Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
International Journal of Medical Microbiology 296 (2006) 179–185
IJMM
www.elsevier.de/ijmm

REVIEW

Infectious diseases – A global challenge

Katja Becker[a,*], Ying Hu[a], Nikola Biller-Andorno[b]

[a]*Interdisziplinäres Forschungszentrum, Justus-Liebig-Universität, Heinrich-Buff-Ring 26-32, D-35392 Giessen, Germany*
[b]*Lehrstuhl für Biomedizinische Ethik, Universität Zürich, Zollikerstr. 115, CH-8008 Zurich, Switzerland*

Received 25 July 2005; received in revised form 9 December 2005; accepted 9 December 2005

Abstract

Infectious diseases represent a continuous and increasing threat to human health and welfare. Due to emerging diseases, increasing resistances, international travelling, and the risk of bioterroristic attacks, infectious diseases concern the whole world and can only be combated by internationally coordinated and interdisciplinary approaches. When assessing the worldwide publication activities on infectious diseases in the years 1994–2004 accessible via the ISI Science Citation Index Expanded®, an overall increase by 24% can be monitored. Furthermore, it becomes evident that highest research priorities are given to HIV/AIDS, hepatitis C, tuberculosis, respiratory infections, and sepsis. Ten countries – including the USA, the UK, France, Germany, and Japan – contributed to more than 80% of these publications; nation-specific research priorities focusing on the current problems in the respective country can be estimated. Countries with the highest disease burdens are still not given the opportunity to contribute adequately to the scientific field. Based on our data, relatively increasing publication activities include those on respiratory infections, tuberculosis, malaria, hepatitis, and sepsis, whereas decreasing activities were determined for AIDS, diarrhoea, meningitis, schistosomiasis, and other diseases. Accordingly, the prevalence of many infectious diseases occurring in tropical countries is not clearly reflected in the worldwide publication activities.

Keywords: Infectious diseases; Research activities; Publications

Contents

*Corresponding author. Tel.: +49 641 993 9121; fax: +49 641 993 9129.
E-mail address: becker.katja@gmx.de (K. Becker).

1438-4221/$ - see front matter © 2006 Elsevier GmbH. All rights reserved.
doi:10.1016/j.ijmm.2005.12.015

Infectious diseases – current situation

Due to multiple drug resistances, migration of populations, and emerging pathogens infectious diseases represent a continuous and increasing threat to human health and welfare. Despite the availability of antibiotics and vaccines against many of the causative pathogens, the mortality rates remain high. According to estimations of the WHO, infectious diseases caused 14.7 million deaths each in 2001, accounting for 26% of the total global mortality (http://www.who.int). AIDS, tuberculosis, and malaria furthermore range among the five major obstacles to increased life expectancies (Feachem, 2004).

Infectious diseases are not only a problem of certain areas in the world, although developing countries are carrying the major part of the burden. As indicated by the appearance and dissemination of the human immunodeficiency virus and the outbreak of the severe acute respiratory syndrome (SARS) (Krilov, 2004), infectious diseases concern the whole world and can only be solved by internationally coordinated and interdisciplinary approaches. In order to enable and facilitate the long-term control of infectious diseases, molecular biologists, biochemists and pharmacologists have to collaborate closely with physicians, epidemiologists and public health researchers in order to insure the transfer and application of scientific data to the field. In parallel, governmental institutions have to collaborate with private funding partners and industrial partners without losing influence on the research agenda. Control of infections can only be successful if priority is given to combating the individual suffering and its structural and socioeconomic causes rather than to serving political or economic interests (Perkins, 2004; Becker et al., 2003).

In order to better understand how we are positioned to meet the global challenge of infectious diseases and to make a real difference in the burden of disease, we looked at three issues: (1) What countries contribute most to what we know about infectious diseases? Do results still come from rich countries or are developing countries starting to have a voice in the international scientific literature? (2) By what criteria do researchers evaluate their peers' work? Do they rely on scientific quality only or do they also consider efforts to bridge the gap between research and application? (3) What contributions to infectious disease research are considered most important? Do researchers mainly think about classical landmark papers or rather about basic research or papers that had impact in terms of shaping public health policy or improving the health of populations?

Publication activities on infectious diseases are still dominated by industrial countries

In order to learn more about the worldwide contributions to infectious disease research, we assessed the publication activities of different countries in the years 1994–2004 which were accessible via the ISI WebPages (http://isi02.isiknowledge.com/portal.cgi?DestApp=WOS&Func=Frame). The database used is Science Citation Index Expanded (SCI-EXPANDED).

