Antibiotic resistance is increasing worldwide and has become a very important threat to public health. The overconsumption of antibiotics is the most important cause of this problem. We created a World Alliance Against Antibiotic Resistance (WAAAR), which now includes 720 people from 55 different countries and is supported by 145 medical societies or various groups. In June 2014, WAAAR launched a declaration against antibiotic resistance. This article describes the process and the content of this declaration.

Keywords. antibiotic resistance; antibiotic consumption; declaration; antibiotic stewardship.

Antibiotic resistance has increased considerably in the past 2 decades and represents a very serious threat for patients and public health [1–3]. The reasons for increasing rates of resistance are many, but overuse of antibiotics is foremost. Unfortunately, antibiotic prescription is still considered a trivial act, both in humans and animals, and both in the hospitals and the community. Each citizen, and especially healthcare professionals, should feel concerned by this worldwide danger. Antibiotics are a treasure that we must protect. We have not been clever enough, in the last few decades, to treat antibiotics as a precious resource [4]. Some 40%–50% of the antibiotics prescribed worldwide are unnecessary. For example, in many countries we use antibiotics to "treat" viral infections, in particular upper and lower respiratory tract infections. General practitioners, in many cases, do not use rapid diagnostic tests, such as that for streptococcal antigen in the throat, or the use of urinary dipsticks for urinary tract infections. Overtreating patients with antibiotics was already a big mistake even when many antibiotics were available. Now, in this period of antibiotic paucity, it is a crime against humanity. Some efforts have been made in the last few years by several countries. Large awareness campaigns, targeting healthcare professionals and the public, have been implemented [5]. In France, antibiotic consumption has been decreased by 25% [6]; in Belgium, a 34% decrease has been achieved [5]. Large European campaigns have been implemented. The annual European Antibiotic Awareness Day, organized several years ago by the European Centre for Disease Prevention and Control (ECDC) [7], has been a great success not only in Europe, but also has been replicated in other places (ie, Canada and Asia). We may anticipate that those international campaigns might help to decrease antibiotic consumption. A large national campaign has been implemented recently in China, with very positive results in term of antibiotic consumption [8]. In India, cooperation between all of the stakeholders came up with a declaration (Chennai Declaration) and a country-wide program to tackle antibiotic resistance [9]. Campaigns to decrease over-the-counter usage of antibiotics have been organized in South America, with discordant results between countries.

THE WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE

The World Alliance Against Antibiotic Resistance (WAAAR) is an alliance created in 2012 to raise and maintain awareness of stakeholders—including politicians, policy makers, healthcare professionals, and the public—to the problem of antibiotic resistance. The
aim was to control (ie, decrease or at least contain) antibiotic resistance by a series of national and international actions. The objectives were to convince all of the stakeholders of the emergency of the threat and the need to act for the protection of antibiotics [4]. Other associations were already present in the worldwide arena, sometimes for a long period of time (eg, Alliance for the Prudent Use of Antibiotics [APUA], Action on Antibiotic Resistance [ReAct], Global Antibiotic Resistance Partnership [GARP]), but without a good implementation in many countries. Therefore, people were keen to create a new alliance rather than joining other nongovernmental organizations (NGOs). Antibiotic action was launched in the United Kingdom at the same time as our alliance. The alliance was initially French, grouping 300 members after a few months, and became international later on. The alliance gathers now 720 people from 55 different countries, coming from various horizons, including medical doctors from many specialities, veterinarians, pharmacists, nurses, ecologists, environmental specialists, advocacy groups of patients, citizens, and politicians. A very strong support from advocacy groups of patients was present since the very beginning. WAAAR is supported by 145 medical specialities and various professional groups, among them some very large societies such as the Infectious Diseases Society of America (IDSA; http://www.idsociety.org/Index.aspx), European Society of Clinical Microbiology and Infectious Diseases (ESCMID; https://www.escmid.org), Society of Critical Care Medicine (SCCM; http://www.sccm.org), American College of Chest Physicians (ACCP; http://www.chestnet.org), American Thoracic Society (ATS; http://www.thoracic.org), European Society of Intensive Care Medicine (ESICM; http://www.esicm.org), International Society of Chemotherapy (ISC; http://www.ischemo.org/index.html), and International Society for Infectious Diseases (ISID; http://www.isid.org).

