

Human and animal health in Europe: the view from the European Academies Science Advisory Council (EASAC) on challenges in infectious disease

ROBIN FEARS⁽¹⁾, VOLKER TER MEULEN⁽¹⁾

ABSTRACT

For the last seven years, the European Academies Science Advisory Council (EASAC) has conducted a series of projects defining and clarifying priorities for European policy in infectious disease. Both human and animal populations are increasingly threatened by emerging and re-emerging infections, including zoonoses, partly attributable to the impact of environmental change on the distributions of pathogens, hosts and vectors. Among the key challenges to be faced are the impact of climate change, the increase of antibiotic resistance and the need to develop novel global surveillance and early warning systems worldwide. Multidisciplinary approaches are required to build the new interfaces between human and animal medicine (One Health), with new connections between epidemiological and environmental data for surveillance, communication and risk assessment. This multidisciplinary involves integration between microbiology, immunology, genetics and genomics, entomology, ecology and the social sciences, among other disciplines. Improved understanding of patterns of both human and animal disease also requires commitment to standardisation of surveillance methodologies and better analysis, co-ordination and use of the data collected. There must be sustained support for fundamental research, for example to explore how pathogens cross the species barrier, encouragement for industry innovation in developing diagnostics, therapeutics and vaccines, and the increased use of scientific evidence to inform coherent strategic development across different policy-making functions and to support international leadership. Our paper is intended as an introduction to some of the issues for building collaboration between human and animal medicine, to be discussed in greater detail in the other contributions to this Issue.

Key words: Zoonoses, Antibiotic resistance, Climate change, One Health, Infectious disease surveillance

(1) European Academies Science Advisory Council, German National Academy of Sciences Leopoldina, 06018 Halle (Saale), Germany

CORRESPONDING AUTHOR: Robin Fears, European Academies Science Advisory Council German National Academy of Sciences Leopoldina, 06018 Halle (Saale), Germany; e-mail: RobinFears@aol.com

INTRODUCTION

This paper draws on work of the European Academies Science Advisory Council (EASAC) formed by the national science academies of the European Union (EU) Member States to enable

them to collaborate with each other in giving advice to European policy-makers. EASAC provides a means for the collective voice of European science to be heard, bringing together a range of skills from all relevant scientific disciplines and utilising a range of experience from diverse

national settings. EASAC addresses those topics where only action at the EU level will be effective or where there will be economy of scale and added impact in acting collectively. Our focus here is on infectious disease and our points are intended to help serve as an introduction to some of the topics which will be addressed in the other contributions to this Special Issue on "Increasing Integration between Human and Animal Medicine". Our scope relates to Europe but many of the points are of global relevance.

IMPACT OF INFECTIOUS DISEASE

There have been major advances in the treatment of infectious disease. In Europe, for example, there has been effective control of diphtheria, tetanus, *Haemophilus influenzae*, hepatitis B and measles and rubella viruses. Successful vaccination campaigns globally have eradicated smallpox and eliminated poliomyelitis from most regions. However, assumptions that most infectious diseases had been conquered were too complacent. Infectious diseases still account for about one-quarter of all deaths worldwide and represent about 10% of the total burden of disease in Europe (1). Tuberculosis is resurgent, antimicrobial drug resistance is a dramatically growing threat and there are newly emerging pathogens, especially those transmitted from animals to humans. The public health burden imposed by communicable diseases is exacerbated by the increasing mobility of humans, animals, vectors and pathogens, and by other effects of environmental change and globalisation.

During the past seven years, EASAC has undertaken a series of analytical studies in infectious disease (2, 3). Over this period, there have been significant changes in disease patterns and in the EU infrastructure for dealing with surveillance, in particular the strengthening of the capabilities of the European Centre for Disease Prevention and Control (ECDC). However, the broad scientific needs associated with setting priorities for tackling infectious disease have not changed substantially and there is still much to be accomplished. From the perspective of EASAC, among the priority tasks for addressing the health consequences of both the established and the new infectious disease threats are the following:

- ***Understanding the demographics of disease patterns*** - this requires improved,

co-ordinated surveillance procedures with networks to gather, analyse and disseminate epidemiological data.

