Pharmaceutical Payments to Japanese Board-Certified Infectious Disease Specialists: A Four-year Retrospective Analysis of Payments from 92 Pharmaceutical Companies between 2016 and 2019

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
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Conflicts of interest:

Dr. Saito received personal fees from TAIHO Pharmaceutical Co. Ltd outside the scope of the submitted work. Dr. Kusumi received personal fees from Otsuka Pharmaceutical outside the scope of the submitted work. Drs. Ozaki and Tanimoto received personal fees from Medical Network Systems outside the scope of the submitted work. Dr. Tanimoto also received personal fees from Bionics Co. Ltd, outside the scope of the
submitted work. Regarding non-financial conflicts of interest among the study authors,

all are engaged in ongoing research examining financial and non-financial conflicts of
interest among healthcare professionals and pharmaceutical companies in Japan.

Individually, Anju Murayama, Hiroaki Saito, Toyoaki Sawano, Tetsuya Tanimoto, and
Akihiko Ozaki have contributed to several published studies addressing conflicts of
interest and quality of evidence among clinical practice guideline authors in Japan and
the United States. The other authors have no example of conflicts of interest to disclose.

Funding sources:

This study was funded in part by the Medical Governance Research Institute. This non-
profit enterprise receives donations from Ain Pharmacies, Inc., a dispensing pharmacy,
other organizations, and private individuals. This study also received support from the
Tansa (formerly known as the Waseda Chronicle), an independent non-profit news
organization dedicated to investigative journalism. None of the entities providing
financial support for this study contributed to the design, execution, data analyses, or
interpretation of study findings and the drafting of this manuscript.
Abstract

Objective

Conflict of interest with pharmaceutical companies is one of the most contentious issues in infectious diseases. However, there is a lack of whole picture of detailed payments in Japan.

Study Design and Setting

This retrospective study assessed financial relationships between pharmaceutical companies and all infectious disease specialists board-certified by the Japanese Association for Infectious Disease, using publicly disclosed payment data from 92 pharmaceutical companies. Descriptive analyses were conducted for the payments. Payment trends were examined by the generalized estimating equations.

Results

Of 1614 board-certified infection disease specialists, 1,055 (65.4%) received a total of $17,784,070 payments, corresponding to 21,680 cases between 2016 and 2019. The mean±SD and median (interquartile range: IQR) were $16,857±$45,010 and $3,183 ($938–$11,250) in payments. All board executive members of Japanese Association of...
Infectious Disease received higher payments averaging $163,792. There were no significant changes in payments per specialist (annual change rate: -1.4% [95% CI: -4.7% to 2.3%), p=0.48) and prevalence of specialists with payments (annual change rate: -1.4% [95% CI: -3.1% to 0.2%), p=0.093) over the four years.

Conclusion

There were substantial financial relationships between pharmaceutical companies and board-certified infectious disease specialists in Japan. Such personal payments must be restricted to a certain level to avoid potential conflict of interest.
Keywords:

Board-Certified Infectious Disease Specialists, Pharmaceutical payments, Physician payment, conflicts of interest, Health policy, Japan

Running title: Pharmaceutical Payments to Japanese Board-Certified Infectious Disease Specialists

Word count: Abstract 197 words, Main text 3432 words
Main text

Introduction

There has been an increasing concern on financial relationships between healthcare professionals, healthcare organizations and pharmaceutical companies, which sometimes become conflicts of interest (COI), because of its potential bias on healthcare.

In response to this concern, many countries have started requesting pharmaceutical companies to disclose data on their donations and honoraria to healthcare professionals and healthcare organizations.[1, 2] Consequently, previous studies utilizing these data have demonstrated that there were substantial financial relationships between pharmaceutical companies.[3-7]

Among several specialties, infectious disease is one where there is a greatest concern about the influence from pharmaceutical companies. As in the case of Lyme disease guideline issued by the Infectious Diseases Society of America (IDSA), the guideline chair and authors manipulated the guideline recommendations and statements for the benefits of testing and insurance companies, leading to inadmissible harms on the patients in the US.[8]
In cases of Japan, 91.7% of authors of clinical guideline for methicillin-resistant *Staphylococcus aureus* issued by the Japanese Association for Infectious Diseases received an average of $28,371 personal payments in 2016, and four pharmaceutical companies’ employees were involved in the guideline development.[9] Moreover, during coronavirus disease 2019 (COVID-19) pandemic, substantial financial relationships were uncovered among healthcare professionals specialized in infectious diseases and pharmaceutical companies worldwide. However, the Japanese government COVID-19 advisory board members did not manage to disclose the detailed information on COI with pharmaceutical companies.[10] Although COI among influential infectious disease experts such as television commentators specialized in infectious diseases[11], guideline authors[7, 9], and government advisory members[10] were investigated, the whole picture of financial relationships with pharmaceutical companies remains to be elucidated. Since board-certified infectious disease specialists directly prescribe drugs for patients, it is crucial to understand financial relationships among pharmaceutical companies and those specialists.

This study aimed to elucidate the prevalence of board-certified infectious disease specialists receiving payment from pharmaceutical companies, the magnitude of the
payments, and payments trend over last few years in Japan.

Methods

Study design and participants

This study was a retrospective analysis evaluating financial relationships among all board-certified infectious disease specialists and pharmaceutical companies in Japan. All infectious disease specialists who were board-certified by the Japanese Association for Infectious Disease (the Association hereafter) as of November 2021 were included in this study. The Association is the largest and most prestigious professional medical society for infectious diseases in Japan, which contributed to improve patient care by promoting research and training physicians for infectious diseases in Japan since its establishment in 1926. Also, the Association is the only organization in Japan that trains and certifies infectious diseases specialists in the country.

As of November 2021, the Association required physicians to complete several requirements to certificate them as infectious disease specialists, such as being a specialist certified by at least one of the 19 major Japanese medical societies[12], having completed at least six years of clinical practice training after having acquired a medical license and at least three years of specialized training in infectious diseases at
an institution accredited by the Association, and having published at least one academic
article on a peer-review journal and at least two conference presentations as the first
author.

