Parliamentary Office of Science and Technology

postnote

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Infectious Disease – EMBL conference

A conference in Heidelberg on 8-9 November 2002 brought together over 100 researchers from a wide range of backgrounds to discuss challenges, threats and responsibilities in the field of infectious diseases. This report summarises the main themes emerging from the conference.

Background

The conference was jointly organised by two bodies:

- EMBL (European Molecular Biology Laboratory), a basic research institute funded by 16 member states, including most EU members, Israel and Switzerland.
- EMBO (European Molecular Biology Organisation), a body that promotes biosciences in Europe funded by some 25 member countries (see www.embo.org for more details).

Both these bodies run science and society programmes to encourage debate on the impact the biosciences have on society at large. This was the third joint conference EMBL/EMBO have organised: previous subjects were "Developing a new dialogue" (2000) and "From genomes to cures" (2001). This years conference focused on two main areas:

- How to meet the challenge presented by the three main 'killer diseases' (see below);
- Biological weapons – abuses of infectious disease.

Killer diseases

The first part of the conference (see box 1 for the programme) focused on the three biggest killers:

- HIV/AIDS - WHO estimates AIDS killed 2,940,000 people worldwide in 2000). The epidemic is still growing: UN AIDS estimates that there were 5M new HIV infections in 2001, compared with 3.2M deaths from AIDS. Speakers expressed particular concerns over the situation in China, Russia and India.

Box 1 The Speakers

Session 1 North – south: the political economy of affliction

Paul Farmer (Harvard Medical School) Infections and inequalities: examples from Haiti and Peru

Marcel Tanner (Swiss Tropical Institute) New challenges for research partnerships to alleviate disease & poverty

Didier Fassin (University of Paris) The embodiment of inequality: political anthropology of AIDS in S. Africa

Carlos Morel (WHO) Neglected diseases, underfunded research, poor health interventions: can we change this

Session 2 The big killers: past, present and future

Robin Weiss (UCL) HIV and AIDS

Paul van Helden (University of Stellenbosch) Politics, research & the control of TB in the developing world

Janet Hemingway (Liverpool School of Tropical Medicine) Past problems and future opportunities for malaria and dengue control

Laurie Garrett (Newsday, USA) The gaps: wealth, life expectancy, public health infrastructure and the big global killers

Session 3 Consequences and responses

Peter Goodfellow (GlaxoSmithKline) The barriers to the production of new antibiotics

Helena Maekelae (Finnish National Public Health Institute) Knowledge: a prime weapon of defence against infectious diseases

Rob Ridley (WHO) Responding to unmet medical and control needs: past experience and future opportunities

Yiming Shao (Chinese National Centre for AIDS Prevention and Control) Infectious disease control in China: shift from Government to PPP

Session 4 Biological weapons: abuses of infectious agents

Jan van Aken (Sunshine project) Bioweapons and genetic engineering: the dual use problem in the biomedical sciences

Volker Beck (adviser German Foreign Office) – Advances in S&T: risks, perspectives and responsibilities

John Walker (FCO) The role of the Biological and Toxins Weapons Convention in combating infectious disease

- Tuberculosis (TB) – WHO estimates that TB killed 1,660,000 people in 2000. According to Professor van Helden, around 1 in 3 of the world's population is infected with the bacterium that causes TB and rates of the actual disease are growing rapidly in some countries. The emergence of multi-drug resistant TB in southern Africa and Russia is a particular worry.
- Malaria – responsible for 1,080,000 deaths in 2000 according to WHO estimates. Major concerns in this area are that the most frequently used diagnostic test is out-dated and inaccurate, and that the current policy of using pyrethroid-impregnated bednets may encourage the emergence of vectors that are resistant to this pesticide.

Social, economic and cultural factors

While these diseases are caused by biological agents, social, economic and cultural factors play a large part in influencing their mode of transmission. These include:

- Poverty – in general, these diseases are most prevalent in the poorest regions of the world, and are strongly correlated with poor nutrition, high unemployment and low spending on health infrastructure. However there are exceptions to this rule of thumb – for instance, Botswana, which has one of the highest standards of living of all the sub-Saharan African countries also has one of the highest HIV sero-positive rates.
- Gender inequality - a factor affecting the spread of sexually transmitted diseases such as HIV/AIDS.
- Migration/conflict – disease rates tend to be highest among populations affected by war or other political instability that causes mass migration of populations.

