Global Health Impact Data and Methodology

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GLOBAL HEALTH
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Abstract

Background
As the world grapples with the Coronavirus pandemic, we need good data on not only the need for treatments for pressing public health problems but also on new interventions' impacts. We present a mathematical model of medicines' health consequences using disease surveillance data to inform health policy and scientific research that can be extended to address the current public health crisis.

Methods
The Global Health Impact (GHI) index calculates the amount of mortality and morbidity averted by key medicines using data on outcomes in the absence of treatment, treatment effectiveness, and access to needed treatment. We conducted a systematic review of random control trials assessing the efficacy of medical treatments on malaria, TB, HIV/AIDS, and several NTDs. Country-level data on DALYs and treatment coverage were extracted from data repositories maintained by the Global Burden of Disease study, Global Health Observatory, WHO, and UNICEF.

Findings
The index aggregates drug impact by country, disease, company, and treatment regimen to identify the spatial and temporal patterns of treatment impact and can be extended across multiple diseases. Approximately 62 million life-years were saved by key drugs that target malaria, TB, HIV/AIDS, and NTDs in our latest model year. Malaria and TB medicines together were responsible for alleviating 95% of this burden, while HIV/AIDS and NTD medicines contribute 4% and 1% respectively. However, the burden of disease in the absence of treatment was nearly evenly distributed among malaria, TB, and HIV/AIDS.

Interpretation
A common framework that standardizes health impact across diseases and their interventions can aid in identifying current shortcomings on a global scale.

Funding

Introduction

As the world grapples with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, we need good data on both the need for treatments but also on the impact of new interventions as they are developed. We present a mathematical model of medicines' health consequences using disease surveillance data to inform health policy and scientific research that can be extended to address the current public health crisis (http://globalhealth.pythonanywhere.com/).

The SARS-CoV-2 pandemic is currently devastating the health care infrastructure in many developed countries but is likely to have even more profound effects in poorer countries. The United Nations' Sustainable Development Goals (SDGs) are focusing global efforts on providing universal health coverage and access to essential medicines for infectious and chronic diseases.[1] Governmental and non-governmental organizations direct substantial aid toward these needs.Globally, governments gave $13.6 billion in official development assistance for health in 2017, for instance.[2] However, existing resources are not inadequate even to address many pre-existing global health challenges. Organizations attempting to improve health need a broad and accurate picture of medicines' health impact, as well as the need for treatment, in order to target resources, evaluate performance, and improve health. Data on treating communicable diseases is tremendously important for many stakeholders – from international institutions, like the World Health Organization, to bilateral or multilateral health assistance organizations, like the United States Agency for International Development, and philanthropies, like the Gates Foundation, to national governments and their economies. Good data about medicines' impacts can help international and multilateral institutions (and other stakeholders) prioritize funding across countries, diseases, and interventions. Country-level health systems similarly aim to allocate their resources, and secure new resources, to have a greater impact. Information on medicines' health consequences might, for instance, help countries see how drugs' impacts will change as they are made more accessible. This can help them decide whether to invest in efforts to lower drug prices or extend access more broadly in other ways. Moreover, impact assessments may help shape trade and other policies associated with globalization.

Information on health needs greatly influences health policy and practice, but organizations attempting to address those needs require similarly detailed information on essential medicines' global health consequences. The Global Burden of Disease project gathers data on different countries' health needs and the data they provide has helped allocate health spending.[3] But the Global Burden of Disease project does not provide any information about where we are succeeding in meeting health needs with different health interventions. The vast majority of mathematical models that look at health interventions' consequences are disease- or region-specific, and few estimate the impact of specific medicines the global pharmaceutical supply chain provides.[4-6]

The Global Health Impact (GHI) models provide the first comprehensive effort to evaluate the global health consequences of treatment across a wide range of diseases and interventions. To accurately capture these effects, our model considers: 1) outcomes in the absence of treatment, 2) the effectiveness of treatment, and 3) how many people who need treatment access it. The GHI model currently calculates the impact of drugs used to treat diseases affecting many impoverished people around the world: tuberculosis (TB), HIV/AIDS, malaria, and Neglected Tropical Diseases (NTDs). Each of these diseases pose its own threat and requires a different form of treatment and prevention. TB is the leading cause of death from a single infectious agent-- causing 1.2 million deaths in 2018, with 95% of those deaths occurring in low or middle-income countries.[7] Most TB can be cured with low cost medicines, making access to treatment vital. HIV/AIDS is a viral infection for which there is no cure: at the end of 2018 approximately 37 million people were living with HIV/AIDS, but only 62% of infected individuals worldwide were receiving antiretroviral therapy (ART).[8] There were 219 million cases of malaria in 2017, although it is both preventable and curable.[9] Finally, there is insufficient research and development of drugs for many NTDs, despite their detrimental impact on lifespan and livelihood in endemic regions. In focusing on these diseases and their treatments, we hope to shed light on pharmaceuticals' impact on people's lives and to pave the way for improvements in the future. It is possible to expand our model to address other pressing global health problems including the current SARS-CoV-2 pandemic.

Results

The GHI model approximates the global impact of treatment of key drugs that target malaria, TB, HIV/AIDS, and NTDs, in 2015, is 62 million life-years saved. This is equivalent to saving almost a year of life for 1% of the world's population. Malaria and TB medicines together provide 95% of the total life-years saved, while HIV/AIDS and NTD medicines contribute 4% and 1% respectively (in part because we divide total impact by the required length of treatment, which is much longer for HIV/AIDS as the disease cannot be cured). However, the estimated need, or burden of disease in the absence of treatment, for malaria, TB, and HIV/AIDS drugs are approximately equivalent. Figure 1 provides an overall picture of aggregate drug impact over time. The model suggests that malaria and TB drugs are having a decreasing impact on death and disability while HIV/AIDS and NTD medicines have relatively flat impact outcomes over time.

Figure 1. Global DALYs Alleviated Over Time

Global DALYs alleviated in the years 2010, 2013, and 2015 aggregated by disease. Malaria is blue,TB is yellow, HIV/AIDS is red, and NTDs are green.
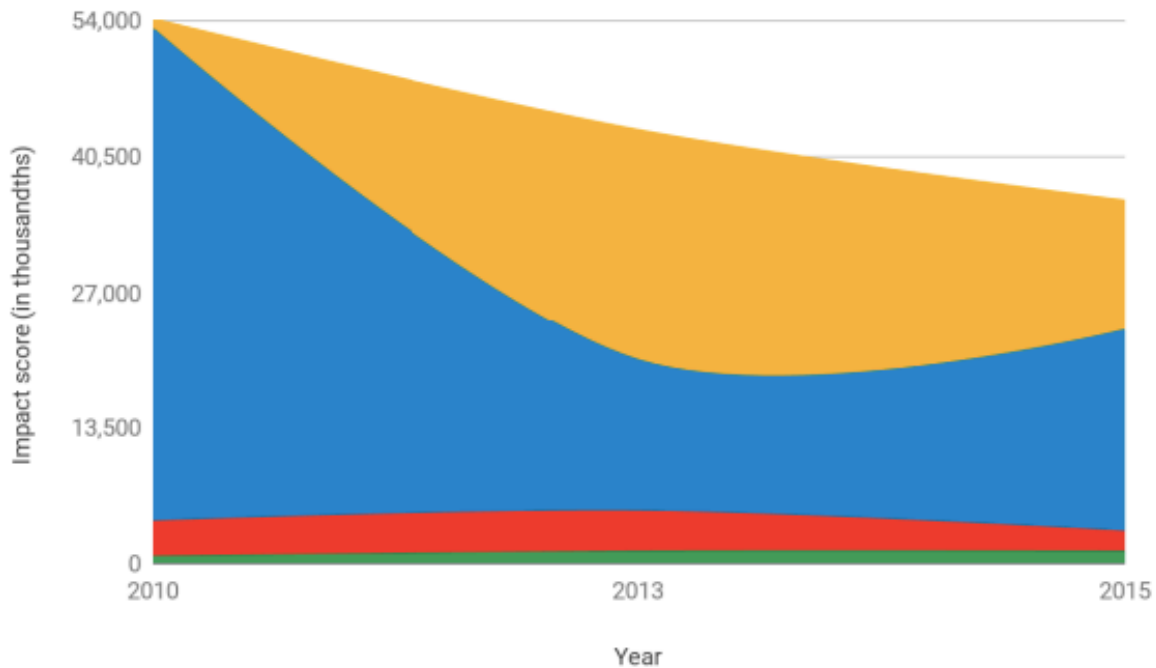
The model provides estimates of the impact of drugs on malaria, TB, HIV/AIDS, and NTDs. Key malaria treatments such as artemether-lumefantrine (AL) and artesunate plus amodiaquine (AS+AQ) have the largest impact, possibly because they are widely recommended and among the most effective treatments. Together they helped alleviate 35% of the 62 million total DALYs alleviated in 2015. Figure 2 illustrates that even with the many highly efficacious drugs available, 73% of the burden of these diseases remains unalleviated.

*Figure 2. Impact of Drugs on the Global Burden of Disease*

Global DALYs alleviated in 2015, separated by drug. Includes global DALYs unalleviated.
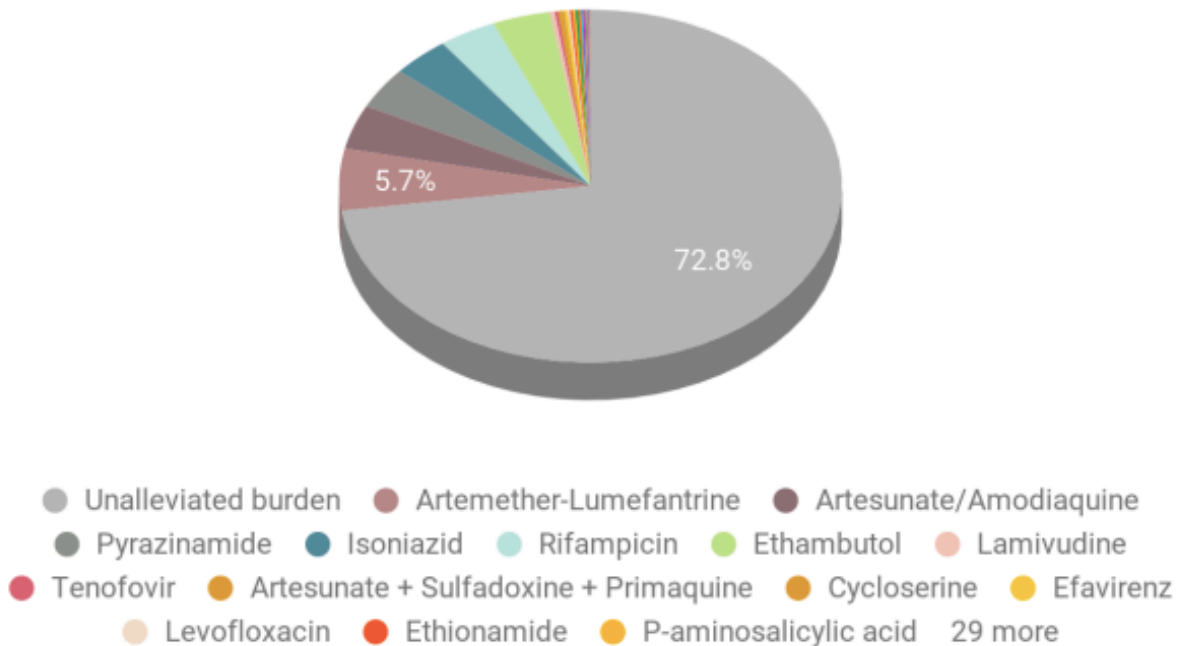
The GHI model makes it possible to study the global distribution of DALYs alleviated across countries. Figure 3 suggests that key medicines are having the most impact in Africa. This is due to the fact that malaria treatment is highly concentrated in this region. The global reach of HIV/AIDS and TB is far more extensive, which is why we see greater uniformity in the distribution of drug impact for those diseases. The treatment of these diseases has the largest impact in India, with the vast majority of lives saved coming from effective TB treatment. Medicines targeting malaria are having a high impact in Nigeria and Uganda. These large impact scores reflect a combination of high disease burden and efficacious treatment. However, there are areas with great need but correspondingly little impact. The most glaring examples of this failure can be found in sub-saharan Africa and South America; the ratio of impact to need in Suriname is lower than 5%, suggesting a substantial amount of unmet need.

Figure 3. DALYs Alleviated by Country

Top 10 countries by DALYs alleviated in 2015, aggregated by disease. Malaria is blue, TB is yellow, HIV/AIDS is red, and NTDs are green.
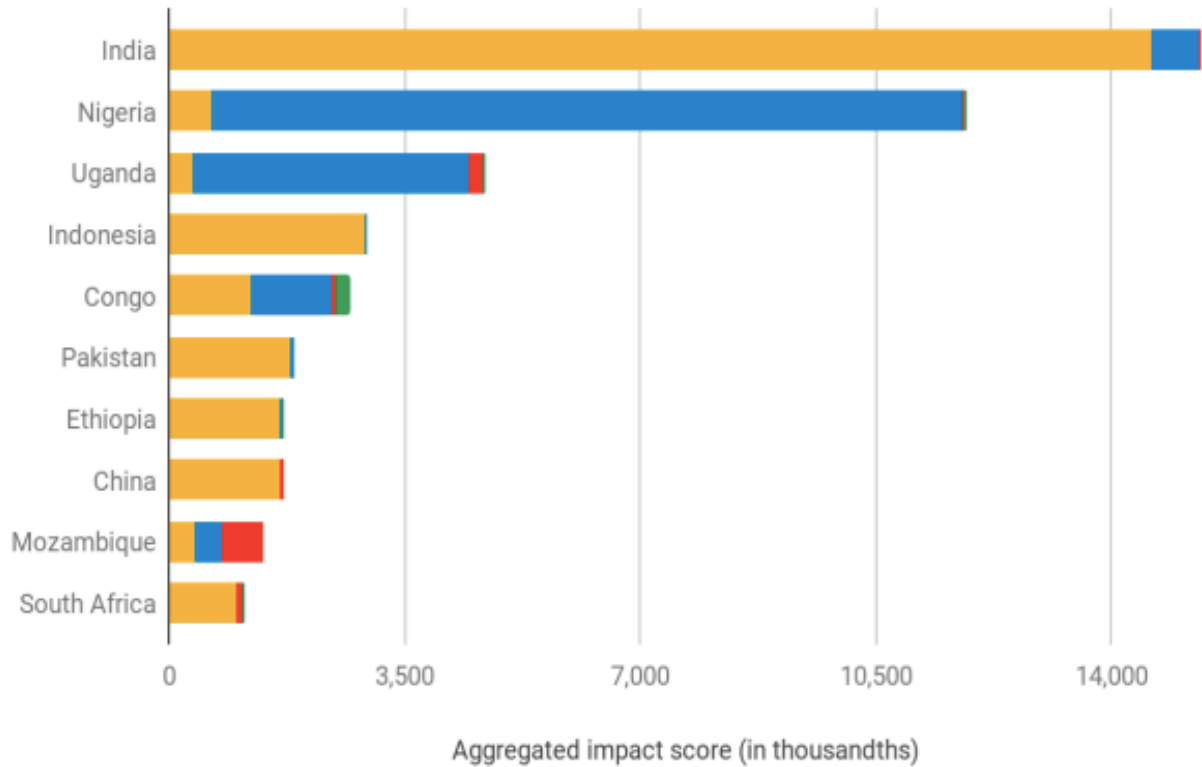
The GHI model also provides drug impact data aggregated by manufacturer. Ajanta Pharma Ltd. and Laboratorio Reig Jofre S.A. are manufacturers of drugs with comparatively high impact scores. Ajanta Pharma Ltd. produces artemether, a drug which alleviated a significant production of the global malaria burden. Streptomycin, produced by Laboratorio Reig Jofre S.A., alleviated a large proportion of the estimated burden of TB that would have been lost in the absence of treatment. However, Svizera Europe, Lupin, and Imres Medical Solutions provide the most cost effective medicines for malaria, TB, and HIV/AIDS.

Figure 4. DALYs Alleviated by Manufacturer

Top 10 manufacturers by global DALYs alleviated in 2015.
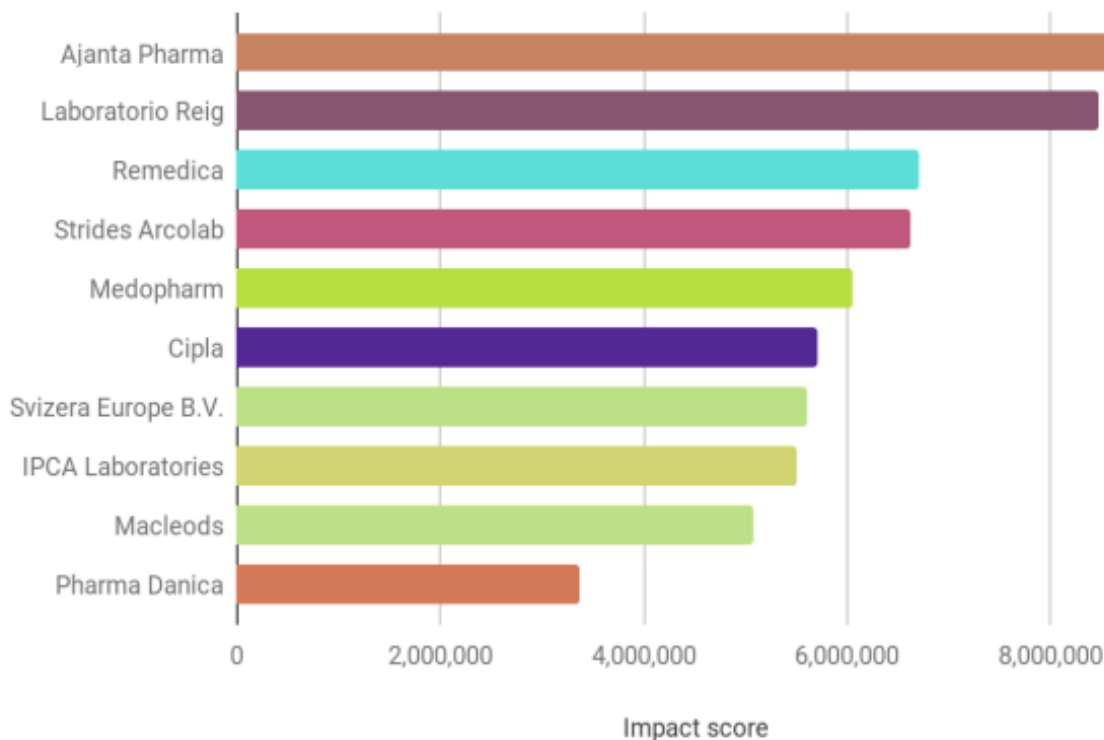
The model allows us to explore the impact of patent holder companies. The complex nature of the drug development process makes any impact allocation controversial, however, we aggregate drugs by the company with the original patent to incentivize new innovation. Sanofi and Novartis are the clear leaders in having originated drugs that reduce morbidity and mortality. Drugs patented by Sanofi averted the loss of more than 18 million DALYs in 2015. Figure 5 illustrates that drastic changes in company rank that occur when company impact scores are divided by revenue earned. Before considering this measure of company size, drugs from Sanofi, Novartis, Pfizer and Merck have the greatest impact. Accounting for size, GlaxoSmithKline, Gilead, Boehringer Ingelheim, and Daiichi Sankyo have a greater impact. We can also examine the timing of the development of medicines across the diseases in our model. Figure 6 demonstrates that many key patents for TB were filed more than 50 years ago.