Data collection

Data concerning name and affiliations for all of those board-certified specialists were
extracted from the official webpage of the Association
(https://www.kansensho.or.jp/modules/senmoni/index.php?content_id=29) on
November 10, 2021. Also, the Association webpage provided us names of all executive
board members as of 2021. All drugs with additional or new indications for infectious
diseases between 2015 and 2019 were extracted from the database of the
Pharmaceuticals and Medical Devices Agency[13], the Japanese regulatory authority for
drugs and medical devices.

Payment data from 2016 to 2019 to all healthcare professionals and healthcare
organizations for lecturing, writing, and consulting were collected from all 92
pharmaceutical companies affiliated with Japan Pharmaceutical Manufacturers
Association (JPMA).[14-16] JPMA required that the member companies disclose only
the payment for lecturing, writing, and consulting on the individual basis. However, payment categories such as meals, travel, and accommodations were not disclosed on each individual specialist. Thus, we could only analyze personal payments concerning lecturing, writing, and consulting.

Then, we stored all payment data collected from 92 companies into an excel file and structured the searchable payment database. By searching for the specialist names in the payment database, the payment data to the infectious disease specialists were extracted from the payment database. The extracted data included recipient names, recipient affiliations, monetary amount, number of payment cases, payment category, and name of pharmaceutical company making the payment. To remove payment data of different persons with duplicate names in the database, we checked and compared the affiliations, affiliation address, and recipient specialties among the data from the Association and the pharmaceutical companies. In cases where affiliation reported by the company differed from the one reported by the Association, we manually googled the name of specialists and collected other data from the official institutional webpages and other sources to verify that they were the same person. The detailed process can be found in our previously published papers.[5, 14-16]
Data Analysis

Descriptive analyses were performed for payment values and number of cases on individual specialist and pharmaceutical company levels. Average and median payments, cases, number of companies making payments per specialist were calculated based on the only specialists receiving payment in each year, as in other studies assessing pharmaceutical payments to physicians.[17-20] To compare the payments among the specialists with and without a leading role in the Association, the average mean and median payments were evaluated by the specialists with and without the executive board membership. The difference between two groups was assessed by the Mann-Whitney U test, as the payments data were not normally distributed.

The Gini index and the shares of the payment values held by the top 1%, 5%, 10%, and 25% of the specialists were calculated to examine distribution and concentration of payments. The Gini index ranges from 0 to 1, and the greater the Gini index is, the greater the disparity in the distribution of payments on the specialist basis, as performed previously.[14, 21, 22] Also payment distributions were geographically examined on prefectures and regions, as there were differences in number of the specialists and the medical institutions accredited by the Association.
The population-averaged generalized estimating equations (GEE) were performed to evaluate the payment trends. As the payment distribution was highly skewed (Supplemental Material 1), negative binomial GEE model for the payment values per specialist, and linear GEE log-linked model with binomial distribution for the prevalence of specialists with payments were used. The year of payments was set as independent variable, and the payment values per specialist and proportion of physicians receiving payments were set as dependent variables. The average annual changes in independent variables, payment values per specialist and prevalence of specialists with one or more payments, were reported as a relative percentage. As several pharmaceutical companies among all 92 companies disaffiliated from the JPMA and newly joined the JPMA, there were 18 companies without payment data over the four years. Thus, the average and median payments for each year and the trend of payments were calculated based on payments from all 92 companies and 74 companies with payment data for the four years between 2016 and 2019, as previously described.[3, 4, 23]

Finally, we assessed association between number of drugs with new or additional indications and (1) total payments and (2) number of specialists with payments on company level using the Spearman’s correlation.
Japanese yen (¥) was converted into US dollars ($) using 2019 average monthly exchange rates of ¥109.0 per $1. All analyses were conducted using Microsoft Excel, version 16.0 (Microsoft Corp.) and Stata version 15 (StataCorp.).

**Ethical approval**

The Ethics Committee of the Medical Governance Research Institute approved this study (approval number: MG2018-04-20200605; approval date: June 5, 2020). As this study was a retrospective analysis of the publicly available information, informed consent was waived by the Ethics Committee.

**Results**

We identified 1,614 infectious disease specialists certified by the Association as of November 10, 2021. The Association stated that there were a total of 1,622 infectious disease specialists in Japan, and therefore, names of eight specialists missing were not disclosed on the webpage, as the specialists could have wished not to disclose their names on the webpage.

**Overview and Per-Specialist Payments**
Of 1,614 eligible board-certified infectious disease specialists, 1,055 (65.4%) received one or more payments, totaling $17,784,070 corresponding to 21,680 payment counts between 2016 and 2019. Among 92 companies, 78 (84.8%) made at least one payment to the specialists over the four-year period. The average (standard deviation: SD) and median (interquartile range: IQR) were $16,857 ($45,010) and $3,183 ($938-$11,250) in payments; 20.5 (41.6) and 6.0 (2.0-19.0) in payment cases; and 5.6 (5.2) and 4.0 (2.0-8.0) in number of pharmaceutical companies per specialist. (Table 1)

Regarding the payment distribution, although 34.6% of specialists had no payments, 5.1% and 2.7% received more than $50,000 and $100,000, respectively. The Gini index for the four-year cumulative payments per specialist was 0.86. Top 1%, 5%, 10% and 25% of the specialists occupied 26.3% (95% confidence interval (CI): 21.4%-31.2%), 61.5% (95% CI: 57.0%-65.9%), 77.2% (95% CI: 73.9%-80.4%), and 93.6% (95% CI: 92.5%-94.7%) of total payments, respectively. (Supplemental Material 2) One specialist received a maximum of $711,965 payments over the four-year from 21 pharmaceutical companies.

Of 18 executive members of the Association as of November 2021, 17 (94.4%) had
certification of infectious disease specialists. All the 17 members with the specialist certification, including the current Association president, received more substantial payments averaging $163,792 (SD: $173,475; median: $95,551; IQR: $54,227−$207,948) than the specialists without executive board membership (p<0.001 in Mann-Whitney U test) over the four-year.

Payment trend between 2016 and 2019

The average annual payments per specialist ranged from $5,775 (SD: $13,410) in 2017 to $6,134 (SD: $15,283) in 2016, and median payments were from $1,430 (IQR: $511−4,531) in 2017 to $1,737 (IQR: $642−$5,286) in 2018. The payment values per specialist remained constant, with an average annual change of -1.2% (95% CI: -4.7% □ 2.3%, p=0.49). The prevalence of specialists with payments decreased by -1.3% (95% CI: -2.9 □ 0.4, p=0.13) in each year from 47.1% (760 out of 1614) in 2016 to 44.9% (724 out of 1614) in 2019, but were not statistically significant (p=0.12).