The 22 infectious diseases which – according to the estimations of the World Health Organization – caused more than 5000 deaths each in 2002 worldwide were included in this study. (http://www3.who.int/whosis/menu.cfm?path=evidence,burden,burden_estimates,burden_estimates_2002N,burden_estimates_2002N_2002,burden_estimates_2002N_2002_Region&language=english).

Since for the key word "maternal sepsis" only few hits were found in the database and since research on sepsis contributes scientifically also to the field of maternal sepsis, we decided to use the key word "sepsis" for our study.

The five countries with the highest publication activities over the last 10 years – as deduced from the data we obtained – were then chosen to assess the national research activities in the different fields of infectious diseases.

Our literature search yielded the following results: Between 1994 and 2004 more than 5% of the articles listed in the Medline database addressed the 22 infectious diseases we had selected for our sample. The total number of articles on these diseases increased from 51,267 published in the years 1994 and 1995 to 63,983 published in the years 2002 and 2003. Ten countries contributed to more than 80% of these publications. The 15 countries with the highest publication activities are listed in Table 1. The top five countries are USA, UK, France, Germany, and Japan. When analyzing the

Table 1. Ranking of different countries based on their contribution to publications in the field of infectious diseases between 1994 and 2004

Rank	Country	Number of articles	Percentage
1	USA	127,978	39.87
2	UK	34,369	10.71
3	France	26,060	8.12
4	Germany	20,622	6.42
5	Japan	17,828	5.55
6	Italy	16,131	5.03
7	Spain	11,454	3.57
8	Canada	11,076	3.45
9	The Netherlands	8340	2.60
10	Switzerland	8192	2.55
11	Australia	8063	2.51
12	Brazil	6506	2.03
13	India	6386	1.99
14	Belgium	5800	1.81
15	Sweden	5397	1.68

Data collected from the ISI Science Citation Index Expanded.

contributions of the different countries to the publications over the last 10 years, USA and France show a decreasing trend (since the overall number of publications on the selected diseases is increasing), the UK is stable, and Germany as well as Japan show increasing trends (for all trends $P<0.05$ according to the Cochran-Armitage Trend Test).

Our results concerning the ranking and developments of publication activities by countries are comparable to data reported by Takahashi et al. (2002), who analyzed the contribution of different countries to articles related to infectious diseases and published in selected journals. Whereas the share of articles from USA and Canada went down, the percentage of articles published by groups from Italy, Spain, and Brazil increased (Takahashi et al., 2002). As our analysis shows, Brazil and India are among the top 15 countries when taking the last 10 years into account. Once developing countries start to be among those who are highly active in the area of infectious disease research, chances are better that they will in fact participate fully in shaping the research agenda. Well-known experts from developing countries that have published in high-impact journals are certainly instrumental for reminding the scientific community as well as political and economic leaders of the so-called 10–90 gap indicating that less than 10% of the global health research resources are allocated to the health problems of developing countries, which account for over 90% of the world's health problems (http://www.globalforumhealth.org/site/003__The%2010%2090%20gap/001__Now.php).

Research priorities vary among different countries

As indicated in Fig. 1, over the last 10 years greatest attention has been given to HIV/AIDS-related research. Worldwide high priority has also been given to respiratory diseases, tuberculosis, and hepatitis C. This group of diseases is followed by sepsis, hepatitis B, diarrhoea, and malaria. It is notable to see that although diarrhoea and malaria represent the third and fifth most frequent causes of death worldwide they only rank on positions 7 and 8, respectively, in the research priorities. It might be speculated that one of the reasons for this constellation is the fact that these diseases seem to be less threatening for industrial countries.

Based on our data, publications on respiratory infections, tuberculosis, malaria, hepatitis B and C, sepsis, Dengue fever, Chagas' disease, Japanese encephalitis, and chlamydial infections increased over the last 10 years. Unfortunately, a decrease in worldwide publication activities was determined for AIDS, diarrhoea, pertussis, tetanus, meningitis, syphilis, schistosomiasis, leprosy, and diphtheria. Publications on measles, leishmaniasis and trypanosomiasis did not change remarkably (Cochran-Armitage Test for Trend, $P>0.05$ for all trends described).

The emergence of microbes resistant to antibiotics is considered to be a most serious threat to humanity (Hacker and Klenk, 2005). This fact is also reflected by the worldwide publication activities on drug resistance which more than doubled over the last 10 years.

