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EPIDEMIOLOGICAL STUDY

Knowledge mapping analysis of Ebola research

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ABSTRACT

OBJECTIVE: To reveal the overall situation of research on Ebola virus via visual knowledge mapping analyses of the literatures regarding Ebola virus all around the world, e.g., literature metrology and topic evolvement.

METHODS: On the basis of the database Web of Knowledge (SCI), a knowledge graph was built by comprehensively utilizing software such as BIBEXCEL, GEPHI, VOSVIEWER, and HistCite.

RESULTS: According to the results of literature analysis, publications on Ebola virus boomed in 2014, and the research focus transferred gradually from basic research (viral glycoprotein) in 1999 to the prevention and treatment research (vaccine). The United States are in a dominant position in the field of Ebola virus research, wherein the US army (United States Army Medical Research Institute of Infectious Diseases) has the strongest research capacity.

DISCUSSION: Ebola virus is an important potential biological warfare agent, and some researches may not be published in the form of literature. So the result of literature metrology can only partially reflect the situation of Ebola virus research. In addition, close attention should be paid to the biosafety risk of Ebola research *(Tab. 5, Fig. 5, Ref. 14)*. Text in PDF *www.elis.sk.*

KEY WORDS: Ebola, visualization, bibliometrics.

Introduction

The outbreak of the Ebola hemorrhagic fever (EHF) in February 2014 in West Africa is the worst Ebola epidemic in the history, and is one of the most serious public health crises which the mankind has ever encountered in the 21st century. EHF is an acute hemorrhagic disease caused by Ebola virus (EBOV), and it is classified as one of the most dangerous viruses by WHO as there are still no effective antiviral drugs and vaccines for EBOV9 (1). In this research, the Web of Knowledge (SCI) of Institute for Scientific Information of USA is used as the source of core data, with which the global research status and tendency of the Ebola virus are analyzed in order to provide data support and research ideas for the researchers who are occupied in the research of Ebola virus (2).

Research method and data sources

On December 16th, 2014, based on the platform of Web of knowledge (SCI) of Institute for Scientific Information of the USA, the keyword "ebola" was searched in the time range of 1986–2014, and 1335 related articles are retrieved. The full records including the references were downloaded and analyzed with the BIBEXCEL software. The knowledge graph was built with the software GEPHI, VOSVIEWER and HistCite to show the main research institutes, authors and hotspots in the research field of Ebola virus in the world (3).

Research results

Overall situation of Ebola virus research

From 1995 to 2013, the quantity of worldwide literatures regarding Ebola virus is relatively stable and small (Fig. 1). The rising and falling on the curve of literature quantity is basically consistent with the curve of outbreak time of Ebola epidemics within the recent 20 years. In 2014, the quantity of the published articles increased sharply to 353, which is in close relation to the outbreak of the largest and the most serious Ebola epidemic. The total citation frequency of the 1335 articles is 29440, the self-citation frequency within this field is 10919, the average citation frequency of each article is 22.02, and the h-index of this field is 88. The self-citation rate within the field is 0.37 (relatively low), which means that the development of the field is relatively mature, and there is a certain degree of intersection with other fields.

Distribution of Country and Region Involving Ebola Virus Research

The regions where a larger number of articles on Ebola virus are published is concentrated in the USA and Europe, and the USA is the global leader of this research field. In terms of the number of the published articles, the USA is at the top with the quantity of 665, accounting for half of the total quantity of the published articles in the field worldwide. In terms of the quality, the average

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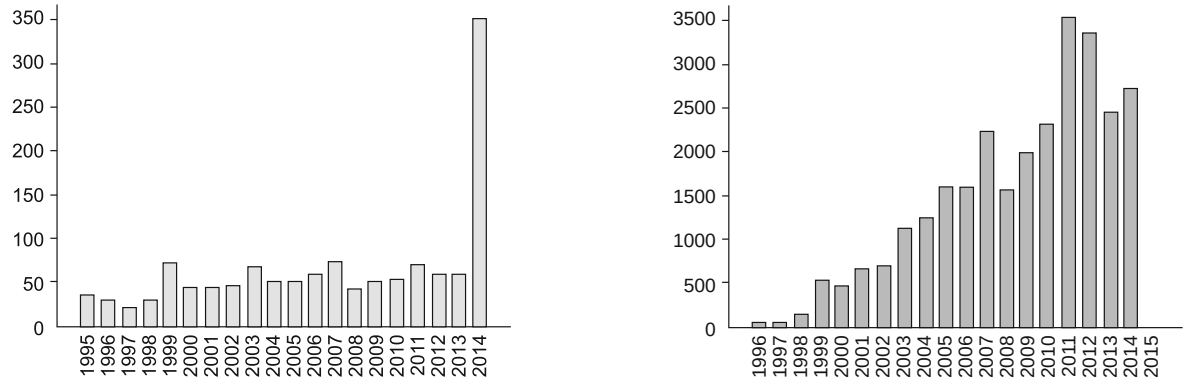

