneck has been identified by one or more individuals in one stakeholder group*
●	Risk/bottleneck has been identified by one or more individuals in more than one stakeholder group*
	Legend, Literature column (i.e. the literature survey, included as Appendices 4 and 5)
○	Risk/bottleneck has not been mentioned
◗	Risk/bottleneck has been identified in one paper/reference
●	Risk/bottleneck has been identified in two or more papers/references

*Stakeholder groups for the **Survey** category are Academic researchers, SMEs, EFPIA members, Venture capitalists, and Philanthropists.

We have not identified authors from the literature review as belonging to specific stakeholders. There may be literature survey authors also 'doubling' as survey interviewees.

The choice of criteria for 'half moon' symbols and 'full moon' symbols may seem somewhat arbitrary, but they turned out to be easily operationalizable for analyzing the material in the Nvivo software. We believe these symbols provide an appropriate indication of the extent to which each point has been expressed in surveys and in literature. We would like to caution that the symbols are just indications. For instance, the fact that a specific point has been raised in scientific literature does not imply that it should be taken as a scientific fact, and vice versa, the

'new moon' symbol in the literature column does not rule out the possibility that the point in question has been scientifically corroborated in papers that escaped our limited literature review. Moreover, there is the caveat that in many cases it is a matter of interpretation and inference to determine whether a specific point made in the list is supported by a specific statement found in literature or in the survey material. At any rate, it will be up to the Task 7 and Task 11 teams to further process these points as suitable for their respective purposes.

Several points have been added by the WP2 team members while circulating and discussing previous drafts of this document. Whenever any of these points have not been corroborated in the interview survey or the literature review, two 'new moons' have been applied.

The identified risks and bottlenecks fall into any of the following six categories:

1. Lack of general scientific or methodological progress in the field, and technical challenges
2. Industry structure issues
3. High R&D costs to the developer and lack of financing for R&D
4. Low revenues accruing to antibiotics developers, and market risks
5. Regulatory and legal issues
6. Access issues

The risks and bottlenecks list

1. Lack of general scientific or methodological progress in the field, and technical challenges

Root causes	Literature	Survey
Technical issues		
Technical challenges are becoming increasingly more demanding (the low hanging fruits have been taken).	◗	◗
It is difficult to identify new compounds via both traditional and newer (such as genomics, etc.) discovery methods. Moreover, the modern "rational" linear drug development approach (for instance high throughput screening and single targets) might not be superior to the "older" empirical "chance" discovery approach.	●	◗
In antibiotics there is increased attrition rates, specifically the challenge of optimizing leads to development candidates is greater, given that antibacterials require higher blood levels than almost all other medicines. I.e. dose must be toxic to bacteria but not the host.	●	●

Root causes	Literature	Survey
Current chemical libraries are inadequate for antibiotic discovery. Specifically, there is a lack of platforms for extracting natural products from uncultureable microbes. Libraries are also poor in understanding of the necessary physicochemical requirements for entry into bacteria and prevention of efflux (active expulsion) from bacterial cells. While many antibiotics were discovered through the screening of natural product compound libraries, few new drugs have been identified in recent screens of synthetic chemical libraries. Synthetic compound collections held by firms and most proprietary compound vendors might not represent the range of compound types that might be explored to yield new classes of antibiotics.	●	◗
There appear to be multiple resistance mechanisms that work simultaneously, and it is challenging to develop a drug that targets all the mechanisms.	◗	○
Efflux pumps (and biofilms) in bacteria are poorly understood and difficult to overcome although they are the an important aspect of successful antibacterial development.	●	◗
It is difficult to find molecules that will affect Gram-negative bacteria due to the difficulties in penetrating their outer membrane.	●	○
Safety and adverse event risks are high as antibiotics interact with both the host and the bacteria, and many off-target effects (i.e. effects on the host) escape discovery *in vitro*, and are only discovered *in vivo* in clinical trials.	○	○
There is a clinical need for broad-spectrum drugs that could be used for empiric treatment (i.e. treatment prior to lab results that indicate the specific pathogen that causes illness). Such drugs have to be effective against a broad range of different pathogens, and there is a limited number of targets that are present in many species of bacteria.	○	○
There is a lack of access to good quality resistance data.	○	○
Various factors inhibit sharing of failures and potentially lead to duplication of efforts. Such factors include lack of time and support for curating information on failed projects into a useful format, lack of avenues for publishing data on failed projects, lack of access to old data as personnel retire or leave companies, difficulty in formatting raw scientific data so that it is useful. In some cases, data may not be shared because of continuing work on similar drug candidates and the need to protect against competition.	◗	○

