Report

Antimicrobial resistance in humans and animals in low and middle income countries

How can knowledge and action be strengthened at national level?

Friday 13 – Sunday 15 March 2015 | WP1399
The rapid emergence of antimicrobial resistance (AMR) is a major global health risk with potentially immense medical, economic, and social ramifications. At a minimum, the gradual loss of effective antibiotics will undermine our ability to fight infectious diseases. Beyond that, it also places at risk other widespread, life-saving medical interventions – like surgery, organ transplantation and cancer chemotherapy. However, it has become increasingly clear that this issue runs deeper; antibiotic resistance threatens the health of animals and hence the livelihoods of farmers, the security and safety of food and the environment. It is also recognised that low and middle income countries (LMICs), where the majority of the world’s population live, will face a disproportionate burden.

The far reaching drivers of AMR mean tackling the issue requires a complex set of approaches under the One Health paradigm (humans, animals and the environment). Such responses require mobilising political action at the national and global level. Recent national and international actions have raised the political profile of AMR and there is a general consensus that we have reached a critical juncture to tackle the issue. The global nature of this threat means all countries need to coordinate a response. Resolution 67.25 adopted at the World Health Assembly (WHA) in May 2014 reflected the global consensus that antimicrobial resistance poses a profound threat to human health. The resolution requested a draft global action plan to combat antimicrobial resistance, for presentation to the World Health Assembly in 2015. It is expected that countries will develop their own national action plans on antimicrobial resistance in line with the global plan. However, in order to provide a sustainable response to AMR there are still many challenges, in particular, for LMICs.

This Wilton Park meeting convened a unique mix of expertise with the purpose of sharing experiences, concerns and knowledge regarding the challenges and opportunities for tackling AMR at LMIC level. This report sets out the main themes of discussion during the meeting.
Key points

- The discourse is increasingly evolving to recognise the importance of the One Health concept in tackling AMR. For a truly sustainable response, action must be pursued at the human, animal and environmental level to acknowledge the ability of resistance to spread through ecosystems and into the food chain. Furthermore, it is also becoming increasingly apparent that the scope of the issue necessitates the inclusion of trade, finance and development institutions in the discussions.

- The relative lack of data regarding the level, spread and patterns of resistance in human, animal and agricultural contexts prevents many countries from recognising the true extent of the problem and also prevents the formulation of evidence-based intervention design and monitoring. Whilst there needs to be increased general data collection and strengthening of surveillance and monitoring systems this must be balanced with the urgency of the issue and the requirement in many situations to implement immediate interventions to tackle AMR.

- AMR needs to be capped at the source. Behaviour change interventions need to reflect the local context and be relevant to those being targeted. Bottom-up approaches at the individual and organisational levels are essential for modifying behaviour; top-down, policy-level approaches and social measures are also needed to sustain behaviour change.

- Antibiotics need to be used judiciously but this must be balanced with the principle that people need to have equitable access to effective antibiotics and, prudently used, antibiotics are necessary for animal health.

- Choosing the right paradigms for sustainably stimulating research and development (R&D) requires new measures to align the financial incentives for drug and diagnostics development with public health needs. Understanding how the risks of drug development can be shared amongst the public and private sector will be important.

- There are inherent issues which present barriers to tackling AMR in LMICS, such as the fragile state of health systems, poor infrastructure, poor sanitation, weak leadership capacity and competing priorities.

- There is a need to ensure that the future growth of populations and intensification of livestock production due to an increased desire for protein-based foods are met with intelligently designed systems and a focus on improved biosecurity and better husbandry practices.

- The cross-cutting nature of AMR means as an issue it often suffers from a lack of leadership. In building effective advocacy and awareness the role of champions, civil society and forming multi-sector alliances and networks are all key elements to effective policy change.

- The complexity and far-reaching drivers and impacts of AMR make action particularly challenging in countries with already stretched resources. Nations will benefit from developing a coherent set of priorities and actions based on what resources they do have, these can eventually be scaled up; capitalising on existing efforts where possible and forming regional alliances can help countries achieve their goals.

- Resistant microbes do not respect borders. The need to tackle the problem in a coordinated global way is key. Defining what a coordinated global response looks like is essential. Some of the key elements of a global response include raising the political profile of AMR, lesson learning from other countries, awareness raising at the national, regional and international level, sharing positive and negative experiences and establishing guidelines. Notwithstanding

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the importance of differing contexts, there are many similarities in the gaps and challenges countries face and in the possible responses.