Among 78 companies making payments, 10 companies were devoid of the four-year continuous payment data. Excluding payments from ten companies, the specialists received payments averaging from $5,562 (SD: $13,383) in 2017 to $6,105 (SD:
in 2018. There were also no statistically significant annual changes in payments per specialist (average annual change rate: -1.3% [95% CI: -4.7% to 2.3%], p=0.48) and prevalence of specialists with payments (average annual change rate: -1.4% [95% CI: -3.1% to 0.2%], p=0.093) between 2016 and 2019. (Table 2)

Payment by pharmaceutical companies

The top companies made 63.8% of the total payments, representing $11,340,870 and 13,247 cases. (Figure 1) In company level analysis, the average and median number of specialists with payments per company were 74.9 (SD: 98.8) and 27.0 (IQR: 5.0–113.0), respectively. The average payments and number of cases per specialist were $2,333 (SD: $2,578) and 2.8 (SD: 1.9) cases, respectively. In short, each company made an average of $2,333 payments, entailing 2.8 cases per specialist, to 74.9 specialists in average for the reimbursement of lecturing, consulting and writing.

MSD made the largest payments of $2,493,244 to 460 (28.5%) specialists. Pfizer with the second largest payments distributed a total of $1,376,045 payments to 267 (16.5%) infectious specialists. The average payments per specialist were the highest from FujiFilm Toyama Chemical ($7,269), followed by MSD ($5,456), Pfizer ($5,154), Boehringer Ingelheim ($5,002), and AstraZeneca ($4,990). Payment categories by each
company were described in Supplemental Material 3. MSD also had the largest number
of drugs with new and additional indications (8 drugs), followed by Daiichi Sankyo
Company (5 drugs) and GlaxoSmithKline (5 drugs). (Supplemental Material 4) There
were moderately positive correlations between number of new or additional indications
and (1) total payments ($r(76)=0.46, p<0.001$) and (2) number of specialists with
payments ($r(76)=0.43, p<0.001$).

Geographical payment distribution

There were geographical differences in distribution of infectious disease specialists.
(Supplemental Material 5A and 5B) Number of infectious disease specialists per million
populations ranged from 0.8 in Iwate Prefecture to 47.9 in Nagasaki Prefecture, while
the average number of specialists per million was 12.7 in nationwide. There were
geographic differences in total and per-specialist payment distribution as well.
(Supplemental Material 5C and 5D) The average payment values per specialist were the
highest in Okayama Prefecture ($21,750) and lowest in Ibaraki Prefecture ($1,574).
In the analysis by region, the number of specialists per million populations ranged from
7.8 in the Hokkaido region (northernmost of Japan), and 8.7 in the Tohoku region
(northernmost of main Japanese islands) to 20.6 in the Kyusyu region (southernmost of
Japan). Meanwhile, the average payments per specialist were the highest in Tohoku region ($15,057), followed by Chugoku (the western part of main Japanese islands, $13,980) and Kyusyu regions ($13,394).

**Discussion**

This study demonstrated that a total $17,717,264 personal payments, equal to 1.8% of all payments were distributed to the board-certified infectious disease specialists over the period of four years in Japan. Among all Japanese board-certified infectious disease specialists, 65.4% (1,055 out of 1,614) of the specialists received an average of $16,794 and a median of $3,183 personal payments from 78 pharmaceutical companies between 2016 and 2019. The payments per specialist and proportion of specialists with at least one payment remained stable between 2016 and 2019.

First, this study found that there were substantial financial relationships among the board-certified infectious disease specialists and pharmaceutical companies in Japan. Although the prevalence of specialists with payments were similar to the previous findings, ranging from 62.0% among hematologists to 70.6% among medical oncologists[3, 4, 15, 23], payment values per specialist among the infectious disease
specialists ($3,183 in median four-year combined payments and $1,430–$1,720 in median single-year payments) were higher than all of the available evidence among pediatric oncologists ($2,961 in average)[23], pulmonologists ($2,210 in median)[3], hematologists ($2,471 in median)[23], and medical oncologists ($1,103 in one-year median)[15] in Japan. Overall, compared to the previous studies, Japanese infectious disease specialists have higher financial relationships with pharmaceutical companies.

Second, we found that the payment values and prevalence of specialists with payments did not significantly change between 2016 and 2019. Kusumi et al. found that the pharmaceutical companies increasingly prioritized the payments to hematologists in Japan, with a 11.2% annual increase in payments per specialist.[4] Also, similar trends were observed by Murayama et al. among Japanese pulmonologists, with 7.8% annual increase in payments.[3] Our finding was different from these studies, indicating that the financial relationships among infectious disease specialists and pharmaceutical companies did not decline nor increase, but remained stable for the last four years. Although we found that there were many drugs newly approved or gained additional indications for infectious diseases, the Japanese government now recommends physicians to refrain from using new antibiotics to prevent antimicrobial-resistant
bacteria. This trend in payments might be due to the demand for fewer use of new antibiotics.

Furthermore, we found that vast majority of payments disproportionately concentrated only on a small portion of the infectious disease specialists in Japan. Surprisingly, a small portion of the specialists included authoritative specialists such as leaders of the Association and other medical societies. For example, the specialist with the largest payments ($711,965) was in various authoritative positions such as a full professor at a private medical university and a very influential television commentator for infectious disease.[11] Also, he was the current executive member of the Association and other medical societies.

The specialist with the second-largest payments ($421,678) was also in authoritative positions such as a full professor at a national university and an executive or council member at several medical societies, including the Association, and the Japanese Respiratory Society. He also served on public authorities as an author of the clinical guidelines for COVID-19 issued by the Japanese Ministry of Health, Labor and Welfare[7] and as a member of government scientific advisory committee.