Root causes	Literature	Survey
Methodological issues		
Appropriate animal models are lacking.	◗	◗
Diagnostics are lacking. Rapid diagnostics would facilitate recruitment to clinical trials and improve clinical practice.	◗	◗
There is a lack of incentives (i.e. financing) to create platforms to track and forecast resistance patterns. Therefore resistance potential is insufficiently addressed in antibiotics discovery and development methodology. Such a platform would respond in a coordinated way to the uncertainty inherent in the unpredictable rate of resistance progression. The response needs to take place in advance of resistance reaching crisis.	○	◗
Clinical trials issues		
There is a lack of established clinical trial networks and infrastructure in areas of greatest resistance which makes site recruitment and retention more difficult and expensive. This is in a way a vicious circle: the limited number of new antibiotics over many years also means that there are few sites with antibiotics trial experience.	○	○
Declining investigator and patient participation rates makes later stage antibiotics development more demanding.	●	●
In clinical trials of severe infections, it is challenging to demonstrate benefit specifically attributable to the antibiotic given many co-morbidities in population with highest unmet need. (This is also true for many drugs other than antibiotics.)	○	○

2. Industry structure issues

Root causes	Literature	Survey
Academic studies are not necessarily conducted under conditions required for regulatory compliance or industrial application.	◗	◗
Academic researchers' incentives to publish can run counter to industry desires to preserve and protect IP.	◗	●

Root causes	Literature	Survey
Single-drug companies tend to pursue lower-value drug candidates than companies based on a discovery platform. A narrow range of project increases risk.	○	●
There is a knowledge gap, and there are also lack of shared objectives, between pharmaceutical companies and venture capitalists on the one hand and the academic research community on the other. The former are unaware of what is going on in research, and the academic researchers are unaware of which products have the greatest commercial potential.	◗	●
From an SME point of view, Venture Capitalists display certain behavior that creates challenges for SMEs: - VCs have limited expertise of the antibiotic field to be able to identify the true potential of an antibiotic venture - VCs demand business models with short-term returns which are unfeasible for SMEs working on antibiotics - there is a communication and goal mismatch between VCs and antibiotic SMEs, with the former focusing exclusively on financial returns and the latter focusing to a large extent also on medical needs rather than financial forecasts and performance - risk aversion and limited expertise of VCs seem to induce a particular herd behavior whereby VCs invest in a particular area only after some other VCs has already done it.	●	●

Secondary causes	Literature	Survey
It is difficult for SMEs to find partners for late-stage clinical trials due to unpredictable commercial returns for investors.	○	◗
Industry consolidation has resulted in a major decrease in the hunt for novel antibiotic agents	◗	○
Industry has reduced R&D efforts in antibiotics.	●	●
Lack of robust investment in the antibiotics development space over the past 15 years and exit of many pharmaceutical companies from this space, has resulted in deterioration of the development infrastructure and declining number of experts across basic research, clinical microbiology, and among infectious disease physicians.	◗	●

Secondary causes	Literature	Survey
Single-drug companies tend to pursue lower-value drug candidates than companies based on a discovery platform. A narrow range of project increases risk.	○	●
The limited number of big pharma from the antibiotics field means few potential exit partners for SMEs, which in turn diminished bargaining power for SMEs.	○	◗

3. Challenges in antibiotics R&D financing

Root causes	Literature	Survey
There is a funding gap for optimization and toxicity studies and other early stage activities. It is too applied for science funders and too 'basic' for venture capitalists.	●	●
Clinical Research Organization fees are costly to SMEs, and clinical trials are costly as such, in particular for narrow-spectrum products.	●	●
There is a high barrier of entry for companies wishing to enter the antibiotics field, due to large initial costs of building up the internal competencies and equipment.	○	◗