Figure 5. Originator Company Impact versus Revenue
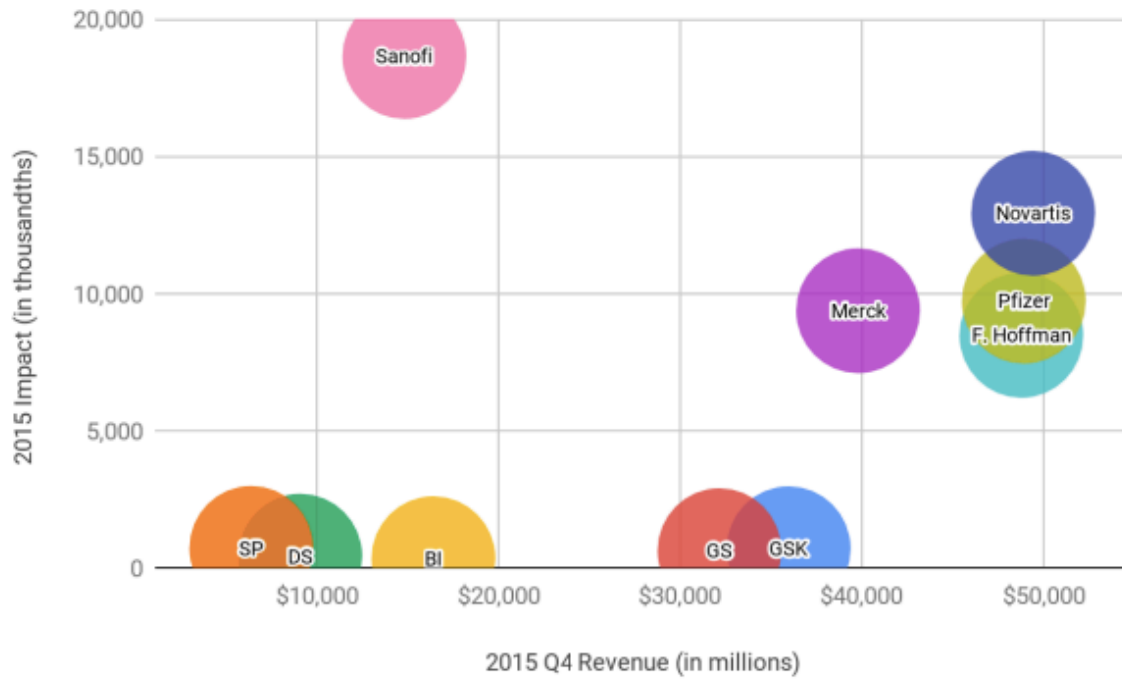
Comparison between an originator's global DALYs alleviated and its Q4 revenue in 2015. SP is Shire Pharmaceuticals, DS is Daiichi Sankyo, BI is Boehringer Ingelheim, GS is Gilead Sciences, and GSK is GlaxoSmithKline.

Figure 6. Global DALYs Alleviated by Patent Date
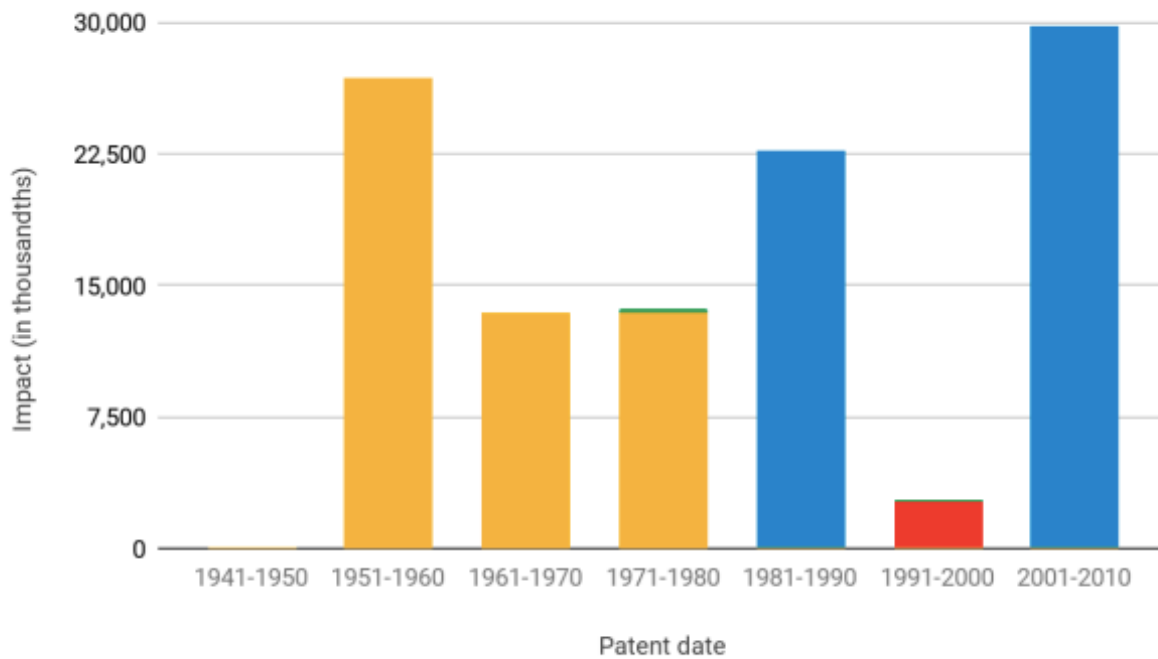
Total impact of drugs organized by patent date in bins of 9 years, aggregated by disease. Malaria is blue, TB is yellow, HIV/AIDS is red, and NTDs are green. Note that 18% of patented drugs from 1941-1950 impacted NTDs (though the proportion is not visible on the graph).

Research in Context

Evidence before this study
We performed an extensive literature search for articles containing the key words: impact, medicine, disease, and model on PubMed and Google Scholar, with no time limitation.. However, previous attempts to model the global burden of disease alleviated across multiple interventions were not available. We conducted a systematic review of PubMed and Google Scholar for drug efficacy studies with no limitation of time until Dec 31, 2015, selecting random control trials with a confidence threshold of 0.9 or greater. A combination of search terms: drug name, efficacy, and the disease's technical name were used. Data for total DALYs lost to malaria, TB, HIV/AIDS, and several NTDs are extracted from the Global Burden of Disease Study (GBD). As the GBD study provides only total DALYs for malaria, we gather data on the percent of prevalent plasmodium falciparum from the WHO World Malaria Report. Case notifications are used to allocate GBD's total TB DALYs between drug susceptible, multidrug resistant, and extremely drug resistant TB. Epidemiological data on the treatment coverage of TB was collected from the WHO Global Tuberculosis Report (2011, 2014, and 2016). Data published on country-level HIV/AIDS treatment was taken from the Global Health Observatory data repository. The percentage of febrile children receiving artemisinin-based combination therapy was used as an estimate of malaria treatment coverage, gathered from the UNICEF Data Warehouse. The number of individuals receiving treatment for several NTDs was collected from the WHO Preventive Chemotherapy and Transmission Control databank.

Added value of this study
Our model uses data on the global burden of disease, disease incidence, treatment percentage, and drug effectiveness to estimate the burden of disease that occurs in the absence of treatment, the impact of drugs on this burden over time, and the contribution of generic firms to alleviating the burden. Previous models of impact on disease burden focus largely on one disease and its transmission and mortality rates, leaving out a large component of an intervention's impact. The GHI model differs significantly from models that do consider a more holistic view of health impact by estimating, in a simple, transparent way, the health consequences of drugs for malaria, TB, HIV/AIDS, and several NTDs. To our knowledge, our study is the first attempt to create a framework for judging the burden of disease alleviated by treatment that can be extended to many other diseases and health interventions.

Implications of all the available evidence
A common framework for estimating global health impact is critical in evaluating performance, setting targets, and guiding the distribution of scarce health resources in order to advance access to essential medicines. The GHI models provide a robust methodology that can be applied to many diseases to create a comprehensive picture of the impact of interventions and determine where large need remains unmet.

Discussion

What would happen to our impact on malaria if resistance to first-line drugs became widespread and governments had to rely only on chloroquine to treat the disease? What if an international organization like the Global Fund worked with Merck to introduce a medicine 5% more effective than current first-line HIV/AIDS medicines, would there be a noticeable impact on the global burden of disease? If global resistance rates to TB drugs rise and prices fall, would individuals get greater access to necessary drugs? Governments, corporations, and non-governmental organizations (NGOs) are absolutely critical to disease management but it is tough and time-consuming to translate their potential actions into a quantifiable what-if scenario. A crucial capability of the GHI Index is that it can be used to forecast estimates of the impact of these various efforts. The results of these simulations can aid in determining which policies will be most effective, and thus provide evidence-based data to determine and justify policy decisions.

Policy researchers are able to use the GHI Index to examine the determinants and consequences of a medicine's impact on the global burden of disease. It is possible, for instance, to study the differences in efficacy on particular diseases in the model across countries. NGOs can wield the data offered to evaluate performance, set targets, and direct the distribution of critical resources to nations that need it the most. Additionally, international organizations and governmental departments of health can use the information from the Index to determine how they can have a larger health impact.

The GHI Index allows policy makers to better treat, and prevent, infectious diseases that threaten millions of human lives. It is clear that policy makers need to pay greater attention not just to the burden of disease but also its alleviation. Comparing global data collected on need versus impact shows that we are failing to address the unmet needs of HIV/AIDS and NTD patients.

The model's methodology is significantly different than, but is complementary to, that embodied in alternative models.4–6,10–12 It is important to have a variety of useful, comprehensive models. For example, Spectrum Health produces several dynamic models focused primarily on maternal and child health and HIV/AIDS.13 However, none of the other models combine -- in a simple, transparent, consistent way -- estimates of the mortality and morbidity averted by medicines for malaria, TB, HIV/AIDS, and NTDs. Because it uses the Institute for Health Metrics Evaluation's DALY information, the GHI model includes comparable estimates of the interventions' impacts on disability as well as death across several different diseases.

We need a mechanism that can be used to evaluate international institutions' and country-level contributions to global health and can assist country-level policy makers in developing health policy. The GHI index demonstrates which drugs are alleviating the largest amount of death and disability in each country in the world, where great needs remain unmet, and to what extent this is due to lack of access. Moreover, the index provides a mechanism for incentivizing positive change.14 Just as the Global Fund uses its estimate of lives saved in different countries in evaluating performance and distributing aid, the Index can be used to guide the distribution of health resources between different countries as well as within them. Additionally, if governments and funding agencies have greater confidence that certain interventions will be effective, they are

more likely to make the political decision to maintain, or even increase, national health budgets and international health assistance.

Conclusion

Good data is essential for improving decision making in addressing the SARS-CoV-2 pandemic and other pressing public health crises. Researchers should consider expanding the Global Health Impact model of medicines' health consequences using disease surveillance data to inform health policy and scientific research. Comprehensive information on interventions' health impact, as well as need, is essential for combatting the SARS-CoV-2 pandemic and other major public health crises. Millions of lives hang in the balance.

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Supplementary Materials for
Global Health Impact Data and Methodology

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Materials and Methods

Methods

The equation below is the impact formula that is used throughout our models to calculate a drug's lives saved in a single country; for the derivation of this formula see.[3]

$$I = \frac{D * \in * \theta}{1 - \in * \theta}$$

In this calculation: I = DALYs saved, D = DALYs lost, $\in$ = efficacy (%), and θ = treatment coverage (%).

Our models cover the years 2010, 2013, and 2015. We move beyond previous models in estimating the burden of disease that occurs in the absence of treatment, the impact of drugs on this burden over time, and the contribution of generic firms to alleviating the burden. The current models also include estimates of medicines' impacts on several NTDs, specifically: onchocerciasis, schistosomiasis, lymphatic filariasis (LF), and soil transmitted helminthiasis (STH). Where treatment length exceeds one year for infected patients, we also divide by the length of treatment.[15]

In the case of NTDs, we multiply the impact formula by prevalence to account for the fact that treatment is primarily delivered via mass drug administration (MDA) which is provided to almost all individuals in a given area (as only a percentage of the treated population will be infected with an NTD). This reduces our final impact score to account for the difference between the population requiring preventive chemotherapy and the actual number of people with the NTD as we intend to measure only the direct impact of treatment.

In what follows, we detail the more specific methodological choices we made for each disease sub-model and how we looked at different parts of the pharmaceutical supply chain. After we arrive at individual drug scores within each country, we aggregate them across countries and then by disease type as well as by both originator and manufacturing company. We briefly explain the company attribution below as well.

TB Model

Our current TB model investigates the impact of drugs on three patient groups: those with drug susceptible TB (DS-TB), multidrug resistant TB (MDR-TB), and extensively drug-

resistant TB (XDR-TB). The model also makes a distinction between the drug impact of treatment for DS-TB on patients with HIV/AIDS and without.

To illustrate how we calculate TB impact scores we will walk through a demonstration for the Dominican Republic in 2013. This section first explains how the inputs for the total DS-TB impact score were derived, then computes the impact score, and finally disaggregates the score among the drugs used to treat each case. This explanation is repeated for the MDR-TB and XDR-TB impact scores.

To calculate the final impact score for DS-TB we must first determine DALYs lost to DS-TB/HIV+ and DS-TB/HIV-. Approximately 18,000 DALYs were lost to TB in the Dominican Republic in 2013.[16] It is assumed that DALYs lost to TB are the sum of DALYs lost to DS-TB, MDR-TB, and XDR-TB. We estimate that DALYs lost to MDR-TB and XDR-TB are 1,958.06 and 207.94, respectively. The derivation of these estimates are explained further in the appendix. Thus, we can infer that 15,834.01 DALYs were lost to DS-TB (18,000 - 1,958.06 - 207.94). We still need to decouple DS-TB/HIV+ DALYs from DS-TB/HIV- DALYs. The WHO reported 4,331 incidence cases of TB with known HIV status: with 24.72% testing positive and 75.28% testing negative.[16] We can then determine DS-TB/HIV+ to have 3,9139.97 DALYs and DS-TB/HIV- to have 11,920.04 DALYs.

We also require data on treatment coverage and efficacy to calculate DS-TB impact. We lack accurate treatment coverage data for the Dominican Republic so we utilize the WHO's estimate of directly observed treatment coverage of 58% for every case.[16] The WHO's 2015 Global Tuberculosis Report estimates 73% efficacy for HIV+ cases and 88% efficacy for HIV- cases.[17]

The data collected above can now be inserted into the overall impact formula to derive the final impact score for both diseases.

$$I_{\text{DS-TB/HIV+}} = \frac{3{,}913.97 * 58\% * 73\%}{1 - 58\% * 73\%} = 2{,}874.05$$

$$I_{\text{DS-TB/HIV-}} = \frac{11{,}920.04 * 58\% * 88\%}{1 - 58\% * 88\%} = 12{,}426.44$$

Consider how the DS-TB impact score is split up to estimate individual drugs' impact on HIV+ and HIV- patients. For DS-TB, we assume that the impact of each drug in the standard 6 month regimen is equal. DS-TB is characterized by the absence of resistance to first-line TB drugs and is treated using a 6 month rifampicin-based regimen involving 2 months of H+R+E+Z and 4 months of 2HRZE/4HR.[18] We assume that each first-line drug receives equal credit. This means that the total DS-TB impact score for the Dominican Republic will be divided by four with each drug receiving equal credit.

To calculate the impact score for MDR-TB we must differentiate MDR-TB cases from TB cases. The WHO tells us that there are an estimated 30 MDR-TB cases among newly treated TB cases and an estimated 62 MDR-TB cases among previously treated TB cases.[16] The

WHO also tells us that 6.6% of new TB cases were MDR-TB while 20% of previously treated TB cases were MDR TB.[19] Using this data we can estimate new cases of any type, 30/6.6% = 454.55, and retreatment cases of any type, 62/20% = 310. From this, we can calculate the overall percentage of MDR TB among prevalent TB: (30 + 62)/(454.55 + 310) = 12.03%. If the WHO reports zero new and retreatment MDR-TB cases at the country-level, the model will substitute the global average of the proportion of new and retreated MDR-TB cases out of total TB cases. Countries with this fallback data will maintain a total MDR-TB impact score but we do not further disaggregate impact among treatment regimens for these countries as we lack resistance rate data for new and retreated MDR-TB cases at the country-level. We can then multiply this by the total DALYs lost due to TB of all types: 12.03%*18,000 = 2,167.02. This is subtracted by 207.94, the number of DALYs lost to XDR-TB, to reach an estimate of 1,958.06 DALYs lost to MDR-TB. The calculation to derive the number of XDR-TB DALYs can be found further in the appendix.

Next, we estimate treatment coverage and efficacy for MDR-TB. The WHO estimates that there are 7,600 prevalent cases of TB in the Dominican Republic.[19] Multiplying this by the overall percentage of MDR-TB among prevalent TB yields 915, the number of MDR-TB cases needing treatment. Data from the WHO states that 105 Dominican Republic citizens received treatment for MDR-TB in 2013.[19] This number allows us to then estimate treatment coverage in the DRC: 105 individuals receiving treatment divided by 7,600 individuals needing treatment, or 11.48%. The WHO's Global Tuberculosis 2016 Report suggests MDR-TB treatment is 52% effective.[20]

We can now use the overall impact formula to calculate the final 2013 impact of MDR-TB treatment in the Dominican Republic. Given that MDR-TB treatment typically takes two years, we divide the estimated impact scores by two to arrive at an estimate for a single year:[21]

$$I_{MDR\text{-}TB} = \frac{1{,}958.06 * 11.48\% * 52\%}{1 - 11.48\% * 52\%} / 2 = 6$$

Now that we have derived the overall impact of all three MDR-TB regimens in 2013 we can give credit to the individual regimens (and drugs within the regimens). We find regimen-level impact scores using resistance rate data, and explain our disagreggation methodology below.