The specialist with the fourth largest payments ($318,565) was the former president of
the Association who served from 2017 to 2020. He was also a current executive member of the Association and the deputy chairperson of the Japanese government COVID-19 scientific advisory board, but his COI was not publicly disclosed by neither the Association nor the Japanese government.[10]

The receipt of substantial personal payments by executive members of medical societies was widely prevalent in Japan and other countries such as the US. Saito et al. found that 86.9% of Japanese executive members received a median of $7,486 personal payments in 2016, and especially members specialized in internal medicine had higher financial relationships with pharmaceutical companies.[24] Moynihan et al. elucidated that 72% of the US influential medical society leaders had financial ties with pharmaceutical companies,[25] and that 93% of the leaders of Infectious Diseases Society of America received $31,805 in median total payments for six years, where the payments were the most prevalent of ten influential medical societies in the US.[25] Although we did not evaluate financial relationships during the tenure of the board membership, our findings indicated that the current board members of Japanese Association for Infectious Diseases had much larger financial relationships with pharmaceutical companies over the past several years, with 3.2 times higher median annual payments than those among
board members of other Japanese medical societies or at least 4.5 times higher median annual payment values than that of the Infectious Diseases Society of America.

A number of studies have shown that financial relationships with pharmaceutical companies influence physicians' behavior in prescribing drugs,[26-30] recommending clinical guidelines,[5, 8, 31-33] and commenting on drugs in pharmaceutical advisory committees.[34-37] Pharmaceutical companies sometimes spend more payments for marketing less effective and less advantageous drugs[38, 39] but with more harms to patients.[40, 41] Despite these influences, the trends of the physicians' acceptance of personal payments from industries are still common[17, 42, 43] and are even increasing in several specialties.[3, 4, 23, 44] More transparency is required to reduce the undue influences of financial relationships with pharmaceutical companies on physician behaviors and potentially patients care,[28, 45] to increase trust in healthcare, and to provide patients with more information about their treatment.[46-49] However, there is no consensus on how to manage the financial relationships, and how to increase independency of healthcare professionals toward their primary interest of treating patients based on their best knowledge and conscience.[50] Restriction of these personal payments to the specialists to a certain degree would be a simple and reasonable
solution, but it is equally hard to implement by the professional medical societies when many of the society board members and societies themselves are financially tied to pharmaceutical companies. In the case of the Association, financial COIs self-declared by the board members were not publicly disclosed, and there was no restriction of the financial relationships among pharmaceutical companies and the board-certified specialists as of now.

This analysis has few limitations. As we previously noted, our manual collection of payment data from 92 pharmaceutical companies’ webpages might have included unavoidable human errors, despite our careful cross-checks to exclude duplicate physicians from the data. Second, currently, pharmaceutical companies do not disclose their payments concerning meals, beverages, accommodations, travel and stock ownerships, according to the JPMA guidance. This could have underestimated the extent and prevalence of overall financial relationships among the specialists and industries. Third, the data disclosed by the Association and pharmaceutical companies did not provide us many of detailed demographics of the specialists such as the specialists’ gender, affiliation characteristics, positions within their affiliations, and their academic and clinical performances. Therefore, there would have been influence of
many unavoidable confounders on the personal payments at individual specialist level.

However, our robust statistical analysis with GEE modeling has helped nullify effects of such confounders to some extent. Still, further studies should have elucidated the relations among the specialists’ characteristics and the personal payments. Finally, this study was based on the open-access payment data and Japanese board-certified infectious disease specialists. Thus, the payment magnitude and trend may not be exactly replicable to other countries’ specialists. However, this might serve as a pathway for prospective researchers to explore the same in other countries as well.

Conclusion

The majority of the certified infectious disease specialists received substantial personal payments for the reimbursements of lecturing, consulting and writing from the pharmaceutical companies in Japan. These financial relationships with those companies remained stable for the past four years in Japan. Furthermore, high ranked specialists such as those in the executive board had stronger financial ties with the companies. Such personal payments must be restricted to a certain level to avoid potential conflict of interest.
Acknowledgment

The authors thank the Tansa (formerly known as Waseda Chronicle) for providing payment data. Also, we appreciate Mr. Souto Nagano, an undergraduate student from the Faculty of Letters, University of Tokyo; Mr. Kohki Yamada, a medical student at the Osaka University School of Medicine; Mr. Takuto Sakaemura, an undergraduate student from Faculty of Applied Science, Simon Fraser University; and Ms. Megumi Aizawa, a graduate student from the Department of Industrial Engineering and Economics, School of Engineering, Tokyo Institute of Technology, for their dedicated contributions on collecting and cross-checking the payment data.

References

1. Agrawal S, Brennan N, Budetti P. The Sunshine Act--effects on physicians. N Engl J Med 2013; 368(22): 2054-7.
2. Pham-Kanter G. Act II of the Sunshine Act. PLoS Med 2014; 11(11): e1001754.
3. Murayama A, Hoshi M, Saito H, et al. Nature and Trends of Pharmaceutical Payments to Board Certificated Respiratory Specialists in Japan between 2016 and 2019. medRxiv 2022: 2022.01.16.22269188.
4. Kusumi E, Murayama A, Kamamoto S, et al. Pharmaceutical Payments to Japanese Certificated Hematologists: A Retrospective Analysis of Personal Payments from Pharmaceutical Companies between 2016 and 2019. medRxiv 2022: 2022.01.17.22269284.
5. Murayama A, Kida F, Ozaki A, Saito H, Sawano T, Tanimoto T. Financial and Intellectual Conflicts of Interest Among Japanese Clinical Practice Guidelines Authors for Allergic Rhinitis. Otolaryngol Head Neck Surg 2021; 0(0): 1945998211034724.
6. Kida F, Murayama A, Saito H, Ozaki A, Shimada Y, Tanimoto T. Pharmaceutical company payments to authors of the Japanese Clinical Practice Guidelines for Hepatitis C treatment. Liver International 2021; 41(3): 464-9.
7. Hashimoto T, Murayama A, Mamada H, Saito H, Tanimoto T, Ozaki A. Evaluation of Financial Conflicts of Interest and Drug Statements in the Coronavirus Disease 2019 Clinical Practice Guideline in Japan. Clin Microbiol Infect 2021.

8. Johnson L, Stricker RB. Attorney General forces Infectious Diseases Society of America to redo Lyme guidelines due to flawed development process. J Med Ethics 2009; 35(5): 283-8.

9. Saito H, Tani Y, Ozaki A, et al. Financial ties between authors of the clinical practice guidelines and pharmaceutical companies: an example from Japan. Clin Microbiol Infect 2019; 25(11): 1304-6.

