

Accelerating R&D for emerging infectious diseases: lessons learnt from Ebola

Yangmu Huang (✉ ymhuang@bjmu.edu.cn)

Peking University Health Science Centre <https://orcid.org/0000-0002-3660-1276>

Chao Li

Centers for Disease Control and Prevention

Jingyi Chen

Harvard University T H Chan School of Public Health

Jiyan Ma

Peking University Health Science Centre

Research article

Keywords: Ebola Virus Disease, Emerging Infectious Disease, Research and Development

Posted Date: July 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-42486/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Both China and the U.S. developed high-quality vaccines for the Ebola outbreak. This study compared the R&D activities of Ebola products in two countries, as a way to present the influential factors of R&D for emerging infectious disease (EID) and to provide suggestions for timely and efficient response to the COVID-19 pandemic.

Methods

R&D activities were analyzed in terms of research funding, scientific research outputs, R&D timeline, and governmental mechanisms. Quantitative analysis was performed using data retrieved from national websites, clinical trial registries and databases. Qualitative semi-structured interviews were conducted to explore perspectives of key informants involved in Ebola product development.

Results

The funding gap between China and the U.S. was significant before 2014 and narrowed after the Ebola outbreak. Both research teams started basic studies prior to the outbreak; however, the U.S. got FDA approval for clinical trials 5 months earlier than China. The underlying gap reveals the lack of participation and support by private sectors, stagnant transformation platform, and inadequate government incentives in China.

Conclusions

R&D pre-planning and resource deployment mechanisms are crucial for EID preparedness and response. Building private and public collaboration, and strengthening government support for clinical trials may accelerate the translation of basic research.

1. Background

The dreadful influence of COVID-19 sounded alarm on the evolving emerging infectious disease (EID) challenge and the need for prompt and effective countermeasures research and development (R&D) [1]. Since the announcement of the outbreak, global community has been working collaboratively to uncover possible drug regimens, diagnostic tools, and vaccines for reducing case-fatality rate and halting transmission. As the previous disease declared the Public Health Emergency of International Concern (PHEIC), Ebola's R&D experience has demonstrated the feasibility and success of accelerating more than 40 products to clinical phases under continuous and inclusive efforts [2]. To support the development of

countermeasures for COVID-19 and future epidemic, global public health community needs to draw lessons from the top R&D contributors to Ebola response that reflect strengths and weaknesses.

As the leading force driving international pharmaceutical innovation, the U.S. government has worked closely with research institutions and biopharmaceutical companies during the 2014–2016 outbreak and provided strong support for developing the Ebola drug ZMapp [3]. It also contributed nearly half of the vaccine candidates to clinical trials, as reported by the WHO Ebola Response Roadmap [4]. The rVSV-ZEBOV, also known as the Ebola Zaire vaccine, demonstrated highly effective performance in a phase III trial of Guinea and was approved for compassionate use in the 2018–2020 Kivu Ebola epidemic [5].

Meanwhile, as the second country bringing Ebola vaccine to market, China's rapid development and manufacture of medical products give hope to the developing world. After the lessons learnt from SARS, China has put intensified efforts and investment in rebuilding public health infrastructure, laboratory capacity and capability, as well as science and technology innovation for major EIDs [6]. It has successfully launched a portfolio of vaccines for SARS, H5N1 and H7N9, and become the first country approved to mass-produce the H1N1 vaccine. Before the Ebola outbreak, China focused its R&D innovation on the main causes of domestic EID burden. With growing responsibility in global health and more multilateral engagement, China carried out its largest foreign health aid campaign in history and provided prompt and substantial financial and technical support for Ebola R&D. As a result, China has independently developed a restructured Ebola vaccine named Ad5-EBOV, which got approved for emergency use by CFDA on Nov 2017.

