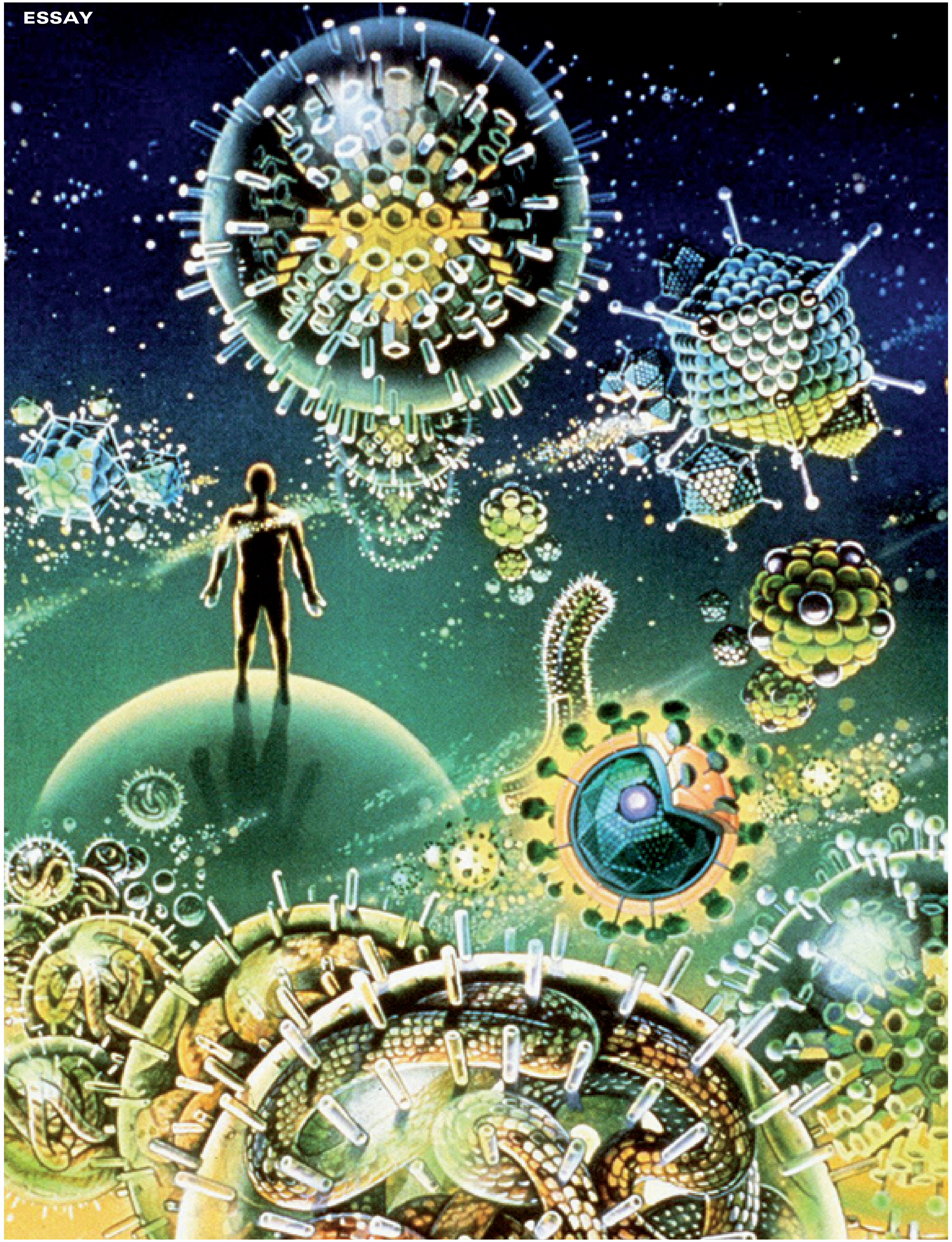


Taking Arms Against a Sea of Troubles …

Every two seconds somebody somewhere in the world dies from an infectious disease. And epidemics such as influenza or recently SARS serve to remind us again and again that we share this world with microscopically small infectious agents that continually haunt us. How severe is the threat from ancient and newly emerging diseases? How can – and must – medicine, basic research and politics defuse this situation? These are the questions that are of great concern to **PROF. STEFAN H. E. KAUFMANN**, *Director at the* **MAX PLANCK INSTITUTE FOR INFECTION BIOLOGY** *in Berlin.*