10. Mamada H, Murayama A, Ozaki A, et al. Financial and Non-financial Conflicts of Interest Among the Japanese Government Advisory Board Members Concerning Coronavirus Disease 2019. medRxiv 2021.

11. Murayama A, Ozaki A, Saito H, Sawano T, Sah R, Tanimoto T. Coronavirus disease 2019 experts appearing on Japanese television: their characteristics and financial conflicts of interest with pharmaceutical companies. Clinical Microbiology and Infection 2020.

12. Koike S, Matsumoto M, Ide H, Kawaguchi H, Shimpo M, Yasunaga H. Internal medicine board certification and career pathways in Japan. BMC Medical Education 2017; 17(1): 83.

13. Pharmaceuticals and Medical Devices Agency. List of approved products. Available at: https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html. Accessed February 24.

14. Murayama A, Ozaki A, Saito H, et al. Pharmaceutical company payments to dermatology Clinical Practice Guideline authors in Japan. PLoS One 2020; 15(10): e0239610.

15. Ozaki A, Saito H, Onoue Y, et al. Pharmaceutical payments to certified oncology specialists in Japan in 2016: a retrospective observational cross-sectional analysis. BMJ Open 2019; 9(9): e028805.

16. Saito H, Ozaki A, Sawano T, Shimada Y, Tanimoto T. Evaluation of Pharmaceutical Company Payments and Conflict of Interest Disclosures Among Oncology Clinical Practice Guideline Authors in Japan. JAMA Netw Open 2019; 2(4): e192834.

17. Tarras ES, Marshall DC, Rosenzweig K, Korenstein D, Chimonas S. Trends in Industry Payments to Medical Oncologists in the United States Since the Inception of the Open Payments Program, 2014 to 2019. JAMA Oncology 2021; 7(3): 440-4.

18. Tringale KR, Marshall D, Mackey TK, Connor M, Murphy JD, Hattangadi-Gluth JA. Types and Distribution of Payments From Industry to Physicians in 2015. JAMA 2017; 317(17): 1774-84.

19. Tringale KR, Hattangadi-Gluth JA. Types and Distributions of Biomedical Industry Payments to Men and Women Physicians by Specialty, 2015. JAMA Intern Med 2018; 178(3): 421-3.

20. Feng H, Wu P, Leger M. Exploring the Industry-Dermatologist Financial Relationship: Insight From the Open Payment Data. JAMA Dermatol 2016; 152(12): 1307-13.
21. Yamamoto K, Murayama A, Ozaki A, Saito H, Sawano T, Tanimoto T. Financial conflicts of interest between pharmaceutical companies and the authors of urology clinical practice guidelines in Japan. Int Urogynecol J 2021; 32(2): 443-51.

22. Ozieranski P, Csanadi M, Rickard E, Thilingerian J, Mulinari S. Analysis of Pharmaceutical Industry Payments to UK Health Care Organizations in 2015. JAMA Netw Open 2019; 2(6): e196253.

23. Kusumi E, Murayama A, Kamamoto S, et al. Pharmaceutical Payments to Japanese Certificated Pediatric Hematologist/Oncologists: a cross-sectional analysis of personal payments from pharmaceutical companies between 2016 and 2019. Authorea Preprints 2022.

24. Saito H, Ozaki A, Kobayashi Y, Sawano T, Tanimoto T. Pharmaceutical Company Payments to Executive Board Members of Professional Medical Associations in Japan. JAMA Intern Med 2019; 179(4): 578-80.

25. Moynihan R, Albarqouni L, Nangla C, Dunn AG, Lexchin J, Bero L. Financial ties between leaders of influential US professional medical associations and industry: cross sectional study. BMJ 2020; 369: m1505.

26. Perlis RH, Perlis CS. Physician Payments from Industry Are Associated with Greater Medicare Part D Prescribing Costs. PLOS ONE 2016; 11(5): e0155474.

27. DeJong C, Aguilar T, Tseng C-W, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical Industry-Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries. JAMA Internal Medicine 2016; 176(8): 1114-22.

28. Mitchell AP, Trivedi NU, Gennarelli RL, et al. Are Financial Payments From the Pharmaceutical Industry Associated With Physician Prescribing? : A Systematic Review. Ann Intern Med 2020.

29. Goupil B, Balusson F, Naudet F, et al. Association between gifts from pharmaceutical companies to French general practitioners and their drug prescribing patterns in 2016: retrospective study using the French Transparency in Healthcare and National Health Data System databases. BMJ 2019; 367: l6015.

30. Inoue K, Figueroa JF, DeJong C, et al. Association Between Industry Marketing Payments and Prescriptions for PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibitors in the United States. Circulation: Cardiovascular Quality and Outcomes 2021; 14(5): e007521.

31. Nejstgaard CH, Bero L, Hrobjartsson A, et al. Association between conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: systematic review. BMJ 2020; 371: m4234.

32. Coyne DW. Influence of Industry on Renal Guideline Development. Clinical Journal of the American Society of Nephrology 2007; 2(1): 3-7.

33. Steinbrook R. Guidance for guidelines. N Engl J Med 2007; 356(4): 331-3.

34. Arthur W, Austin J, Wayant C, Vassar M. Association of Conflicts of Interest for Public Speakers
for the Peripheral and Central Nervous System Drugs Advisory Committee of the US Food and Drug Administration With Their Statements. JAMA Neurology 2019; 76(3): 368-9.

35. Bickford T, Kinder N, Arthur W, Wayant C, Vassar M. The Potential Effects of Financial Conflicts of Interest of Speakers at the US Food and Drug Administration’s Pulmonary-Allergy Drug Advisory Committee Meetings. Chest 2021; 159(6): 2399-401.

36. Johnson BS, Roberts W, Riddle J, Wayant C, Scott J, Vassar M. Potential Financial Bias From Speakers at US Food and Drug Administration’s Bone, Reproductive, and Urologic Drugs Advisory Committee Meetings. Urology 2020; 137: 1-6.

37. Cooper CM, Jellison S, Vassar M. Characteristics of Open Public Hearing Speakers of the Tobacco Products Scientific Advisory Committee meetings. Tob Prev Cessat 2018; 4: 35-.