Context: a complex, multi-sector issue

AMR is a fundamental and growing global health threat. According to the initial report produced in December 2014 by the Review on AMR, chaired by Jim O’Neill, up to 10 million people per year could die by 2050 due to resistance, compared to an estimated 700,000 deaths annually at present. Furthermore, this figure does not capture the indirect impacts of AMR beyond the risk to mortality; economic losses due to reduced productivity caused by sickness and higher costs of treatment, the effects on animal health, the effects on the livelihood of millions of producers that rely on livestock, poultry and fish, the effects on food security, food safety and environmental risks. The complexity of this issue is impacted by the broad and multi-sector drivers that are believed to be exacerbating resistance across the human, animal and agricultural/environmental sectors. Compounded by the lack of available new antibiotics and limited research into alternatives AMR is a global problem, however, it is clear that LMICs will face a significant and disproportionate burden.

Despite an incomplete evidence base, it is recognised that the main areas that need to be tackled are poor stewardship and inappropriate use of antibiotics, improving data and surveillance of resistance, infection prevention and control, raising awareness and advocacy building for AMR, increased R&D of new antibiotics or alternative treatments and fostering coordinated national, regional and international responses under the One Health paradigm. Some countries have already taken steps to tackle these themes, albeit with varying levels of success, but there are key lessons that can be transferred.

The complexity of tackling AMR is highlighted by the fundamental questions we are still grappling with; for example, how do you change cultural norms regarding antibiotic use? How do we achieve sustainable use of these medicines with a growing population and market demands for increased animal products? How can the risks for new drug development be shared? Addressing these issues poses a number of key challenges for LMICs, in particular, those with already over-stretched fragile health systems, poor infrastructure and few resources to devote to tackling AMR.

Providing the evidence base: data, surveillance and monitoring

1. There is still insufficient evidence regarding the current use of antibiotics and prevalence of AMR. Despite a number of studies underway, there is currently limited understanding of the role of agriculture in antibiotic resistance, and data for resistance in aquatic and companion animals is lacking. Furthermore, the level of data collection and surveillance has not captured the full scope of the issue, in particular in recognising the ability of microbes to transfer through ecosystems to affect humans and animals. Whilst it is important to capture the specific contributions of different sectors in terms of resistance it is essential to view resistance within the One Health paradigm to help design sustainable, comprehensive solutions to tackle the problem.

2. The availability of data can be a key driver for engaging governments on the issue. Both the South African and Canadian governments mobilised resources to tackle AMR once they were presented with the reality of the situation in their local context. In addition, national-level evidence is a driver for governments to mobilise resources and foster political action. In Thailand, teaching hospitals were encouraged to replicate studies from neighbouring countries looking at rates of resistance to highlight the similarities.

3. There is a tension between expediency versus quality and quantity regarding the collection of data. The need to ensure a reliable scientific basis for evidence-based decision making must be balanced with the urgency of the issue and a requirement, in many cases, to begin implementing responses immediately.
4. The issue of poor infrastructure for data collection and surveillance and the sheer scale of data that should be collected is a challenge for many countries. However, where possible, starting in a small and focused way can provide enough information for action. Ghana began data collection by focusing on the resistance to 5 key antibiotics which they will then use to inform monitoring practices. Once countries begin to collect data a network can then be established. China instituted a national monitoring network in 2004 involving just 15 tertiary hospitals; this has now grown to involve 1427 tertiary and secondary hospitals and consists of sub-monitoring networks.

5. Much emphasis is placed on the requirement to guarantee data collection and for monitoring to be transparent and made available in electronic form to ensure it can be used in the most effective way possible by all stakeholders.

6. Monitoring data will be an essential component for lesson learning regarding the success of various interventions, an area which is lacking much attention.

7. Data regarding the role of tourism and medical tourism in the spread of AMR presents a major gap and therefore creates a lack of understanding as to how this is contributing to the global picture of AMR.