Fig. 1. The quantity of annually published articles in the field of Ebola virus research worldwide (left) and the citation frequency (right).

citation frequency of articles published in the USA is 33.95 and the h-index is 80, which are apparently higher than those of other countries. Moreover, Canada, Germany, France, Japan, the UK, Russia, Gabon, Belgium and Switzerland also have published a large quantity of articles regarding Ebola virus (Tab. 1).

Comparison of the strength of Ebola virus research institutions

Judging from the quantity and quality of the published articles, the US Army Medical Research Institute of Infectious Diseases (USAMRIID) is a giant in the field of Ebola virus research. This institute has published 165 articles in total in this field, with the average citation frequency of 48.78 and the h-index of 56, and the quantity and quality of the published articles are significantly higher than other institutes. The other leading institutes include the Centers for Disease Control and Prevention in the USA (CTR DIS CONTROL PREVENT), National Institute of Allergy and Infectious Diseases of National Institutes of Health in the USA (NIAID, NIH), National Microbiology Laboratory of Public Health Agency of Canada (PUBL HLTH AGCY CANADA), University of Manitoba in Canada (UNIV MANITOBA), Philipps University of Marburg in Germany (UNIV MARBURG), the University of Tokyo in Japan (UNIV TOKYO), the University of Pennsylvania in the USA (UNIV PENN), the University of Wisconsin in the USA (UNIV WISCONSIN), and International Center for Medical Research of Franceville in Gabon (CTR INT RECH MED FRANCEVILLE) (Tab. 2). Through the analysis on the cooperation between the global institutions it was found that of the top 10 research institutions with the highest number of relevant articles, 6 are located in the core of the cooperation network, with high influence during cooperative processes. They are the US Army Medical Research Institute of Infectious Diseases, the Centers for Disease Control and Prevention in the USA, National Institute of Allergy and Infectious Diseases of National Institutes of Health in the USA, University of Manitoba in Canada, Philipps University of Marburg in Germany and the University of Tokyo in Japan (Tab. 2). The quantity of the published articles of the International Center for Medical Research of Franceville in Gabon ranks num-

Tab. 1. Top 10 countries with the largest quantity of articles regarding Ebola virus.

Country	Quantity of the Published Articles	Percentage (%)	Average Citation Frequency	h-index
The USA	665	48.99	33.95	80
Canada	118	8.826	25.84	32
Germany	115	8.601	41.62	37
France	92	6.881	37.49	31
Japan	87	6.507	24.78	25
The UK	62	4.637	12.31	10
Russia	39	2.917	15.62	11
Gabon	39	2.917	51.23	23
Belgium	38	2.842	19.87	15
Switzerland	38	2.842	23.58	13

Tab. 2. Top 10 institutions with the highest quantity of published articles regarding Ebola virus in the world.

Name of Institution	Quantity of Published Articles	Total Citation Frequency	Average Citation Frequency	h-index
US Army Medical Research Institute of Infectious Diseases (USAMRIID)	165	8048	48.78	56
Centers for Disease Control and Prevention of the USA	124	6093	49.14	47
National Institute of Allergy and Infectious Diseases of the National Institutes of Health of the USA	106	3010	28.4	30
National Microbiology Laboratory of Public Health Agency of Canada	85	2209	25.99	27
University of Manitoba, Canada	74	1910	25.81	24
Philipps University of Marburg, Germany	67	3327	49.66	31
University of Tokyo, Japan	65	1680	25.85	24
University of Pennsylvania, the USA	52	2182	41.96	21
University of Wisconsin, the USA	50	1960	39.20	24
International Center for Medical Research of Franceville in Gabon	30	1540	54.73	18