The five countries with the highest publication activities were then in our study chosen for further analysis to assess the national research activities in the different fields of infectious diseases. In most countries, HIV/AIDS research is given the highest priority. In the USA (Fig. 2A) this is followed by respiratory diseases; for hepatitis C a strong increase can be monitored. A similar pattern becomes evident for France (data not shown). In the UK (Fig. 2B), HIV/AIDS, tuberculosis, and malaria research are particularly strong. In Germany – apart from HIV/AIDS research – priority is given to sepsis and hepatitis C research followed by respiratory infections (data not shown). In contrast, Japan focuses on hepatitis C followed by HIV/AIDS, respiratory infections and hepatitis B.

When we look at the development of research priorities over the last decade (Fig. 1) it is obvious that the burden of disease is certainly not the only factor in determining research intensity. For instance, the fact that diarrhoeal diseases are among the three most severe health problems (http://www.who.int) is not clearly reflected in worldwide publication activities. The top five countries with most publication activities on infectious diseases each seem to focus on diseases that are relevant within their own borders, like hepatitis B and C, sepsis, and HIV/AIDS. Countries with a colonial past, like the UK, seem to put more emphasis on diseases like malaria that are of particular relevance to developing countries.

The experts' view

In order to facilitate the interpretation of the statistical data and add some qualitative aspects to the quantitative analyses, we addressed senior scientists in the field of infectious diseases in autumn 2004 and sought their written opinion on the perception of infectious disease research and strategies that should be undertaken in the future. As a result, the input of 78 experienced group leaders (28% from Germany, 5% each from India, Switzerland, UK, and USA, 1–4% from 27 other countries in the world) could be included into this work. Of these 78 scientists, 32% declared that their main field of current research was virology, for

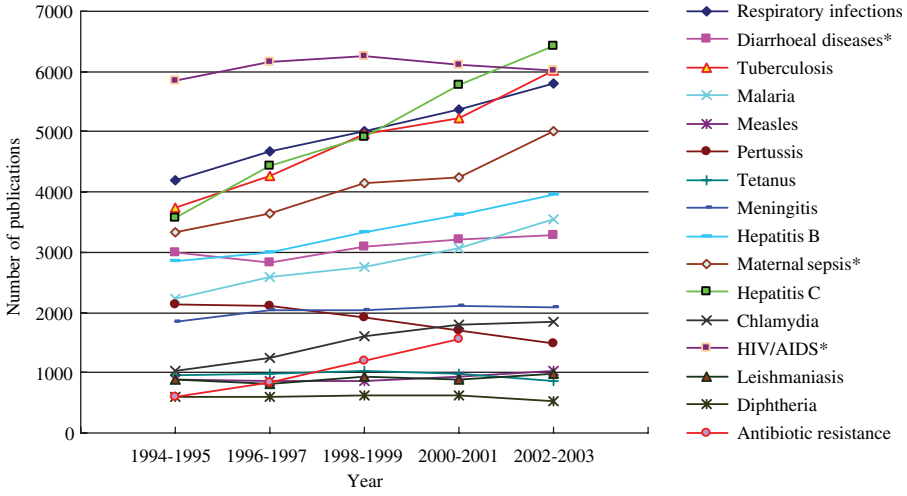

Fig. 1. The number of articles on selected infectious diseases and antibiotic resistance published between 1994 and 2003 worldwide. The 15 most important infectious diseases were included in this figure. *The search key word for "HIV/AIDS" was "(acquired immunodeficiency syndrome) OR (acquired immune deficiency syndrome) OR (HIV) OR (human immunodeficiency virus) OR (human immune deficiency virus)". The number of articles on "HIV OR AIDS" in the graph has to be multiplied by 3. The search key word for "diarrhoeal disease" was "diarrhoea"; the search key word for "maternal sepsis" was "sepsis".