8. Capitalising on existing data collection mechanisms and surveillance infrastructure is one way to make rapid gains on data collection for AMR. Partnerships already exist looking at counterfeit medicines which could be expanded upon to look at antibiotic quality, and microchips used to monitor livestock movement and track thefts could also be used to monitor AMR. The possibility of integrating surveillance mechanisms to include both animals and humans is also an efficient way forward, as seen in Kenya with the FAO/WHO integrated surveillance programme of food-producing animals and humans.

9. Lessons can be learnt from malarial resistance data sharing, for example in the South-East Asia region, where a great deal of emphasis was placed on the importance of sharing data at the regional level to provide bigger picture analysis of resistance. Linking up national systems to regional monitoring is seen as a priority for AMR and a robust sustained network of sentinel sites is seen as key to providing this.

**Behaviour change: responsible and prudent use of effective antibiotics**

10. There is a tension between access and excess. Access to effective antibiotics is still an issue for many, whilst in certain settings antibiotics can be obtained and used freely with little or no effective regulation. Decisions surrounding how to ensure antibiotics are used prudently need to be founded on principles of equity.

11. Behaviour change on both the supply and demand side (prescription, dispensing and use) is required to ensure antibiotics are used appropriately. Furthermore, factors such as the strength of the health system, the existence of both private and public health systems, informal health markets and the migration of people/livestock, all need to be taken into context. Poor use cannot simply be 'regulated', 'reformed' or trained away and despite poor education and training of antibiotic use, behaviour change will only partly be achieved through effective education. Attention needs to be paid to the complex interplay of knowledge, attitudes and behaviour and to the contextual influences emanating from specific health-care settings and communities. Multifaceted, multilevel interventions are essential.

12. Inherent to the rational use debate is the issue of medicine quality; the availability of substandard antibiotics in both the human and animal sector is a significant problem. Strong regulation needs to be supported by testing laboratories and this should be achieved at the regional level which will foster sharing of data but also sharing of training.

13. There is a need to be mindful of the growing rise in livestock production required to
Estimates suggest that without any policy change there will be a 60% rise in the use of antibiotics in livestock in the next decade. How can the increasing demand for animal protein be met without causing a tension between tackling antibiotic resistance and ensuring future food security? Since many antibiotics commonly used in sub-therapeutic concentrations are the same as or similar to antibiotics used in human medicine there is a serious threat to public health. Tackling the use of antibiotics as growth promoters is a key area of intervention, but efforts focusing on the prescription of antibiotics should be attentive to the way antibiotics are used in rural communities and by pastoralists, for example. Whilst prudent use of antibiotics is required in all sectors, it is important that policies do not undermine efforts in other areas.

14. Countries such as the Netherlands, China, and the UK have all set targets in terms of antibiotic use in certain sectors. The Netherlands declared a target of 20% reduction in veterinary use in 2011, then a 50% reduction in 2013. For the UK, in primary human healthcare the target is to reduce the number of antibiotic prescriptions by 1% (from 2010) whilst reducing antibiotic prescription from certain classes by 10%. Targets are thought to be useful for mobilising action despite the agreed target levels not always being evidence-based.

15. Unannounced inspections, antibiotic use audits and restriction on antibiotics that can be prescribed are all measures that are being implemented in various contexts.

16. In response to anti-malarial resistance in South-East Asia, availability of medicines was limited to hospitals and malaria clinics whilst certain anti-malarials were kept out of circulation and regimens were changed. There are lessons to learn from this. In Canada certain antibiotics have been categorised as ‘category 1’ drugs now reserved solely for human applications.

17. Health systems that reimburse doctors for prescribing antibiotics need to be changed. In China this system was approached by “pay for performance” incentives, but there is some question as to the success of this method. Where doctors feel pressure from the public to prescribe, the use of diagnostics should be relied upon. In Thailand, such measures have been employed in surgeries where patients can distinguish between bacterial and viral infections themselves with the aid of diagnostics.

18. The value of more punitive measures to change behaviour, such as through ‘name and shame’ type exercises needs further exploration. The Netherlands employed a penalty system for those vets who were prescribing inappropriately with success.