MDR-TB is treated with one of three regimens - which is appropriate for a given individual depends how their disease resists treatment with particular drugs. So we use resistance rates to estimate the proportion of people that receive each regimen.[19] The WHO provides country-level information on the number of individuals who test positive for MDR-TB in both new and retreatment cases as well as the overall number of individuals who are tested for drug resistance.[19] Therefore we are able to calculate the percentage of cases that are MDR-TB as the proportion of those who have been tested who are resistant.

A summary of the regimens and their respective drug resistance rates can be found in an analysis done by the Global Project on Anti-Tuberculosis Drug Resistance Surveillance.[22] The regimens for MDR-TB are listed in table S1.

The WHO maintains databases relating to the country-level percentage of drug resistance to DS TB treatments. For example, the WHO estimates resistance to H+R in previously treated cases in the Dominican Republic to be 33.70%.[19] The resistance rates for H+R+E+S are unavailable at the country level so regional averages of 3.81% and .5% respectively are used. Similarly, we use the global averages for resistance to H+R+E (3.3%), and H+R+S (11%).[23] We will use the Dominican Republic as an example of how this data is used. Drug resistance rates in the Dominican Republic are illustrated in table S2.

We must estimate MDR-TB resistance to regimens that include pyrazinamide (Z) because the WHO database does not include resistance data concerning Z. Studies in South Africa indicate that 42.25% of MDR-TB cases are resistant to Z.[24] We use this value as a global estimate for the resistance of Z due to the absence of data for the resistance of Z as a part of a treatment regimen. Both H+R+E and H+R+E+S are taken with or without Z. Therefore, we split both treatments according to the 42.25% resistance rate. This is visualized in table S3.

We can estimate a drug's resistance rate in comparative relation to total drug resistance. For example, 65% of previously treated people in the Dominican Republic who consume MDR-TB treatment are resistant to H+R. This was derived by dividing 33.7%, the resistance rate for H+R, by 51.8%, the sum of all previously treated drug resistances. The results of these calculations can be found in table S4.

Given the proportional resistance rates for TB drugs, we can estimate the distribution of MDR TB treatments consumed in the Dominican Republic. This is done by summing a TB drug's proportional resistance rate according to the proposed treatment regimen. The result can be seen in table S5.

With the proportion of MDR-TB treatment for each regimen calculated for both newly and previously treated cases, we can calculate the proportional use of each MDR-TB regimen. There are a total of 92 MDR-TB cases in the Dominican Republic: 32.6% are new cases and 67.4% are retreatment cases.[19] The proportion of new cases was multiplied by a treatment regimen's proportional use by new cases. Similarly, the proportion of previous cases was multiplied by a treatment regimen's proportional use by previous cases. These two values were summed to derive the weight of a treatment regimen. The results of these calculations are found in table S6.

The final step is to simply multiply the total MDR-TB impact score by the proportional use of each regimen to get individual regimen's scores. In the case of the Dominican Republic, we see that:

$$I_{Z+S+Lfx+Eto+Cs+PAS} = 62.16 * 72.43\% = 45.03$$
$$I_{S+Lfx+Eto+Cs+PAS} = 62.16 * 2.52\% = 1.56$$
$$I_{Km+Lfx+Eto+Cs+PAS} = 62.16 * 25.05\% = 15.57$$

We can calculate DALYs lost to XDR-TB by multiplying total TB DALYs, 18,000, by the overall percentage of MDR-TB among prevalent TB, 12%, and then multiplying the result by 9.6%, the percent of MDR-TB cases that are XDR-TB.[19,25] Thus, 15,184.71 DALYs were lost to XDR TB. The WHO's Global Tuberculosis 2014 report states that there is a global average of 57% of treatment coverage for XDR-TB.[19,26] The approximate global efficacy of XDR-TB treatment is 28% according to the WHO.[19] The data acquired can be inserted into the overall impact formula:

$$\text{XDR-TB} = \frac{15{,}184.7 * 28\% * 57\%}{1 - 28\% * 57\%} / 2 = 1{,}441.86$$

We further separate the XDR-TB impact score by the components used to treat it. XDR-TB is categorized as TB resistant to H+R as well as a fluoroquinolone and a second-line injectable drug.[27]

The combination used to combat XDR-TB is Cs + Km(or)Amk(or)Cm + Lfx(or)Mfx(or)Gfx(or) Ofx.[27] Successful treatment always requires cycloserine, one injectable second-line agent, and a fluoroquinolone. Each of these is credited with one third of the XDR-TB impact score, which is then broken up further among each drug in a respective classification. Cycloserine receives 33% of the credit. Km, Amk, or Cm, the injectable second-line agents, receive 11% of the credit. Lfx, Mfx, Gfx, or Ofx, the fluoroquinolones, receive 8% of the credit impact. We calculate the impact of an individual drug by multiplying the total impact by the credit given to the drug's respective classification. For example, Km has a score of 160.2. Total regimen scores are the sum of impact scores in each individual country. Each drug in a given regimen is credited in proportion to its use. An individual drug's score is the sum of its proportion of each regimen's score in which it is a part.

HIV/AIDS Model

To understand the HIV/AIDS model we will determine the impact of the antiretroviral drug AZT in Benin in 2013. The HIV/AIDS model uses data collected from the WHO AIDS Medicines and Diagnostics Service (AMDS) survey that splits countries into two groups: Group A and Group B. Group A countries are defined as low and middle income countries excluding the region of the Americas. Group B countries are low and middle income countries in the Americas. We then extrapolated this methodology to include high income countries as well.

To start determining impact we must first gather DALY data. The WHO produces statistics for adults (15 years old and above) and children (below 15 years old), therefore the model starts by calculating impact for these patient groups. The Global Health Data Exchange provides country specific DALY data according to these age groups. In 2013 Benin lost 106,998.33 adult DALYs and 40,703.47 child DALYs to HIV/AIDS.[16]

Next we estimate treatment coverage. The WHO estimates the number of individuals in all age groups that need treatment as well as the number of individuals in all age groups that are receiving treatment. This data allows us to determine treatment percentages, or the proportion of people who receive needed treatment, split by age group). In 2013, Benin had a treatment coverage of 38.82% and 21.0% for adults and children, respectively.[16]

Efficacy is the last variable to calculate. We utilize proportional use and efficacy information for adults and children using first or second-line antiretroviral regimens.[28] Each unique grouping of age and regimen can be considered a quadrant. An example of a quadrant is "second-line adults" or "first-line children". If we lack regimen-specific efficacy or proportion data we average all data points in the relevant quadrant. If this estimate does not yield results we average all original data points regardless of quadrant. The instances in which there is missing data represent cases where we cannot make an accurate estimate due to a lack of original data points. These quadrants are further separated by group A and group B countries in the 2010 and 2013 models to reflect variations in access to medicines. The lack of efficacy data separated by country grouping in 2015 prevents us from employing this aspect of the methodology for the 2015 model. The full list of antiretroviral treatment regimen proportions and efficacies for group A and group B countries can be found in tables S7 and S8.

The WHO produces information concerning the percentage of adults and children that are receiving first and second-line regimens by country group A and B.[29] We assume that the DALYs each regimen can recover are proportionate to their use in each population. The data can be found in table S9.

The percentage of adults and children using first or second line treatments in group A or B can be derived using these figures. For instance, the percentage of adults receiving first line regimens in group A is the number of adults receiving first line regimens in group A divided by the total number of adults using either first line or second line treatment in group A = 9,958,772 / (9,958,772 + 388,630) = 96.24%.[29] Consider how we calculate AZT's score in Benin, a Group A country. First, we estimate AZT's impact in the adult first-line treatment regimen "AZT + 3TC + NVP". Recall that in 2013 Benin lost 106,998.33 adult DALYs to HIV/AIDs.[16] It is also important to remember that in 2013 Benin had a treatment coverage of 38.82% for adults.[8] We multiply these two data points by three variables: 96.24%, the percent of adults that receive first-line treatment, 32%, the proportion of those adult first-line treatments that receive AZT + 3TC + NVP in Group A, and 81.93%, the efficacy of this particular treatment.[29] Now it is possible to plug these data points into the overall impact formula to derive impact:

$$I_{AZT+3TC+NVP} = \frac{(106{,}998.33 * 81.93\% * 96.24\% * 32\% * 38.82\%)}{(1 - 81.93\% * 96.24\% * 32\% * 38.82\%)} = 11{,}618.49$$

Since AZT is one of three drugs in this regimen, we divide the impact score by three to get 3,872.83. This calculation is repeated for each regimen that includes AZT and that is classified as a regimen used in Group A countries. This includes all subgroups such as 1st-

or 2nd-line treatments that are used to treat adults, or used to treat children. This leaves four categories of regimens that could contain AZT. Group B countries undergo the same process, but use data specific to that group of countries. The full list of impact scores for regimens containing AZT in Benin in 2013 can be seen in table S10; note that regimens lacking efficacy data have been excluded from this section.

We can now sum the impact of AZT in each regimen for all patient and country groups, 6,554.89. We now divide this sum by estimated retention rates. We do this to split up the impact of a treatment that is carried out over a course of several years. Retention rate is a measure of the percentage of patients that have begun treatment and remain in treatment.[30] It can be used to estimate the average period of treatment that patients will complete with this formula: 100%/(100% - retention rate); for an 80% retention rate, the average period would be 100%/(100%-80%), or 5 years. What we do is take the total impact that the drug had for the given year and divide it by 5, since the full impact of treatment was not completed in that year, but rather over the 5 years that the average patient will be treated. There is a maximum retention rate of 97.14 instituted, so the formula will choose the number that is smaller between the country level data and 97.14; if no data is available for that country, it uses 97.14 as the default retention rate. Sensitivity analysis on this variable yields no significant change in ranking when increased or decreased.

We divide the sum by (100/100-97.14)=35:

6571.56 / 35 = 187.47

The overall impact for AZT in Benin in 2013 is 187.47. We calculate other drugs' scores in Benin (and in other countries) in a similar way.

Malaria Model

Our model estimates the impact of medicines on p. falc and p. vivax malaria. Consider an example of how we calculate the impact that the first-line p. falc. treatment, Artesunate-Mefloquine (AS+MQ), had in Cambodia during the year 2013. 64,100 DALYs were lost to malaria in 2013; 55% of this can be attributed to p. falc., the remaining 45% being attributed to p. Vivax.[31] Therefore, p. falc. DALYs for 2013 are equal to 64,100 * .55, or 35,255. Treatment coverage, or the percentage of febrile children receiving artemisinin-based combination therapy (ACT) treatment, is taken from the UNICEF database "Malaria mortality as a cause of death in children under 5".[32] This percentage, 2.6%, is an average of treatment coverage in the West Pacific region because no country-specific data is available in Cambodia.[33] Finally, regional level efficacy data for AS+MQ in Cambodia is 97.23%.[34] So, using the overall impact formula, the impact due to AS+MQ treatments is equal to:

$$I_{AS+MQ} = \frac{(35,255 * 2.6\% * 97.23\%)}{(1 - 2.6\% * 97.23\%)} = 914$$

This same process is repeated for every country in which AS+MQ was administered. In countries where multiple regimens were utilized, the impact score for a given treatment is divided by the number of separate regimens. For example, Burkina Faso recommended administering either Artesunate-Amodiaquine (AS+AQ) or Artemether-Lumefantrine (AL), so we assume half of the patients were administered AS+AQ, and half AL. In this manner, we calculated every country's impact score for each drug. Summing these, we estimated that the global impact for the p. falc drug AS+MQ in 2013 was 18,025.10. Finally, the above method to derive impact is used for p. vivax drugs as well.

NTD Model

The general impact formula is used to calculate the impact of treatment for several NTDs, however, there are a number of modifications to the original methodology to account for differences in the available data and for the general nature of the treatment for NTDs -- MDAs. The most significant change is that we reduce MDA impact scores by estimated prevalence as only a percentage of the treated population will be infected with a given NTD.[15] This reduces the final impact score to account for the difference between the population requiring preventive chemotherapy and the actual number of people with the NTD as the model intends to measure only the direct impact of treatment. Additionally, we divide the impact score for onchocerciasis by 30 because treatment is required twice a year for the 15-year lifespan of the adult worm.[35]

To determine which MDA was initiated in each country, we applied two algorithms provided by the WHO's guidance for preventive chemotherapy in human helminthiasis (PCHH). There are instances in which a targeted treatment is to be administered along with the MDA. The PCHH defines a targeted treatment as the group-level application of drugs irrespective of infection status, therefore we model these treatments the same as we do MDAs[36].

We gather data on endemicity from the WHO's PCT database.[36] The decision trees rely on endemicity data that is not publicly available, leaving us to estimate a country's disease endemicity level. We assume that a disease is endemic to a country if it has a population requiring treatment as stated in the WHO's PCT database.

Consider how we estimate drugs' impacts for Ghana. The WHO's PCT database tells us that Ghana is endemic for LF, onchocerciasis, and schistosomiasis. Using our algorithm we can see the corresponding MDA type is MDA1+T2 and people in Ghana are treated with IVM+ALB and PZQ. IVM+ALB is used to treat LF and PZQ is used to treat schistosomiasis. We will first calculate the impact score for IVM+ALB. The first step is to locate DALY data for LF in the year 2010. Through the IHME's database, we find this to be 21,374.72.[16] The next step is to calculate efficacy data for LF in 2010. We do so by averaging the efficacy data of IVM+ALB on LF from multiple sources.[36] We found this number to be 39.46%. Next we estimate treatment coverage by dividing reported prevalence with the reported number of people treated. Both of these data points are national and were taken from the WHO's PCT database. Estimated treatment coverage was 62.82%.[36] Finally, IHME estimates LF

prevalence at 1.8%.[36] We are now able to enter these values into our overall impact formula for NTDs to derive IVM+ALB's alleviated DALYs:

$$I_{IVM+ALB} = \frac{(21{,}374.72 * 39.46\% * 62.82\%)}{(1 - 39.46\% * 62.82\%)} * 1.8\% = 126.82$$

We calculate PZQ's alleviated DALYs in the same way. Due to the lack of available data, there is a critical difference in the way we calculate efficacy and treatment coverage for PZQ. While we were able to find studies containing relevant efficacy and treatment coverage information for IVM+ALB, we were unable to do the same for PZQ. For both variables, we average available data in the same WHO region as Ghana. We employ a similar methodology to derive impact scores for targeted NTD drugs in endemic countries. Here is our overall impact formula for PZQ's alleviated DALYs:

$$I_{PZQ} = \frac{(50{,}239.32 * 64.44\% * 25.2\%)}{(1 - 64.44\% * 25.2\%)} * 20\% = 1{,}984$$

Company Attribution

Originator companies were located via a patent search confirmed by Cornell Law School. We searched only for the original patent holder or licensee as opposed to companies or organizations that have acquired the technology in the interim as we now evaluate company contributions post development separately. We show results for originator companies by patent date and impact/ revenue. The sources for our attribution decisions are available in the appendix.

Our impact scores can be used to assess the performance of companies involved in drug development and the manufacturing sector of the pharmaceutical industry for malaria, TB, and HIV/AIDS. We use manufacturing and distribution data provided by the WHO Global Price Reporting Mechanism to evaluate company contributions post-development.[37] The database provides important information such as cost, drug strength, and the total number of units (TNU) of each drug that are involved in shipments of a variety of medicines. This data can be used to determine the proportion of certain classes of drugs that each manufacturer in the database is responsible for shipping. This can help highlight which manufacturers are doing the most to extend access of essential medicines to the countries that would benefit from the medicine. However, the way the data is provided from the Global Price Reporting Mechanism does not contain data on the impact one shipment makes compared to another. The formula below estimates the lives saved by each shipment of drugs (and subsequently we estimate the DALYS alleviated by manufacturer). In this formula TNU stands for total number of units, and is the quantity per package times the number of packages in the shipment. For example, if the drug comes in tablet form, and there are 20 tablets per package and 1,050 packages per shipment, the TNU is 21,000. DD represents the daily dosage (the quantity of medication at the strength of that shipment given per day of treatment) and 365 represents the number of days in a year. In other words, the Lives Saved calculation

provides an estimate of how many years of treatment a particular shipment could potentially provide.

Next, we find what percent of the total potential lives saved a shipment represents. Note that if a shipment contains a combination of drugs, we credit both drugs separately and equally to that manufacturer of the shipment. We then sum the potential lives saved for that drug (both from individual drug shipments and shipments where that drug was part of a combination) due to each individual manufacturer. Next, we divide that sum by the potential total lives saved due to that drug, to calculate the proportional percent of the lives that a manufacturer saves with that drug for all shipments. Using the total DALYs alleviated by each drug calculated from our model, we use the proportional percent of total potential lives saved by that manufacturer calculated above to estimate the proportional percent of the total DALYs alleviated that will be attributed to that manufacturer. For instance, the sum of all shipments of Ethambutol (both as an individual drug and as part of a combination) is found to potentially save 7,322 lives, and Lupin Ltd. is responsible for potentially saving 46 of those. So, it is responsible for .63% of the total lives Ethambutol saved. Ethambutol has alleviated 8,470,126 DALYs. So, we can estimate that Lupin Ltd. has alleviated 53,686 DALYs, or 8,470,126*.63%.

There are slight differences in the way that the various components of the lives saved formula is calculated, based on disease type. For example, to calculate daily dose for the malaria model we use guidelines that are based on the weight of the patient. By determining the proportion of malaria incident cases within children and adults, and the average global weight of people in these age groups, we are capable of estimating a weighted proportional average of malaria patients. Additionally, the daily dosage for HIV/AIDS drugs was not calculated but rather provided by the WHO's HIV section.

Using the data that is available from the Global Price Reporting Mechanism on the price of shipments and data that was generated in the previous section regarding each manufacturer's DALYs saved, it was possible to generate a cost effective analysis model that evaluates the cost for a manufacturer to alleviate one DALY. For example, Micro Labs Ltd. alleviated 12,415 DALYs at a price point of $21,662. It receives a cost effectiveness value of 0.57 DALYs/$. That is, one dollar spent on its shipments alleviated a little more than half a DALY. This calculation allows us to compare different manufacturing companies' drugs' cost effectiveness.

Monte Carlo Analysis

We conducted sensitivity analysis to quantify uncertainty in our models. We ran a Monte Carlo (MC) simulation with 100 iterations for individual tests first and then we ran an MC for all tests together for 1,000 trials. For each trial, a value was randomly chosen from the assigned distribution. The company rank was then recalculated and changes in rank were noted. If a test consisted of multiple parameters we used a maximum likelihood estimation, otherwise we chose a particular mean based on our assumption with small variance (0.05).