THE DECLARATION AGAINST ANTIBIOTIC RESISTANCE

Twelve months ago, WAAAR decided to program the release of a declaration against antibiotic resistance. The idea was to widely diffuse a consensus document signed by all our supporters. The initial idea was discussed in the French executive committee of the alliance (17 persons) and was welcomed very warmly. The next step was to create an international scientific committee of 22 members worldwide. We circulated a first draft written by this international scientific committee, taking advantage of the available literature, but without any grading of the different proposals. It was not easy to come to a consensus among 720 people (Table 1). We used a method similar to the Delphi technique. Altogether, 10 different versions of the document circulated during the last 6 months of the process. The declaration was sent to all 145 supporting societies, which made some proposals, sometimes extensive. In particular, some veterinarians made very strong proposals, conditioning their participation to the declaration to a couple of points. We wanted, for example, to ban the usage of antibioprophylaxis in the animal world, but some veterinarians were in disagreement with this. However, other veterinarians were in agreement with us. We came to a consensus: Antibioprophylaxis should be used only exceptionally. This consensus was very important for us to reach, as it was key to keep veterinarians with us, in a One Health philosophy. We had similar discussions with several other partners, and a consensus was in general relatively easy to reach. We had some comments according to country; the representatives of low- and middle-income countries mentioned for several actions the difficulty of implementing such a program, due to a lack of resources. Participants from high-income countries were in agreement with the consensus, and had no major concerns.

We attempted to get support from many international agencies, such as the World Health Organization (WHO), the World Organisation for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO), the US Centers for Disease Control and Prevention (CDC), the ECDC, the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA). All answered that the topic was of paramount importance and that they were highly in agreement with our actions, but only the CDC agreed to support us officially. The other agencies thought that it was not logical to be both the stakeholders and the supporters of the declaration. It is true that the issue of antibiotic resistance is highly political [10], and the above-mentioned agencies were not keen to cooperate with NGOs.

A meeting, gathering 25 people, occurred during the 24th Congress of ESCMID, in Barcelona, Spain, in May 2014. During this meeting, the document was discussed in depth, and was refined. Many alterations were made, but nobody was in opposition with the core of the document. The document was then sent again to all the members and the societies supporting the declaration for a final evaluation. Some additional comments were made by the members and the supporting societies. Finally, the document was validated by everybody. The declaration was launched on 23 June 2014. A press release was organized in France and internationally, with a very good result. The declaration was diffused locally by all the members, was sent to many local and international journals, and was stressed in newsletters of many societies. Some manuscripts have been published [11, 12] or are in the review process. The final document was sent to policy makers, some politicians, and national and international agencies. We can therefore consider that this declaration has been a success in term of communication. The next steps are currently being discussed by the scientific committee. An updated version of the declaration will certainly be
useful in the near future. A document grading the different measures according to their urgency to the economic level of the countries would be of interest.

The aim of this declaration was to propose to both professionals and consumers a series of consensual actions to tackle antibiotic resistance. The strength of this activity is that the declaration has been validated by 720 people, therefore increasing its value. We anticipate that the different countries could improve the level of their programs against antibiotic resistance using this declaration. The document was relatively short and concrete, increasing its impact, compared with the many documents already available, which are usually very long and very generalized.

### THE 10 ACTIONS PROPOSED IN THE DECLARATION

WAAAR advocates a number of actions within 10 main topics. For some of these topics, achieving consensus was straightforward; other topics needed more discussion (Table 1).

The first 3 actions were very general, and consensus was not a problem. In particular, everybody agreed that WHO has the legitimacy to take charge of the crusade against antibiotic resistance [13].

1. Awareness of all stakeholders on the threat represented by AMR

2. Financed national plan in each country

3. Permanent access of AB of assured quality

4. Antibiotic stewardship
   a. ABS in animals
   b. AB as growth factors
   c. ABS over the counter
   d. ABS in the hospitals

5. Infection prevention

6. Use of diagnostic tests

7. Education information

8. Surveillance

9. Basic and applied research: R&D for new drugs

10. AB in UNESCO list

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**Table 1. Consensus Process for the 10 Actions of the Declaration**