Both China and the U.S. stepped up timely to offer Ebola vaccination for those who may have been exposed. As two great power representing the developing and developed world, the two countries' R&D practice should be compared and summarized in order to provide insights in accelerating R&D for global public health emergencies. Previous R&D studies mainly focused on parts of the R&D process, such as comparing the clinical trial progress, protective effect and efficacy, and funding flow for Ebola-related medical products in various countries [7, 8, 9]. While our study aims to draw a more comprehensive picture, for comparing the R&D activities of products, in regards to research funding, scientific research outputs, R&D timeline, and government incentive and coordinated mechanisms. It will help present the influential factors of R&D efficiency for EIDs, depict a proven R&D pathway of success in both developing and developed world contexts, thereby providing suggestions for timely and efficient R&D response to the COVID-19 pandemic.

2. Methods

Mixed methods were employed in this study, including a quantitative analysis for comparing R&D activities between China and the U.S.; and a qualitative analysis to explore the underlying gap in China and suggestions for accelerating the R&D process. Informed consent and human or animal experimentation guidelines are not applicable in this study.

2.1 Quantitative Data

Research funding

The Chinese government's R&D research funding was sourced from the National Natural Science Foundation of China (NSFC) website. Relevant data in the U.S. was derived from the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools (projectreporter.nih.gov). We included projects supported by individual governments between 2008 and 2016 using "Ebola" and "Ebola virus" as search terms, and excluded those irrelevant based on project summaries. For example, research on information platform, epidemic model, and clinical pharmacokinetics were excluded.

Scientific research outputs

Clinical trial was extracted from the NIH web-based clinical trial resource (clinicaltrials.gov), which contains global trial data registered by study sponsors or principal investigators. Pipeline candidate information was extracted from the WHO Ebola R&D Landscape of Clinical Candidates and Trials Report. The patent application data of China was mainly extracted from the Patent Search System of the State Intellectual Property Office (sipo.gov.cn). We also searched the Patent Search and Analysis of SIPO database (pss-system.cnipa.gov.cn) for China and U.S.'s Ebola-related medical products patent application information. Patents were included based on their patent descriptions, and then classified into at least one category of "drugs", "vaccines" and "diagnostics". For publications, bibliometric analysis was conducted using the literature search tool Gopubmed. China and U.S.'s Ebola R&D scientific papers (English-version) were screened using "Ebola virus" as the MeSH term, from Jan 1st 2006 to Dec 31st 2016. Articles were then classified by "Chemistry and medicine", "Vaccination", and "Diagnostics" according to their topics and abstracts. Full articles were obtained for further exclusion if needed.

R&D Timeline

Key time points for China's R&D phases were obtained through relevant announcement and articles issued by the Chinese agencies, and time points of the U.S. was obtained from official reports from National Institutes of Health and Biomedical Advanced Research and Development Authority (BARDA).

All the quantitative data was double-screened and cross-checked by two trained researchers to reach a consensus. Accordingly, data was double-entered into Microsoft Excel and checked for consistency. Microsoft Excel was also used for data description and analysis.

2.2 Qualitative Data

Participants

Interviewees were mainly from three categories: professionals directly involved in Ebola pharmaceutical R&D; professionals involved in EID-related R&D; and policymakers and researchers who have been working in this field and can provide policy recommendations for accelerating EID-related R&D process.

Sampling

The key informants were selected through non-random and purposeful snowball sampling. The sampling stopped until the obtained information was saturated. A total of 15 key informants were interviewed. Six were directly involved in the R&D of Ebola medical products; six engaged in the development of EID-related pharmaceutical products; and three contributed to providing relevant policy recommendations.

Interview Content and Analysis

A semi-structured qualitative outline was compiled before the interview. The content mainly focused on the influential factors of R&D efficiency for EID, including coordination within government agencies, implementation barriers during the R&D cycle, R&D funding resources, as well as policy recommendations for accelerating R&D process. Thematic analysis was conducted by two trained researchers with principles of constant comparison and facilitated by Nvivo software (version 11.0).

