Current Topics

WHO develops artesunate for emergency treatment of malaria

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Traditionally, the development of new drugs relies to a great extent on the ability of the pharmaceutical industry to carry out scientific and technological research on behalf of public health. In such a setting, drug development tends to be directed to health problems which give a return on the significant investment of time and money needed to obtain a commercially successful product. The provision of new medicines for diseases endemic in developing countries where a commercial gain is not possible remains a dilemma (1).

A new initiative in public health delivery has recently been launched by WHO with the development of the antimalarial, artesunate. The pace of artesunate development has been fast and focused and is targeted to those populations at risk of severe malaria. Although the development strategy for artesunate originated within WHO's Special Programme for Research and Training in Tropical Diseases, it relies heavily upon an alliance of scientists, laboratories, industry, regulators and ministries of health for its implementation.

The malaria setting

It is estimated that malaria is responsible for up to 500 million episodes of clinical infection annually, killing 2.7 million people with severe and cerebral disease. Existing data indicate that in some African settings, 44% of all mortality in children under the age of 5 is associated with malaria and 82% of these deaths occur at home since many children are not fortunate enough to reach a hospital.

The commonest presenting symptoms associated with significant mortality are cerebral malaria, recurrent convulsions, metabolic dysfunction, or symptomatic anaemia (2). In the population most at risk of death — infants and children in Africa — a significant number soon become too ill to take any form of medication orally and must be referred to hospital for parenteral treatment. Data confirm that the illness progresses rapidly. Children with severe anaemia may present with longer histories of illness, and acute decompensation, manifesting as respiratory distress, often precipitates admission to hospital. The risk of death at hospital is highest within the first 24 hours after admission, and varies from 10% to 40%. Survival thus depends on two factors: the time elapsed between first symptoms and initiation of treatment, and the health facility's ability to manage complications.

It follows that the earlier a patient receives therapeutic concentrations of an effective antimalarial, the lower the risk of mortality. Since the need is to provide early, affordable treatment to patients with suspected malaria who do not have easy access to hospital, it was urgent for WHO to develop a product which met these criteria.

The clinical efficacy of currently marketed antimalarials is generally demonstrated by parasite clearance rates. However, the circumstances of malaria illness are complicated and require a formulation which can be administered easily and safely by untrained health workers while being acceptable to young children. Once the patient has reached an equipped health facility, a more precise diagnosis can be made and treatment administered as required. Given these circumstances, the WHO strategy aims to achieve full development and distribution of artesunate in suppository form for emergency use in patients prior to hospital admission.

The development strategy

The Artesunate Task Force was set up in 1996 and operates as a "virtual" pharmaceutical company. It meets twice a year to oversee the development of artesunate with the aim of providing national pro-

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grammes with additional means to control malaria. It is comprised of a core group of 4 members consulting on an ad hoc basis with experts, regulatory officials and the scientific community. This approach, aside from being flexible, has many advantages:

- A plan of work is created with the ultimate goal of providing national programmes with access to an antimalarial with life-saving potential.
- World experts in chemotherapy, toxicology, chemistry, regulatory affairs, and pharmacokinetics can be called upon on an expenses-only basis (although many give advice and evaluate material for a symbolic fee).
- A high level of collaboration can be achieved when parties are engaged in a common aim.
- Research capacity for related public health drug development is established in many areas involving safety monitoring, good clinical practice and laboratory capacity.

Demonstration of benefit

Evidence of the potential role of the artemisinin derivatives in the control of severe malaria and associated mortality was provided by a sharp decline in malaria levels following their introduction in Viet Nam. Although artesunate is widely regarded as the most efficacious of the artemisinin derivatives, it is not under patent and has not been subject to full registration by a highly developed regulatory authority. Furthermore, no pharmaceutical company has shown willingness to pursue full registration because of the investment needed to constitute a registration dossier. WHO has thus been able to develop the product to full registration requirements.