- ***Sustaining commitment to basic research and training the next generation of scientists*** - to support fundamental science and its translation, improve interdisciplinary linkages and revive neglected scientific disciplines, streamline the regulation of clinical research and develop new research infrastructure.
- ***Reducing barriers to innovation*** - to develop new models of public-private partnership and support for smaller companies. Obstacles to the development and use of novel, smart diagnostics, therapeutics and vaccines need to be dismantled.
- ***Achieving better integration of the agendas for human and animal health*** - in surveillance, communication and risk assessment.
- ***Ensuring coherent action across different policy-making departments*** - to recognise that health issues are often very relevant to strategic decisions in other policy areas and that there must be accurate and timely communication about infectious diseases and their management to the public.

For each of these tasks, improved responsiveness to current threats needs to be combined with improved preparedness for the future: new diseases will emerge even if their specific characteristics are presently unknown. The term One Health was introduced to capture the interrelatedness between human and animal health (domestic animals and wildlife), providing a framework for seeking new linkages between medical and veterinary services in clinical care, surveillance, education and research (4). The remainder of our paper will draw on the work of EASAC (2, 3) to explore some of these priorities for developing the integrated knowledge base.

ZOONOSES – ISSUES FOR CO-ORDINATING SURVEILLANCE AND MANAGEMENT

A zoonosis is any infection that is naturally transmissible, directly or indirectly, between vertebrate animals and humans. Some agents cause disease both in the animal host and humans, others are commensal in the animal host. Approximately 60% of all human pathogens and

most of those emerging in the past few decades are zoonotic. Major changes in modern societies are creating new opportunities for infections to emerge and adapt: new zoonoses arise because of the complex interplay of multiple factors (5) from agriculture, trade, urbanisation and other changes in land use, migration, and use of medical technologies. According to the World Bank (6), the direct cost of zoonotic diseases worldwide over the last decade was greater than \$20 billion with indirect losses of more than \$200 billion to the affected economies.

In 2004, The Netherlands Presidency of the EU Council set a priority for developing a strategy and programme on zoonoses (7). Since that time there has been increasing recognition of the importance of zoonoses in public health in the EU. For example, there are now clear reporting systems and strong surveillance networks for certain pathogens relating to food safety. Some emerging zoonoses have been well characterised, for example bovine spongiform encephalopathy. However, as EASAC noted in 2008 (7), other emerging zoonotic pathogens have been relatively neglected or not addressed in terms of an integrated human-veterinary strategy, for example, campylobacteriosis and verotoxigenic *Escherichia coli*. Growing problems with these two pathogens were highlighted in the most recent annual report of ECDC and the European Food Safety Authority (EFSA) (8). More generally, there have been continuing problems in sharing and standardising molecular methods of diagnosis across the EU and commitment is still lacking in providing real-time analysis of data collected to inform policy and action.

The concept of One Health requires very good collaboration between the ECDC, EFSA and others to remove unnecessary barriers in integrating surveillance mechanisms for human and animal infections. In EASAC work (2, 7), several areas were emphasised that required collective attention:

1. Coherent, longer-term efforts - in monitoring domestic, companion and wild animals, integrating epidemiological and environmental data, and building linkages between agriculture and health. The recent emergence of a new orthobunyavirus isolated from infected cattle and small livestock, the Schmallenberg virus (9), although judged to be unlikely to cause disease in humans, provides a good example of the importance of maintaining

close collaboration between human and animal health services and using modern molecular diagnostic techniques, to ensure that there can be rapid detection of any changes in epidemiology.

Surveillance is multidisciplinary and must extend beyond centralised expert systems. Most new disease patterns of public health importance will be detected locally by farmers, veterinary surgeons, nurses and primary care physicians. Therefore, it is important to improve awareness and competence within this wider population to detect and report disease. And it is vital for the information from the local level to be communicated consistently and effectively, and to be heeded by the public health authorities.

2. Surveillance must extend to vectors and hosts, including wildlife, as well as pathogens -

as part of the assessment of the ability to transmit infection. Currently, there are several relatively neglected areas of study: for example, the biology and distribution of arthropod vectors according to standardised protocols; changes in zoonoses related to changes in the distribution of vector populations; changes in vector competence and pathogen movement into new vectors; changes in distribution and population density of wildlife animal species which serve as important reservoirs for transmission to human (for example, foxes, wild boars, rodents, birds, bats and racoons). Although the well-managed use of rabies vaccine in foxes in Europe is an example of best practice, too often wildlife control strategies fail because they do not take proper account of the ecological and evolutionary relationship of pathogen to host. For example, the control of severe acute respiratory syndrome (SARS) in China targeted an accidental host, the Asian palm civet, missing the actual primary host, fruit bats.