19. In Thailand the Antibiotics Smart Use (ASU) program used a phased program approach to change behaviour. During phase 1 (2007–2008), behaviour change interventions targeting antibiotic prescription practices were implemented and assessed; in phase 2 (2008–2009), the feasibility of scaling up the programme was examined; in phase 3 (2010–present), in progress, steps are being taken to identify mechanisms for programme sustainability. The behaviour change interventions operated on the supply and demand side and were all adapted to the local context of the hospital physicians. The overall strategy involved educational materials for health professionals for display or distribution to patients, along with instructions on their proper use. Health-care workers were told, for example, to display posters or play DVDs in waiting areas and to distribute brochures to patients during consultations. They were also given ASU treatment guidelines for upper respiratory infections, diarrhoea and simple wounds, posters showing diagnosis and treatment algorithms, and diagnostic tools such as white light illuminators for throat examination. Hospitals received seed money for project implementation and evaluation.

20. Bottom-up approaches at the individual and organisational levels are essential for modifying behaviour; top-down, policy-level approaches and social measures are also needed, on the other hand, to sustain behaviour change. A policy that does not reflect the many facets and complexities of AMR within the country context and focuses solely...
on creating strict guidelines will not work; an implementable strategy and not necessarily a perfect policy is the way to achieve meaningful change.

**Infection prevention and control**

21. The close relationship between animals, humans and the environment, as emphasised with examples of livestock and pastoralists and companion pets and their owners, present intensive microbial exchange pathways. Notwithstanding the need to ensure infections are contained within human and animal medicine, there is a requirement to view infection prevention and control in a more holistic manner to acknowledge the ability of resistance to spread through ecosystems and into the food chain.

22. There is still concern that despite the need for better infection prevention and control in combating resistance, many LMICs still grapple with poor sanitation issues and have fragile health systems which need strengthening in order to tackle resistance. Consideration needs to be given to ensuring strengthening these systems is included in the discourse of AMR. The post-2015 Development Agenda is seen as a key opportunity for countries to ensure health infrastructure features as a priority; this will be essential for sustainable AMR responses.

23. Ensuring systems of agricultural production and the intensification of livestock production incorporate improved biosecurity and better husbandry to decrease the need for antibiotic use is the key to the future sustainability of tackling AMR. Areas of bad design in these systems need to be identified and addressed.

24. Simple messages to target improved hygiene practices for infection prevention should be the foundation of any response. In Ghana, hand washing campaigns targeted at children were successful in transferring knowledge from children to parents; the challenge then arises with building on this to target institutes and hospitals.

25. Infection prevention presents a major opportunity for technological investment, for example with rapid diagnostics, as encouraged by the Longitude Prize, a £10m UK led challenge to find a cheap, accurate, rapid and easy-to-use test kit for bacterial infections, and for improved sanitation. Provided they are suitable for LMIC settings, a spectrum of tools and technologies could have an impact. Vaccination also has an important role in tackling AMR.

**Awareness building and advocacy**

26. Due to the cross-cutting nature of AMR and complexity of the issue one of the biggest challenges is building awareness and advocating for the issue.

27. It is essential to find ways to energise the public on the issue of AMR; local evidence is key to make AMR personal and encourage action, this also needs to be tempered with effective risk communication messages. The most effective methods and vehicles for this communication need to be found. The message of food safety and encouraging public demand for animal products that are free from antibiotic residues is an area with promise.

28. Mobile technology has an important role to play in raising awareness and transferring key messages in particular to rural communities and mobile livestock owners.

29. Many lessons can be learnt from other disease areas, in particular efforts in TB and HIV advocacy. Malaria advocacy relied on ensuring messages were customised at the country level. For AMR, the economic case is incontrovertible and seen as a key message, China is currently using the economic argument to drive action forward. For the Netherlands there was an element of national pride that helped foster action to tackle the high levels of antibiotic use in agriculture.

30. One of the key barriers for advocacy is funding. Many donors seek quantifiable outcomes, but for AMR many of the efforts will be focused on influencing policy and
30. There is a strong view that for AMR a political movement to create awareness for change is required.

31. There is concern that opportunities are not being seized which could highlight many of the simple messages key to tackling resistance at the patient level, for example Ebola is a One Health issue that could be used to highlight other infectious threats. Likewise, such opportunities should be used to sustain the momentum of AMR awareness campaigns.

32. Much emphasis is placed on the importance of champions in serving as ambassadors for the cause and facilitating collective action; champions have the ability to raise awareness across sectors, encourage countries to take initiative and scale up actions.