Raw data on the safety of artesunate in South-East Asia have been collected by investigators over the past ten years and clinical data have been provided through WHO studies on artesunate use in moderately severe malaria. Effectiveness in an emergency situation will now be evaluated through the community trials initiated in several countries. These trials will be crucial in demonstrating whether early administration of rectal artesunate halts severe disease and prevents a fatal outcome. Additionally, they will define the conditions of use and follow-up treatment, and provide a platform for subsequent development of health education programmes.

Regulatory mechanisms

WHO will be the sole applicant for marketing of rectal artesunate for the emergency treatment of severe malaria. Registration dossiers will be submitted in Switzerland, the United Kingdom and the United States of America in late 1999 and registration elsewhere is likely to be made by mutual agreement with the national drug regulatory authority.

The new drug application to be submitted to the FDA will be filed under orphan drug status and within the expedited approval process. Orphan drugs are those drugs that involve a condition or disease affecting fewer than 200 000 diagnosed cases in the USA and expedited approval is reserved for products addressing serious or life-threatening illnesses. In these circumstances, approval is based on evidence of benefit on a surrogate endpoint pending the outcome of community-based studies designed to provide definitive survival data.

Elements of a model strategy

Collaboration is possible wherever parties benefit mutually and share a common aim. The following steps outline how WHO achieved this goal by exploiting its unique international role and expertise in public health.

- A common aim was identified to develop and register a product of public health benefit.
- Collaborative links were established with the pharmaceutical industry, regulatory authorities, scientists, experts, national authorities and community health centres in endemic areas.
- Global expertise was harnessed cost-effectively.
- On behalf of WHO, scientific experts planned, followed-up and executed components of the strategy.
- Industrial partners manufactured a final product in compliance with the highest quality, safety and efficacy requirements.
- A focused path to registration was planned by the application of orphan drug status and accelerated approval.
- Postmarketing surveillance and health education programmes are under development to enable optimal use of the final product by public health agencies and programmes such as UNICEF, Roll Back Malaria, and national control programmes.

References

1. Garattini, S. Financial interests constrain drug development. *Science*, **275**: 287 (1997).

2. Newton, C.R., Krishna, S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. *Pharmacology and Therapeutics*, **79**(1): 1–53 (1998).

Vitamin A supplementation strategies

Vitamin A deficiency has been identified as a problem of public health importance in over 118 countries worldwide and about 250 million children are estimated to be at risk of this deficiency. Among children under 5 years of age, some 3 million have clinical signs of xerophthalmia.

Reducing vitamin A deficiency requires long-term approaches which include food fortification or increased dietary intake of foods rich in vitamin A. Periodic supplementation is a rapid, low-cost way to ensure that children at risk receive enough vitamin A. The Expanded Programme on Immunization (EPI) is now linking delivery of vitamin A to its routine and supplementary immunization programmes (1).

In the correct dosage, vitamin A is safe and has no negative effect on seroconversion rates for oral poliovirus vaccine (OPV) or measles vaccine. Occasionally, side effects such as headache, loss of appetite or vomiting may occur the day following vitamin A administration. These symptoms are minor and transitory. Vitamin A supplements should not be given to any pregnant woman or a woman of reproductive age because of the risk of teratogenicity (2).

Children aged 6 months and above should ideally receive high-dose supplements at intervals of 4–6 months. The recommendation for postpartum supplementation for mothers is one 200 000 IU dose to be administered within 6 weeks after delivery, which is usually a period of infertility in breast-feeding mothers (2). If children show signs of xerophthalmia, they should be treated and receive an appropriate dose of vitamin A on 2 successive days and another dose two weeks later. To avoid multiple dosing, vitamin A supplementation should be recorded on the child's health card.

Vitamin A supplementation is the easiest intervention to add to routine EPI schedules or national immunization days and requires a minimum of training and equipment. EPI and nutrition staff should collaborate closely to design and implement vitamin A supplementation through immunization encounter points. Good planning is essential for the successful integration of vitamin A supplementation with immunization. The following are useful steps to follow when undertaking such an event.