3. Global co-operation - there is increasing consensus that any surveillance strategy to identify disease outbreaks in animals before they spread to humans should be accompanied by attempts to characterise and prevent environmental disturbances that contribute to disease emergence and spread in animal populations (10). There is evidence of greater co-operation between the EU and international intergovernmental organisations although, of course, more can be attempted. A "Tripartite Concept" from the Food and Agriculture Organisation-World Health Organisation - World Organisation for Animal Health (11) describes an approach to sharing responsibilities and co-ordinating global activities to

address health risks at the animal-human-ecosystem interfaces. However, the problem remains that no global body has overall responsibility for surveillance, and international leadership is currently lacking (12). This weakness, undermining effective routine surveillance, has been made even more visible recently by the growing awareness of the potential public health opportunities in monitoring for mutations of the influenza virus that might increase transmission between mammals. Despite advances in the science, because of the capacity problems, *“current surveillance can barely identify threats, let alone track them”* (13).

Apart from the moral responsibility of the EU to help developing countries, one essential element in European control of zoonoses such as rabies, echinococcosis, brucellosis as well as influenza is to focus on the animal reservoir, and this requires partnership with developing countries. The imperative is to increase preventive efforts earlier in the chain of transmission, at a stage where the microbe crosses species and when direct transmission first occurs person-to-person. This necessitates global surveillance and early warning systems focusing on systematic sampling and phylogeographic analysis in diverse species (14). The global perspective is also vital in the inter-sectoral assessment of societal impact and evaluation of the cost-effectiveness of interventions (15).

4. Recognising the impact of climate change - climate exerts both direct and indirect effects on the appearance and spread of human and animal infectious disease (16, 17). The impact of climate change on the transmission and geographical distribution of disease has been associated with changes in the replication rate and dissemination of pathogen, vector and animal host populations, which are often sensitive to changing temperature and rainfall. The available evidence (16) indicates, for example, the potential for an increasing challenge to European public health from arboviral (arthropod-transmitted) diseases such as tick-borne encephalitis, West Nile fever, chikungunya, diseases caused by rodent-borne hantaviruses, and parasitic diseases such as dirofilariasis and leishmaniasis. The latter was discussed recently in the context of a One Health approach to canine and human patients (18). In the latest West Nile virus surveillance data (19), cases have been reported in newly-affected geographical areas in Europe and further geographical expansion is expected,

attributable to favourable ecological parameters for the interaction between migratory birds, resident birds, competent mosquito vectors and humans. Climate change is anticipated to have other impacts on animal health in Europe and among the newer priorities for attention (20) are blue tongue virus, Rift Valley fever, leptospirosis and African horse sickness.

Overall, however, the evidence base is still fragmented and it is necessary to continue evaluating other determinants of changes in habitat and human behaviour that may confound an understanding of the impact of climate change. Intensive and multidisciplinary study of the impact of environmental change (21) must be integrated with international epidemiology (22). More research is needed to test hypotheses, explore cause-and-effect and provide a stronger evidence base from which to extrapolate, in modelling future impacts. It is likely that new vectors and pathogens will emerge and become established in Europe. Additionally, the spread of pathogens to new habitats and their interaction with new hosts may offer new evolutionary opportunities and lead to the emergence of pathogens with distinctive virulence (23).

5. Sharing good practice more widely - lessons learned, for example from the 2009 H1N1 influenza pandemic (2), may be generalisable to other emerging infections (24). Among these lessons to be shared are:

- The relevance of surveillance in sentinel animal populations (12, 13) known to pose a risk for humans.
- The avoidance of undue emphasis on proxy indicators of disease, such as numbers reporting influenza-like illnesses.
- The value of basing political opinion on scientific evidence (25).
- The importance of continuing to invest in vaccine innovation (26) to take account of antigenic drift and the potential for virus reassortment.
- Not to become complacent merely because the H1N1 pandemic was not as severe as initially feared.

6. Syndromic surveillance and biosecurity - new methods are available to improve the detection of novel pathogen signals superimposed on a background of variable “noise” level. Informatics-based approaches have much to contribute by capitalising on the advances in interpretation of large

datasets in other sectors. Syndromic surveillance has emerged as a mechanism to complement other, passive and active, surveillance systems. However, the automated extraction of relevant information from routine laboratory and clinical databases remains technologically challenging (2).