ILLUSTRATION: TG2-OSTERWALDER

SARS – this acronym shook the world at the beginning of the year, as "Severe Acute Respiratory Syndrome", an infectious pulmonary disease, spread worldwide. The disease started out at the end of 2002 from Guangdong in south China, probably from meat markets. Since then, in about 30 countries worldwide, more than 8,000 people have become ill and more than 800 have died from SARS, most of them in China.

As distressing as these figures may be, they only represent the tip of the iceberg. Compared to the 800 victims claimed by SARS so far, 500 individuals are stuck down every hour on this planet by AIDS and tuberculosis; last year five million people died worldwide from these two diseases. And stacked against the 8,000 SARS sufferers in the first half of 2003, more than 30,000 people are infected every day with TB and AIDS. In Germany alone, more than 40,000 people are HIV-positive, and in 2002 there were more than 1,800 new HIV infections and 600 AIDS-related deaths. The situation with TB is very similar: Last year in Germany nearly 8,000 people became infected and around 500 died – although the majority can be defined as socially disadvantaged and foreigners. Perhaps this is why the problem has not penetrated into general awareness ...

Of the 56 million premature deaths lamented annually in the world, infectious diseases account for around 17 million of these – claiming a victim every two seconds: almost as many as cardiovascular diseases, and more than those dying from cancer and all other disease groups. The number of deaths resulting from AIDS or TB alone is greater than the sum of all those who die due to wars (including the Iraq war), diabetes, Alzheimer's, Parkinson's, multiple sclerosis, breast cancer and rheumatic diseases.

However, the number of victims still says nothing about the disease's significance for a country's local economy. The death of 15 to 50-year-olds is a greater economic burden than that of small children or old people. Experts at the World Bank therefore introduced the concept DALY – Disability Adjusted Life Years – which provides a measure for healthy life years lost due to disease and invalidity. Even if this measurement ignores individual human suffering, it is informative as a purely economic statistical formula, since not only do ill people and invalids drop out of the workforce, caring for them costs money.

According to this calculation almost 40 percent of all lost life years can be accounted for by infectious diseases – many more than through accidents, wars, all neuropsychiatric disorders, cardiovascular diseases or cancer, which occupy the next positions in the statistics, and which, only when added together and measured by DALY, reach the same order of magnitude as infectious diseases.

Fear of the Invisibly Small

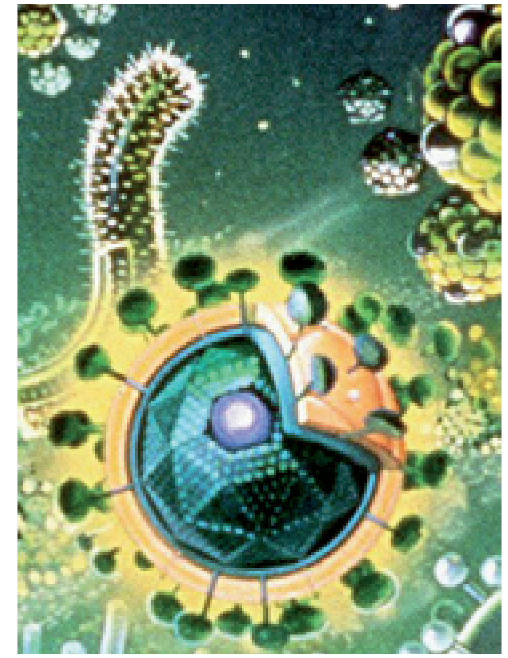
Against this background, even if they seem somewhat marginal, diseases such as SARS ensure a growing "epidemic awareness" and serve to remind us that infectious diseases are in no way extinct and remain a real threat – as they always were for humans: Epidemics have written history, caused mass migrations, wiped out whole populations and decided wars. The artists Raffael and Holbein, the composers Schubert and Mozart, the philosophers Nietzsche and Marx all died from infectious diseases.