EPI schedule for vitamin A supplementation *(3)*

Target group	Immunization contact	Vitamin A dose
Routine schedule: All **mothers** irrespective of mode of infant feeding up to 6 weeks postpartum if no vitamin A supplement received after delivery	BCG, OPV^0, DTP^1	200 000 IU
Infants 9–11 months	Measles	100 000 IU
Children 12 months and older	Measles	200 000 IU
Children 1–4 years	Booster doses Delayed primary immunization	200 000 IU
Campaigns: Infants 6–11 months	e.g. OPV national immunization days	100 000 IU
Children 12–59 months		200 000 IU

1. Define whether the area or region has a vitamin A deficiency problem.

2. Convince decision-makers of the importance of vitamin A supplementation and engage partners such as WHO, UNICEF, the Red Cross or non-governmental organizations and aid agencies.

3. Inform and educate the public, health care workers and politicians about the advantages of supplementation and the dangers of deficiency.

4. Evaluate success and use this information to improve delivery of vitamin A in subsequent events.

References

1. World Health Organization. Integration of vitamin A supplementation with immunization. *Weekly Epidemiological Record*, **4**: 1–8 (1999).

2. Expanded Programme on Immunization. *EPI Update No. 33*. November 1998.

The microbial threat: Copenhagen recommendations

The increasing resistance of microorganisms to antimicrobial agents is a major public health problem in Europe. The international spread of microorganisms means that this can no longer be regarded as a national, but an international problem and requires a common, global solution.

In September 1998, Ministers of Health from European Union countries met at a conference in Copenhagen, Denmark, to address the growing problem of antimicrobial resistance within Europe. Recommendations from the conference were subsequently drafted and transmitted to all Ministers of Health in the European Union. A summary of the conclusions and recommendations follows.

Participants at the conference agreed that there is an established but complex link between the consumption of antimicrobial agents and the prevalence of drug resistance. Although the full extent of the problem is as yet unknown, resistance is leading to increased deaths and illness, with consequential health expenditure. Although the pharmaceutical industry is making great efforts to develop new antimicrobials, innovative medicines cannot be expected to solve the immediate problem. It is thus a priority to introduce policies which govern the rational use of the antimicrobials currently available.

The provision of good quality data on resistance patterns which are clinically and epidemiologically relevant is essential if effective interventions are to be implemented. A European surveillance system should be established based on existing national systems to monitor trends in antimicrobial resistance of microorganisms of both human and animal origin and the European Union should coordinate the medical and veterinary sectors and seek the active involvement of all parties.

Rational use of antimicrobial agents

Educational initiatives for both health professionals and the general public are of major importance for improving the use of antimicrobial agents. Antimicrobials for therapeutic use should be prescription-only medicines and as such should not be advertised to the public. Guidelines for the rational use of antimicrobials should be introduced into medical and veterinary practice. Guidelines on good practice in prescribing antimicrobials should be drawn up which set out (i) the conditions under which antimicrobials should be prescribed; and (ii) the importance of patient compliance and how this can be achieved. Laboratories carrying out antimicrobial testing should be strengthened.

The majority of participants at the conference considered that use of antimicrobials as growth promoters was not justified and that safer non-antimicrobial alternatives should be developed, including improved farming practice. It was also considered urgent to conduct a full risk assessment and coordinated research on antimicrobial resistance should be given high priority.

Conclusions and recommendations

- Antimicrobial resistance is a major European and global problem.
- Pharmaceutical companies should be encouraged to develop new antimicrobial agents.
- The European Union and Member States should set up a European surveillance system of antimicrobial resistance.
- The European Union and Member States should collect data on the supply and consumption of antimicrobial agents.

- The European Union and Member States should encourage the adoption of a wide range of measures to promote prudent use of antimicrobial agents.
- The European Union, Member States and national research councils should make coordinated research on antimicrobial resistance a high priority.
- A way should be found to review progress of these recommendations and proposals.

Reference: Ministry of Health & Ministry of Food, Agriculture and Fisheries, Denmark. European Union Conference, *The Microbial Threat. "The Copenhagen Recommendations"*. 10 September 1998.

The International Pharmacopoeia: 50 years on

In countries with a robust pharmaceutical market, regulatory control measures ensure that drugs are efficacious, safe and of good quality. However, the extent to which a national health authority is able to provide adequate regulatory control will depend on prevailing conditions, experience and the resources available to it. A prime consideration for WHO is to support national health authorities with reliable expertise, information and technology. One important tool in the overall task of assuring quality is a pharmacopoeia.