38. Greenway T, Ross JS. US drug marketing: how does promotion correspond with health value? Bmj 2017; 357: j1855.

39. Lexchin J. The relation between promotional spending on drugs and their therapeutic gain: a cohort analysis. CMAJ Open 2017; 5(3): E724-e8.

40. Eichacker PQ, Natanson C, Danner RL. Surviving Sepsis — Practice Guidelines, Marketing Campaigns, and Eli Lilly. New England Journal of Medicine 2006; 355(16): 1640-2.

41. Mitchell AP, Winn AN, Dusetzina SB. Pharmaceutical Industry Payments and Oncologists' Selection of Targeted Cancer Therapies in Medicare Beneficiaries. JAMA Intern Med 2018; 178(6): 854-6.

42. Marshall DC, Tarras ES, Rosenzweig K, Korenstein D, Chimonas S. Trends in Industry Payments to Physicians in the United States From 2014 to 2018. JAMA 2020; 324(17): 1785-8.

43. Ahlawat A, Narayanaswami P. Financial relationships between neurologists and industry. Neurology 2019; 92(21): 1006.

44. Putman MS, Goldsher JE, Crowson CS, Duarte-García A. Industry Payments to Practicing US Rheumatologists, 2014–2019. Arthritis & Rheumatology 2021; 73(11): 2138-44.

45. Ozaki A, Murayama A, Saito H, et al. Transparency Is Not Enough: How Can We Improve the Management of Financial Conflicts of Interest Between Pharma and Healthcare Sectors? Clin Pharmacol Ther 2020.

46. Kanter GP, Carpenter D, Lehmann LS, Mello MM. US Nationwide Disclosure of Industry Payments and Public Trust in Physicians. JAMA Network Open 2019; 2(4): e191947-e.

47. Lopez J, Naved BA, Pradeep T, et al. What Do Plastic Surgery Patients Think of Financial Conflicts of Interest and the Sunshine Act? Annals of Plastic Surgery 2019; 82(6): 597-603.

48. Kanter GP, Carpenter D, Lehmann L, Mello MM. Effect of the public disclosure of industry payments information on patients: results from a population-based natural experiment. BMJ Open 2019; 9(2): e024020.

49. Stein GE, Kamlер JJ, Chang JS. Ophthalmology Patient Perceptions of Open Payments
Information. JAMA Ophthalmology 2018; 136(12): 1375-81.

50. Moynihan R, Bero L, Hill S, et al. Pathways to independence: towards producing and using trustworthy evidence. BMJ 2019; 367: l6576.
Table 1. Summary of personal payments from Japanese pharmaceutical companies to infectious disease specialists certified by the Japanese Association for Infectious Disease between 2016 and 2019

| Variables                          | Total          | Average per specialist (SD) | Median per specialist (IQR) | Range               |
|-----------------------------------|----------------|----------------------------|-----------------------------|---------------------|
|                                   |                |                            |                             |                     |
| Payment values, US$               | 17,784,070     | 16,857 (45,010)            | 3,183 (938 to 11,250)       | 31 to 711,965       |
| Cases, n                          | 21,680         | 20.5 (41.6)                | 6.0 (2.0 to 19.0)           | 1.0 to 538.0        |
| Companies, n                      | 78             | 5.6 (5.2)                  | 4.0 (2.0 to 8.0)            | 1.0 to 29.0         |
| Physicians with specific payments, n (%) |                |                            |                             |                     |
| Any payments                      | 1,055 (65.4)   |                            |                             |                     |
| Payments >US$500                  | 930 (57.6)     |                            |                             |                     |
| Payments >US$1,000                | 776 (48.1%)    |                            |                             |                     |
| Payments >US$5,000                | 419 (26.0%)    |                            |                             |                     |
| Payments >US$10,000               | 290 (18.0%)    |                            |                             |                     |
| Payments >US$50,000               | 82 (5.1%)      |                            |                             |                     |
| Payments >US$100,000              | 43 (2.7%)      |                            |                             |                     |
| Gini index                        | 0.857          |                            |                             |                     |
| Category of payments              |                |                            |                             |                     |
| Lecturing                         |                |                            |                             |                     |
| Payment value, US$ (%)            | 14,607,478 (82.1) |                            |                             |                     |
| Cases, n (%)                      | 18,078 (83.1)  |                            |                             |                     |
| Consulting                        |                |                            |                             |                     |
| Payment value, US$ (%)            | 1,981,003 (11.1) |                            |                             |                     |
| Cases, n (%)                      | 2,122 (9.8)    |                            |                             |                     |
| Writing                           |                |                            |                             |                     |
| Payment value, US$ (%)            | 797,929 (4.5)  |                            |                             |                     |
| Cases, n (%)                      | 1,086 (5.0)    |                            |                             |                     |
| Other                             |                |                            |                             |                     |
| Payment value, US$ (%)            | 397,659 (2.2)  |                            |                             |                     |
| Cases, n (%)                      | 459 (2.1)      |                            |                             |                     |
Table 2. Trends of personal payments from Japanese pharmaceutical companies to infectious disease specialists certified by the Japanese Association for Infectious Disease between 2016 and 2019