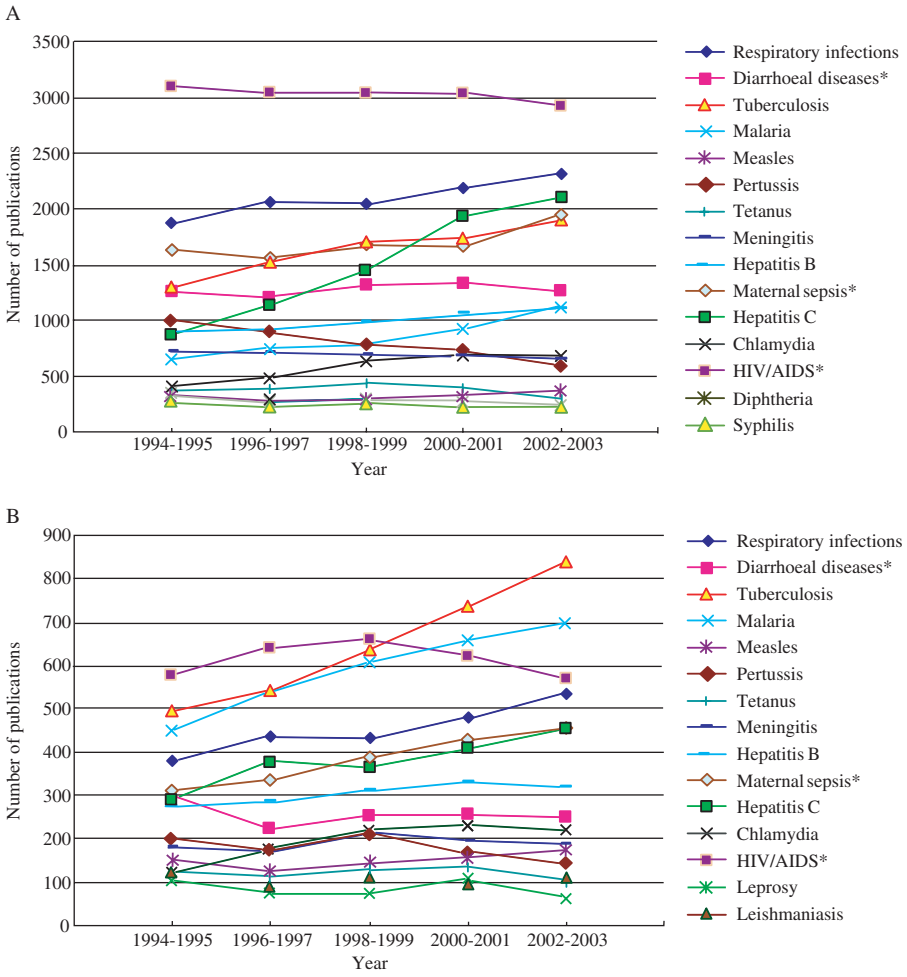

Fig. 2. The number of articles on selected infectious diseases published between 1994 and 2003 in the USA (A) and the UK (B). The 15 most important infectious diseases were included in this figure. *The search key word for "HIV/AIDS" was chosen as described in the legend of Fig. 1; the number of articles on "HIV OR AIDS" in the graph has to be multiplied by 3. The search key word for "diarrhoeal disease" was "diarrhoea"; the search key word for "maternal sepsis" was "sepsis".

31% it was bacteriology, for 27% parasitology, and for the remaining 10% mycology or combined fields.

According to the opinion of these scientists, research priorities within the next years should be given to virology followed directly by bacteriology and then parasitology and mycology. As major source of current funding of the respective groups, the government was listed in 78% of the cases, private funding in 27%. As the most essential factors determining the excellence of infectious disease research were regarded funding (90%), scientific exchange (76%), education (64%), connection between the laboratory and the field (55%), and the country in which the research is carried out (55%).

USA, UK, France, and Germany were regarded to be leading in the field of infectious diseases. This impression was in accordance with the statistical data obtained on publication activity within the frame of this study (see above). An interesting contribution to this phenomenon has recently been made by Man et al. (2004). According to their study, research funding and English proficiency are strongly associated with publication output in the highest ranked general medical journals.

Table 2 shows the most reliable evaluation criteria for a research group working on infectious diseases as judged by the scientists. High priority was given to ''Originality'' and ''Impact factors'' of the journals the respective articles are published in (concerning the use and misuse of impact factors in evaluating research, see, e.g. Seglen, 1997). ''Applicability of the results to the field/clinical work'' was ranked third, having been chosen by about one-third of the scientists as one of the three most reliable criteria for evaluating a research group. ''Interdisciplinarity'' and ''Impact on policy'' were chosen by less then 15%.

Table 2. ''Reliable'' evaluation criteria

Criteria	Percent
Originality	67
Impact factor[a]	41
Applicability of results in field/clinic	37
Continuity of research	33
Number of publications	27
Citation index	27
Training of young scientists	23
Interdisciplinarity	12
Funding profile	12
Impact on policy	8
Patents	4
Academic prizes	3

According to the opinion of 78 senior scientists these criteria were regarded to be reliable for evaluating a research group working on infectious diseases. Three criteria were supposed to be chosen out of the 12 given.