We define stability for an individual company as follows: if the main box of the boxplot is between 2 and -2, we will say the result is stable. If more than 16 companies are stable in the same test we classify our model as stable. The y-axis indicates changes in company rank. The x-axis corresponds to the following companies for each year ordered by initial rank. The numbers assigned to each company can be found in Table S11.

In each plot, each number on the X-axis stands for one company from above. Each number on the Y-axis indicates the rank change for that company (1 stands for rank decrease by 1, -1 stands for rank increase by 1, 0 stands for not changing).

Again, for each company, when we combined all tests together, we did the MC test 1000 times. So there are 1000 new ranks for that company (100 for individual tests alone). For example, Sanofi might be ranked as follows in the different iterations: (4, 5, 6, 1, 8, 9, etc.), and then we compare each company's rank to its original rank to see whether rank increased or decreased. The boxplot for each company represents the changed-rank.

For each boxplot, the bold line in the middle stands for the median (2nd quartile), the box stands for 1st quartile to 3rd quartile. The upper whisker (solid line above the box, below the dot (circle)) stands for [3rd quantile+1.5*(3rd quartile-1st quartile)]. Similarly the lower whisker stands for [1st quantile-1.5*(3rd quartile-1st quartile)]. Any points beyond or below whisker, are outliers. So, if 0 is inside the box, then 50% of the time the middle contains value 0. If the height of the box is between 2 and -2, that means that 50% of the time, the changed-rank will be no higher than 2. There are few outliers, so we focus on the main portion of the boxplots for 2010, 2013 and 2015 below. As we do not consider outliers, we can consider the upper whisker and lower whisker to be the maximum and minimum changed-rank in the 1000 trials.

Here are a few more notes on some particular cases: If you only see one solid bar, that means that all 1000 (or 100) times, the changed-rank is equal to the same value, for example: if it is 0, then in all 1000 (or 100) trials, the company does not change rank. If you do not see the upper/lower whisker bars, that means all the last/top 25% data points are the same. If you see the median is overlapped with the upper/lower edge of the box, that means all data from 50% to 75%(25% to 50%) have the same value.

MC Individual Tests

Test 1

Assumption tested: The model assumes that the proportion of DALYs lost to MDR-TB relative to all DALYs lost to TB is equal to the percent of MDR-TB cases out of all TB cases. **Distribution and parameters:** We assumed that the percentage of MDR-TB cases follows a beta distribution, which picks a random variable that is between 0 and 100%. We used a Maximum Likelihood Estimation (MLE) to do the estimation by replacing the original percentage with new values which are randomly generated from that distribution. **Result:** In 2010, 2013, and 2015 the model is stable. Although for 2013, the ranks of company 2(F. Hoffmann-La Roche) and 14(Novartis) have 1 rank change, they are stable. The results graphs can be found in figures S1-S3.

Test 2

Assumption tested: The model divides the country level impact of HIV by the country's respective treatment length. The model uses regional and global treatment length as fallback data if data for a given country is unavailable.

Distribution and parameters: We assumed treatment length follows a beta distribution, and used MLE to derive estimates. We replaced fallback values for countries missing treatment length data with new values drawn from that distribution.

Result: In three years, all company ranks are stable. There are some changes, like company 2(F. Hoffmann-La Roche), 6(Daiichi Sankyo), 9(Shire Pharmaceuticals), 10(Boehringer Ingelheim), 11(Gilead Sciences), 14(Novartis) and 16(GlaxoSmithKline), but the magnitude of the changes are small, only 1. The models are stable for all three years. The results graphs can be found in figures S4-S6.

Test 3

Assumption tested: Research indicates that overall treatment efficacy for XDR-TB is 20%, 28%, and 30% for the years 2010, 2013, and 2015 respectively.

Distribution and parameters: We assumed that the overall treatment efficacy for XDR-TB is drawn from a beta distribution with a mean equal to 20%, 28%, and 30% in 2010, 2013, and 2015 respectively, and 0.05 variation.

Result: 2010, and 2015 are stable. For 2013, company 18 is not stable its rank has a tendency to move down by 5 but overall the model is stable. The results graphs can be found in figures S7-S9.

Test 4

Assumption tested: Our model uses the regional and global treatment coverage for an HIV/AIDS drug as fallback data if that drug's treatment coverage data is not available for a given country. **Distribution and parameters:** When treatment coverage data is not available for a country, we assume it is drawn from a beta distribution, with a mean equal to global average, and 0.05 variation. **Result:** In 2010, 2013, and 2015, all years, the rank is stable. There is one rank change for 2013. The results graphs can be found in figures S10-S12.

Test 5

Assumption tested: Our model assumes that the proportion of XDR-TB among MDR-TB cases is equal to the proportion of XDR-TB DALYs lost to MDR-TB.

Distribution and parameters: We assumed the proportion of MDR-TB cases that were classified as XDR-TB is drawn from a beta distribution, with mean equal to 9.5% and 0.05 variation. **Result:** In 2010 and 2013, company 1(Kyorin Pharmaceutical) and 17(Johnson and Johnson) are stable in more than 50% times of iterations, for the rest iterations, the change will go up to 2. In 2015, company 12(Eli Lilly), 15(Chongqing Holley), and 18(Guilin Pharmaceutical) will be affected, but the main box is between -2 and 2, so they are stable. Overall the models are stable. The results graphs can be found in figures S13-S15.

Test 6

Assumption tested: Research indicates that drug susceptible TB both with and without comorbid HIV has a treatment coverage of 65.9%, 58%, and 59% in 2010, 2013, and 2015 respectively. **Distribution and parameters:** We assume the treatment coverage for drug susceptible TB both with and without comorbid HIV draws from a beta distribution, with a mean equal to 65.9%, 58%, and 59% in 2010, 2013, and 2015 respectively, and 0.05 variation.

Result: In all three years, the models are stable. Except company 14(Novartis), the others are stable. The results graphs can be found in figures S16-S18.

Test 7

Assumption tested: In the absence of country-specific treatment coverage data, our model uses regional or global data as a fallback for the percentage of febrile children under five receiving antimalarial treatment.

Distribution and parameters: When treatment coverage data is absent, we assume the treatment coverage follows a beta distribution, with mean equal to the global average, and 0.05 variation. **Result:** In 2013 multiple patent holders change rank but only one company 18('Guilin Pharmaceutical') is unstable and the model is stable for all years. The results graphs can be found in figures S19-S21.

Test 8

Assumption tested: We estimate the treatment efficacy for TB with comorbid HIV to be 72%, 73%, and 78% for the years 2010, 2013, and 2015 respectively.

Distribution and parameters: We assume that the treatment efficacy for TB with comorbid HIV follows a beta distribution, with a mean equal to 72%, 73%, and 78% in 2010, 2013, and 2015 respectively, and 0.05 variation.

Result: In both 2010 and 2015, the model is stable. In 2013, the rank of company 14(Novartis) changes, but the main box is between -2 and 2, so it is stable too. The results graphs can be found in figures S22-S24.

Test 9

Assumption tested: We estimate the treatment efficacy for TB without comorbid HIV to be 88% in 2010 and 2013, and 83% in 2015.

Distribution and parameters: We assume that the treatment efficacy for TB without comorbid HIV follows a beta distribution, with mean equal to 88% in 2010 and 2013, and 95% in 2015, and 0.05 variation.

Result: For 2013, company 14(Novartis) is unstable but all companies are stable in 2010 and 2015 and the models are stable for all years. The results graphs can be found in figures S25-S27.

Test 10

Assumption tested: XDR-TB treatment impact is divided among three treatment regimens, each receiving a certain amount of credit.

Distribution and parameters: For the three treatment regimens, we assume it follows a dirichlet distribution dimension 3, and mean equal to 33% for all treatment regimens, with variation 0.05 in each.

Result: For 2010, 2013, and 2015, the model is stable. Although some changes occur, all companies are stable. The results graphs can be found in figures S28-S30.

Test 11

Assumption tested: In the absence of drug-specific efficacy data for malaria, our model uses regional and then global data as a fallback.

Distribution and parameters: When efficacy data is unavailable for a country, for each drug we assume it follows a beta distribution with mean equal to the regional or global efficacy of that malaria drug, and 0.05 variation.

Result: All three years are stable. Only small changes happen in 2013 and 2015. The results graphs can be found in figures S31-S33.

Test 12

Assumption tested: The model determines treatment efficacy for malaria drugs that target p. falc and p. vivax using data collected from the World Malaria Report. If there is no data present for a specific country, the model uses data from our own systematic review of efficacy papers. When data is unavailable for a country, the model uses regional and then global averages.

Distribution and parameters: Here, when efficacy data is unavailable for a country, we assume it follows a beta distribution with mean equal to the estimated regional or global value, and 0.05 variation.

Result: The model is stable for all years, there are only small changes in a few company ranks in 2013 and 2015. The results graphs can be found in figures S34-S36.

Test 13

Assumption tested: Our model constrains the fallback data used to estimate treatment efficacy for NTDs to studies that took place before or during our model year. We tested different time constraints by removing all time constraints.

Result: For all three years, the model is stable. The results graphs can be found in figures S37-S39.

Test 14

Assumption tested: Research indicates that MDR-TB has a treatment efficacy of 48%, 52%, and 54% for the years 2010, 2013, and 2015 respectively.

Distribution and parameters: We assume the treatment efficacy follows a beta distribution, with mean equal to 48%, 52%, and 54% in 2010, 2013, and 2015 respectively, and 0.05 variation. **Result:** For 2010 and 2013, the models are stable. For 2015, company 6 (Daiichi Sankyo) is unstable. Its rank will decrease by 1 or increase by 3 most of the time. However, the model is stable overall. The results graphs can be found in figures S40-S42.

Test 15

Assumption tested: Research indicates that XDR-TB has a treatment coverage of 38%, 57%, and 95% for the years 2010, 2013, and 2015 respectively.

Distribution and parameters: We assume the treatment coverage follows a beta distribution, with a mean equal to 38%, 57%, and 95% in 2010, 2013, and 2015 respectively, and 0.05 variation. **Result:** The model is stable for all three years. There are only some small changes. The results graphs can be found in figures S43-S45.

Test 16

Assumption tested: In our TB model, for countries lacking data on HIV status, we use the global average to estimate the percentage of people with known HIV status. Research indicates that the global average was 34%, 46%, and 55% for the years 2010, 2013, and 2015 respectively. **Distribution and parameters:** For countries lacking data on the percentage of people with known HIV status, we assume it follows a beta distribution, with a mean equal to 34%, 46%, and 55% in 2010, 2013, and 2015 respectively, and 0.05 variation.
Result: In all three years, the model is stable. There are a few small changes in 2013. The results graphs can be found in figures S46-S48.

Test 17

Assumption tested: The model estimates that the percentage of TB cases that have comorbid HIV is 23%, 13%, and 15% for the years 2010, 2013, and 2015 respectively.
Distribution and parameters: We assume the percentage of TB cases that have comorbid HIV follows a beta distribution, with a mean equal to 23%, 13%, and 15% in 2010, 2013, and 2015 respectively, and 0.05 variation.
Result: In all three years, the model is stable. Although some changes happen, they are all very small, only 1 rank changes. The results graphs can be found in figures S49-S51.

Test 18

Assumption tested: In calculating LF'S impact score, the average regional treatment coverage of a drug is used as fallback data for that drug if treatment coverage data is not available for a country. **Distribution and parameters:** When treatment coverage is not available for a given country, we assume it follows a beta distribution, with mean equal to global average and 0.05 variation.
Result: In all three years, the model is stable. Small changes occur in 2013. The results graphs can be found in figures S52-S54.

Test 19

Assumption tested: In calculating schistosomiasis's impact score, the average regional treatment coverage of a drug is used as fallback data for that drug if treatment coverage data is not available for a country.
Distribution and parameters: When treatment coverage is not available for a given country, we assume it follows a beta distribution, with mean equal to the global average and 0.05 variation. **Result:** For 2010, 2013 and 2015, the model is stable. Small changes happen in 2010 and 2013. The results graphs can be found in figures S55-S57.

Test 20

Assumption tested: In calculating LF's impact score, the average regional or global efficacy of a drug is used as fallback data for that drug if efficacy data is not available for a country. **Distribution and parameters:** When efficacy data is not available for a given country, we assume it follows a beta distribution, with mean equal to regional or global average and 0.05 variation. **Result:** In all three years, the model is stable. Small changes occur in 2013. The results graphs can be found in figures S58-S60.

Test 21

Assumption tested: In calculating schistosomiasis's impact score, the average regional or global efficacy of a drug is used as fallback data for that drug if efficacy data is not available for a country. **Distribution and parameters:** When efficacy data is not available for a given country, we assume it follows a beta distribution, with mean equal to the regional or global average and 0.05 variation. **Result:** Small changes occur in 2010 and 2013. In all three years, the models are stable overall. The results graphs can be found in figures S61-S63.

Test 22

Assumption tested: In calculating whipworm's impact score, the average regional or global efficacy of a drug is used as fallback data for that drug if efficacy data is not available for a country. **Distribution and parameters:** When efficacy data is not available for a given country, we assume it follows a beta distribution, with mean equal to the regional or global average and 0.05 variation. **Result:** In all three years, the model is stable. Small changes occur in 2013. The results graphs can be found in figures S64-S66.

Test 23

Assumption tested: In calculating roundworm's impact score, the average regional or global efficacy of a drug is used as fallback data for that drug if efficacy data is not available for a country. **Distribution and parameters:** When efficacy data is not available for a given country, we assume it follows beta distribution, with mean equal to the regional or global average and 0.05 variation.

Result: In all three years, the model is stable. Only small changes in 2013 and 2015. The results graphs can be found in figures S67-S69.

Test 24

Assumption tested: In calculating hookworm's impact score, the average regional or global efficacy of a drug is used as fallback data for that drug if efficacy data is not available for a country. **Distribution and parameters:** When efficacy data is not available for a given country, we assume it follows beta distribution, with mean equal to the regional or global average and 0.05 variation. **Result:** In all three years, the model is stable. Small changes occur in 2013. The results graphs can be found in figures S70-S72.

Test 25

Assumption tested: Our model uses the average regional and then global treatment coverage for an onchocerciasis drug as fallback data if that drug's treatment coverage data is not available for a given country.

Distribution and parameters: When treatment coverage is not available for a given country, we assume it follows a beta distribution, with mean equal to regional or global average and 0.05 variation.

Result: In 2013 and 2015, no change in overall ranking occurred when fallback global treatment coverage was increased to 100% or decreased to 0% (we do not have a 2010 model for this disease). The results graphs can be found in figures S73 and S74.

Test 26

Assumption tested: Our model uses the average regional and then global treatment efficacy for an onchocerciasis drug as fallback data if that drug's efficacy data is not available for a given country. **Distribution and parameters:** When a drug's efficacy is not available for a given country, we assume the drug's efficacy follows a beta distribution, with mean equal to the regional or global average and 0.05 variation.

Result: The model is stable in both 2013 and 2015 with small changes in 2013. Again there is no 2010 model for this disease. The results graphs can be found in figures S75-S76.

Overall Results:

In 2010, most companies are stable, except company 14 (Novartis) -- in more than 50% of the cases, its rank has a tendency to move up by 1 or move down by 3. Overall the model is stable. The results are displayed in figure S77.

In 2013, there are some small changes, but all of them are within 2 and -2, so our model is stable for the whole year. The results are displayed in figure S78.
In 2015, company 2(F. Hoffmann-La Roche) is not stable. Its rank has a tendency to move down by 3 most of the time. The rest of the companies are stable and overall the model is stable. The results are displayed in figure S79.

Tables S1 to S11

Table S1. Regimens proposed to treat TB according to drug resistance

Drug resistance	Treatment regimen
H+R; H+E	Z+S+Lfx+Eto+Cs+PAS
H+R+E+Z	S+Lfx+Eto+Cs+PAS
H+R+S; H+R+E+S; H+R+E +Z+S	Km+Lfx+Eto+Cs+PAS

Table S2. Estimated TB drug resistance rates

Drug resistance	Previously treated	Newly treated
H+R	33.7%	50%
H+R+E	3.3%	3.3%
H+R+S	11%	11%
H+R+E+S	3.8%	0.5%

Table S3. Estimated TB drug resistance rates including treatments with Z

Drug resistance	Previously treated	Newly treated
H+R	33.7%	50%
H+R+E	1.9%	1.9%
H+R+E+Z	1.39%	1.39%
H+R+S	11%	11%
H+R+E+S	2.2%	0.28%
H+R+E+S+Z	1.61%	0.21%

Table S4. Estimated TB drug resistance rates as a proportion of total drug resistance rate

Drug resistance	Previously treated	Newly treated
H+R	65%	77.16%
H+R+E	3.66%	2.93%
H+R+E+Z	2.68%	2.14%
H+R+S	21.23%	16.97%
H+R+E+S	4.24%	0.43%
H+R+E+S+Z	3.1%	0.32%

Table S5. Estimated distribution of treatment regimens used to treat MDR-TB

Drug resistance	Treatment regimen	Previously treated	Newly treated
H+R	Z+S+Lfx+Eto+Cs+PAS	68.72%	80.1%
H+R+E			
H+R+E+Z	S+Lfx+Eto+Cs+PAS	2.68%	2.14%
H+R+S	Km+Lfx+Eto+Cs+PAS	28.59%	17.75%
H+R+E+S			
H+R+E+S+Z			

Table S6. Weight of treatment regimens used to treat MDR-TB

Treatment regimen	Weight
Z+S+Lfx+Eto+Cs+PAS	72.43%
S+Lfx+Eto+Cs+PAS	2.52%
Km+Lfx+Eto+Cs+PAS	25.05%

Table S7. Antiretroviral treatment regimen proportions and efficacies for Group A countries

First line regimens	Adult proportion	Adult efficacy	Child proportion	Child efficacy
AZT + 3TC + NVP	32.00%	81.93%	48.80%	81.93%
d4T + 3TC + NVP	26.00%	84.30%	23.80%	84.30%
AZT + 3TC + EFV	11.40%	75.75%	10.40%	70.67%
TDF + 3TC + NVP	6.50%	75.00%		65.50%
TDF + 3TC + EFV	6.50%	78.00%		78.83%
TDF + FTC + EFV	6.60%	77.50%		77.40%
TDF + FTC + NVP	4.50%	71.03%		69.02%
d4T + 3TC + EFV	4.90%	84.00%	4.60%	78.00%
Others	1.50%	75.07%	4.80%	50.00%
ABC + 3TC + NVP		75.07%	6.00%	50.00%
ABC + 3TC + EFV		70.63%	1.60%	72.98%