<table>
<thead>
<tr>
<th>Actions</th>
<th>Achieving Consensus</th>
<th>Contentious Issues</th>
<th>Concerns of Countries</th>
<th>Concerns of Professionals</th>
<th>Solving the Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Awareness of all stakeholders on the threat represented by AMR</td>
<td>Easy</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2. Financed national plan in each country</td>
<td>Some difficulties</td>
<td>Resources needed</td>
<td>LMIC</td>
<td>LMIC</td>
<td>Help those countries</td>
</tr>
<tr>
<td>3. Permanent access of AB of assured quality</td>
<td>Some difficulties</td>
<td>Difficult to implement</td>
<td>LMIC</td>
<td>LMIC</td>
<td>Help those countries</td>
</tr>
<tr>
<td>4. Antibiotic stewardship</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. ABS in animals</td>
<td>Some difficulties</td>
<td>Antibiotic prophylaxis in animals</td>
<td>Europe</td>
<td>Veterinarians</td>
<td>Consensus efforts</td>
</tr>
<tr>
<td>b. AB as growth factors</td>
<td>Easy</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>c. ABS over the counter</td>
<td>Some difficulties</td>
<td>Slow process</td>
<td>LMIC</td>
<td>LMIC</td>
<td>Determination and patience</td>
</tr>
<tr>
<td>d. ABS in the hospitals</td>
<td>Some difficulties</td>
<td>Resources needed</td>
<td>LMIC</td>
<td>LMIC</td>
<td>Help those countries</td>
</tr>
<tr>
<td>5. Infection prevention</td>
<td>Some difficulties</td>
<td>Cultural and financial issues</td>
<td>LMIC</td>
<td>LMIC</td>
<td>Apply the WHO recommendations</td>
</tr>
<tr>
<td>6. Use of diagnostic tests</td>
<td>Some difficulties</td>
<td>Resources issues</td>
<td>LMIC</td>
<td>Small hospitals</td>
<td>Resources</td>
</tr>
<tr>
<td>7. Education information</td>
<td>Easy</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>8. Surveillance</td>
<td>Some difficulties</td>
<td>Technical issues for laboratories</td>
<td>None</td>
<td>Microbiologists, pharmacists</td>
<td>Resources</td>
</tr>
<tr>
<td>9. Basic and applied research: R&amp;D for new drugs</td>
<td>Some difficulties</td>
<td>Difficult for R&amp;D</td>
<td>None</td>
<td>Pharmaceutical companies</td>
<td>New business models</td>
</tr>
<tr>
<td>10. AB in UNESCO list</td>
<td>Easy</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AB, antibiotic; ABS, antibiotic stewardship; AMR, antimicrobial resistance; LMIC, low- and middle-income countries; R&D, research and development; UNESCO, United Nations Educational, Scientific and Cultural Organization; WHO, World Health Organization.
tries have implemented a system of a sensus on this action, even from US members. Similarly, anti-biophrophylaxis is widely used in certain countries; it should remain the exception. The consensus has been more difficult to reach on this issue. In Europe, some countries are consuming a lot of antibiotics in animals (eg, France, the Netherlands), and in other countries, very few (eg, Scandinavia) [15]. Some countries have implemented a system of a “green card” for the veterinarians who were reaching their target in term of consumption [16]. A pay-for-performance system could be imagined.

There are many countries in which antibiotics are available over the counter. It is very difficult to fight against this problem, because in several countries, it is the only way to access antibiotics [17]. Similarly, many products are outdated or counterfeit in many countries. Controls are necessary in every country, but it will take some time to treat this problem. The representatives of these countries—in particular, India—insisted on the fact that both patience and determination are needed to treat this issue.

Antibiotic stewardship in the hospitals is a very important issue [18], and the discussion around this issue has been very consensual. However, we need resources to implement those actions. The best scenario is to implement a small team in each hospital, with antibiotic referees (if possible, infectious diseases specialists), microbiologists, and pharmacists to help physicians to prescribe antibiotics appropriately (ie, the right drug, with the right dose, for the right duration). An antibiotic stewardship team is mandatory in several countries, such as France, and is planned in the United States in the Medicare program. Those kinds of organization are very efficient and dramatically improve the quality of antibiotic therapy, but cannot be easily implemented in small hospitals or in hospitals from low- and middle-income countries.