33. The Chennai Declaration in India demonstrated the important elements for effective awareness raising leading to policy change. Since its publication in December 2012; the Declaration has had an unprecedented and unexpected impact at national and international levels. The Chennai Declaration is the consensus that evolved from a meeting organised by medical societies in India, including representatives from of governmental bodies such as the office of Drugs Controller General of India, Medical Council of India, National Accreditation Board of Hospitals, and Indian Council of Medical Research. The Declaration consists of realistic goals and objectives to tackle AMR, with a deep understanding of the background Indian scenario. Perseverance, persistence and the use of the media to create pressure on governments was essential in the first stages of the advocacy effort, in order to gain traction on the issue of AMR and the suggestions of the Declaration. This was then built on by engaging with other interested parties and creating a network of stakeholders to apply political pressure. There is a strong view that for AMR a political movement to create awareness for change is required.

34. Civil society can play a vital role in generating awareness of AMR. In South Africa the civil society movement have played a key role in taking forward the AMR issue in the absence of government action in the form of the South African Antibiotic Stewardship Programme. More recently, the government has driven efforts on the ground as space to focus on AMR has been made.

Innovation: new antibiotics, alternative treatments and research

35. Any efforts to conserve existing antibiotics need to be complemented by the development of new ones. Returns on investments in antibiotics can be less attractive to pharmaceutical companies than for traditional blockbuster drugs taken by many people, every day, for long periods and are patent protected. Measures to restrict antibiotic use in order to mitigate the development of resistance are a further disincentive to investing in R&D. Currently, the incentives for pharmaceutical companies to develop and manufacture new antibiotics are limited. There is a consensus that in the case of antibiotics providing a global good should not depend solely on profit but profit needs to be present in order for antibiotics to be produced. Therefore opportunities for sharing the risks of development amongst the public and private sector need to be explored. Canada plan to support innovation through a government collaboration with industry and smaller pharmaceutical companies. A new sustainable business model is key to fuelling antibiotic development in the future.

36. Diagnostics have an important complementary role to play. They are particularly needed to avoid the unnecessary use of antibiotics as a result of pressure from patients or the absence of precise diagnosis. A spectrum of tools and technologies, particularly low-cost rapid diagnostic technologies, could have a significant impact in LMIC settings.

37. Research into new treatments needs to be dovetailed with more research into antibiotic resistance itself; there is a potential role here for genomics and epigenetics.
attention was given to projects such as the novel large-scale experiment between IBM and Mars, Inc., which is producing a "microbial baseline" to understand what triggers contamination and the spread of disease in food globally.

38. Financing and incentivising the production of new antibiotics, alternative treatments research and diagnostics represent only one side of the problem. The regulatory environment can also be a major constraint to development. In which case consideration needs to be made to ensure regulatory mechanisms are re-engineered to enable products to get to market. The Review on AMR, chaired by Jim O’Neill announced by the UK Prime Minister in July 2014 is exploring and developing recommendations on these themes.

Fostering a coordinated response; national, regional and global approaches

39. One of the hurdles at the national, regional and global levels is the lack of coordination and governance in tackling AMR.

National

40. Within countries, one of the key challenges is the lack of communication between responsible ministries; the fact that AMR is a cross-cutting issue and does not have a recognised "home" within government means clear leadership and responsibility are often lacking. Inherent to this is the tension that can exist between ministries regarding ownership, varying mandates, competing priorities, responsibility and funding for the issue. In countries where political leadership changes regularly the sustainability of the issue on the political agenda can wane. A key goal is to build a collaborative spirit and a platform within government from which this issue can be tackled. In the UK, the appearance of AMR on the National Risk Register means the problem will be dealt with as a cross-cutting issue and will remain so regardless of any governmental changes. Kenya’s national authorities established an inter-ministerial task force, uniting human health, animal, fisheries communities etc. Canada is taking a One Health approach and developing a Federal Framework for Action on AMR, linking up with other sectors through an External Advisory Group on AMR. Sweden started their approach by focusing on the human side of the problem initially and then engaged the animal health and agricultural stakeholders to slowly build up the network.