3. Results

3.1 Quantitative Result for Comparing R&D Activities

Research funding

According to the available data, U.S. had more government-funded projects on Ebola (n = 187) from 2008 to 2016, which is 7.5 times of those in China (n = 25). Meanwhile, U.S. input 180 million dollars for R&D, which is 17.5 times higher than that supported by the Chinese government. Both countries contributed consistent efforts between 2008 to 2015 and the gap was gradually narrowing, regarding the granted project number and research funding. However, the difference suddenly re-increased in 2016 (Fig. 1).

Scientific research outputs

For clinical trials, U.S. supported 21 trials for vaccines in total, including 16 in Phase I, four in Phase II, and one in Phase III. As for China, four vaccine clinical trials were supported with three in Phase I and one in Phase II. For pipeline candidates, drugs, diagnostics and vaccines accounted for 51.6%, 32.9%, and 15.5% in China. In comparison, U.S. held 57.4% of candidates in drugs, 23.0% in diagnostics, and 19.5% in vaccines. For patent application, China had no application for Ebola-related medical products before 2009, while U.S. applied for 11 drug-related patents, three vaccine-related patents, and two diagnostic-related patents. The number of Chinese patent applications increased and surpassed the U.S.'s in 2014. For publication, U.S. has been active in Ebola R&D since 2006 (Fig. 2). The total number of publications in the U.S. from 2006 to 2014 is 37.5 times higher than that of China. Drug-related publication accounted the most in two countries. From 2014 to 2015, both countries increased, with a steeper rise in the U.S. After 2015, the number of the U.S. decreased apparently, however, China's still increased.

As a result, CFDA has licensed six Ebola-related medical products, including five diagnostic reagents and one vaccine products approved for emergency use. U.S. has licensed ten Ebola diagnostic tests for

emergency use under FDA's Emergency Use Authorization (EUA) authority. On December 19, 2019, FDA approved the rVSV-ZEBOV, as the first licensed vaccine for Ebola prevention [10].

R&D timeline

Our study focuses on comparing the R&D timeline of the first two Ebola vaccines successfully developed by China and the U.S.: the Ad5-EBOV and the rVSV-ZEBOV (Fig. 3). Both China and the U.S. research teams started basic studies prior to the Ebola outbreak. The U.S. got FDA approval for clinical trials on Sept 2014, which is five months earlier than China. However, the initial time of Phase I trials in two countries was only one month apart. For the preparation of oversea clinical trial sites, China spent five months waiting for the approval by Sierra Leone, and another five months for volunteer recruitment and laboratory preparation. Comparatively, the U.S. took only four months, in total, for going through all the process of resource allocation and preparation in Liberia. In the end, the Ad5-EBOV got CFDA approval for emergency use in China, whereas the rVSV-ZEBOV was adopted by the WHO as the only vaccine applied in the re-emerging Ebola outbreak in the Democratic Republic of the Congo [11].

3.2 Qualitative Result for Exploring the R&D Differences in China

Research funding

According to interviewees, funding for basic research was sufficiently supported by the NSFC programs. Meanwhile, funding for clinical trials mainly came from the Ministry of Science and Technology (MOST), and the R&D grants were only allocated after candidate products demonstrated promising. This funding process lagged the implementation of consistent scientific research. Many teams had to use funding from other projects for Ebola before the government funding got approved. Our interviews suggested that the successful development of the Ad5-EBOV vaccine highlighted the significance of early research accumulation. China needs to establish R&D pre-planning and resource deployment mechanisms for EID preparedness and response.

Scientific research outputs

Although China's basic research had achieved satisfying progress, most researchers found it challenging to transform results into applicable products. The underlying gap mainly attributed to the lack of participation and support by private sectors, the stagnant transformation platform, and the inadequate government incentives in China. The lack of economic and monetizing value of EID products disincentivizes biopharmaceutical enterprises to carry on studies and manufacture. Furthermore, academic institutions are incapable of translating basic research into clinical trial phases. Military affiliated research institution seems as the first choice for pushing forward oversea clinical trial; however, many things need to be coordinated under government support. Considering there is no existing department providing such guidance, the inadequate incentive mechanisms impede public and private sectors from transforming outputs into downstream timely and effectively.