One of the main themes emerging from the conference was the importance of taking such factors into account when devising measures to tackle infectious disease. It was recognised that while the biomedical sciences could produce new tools – drugs, vaccines, pesticides, etc. – to control disease, such tools were most effective when deployed in programmes that took account of local social, economic and cultural factors. The social sciences – along with biomedical, clinical and public health research - thus have a crucial role to play in informing policy on infectious disease.

Interventions

The conference considered ways in which biomedical research could deliver new diagnostics, treatments and vaccines for each of the main killer diseases.

Tuberculosis

Current policy for treating TB is based on the WHO DOTS (directly observed treatment, short course) scheme. This includes detection by sputum smear microscopy and a treatment regime using a combination of antibiotics lasting 6-8 months in total, of which at least the first 2 months is directly observed (to ensure compliance). The conference heard that there was considerable scope for research to improve TB interventions:

- Diagnosis – sputum microscopy is rapid, but not very accurate and can thus lead to significant under-diagnosis. More accurate and rapid diagnostic methods have been developed for TB. One such method is a phage amplification test which uses viruses to detect the TB bacterium, is rapid, has specifically been designed for use in developing countries and delivers information about drug resistance. The test has proved to be highly specific and sensitive in field trials in South Africa.
- Better ways of delivering currently available drugs. Delivery is often hampered by the lack of healthcare infrastructure in many developing countries. The conference heard of initiatives where community health workers were recruited to deliver treatment and increase compliance with drug regimes.
- Research to develop new antibiotics. No new anti-TB therapy has been introduced in the last 40 years. The ideal antibiotic would be a small molecule, with a broad spectrum, and an entirely new mode of action. Pharmaceutical companies are conducting research into new antibiotics, but the technical barriers to developing such products are considerable and the commercial incentives somewhat limited. For instance, it was suggested that even if such a product were developed, it would be used sparsely (e.g. as a last resort) to prevent resistant bacteria emerging.

HIV/AIDS

A number of research priorities were discussed:

- Vaccine development – development of an effective vaccine was seen as the greatest priority. However, the prospects of such a development were seen as being somewhat limited because of the genetic diversity of the various different HIV strains. There was discussion of how effective any vaccine would need to be before its use was deemed to be justifiable. A particular concern was the possibility of HIV strains recombining in people with multiple infections to form new, possibly more virulent, strains.
- Treatments – it was agreed that there was a need for better antiretroviral therapies. But the biggest challenges was seen as ensuring that developing countries had access to the drugs that were already available and compliance with drug regimes.
- There was also seen to be a need for more clinical trials to assess the efficacy of anti-HIV treatments (e.g. to assess the use of nevirapine for reducing mother to infant transmission).
- The need to take account of local cultural and social factors in setting strategies aimed at reducing the spread of HIV. It was pointed out that women in developing countries were often not in a position to insist their partners wear condoms, or to change their behaviour based on education programmes.

Malaria

Research priorities for malaria included:

- Improved diagnosis – in developing countries malaria is usually diagnosed clinically, on the basis of reported symptoms. This leads to significant over-diagnosis. More accurate diagnostic methods have been developed based on detection of antibodies, DNA amplification or microscopy but have yet to be deployed in developing countries.

- Vector control – one approach to controlling malaria is by spraying pesticides to kill the mosquitoes that act as vectors for the disease. Another is to use pyrethroid-impregnated bednets. Concerns were expressed that the agrochemical industry was not developing new pesticides for disease vector control. This could become an increasing problem if wide-spread use of impregnated bednets leads to the emergence of pyrethroid-resistant vectors.
- Genetically modified vectors – another approach to vector control is to develop male GM insects that carry dominant lethal mutations. Releasing large numbers of such insects to mate in the wild could produce a generation of insects with lethal mutations that would 'self-destruct', thus decimating the population. But concerns were expressed over the potential costs of such a scheme and as to whether the approach would gain public acceptance. It was pointed out that any such scheme would require approval from *all* governments in the affected area: mosquitoes do not carry passports nor respect national boundaries.
- Development of effective vaccines and treatments – the recent publication of the sequence of the genome of the main cause of malaria (*Plasmodium falciparum*) and one of the vectors (the mosquito *Anopheles gambiae*) has raised hopes of accelerating the development of new vaccines and drugs. However, it was noted that any such developments would take many years to come to fruition.