Second line regimens	Adult proportion	Adult efficacy	Child proportion	Child efficacy
ABC + 3TC + LPV/r	2.70%	63.00%	35.60%	63.00%
AZT + 3TC + LPV/r	19.40%	50.00%	18.30%	50.00%
ABC + ddl+ LPV/r	4.90%	74.18%	10.70%	83.40%
AZT + ABC + 3TC + LPV/r		74.18%	3.90%	83.40%
TDF + 3TC + LPV/r	25.50%	83.00%	4%	83.00%
AZT + ddl + LPV/r		74.18%	3.70%	83.40%
Others	16.50%	74.18%	24.20%	83.40%
AZT + 3TC + TDF + LPV/r	5.80%	74.18%		83.40%
TDF + 3TC + EFV	4.40%	78.83%		78.83%
d4T + 3TC + LPV/r	3%	74.18%		83.40%
TDF + AZT + LPV/r	2.30%	74.18%		83.40%
TDF + FTC + LPV/r	15.50%	65.20%		71.25%

Table S8. Antiretroviral treatment regimen proportions and efficacies for Group B countries

First line regimens	Adult proportion	Adult efficacy	Child proportion	Child efficacy
AZT + 3TC + NVP	9.90%	81.93%	9.90%	81.93%
ABC + 3TC + LPV/r	6.40%	63.00%	6.40%	63.00%
AZT + 3TC + EFV	35.00%	73.00%	35.00%	70.67%
TDF + 3TC + NVP	2.70%	65.50%	2.70%	65.50%
TDF + 3TC + EFV	18.20%	78.00%	18.20%	78.83%
TDF + FTC + EFV	12.40%	75.11%	12.40%	77.40%
TDF + FTC + NVP	1.00%	63.90%	1.00%	69.02%
TDF + 3TC + LPV/r	1.40%	83.00%	1.40%	83.00%
TDF + FTC + LPV/r	1.40%	67.50%	1.40%	71.25%
TDF + FTC + ATV/r	2.90%	78.58%	2.90%	79.42%
ABC + 3TC + EFV	3.60%	66.00%	3.60%	72.98%
AZT + 3TC + ATV/r	2.30%	75.70%	2.30%	75.70%
TDF + 3TC + ATV/r	1.40%	65.00%	1.40%	65.00%

Second line regimens	Adult proportion	Adult efficacy	Child proportion	Child efficacy
TDF + 3TC + ATV/r	21.00%	65.00%	21.00%	65.00%
AZT + 3TC + LPV/r	25.00%	50.00%	25.00%	50.00%
ABC + ddl + LPV/r	1.00%	65.20%	1.00%	65.20%
ABC + 3TC + LPV/r	3.00%	63.00%	3.00%	63.00%
TDF + 3TC + LPV/r	21.00%	83.00%	21.00%	83.00%
ABC + 3TC + ATV/r	2.00%		2.00%	
TDF + FTC + ATV/r	3.00%	79.42%	3.00%	79.42%
TDF + FTC + LPV/r	2.00%	71.25%	2.00%	71.25%
AZT + 3TC + ATV/r	19.00%	75.70%	19.00%	75.70%
3TC + TDF + FPV/r	3.00%		3.00%	

Table S9. Antiretroviral treatment breakdown in 2013

Group	Treatment type	Number of adults receiving ART	Number of children receiving ART
A	First-line	9,958,772	881,335
A	Second-line	388,630	31,525
B	First-line	772,553	19,624
B	Second-line	131,780	4,279

Table S10. Impact of regimens containing AZT in Benin

Adult regimen	Adult regimen impact
AZT + 3TC + NVP	3,873
AZT + 3TC + EFV	1,189
AZT + 3TC + LPV/r	50.6
AZT + ABC + 3TC + LPV/r	0
AZT + 3TC + TDF + LPV/r	16.8
Child regimen	**Child regimen impact**
AZT + 3TC + NVP	1,197
AZT + 3TC + EFV	205.2
AZT + 3TC + LPV/r	9
AZT + ABC + 3TC + LPV/r	2.4
AZT + ddl + LPV/r	3.03

Table S11. Company Index Across Years 2010, 2013, and 2015

Index	Company (2010)	Company (2013)	Company (2015)
1	Kyorin Pharmaceutical	Kyorin Pharmaceutical	Kyorin Pharmaceutical
2	F. Hoffmann-La Roche	F. Hoffmann-La Roche	F. Hoffmann-La Roche
3	Merck	Merck	Merck
4	Bayer Healthcare	Bayer Healthcare	Bayer Healthcare
5	Sanofi	Sanofi	Sanofi
6	Daiichi Sankyo	Daiichi Sankyo	Daiichi Sankyo
7	Bristol-Myers	Bristol-Myers	Bristol-Myers
8	Pfizer Inc.	Pfizer Inc.	Pfizer Inc.
9	Shire Pharmaceuticals	Shire Pharmaceuticals	Shire Pharmaceuticals
10	Boehringer Ingelheim	Boehringer Ingelheim	Boehringer Ingelheim
11	Gilead Sciences	Gilead Sciences	Gilead Sciences
12	Eli Lilly	Eli Lilly	Eli Lilly
13	Abbott Laboratories	Abbott Laboratories	Abbott Laboratories
14	Novartis	Novartis	Novartis
15	Chongqing Holley	Chongqing Holley	Chongqing Holley
16	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline
17	Johnson and Johnson	Johnson and Johnson	Johnson and Johnson
18	Taisho Pharmaceuticals	Guilin Pharmaceutical	Guilin Pharmaceutical
19	Artepharm	Artepharm	Artepharm
20	Imperial Chemical Industries	Imperial Chemical Industries	Imperial Chemical Industries

Figures S1 to S79

Fig. S1.

Results 2010
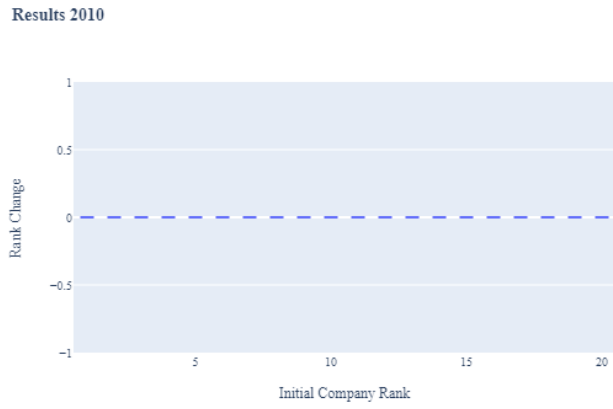
Fig. S2.
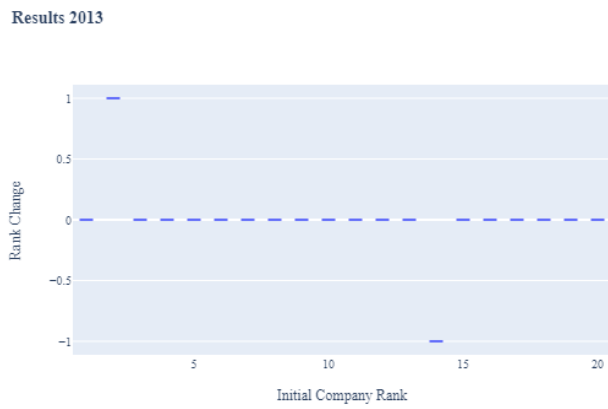
Results 2013

Fig. S3.
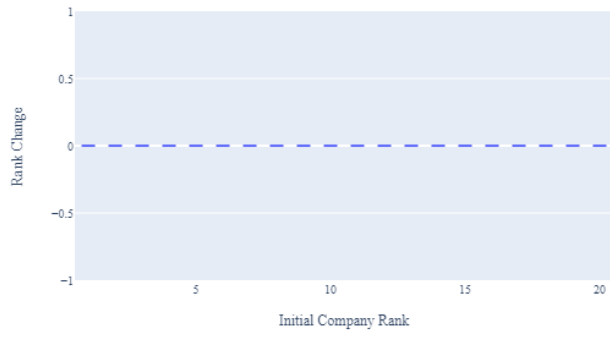
Results 2015

Fig. S4.

Results 2010
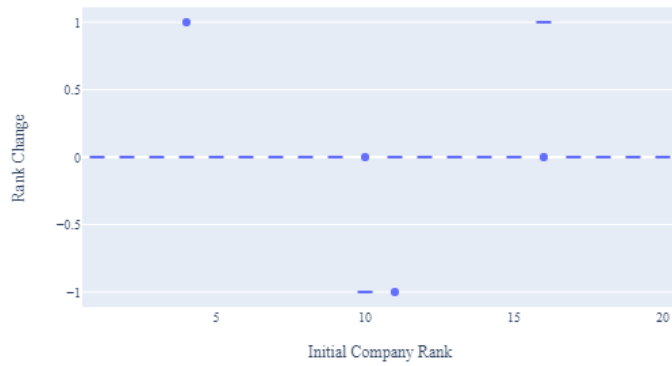
Fig. S5.

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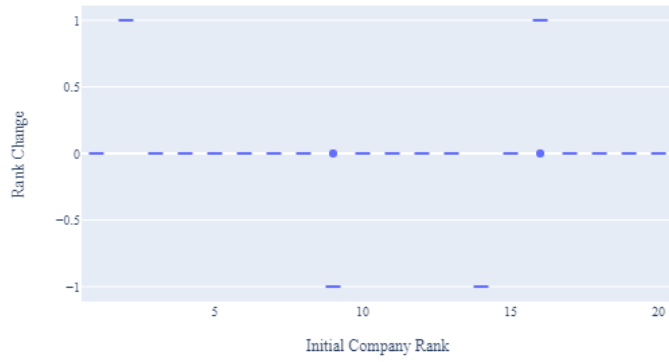
Fig. S6.

Results 2015

Fig. S7.

Results 2010
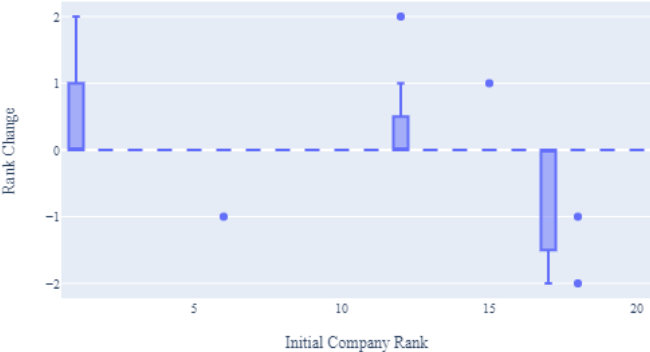
Fig. S8.

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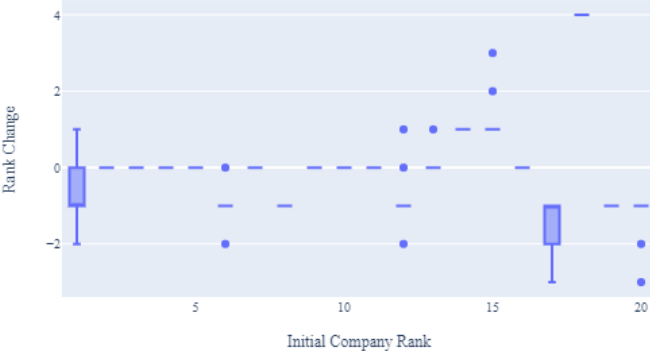
Fig. S9.

Results 2015

Fig. S10.

Results 2010
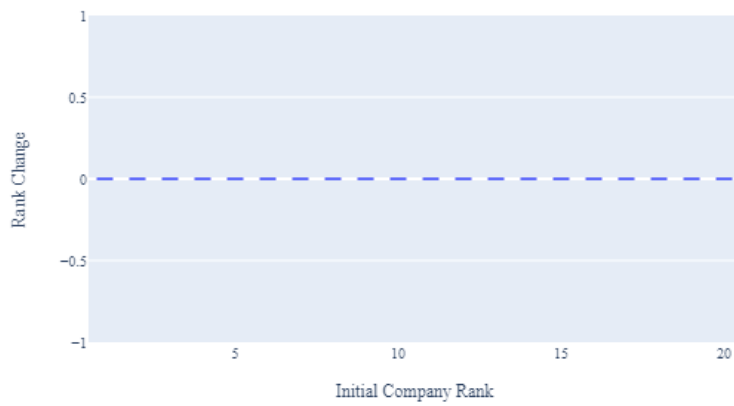
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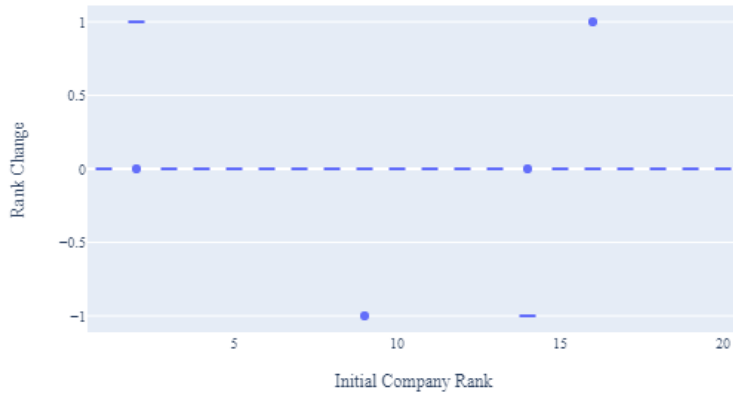
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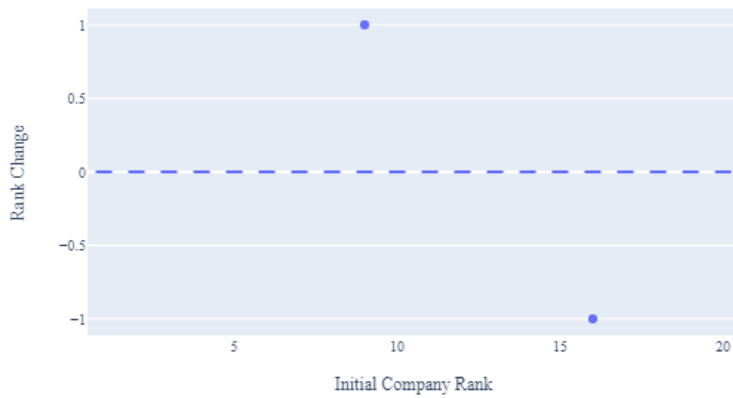
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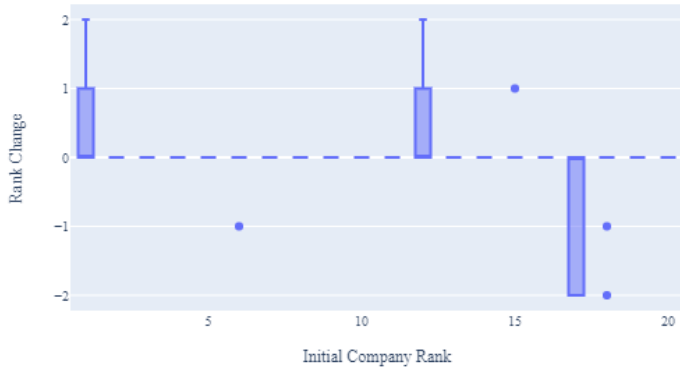
Fig. S14.

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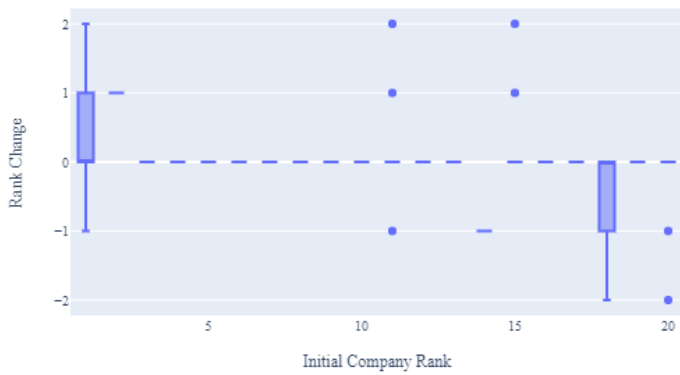
Fig. S15.

Results 2015

Fig. S16.

Results 2010
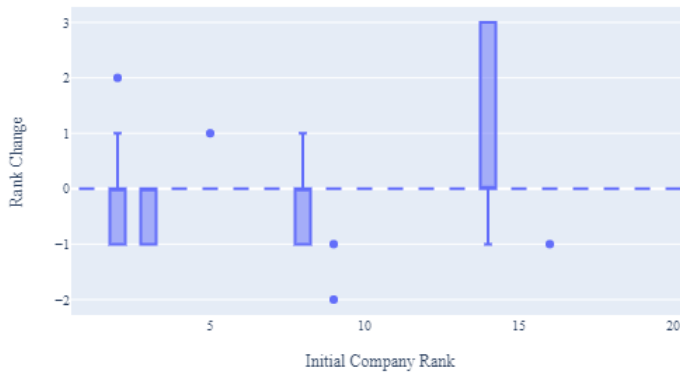
Fig. S17.

Results 2013

Fig. S18.
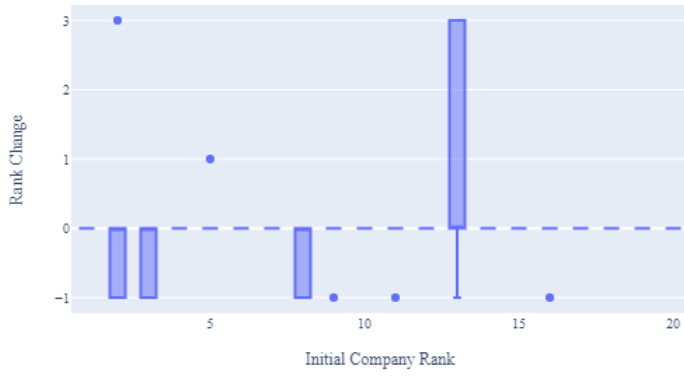
Results 2015

Fig. S19.

Results 2010
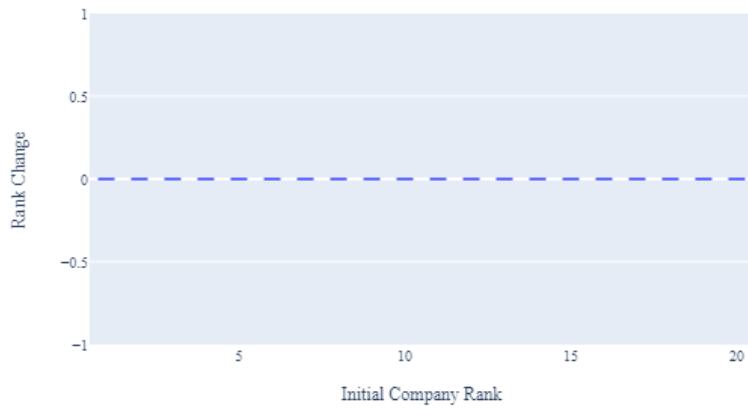
Fig. S20.