R&D timeline

Interviewees agreed that the special review process established by CFDA and the technical guidance provided by its subsidiary evaluation center significantly accelerated the product licensing procedure. Still, the government agencies should have enhanced regulatory support for promoting oversea clinical trials. The insufficient experience and lack of well-established coordination mechanisms placed significant workloads on individual research teams. Most interviewees expressed that the time spent on communication at work could have been shortened and more efficient.

4. Discussion

This study aims to compare the R&D activities between China and U.S. and to explore the underlying barriers to accelerating R&D process. Our research found that both countries put major efforts in Ebola countermeasures development. The difference in R&D activities implied diverse governmental support and regulatory environment. China has achieved substantial progress in basic research, patent application and vaccine licensing. However, the U.S. government started funding for Ebola much earlier than China, and developed the rVSV-ZEBOV as the only vaccine adopted by WHO. The gap attributed to the lack of national R&D pre-planning, incentive and coordinated mechanisms in China before and during EID outbreak.

Our results indicated that a responsive and systematic pre-planning and resource deployment mechanism is crucial for achieving timely R&D. The U.S. government has a complicated coordinating body to assess the chemical and biological threats and enhance national health security through effective procurement and use of medical countermeasures [3, 12]. It established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) on Jul 2006 and determined that the EVD and related viral hemorrhagic fever viruses presented material threats to the U.S. population [12]. However, China's emergency response plan for EIDs was primarily based on emergency investigation, tracing and control of new infected cases [13]. The EVD had not been listed as a potential national security threat prior to the 2014 outbreak. Early Ebola projects started merely based on team's interests and most of the R&D projects initiated after the virus blasted. Funding for Ebola was further curtailed when outbreak got contained. The pivoted focus of Chinese scientific research agencies neglected re-emerging risk of EIDs [14].

Furthermore, the rapid delivery of large-scale clinical trials within efficient and streamlined R&D process requires a set of incentive and coordinated mechanisms. For example, the public-private partnership plays an important role in linking upstream basic research and downstream manufacture [15], as well as in facilitating collaboration between agencies and private sectors [16]. It is widely used in the U.S. and leads to successful development of the vaccine Ad26.ZEBOV and the drug ZMapp [17, 18]. China's current public-private partnerships were mainly driven by military research institutions, and the coordination and communication between companies and research institutions are still impeded due to the lack of efficient R&D partnership. Interviewees suggested that the lack of incentive and coordinated

mechanisms in China has led to a considerable waste of time and resources. China needs to establish a unique government-led model that integrates participation from all sectors. For scientific research institutions, bridges need to be established with private sectors for technical cooperation and communication. To ensure the profitability of private sectors, government should provide tax support, procurement guarantees, and technical guidance to help enter the global market with labels that assure product qualifications in alliance with WHO standards.

The Chinese government has a unique advantage in promoting forceful and practical regulatory procedure, as exemplified during the coordination for COVID-19 R&D,[19]. Besides emergency R&D response, the ongoing reform initiated by CFDA implies a consistent effort to address the lengthy review process for new drug development. It helps reduce the time and cost of clinical studies by minimizing regulatory and application backlogs and facilitating market access,[20]. However, the government agencies should continue enhancing regulatory support, especially for promoting oversea clinical trials. Limited by insufficient participants and pivoted research priorities, the Ad5-EBOV vaccine is currently terminated on long-term efficacy studies and labelled for emergency use. The termination could bring potential risks for a timely and efficient R&D response to future Ebola outbreaks. Lessons learnt from Ebola highlighted the consistent government support through R&D life cycle and WHO's call for global collaboration to accelerate R&D and equitable access to COVID-19 countermeasures.

Although this study is the first study to compare China's Ebola R&D process with developed countries, several limitations still existed. First, though we tried to include all the available official data for quantitative research, some of the data was not available, which might under-estimate the funding or outputs. Second, the possible differences of inclusion standards and categories between China and the U.S might impact the quantitative comparison. Third, in our analysis, qualitative study results were mainly represented by paraphrases or quotations, however a more thorough and systematic qualitative analysis should be conducted in future studies.