Secondary causes	Literature	Survey
Higher predictability and profitability of treatments for other diseases, as well as high R&D costs for antibiotics, create high opportunity costs, i.e. it becomes difficult to prioritize antibiotics R&D.	●	●
Low valuation makes it difficult to attract investors to SMEs at early stages, when uncertainty of regulatory approval is very high.	◗	◗
Low revenues increase the sensitivity to cost of antibiotics R&D.	○	○
Various regulatory issues increase costs, unpredictablity, and risk (see Section 5).	●	○

4. Low revenues accruing to antibiotics developers, and market risks

Root causes	Literature	Survey
Antibiotics prices do not reflect their life-saving potential and societal value. For instance, antibiotics are generally priced at a lower level than treatments in	●	●

other therapeutic areas or for other infectious diseases, such as the recently launched drugs against hepatitis C infection. No premium is placed on having new products as "insurance" against resistance. For example, the fact that resistant N. gonorrhea clones are present 1% of the cases indicates that a serious resistance problem is imminent. Nevertheless, it is not until the resistance rate passes the 2% threshold that it becomes a public health priority, which would then improve the commercial potential for a targeted antibiotic.		
Although the antibiotics market as such is big, it is fragmented into multiple segmented markets. Thus, the markets for each of the different drugs can be comparatively small.	●	○
Competition from generics keeps prices low and limits market size.	●	●
Stewardship properly limits uptake of new antibiotics, especially the most clinically valuable drugs, but this leads to lower revenue and decreased attractiveness to pharmaceutical companies. For instance, new therapies are relegated to later line of therapy leading to lower sales in the early years of launch.	●	◗
Budget constraint in the hospital setting related to the use of DRG (Diagnosis-Related Group), fixed hospital pharmacy budget, and challenges in obtaining central funding encourage use of the cheapest drug and limit hospitals in adopting use of new and more expensive antibiotics. Such bundled payment arrangements imply that the hospital is reimbursed at a rate determined by the diagnosis and not actual cost of treating the patient.	●	●

Secondary causes	**Literature**	**Survey**
It is difficult to command premium prices as non-inferiority studies (comparing to generics) are the predominant regulatory pathway. Because superiority is not demonstrated, reimbursement authorities often use generics as comparators for reference prices.	○	○
SMEs have limited options for exit due to the small number of pharma companies in the antibiotics field. This also weakens their bargaining power in acquisition negotiations.	○	◗

Secondary causes	Literature	Survey
The lack of real-world evidence increases the risk of lower price or limited uptake by the hospitals. Hospitals demand that the benefits of a new antibiotic demonstrated in clinical trials are replicated in real world setting, due to the difference between clinical trial population and real life hospital population (e.g. in clinical trials patients receive new antibiotic treatment within 96 hours, while in real-life patients may receive new antibiotic treatment beyond 96 hours). It is difficult to show real-world evidence that a new antibiotic is superior to existing antibiotic in treating resistant bacteria, due to lack of rapid diagnostics and stewardship.	○	○
It is challenging to recruit patients with resistant infections in clinical trials due to low number of patients and lack of available rapid diagnostics, which means it is unlikely sufficient numbers will be included in the studies to demonstrate statistical superior outcomes. In turn, this results in lack of evidence to support reimbursement.	●	○
Targeting a specific resistance mechanism reduces market size, and currently reimbursement and pricing authorities do not properly value such a targeted approach.	●	○
It is difficult to forecast market size for novel/pathogen-specific drugs due to unpredictable resistance trends and uncertainty in clinical adoption.	◗	◗