A pharmacopoeia is an official, legally binding document which, in the majority of countries, is incorporated into the framework of national health legislation. This means that any pharmaceutical product being manufactured within its boundaries must conform to the nationally adopted pharmacopoeia which will contain quality specifications for the determination of finished drug products, drug substances and excipients. A quality specification describes appropriate tests to confirm identity and purity, and to determine the strength or content, of an active substance.

The underlying principles of a pharmacopoeia are that pharmaceutical substances and products intended for human use should be manufactured in adequately equipped facilities which are managed by competent professionals and operated by qualified staff. General rules governing pharmaceutical manufacture are contained in good manufacturing practices (GMP). Processes, premises, and installations should also comply with regulations under which the product licence or marketing authorization has been granted and with any binding international standards in the case of those products destined for export.

Pharmaceutical preparations are usually produced on a large scale and are stored while they await transport. During storage, pharmacopoeial testing should be undertaken to verify physical and chemical stability during the claimed shelf-life. Such pharmacopoeial tests will allow for the inevitable variations that occur during production and packaging as well as for subsequent degradation during storage.

The following important principles should be considered when pharmacopoeial standards are used to establish compliance with regulatory requirements:

- the application of a monograph is understood as compliance with **all** general requirements contained therein and testing methods, texts, or notices pertaining to it;
- a product is not of pharmacopoeial quality unless it complies with **all** the stated requirements.

A clear distinction exists between pharmacopoeial standards and release specifications, although both comprise identical or similar tests. Release specifications are applied by the manufacturer of a pharmaceutical product to confirm quality. However, since the manufacturer is responsible for the quality of the product throughout its shelf-life, tests must also be predictive. Thus, manufacturers' release specifications are generally more exacting than the corresponding pharmacopoeial requirements. As a general rule, quality must be built into a product throughout the manufacturing process and cannot be added at a later stage of production.

The International Pharmacopoeia

The history of *The International Pharmacopoeia* dates back to 1874 when the strengths and composition of drugs and their terminology were documented in the *Unification of the Formulae of Potent Drugs*. In 1929, an agreement drawn up between 19 countries proposed that the League of Nations should collaborate in the task of preparing an "international pharmacopoeia".

In 1948, the First World Health Assembly approved the establishment of an expert committee to support the work on *The International Pharmacopoeia*. Within the same context, the Programme on International Nonproprietary Names (INN) for Pharma-

ceutical Substances was set up in 1950 to create a single nonproprietary name to identify pharmaceutical substances unambiguously worldwide.

In collaboration with national commissions, the first edition of *The International Pharmacopoeia* was prepared by adapting and harmonizing monographs which were already published in major pharmacopoeias and by the development of new standards. Drug substances were chosen with the needs of developing countries in mind and with emphasis on treatments for tropical diseases. The first edition of *The International Pharmacopoeia* appeared in English, French and Spanish, and was subsequently translated into German and Japanese. It comprised 422 monographs and 59 appendices, including monographs on pharmaceutical starting materials.

The second edition of *The International Pharmacopoeia* saw the addition of a number of new monographs. Specifications were tested by national pharmacopoeia commissions, national quality control laboratories, pharmaceutical manufacturers and national institutes and 162 pharmaceutical preparation specifications were added, while 114 monographs were deleted. The appendices included a number of new analytical control methods using infrared spectrophotometry, chromatography (column, paper and thin-layer), nonaqueous titration, and radioactivity.

By 1975, a trend was developing among the major pharmacopoeias to include techniques requiring expensive analytical instrumentation of the kind that is not readily available in smaller drug testing laboratories operating on low budgets. In response, it was decided that *The International Pharmacopoeia* should focus on providing information adapted to the needs of developing countries and recommend only simple, classical techniques which would give a reasonable assurance of identity and quality. Priority was given to monographs for those drugs that are most widely available throughout the world and used in national control programmes or contained in the Model List of Essential Drugs. Information was also provided on drugs likely to contain impurities arising from degradation during storage, or which are difficult to manufacture.