Fear of infectious diseases is inseparable from the knowledge that they are spread by microscopically small organisms: by bacteria, viruses, fungi or protozoa, also sometimes by worms or – as we now know from BSE – by simple proteins, the prions. From the outset, humans have lived in close contact with microorganisms; they existed long before human beings appeared, and have survived every catastrophe on this planet. It is therefore somewhat arrogant to assume we can keep microbes in check. Rather, there is more to support the opposite view: Humans are here for the benefit of microorganisms.

Microbes developed more than three billion years ago. They had already occupied every niche on earth before human beings appeared on the scene five million years ago. About 30,000 years ago human communities had reached densities sufficient to provide pathogens with conditions conducive to their spread. In other words: if the three billion years since the beginning of bacteria corresponds to 3,000 kilometers on a map, then human origins lie only five kilometers away – and on this scale the 30,000-year history of human infections just reaches 30 meters.

The microorganisms' secret of success lies in a quite simple, yet at the same time very reliable trick: The combination of rapid replication and swift alteration. Many bacteria divide every half hour. That which takes humans with their long generation time a thousand years, can be managed by bacteria and viruses within several days. And even if the majority of mutations and recombinations (i.e. genetic alterations) are damaging or even lethal for the newly created organism, the few advantageous changes rapidly prevail and those carrying them invade a new niche. This makes microorganisms masters of adaptation.

Human development took a different path – that of distribution of labor through specialization and complexity. Humans generally see themselves as the most complex of all living forms and award themselves, quite unjustifiably, the title "crown of creation". Their organs see to the various tasks: stomach, intestine and liver cope with digestion, the lungs serve for breathing, the heart powers the blood circulation and the brain is responsible for sensory perception and thinking. Also in the battle against microorganisms humans rely on specialization. They have a special defense – the immune system that detects and attacks microorganisms in the body. The pathogen's speed and variation talents constantly compete with the human strengths, specialization and complexity: Only time will tell who will win in the end. With the development of vaccines humans, thanks to their capacity to think, discovered a strategy to effectively support their special forces for defense against the deadly invaders. Vaccinations prepare and train the immune system for attacks.



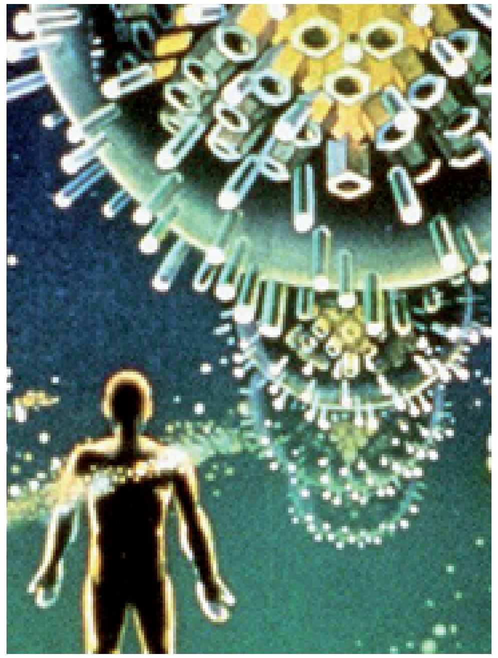
However, and this is regrettable, biomedical knowledge can also be abused. At the end of 2001 the world was confronted with a new dimension to the threat from infectious agents: intentional pathogen misuse for bio-terroristic goals. In the USA anthrax attacks led to four deaths and numerous anthrax infections, and triggered hysteria among the population. The warning that smallpox viruses – which actually count as being eradicated and should only still exist for safekeeping in two secure locations in the USA and Russia – could land up in the wrong hands has resulted in the stock-piling of smallpox vaccines in many countries. Although an attack with bio-weapons represents a low probability risk, the consequences could be catastrophic should it occur.