| Variables | 2016       | 2017       | 2018       | 2019       | Average yearly change (95%CI), % | p-value | Combined total |
|-----------|------------|------------|------------|------------|---------------------------------|---------|----------------|
| **All pharmaceutical companies** |            |            |            |            |                                 |         |                |
| Total payments, US$ | 4,662,217   | 4,215,566  | 4,538,520  | 4,367,767  |                                 |         | 17,784,070    |
| Average payments (SD), US$ | 6,134 (15,283) | 5,775 (13,410) | 6,108 (13,324) | 6,033 (11,837) | -1.2 (-4.7 to 2.3) | 0.49    | 16,857 (45,010) |
| Median payments (IQR), US$ | 1,604 (511-5,646) | 1,430 (511-5,431) | 1,737 (642-5,286) | 1,554 (662-5,258) | 3,183 (938-11,250) |         |                |
| Payment range, US$ | 92-216,035  | 92-160,610  | 95-190,726  | 31-144,593  |                                 |         | 31-711,965    |
| **Pharmacists with specific payments, n (%)** |            |            |            |            |                                 |         |                |
| Any payments | 760 (47.1%) | 730 (45.2%) | 743 (46.0%) | 724 (44.9%) | -1.3 (-2.9 to 0.4) | 0.13    | 1,055 (65.4%) |
| Payments >US$500 | 612 (37.9%) | 594 (36.8%) | 628 (38.9%) | 616 (38.2%) | 0.8 (-1.1 to 2.6) | 0.43    | 930 (57.6%)   |
| Payments >US$1,000 | 482 (29.9%) | 436 (27.0%) | 485 (30.0%) | 453 (28.1%) | -0.8 (-2.9 to 1.3) | 0.45    | 776 (48.1%)   |
| Payments >US$5,000 | 175 (10.8%) | 178 (11.0%) | 193 (12.0%) | 187 (11.6%) | 2.8 (-0.8 to 6.5) | 0.13    | 419 (26.0%)   |
| Payments >US$10,000 | 106 (6.6%) | 94 (5.8%) | 113 (7.0%) | 103 (6.4%) | 1.0 (-3.6 to 5.7) | 0.68    | 290 (18.0%)   |
| Payments >US$50,000 | 16 (1.0%) | 14 (0.9%) | 17 (1.1%) | 14 (0.9%) | -1.9 (-15.9 to 14.5) | 0.80    | 82 (5.1%)     |
| Payments >US$100,000 | 4 (0.2%) | 3 (0.2%) | 1 (0.1%) | 2 (0.1%) | -28.3 (-52.4 to 8.1) | 0.11    | 43 (2.7%)     |
| Gini index | 0.878 | 0.881 | 0.870 | 0.876 | 0.860 | 0.860 |

Pharmaceutical companies with four-year payment data: 4,597,653 4,205,920 4,492,988 4,314,421 17,610,982

| Variables | 2016       | 2017       | 2018       | 2019       | Average yearly change (95%CI), % | p-value | Combined total |
|-----------|------------|------------|------------|------------|---------------------------------|---------|----------------|
| Total payments, US$ | 6,074 (15,169) | 5,562 (13,383) | 6,105 (13,312) | 5,992 (12,825) | -1.3 (-4.7 to 2.3) | 0.48    | 16,788 (44,820) |
| Median payments (IQR), US$ | 1,603 (511-4,642) | 1,430 (511-4,525) | 1,737 (613-5,280) | 1,552 (662-5,258) | 3,183 (923-11,238) |         |                |
| Payment range, US$ | 92-215,089  | 92-160,610  | 95-190,726  | 31-143,571  |                                 |         | 31-709,997    |
| **Pharmacists with specific payments, n (%)** |            |            |            |            |                                 |         |                |
| Any payments | 757 (46.9%) | 730 (45.3%) | 736 (45.6%) | 720 (44.6%) | -1.4 (-3.1 to 0.2) | 0.093   | 1,049 (65.0) |
| Payments >US$500 | 609 (37.7%) | 593 (36.7%) | 620 (38.4%) | 610 (37.8%) | 0.5 (-1.4 to 2.4) | 0.60    | 927 (57.4)   |
| Payments >US$1,000 | 478 (29.6%) | 436 (27.0%) | 481 (29.8%) | 452 (28.0%) | -0.7 (-2.8 to 1.4) | 0.51    | 768 (47.6)   |
| Payments >US$5,000 | 172 (10.7%) | 179 (11.1%) | 191 (11.8%) | 186 (11.5%) | 3.1 (-0.6 to 6.8) | 0.10    | 415 (25.7)   |
| Payments >US$10,000 | 106 (6.6%) | 94 (5.8%) | 112 (7.1%) | 103 (6.4%) | 0.9 (-3.7 to 5.6) | 0.71    | 289 (17.9)   |
| Payments >US$50,000 | 14 (0.9%) | 14 (0.9%) | 17 (1.1%) | 14 (0.9%) | 0.0 (-13.7 to 15.9) | 1.0     | 82 (5.1)     |
| Payments >US$100,000 | 4 (0.2) | 3 (0.2) | 1 (0.1) | 2 (0.1) | -28.3 (-52.4 8.1) | 0.11 | 42 (2.6) |
|----------------------|---------|---------|---------|---------|-------------------|-------|---------|
| Gini index           | 0.879   | 0.881   | 0.871   | 0.876   |                   |       | 0.860   |

IQR: interquartile range; SD: standard deviation
Figure 1. Total payment by company
Supplemental Material 1. Distribution of payment values per specialist

![Graphs by year](image-url)

| Year | Payment Year | Number of Infectious Disease Specialists |
|------|--------------|------------------------------------------|
| 2016 | 2017         |                                           |
| 2018 | 2019         |                                           |
Supplemental Material 2. Payment concentration

![Graph showing cumulative percent of total payments vs. percent of infectious disease specialists.](image-url)
Supplemental Material 3. Payment category by company
### Supplemental Material 4. New and additional indications for infectious diseases in Japan between 2015 and 2019