Volume 5 of the third edition is now in the final stages of preparation. It contains additions to the list of monographs for active pharmaceutical substances and a number of important general texts on dissolution tests, nomenclature and specifications for tablets. It will include the newly developed antimalarial drug substances.

Future activities

In the future, work on dissolution tests for predicting the capacity of equivalence testing of groups of drug products will be undertaken. WHO will also continue to provide monographs for starting materials using simple test methodologies. The importance of this activity was emphasized following incidents of contamination of pharmaceutical products with diethylene glycol.

Future activities of *The International Pharmacopoeia* should be regarded in the context of quality control of pharmaceuticals in general. Many countries still do not have their own national pharmacopoeia and depend either totally or in part on the monographs included in *The International Pharmacopoeia.*

It must be emphasized that the trend of advocating expensive methods for drug testing is driven by increasingly large-scale drug manufacture and does not consider the more varied practical needs of developing countries. This renders the major pharmacopoeias less and less adapted for the practice of drug quality control in countries that need drug testing methods for various other reasons, such as on-the-spot identification of counterfeit pharmaceuticals.

Artemisinin: guidelines for use

Artemisinin products were first developed as antimalarials in China. They resolve fever and clear parasites more rapidly than any other known antimalarial agent. Moreover, they are the only group of antimalarial drugs to which *Plasmodium falciparum* has not yet developed resistance and, as such, play an essential role in malaria control. Protection of this product from resistance will depend on controlled, rational use requiring the urgent development and implementation of global and national policies concerning management, availability and prescription.

In order to address these issues, a meeting was held in Geneva from 10 to 12 June 1998 to review the use of artemisinin products in the light of experience now available from several countries. Participants at the meeting gave advice on policy and drafted guidelines for the selection and correct use of artemisinin products in different epidemiological situations. A summary of the report of the meeting follows. More information is available from the report itself, which includes information on recom-

mended regimens and clinical use of artemisinin products as well as priority areas for further research*.

In practice, the process of registration and availability of artemisinin products varies depending on the particular circumstances of each country. Some countries, such as Bangladesh and the Philippines, do not have a problem with multidrug-resistant malaria and have not allowed these drugs onto the market. Others, such as Myanmar and Viet Nam, face problems of resistance to antimalarials and consequently allow artemisinin products to be traded by pharmacies and market sellers where populations do not have access to public health services.

Thailand was one of the first countries outside China and Viet Nam to use artemisinin products in the public sector. During the early 1990s, it was facing acute problems of multidrug resistance with failure rates of antimalarials, and particularly mefloquine, reaching over 50% in some areas. In view of the lack of full registration of artemisinin products in any highly developed country, the Thai authorities allowed probational use of the drug in the public health sector on the understanding that reinforced postmarketing surveillance would be carried out. All batches of imported artemisinin products were controlled for quality by the Thai Food and Drug Administration.

Faced with an unacceptable level of chloroquine failures, Papua New Guinea has also revised its antimalarial drug policy. A combination of chloroquine plus sulfadoxine/pyrimethamine is the first-line drug of choice with oral artesunate in reserve. Parenteral or rectal artesunate is available for the treatment of severe malaria. In Brazil, dispensing of artemisinin products is restricted to approved public sector hospitals, but only for the treatment of severe malaria.

By contrast, artemisinin products are widely available in Africa despite warnings recommending caution. Injectable artemether and oral artesunate produced by French-based companies have now been registered in 38 countries in Africa. Formulations from China are also circulating.

A weak regulatory system is one of the greatest obstacles to the correct deployment and rational use of antimalarials. Even in countries where regulatory mechanisms are well established, the system is bypassed by illegal activities which lead to the sale of substandard and counterfeit drugs. The WHO Certification Scheme is a useful way of verifying the status of imported products. Alternatively, many countries insist on the provision of a certificate of registration and free sale from the country of origin. However, a free-sale certificate will not give information on the quality and stability of the product under local conditions.