And that's not all: Modern methods of biotechnology and immunology could be misused to generate infectious agents with new properties. As shocking as the anthrax attacks at the end of 2001 in the USA were, they involved "classical" strains sensitive to antibiotics. However, the former Soviet Union bioweapon program has already constructed recombinant anthrax strains that are resistant to most of the available major antibiotics. Similarly, plague bacteria were genetically modified so that they can also produce diphtheria toxin, thus combining the risk of plague and diphtheria.

Also the ability to influence the body's own mechanisms has been subverted for war purposes, with the creation of endorphin-expressing pathogens: They are meant to induce good feelings in those infected tricking them to leave their sick bed rather than recover – and to walk about infecting more people. Similarly, a procedure was devised that provokes the body's own immune system into waging a form of "civil war". Here, the pathogen causing Legionnaire's disease was modified to produce the nerve component myelin and thus to provoke an aggressive auto-immune reaction that results in severe nerve damage. Added to all this are new results from Australian scientists: They generated mouse-pox viruses that release one of the body's own soluble mediators; this stimulates the production of antibodies, but at the same time represses protective immunity against the virus. The result is a pox virus against which every vaccine fails: a horrible idea that this could also apply to human pox viruses!

In principle, however, bio-terrorism needs no biotechnology, since the natural pathogen arsenal is more than sufficient to plunge the world into fear and panic. The lessons learned from recent disease outbreaks: Nature is the worst bio-terrorist. Here, humans also unwittingly contribute to new pathogens emerging: AIDS arose in African jungles where close contact between monkeys and humans led to transfer and subsequent spread of HIV. And SARS is the result of south Chinese markets' unhygienic preparation of civet cats and other animals destined for the dinner table.

AIDS and SARS, but also BSE and the new influenza viruses appearing every year show that infectious agents can jump from animals to humans and precipitate new epidemics. Most of these pathogens' survival strategies are directed at the animal host. Only a



few are equipped to adapt to a new host. That they sometimes then cause threatening diseases is a possible but not inevitable consequence. So we can be thankful that most pathogens fail at the cross-species jump and that only a few are successful.

Animal reservoirs, however, present a huge problem. They impede the battle against a pathogen and make its elimination impossible – particularly if the animals show no symptoms. Since corona-viruses have now been detected in various animals, we have to conclude that SARS will not quickly disappear from the planet. This summer SARS could be brought under control; but in winter it might possibly return. Such cycles are familiar with common colds, which are also caused by corona-viruses. Even when epidemics emerge far from Europe it is completely wrong to feel secure. Pathogens pay no attention to political borders: More than 1.5 billion flight passengers and more than 500 million border crossings per year make any containment impossible. In the global village no one is safe from disease. No disease has brought this to our attention better than SARS.

Pathogens Know No Borders

Instead of containment we must turn to defense – and here in the front line to vaccination. Worldwide vaccinations save 8 million people every year, a human life every 5 seconds. And this at an exceptionally modest price, since vaccinations are without doubt medicine's most cost-effective instrument. Unfortunately, their application has not been put to full use: Even today a further 2 to 3 million people, mostly children, could be saved if only they had the chance to be vaccinated.

Wherever vaccination programs are routinely carried out, they achieve astonishing success – with, for example, measles, polio, rubella, mumps, whooping cough and diphtheria, they reduce the disease rate to almost zero. The few cases that do arise are usually due to an incomplete protective vaccination course rather than vaccine failure.

Previously, vaccines were mainly developed empirically, which seldom uses the rapid advances in knowledge gained from basic research. But this strategy has now reached its limits. In principle, vaccines available today target those agents that cause disease directly. In contrast, many pathogens still awaiting a vaccine operate as sophisticated, sometimes persistent "guerilla" fighters that use refined strategies to escape the body's defense mechanisms. Vaccines against these pathogens can only be developed with the help of modern infection biology – the branch of basic research focusing on cellular and molecular events at the interface between infectious agents and human beings.

The new vaccine generation's priority goal is the battle against new as well as old infectious diseases, particularly the three greatest scourges of humankind: malaria, tuberculosis and AIDS. Next in line are new vaccines against agents for diseases that until recently were not considered infectious: hepatitis B virus, which causes liver carcinoma, papilloma viruses that cause cervical cancer, followed by Helicobacter pylori which promotes stomach ulcers and certain kinds of stomach cancer, as well as Chlamydia pneumoniae, now a suspected cofactor in cardiovascular diseases. Added to this are agents for new diseases whose potential danger is still difficult to assess – such as SARS.