Encouraging research

A main theme emerging from the conference was the need to encourage more research to develop better vaccines, drugs and pesticides to control infectious diseases in developing countries. Implicit in this was a recognition that the current system was failing to deliver the goods. The conference heard that one of the main problems is that the development of such products was not a particularly attractive commercial proposition. For instance, while there is an urgent need for new antibiotics to combat multi-drug resistant TB, there is little commercial incentive for companies to spend the several hundred million dollars required to develop them. This is partly a reflection of the fact that the main intended customers (developing countries) will not be able to pay a sufficiently high price for any new product to guarantee an attractive return on investment. Furthermore, potentially more lucrative markets in developed countries are unlikely to yield high returns, as any new antibiotic would probably be used sparingly to minimise the development of resistance.

Various ways of providing companies with greater incentives to fund research were discussed. The WHO sees public-private partnership (PPP) as the way forward, and is already involved in a number of such projects. Examples include the International AIDS Vaccine Initiative, Medicines for Malaria Venture and the Global Alliance for TB Drug Development. These PPPs all share a number of operational features:

- A focus on disease-specific indications (anti-TB drugs, anti-malarial drugs and HIV vaccines);
- Funding primarily from the public/philanthropic sectors with in-kind contributions (e.g. of expertise) from the private sector;
- Registration and licensing of products for commercialisation;
- Contractual arrangements to develop affordable products.

However, some are suspicious of PPP arrangements and the jury is still out over whether such approaches will prove effective. Alternative ways of encouraging research discussed at the conference included:

- Spending more public money on centralised research into infectious disease. The EU's 6th Framework Programme was cited as a missed opportunity as it places little emphasis on such research;
- Providing greater incentives for the involvement of private companies. Examples included differential pricing of drugs, relaxation of regulatory requirements, fast-tracking of clinical trials, guarantees by international agencies such as WHO to buy products once developed, and extension of patent life for certain types of products (e.g. antibiotics, vaccines).

Implementation

Developing new treatments, vaccines, etc. is only part of the story. Delivering them to the people that need them in a timely, effective, affordable and acceptable manner is just as big a challenge. Such issues can be addressed at the research stage to a certain extent. For instance, vaccines can be developed that contain multiple antigens (giving immunity to a number of diseases), are easy to administer (e.g. oral rather than injected) and are effective after a single dose. But effective implementation also raises a number of other issues:

- Health infrastructure - this was seen as one of the biggest needs, and requires significant investment. For instance, one speaker suggested that a basic network of integrated laboratories capable of diagnosing/treating HIV/AIDS, malaria and TB would cost around $32,000 per laboratory. The current lack of infrastructure in many developing countries was one factor cited as discouraging pharmaceutical companies from developing new treatments: the attitude being that there was little point developing new products if the basic means to dispense them was lacking.
- Programme design – as discussed previously, it was seen as essential that knowledge of the prevailing cultural, economic and social factors was built into the programme design at all stages. In practice this requires local consultation, good communication, a 'local driving force' and effective monitoring of programmes.
- Public health and sustainable development. The conference heard that HIV/AIDS was increasingly being seen in a wider, development, context and that this opened up potential new areas of funding (e.g. international development budgets). The WHO was seen as the appropriate agency for implementing health programmes. The need for a new body – a World Development Agency - to implement cross-cutting development programmes was not discussed.

Biological weapons

Background

Most of the countries that had programmes to develop biological weapons (BW) after World War II had discontinued their efforts by the 1960s. It had become apparent that there were significant technological difficulties in developing effective BW, and that it made little sense for countries with a nuclear capability to continue such programmes. It was against this background that the Biological and Toxin Weapons Convention (BTWC) was agreed in 1972. This prohibited the development, testing, production and stockpiling of BW and has been signed by 144 nations. However, the BTWC does not include a mechanism for verifying that nations are complying with its terms.

