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Ten tips on how to win the war against resistance to antibiotics

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Antibiotic resistance has increased dramatically in the past few years and nowadays represents a serious threat to public health [1-3]. Reasons are multiple, the excess in antibiotic consumption being the most important one. Therefore, antibiotic prescription must be carefully discussed for each patient. Unfortunately, antibiotic prescription is still considered as a trivial act in both humans and animals, in both the hospitals and community. Antibiotic resistance is a worldwide issue. The prevalence of Enterobacteriaceae resistant to third generation cephalosporins reaches 70–80 % in several countries, the prevalence of carbapenemases in Klebsi-<u>ella</u> <u>pneumoniae</u> being <u>more</u> <u>than</u> <u>50</u>% in many countries [4, 5] (Fig. 1). In the ESAC network in Europe [6], antibiotic consumption in the community ranges from 11 to 32 DDDs per 1,000 inhabitants per day. Similar differences are seen in other continents. Between 2000 and 2010, consumption of antibiotics increased in 71 countries by 36 %, Brazil, Russia, India, China and South Africa accounting for 76 % of this increase [7]. Animal consumption represents 80 % of total antibiotic consumption. Large differences are seen in the consumption in animals [8]. In Europe, France and The Netherlands were the highest consumers. The Netherlands has been able to reduce its

consumption by more than 60 % and France by 35 % in the last 5 years.

The World Alliance Against Antibiotic Resistance (WAAAR)

The WAAAR is an alliance created 2½ years ago in order to raise awareness of politicians, policy makers, health care professionals and citizens. It comprises 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 and citizens. It is supported by 145 medical specialities and various groups. The WAAAR proposes the ten following actions.

- 1. Awareness of all the stakeholders, including the general public, of the threat represented by antibiotic resistance. Strong cooperation among the WHO, OIE and FAO, which must take the lead in the world program against antibiotic resistance.
- 2. Organization, in each country of a financed national plan for the containment of antibiotic resistance, with the involvement of all the actors, including consumers.
- 3. Permanent access to antibiotics of assured quality, in particular in middle- and low-income countries.
- 4. Cautious, controlled and monitored approaches to the use of antibiotics (antibiotic stewardship).

A list of "protected" antibiotics must be available in each hospital. These antibiotics can only be prescribed by referents or infectious diseases specialists. Each antibiotic prescription must be carefully balanced according to advantages and risks of the product. The



Fig. 1 The worldwide dissemination of the OXA-48 and OXA-48-like carbapenemases

risks include side effects of the drug (early events) and the risk of resistance (late events). Antibiotic therapy must be reserved for bacterial infections. In practice, many viral infections, including those of the upper respiratory tract, are treated with antibiotics. Rapid diagnostic tests would help greatly to differentiate viral and bacterial infections. In the ICU, all these measures are of paramount importance, since 60 to 70 % of the patients are treated with antibiotics. A systematic re-evaluation must be performed and a deescalation must be systematically discussed [9]. The antibiotic dose must be increased because of particularities of PK/PD parameters in ICU patients. Combination therapy must be applied rarely and limited to therapy of ventilator-associated pneumonia, severe sepsis and septic shock. The duration of antibiotic therapy must be reduced as much as possible [10].

Antibiotherapy in animals is also an important issue. Antibiotic usage as a growth factor, which is implemented in many countries, including the USA, must be abandoned (this has been the case in Europe since 2006). Similarly, the prophylactic prescription of antibiotics must be a very rare event. Antibiotics must be prescribed for a precise duration, with an appropriate dosage. Performing a reevaluation at day 2 or 3 is very important. In most cases, the initial antibiotic therapy, which is often empiric, can be altered for drugs with less antibiotic pressure or can be stopped. In developing countries, antibiotics are often available over the counter, without any prescription. This must be combatted.

5. Development of new and use of available rapid and accurate diagnostic tests

These must be developed to aid in distinguishing bacterial and nonbacterial etiologies and rapidly select appropriate, targeted antibiotics, avoid unnecessary treatments and modulate the duration of therapy.

6. Prevention of bacterial transmission

Hand disinfection with hydro-alcoholic solutions is the most important action to interrupt spread of resistant microorganisms. <u>Antibiotic screening</u> is a <u>very controversial</u> topic. It <u>should not be generalized</u>. In the ICU, some studies show that excellent usage of standard precautions and daily bathing with chlorhexidine is more effective than screening and isolation [11].

7. Education and information

A strong educational program for both health care professionals and the public is necessary. Education and training programs for health care professionals (medical and veterinary schools and continuing medical education) must be accelerated. Large awareness educational campaigns have been shown to be effective.

8. Surveillance of antibiotic resistance and consumption

It is very important to have precise information on antibiotic resistance and consumption in each country. Therefore, local networks must be set up as well as participation in large networks, allowing some benchmarking. We are lucky enough to have these networks in Europe [4, 6]. Specific data are necessary for ICUs.

9. Promotion of basic and applied research. Research and development (R/D) of new drugs

Many resources are mandatory for both fundamental and applied research. An important budget has been devoted to research by the European commission and by the NIH in the last few years. Very recently a public/private cooperation (IMI) has been developed in Europe. The research resources must be increased for both human and veterinary medicine. Very few drugs have been made available in the past few years [12]. This is due to the fact that R&D takes a long time and is costly, with an insufficient return on the investment for companies (short duration of therapy, low price). New development models must be found. Fast-track R&D is a possibility, considering for example antibiotics such

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as orphan drugs. Pricing must be discussed according to the ability of new drugs to be really innovative, with a delinking between return to investment for the companies and volume of the prescriptions.

Development of new antibacterial vaccines and nonantibiotic compounds is of paramount importance

10. Inclusion of antibiotics in UNESCO's world intangible heritage

This would have an exemplarity effect for all countries and for the public. Antibiotics are very special drugs, being like a treasure that we need to protect [13], with a philosophy of sustainable development.

Can we win the war against antibiotic resistance?

This war will be very long, and we need a great deal of perseverance. We also need the strong commitment of politicians, with sustainable actions [14]. Repeated campaigns must be organized in order to convince health care professionals and consumers that the problem is very serious, even if they do not see a lot of resistant bacteria in their daily life. International cooperation is urgently needed. The WHO is the appropriate structure to lead the crusade. Yes, we can!

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