Syndromic surveillance is also relevant to the defence against bioterrorism and it is prudent for the biomedical community to be alert to the possibility that natural or modified pathogens might be released deliberately. An early US Central Intelligence Agency report (27) warned that synthetic biology could produce engineered infectious agents worse than any known disease. Given the uncertainty surrounding synthetic biology, and prior to considering new regulations, it is desirable for the research community and companies involved in synthesising new genetic sequences to develop and implement voluntary codes of conduct. This raises issues for global research governance, harmonisation of security standards, disclosure of experimental protocols and education on “dual-use technologies” (28). The controversy surrounding dual-use issues was accentuated by the discussion of research on avian influenza (29) and this was also among the subjects of a recent Royal Society meeting on H5N1 influenza research (30).

7. Integrating research agendas - capitalising on the value accruing from integrating epidemiology in human and animal health involves sharing other research priorities, for example in studying how pathogens cross the species barrier and extend their host range (13, 24, 31). Such research may also help to focus surveillance on those species most likely to be hosts. Research in disciplines such as entomology, vector biology and microbial ecology has been relatively neglected but is fundamental to understanding the spread of infections in humans and animals as a result of environmental pressures. The study of human behaviour is equally important - in understanding the human population responses to environmental change and the associated new leisure and land use patterns that may increase exposure to pathogens, vectors and animal hosts.

Research is important to generate new evidence but it is also essential to make better use of the evidence already available, for example in modelling. Systems biology can be used to bring together all relevant surveillance and research data, from the social as well as

biological sciences, to provide the earliest intelligence on threats, anticipate trends, test hypotheses and inform the policy debate. Long-term research encompassing the multiple disciplines associated with understanding infectious disease is costly and will only thrive at the EU level if supported by new types of research funding model. A good case can be made for identifying Grand Challenges (2) for research support by the European Commission with the potential for additional funding to be contributed by Member States. The broad area covered by human and animal infectious disease fulfils the criteria for what can be considered a Grand Challenge - an agreed societal need, tangible goals, excellent science base and industrial capability.

8. Aligning vaccine innovation - there are also opportunities for better co-ordination between the human and veterinary innovation agendas, capitalising on scientific advances. Animal vaccines are important both in the context of reducing animal reservoirs of human pathogens and in veterinary care. Veterinary vaccines can provide proof-of-principle to aid development of human vaccines, for example as occurred for the DNA vaccines (32). There are significant challenges in producing new veterinary vaccines: many infections are caused by multiple serotypes; there are major immunological differences between host species and the rapid completion of genome sequencing of the relevant target species must be accompanied by more research on basic and applied immunology; there may be lack of public acceptance for vaccination of food-producing species; and there may be environmental constraints in vaccine use. The EU must continue to identify new incentives for industry to continue vaccine innovation for animals and humans (2).

ANTIBIOTIC RESISTANCE

Antibiotic resistance has been exacerbated by the inappropriate use of antibiotics in human and veterinary medicine. The problem can be viewed as a collective failure of society (33). The combination of resistance to multiple antibiotics and the ready transmission of genes between bacterial species creates a potent threat worldwide (3). While it had sometimes been difficult to quantify the socio-economic impact of antibiotic resistance (2), there is now an accumulating body

of evidence to document the excess mortality and burden on health systems (for example, attributable to infections by *Staphylococcus aureus* and *Escherichia coli*) (34).

Multi-drug resistant bacteria, both pathogenic and commensal, are very common in farm animals in parts of Europe. An Opinion published by the European Medicines Agency together with ECDC and EFSA (35) noted the problem of increasing antibiotic resistance in humans with infections of *Salmonella* and *Campylobacter*, as a consequence of transmission from animals and food. Other evidence for the transmission of antibiotic resistance to humans through the food chain is exemplified by a rise in the number of bacteria producing extended spectrum beta-lactamases (36). However, the link between the use of antibiotics in animals and the development of resistant bacteria in humans still attracts scientific controversy. For example, one recent study (37), based on collecting resistant *Salmonella typhimurium* strain DT 104 from animals and humans in the same geographical areas and over the same time period, concluded that the animal population is unlikely to be the major source of resistance in human populations. It is vitally important for more research to be conducted on how antibiotic resistance arises and spreads; the recent commitment to a research programme organised through the Innovative Medicines Initiative, a public-private partnership funded by the European Commission and the pharmaceutical sector, is welcome. The analytical techniques of evolutionary biology in population genome analysis have much to contribute when combined with the more traditional approaches to pathogen biology (38) to elucidate the timing of emergence of drug resistance, helping to predict and limit its spread.

