



The future of vaccines

Vaccines have played a vital role in the on-going battle against infectious diseases.

Maria Lattanzi, Rino Rappuoli and **Tiziana Tonini** explore the developments and challenges that lie ahead.

Infectious diseases are one of the most terrible enemies mankind has faced during its whole existence. They have changed human fate and the course of history, and influenced national economies more than any war.

The history of vaccine development

The observation that people who survive an infectious disease do not get it again is extremely old. The historian Thucydides, describing the Peloponnesian War, reports that during the plague of Athens in 430 BC, it was common practice to use those who had recovered from the disease to take care of the sick, because 'the same man was never attacked twice'.

The practice of inducing artificial immunity by deliberate infection of healthy people is also very old, like variolation, which goes back to 590 AD in Asia. The procedure was to transfer infected material from a smallpox lesion to healthy people to make them resistant to subsequent exposures to this deadly disease. Nevertheless, the practice was still a desperate undertaking, because up to 4% of the healthy individuals treated developed a severe form of the disease and died, but this was still much lower than the 20–30% fatality rate from natural smallpox. A more success-

ful approach came in 1796 with Edward Jenner, an English physician who, during his practice in the countryside, had noticed that farmers exposed to infected material from cows did not develop smallpox, but acquired immunity to the disease.

The scientific approach to vaccination came only a century later, when Louis Pasteur introduced the concept that infectious diseases were caused by micro-organisms. Using this empiric approach, Pasteur developed the first vaccine against rabies, which, on 6 June 1885, was successfully used to inoculate Joseph Meister, an Alsatian boy bitten by a rabid dog. Large-scale vaccination came only following the discovery of a safe and reproducible way to inactivate toxins and pathogens with formaldehyde treatment, performed by Glenny & Hopkins in 1923 and Ramon in 1924, and of the stable attenuation of pathogens by serial passage *in vitro*.

Between 1920 and 1980, using these simple, basic technologies, vaccines were developed to control many infectious diseases. The achievements made during this period were remarkable. The introduction of routine mass vaccination was responsible for the eradication of smallpox virus in 1977, and of poliomyelitis in the WHO American, Pacific and European regions. Moreover, seven other threatening diseases [diphtheria, measles, rubella, mumps, pertussis, *Haemophilus influenzae* type b (Hib) and tetanus] have been reduced by more than 97% in those countries in which the respective vaccines have been introduced.