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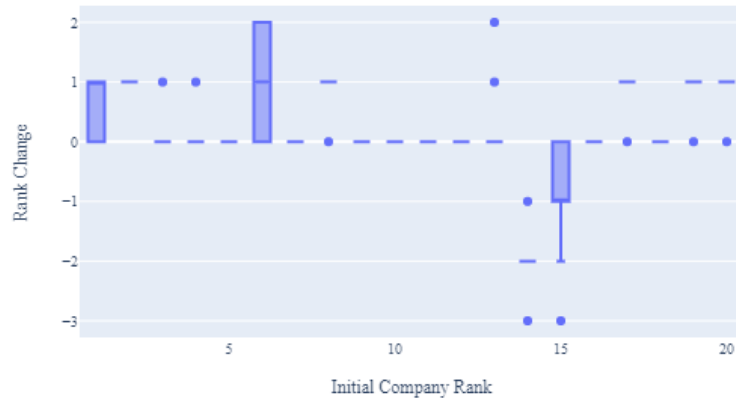
Fig. S21.

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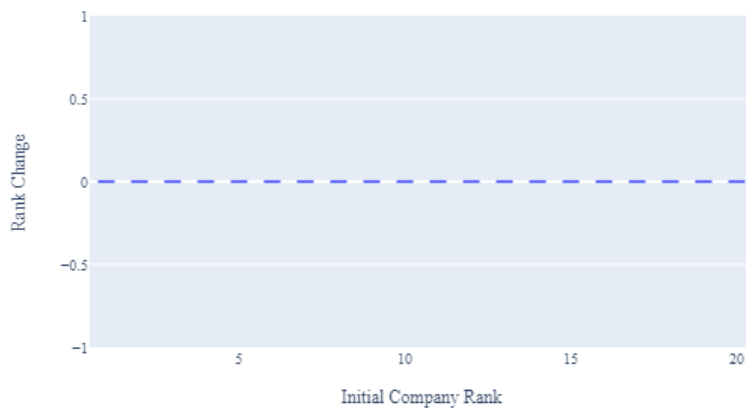
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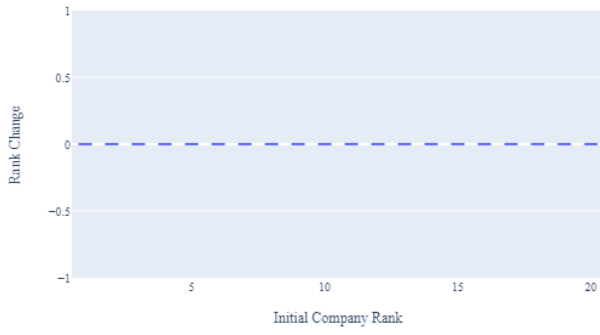
Fig. S23.

Results 2013

Fig. S24.

Results 2015
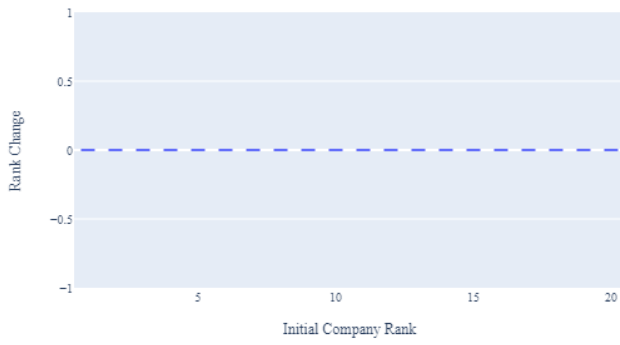
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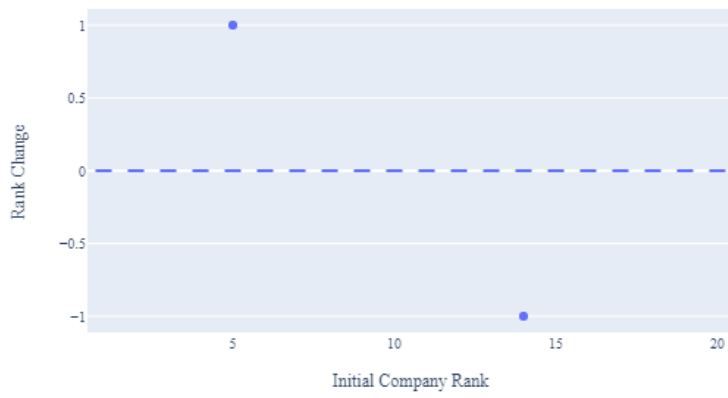
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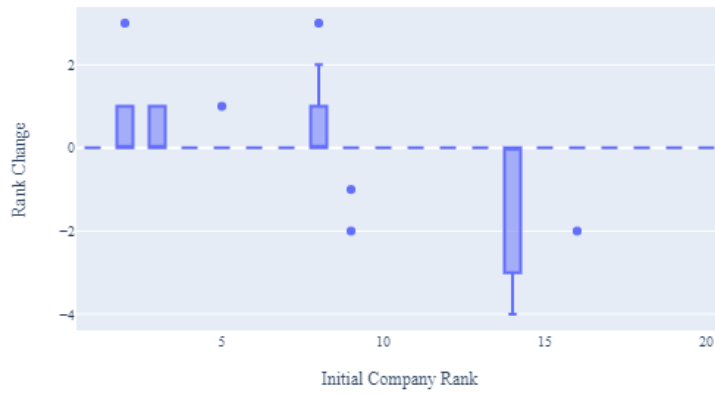
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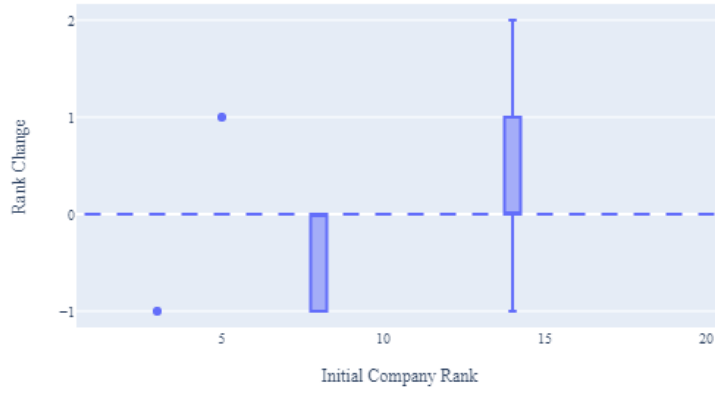
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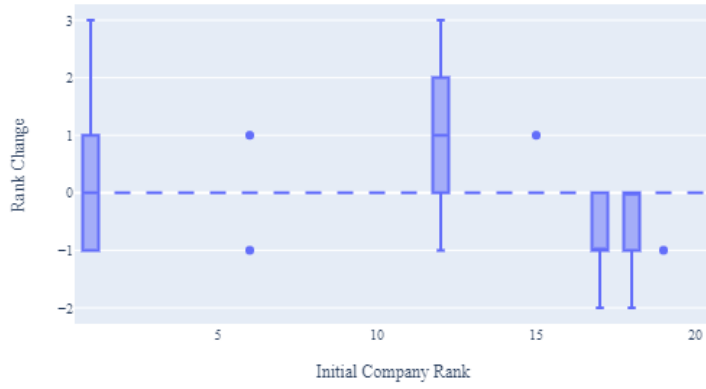
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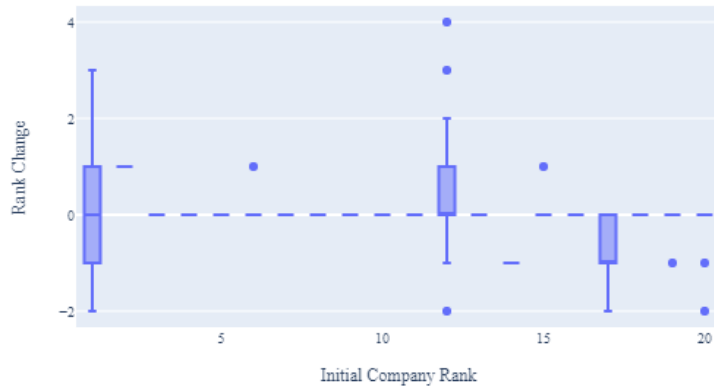
Fig. S30.

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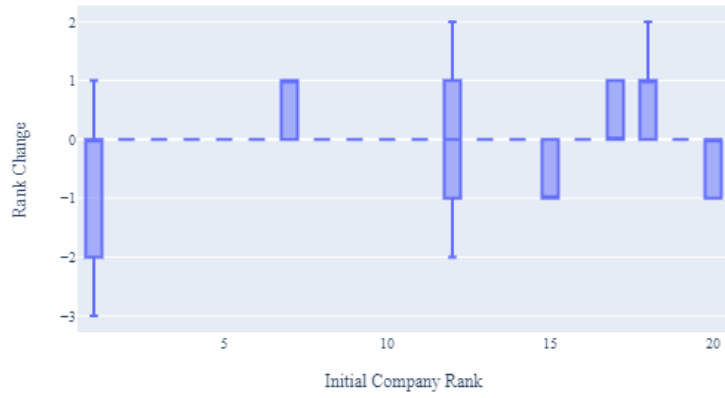
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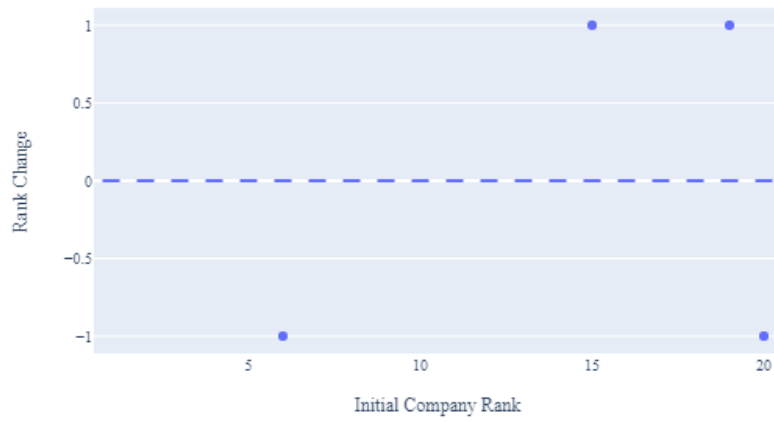
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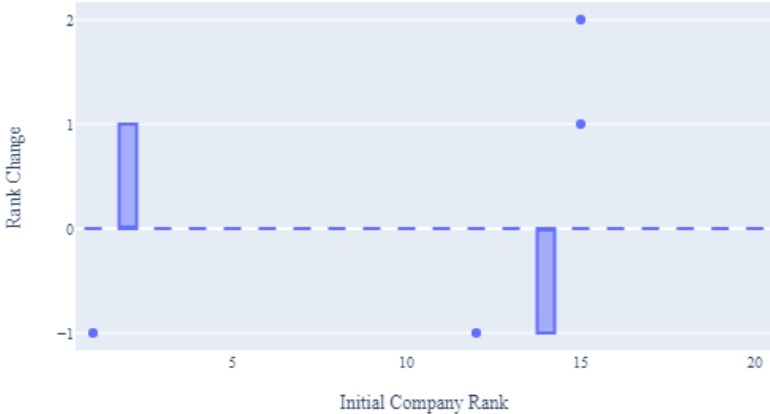
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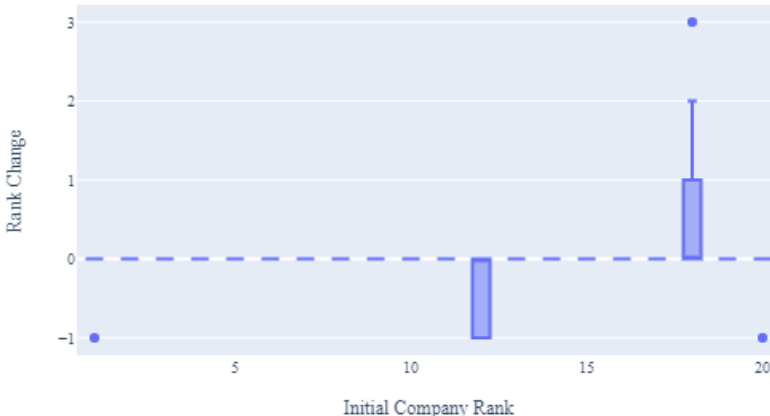
Fig. S34.

Results 2010

Fig. S35.

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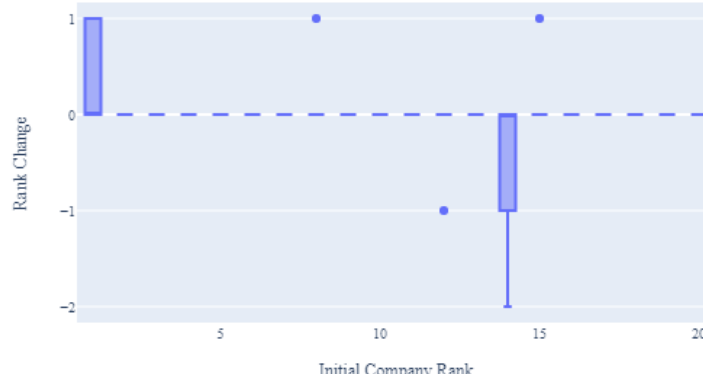
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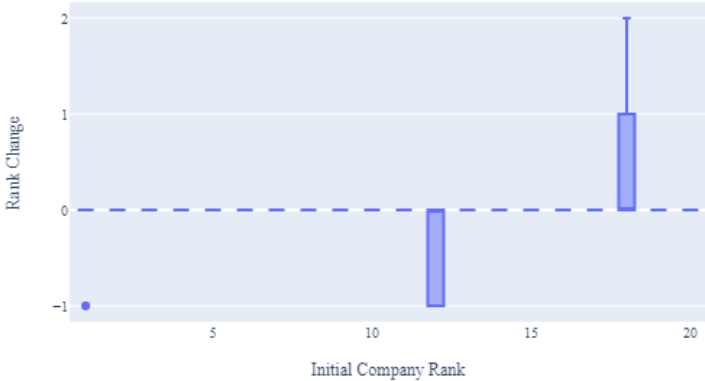
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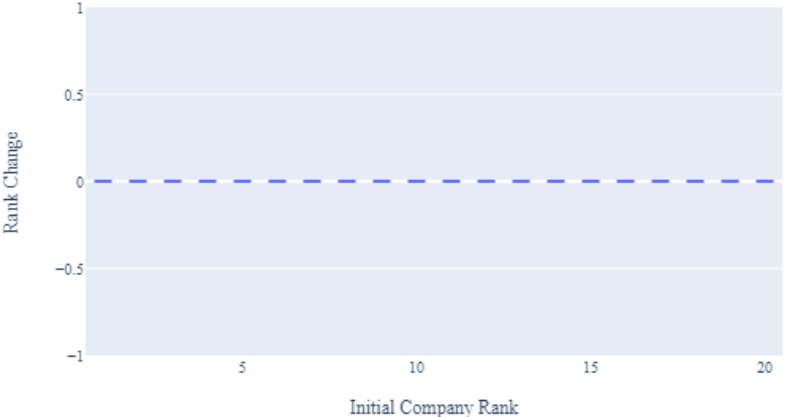
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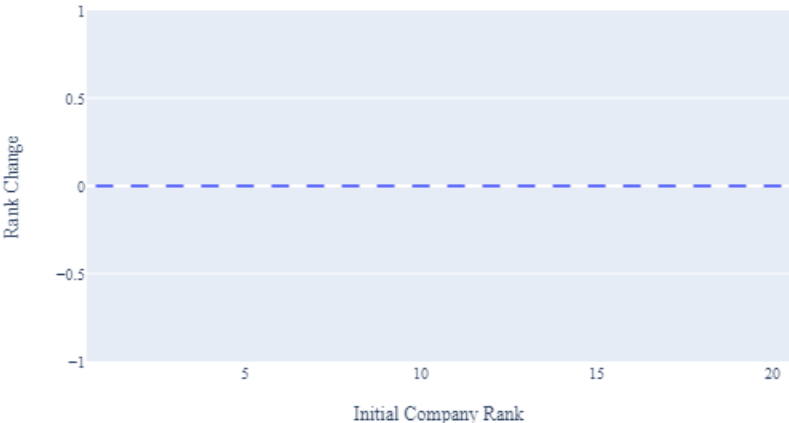
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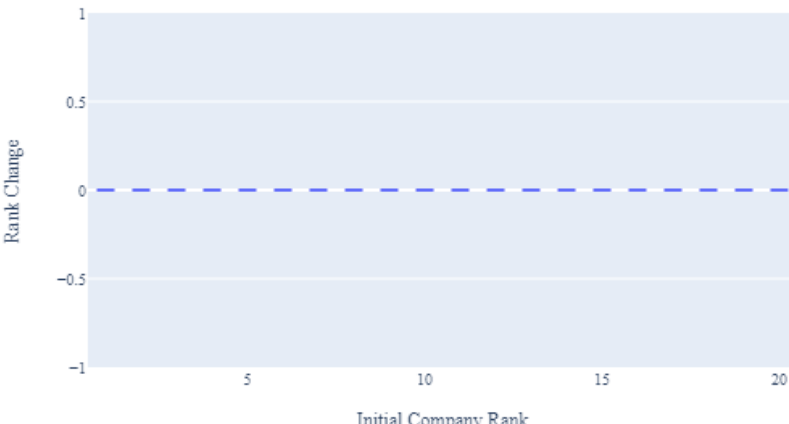
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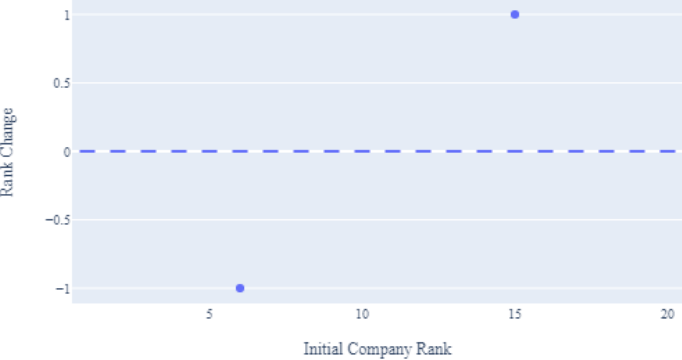
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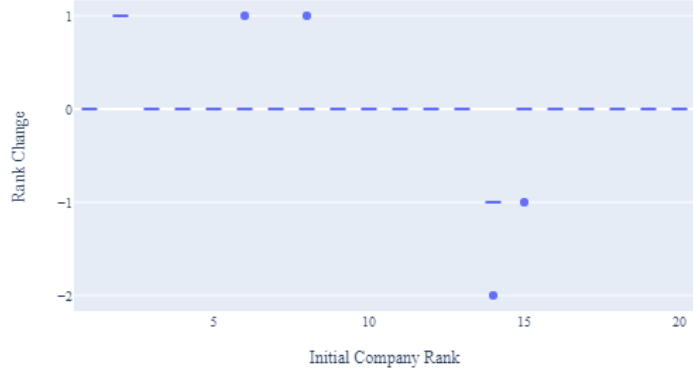
Fig. S42.

