

Original Research Article

Addressing the unmet need in respiratory viruses: an interdisciplinary analysis of product development pipeline in Asia

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ABSTRACT

Background: Respiratory tract infections (RTIs) pose a significant burden on health systems worldwide. Progress has been booked in reducing RTI disease burden through development of diagnostics, therapeutics and vaccines, though most efforts often fail to address the contribution of non-influenza viruses. Increasing awareness and the prevailing unmet need has resulted in the establishment of initiatives that aim to explore ways in which to extend innovation efforts for influenza to the broad range of respiratory viruses. This study will provide a detailed description of the state of the RTI market in Asia.

Methods: By developing a dataset containing data from patent documents and clinical trials (CTs) we aimed to provide a detailed description of the RTI market in Asia.

Results: We found a downward patent filing trend in respiratory diagnostics but a high number of phase 3 studies. A strong preference for the development of therapeutics and vaccines targeting bacterial pneumonia and influenza became apparent, whereas less attention is given towards product development targeting non-influenza viruses.

Conclusions: The findings indicate a mature respiratory diagnostics market with minor industrial interest but at the same time an evolving RTI CT market with a strong late-stage pipeline. Asia represents only a handful of studies related to non-influenza viruses, mostly conducted by non-profit organisations. The business segment appears to focus upon product development for more profitable respiratory infections thereby suggesting that involvement and engagement of the industry within global initiatives and efforts to increase innovation for non-influenza viruses is not optimal.

Keywords: Respiratory tract infections, Non-influenza respiratory viruses, Respiratory diagnostics, Patents, Clinical trials

INTRODUCTION

Respiratory tract infections (RTIs) are amongst the most common causes of morbidity and mortality worldwide.¹ While substantial progress has been booked in reducing RTI disease burden, there is still much ground to cover. Action plans by UNICEF and the WHO aim to further reduce morbidity and mortality through better bacterial treatment and increased prevention, mainly by establishing wider coverage of vaccines for *Haemophilus*

influenza type B and *Streptococcus pneumoniae*.² While such plans could indeed result in further reduction of morbidity and mortality, they often fail to address the contribution of RTIs caused by viruses. Various studies reported that more than half of pneumonia cases are caused by viral agents, much larger than previously estimated.^{3,4} This hidden burden of viral agents is not well appreciated, even more so in low-resource parts of the world where it may be disproportionately high. Additionally, one has to realize that respiratory infections

caused by a bacterial agent often have a preceding or concurrent viral component. Especially in risk-populations, such as infants and the elderly, co-infection with more than one pathogenic agent is not unusual and can be present in as many as two third of the RTI cases.⁵ Therefore, increasing coverage through bacterial vaccines will not solely provide clinical benefit, but also increase the proportion of respiratory infections attributable to respiratory viruses.

In the past several years, some progress has been made in developing novel influenza diagnostics, therapeutics and vaccines. However, the overrepresentation of studies focused upon influenza and the scarcity studies of regarding non-influenza respiratory viruses (NIRVs) remains evident.⁶ While much attention is given to the impact influenza, is it not recognized that the cumulative burden caused by NIRVs, such as Rhinovirus (RV), Human Metapneumovirus (hMPV), respiratory syncytial virus (RSV) and coronaviruses (CoV), often outweighs that of influenza.⁴ The use of influenza antivirals during the pandemic response in Japan in 2009 shows the potential value of antivirals for other respiratory viruses, though the pipeline for other viruses seems much more limited.^{7,8} It seems that R&D investments by the industry are not in line with the medical needs of the global population and the number of market entries per therapeutic area appears not in sync with the prevalence of diseases.^{9,11} Even more so, in continents where the respiratory burden by viruses is highest, such as Africa and Asia, industries' interest and engagement appears to be low and the pipeline seems to be running dry.^{3,12}

Increasing awareness in the scientific community regarding this matter has resulted in the establishment of the Battle against respiratory viruses initiative (BRaVe) in 2012.¹³ The initiative aims to explore ways in which to extend innovation efforts for influenza, to the broad range of NIRVs. The importance of identifying research activities that would contribute to reducing viral RTI mortality in low-resource settings, where the burden is greatest, was vastly emphasized. Amongst the research priorities was the need for fast and accurate diagnostic tools that enables healthcare professionals to distinguish patients with viral from those with bacterial infections. The absence of such diagnostics is not only considered to be one of the reasons why RTIs pose enormous burden of disease in developing countries but is also a major cause of misprescription of antibiotics and growing bacterial resistance.^{12,14} Even in well-resourced settings, the performance characteristics and costs of available diagnostics do not necessarily justify their use in patient management. This inability to rapidly and accurately identify between bacterial and viral pathogens is considered a major drawback in the clinical management of RTIs.