Essential requirements for the rational use of artemisinin products are:

- A drug registration authority which will regulate the import and distribution of drugs and will be able to resist commercial pressure to make drugs freely available.
- Development of a sound national antimalarial drug policy and inclusion in the national essential drugs list.
- Awareness campaigns to prescribers on the rational use of drugs.
- Information, education and communication to the general public on appropriate treatment-seeking behaviour.

An assessment of the quality of artemisinin products can be made using several methods, ranging from the relatively cheap thin-layer chromatography (TLC), to high performance liquid chromatography (HPLC) with ultraviolet detector allowing accurate quantification of diluents and breakdown products. The former system may be used at entry ports or for on-the-spot testing, with confirmation from the second method situated, for example, in a national control laboratory when regulatory action needs to be taken. WHO is presently developing *in vitro* dissolution profiles for dosage forms, and quality specifications for the artemisinin products will soon be published in *The International Pharmacopoeia*.

Recommendations

1. Use

- Artemisinin is a safe and effective alternative to quinine for the treatment of **severe malaria**. In areas where sensitivity to quinine is reduced,

*World Health Organization. *The use of artemisinin and its derivatives as antimalarial drugs.* Report of a joint CTD/DMP/TDR Informal Consultation. Unpublished document WHO/MAL/98.1086.

artemisinin is the treatment of choice. In other areas, a change from quinine to artemisinin will not necessarily improve survival, but may be preferred in view of ease of administration and lessened side effects.

- Artemisinin is a potent and effective drug for the treatment of **uncomplicated malaria.** However, use should be limited to patients with multidrug-resistant malaria.

- To improve efficacy of the drug and **delay onset of resistance** artemisinin should always be used in combination with another effective antimalarial. Under certain circumstances, such as a history of adverse reactions to the combination, monotherapy may be indicated. In this case, a 7-day course of treatment is recommended as long as compliance can be assured.

- In areas where mefloquine is the first-line drug of choice, or a change to mefloquine is being considered, a 3-day course of artemisinin in combination with mefloquine is recommended.

- Combination therapy using artemisinin and artemisinin derivatives could slow resistance to each component and is a promising strategy. However, studies have not yet evaluated the tolerability, efficacy, effectiveness and cost benefit of this approach.

- The use of parenteral preparations of artemisinin in patients able to take oral medication is not indicated.

- Artemisinin and its derivatives should not be used for chemoprophylaxis.

2. Registration

- National authorities should develop policies on the manufacture, import, distribution, promotion and use of artemisinin products with a view to preventing or delaying the development of resistance. It is important that health care providers, together with those involved in distribution and sale of these products, health organizations and community service agencies should comply with national policy.

- Only artemisinin products manufactured according to good manufacturing practices (GMP) should be used.

- In order to ascertain the regulatory and GMP status of products, the WHO Certification Scheme may be used by governments to provide information on the status of the product in the exporting country.

- Governments lacking expertise may call on the assistance of WHO when developing systems of GMP, quality assurance or testing.

- In order to maintain stability, special attention should be paid to conditions of transport, distribution and storage.

3. Drug susceptibility monitoring

- Monitoring is the responsibility of the national control programme and should be conducted in sentinel sites on a regular and sustained basis. Patient response should be monitored to detect changes in susceptibility.

- Wherever artemisinin products are used, postmarketing surveillance should be in place. Although there is now a body of information confirming the safety of standard artemisinin regimens, information is still needed on the long-term effects, particularly among pregnant women and following repeat treatments.

4. Information

- Guidelines on the use of artemisinin products should be made available by national authorities and distributed to all health care providers, distributors and sales outlets. This information may complement the national formulary, prescribing information or guidelines for pharmacists.

- To avoid consumer misuse, it is important to educate the general public on the correct use and need for compliance when taking these products.

- Donor agencies, consumer service organizations and pharmaceutical companies should be discouraged from promoting or importing these drugs outside of official channels.

- Countries facing problems of multidrug resistance should develop mechanisms whereby they may share information and experience with other countries.

In order to achieve implementation of these recommendations, collaboration will be required not only from the public and private health care sectors but the community at large.