Results 2015

Fig. S43.

Results 2010
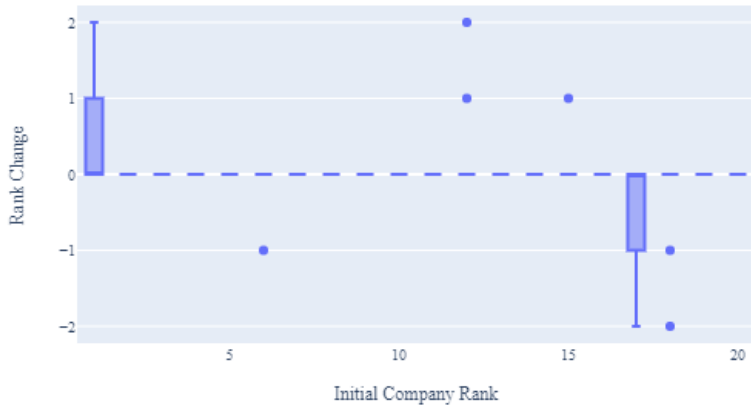
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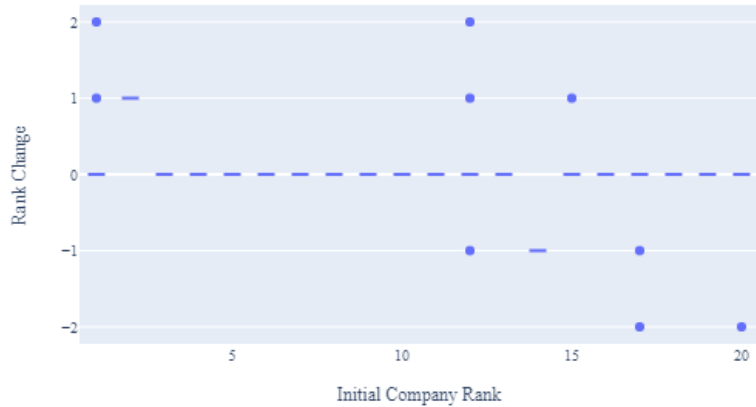
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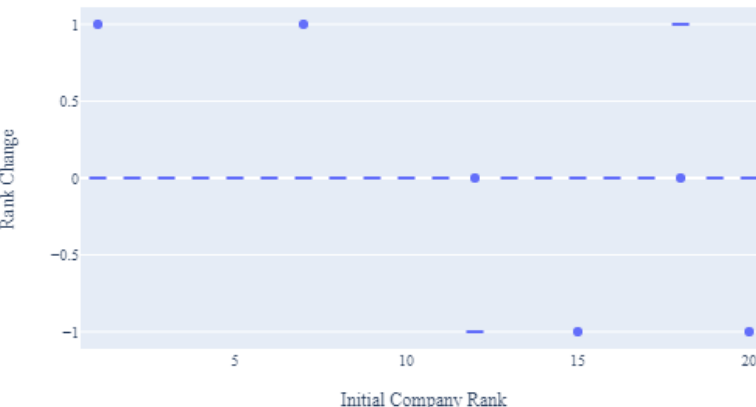
Fig. S46.

Results 2010

Fig. S47.

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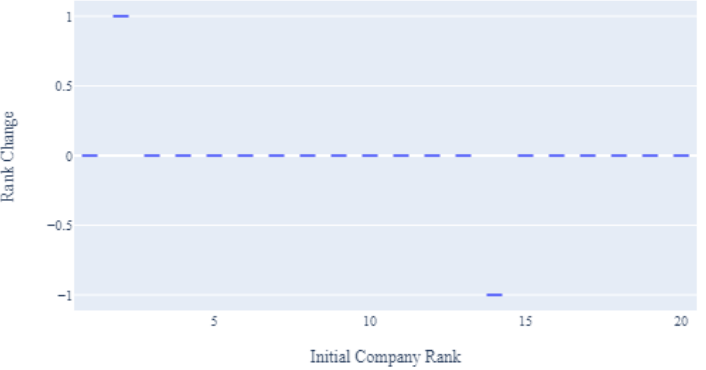
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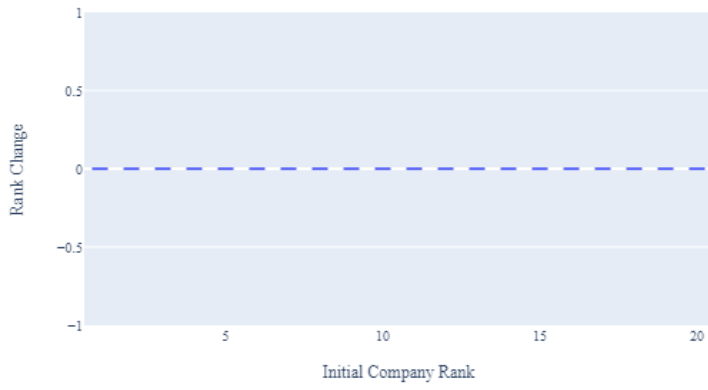
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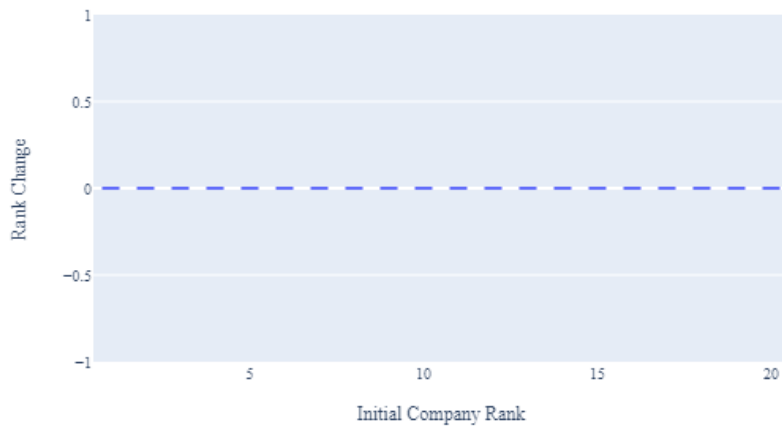
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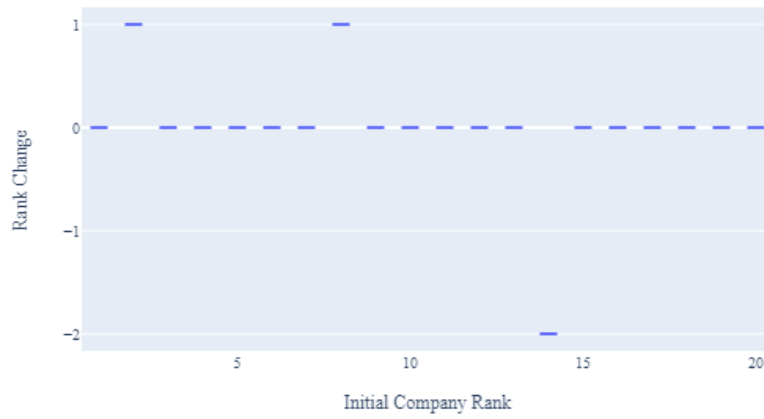
Fig. S51.

Results 2015

Fig. S52.

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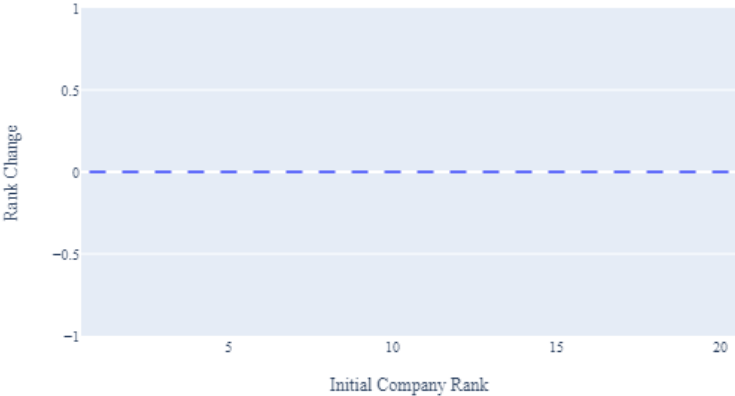
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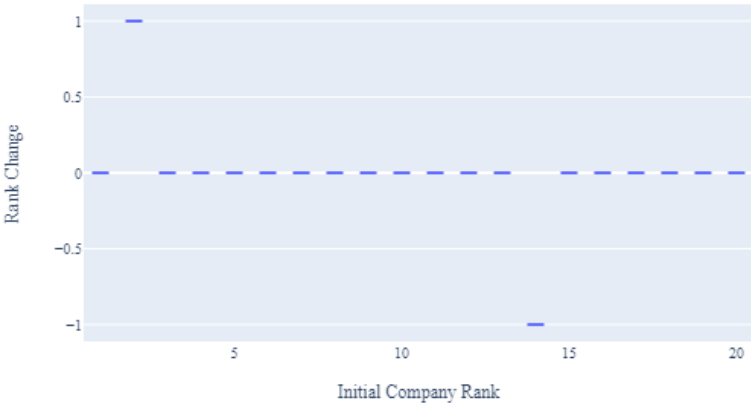
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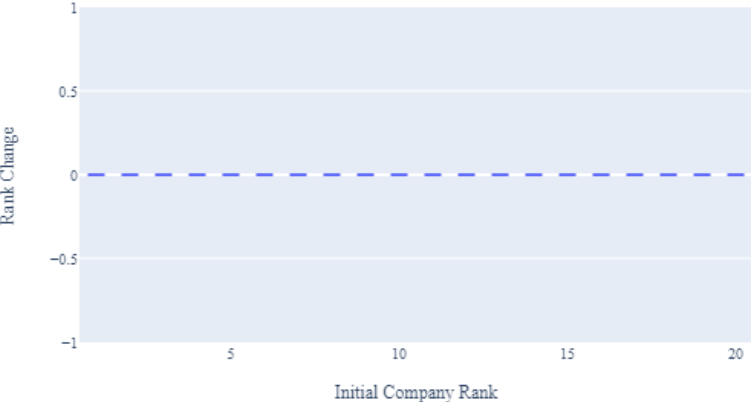
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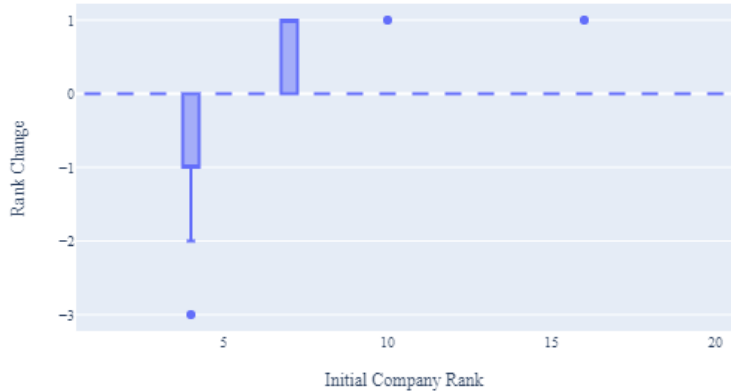
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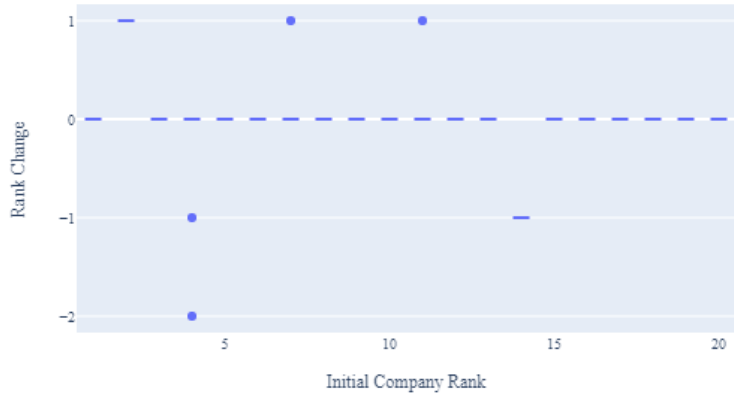
Fig. S57.

Results 2015

Fig. S58.

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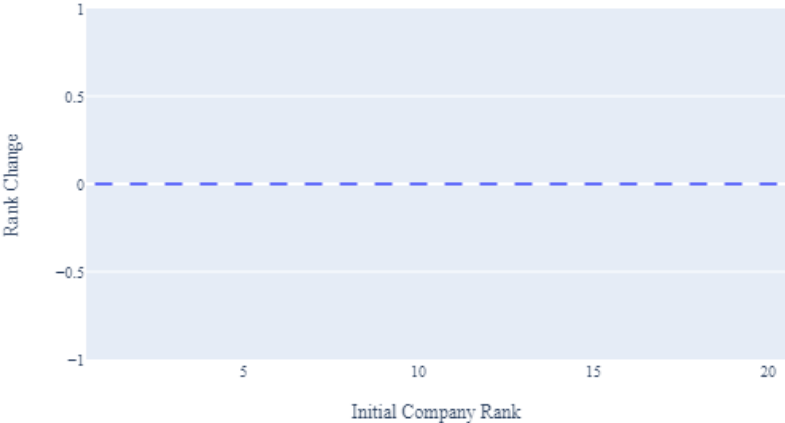
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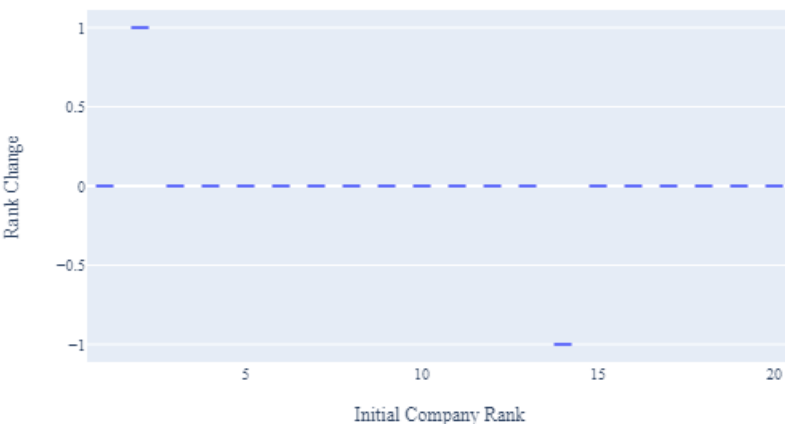
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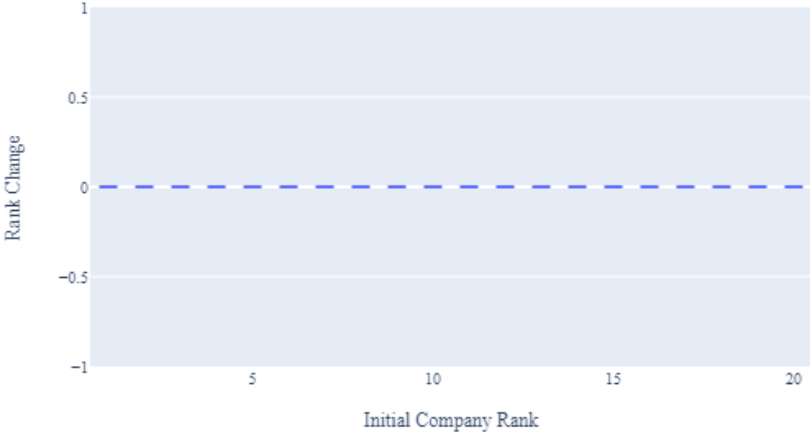
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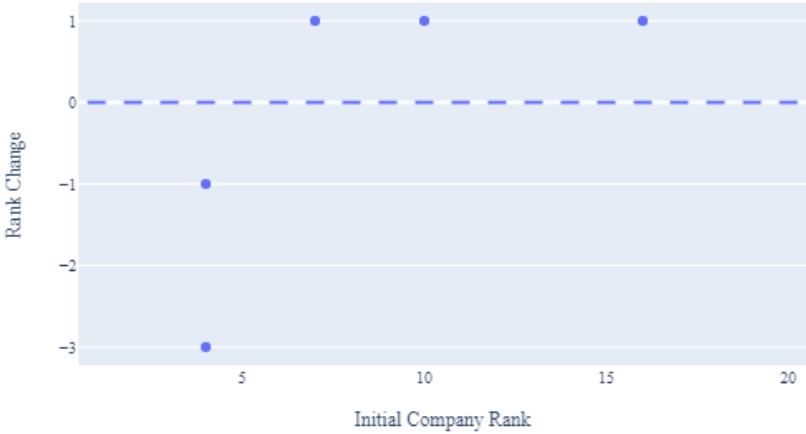
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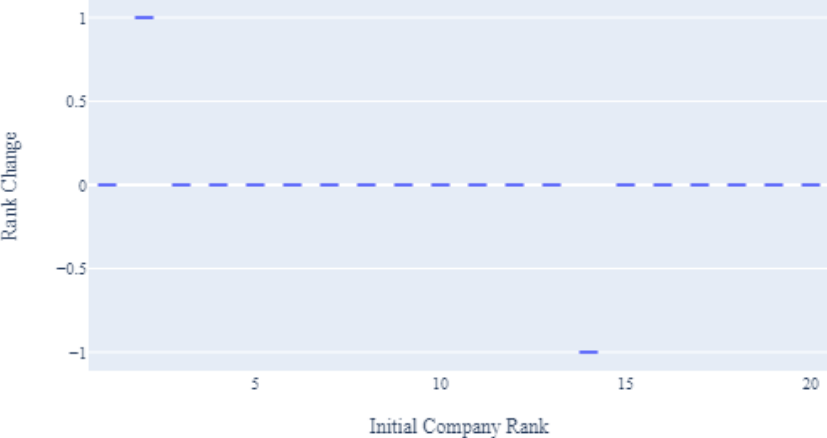
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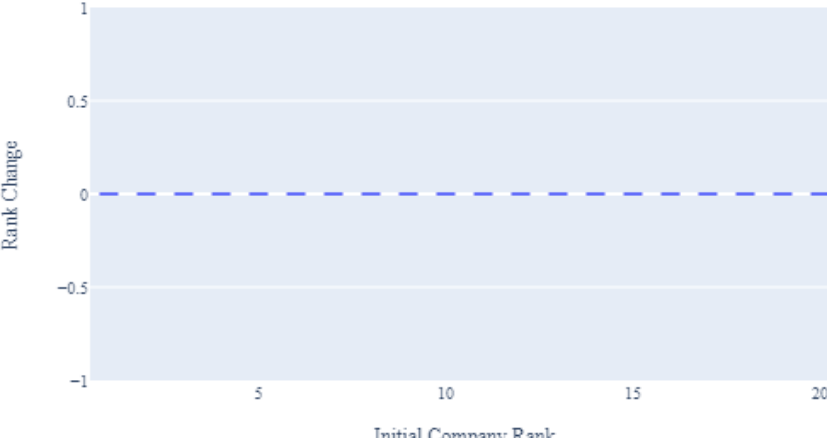
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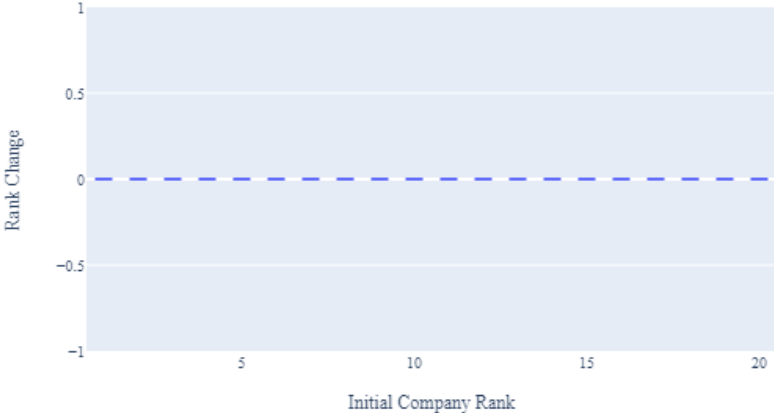
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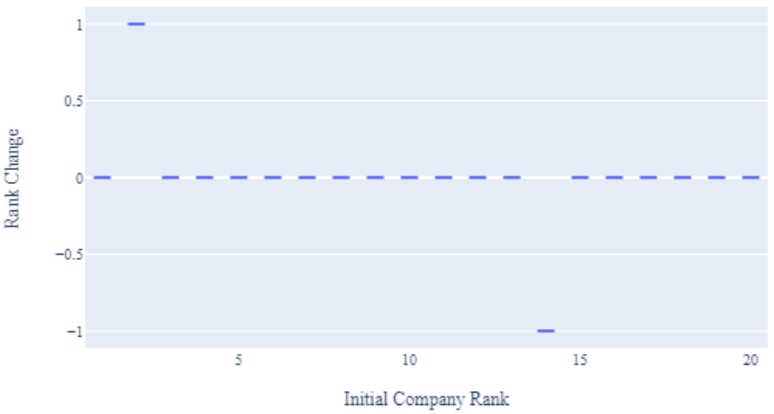
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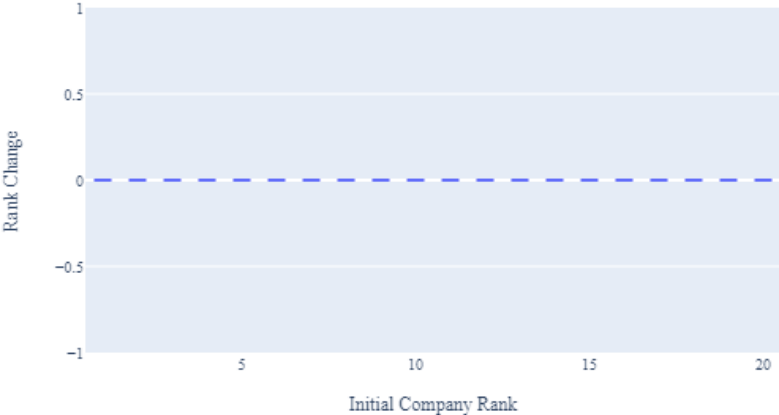
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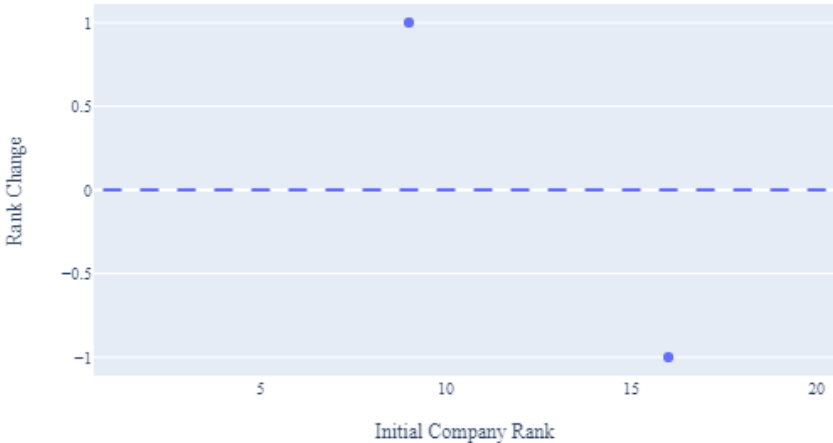
Fig. S68.