This study will provide insight in the market surrounding acute RTIs. The aim was to present an overview of the market through patent analysis, as well as providing a

detailed description of the product pipeline in Asia. Additionally, we investigated the therapeutic focus of the industry by analysing ongoing CTs. In doing so, we narrowed down the research to the Asian market as we believed the unmet need within this continent to be amongst the highest. Hence, the main objective of this study was to present a thorough overview regarding the current state of the RTI market in Asia by developing and analysing a dataset containing data from patent documents and clinical trials (CTs).

METHODS

Patent analysis

The purpose of the patent analysis was to identify and evaluate trends in diagnostic technologies related to RTIs. Patents present the state-of-the-art technologies and are a valuable source of information for the early detection of market changes. Patent activity is oriented towards the commercialisation of new technologies and there is a positive relationship between patent activity and market dynamics.¹⁵ We therefore considered them an effective method for evaluating the Asian market.

Data needed for the patent analysis was obtained from EPO database Espacenet with the help of a patent specialist from the Dutch Enterprise Agency. The initial search strategy used for this research focused upon the classification search and the Cooperative Patent Classification (CPC) system. Making use of the CPC system allowed us to increase the total number of patents analysed, since not all patent applications are written in English. The following four CPCs were chosen: C12Q1/xx, G01N33/xx, G01N2333/xx and G01N2800/xx. Subsequently, these classification codes were combined various search specific terminology retrieved from literature to specify and narrow down our search. The CPCs combined with the search terminology, Boolean operators and the number of hits can be found in the Table 1.

Combining the four categories and deduplicating similar patents resulted in a dataset containing 23.931 unique patents worldwide. The following Asian nationalities were present in the dataset: China, Hong Kong, Israel, Japan, Korea, Russia, Singapore and Taiwan. Country codes of these countries were used to search within the patent application and patent priority field and resulted in a total number of 9.929 individual patents in Asian countries as can be seen in Figure 1.

In Excel, each patent applicant was labeled a company, institute or an individual based upon the name and information found on the internet. Patent applicant names written differently but referring to applicant were merged. Data was then exported to Excel 3D maps for geographic visualisation of the patent density, including the top ten companies and institute applicants. Additionally, patent

filing dates of all patents included were used to design a graph showing the patent filing timeline. Starting point of

the graph was 1980, leading only to the exclusion of 5 patents filed in 1967.

Table 1: CPC codes combined with search terminology used for the patent search.

CPC-code	Search query's	Number of hits
C12Q1/xx	Measure or testing processes involving enzymes, or microorganisms AND lung* OR pulm* OR pneum* OR bronch* OR respir*	11.969
G01N33/xx	Investigating or analysing materials by specific methods not covered by the preceding groups AND lung* OR pulm* OR pneum* OR bronch* OR respir*	14.314
G01N2333/xx	Assays involving biological materials from specific organisms or of a specific nature AND lung* OR pulm* OR pneum* OR bronch* OR respir*	5.349
G01N2800/xx	Detection or diagnosis of diseases AND lung* OR pulm* OR pneum* OR bronch* OR respir*	3.801

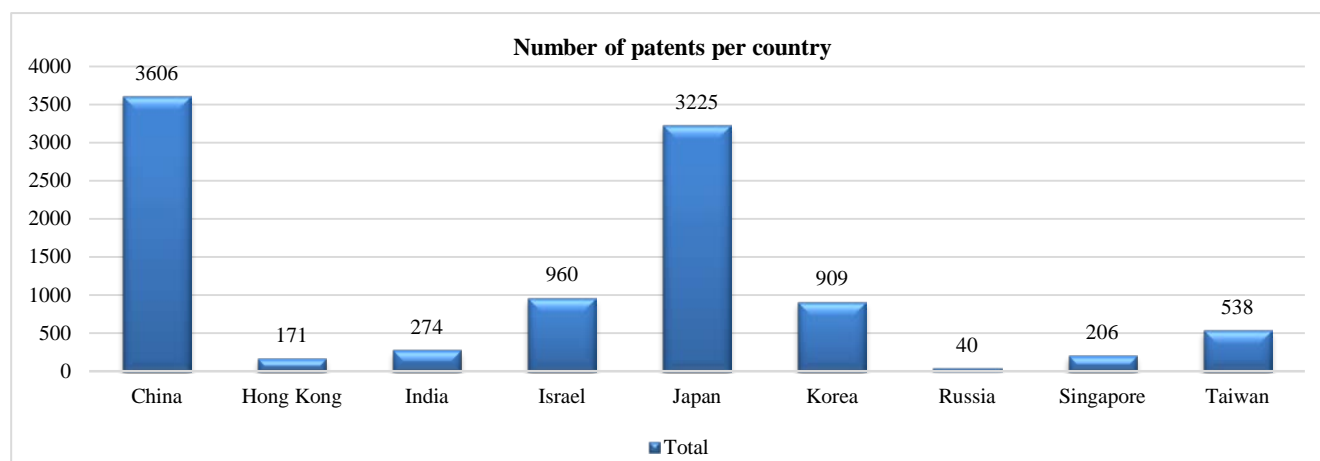


Figure 1: Patent distribution per country.