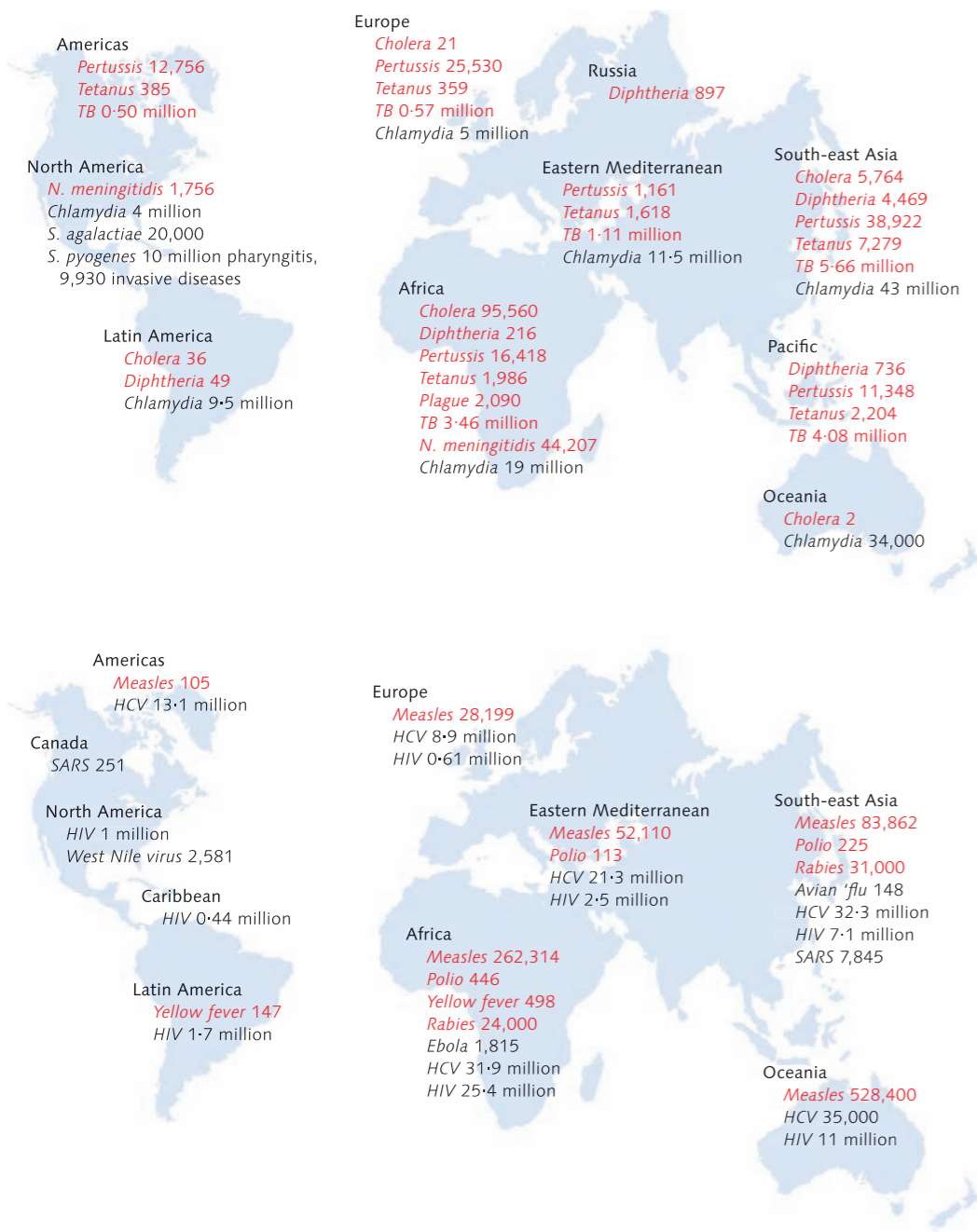
The need for new approaches

The emergence of new diseases such as AIDS, hepatitis C, Lyme disease, West Nile virus, SARS and avian 'flu, as well as the re-emergence of diseases thought to be under control, such as tuberculosis, together with the dramatic spread of resistance to antimicrobial agents by *Neisseria gonorrhoeae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and other pathogens, has increased the need for the development of new vaccines based on modern approaches (Fig. 1; see also Table 1 with the online version of this article for a list of websites and resources for infectious diseases). With conventional approaches to vaccine development, a pathogen is first studied to identify the factors capable of eliciting protective immunity, and these factors are then purified from large-scale cultures of the organism. This approach has severe limitations, not only because of safety issues, but also because several pathogens are very difficult, or even impossible, to grow *in vitro*.

Recent developments

From the early 1980s, emerging technologies stimulated a new enthusiasm in vaccine research. The advent of recombinant DNA technologies led to the production of subunit vaccines based on specific antigens. Once the protective antigens of a pathogen have been identified, the corresponding coding genes can be cloned in other organisms, which become the vaccine factories. This approach has generated two very efficacious recombinant vaccines: the hepatitis B vaccine and the

◀ Doctor holding a syringe containing influenza vaccine. Saturn Stills / Science Photo Library



acellular vaccine against *Bordetella pertussis*.

Novel vaccine components are also being vigorously explored, like DNA vaccines, conjugated vaccines, new combination vaccines, new formulations, fresh delivery routes and new adjuvants.

Similarly, new and powerful scientific approaches have revolutionized the way in which microbial pathogenesis and vaccine design are studied (Fig. 2). These include genome sequencing, *in silico* analysis, proteomics (including 2D polyacrylamide gel electrophoresis, multidimensional high-performance liquid chromatography, mass spectrometry and protein arrays), DNA microarrays, *in vivo* expression technology and signature-tagged mutagenesis.

Computational vaccinology has, and will have, a major support role in the analysis of antigen presentation and in the characterization of the most effective targets for immune response. Studies of the surface of microorganisms are leading to the use of synthetic peptides and monoclonal antibodies in vaccinology.

'Reverse vaccinology' is based on a genomic approach, by which the protective molecule is developed using the information contained in its genetic code. This has been applied for the first time to tackle *Neisseria meningitidis* group B (MenB) vaccine development, which has been unsuccessful until now. The reverse vaccinology approach can be used with any other pathogen for which conventional vaccinology has failed and has been applied to many other bacteria like *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Staphylococcus*

aureus, *Porphyromonas gingivalis* and *Chlamydia pneumoniae*, and parasites such as *Plasmodium falciparum*.