5. Conclusions

In conclusion, pre-planning and resource deployment mechanism for R&D on EID should be established to achieve a timely and more efficient R&D process. Funding should be allocated to support diversified R&D institutions for coping with the risks. Building private and public collaboration and communication, and strengthening government support in clinical trials may accelerate basic research translation.

Abbreviations

EID	Emerging infectious disease
R&D	Research and development
PHEIC	Public Health Emergency of International Concern
NSFC	National Natural Science Foundation of China
NIH	National Institutes of Health
BARDA	Biomedical Advanced Research and Development Authority
EUA	Emergency Use Authorization
MOST	Ministry of Science and Technology
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

<https://bmcinfectdis.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article>

Competing interests

The authors declare that they have no competing interests.

Funding

This study was co-supported by the National Natural Science Foundation of China [No. 72042014], the Special Research Fund of Peking University for Prevention and Control of COVID-19, and the Fundamental Research Funds for the Central Universities.

Authors' contributions

CL and JC drafted the manuscript, JC did the data collection, data analysis. YH and JM contributed to study design, editing and revising the paper. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Fauci AS, Clifford Lane H, Robert R. Redfield. "Covid-19—navigating the uncharted." (2020): 1268–1269.
2. World Health Organization. WHO R&D Blueprint. Retrieved from http://www.who.int/research-observatory/analyses/rd_blueprint/en/.<https://www.who.int/ebola/en/>. [Accessed 6 Sep 2018].
3. US Department of Health and Human Services. "2015 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) strategy and implementation plan." (2015).
4. World Health Organization. Ebola Response Roadmap. Aug 28. 2014. Retrieved from <http://apps.who.int/iris/bitstream/10665/131596/1/EbolaResponseRoadmap.pdf?ua=1> [Accessed 6 Sep 2018].
5. Potluri R, Kumar A, et al. Impact of prophylactic vaccination strategies on Ebola virus transmission: A modeling analysis. *PLoS ONE*. 2020 Apr;27(4):e0230406. 15(.
6. Wang L, Wang Y, et al. Emergence and control of infectious diseases in China. *The Lancet*, 372(9649), pp. 1598–1605.
7. Fitchett JR, Lichtman A, et al. Ebola research funding: a systematic analysis, 1997–2015. *J Glob Health*, 6(2).
8. Osterholm MT, et al. Transmission of Ebola viruses: what we know and what we do not know. *MBio*. 2015;6(2):e00137-15.
9. Wang H, et al. Ebola viral glycoprotein bound to its endosomal receptor Niemann-Pick C1. *Cell* 164.1-2 (2016): 258–268.
10. Biologics Evaluation and Research. (2019). ERVEBO. Retrieved from <https://www.fda.gov/vaccines-blood-biologics/ervebo>.
11. Pagliusi S, et al. Vaccines: Shaping global health. *Vaccine*. 2017;35(12):1579–85.
12. Board on Health Sciences Policy; Institute of Medicine; National Academies of Sciences, Engineering, and Medicine. *Global Health Risk Framework: Research and Development of Medical Products: Workshop Summary*. Washington (DC): National Academies Press (US); 2016 May 6. 3, *Discovery Research*. Retrieved from: <https://www.ncbi.nlm.nih.gov/books/NBK367991/>.
13. Sun M, et al. The public health emergency management system in China: trends from 2002 to 2012. *BMC Public Health*. 2018;18(1):474.
14. Li C, Chen J-Y, Huang Y-M. Challenges and opportunities for China entering global research and development for emerging infectious diseases: a case study from Ebola experience. *Infect Dis Poverty*. 2020;9(1):1–10.
15. Nwaka S. Drug discovery and beyond: the role of public-private partnerships in improving access to new malaria medicines. *Trans R Soc Trop Med Hyg* 99.Supplement_1 (2005): S20-S29.