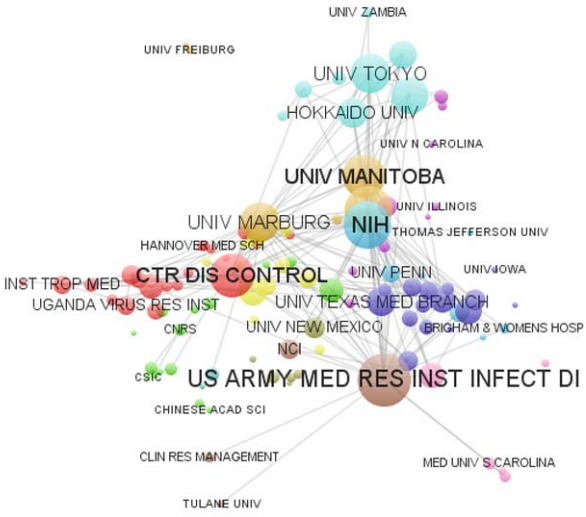

Fig. 2. Global cooperation network of the institutions in the field of ebola virus research.

ber 10, but its average citation frequency of the published article (54.73) is the highest. The reason may be that the research center received the Ebola patients directly during many outbreaks and can separate firstly the pathogenic viral strain. Most of these articles are published by cooperating with the research institutions of other countries including the USA, France, the UK, Germany, Switzerland, Thailand and South Africa (Fig. 2).

Distribution of core authors engaged in the research of Ebola virus

After data cleaning, the top 10 scientists (corresponding author) who published the largest number of articles in the field of Ebola virus research are ranked, wherein 9 scientists are employed in the institutions of the USA, including NIAID (under NIH), University of Texas, Centers for Disease Control and Prevention, University of Wisconsin and the USAMRIID. Only 1 scientist is employed in University of Marburg, Germany (Tab. 3). By analysing the global coauthoring network of Ebola virus research, it was found that among the top 10 corresponding authors, 6 are in the core of the coauthoring network and are active scientists participating in much cooperation and with higher influence. They are Feldmann (No. 1), Geisbert (No. 2), Rollin (No. 3), Jahrling (No. 5), Kawaoka (No. 6) and Ksiazek (No. 10). Close cooperation relationship is established between them, and they also have their own cooperation networks.

Among them, Feldmann H, who is employed in NIH USA, ranks No.1 with 124 published articles and the h-index of 34. After graduation with the doctoral degree in 1988, Feldmann worked in the Institute of Virology of the University of Marburg in Germany at first, and then was in charge of the special pathogen project of the National Microbiology Laboratory of the Public Health Agency of Canada from 1999 to 2008. Now he works in the NIAID of NIH of the USA. Feldmann is an expert in the management of high level (BSL-4) laboratory and a consultant of the WHO on the viral hemorrhagic fever and related pathogens. He is mainly engaged in the pathogenic mechanism, animal model, diagnosis, medicine and vaccine research of hemorrhagic fever (4).

Geisbert TW from the University of Texas in USA ranks No. 2 in the quantity of the published articles, and the total citation frequency and the h-index of his articles both ranks the first in the world. Geisbert graduated from the West Maryland College (now McDaniel College), and obtained a doctorate from the Uniformed Services University of the Health Sciences. Now Geisbert is a professor of the Department of Microbiology and Immunology, University of Texas, and his main research direction is to develop the Ebola vaccine by utilizing the recombinant vesicular stomatitis virus as the vaccine vector (5). The research projects that he is carrying out are as follows: modifying the vesicular stomatitis virus vector to improve its security and immunogenicity; identifying the antigen needed for the preparation of polyvalent vaccine; determining the roles of the cell and host immune response in the immune protection (6).

Ranked No. 6, Kawaoka Y (Yoshihiro Kawaoka) receives much attention for the successful synthesis of Ebola virus and the attenuated Ebola virus. Yoshihiro Kawaoka, a Japanese American, is a virology professor at the University of Wisconsin–Madison. He once worked in the Institute of Medicine, University of Tokyo, and learned from Professor Robert (a globally recognized author-

Tab. 3. Top 10 Authors of the World with the largest quantity of articles on Ebola virus research.