Moreover, reverse vaccinology can be applied to viruses. In fact, even though viral genomes, due to their small size, have been available for more than two decades, the approach to vaccine development has always been conventional. Only structural (envelope and core) antigens have been usually considered to date. Promising results with HIV early proteins such as Tat, Rev, Pol, etc., show that this approach may provide effective new weapons in the fight against AIDS.

Progress in DNA sequence technology shows that it is now possible to obtain the genome map of any micro-organism in a relatively short time.

Formulation and delivery of vaccines

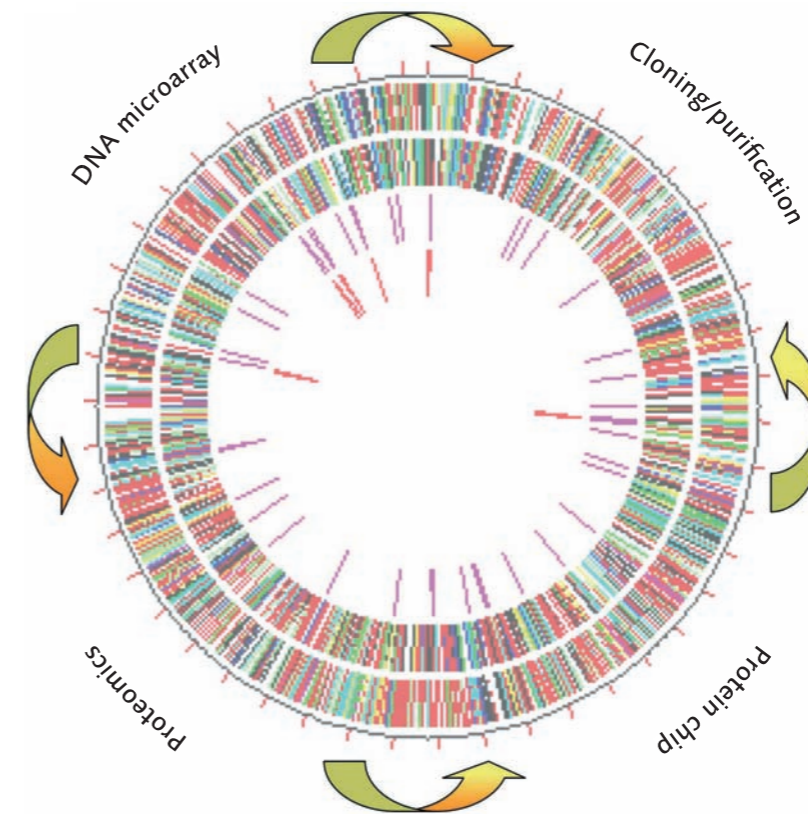
In addition to finding the most suitable vaccine candidate, increasing attention has been paid to the importance of the formulation and delivery of vaccines to maximize their potential. With a few exceptions, most vaccines are presently given by intramuscular injection, which is a primitive way of delivering drugs. Development of mucosally delivered

vaccines has many advantages: not only will this technology provide a more convenient method that increases compliance among recipients as well, but it will stimulate an immune response at the mucosal sites, the entry point of most pathogens, responses that are usually not stimulated by systemic vaccines. It is anticipated that within the coming decades we will have more convenient oral and mucosal delivery of vaccines.

What next?

We now have the technology to make vaccines against most pathogens. In theory, we could free mankind from the majority of infectious diseases. However, despite the enormous technical advances, today vaccines are no easier to develop because of the increase in regulatory and liability burdens that have made investing in vaccine development rise to the highest levels ever seen. Nevertheless, experts have calculated that vaccines are cost-effective because they are less expensive than the cumulative cost of treatment, hospitalization, lost working days, etc. But we believe that the benefits of vaccines go far beyond the money saved in treating diseases. What is the value of being alive? What is the value of being healthy? What is the value of the lost opportunity for economic growth?

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◀ Fig. 1. The annual number of cases of selected bacterial (upper panel) and viral (lower panel) diseases. Vaccine-preventable diseases are indicated in red.

▶ Fig. 2. The genomic revolution.

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