Table 2: Search queries used in the clinical trial search.

Database	Search queries	Number of hits
ICTRP-database	Infect* AND Lung* OR respir*OR pulm* OR pneum* OR bronch*	381 unique trials
	Diagnos* OR detect* AND bronch* OR pneum* OR lung* OR respir*	
	Treat* OR vaccine* AND bronch* OR pneum* OR lung* OR respir*	
ClinicalTrials database	Infection AND Lung OR respiratory OR pulmonary OR pneumonia OR bronchitis	164 unique trials
	Diagnosis OR detection AND bronchitis OR pneumonia OR lung OR respiratory	
	Treatment OR Vaccine And bronchitis OR pneumonia OR lung OR respiratory	

Clinical trial analysis

Analysis of CTs enabled us to reveal clinical trends over the last years, while at the same time proving us with information related to ongoing CTs and pipeline products. We decided to also include CTs related to the development of drugs and vaccines for RTIs. Besides providing a more accurate pipeline presentation, this also enabled us to interpret the findings on diagnostic studies in regard to drug and vaccine studies.

A combined dataset was composed, consisting of data from the WHO ICTRP database as well as the U.S.

National Library of Medicine (NLM) database on ClinicalTrials.gov.^{16,17} In addition to the ICTRP database, the ClinicalTrial.gov database also includes completed CTs, thereby enabling us to provide a more reliable picture in regard to the trends over recent years. Various search queries were used to retrieve data from both databases as can be seen in Table 2. Data was deduplicated and the complete list was reviewed to make sure only relevant CTs were included in the analysis. Trials targeting acute RTIs were considered relevant, meaning that trials regarding chronic conditions such as asthma were excluded. Trials were included when the following data was present: trial country, trial status, trial subject, sponsor, condition studied, trial phase, and

registration date. The end result was a list of 545 unique CTs; 381 trials retrieved from the ICTRP database and 164 trials retrieved from the ClinicalTrials database.

Trials were categorized according to the intervention type tested within the trial. Four categories were composed; RTI drug/therapy trials, diagnostic trials, vaccine trials, and lastly, trials that did not fall under any of the previously named categories such as observational studies. Starting date of trials included in this study was 2001 since this was the earliest registration data found in both databases for relevant CTs. Data was retrieved in March 2018, so only ± 3 months of the year 2018 were included.

RESULTS

Patent literature

The total number of patents that were included in this study was 9,929. All patent documents dating from the year 1980 onwards up until 2017 were added to geographical map in Figure 2 which delineates the patent density for 9 Asian countries. Two patent filing timelines have been added to Figure 2, including a cumulative filing timeline.