Author	Affiliation	Quantity of Published Articles	Total Citation Frequency	Average Citation Frequency	h-index
Feldmann H	National Institute of Allergy and Infectious Diseases of National Institutes of Health, the USA	124	3468	27.74	34
Geisbert TW	University of Texas, the USA	71	3888	54.76	36
Rollin PE	Centers for Disease Control and Prevention, the USA	66	3381	51.23	33
Becker S	University of Marburg, Germany	65	2047	31.02	26
Jahrling PB	National Institute of Allergy and Infectious Diseases	63	3232	59.85	32
Kawaoka Y	University of Wisconsin, the USA (2014)	59	2333	39.54	25
Bavari S	US Army Medical Research Institute of Infectious Diseases (USAMRIID)	59	1819	30.32	23
Hensley LE	US Army Medical Research Institute of Infectious Diseases (USAMRIID)	58	2290	44.90	25
Nichol ST	Centers for Disease Control and Prevention, the USA	51	2418	48.36	27
Ksiazek TG	University of Texas, the USA	46	2039	46.34	26

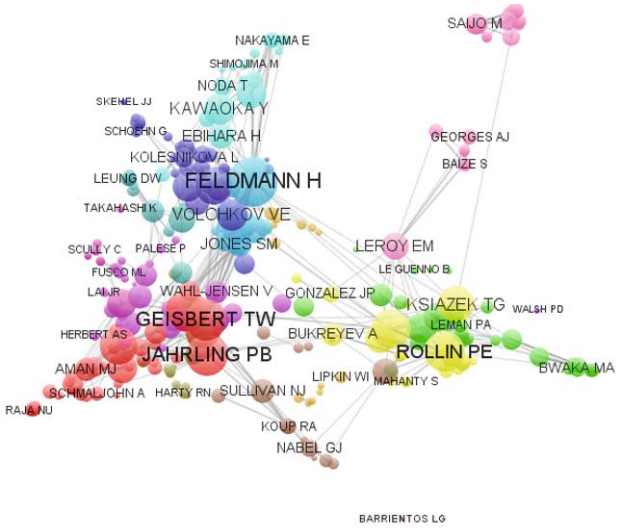

Fig. 3. Global coauthoring network of the Ebola virus research.

ity in the avian influenza research) of St. Jude Children's Research Hospital in the USA. Using the technology of synthesis of influenza virus, Yoshihiro Kawaoka and his team transferred the genes with which the Ebola virus produces RNA and protein into the cells for test, and then the artificial viruses could be formed on the cell surface. The appearance and structure of this artificial Ebola virus was quite similar to the natural Ebola virus, but its virulence was much weaker. So it can be used to study the interference and virulence mechanisms of Ebola virus or to develop the Ebola vaccine (7). His research articles are valuable for either controlling biological risk or developing vaccine (Fig. 3).

Analysis of the highly cited articles on Ebola virus research

The academic influence of articles can be reflected by the citation frequency. The more frequently an article is cited, the greater the influence of this article in the related field is. Most of such articles reveal a great discovery or provide important experimental data in some research field. Table 4 shows the 10 articles on Ebola virus research included in SCI which are cited most frequently, wherein 8 articles come from the USA, and 2 come from Gabon and Spain, respectively. All these 10 highly cited articles are completed cooperatively by two or more institutions.

In terms of the research content, 7 of the 10 highly cited articles mainly involve the structure and nosogenesis of the Ebola virus, 2 involve the animal experiment for Ebola vaccine, and 1 involves the host of Ebola virus. Among them, the article cited most frequently was published in 2001, which has been cited for 434 times in total, with the annual average citation frequency of 31. This article focused on the function of small molecule peptides encoded by the Ebola virus in accelerating the transfer of the virus, which was published collaboratively by Aaron Diamond AIDS Research Center and Rockefeller University (8). The article with the second highest citation frequency was published in 2000, which has been cited for 378 times in total, with the annual average citation frequency of 25.2. This article studied the effect

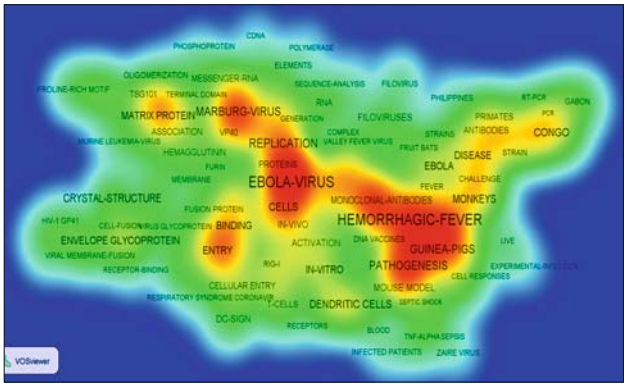

Fig. 4. Hot Keywords of the global Ebola virus research.

of Ebola vaccine on the primates via experiments and was published collaboratively by NIH and Centers for Disease Control and Prevention (9) (Tab. 4).