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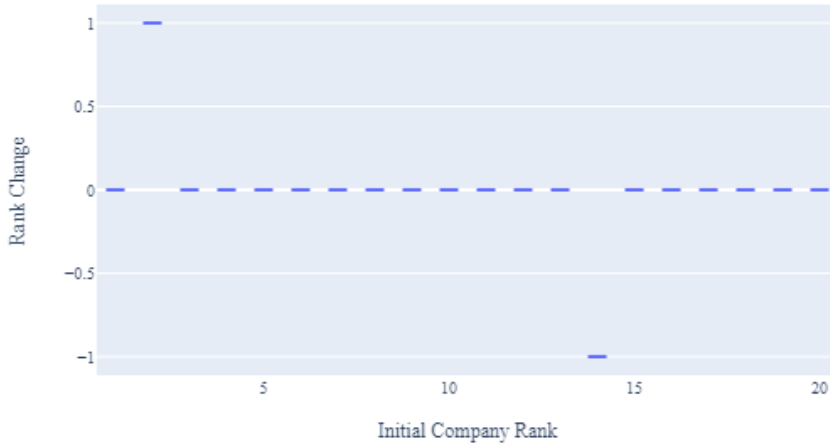
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Results 2015
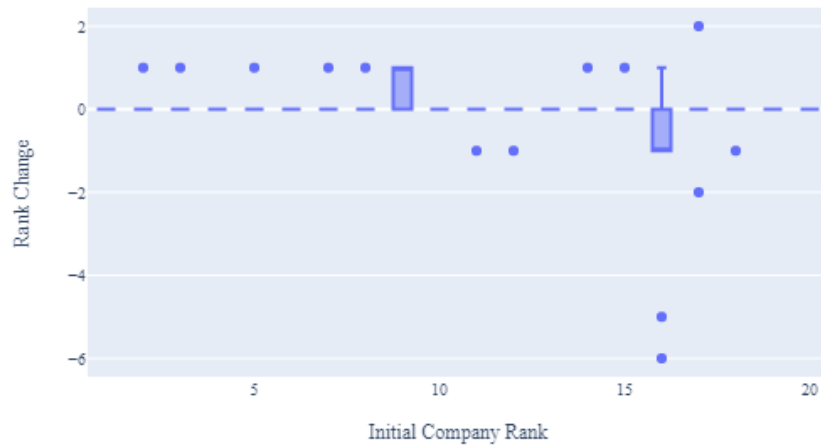
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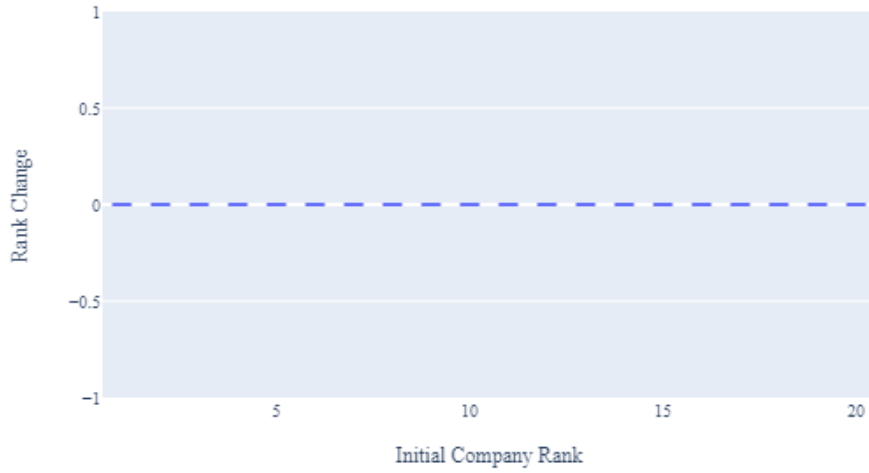
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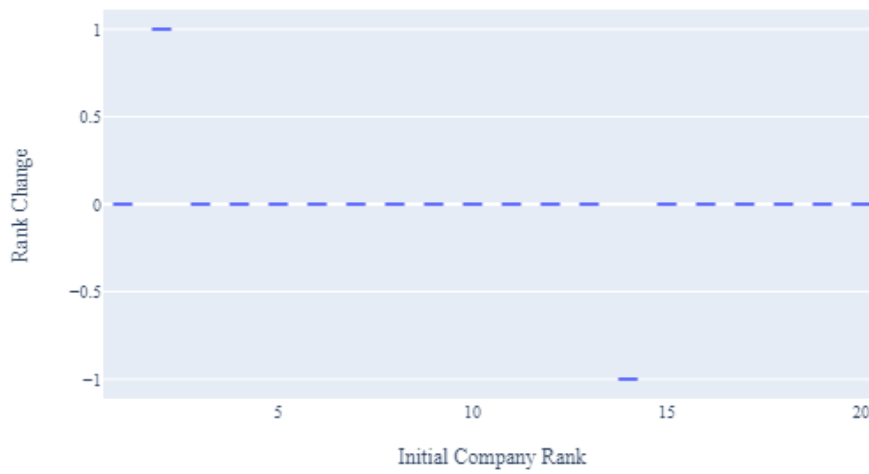
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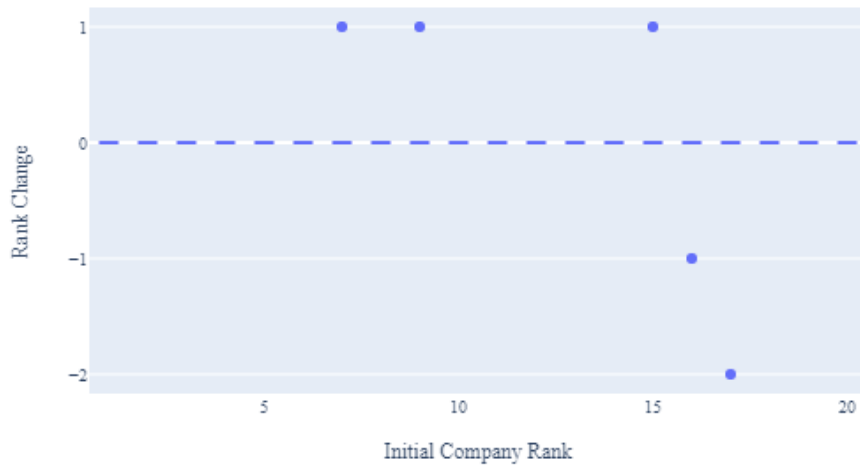
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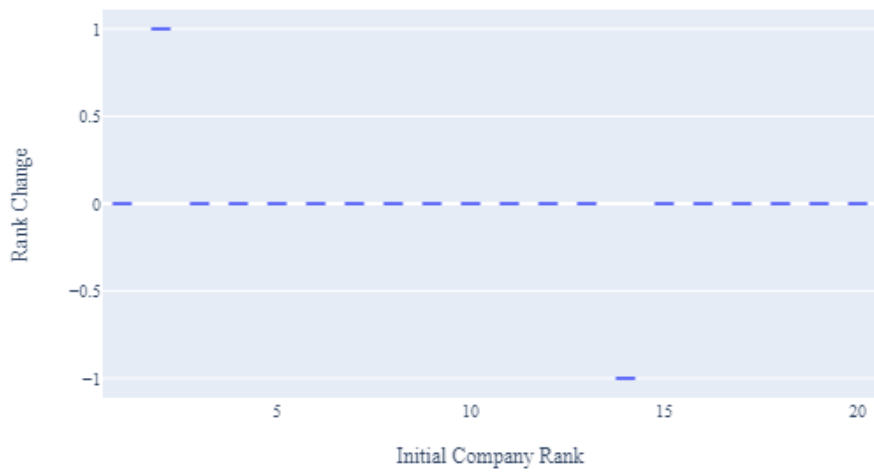
Fig. S74.

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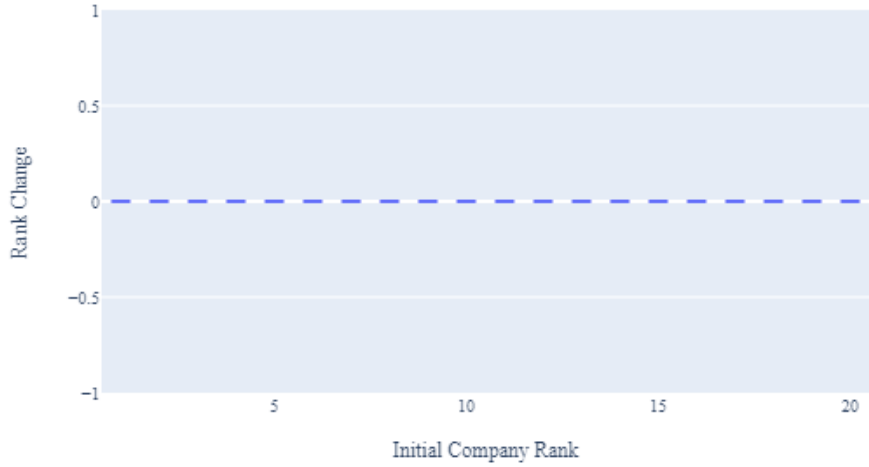
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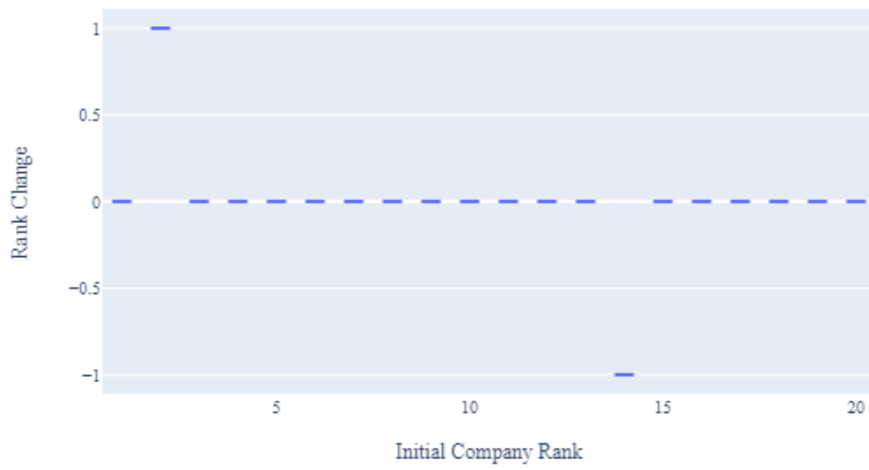
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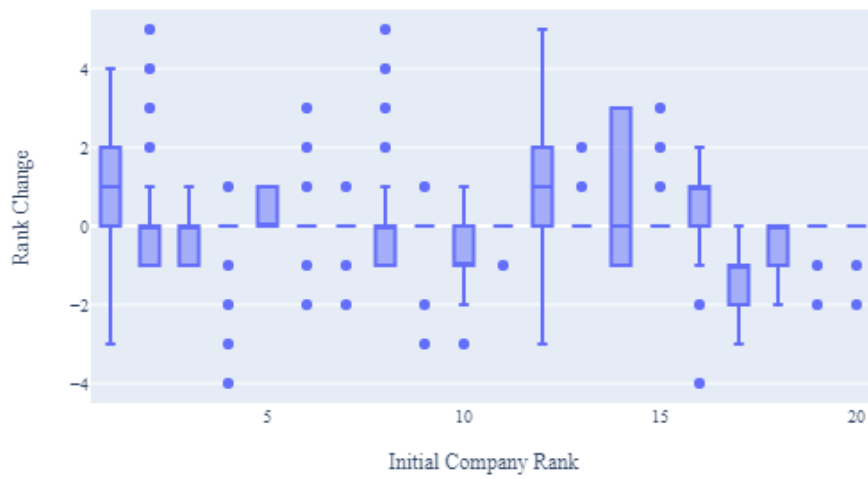
Results 2015
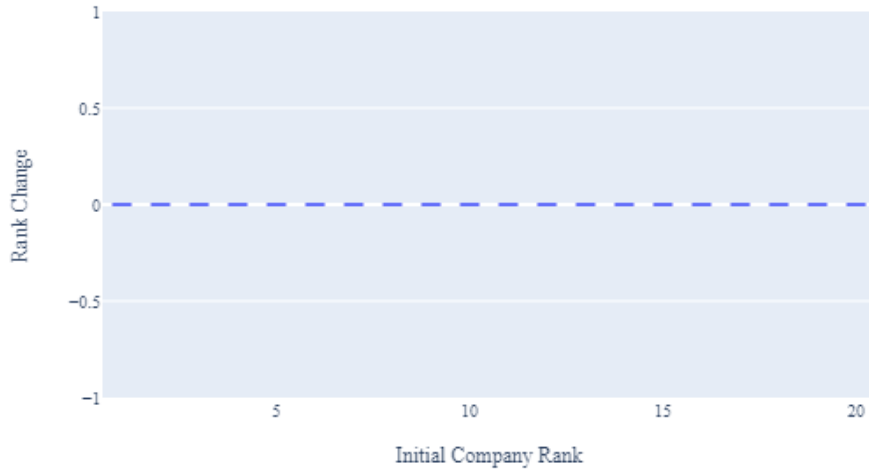
Fig. S77.

Results 2010

Fig. S78.

Results 2013

Fig. 79.

Results 2015