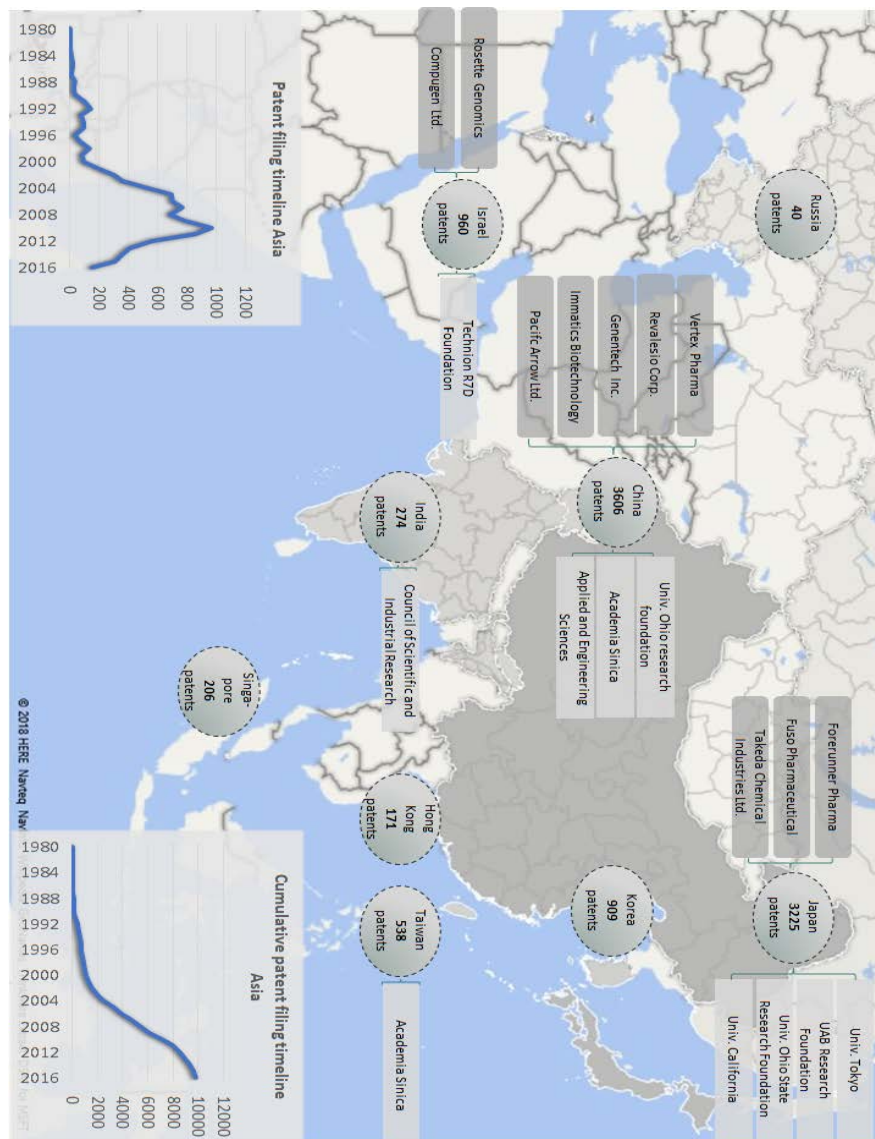


Figure 2: Patent density based on the number of patents per country. Top companies and institutes have been added to the map, together with two patent filing timelines over the years 1980 to 2016.

Data for the year 2017 and 2018 was not included in both timelines due to the 18 months delay between patent filing and publication date. The timelines reveal that the number of patents filings in the respiratory diagnostics

segment has dropped with every year since 2010. Additionally, we see that between 1980 and 2018 most patents were filed in China, followed by Japan, Israel, Korea, Taiwan, India, Singapore, Hong-Kong and Russia.

Top companies and institutes involved in patent filing were identified and ordered based upon the number of patents they own (Figure 3B/3D). Numbers found behind the company or institute name correspond to the number of patents they filed in that country. Academia Sinica, the national academy of Taiwan, appears more than once in the list of top institute patent filers, indicating that they actively file patents in Taiwan as well as in China. Eight out of the top ten patent filing companies filed their patents either in China or in Japan. Foreign companies

filed most patents in China whereas patent filing in Japan was mainly done by domestic companies. The top three companies that filed most patents included Vertex Pharma in China, and Compugen Ltd and Rosetta Genomics in Israel. Patent filing amongst institutes revealed a similar trend; seven out of the ten top filing institutes filed their patents in China or Japan. The top three institutes included Academia Sinica in Taiwan, the Ohio State University Research Foundation in China, and the University of Tokyo in Japan.