New BW risks

Since the BTWC was introduced, significant advances in science and technology have occurred, and these have opened up new possibilities for the development of BW. A number of potential new risks were discussed at the conference. For instance, it was noted that genetic modification (GM) had the potential to increase the pathogenicity of the viruses (e.g. the smallpox virus) and bacteria (e.g. those causing anthrax and the plague) that are of most current concern. It is now also relatively straightforward to produce GM pathogens which resist the most commonly used antibiotics. But it was also recognised that the pace of scientific development was such that it posed potential novel BW risks in the longer term. Some of the examples discussed are given in the following section.

'Synthetic' viruses

It was noted that it is now possible to synthesise simple viruses from scratch. For instance, US researchers recently announced they had synthesised viable polio virus using only commercially available chemicals and publicly available genome sequence. They did this by ordering short sections of DNA from companies selling made-to-order sequences, and then 'stitching' these together to obtain a DNA copy of the polio virus genome. This was converted to RNA using an enzyme, and this synthetic polio genome was used (along with cell extracts) to manufacture virus particles. This research has shown it is possible to synthesise simple viruses, but it is not clear what the implications are for developing BW (polio virus would not be a particularly effective BW). Viruses such as smallpox are of greater concern, but would be much more difficult to synthesise. This is partly because they are bigger (smallpox virus has 200,000 base pairs in its genome compared with 7,500 for polio virus) and partly because some of the virus's pre-formed proteins are needed to start replication.

Modified viruses

Recent research has shown that it is possible to increase the pathogenicity of a virus using GM techniques. Australian researchers attempting to produce an effective contraceptive for mice inserted two new genes into the mousepox virus. Rather than having the desired contraceptive effect, the modification transformed the virus from an agent that usually only causes a very mild illness into one that killed all the mice infected with it. Other concerns focus on the possibility of using GM to produce new virus strains. For instance, smallpox virus belongs to a family of very closely related viruses that include those responsible for chickenpox and mousepox. The genomes of these viruses are highly conserved, so it is possible that researchers could use GM to transform one of these closely related viruses into something that behaved very much like the smallpox virus.

Other risks

A wide range of other potential new BW risks were discussed. For instance, it was noted that increasing knowledge of the action of bio-regulators - substances produced in the body naturally that control fundamental biological processes – has potential to be exploited in BW. There was concern that as our knowledge of genetic variation between individuals increases (e.g. from the application of pharmacogenetics), then so does the potential for devising BW to target particular ethnic groups. It was also noted that the technology for production, stabilisation, weaponisation and storage of BW had significantly advanced and that humans were not the only targets for potential BW attack: attacks on agricultural animals and plants had the potential to cause massive economic disruption.

Ways forward

So what can be done to address these potential new BW risks? The conference identified several possibilities:

- Improved surveillance. The conference identified an urgent need for a global, rapid diagnostic/surveillance/reporting system that allowed the early detection of unusual outbreaks of disease. Ideally, such systems would include monitoring of plant and animal disease.
- Verification mechanism for the BWTC. This would be linked to surveillance and include a mechanism for investigating unusual outbreaks of disease (e.g. following accidental release from a BW plant). However, there is a need for baseline data on disease prevalence in order to identify unusual events.
- Stricter regulation of inter-laboratory transfer of 'biomaterials'. Measures could be built in to the BWTC to require verification/inspection of laboratories handling 'biomaterials' and notification of any international trade. The problem is defining what 'biomaterials' such measures would apply to: those with BW potential often also have legitimate (dual) uses in biomedical research.
- Regulation of research and knowledge transfer. It was noted that researchers faced an increasing dilemma over whether to publish research (e.g. the genome sequence of a pathogen) that had both BW and biomedical applications. Opinions differed as to whether self regulation was the best approach (e.g. with researchers judging the balance between public good and potential harm for themselves). Or whether a legally binding biosecurity convention was required to formally regulate research and its dissemination.