41. Much emphasis is placed on leadership and coordinating collaborations. For example, in Thailand the ASU model used a modified ‘starfish model’, in which management has no hierarchical leadership. The local partners include physicians, pharmacists, nurses, health volunteers, local administrators and community leaders who promote the rational use of antibiotics in their health-care settings and communities. They name their own projects and design their own methods for improving the use of antibiotics among health professionals and the public. The central partners play catalytic and supportive roles; they guide and harmonize activities across local partners and disseminate examples of good practice and success stories drawn from local partners. In this manner, ASU gradually came to be owned by the local partners, who work with central partners as part of a collaborative network designed to translate the concept of ASU into practice.

42. Notwithstanding the importance of a coordinated global response, cultural norms are not global and the importance of instituting national action plans to reflect the true needs of nations and interventions that will address the specific behaviours within countries are essential.

Regional

43. Efforts to align at the regional level should involve activities to share expertise, resources, training and technical assistance. The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was created in 2009 with the goal of improving cooperation between the U.S. and the EU in three key areas: (1) appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities, (2)
countries are essential.”

prevention of healthcare and community-associated drug-resistant infections, and (3) strategies for improving the pipeline of new antimicrobial drugs. Similarly, the Global Health Security Agenda is an effort by nations, international organisations, and civil society to accelerate progress on various global health security priorities. AMR forms one of the action packages. GHSA activities are being conducted in collaboration with relevant local, national, and international stakeholders and in coordination with the activities of the WHO, FAO, OIE, and International Criminal Police Organisation (ICPO-INTERPOL) as part of a time-limited project to look at how collaborative efforts can achieve national gains.

44. The Caribbean Public Health Agency (CARPHA) is an example of a regional agency which includes collaboration on tackling AMR as part of its remit. Set up in 2013 it works with 24 member countries. CARPHA and Public Health England (PHE) are exploring efforts to collaborate across regional boundaries. CARPHA and the PHE have combined their efforts to strengthen public health laboratories in the Caribbean region through a twinning and partnership initiative to share expertise and knowledge in the area of AMR.

International

45. There is consensus that the scale and complex, interwoven nature of AMR is still not captured at the international level. Many of the key stakeholders from environment, trade, finance, food safety and food security are still not part of the current discourse. The FAO-WHO-OIE tripartite covers human and animal health but the environmental angle is absent from this international collaboration. Considering the inclusion of the United Nations (UN) Environment Programme would be beneficial and potentially even the UN Development Programme to align the importance of prioritising health infrastructure with AMR. The World Bank could also play a role in financing countries to implement their own national action plans. Involving ministers of finance in the issue and reaching out to trade and finance institutions is seen as a key step.

46. There is genuine concern that international efforts are not moving fast enough. The upcoming Global Action Plan, a request of the 2014 WHA resolution on AMR, will be presented at the WHA in May 2015 and is seen as a key event to engage national governments and stakeholders on AMR, and to foster international collaboration and meaningful efforts at the national level. Efforts need to consistently align with the One Health agenda.

47. AMR is not a new issue, nor a rapidly solvable one, and therefore capturing the urgency of the issue while maintaining longer-term interest is challenging. Understanding how more visibility can be brought to AMR is a key goal. Are there areas that are more urgent than others or where rapid wins can be identified?

48. A major opportunity at the international level is to establish an understanding of what works at the practical level to tackle AMR. International collaboration would also benefit from a system of peer assessment and mentoring arrangement on national actions to provide more evidence on what is working at the national level.

49. Whilst the issue of leadership, norm setting and legitimacy is seen as an unmet need for AMR the idea of creating an international super agency is not seen as an ideal way forward. However, some capacity dedicated to drawing the threads together and connect people at the international level would be beneficial, for example an envoy.

50. Consideration of what cooperation should look like at the international level is important. It could involve expanding research efforts across regions, instituting Commonwealth twinning projects, an expansion or alignment of the UK longitude prize with similar initiatives funded by other countries, or creating a collaborative research laboratory similar to CERN. Similarly, countries need to discuss if a set of international guidelines would be helpful and what they might look like. Much emphasis is placed on the need for agreeing any form of guidelines to not simply distract from the issue at hand and there needs to be a genuine case for how such guidelines will change what
the response is/needs to be. The UN itself could be involved at this level to benefit from
the value of its convening power and universality; giving reassurance to countries that
their steps for action are authoritative and sensible.

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Wilton Park | April 2015

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