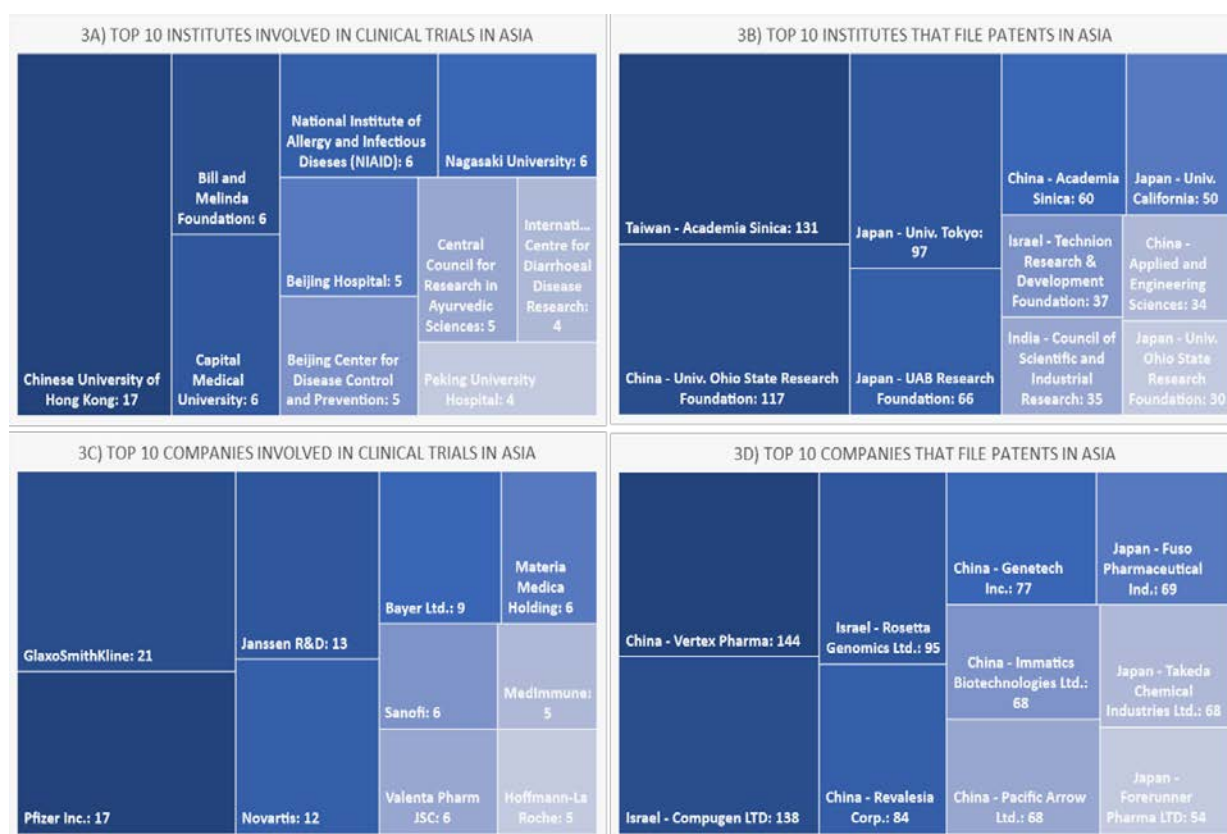


Figure 3 (A-D): Top institutes and companies based on the number of clinical trials run and the number of patents they own. Numbers behind the institutes and companies indicate the amount of trials or patents.

Clinical trials

The total number of CTs included in the analysis was 545. Figure 4 displays the number of recently completed and active CTs with China, Japan and India forming the top 3. Most trials in China were conducted by domestic companies, whereas in Japan the majority was conducted by foreign companies. The remaining countries and their number of CTs over the last years can be found in Figure 5A. Top organisations involved in CTs can be found in Figure 3A/3C. Companies and institutes involved in trials tend to have multiple trials running simultaneously in various countries, making it impossible to assign them to a specific country in contrast to patent filing.

The number of trials per phase is displayed in Figure 5B. The figure clearly shows the number of CTs increasing

towards phase 3. Diagnostic studies have been mentioned separately since these studies tend to be different from the conventional CTs that have distinctive phases. Figure 5C illustrates the CT registration trend between the years 2001 and 2018. A prognosis for 2018 was made based upon the number of CT registration within the first three months. The pie chart in the top left corner of Figure 5C shows that in the majority of trials a drug was tested, followed by vaccines and diagnostics. Lastly, Figure 5D presents the leading conditions and pathogens studied in the trials included in this study. A substantial part of all trials targeted influenza and pneumonia, where the vast majority of pneumonia studies focused upon a bacterial etiology as can be seen in pie chart in the upper right corner of Figure 5D.