Analysis of the hotspots and the topic evolvement in the field of Ebola virus research

Hotspot analysis

Cluster analysis is performed on the main keywords in the field of Ebola virus research (Fig. 4). It is indicated that the current researche of Ebola virus mainly focuses on coat glycoprotein, monoclonal antibody, retrovirus, DNA vaccine, fusion protein, matrix protein vp40, matrix protein vp35, phosphoprotein, nucleoprotein, nucleocapsid protein and crystal structure of the Ebola virus. In addition, a few articles discuss the risk brought by Ebola virus as a biological weapon and its threat to organisms (Fig. 4).

Analysis of topic evolvement

The milestone articles (the bigger circle indicates a higher citation frequency) in the field of Ebola virus research are summarized, and the hotspot evolvement process in the field from 1995 to 2014 is analyzed through the sequence diagram of highly cited articles (Fig. 5) (the relevant articles published before 1995 are not included in the SCI database). It can be seen from the diagram that the Ebola virus research is divided into two phases.

Phase 1: basic research phase (1995–1998). The first highly cited article published in 1995 is an experimental study regarding the isolation and identification of new Ebola virus strains. From 1995 to 1998, the highly cited articles in the field of the Ebola virus research mainly focused on the viral glycoprotein, including the studies of mRNA, encoding and function of glycoprotein, and the mechanism of action of secreted glycoprotein and transmembrane glycoprotein in cells. In addition, along with the heated debate on the possibility of airborne transmission of the Ebola virus in the scientific community, the research articles on this topic published in this period also become highly cited articles.

It should be noted that the US Army Medical Research Institute of Infectious Diseases (USAMRIID) started the research on the airborne transmission of Ebola virus in 1992, and they believed that the Ebola virus can spread through the air among the non-human primates (including Macaca mulatta, Cercopithecus aethiops and

Tab. 4. List of the highly cited articles in the field of Ebola virus research.

Rank	Title	Author	Journal	Publishing Time	Citation frequency	Country
1	HIV-I and Ebola virus encode small peptide motifs that recruit Tsg101 to sites of particle assembly to facilitate egress	Martin-Serrano, J; Zang, T; Bieniasz, PD	NATURE MEDICINE	2001	432	The USA
2	Development of a preventive vaccine for Ebola virus infection in primates	Sullivan, NJ; Sanchez, A; Rollin, PE et al.	NATURE	2000	376	The USA
3	Fruit bats as researvoirs of Ebola virus	Leroy, EM; kumulungui, B; Pourrut, P	NATURE	2005	324	Gabon
4	C-type lectins DC-SIGN and L-SIGN mediate cellular entry by Ebola virus in cis and in trans	Alvarez, CP; Lasala, F; Carrillo, J	JOURNAL OF VIROLOGY	2002	288	Spain
5	Endosomal proteolysis of the Ebola virus glycoprotein is necessary for infection	Chandran, K; Sullivan, NJ; Felbor, U et al.	SCIENCE	2005	276	The USA
6	A system for functional analysis of Ebola virus glycoprotein	Takada, A; Robison, C; Goto, H et al.	PROCEEDINGS OF THE NATIONALACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	1997	266	The USA
7	Crystal structure of the Ebola virus membrane fusion subunit, GP2, from the envelope glycoprotein ectodomain	Weissenhorn, W; Carfi, A; Lee, KH et al.	MOLECULAR CELL	1998	261	The USA
8	Lipid raft microdomains: A gateway for compartmentalized trafficking of Ebola and Marburg viruses	Bavari, S; Bosio, CM; Wiegand, E;	JOURNAL OF EXPERIMENTAL MEDICINE	2002	251	The USA
9	The virion glycoproteins of Ebola viruses are encoded in two reading frames and are expressed through transcriptional editing	Sanchez, A; Trappier, SG; Mahy, BWJ	PROCEEDINGS OF THE NATIONALACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	1996	248	The USA
10	Accelerated vaccination for Ebola virus haemorrhagic fever in non-human primates	Sullivan, NJ; Geisbert, TW; Geisbert, JB	NATURE	2003	244	The USA

Macaca fascicularis) (10, 11). The articles from the University of Manitoba, Canada, show a similar research result (12). Although the conclusions above goe against the current mainstream view that Ebola virus cannot spread through the air and needs further research to verify, it is still worth special attention.