5. Regulatory and legal issues

Root causes	Literature	Survey
There are very few regulatory agencies outside EU and US who have integrated the concept of streamlined development in their guidelines, i.e. there is a lack of regulatory harmonization globally.	●	◗
Antibiotic trial designs are often non-inferiority with the active comparator being the current standard of care. This does not demonstrate clinical superiority to generic antibiotics and subsequent economic benefits. Lack of clear clinical differentiation leads to greater reimbursement risk.	●	○
There are no clear guidelines for some indications including bacteremia, endocarditis, and bone and joint infections.	◗	○
The regulatory pathway for pathogen-specific drugs is unclear. It is not clear how to implement clinical trials by pathogen for pathogen specific drugs. This adds considerable risk to developers of these approaches.	○	○

There are missing guidelines for conducting clinical trials in resistant patients.	○	○
There are missing guidelines for some products, such as preventative, non-bactericidal, and other 'breakthrough' technologies.	○	●
Under the current guidelines, the developer has to study the effect of the drug on each site of infection separately, i.e. for an antibiotic drug candidate it is required to demonstrate its effect on infections in different organs or body parts (e.g. urinary tract infection and blood stream infection). For pathogen-specific antibiotics (e.g. antibiotic that covers only acinetobacter), this requirement makes clinical trials long and difficult to enroll since the antibiotic only covers a small subset of infections.	◗	◗
Some guidelines are not feasible or pragmatic (for example: FDA's guidance on HAP/VAP (Hospital/Ventilator Associated Pneumonia) requires that mortality is the primary outcome endpoint. Commonly, these indications occur in very sick patients, and in many cases the patient dies despite having cleared the infection).	○	○
The labelling of a drug influences physicians' and payers' perception of the superiority of an antibiotic. While there has been significant progress over the past couple of years in US and EU to streamline development of antibiotics for unmet needs, there is a lack of clear regulatory guidelines on how to design clinical trials in a pragmatic way (e.g. required number of patients with resistant infections, which could be rare and difficult to recruit) to ensure appropriate labelling of superiority in treating resistant infections. Specifically, lack of superiority claim in the label increases the hurdle for favorable assessment by payers.	○	○
High patent costs is a burden for SMEs	○	◗

6. Access issues

Root causes	Literature*	Survey
There are differing standards of care between countries.	○	○
Restrictions on hospital formulary across countries restrict access to novel antibiotics. High priced agents will face restrictions to limit overall budget impact and lead to reduced access or potentially no access for patients.	○	○
There are weak health systems in low and lower middle income countries (LICs/LMICs), which impedes uniform access across all population groups and regions.	○	○

Root causes	Literature*	Survey
There is a general lack of public investment in health systems in many LICs and some LMICs, and high competition for existing investment, such as co-financing commitments for vaccines, HIV/TB/Malaria drugs.	○	○
There are weak or nonexistent regulatory systems in low and lower middle income countries.	○	○
There is a lack of procurement capabilities in low and lower middle income countries.	○	○
Access is often driven by donor funding of initiatives. Funding in this area is typically "short-term", i.e. 3-5 years, which can make markets unpredictable from a pharmaceutical R&D perspective.	○	○
Uncontrolled over-the-counter access to antibiotics and even advanced antibiotics (cephalosporins) without prescription drives resistance.	○	○
Generic antibiotics are of uneven quality in many low and lower middle income countries.	○	○
High prices contribute to reducing access in low and lower middle income countries.	○	○

List of references for literature review

Adams C, Brantner V (2006). Estimating the cost of new drug development: is it really $802 million? Health Affairs, 25:420–428.

Alemayehu D., Quinn J., Cook J., Kunkel M. & Knirsch C. A. (2012) A Paradigm Shift in Drug Development for Treatment of Rare Multidrug-Resistant Gram-Negative Pathogens. Clinical Infectious Diseases 2012;55(4):562–7.

Bridging the Gap (2012). Overcoming Bottlenecks in the Development of Therapeutics for Infectious Diseases - Workshop Summary Report. National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Chopra I et al. (2008). Treatment of health-care-associated infections caused by Gram-negative bacteria: a consensus statement. Lancet Infectious Diseases, 8:133–139.

DiMasi J et al. (2003). The price of innovation: new estimates of drug development costs. Journal of Health Economics, 22:151–185.