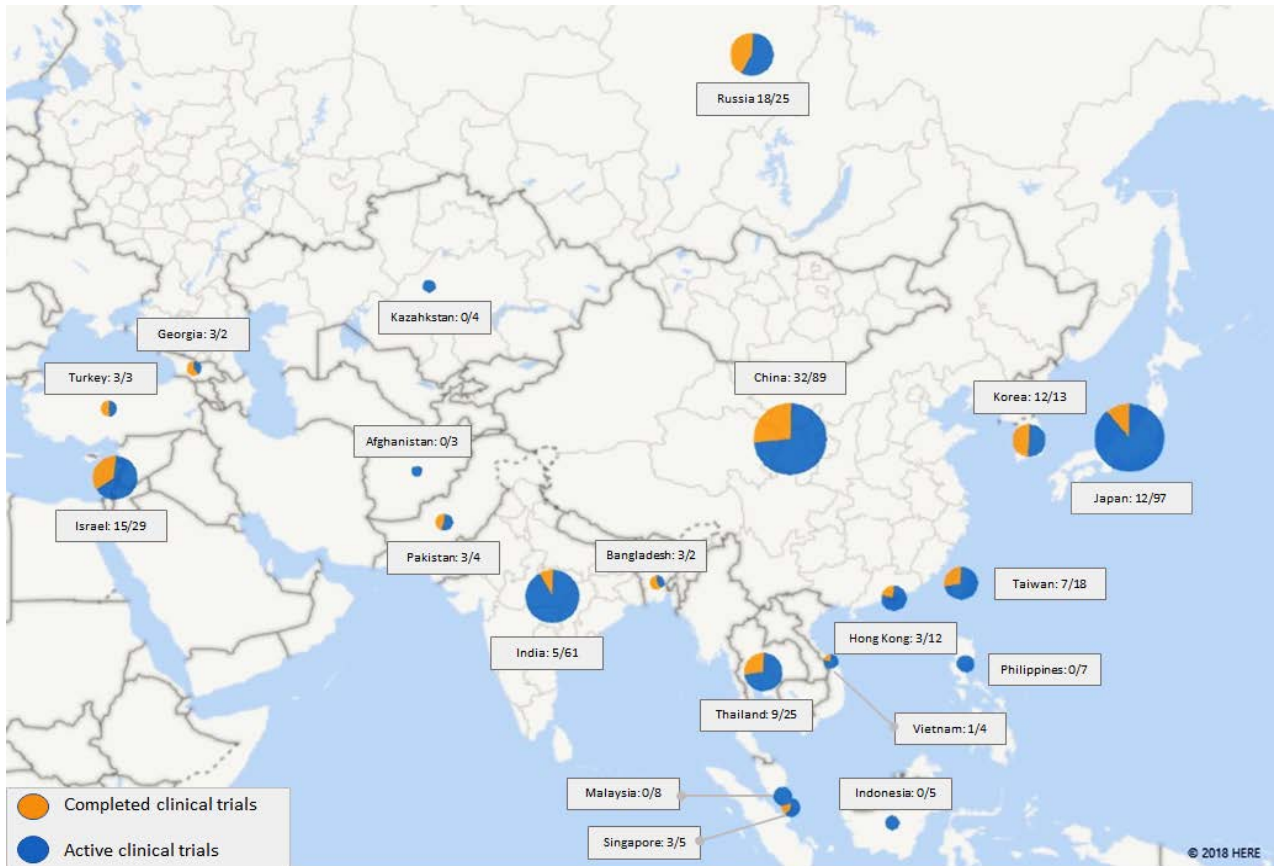


Figure 4: Number of completed and active clinical trials in Asia.

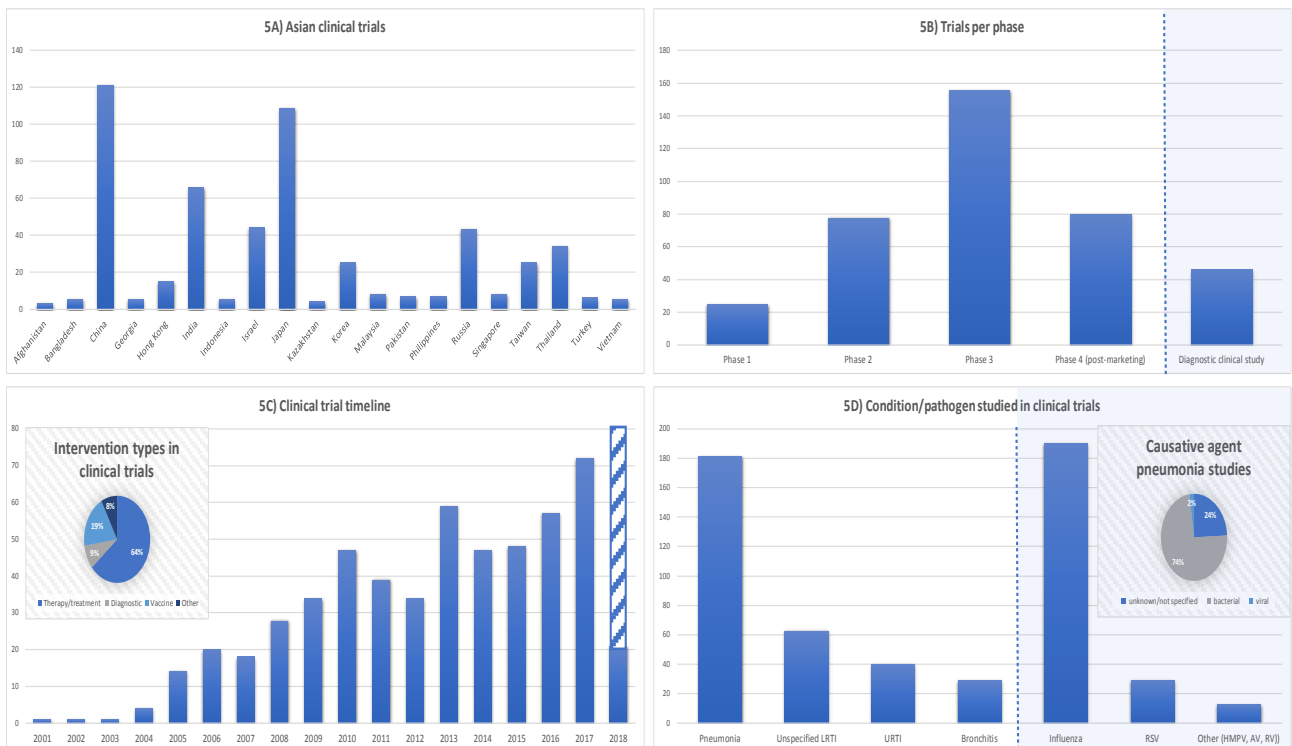


Figure 5: (A) Number of clinical trials per country; (B) number of active trials per phase; (C) clinical trial timeline and intervention types; (D) condition/pathogen studied and causative agent in pneumonia studies.