There is need for urgent action to combat antibiotic resistance and this must include an integrated approach to human and veterinary medicine as emphasised in the priority of the Danish Presidency of the Council of the EU in 2012. The European Commission's Action Plan (39) also emphasises objectives for the prudent use of antibiotics in veterinary medicine, for example relating to use of the third and fourth generation cephalosporins, critically important medicines for humans. Other key objectives include better monitoring of resistance in food-producing animals and using the Animal health

Law to reinforce efforts in infection prevention, by implementing lessons of good practice. For example, in Norway the introduction of effective vaccines in farmed salmon and trout together with improved fish health management reduced the annual use of antimicrobials in farmed fish by 98% between 1987 and 2004 (40). It is also very important to identify and develop new approaches to antibiotic innovation for human use (2, 41) and clarify the issues for developing antimicrobials for selective use in animals (39, 41).

FUTURE DIRECTIONS

Given the interrelatedness of human, animal and ecosystem health, a good case can be made for co-ordinated policy action among those responsible for public health, medical science and veterinary services (6). There has often been a relative neglect of the problems associated with animal health in much policy-making (5), partly because of the lack of resources allocated to veterinary services and under-diagnosis, but also because of the perceived difficulties in disease control mechanisms and the complex challenges for interdisciplinary collaboration in research and practice as well as in policy. However, there are some encouraging developments recently in identifying frameworks for generating and using an integrated knowledge base, in terms of stipulating the research agenda (5) and evaluating societal costs (15).

There is much still to be done: to create novel global surveillance systems (12, 13); to build information exchange between the human and animal health sectors; to agree global health priorities and support national health capacities; and to strengthen the capabilities of health authorities to influence policy-making in other areas. In tackling these challenges, it will be possible to capitalise on the pace of scientific advance across a broad front.

Academies of science and medicine accept their ongoing responsibility to promote research and stimulate dialogue among the scientific, medical and policy communities, and with the public. Collective activity is essential for priority setting across human and animal health and to communicate and use the available scientific evidence in pursuit of agreed goals, while at the same time also evaluating where there is uncertainty that can be reduced by new research.