Phase II, a transition phase from basic research to prevention and treatment research (1999–2011). Since 1999, the highly cited articles involve the humoral immune response and the intravascular cell apoptosis related to Ebola virus infection. From 2000 to 2008, the themes of the highly cited articles began to concentrate on testing method of Ebola virus and animal experiment of Ebola vaccine. Meanwhile, from 1999 to 2011, the structure and function of the glycoproteins of Ebola virus (e.g., vp35 and VP40) is still the research hotspot.

Distribution of the articles of Ebola virus research in major journals

By analyzing the major journals which publish the articles regarding Ebola virus research, it is found that the Journal of Viro-

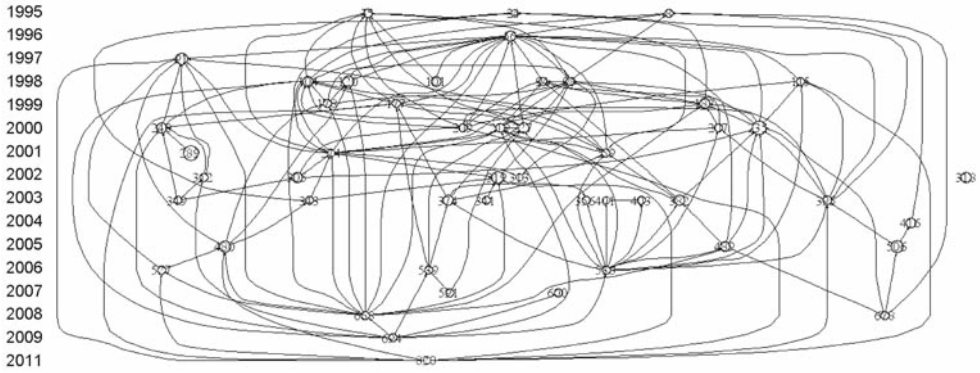

Fig. 5. Sequence diagram of 50 highly cited articles in the field of Ebola virus research.

Tab.5. Top 10 major journals with the largest quantity of articles regarding Ebola virus research.

Name of Journal	Quantity of Published Articles	Impact Factor	Country
Journal of Virology	118	4.648	The USA
Journal of Infectious Disease	107	5.778	The USA
British Medical Journal	65	16.378	The UK
LANCET	63	39.207	The USA
Science	50	31.477	The USA
Virology	46	3.278	The USA
Nature	31	42.351	The UK
Journal of the American Medical Association	29	29.978	The USA
Antiviral Research	25	3.434	Netherlands
New Scientist	24	0.379	The UK

logy ranks the first in the quantity of articles in this field, followed by Journal of Infectious Disease and British Medical Journal. In terms of the journal's impact factor, Nature ranks the first among the top 10 journals with the largest quantity of relevant articles. Among the top 10 journals, 6 are published in the USA, 3 in the UK, and 1 in Netherlands (Tab. 5).

Subsidization for Ebola virus research

Through analysing the major funding situation of the Ebola virus research worldwide, the projects subsidized by the NIH of the USA publish the largest number of articles. The other major funding agencies include the Defense Threat Reduction Agency of the USA, Canadian Institutes of Health Research, Public Health Agency of Canada, German Research Foundation, French National Research Agency, French Foundation for Medical Research, Japan Society for the Promotion of Science, German Schering Foundation and Boston University of the USA (Fig. 5).

Conclusion and discussion

Having an objective view on the results of literature analysis of the Ebola virus research

Literature metrology and visualization analysis can assess the current situation and trend of Ebola virus research from the view of literature, and intuitively reflect the national or regional distribution, core research institutions, important experts and research hotspots in this field (13). Considering that the Ebola virus is an important biological warfare agent, some researches may not be published to the public. So this study can only reflect the basic information of the research in this field. The conclusions are made based on the literature analysis, and can serve as a component of the overall situation of the Ebola virus research (14).

Paying close attention to the biosafety risk of Ebola virus research

Through the analysis on the hotspots of the Ebola virus research, it can be found that the potential biosafety risk of the Ebola virus research has been discussed by many scientists, and scientists from various countries have to be vigilant to this issue when carrying out such research. Therefore, it is necessary for us to follow closely the key research institutions abroad and the research trends of the scientists, and carry out the dual-purpose risk assessment timely so as to get ready for response to terrorist activities. Meanwhile, appropriate laboratory biosafety standards and code of conduct should be established based on the potential risk of the research performed in order to prevent the accidents threatening the biosafety.

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