DISCUSSION

Here we showed a downward trend in Asian respiratory diagnostic patent filing since 2010 but a surprisingly high number of clinical studies in phase 3 and 4. The results also indicate a strong preference and interest of companies for the development of therapeutics and vaccines for bacterial pneumonia and influenza (viral) whereas less attention is given to non-influenza respiratory viruses (NIRVs) and the development of diagnostic tools. Most viable markets in Asia are the Chinese, with substantial foreign R&D investments in patent filings, and the Japanese market, which revealed high involvement of pharmaceutical multinationals in CTs.

The main objective of this study was to present a thorough description regarding the current state of the RTI market in Asia. By analysing patent documents and CTs we aimed to provide a comprehensive overview of the existing pipeline. Patent trend analysis revealed a downward trend in patent filing since 2010. Increasing awareness and efforts through initiatives did not seem to provide incentives for organisations to invest more resources into the development of diagnostics. Instead, industries' interest appeared to be gradually decreasing as the number of patents filed dropped with every year. The cumulative plot revealed a shift in the growth slope. Such transition in growth could mean the opposite, as it indicates a shift in the market from the growth phase into the maturity phase as we described earlier by Manfield's S-curve theory.¹⁸ This transition is confirmed by comparing the non-cumulative patent filing graph with theory on patenting activity, thereby suggesting that optimal market penetration has already been reached.¹⁵

Characteristic for a mature market is the negative technological progress over cumulative R&D expenditures. Further investments into existing technologies is not advised and only results in marginal improvements.¹⁹ Instead, resources should be invested in finding new S-curves that provide higher development potential. Further investments into this segment could no longer be as profitable, thereby providing incentives for companies to shift their focus towards other more lucrative areas despite the high burden and unmet medical need that continuous to exist.

Analysis of CTs in Asia revealed a late-stage pipeline with a high number of phase 3 studies compared to phase 1 studies, which is the opposite of what could be expected considering the phase transition success rates and risk of failure.²⁰ This underrepresentation of phase 1 studies could be because many potential research centers in Asian countries have not been awarded the certification designed by the Medicines and Healthcare products Regulatory Agency.^{21,22} Concerns by companies regarding the lack of skills needed for phase 1 studies is what keeps the industry from conducting phase 1 trials in Asia.²³ At the same time, the overrepresentation of phase

3 studies is in line with a trend that has been visible over the years where big pharma moves their phase 3 trials towards less wealthy countries to save costs.²² Contrary to what the downward patent trend suggested, this late-stage pipeline does not suggest a mature market with decreasing interest and investments of the industry. Instead, it reveals a highly viable market with high investments and many products in its pipeline. It also shows that this market is of much interest to foreign companies since all top 10 companies involved in CTs appeared to be of American and European origin.

The downward diagnostic patent trend together with the high number of products in the late-stage pipeline implicates the industries preference for therapeutic areas other than diagnostics. Further analysis of the CTs confirmed that only a minor part of the diagnostic studies included were financed by the industry, whereas the majority was financed by universities and hospitals. This difference could be even bigger since non-profit organisations tend to underreport CTs to databases.^{6,24} This implies that the industry has little interest in developing respiratory diagnostics, regardless of the high unmet need that exists. Instead, the industry coordinates their R&D towards products aimed at profitable diseases thereby explaining the strong preference towards product development for bacterial pneumonia and influenza, despite growing consensus on the burden of viral RTIs.^{25,26} Of those studies that do focus upon viral pathogens, the majority of companies seems to target vaccines and antivirals for influenza. The result remains a significant underrepresentation of studies concerning NIRVs and a pipeline that is almost dry, which is troubling to say the least. Especially since more and more studies have suggested an association between these viral infections and asthma development later on in life.^{27,28} The relatively few CTs that do focus upon these viruses are mostly conducted by institutes rather than the industry.

This underrepresentation of NIRVs confirmed what was already addressed in 2012 during the establishment of the BRaVe initiative; the lack of attention and investments being put into finding solutions for NIRVs. A recent study in *Nature* concluded the underrepresentation of NIRVs studies was also present in the USA and EU.⁶ They argued the lack of databases containing genome sequencing could be the underlying cause. They suggested that increasing global surveillance of NIRVs could provide incentives for investments into non-influenza viruses. Assessing mutation rates and genetic diversity is crucial for product development, thus baseline data on diversity of viral proteins, or the absence thereof, could affect the choice of development of any future specific antiviral drug or vaccine.