[a]Concerning the use and misuse of impact factors in evaluating research, see e.g. Seglen, 1997.

Considering the challenges that lie ahead – part of which are developing and implementing programs to treat diseases where the causative agents are known and therapies already exist – it seems that an effective infectious diseases research team would also be measured by its impact on policy-making and its interdisciplinary approach. However, both factors have been largely dismissed by the researchers. Applicability to the field and to clinical work, which would seem important given current challenges, was mentioned third by a distance after originality and impact factor. The relatively low priority that was given to impact on policies, interdisciplinarity and applicability can be understood from a purely scientific point of view. In addition, the answers we obtained were certainly biased by the fact that most scientists whose answers are summarized here were from Western industrialized countries. To investigate this phenomenon systematically, further studies would be required. However, the tendency of many scientists to refrain from the transfer of their results and the health policy arena might be one of the reasons why many programs directed against infectious diseases are less successful in reducing the global mortality and burden than they could be.

Apart from the results of our study and political as well as economic strategies, a number of central strategies for efficient control of infectious diseases have to be followed in the future. As concluded at the International Symposium ''Threat of Infection'', conducted in Würzburg, Germany, in July 2004 (Hacker and Klenk, 2005), these include (i) maintainance of vaccination programs and development of novel vaccines, (ii) preservation of the know-how concerning pathogens and diseases which are considered to be in the post-eradication era (like smallpox) in order to be prepared for reappearance of the pathogens and potential bioterroristic attacks, (iii) guaranteed provision of vaccines and drugs for emergencies, (iv) prevention of misuse of know-how, methods, and drugs by increasing national and international security measures, (v) enhanced interdisciplinary research activities including genome and proteome analyses, characterization of known and novel pathogens, studies on mechanisms of transmission, pathogenicity, and resistance as well as drug development including all required preclinical and clinical steps.

The pioneers' work still has the highest impact

Furthermore, we asked the 78 experts which 10 scientific publications were regarded to be the most important ones in the field of infectious diseases. The most frequently mentioned works are listed in Table 3. In addition to those, the following scientific

Table 3. The most important contributions to infectious diseases research as judged by 78 senior scientists in the field in autumn 2004

Rank	Name	Contribution
1	Louis Pasteur	Founder of microbiology, immunization
2	Alexander Fleming	Discovery of penicillin
3	Edward Jenner	Vaccination against smallpox
4	Robert Koch	Etiology of and vaccination against tuberculosis, microscopy
5	Paul Ehrlich	Chemotherapy against infectious diseases
6	Ronald Ross	Link between mosquitoes and malaria
7	Emil von Behring	Discovery of antitoxin

contributions were quoted repeatedly: John Franklin Enders – isolation of the poliovirus, Alphonse Laveran – discovery of the human malaria parasite, Kary Banks Mullis – development of PCR, Pierre Paul Émile Roux – development of the diphtheria vaccine, Jonas Salk – poliomyelitis vaccination, James Watson and Francis Crick – discovery of DNA, and the conduction of genome projects by different authors.

As shown in Table 3, highest credits were given to the pioneers of infectious disease research, whereas the more recent advances did not receive high attention. However, to tackle the global challenge that infectious diseases confront us with today, we need answers that go beyond the identification of micro-organisms and therapeutic or preventive principles that Pasteur, Fleming, Jenner, Koch, Ehrlich, Ross, and von Behring provided us with. Beyond these fundamental and important discoveries we need contextual knowledge about socio-economic, political and cultural factors in order to tailor treatment and prevention programs that will work.

In doing so we will also need to take into account ethical issues. Some of the classic researches on vaccines and chemotherapeutic agents aroused moral suspicion and debate already when it was conducted in the late 19th and early 20th century. Studies, among them Robert Koch's and Paul Ehrlich's experiments with Salvarsan and other chemicals, were criticized for insufficient informed consent of study participants and for using vulnerable populations, like people living in ''the colonies'', prisoners, children, or prostitutes (Reuland, 2004; Roelcke and Maio, 2004). The guidelines of the German Reich's Ministry of the Interior of 1930 reacted to the increasingly intense political debate by specifically emphasizing the necessity of explicit informed consent und the moral inadequacy of exploiting a person's difficult social situation for performing studies that pose a risk to the participant's health (Steinmann, 1975). Since then, ethical standards have been further elaborated and laid down in international guidelines, like the Nuremberg Code (1947), the Declaration of Helsinki (1964/2000), and the CIOMS International guidelines on research involving human subjects (2002). When building research capacity in developing countries and intensifying efforts to meet the global challenge of infectious diseases today, we need to make sure that ambition, greed, or even the genuine wish to alleviate and prevent suffering do not compromise these ethical principles that have been agreed on worldwide. It is true that not all questions regarding research ethics have already been settled. Particularly clinical trials that include some form of collaboration between rich countries and developing countries are raising issues, like permissible standards of care for control groups and after-trial obligations, that need to be addressed in a fair and transparent manner.