DiMasi J et al. (2004). Assessing claims about the cost of new drug development: a critique of the public citizen and TB Alliance reports. Boston, MA, Tufts Center for the Study of Drug Development, Tufts University (http://csdd.tufts.edu/files/uploads/assessing_claims.pdf, accessed 26 April 2010)

Finch R, Hunter P (2006). Antibiotic resistance – action to promote new technologies: report of an EU Intergovernmental Conference held in Birmingham, UK, 12–13 December 2005. Journal of Antimicrobial Chemotherapy, 58:3–22.

Frank RG (2003). New estimates of drug development costs. Journal of Health Economics, 22:325–330.

Friedman, D. & Alper, J. (2014). Technological Challenges in Antibiotic Discovery and Development: A Workshop Summary. Chemical Sciences Roundtable; Board on Chemical Sciences and Technology; Division on Earth and Life Studies; National Research Council

Global Alliance for TB Drug Development (2001). The economics of TB drug development. New York, NY, Global Alliance for TB Drug Development (http://www.tballiance.org/downloads/ publications/ TBA_Economics_Report.pdf, accessed 26 April 2010).

Harbarth S., Theuretzbacher U., & Hackett J. (2015) Antibiotic research and development: business as usual? Journal of Antimicrobial Chemotherapy Advance Access, 70(6):1604-7.

Howell L. (ed.) 2013 World Economic Forum Global Risk Report 2013. Eighth Edition. Insight Report.

Katz, M. L., Mueller, L. V. Polyakov, M. & Weinstock, S. F. (2006). Where have all the antibiotic patents gone? Nature Biotechnology, 24:1529–1531.

Kraus, C. N. 2008. Low hanging fruit in infectious disease drug development. Current Opinions in Microbiology, 11(5): 434–438.

Laxminarayan R, Powers JH. (2011) Antibacterial R&D incentives. Nature Reviews: Drug Discovery, 10(10):727-8.

Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O. (2014) Antibiotic resistance—the need for global solutions. Lancet Infectious Diseases. 13(12):1057-98.

Love J (2003). Evidence regarding research and development investments in innovative and non-innovative medicines. Washington, DC, Consumer Project on Technology.

Morel C. & Mossialos E. (2010) Stoking the Antibiotic Pipeline. BMJ 2010;340:c2115

Mossialos, E. (2010) Policies and incentives for promoting innovation in antibiotic research, European Observatory on Health Systems and Policies.

NIAID (2014). NIAID's Antibacterial resistance Program: Current Status and Future Directions. Report.

O'Neill Commission (2015). Securing New Drugs for Future Generations: The Pipeline of Antibiotics. The Review on Antimicrobial Resistance.

Outterson, K., Samora, J.B., & Keller-Cuda, K. (2007). Will longer antimicrobial patents improve global public health? Lancet Infectious Diseases, 7(8): 559-66.

Payne D et al. (2007). Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nature Reviews Drug Discovery, 6:29–40.

Payne D. J., Federici Miller, L., Findlay D., Anderson J. & Marks L. (2015) Time for a change: addressing R&D and commercialization challenges for antibacterials. Phil. Trans. R. Soc. B 370: 20140086.

Payne, D. J., Gwynn, M. N., Holmes, D. J. & Pompliano, D. L. (2007). Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nature Reviews, Drug Discovery.

Poupard J (2006). Is the pharmaceutical industry responding to the challenge of increasing bacterial resistance? Clinical Microbiology Newsletter, 28:13–15.

Power E (2006). Impact of antibiotic restrictions: the pharmaceutical perspective. Clinical Microbiology and Infection, 12:25–34.

Pray L (2008). Antibiotic R&D: resolving the paradox between unmet medical need and commercial incentive. Needham, MA, Cambridge Healthtech Institute (Insight Pharma Reports).

Projan S. (2003). Why is big pharma getting out of antibacterial drug discovery? Current Opinion in Microbiology, 6:427–430.

Projan, S. J., & Shlaes. D. M. (2004). Antibacterial drug discovery: is it all downhill from here? Clinical Microbiological Infections, 10:18–22.

ReAct (2011). Collaboration for Innovation The Urgent Need for New Antibiotics. ReAct policy seminar, Brussels, 23 May 2011.