Our results reveal a large portion of respiratory products in the late-stage pipeline, some of which will be hitting the market within the next couple years. Amongst the most promising markets in Asia are the markets in China

and Japan. These countries are responsible for almost 70% of all diagnostic patents filed and the attractiveness of these markets was already implicated in our result section where we revealed that the majority of organisations filed their patents in either of these two countries. Difference between both countries is the fact that almost all top patent filing organisations in China appear to be foreign, whereas the majority of top companies and institutes in Japan are domestic (Figure 6).

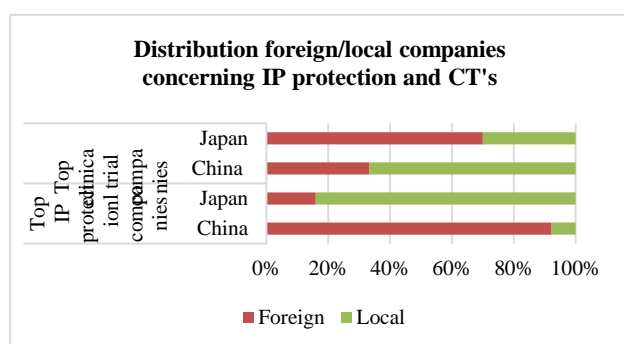


Figure 6: Skewed distribution of foreign and domestic companies in Japan and China regarding patent filing and clinical trials.

The popularity of these two markets isn't surprising since both countries present a large and rapidly aging population, thereby offering unique business opportunities. The high number of international companies filing for patents in China is more surprising since intellectual property (IP) protection there is ranked poorly and often presents challenges for foreign companies.²⁹ Increasing efforts by the Chinese government, however, to keep IP protection high on the agenda seem successful. Patent litigation and foreign investments have drastically increased over the last decades and successful IP cases by GSK and Pfizer demonstrate that foreign companies should have confidence that their IP will be protected.³⁰

Contrary to China, IP protection in Japan is ranked amongst the best worldwide and foreign companies have to worry less about IP infringement.²⁹ Despite this, our results indicate relatively few foreign companies amongst the top patent filing companies which could be due to Japan's mature market, driven by strong local companies and the fact that cultural business differences between Western and Japanese companies pose significant challenges. These differences in culture appear to be less problematic in China where similarities with the Western business culture can be found.³¹

Together, China and Japan conduct 40% of RTI-related trials in Asia. The rising number of trials throughout Asia (Figure 3C) appears to be the consequence of an increase in CTs in China and other developing countries such as Vietnam and Thailand, but less so because of Japan where numbers appear relatively stable.³² Contrary to

what was described above, the majority of organisations responsible for this increase in China were found to be domestic organisations, whereas the majority of companies conducting trials in Japan were foreign. This could have something to do with the fact the Japanese CT infrastructure is superior to China's, yet costs per patient are still significantly less compared to the US or Western European countries.^{33,34} Also, China offers relatively few CT sites compared to Japan and the quality of trials in Japan has developed to such an extent that there is no reason for big pharma to maintain a bias in favor of Europe or the US.^{35,36}

There are several limitations to this study that we have to take into consideration. The fact that multiple diseases are considered RTIs required us to construct a search query used in patent and CT search that aimed to encapsulate these conditions as accurate as possible. The design of such a search query could have resulted in the inclusion of non-relevant data, particularly in the patent analysis since these search results were not reviewed and checked for relevance. To minimize the degree to which this could affect our data collection, we verified the search criteria with experts at patent offices and the ICTRP database.

Additionally, since we made use of the publicly available patent database Espacenet, we cannot say with complete certainty how trends have evolved over the last years. Particularly recent developments in market trends remain uncertain because publication of patent literature takes 18 months after initial filing.

Lastly, since we used patent applicant information to describe filing trends, we have to realize there's a chance of underreporting. In some cases, organisation names are not registered as the patent applicant. Instead, names of individuals are filled in which are often untraceable to the specific organisation. Thus, in reality the numbers of patents filed by companies and institutes could be higher.

This study showed a downward patent filing trend and decreasing investments, thereby implying a mature respiratory diagnostics markets in Asia. Minor industrial interest was seen in the diagnostics segment which was explained by the fact that resource investments into a seemingly mature market could be less lucrative for profit-driven companies. At same time we revealed an evolving respiratory CT market with increasing R&D investments that seemed particularly attractive for foreign companies. Primary focus of these companies appeared to be towards profitable segments such as treatments and vaccines for bacterial pneumonia and influenza, which both presented strong pipelines. The handful of studies related to NIRVs and respiratory diagnostics in Asia appeared to be financed and conducted by non-profit organisations, which suggests that involvement of the business sector in initiatives such as the BRaVe initiative is not optimal. Future research should therefore aim to study how to improve involvement and engagement of

the industry in such initiatives and how to provide incentives to increase investments in these segments. Research and establishment of genome databases for NIRVs could produce the right stimulus for innovative companies in emerging markets where the unmet medical need is high.

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