Conclusions

In conclusion, overall increase in publication activities on infectious diseases during the last 10 years is a very promising sign. However, concerning research priorities, the scientific community should focus on the most prominent diseases affecting large parts of the world's population like diarrhoeal diseases and malaria, but also on neglected diseases like schistosomiasis and trypanosomiasis. Taking into account that national research activities are of course driven by national funding this is a difficult task. Based on the publication activities, the countries with the highest infectious disease burdens are still not given the opportunity to contribute adequately to the scientific field. More political engagement of the scientific community might help to overcome this problem in the long term. According to our survey, the pioneer discoveries in infectious diseases still have the greatest impact; most of these pioneer studies were directly related to (chemo)therapy, prophylaxis or aetiology indicating that applied research is still considered most important.

As delineated above, there is no doubt that good basic research is needed in order to reduce the global mortality and global burden of infectious diseases. But beyond basic research intense efforts are needed to translate these findings into the realm of public policy and public health. And sometimes, mere translation will not be enough. In order to really make a difference we will continuously have to check if our research agenda responds to the most pressing needs rather than to the biggest markets. In order to actually tackle the global challenge of infectious diseases we need to find the best and most efficient ways to transfer knowledge from the labs to the field. As developing countries are the ones for whom the burden of disease is greatest, their participation in the definition of research goals and the

implementation of results is essential. Clinical trial partnerships between rich and developing countries are an important step in that direction (cf. for example the European & Developing Countries Clinical Trials Partnership, http://www.edctp.org/). We will have to make sure, however, that blind enthusiasm or conflicts of interest do not compromise the ethical dimension of an urgently needed global effort to reduce mortality and burden of infectious diseases.

Acknowledgments

The survey was carried out by the working group "Infectious Diseases" of Die Junge Akademie at the Berlin-Brandenburgische Akademie der Wissenschaften and the Deutsche Akademie der Naturforscher Leopoldina supported by the Bundesministerium für Bildung und Forschung and the VolkswagenStiftung. We would also like to thank Dr Annette Schulz-Baldes and Dr. Jörg Hacker who helped to gather addresses for the survey and who gave valuable feedback in the early stages of the project.

References

Becker, K., Engelen, E.M., Vec, M. (Eds.), 2003. Ethisierung–Ethikferne. Wieviel Ethik braucht die Wissenschaft? Akademie-Verlag, Berlin.

Feachem, R.G.A., 2004. The research imperative: fighting AIDS, TB and malaria. Trop. Med. Int. Health 9, 1139–1141.

Hacker, J., Klenk, H.-D., 2005. Threat of infection. Microbes of high pathogenic potential – strategies for detection, control and eradication. Nova Acta Leopold. N. F 92 (344).

Krilov, L.R., 2004. Emerging infectious disease issues in international adoptions: severe acute respiratory syndrome (SARS), avian influenza and measles. Curr. Opin. Infect. Dis. 17, 391–395.

Man, J.P., Weinkauf, J.G., Tsang, M., Sin, D.D., 2004. Why do some countries publish more than others? An international comparison of research funding. English proficiency and publication output in highly ranked general medical journals. Eur. J. Epidemiol. 19, 811–817.

Perkins, J., 2004. Confessions of an Economic Hit Man. Berrett-Koehler Publishers Inc., San Francisco.

Reuland, A., 2004. Menschenversuche in der Weimarer Republik. Books on Demand, Norderstedt.

Roelcke, V., Maio, G. (Eds.), 2004. Twentieth Century Ethics of Human Subjects Research. Historical Perspectives on Values, Practices, and Regulations. Franz Steiner Verlag, Stuttgart.

Seglen, P.O., 1997. Why the impact factor of journals should not be used for evaluating research. BMJ 314, 498–502.

Steinmann, R., 1975. Die Debatte über medizinische Versuche am Menschen in der Weimarer Zeit. Dissertation, Universität Tübingen.

Takahashi, O., Mahlbubur, R., Tsuguya, F., 2002. Japan's contribution to research on infectious disease. Jpn. J. Infect. Dis. 55, 139–141.