5. Infection prevention.

Cross-transmission of resistant strains in the hospitals and in the community is a very important mechanism of antibiotic resistance. Hand hygiene with hand-rub alcoholic solutions is the most efficient weapon to prevent-cross transmission. It is this method which allowed the good results that many countries achieved in reducing the transmission of methicillin-resistant Staphylococcus aureus [19]. There are many countries, especially, but not only, low- and middle-income ones, in which hygiene is very poor. The problem is economic, but also cultural. It is not difficult to locally produce very inexpensive hand-rub alcohol solutions, and many countries are now embarking in this direction.

Screening is another important method to rapidly detect patients carrying multidrug-resistant microorganisms. This allows healthcare providers to isolate patients very quickly. There are still some controversies on whether we should use targeted screening or universal screening [20]. Again, this cannot be done in low- and middle-income countries, nor in small hospitals. We had no formal recommendation for this issue.

6. Use of diagnostic tests.

Diagnostic tests are of paramount importance. Some tests are already available, such as that for streptococcal antigen in the throat, which allows healthcare providers to treat only patients with a positive test. This test is underused, with physicians deciding that it is too long to be performed. The procalcitonin test has been used in lower respiratory tract infections. This test differentiates viral and bacterial infections and could be useful in specific cases, but cost is an issue.

Recent tests, such as matrix-assisted laser desorption/ionization–time of flight and rapid polymerase chain reaction (PCR), are able to shorten the time to identification of the microorganism, and the access to its susceptibility to antibiotics. However, it is still too long to curtail empiric treatment of severe infections. Ultrarapid PCR, giving a result within 30–60 minutes, will be an important progress. Those techniques are only available in resource-rich countries, and mostly in tertiary hospitals.

7. Education and information.

A strong educational program, of both healthcare professionals and the public, is necessary in every country. Some large national awareness campaigns have been performed in some countries, with interesting results [5]. The results of those campaigns are not sustained, and regular reminders must be performed. Education and training programs for healthcare professionals (students in medical and veterinary schools and in continuing medical education) must be improved.

8. Surveillance of consumption of and resistance to antibiotics.

It is key to have information on the consumption of [21] and the resistance to antibiotics [18]. Several large networks are in place in several regions and countries, including Europe, South America, Australia, Canada, and, to some extent, the United States. These networks allow some benchmarking. National networks are available in many countries. It is very important to have local information on the susceptibility of microorganisms. However, there are many countries in which those networks are still missing, in particular, in low- and middle-income countries. It is urgent to help those countries implement those surveillance systems. Laboratory capabilities must be improved.

9. Promotion of basic and applied research, and research and development of new drugs.

It is mandatory to find resources for both basic and applied research. An important budget has been devoted to research by the European Commission and by the US National Institutes of Health in the last few years. Very recently, a public–private collaboration (the Innovative Medicines Initiative) has been developed in Europe. Research resources must be increased, for both human and veterinary medicine, and made accessible to low- and middle-income countries.
Very few drugs have been made available in recent years [22]. This is due to the fact that research and development (R&D) is very long and costly, with an insufficient return on investment for the companies (ie, short duration of therapy and low price). New models of development must be invented. Fast-track R&D is a possibility, considering antibiotics such as orphan drugs. Pricing must be discussed according to the ability of new drugs to be truly innovative, with a delinking between return on investment for the companies and consumption. All these concepts have been largely discussed by the EMA and the FDA, but nothing has happened in practice. It is urgent to implement some of those measures. The price of antibiotics has been discussed by WAAAR. Prices should probably be higher in developed countries, but this would raise a problem for low- and middle-income countries. Similarly, the use of generic drugs, which encourages the use of antibiotics, could be reduced in resource-rich countries, but not in resource-limited countries.

10. Inclusion of antibiotics (or lives saved by antibiotics) in the UNESCO’s intangible cultural heritage (the United Nations Educational, Scientific and Cultural Organization).

This action would have an exemplary effect for all countries, in particular for the public. Antibiotics are very special drugs. They need protection, in a philosophy of sustainable development.

CONCLUSIONS

Building this consensual declaration has been an outstanding experience. It was not easy to come to this consensus. Some countries have very high levels of resistance to antibiotics, and others have very low levels. The feeling of urgency differs between countries. Veterinarians do not have the same objectives as medical doctors. For veterinarians, the production of goods is an important objective. Low- and middle-income countries will have difficulties in implementing most of the measures, due to cultural issues, lack of infrastructure, and limited resources. It will take much time to finalize all those measures. Patience and determination are needed.

References