Renwick M., Brogan D., & Mossialos E. (2014) A Critical Assessment of Incentive Strategies for Development of Novel Antibiotics. Report, LSE.

Royal Society (2008). Innovative mechanisms for tackling antibacterial resistance. London, The Royal Society (RS Policy Document 14/08) (http://www.bsac.org.uk/_db/_documents/ Innovative_mechanisms_for_tackling_antibacterial_resistance.pdf, accessed 26 April 2010).

Rubin P (2004). The FDA's antibiotic resistance. Regulation, 27:34–37.

Silver, L. (2011a). Scientific Obstacles to Discovery of Novel Antibacterials. Background document commissioned by ReAct for the seminar "Collaboration for Innovation – The Urgent Need for New Antibiotics", Brussels May 23 2011.

Silver, L. L. (2011b). Challenges of Antibacterial Discovery. Clinical Microbiology Reviews, 24(1): 71-109.

Spellberg B (2008a). Trials and tribulations of antibiotic development. Lancet Infectious Diseases, 8:209.

Spellberg B (2008b). Antibiotic resistance and antibiotic development. Lancet Infectious Diseases, 8:211–212.

Spellberg B., Bartlett J., Wunderind R. & Gilbert D.N. (2015). Novel Approaches Are Needed to Develop Tomorrow's Antibacterial Therapies. American Journal of Respiratory and Critical Care Medicine, 191(2): 135-140.

Spellberg, B., Powers, J. H. Brass, E. P. Miller, L. G. & Edwards, J. E. Jr. (2004). Trends in antimicrobial drug development: implications for the future. Clin. Infect. Dis. 38:1279–1286.

Stewart P, Costerton J (2001). Antibiotic resistance of bacteria in biofilms. Lancet, 358:135–138.

Wright G.D. (forthcoming) Solving the Antibiotic Crisis. ACS Infectious Diseases.

Zorzet, A. (2014). Overcoming scientific and structural bottlenecks in antibacterial discovery and development. Upsala Journal of Medical Sciences, 119(2): 170–175.

List of references for additional literature review

Baltz, R.H., (2006). Marcel Faber Roundtable: is our antibiotic pipeline unproductive because of starvation, constipation or lack of inspiration? Journal of Industrial Microbioogy and Biotechnology, 33(7):507-513.

Center for Drug Evaluation and Research, (2010). Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. U.S. Department of Health and Human Services, Food and Drug Administration, Washington, D.C.

Hamad, B., (2010). The antibiotics market. Nature Reviews Drug Discovery, 9, 675–676.

Outterson, K., Powers, J.H., Daniel, G. W., & McClellan, M., B. (2015). Repairing the Broken Market for Antibiotic Innovation. Health Affairs (Millwood), 34(2): 277-285.

Outterson, K., (2010). The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation. Cardozo Law Review, 31, 613.

Outterson, K., New Business Models for Sustainable Antibiotics (2014). Centre on Global health Security Working Group Papers, Chatham House (The Royal Institute of International Affairs), Working Groups on Antimicrobial Resistance, Paper 1, Boston Univ. School of Law, Public Law Research Paper No. 14-10; Boston Univ. School of Law, Law and Economics Research Paper No. 14-10.

Kesselheim, A,. & Outterson, K. (2011) Improving antibiotic markets for long-term sustainability. Yale J Health Policy Law Ethics, 11(1): 101-167.

So, A.,D., Gupta, N,, Brahmachari, S., K,. Chopra, I., Munos B., Nathan, C., Outterson, K., Paccaud, J., P., Payne, D., J., Peeling, R., W., Spigelman, M., Weigelt, J. (2011). Towards new business models for R&D for novel antibiotics. Drug Resistance Update, 14(2): 88-94.

Tsouderos, T., (2010). Antibiotics caught in stalemate over clinical trials. Richmond Times-Dispatch. U.S. Government Accountability Office, (2010). New drug approval: FDA's consideration of evidence from certain clinical trials. U.S. Government Accountability Office, Washington, D.C.