Unfortunately, the path from basic research to vaccine use is long and goes far beyond research institutes' capabilities. Basic research certainly provides the basis for rational vaccine development; but the subsequent pre-clinical investigations often burst the basic researcher's resources. At the very latest, the basic researcher reaches the end of the road when clinical studies are lined up.

Here above all one must look to industry – who of course are looking out for the amortization of their own investments. The eradication of smallpox, and soon the polio virus, illustrates the vaccine research dilemma: the goal is to eliminate the disease. However, the faster and more thoroughly this is achieved, the less money is earned in the end.

Moreover, vaccines against many diseases are most urgently needed in the countries that have the least money available. It is no wonder that the industry is not particularly motivated to implement modern immunology and molecular biology opportunities at full power to develop vaccines. For the industry profits are too low. Therefore, public and private sectors must join forces – and not only for material reasons, but because it will especially benefit public health services.

In order to arouse the industry's interest one has to create suitable stimuli: guaranteeing tax benefits for vaccine producers, ensuring secure retail markets in developing countries, tiered prices (i.e. higher prices in industrial countries, lower in developing countries) as well as reasonable interest rate loans – up to debt relief – arranged through the World Bank for broad-based vaccination campaigns. Can we afford this at all? Is it worth it? From worldwide health expenses estimated at nearly 600 billion US dollars in 1996, less than 0.2 percent flowed into vaccinations. And from the money used in the same year worldwide for research and development in the health sector – nearly 60 billion US dollars - one billion US dollars, i.e. less than 2 percent was allotted to vaccine research. Even if these figures are likely to be somewhat higher today, the proportions have changed little. Some more numbers to add to the costs of epidemics: SARS exhorted a toll of more than 11 billion US dollars on the Asian economy and brought the entire flight industry 6 billion US dollars in losses – Lufthansa alone more than 500 million euros.

Things have also changed a little in the last few years. As an answer to 9/11 and the anthrax attacks in October 2001 the US government made 1.7 billion US dollars available for research on infection and immunity in 2003. True, this money was primarily intend-ed for internal security as well as prevention and treatment of diseases with bio-terrorist origins. In parallel, however, general problems in infection biology should also be addressed, which will lend powerful impetus to research into tackling the major endemic diseases.

In this respect the German research landscape remains virtually untouched. The EU did however allocate high priority to the so-called poverty related diseases such as AIDS, tuberculosis and malaria within the 6th framework project. One now has to establish a platform for clinical vaccination studies for these diseases. Also a valuable step in the right direction is the fact that soon in Germany, with support from the government research ministry, Vaccine Management GmbH will be created to improve connections between public and private sectors.

Research is Stuck in a Dilemma

Research and development cost money. But the fact that investments in research bring dividends in the long term is seldom discussed. Here, precisely vaccine development provides an impressive example of how well research money pays off. Experts from the World Bank and WHO have determined the value of vaccinations and other measures. According to them, vaccinations count as the most economical medical measure: every euro spent on vaccination against measles, mumps, rubella, diphtheria, whooping cough or tetanus saves 10 to 20 euros. Vaccination against infant tuberculosis, tetanus, polio, measles or hepatitis B, at a price of 10 to 40 euros per vaccination, extends a healthy life by one year. Not only does every one of us profit from vaccination – but the population at large is also saved enormous costs.

Research investments for vaccines available today, however, date back decades ago. So in fact we profit from financial input from earlier generations. Money invested in vaccine development now could bring dividends of similar magnitude in this millennium – and all the more so since now the path is also paved to developing vaccines against autoimmune diseases, allergies and cancer.

The epidemic clock is ticking – and we don't know how late it is: if it is 5 to, or already 5 past 12. But in any case it is urgent that we react now. As Voltaire so precisely put it: "We are responsible for what we do – but equally for what we do not do."