References

- (1) Jakab Z. Why a burden of disease study? *Eurosurveillance* 2007; 12: 300
- (2) EASAC. European public health and innovation policy for infectious disease: the view from EASAC. Halle (Saale), Germany, 2011. Available from: <http://www.easac.eu> [last accessed March 23, 2012]
- (3) Fears R, van der Meer JWM, ter Meulen V. The changing burden of infectious disease in Europe. *Science Transl Med* 2011; 3: 103cm30
- (4) Gibbs EPJ, Anderson TC. "One-world-one-health" and the global challenges of epidemic diseases of viral aetiology. *Veterinaria Italiana* 2009; 45: 35-44
- (5) Coker R, Rushton J, Mounier-Jack S, et al. Towards a conceptual framework to support one-health research for policy on emerging zoonoses. *Lancet Infect Dis* 2011; 11: 326-31
- (6) World Bank. People pathogens and our planet. Volume 1: Towards a one health approach for controlling zoonotic disease. The World Bank Report No. 50833-GLB, 2010. Available from: http://siteresources.worldbank.org/INTARD/Resources/PPP_web.pdf [last Accessed March 23, 2012]
- (7) EASAC. Combating the threat of zoonotic infections. London, UK, 2008. Available from: <http://www.easac.eu> [Accessed March 23, 2012]
- (8) EFSA. EU summary report on zoonoses, zoonotic agents and food-borne outbreaks 2010. *EFSA J* 2012; 10: 2597
- (9) ECDC. Risk assessment: new orthobunyavirus isolated from cattle and small livestock - potential implications for human health. Stockholm, Sweden, 2011. Available from <http://ecdc.europa.eu> [last Accessed March 23, 2012]
- (10) Kuehn BM. Human, animal, ecosystem health all key to curbing emerging infectious disease. *J Am Med Ass* 2010; 303: 117-118
- (11) FAO-OIE-WHO. A tripartite concept note, 2010. Available from http://www.oie.int/download/FINAL_CONCEPT_NOTE_Hanoi.pdf [last Accessed January 7, 2011]
- (12) Butler D. Flu surveillance lacking. *Nature* 2012; 483: 520-2
- (13) Under surveillance [editorial]. *Nature* 2012; 483: 509-10
- (14) Wolfe ND, Panosian DC, Diamond J. Origins of major human infectious disease. *Nature* 2007; 447: 279-83
- (15) Narrod C, Zinsstag J, Tiogco M. A one health framework for estimating the economic costs of zoonotic diseases on society. *Ecohealth* 2012; DOI: 10.1007/s10393-012-0747-9
- (16) EASAC. Climate change and infectious diseases in Europe. London, UK, 2010. Available from: <http://www.easac.eu> [last Accessed March 23, 2012]
- (17) Semenza JC, Suk JE, Estevez V, et al. Mapping climate change vulnerabilities to infectious disease in Europe. *Environ Health Perspect* 2012; 120: 385-92
- (18) Palatnik-de-Sousea CB, Day MJ. One health; the global challenge of epidemic and endemic leishmaniasis. *Parasit Vectors* 2011; 4: 197
- (19) ECDC. Rapid risk assessment: review of the epidemiological situation of West Nile virus infection in the European Union. Stockholm, Sweden, 2011. Available from: <http://ecdc.europa.eu> [last Accessed March 23, 2012]
- (20) De la Rocque S, Morand S, Hendricks G. Climate change: impact on the epidemiology and control of animal diseases. *OIE Scientific and Technical Review* 2008; 27: special issue
- (21) Keesing F, Belden LK, Daszak P, et al. Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature* 2010; 468: 647-52
- (22) Himsforth CG. If a pig coughs in Mexico the whole world should hear it. *Lancet Infect Dis* 2010; 10: 511-2
- (23) Pallen MJ, Wren BW. Bacterial pathogenomics. *Nature* 2007; 449: 835-42
- (24) Peiris JS, Poon LLM, Guan Y. Surveillance of animal influenza for pandemic preparedness. *Science* 2012; 335: 1173-4
- (25) A pandemic of hindsight [editorial]. *Nature* 2010; 465: 985
- (26) Pandemic influenza - (some) reasons to be cheerful [editorial]. *Lancet* 2010; 376: 565
- (27) CIA. The darker bioweapons future. Office of Transnational Issues, 2001. Available from: <http://www.fas.org/irp/cia/product/bw1103.pdf> [last accessed February 27, 2011]
- (28) EASAC. Realising European potential in synthetic biology; scientific opportunities and good governance. Halle (Saale), Germany, 2010. Available from: <http://www.easac.eu> [last accessed March 23, 2012]
- (29) Avian influenza and the dual-use research debate [editorial]. *Lancet Infectious Diseases* 2012; 12: 167
- (30) Royal Society. H5N1 research: biosafety, biosecurity and bioethics. The Royal Society, London - 3-4 April 2012 - Available at <http://royalsociety.org/events/2012/viruses> [last Accessed April 16, 2012]
- (31) Streicker DG, Turmelle AS, Vanhof MJ, et al. Host phylogeny constrains cross-species emergence and establishment of rabies virus in bats. *Science* 2010; 329: 676-9
- (32) EASAC. Vaccines: innovation and human health. London, UK, 2006. Available from: <http://www.easac.eu> [last accessed March 23, 2012]
- (33) Carlet J, Collignon P, Goldmann D, et al. Society's failure to protect a precious resource: antibiotics. *Lancet* 2011; 378: 369-71
- (34) De Kraker MEA, Davey PG, Grundmann H, on behalf of the BURDEN study group. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of

- antibiotic resistance in Europe. *PLoS Medicine* 2012; 8: e1001104
- (35) EMA. Better surveillance needed to fight antimicrobial resistance in zoonotic infections. EMEA-ECDC-EFSA Joint Press release, November 2009. Available from: <http://www.ema.europa.eu> [last Accessed December 2, 2009]
- (36) Sheldon T. Dutch doctors warn that the overuse of antibiotics in farming is increasing resistance. *Br Med J* 2010; 341: 801
- (37) Mather AE, Matthews L, Mellor DJ, et al. An ecological approach to assessing the epidemiology of antimicrobial resistance in animal and human populations. *Proc Roy Soc B: Biol Sci* 2012; 279: 1630-9
- (38) Little TJ, Allen JE, Babayan SA, et al. Harnessing evolutionary biology to combat infectious disease. *Nature Med* 2012; 18: 217-20
- (39) European Commission. Action plan against the rising threats from antimicrobial resistance. COM (2011) 748, 2011. Available from: http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf [last accessed March 23, 2012]
- (40) WHO. The evolving threat of antimicrobial resistance - options for action. Geneva, Switzerland, 2012
- (41) Piddock LJV. The crisis of no new antibiotics - what is the way forward? *Lancet Infectious Diseases* 2012; 12: 249-53