16. National Center for Advancing Translational Sciences. Issues in Translation. (2018, July 12). Retrieved from <https://ncats.nih.gov/translation/issues>.
17. Pharmaceutical Public-Private Partnerships in the United States and Europe. Moving from the Bench to the Bedside. Retrieved from <https://digitalcommons.law.yale.edu/cgi/viewcontent.cgi?referer=https://www.google.com.hk/&httpsredir=1&article=1011&context=yas>.
18. National Academies of Sciences, Engineering, and Medicine. Rapid Medical Countermeasure Response to Infectious Diseases: Enabling Sustainable Capabilities Through Ongoing Public-and Private-Sector Partnerships: Workshop Summary. National Academies Press, 2016.
19. Parry J. China enters the global vaccine market. World Health Organization. Bull World Health Org. 2014;92(9):626.
20. Cyranoski D. China announces plans to fast-track drug approval. Nature News (2017).

Figures

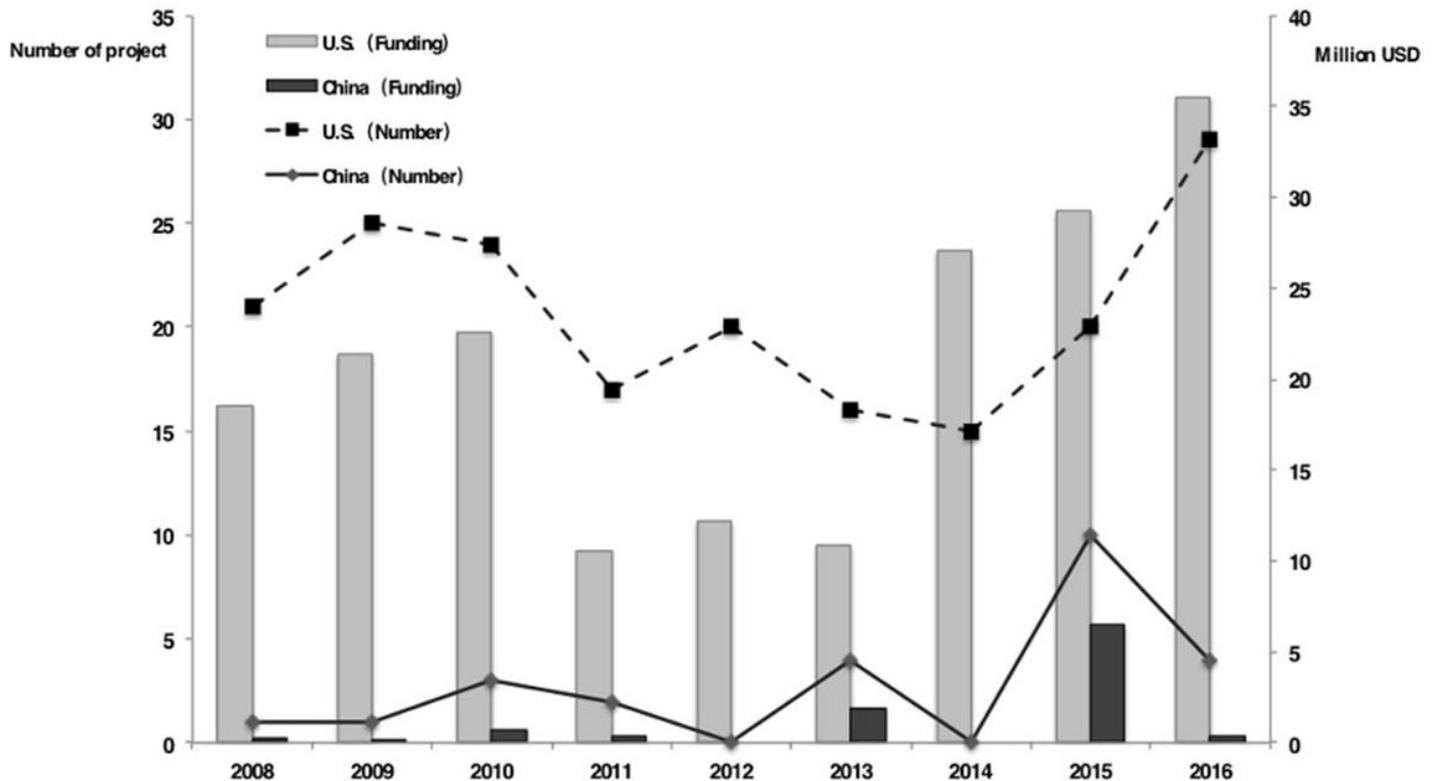


Figure 1

Government-funded projects for Ebola in the U.S. and China

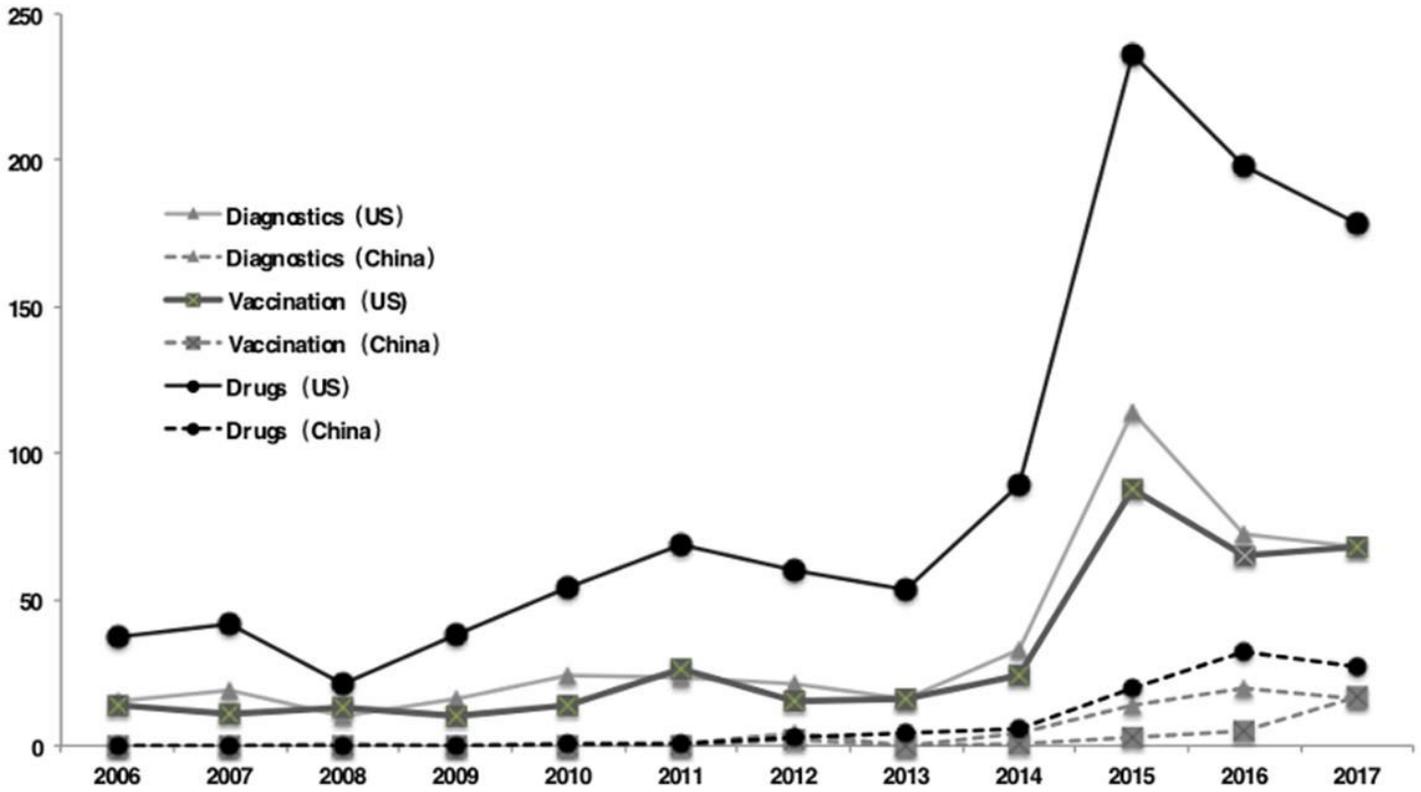


Figure 2

Publications for Ebola R&D in the U.S. and China

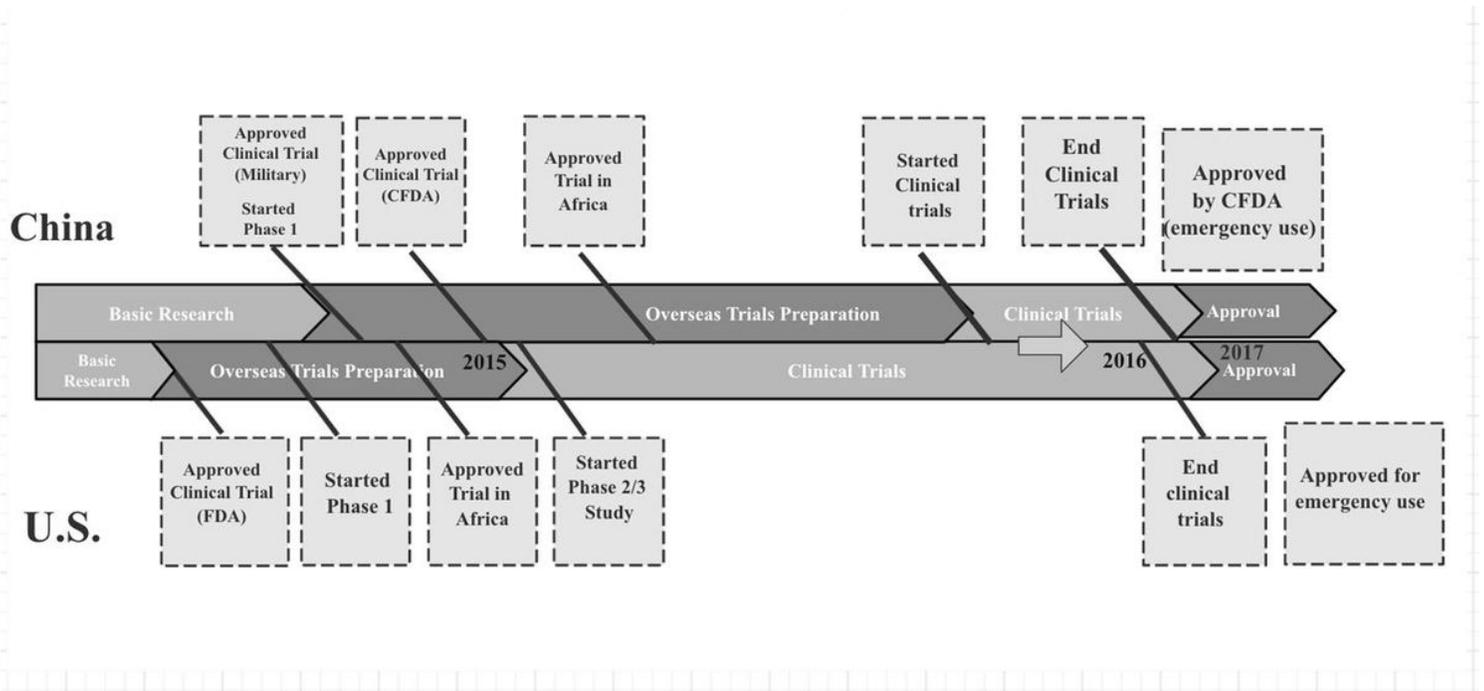


Figure 3

R&D timeline for the first two Ebola vaccines developed by China and the U.S.