| Brand name | Name | Pharmaceutical companies | Approval date | Price per drug unit, US$* | Indication | Category |
|------------|------|--------------------------|--------------|---------------------------|------------|----------|
| ZERBAXA   | Ceftolozane sulfate/Tazobactam sodium | Manufacturer and distributor: MSD K. K | December 20, 2019 | $59 (1.5g/bottle) | Treatment of sepsis and pneumonia caused by Serratia and Hemophilus influenzae | Additional indication |
| LASVIC    | Lascufloxacin hydrochloride | Manufacturer and distributor: Kyorin Pharmaceuticals | September 20, 2019 | $3 (75mg/pill) $37 (150mg/ intravenous infusion kit) | Treatment of laryngopharyngitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory disease, otitis media and sinusitis | New approval |
| MAVIRET   | Glecaprevir hydrate/Pibrentasvir | Manufacturer and distributor: AbbVie GK | August 22, 2019 | $168/pill | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C | Additional indication |
| AZIMYCIN  | Azithromycin hydrate | Manufacturer and distributor: Senju Pharmaceuticals Distributor: Takeda Pharmaceutical | June 18, 2019 | $3 (1%1ml eye-drops) | Treatment of conjunctivitis, blepharitis, hordeolum and dacyrocystitis | New approval |
| SYMTUZA   | Darunavir ethanolate/Cobicistat/Emtricitabine/Tenofovir alafenamide fumarate | Manufacturer and distributor: Janssen Pharmaceutical K. K | June 18, 2019 | $44/pill | Treatment of HIV-1 infection | New approval |
| INAVIR    | Laninamivir octanoate hydrate | Manufacturer and distributor: Daiichi Sankyo | June 18, 2019 | $20 (20mg/inhalation kit) $39 (160mg/bottle) | Treatment of influenza A or B virus infection | New approval |
| GENVOYA   | Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide fumarate | Manufacturer and distributor: Gilead Sciences | May 22, 2019 | $65/pill | Treatment of HIV-1 infection | Additional indication |
| BIKTARVY  | Bictegravir sodium/Emtricitabine/Tenofovir alafenamide fumarate | Manufacturer and distributor: Gilead Sciences | March 26, 2019 | $65/pill | Treatment of HIV-1 infection | New approval |
| ZERBAXA   | Ceftolozane sulfate/Tazobactam sodium | Manufacturer and distributor: MSD K. K | January 8, 2019 | $59 (1.5g/bottle) | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C who have previously been treated. Improvement of viremia in patients with decompensated cirrhosis type C | New approval |
| EPCLUSA   | Sofosbuvir/Velpatasvir | Manufacturer and distributor: Gilead Sciences | January 8, 2019 | $562/pill | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C who have previously been treated. Improvement of viremia in patients with decompensated cirrhosis type C | New approval |
| REBETROL  | Ribavirin | Manufacturer and distributor: ViV Healthcare Distributor: GlaxoSmithKline K. K Promotional partner: Shionogi | January 8, 2019 | $4 (200mg) | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C who have previously been treated | Additional indication |
| JULUCA    | Dolutegravir sodium/Rilpivirine hydrochloride | Manufacturer and distributor: ViV Healthcare | November 26, 2018 | $50/pill | Treatment of HIV-1 infection | New approval |
| Brand Name | Drug Name | Manufacturer and distributor | Approval Date | Price | Indication |
|------------|-----------|------------------------------|---------------|-------|------------|
| **ODEFSEY** | Rilpivirine hydrochloride/Emtricitabine/Tenofovir alafenamide fumarate | Manufacturer and distributor: Janssen Pharmaceutical K. K | August 21, 2018 | $56/pill | Treatment of HIV-1 infection | New approval |
| **ISENTRESS** | Raltegravir potassium | Manufacturer and distributor: MSD K. K | May 14, 2018 | $15 (400mg/pill) $15 (600mg/pill) | Treatment of HIV infection | New approval |
| **KAKETSUKEN** | Emulsion-adjuvanted cell-culture derived influenza HA vaccine (H5N1) | Manufacturer and distributor: The Chemo-Sero-Therapeutic Research Institute | March 23, 2018 | NA | Prevention of pandemic influenza (H5N1) | Additional indication |
| **KAKETSUKEN** | Emulsion-adjuvanted cell-culture derived influenza HA vaccine (prototype) | Manufacturer and distributor: The Chemo-Sero-Therapeutic Research Institute | March 23, 2018 | NA | Prevention of pandemic influenza | Additional indication |
| **XOFLUZA** | Baloxavir marboxil | Manufacturer and distributor: Shionogi | February 23, 2018 | $14 (10mg/pill) $22 (20mg/pill) | Treatment of influenza A or B virus infections | New approval |
| **HARVONI** | Ledipasvir acetonate/Sofosbuvir | Manufacturer and distributor: Gilead Sciences | February 16, 2018 | $509/pill | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in serogroup 2 | Additional indication |
| **ZINPLAVA** | Bezlotoxumab | Manufacturer and distributor: MSD K. K | September 27, 2017 | $3081 (625mg/25ml bottle) | Prevention of recurrent Clostridium difficile infection | New approval |
| **MAVIRET** | Glecaprevir hydrate/Pibrentasvir | Manufacturer and distributor: AbbVie GK | September 27, 2017 | $168/pill | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C | New approval |
| **TAMIFLU** | Oseltamivir phosphate | Manufacturer and distributor: Chugai Pharmaceutical | March 24, 2017 | $2 (75mg/pill) $2 (3%/g dry syrup) | Treatment of influenza A or B virus infection | Additional indication |
| **SOVALDI** | Sofosbuvir | Manufacturer and distributor: Gilead Sciences | March 24, 2017 | $395 (400mg/pill) | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in neither Serogroup 1 (genotype 1) nor Serogroup 2 (genotype 2) | Additional indication |
| **REBETOL** | Ribavirin | Manufacturer and distributor: MSD K. K | March 24, 2017 | $4 (200mg/pill) | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in neither Serogroup 1 (genotype 1) nor Serogroup 2 (genotype 2) | Additional indication |
| **OZEX** | Tosufloxacin tosylate hydrate | Manufacturer and distributor: Fujifilm Toyama Chemical | March 2, 2017 | $1.1 (60mg/pill) $0.5 (75mg/pill) $0.6 (150mg/pill) $1.2 (0.3%/ml eye-drops) | Treatment of mycoplasma pneumonia caused by Mycoplasma pneumoniae | Additional indication |
| **RIAMET** | Artemether/Lumefantrine | Manufacturer and distributor: Novartis Pharma K. K | December 19, 2016 | $2/pill | Treatment of malaria | New approval |
| **VAXEM HIB** | Hemophilus influenzae type b vaccine adsorbed | Manufacturer and distributor: Takeda Pharmaceutical | December 19, 2016 | NA | Prophylaxis of Hemophilus influenzae type b infections | Additional indication |
| **XIMENCY** | Daclatasvir hydrochloride/Asunaprevir/Beclabuvir hydrochloride | Manufacturer and distributor: Bristol Myers Squibb | December 19, 2016 | $99/pill | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in serogroup 1 (genotype 1) | New approval |
| **DESCOY** | Emtricitabine/ Tenofovir alafenamide fumarate | Manufacturer and distributor: Gilead Sciences | December 9, 2016 | New approval |
| **PREZCOBIX** | Darunavir ethanolate/ Cobicistat | Manufacturer and distributor: Janssen Pharmaceutical K. K | November 22, 2016 | Treatment of HIV infection |
| **ERELSA** | Elbasvir | Manufacturer and distributor: MSD K. K | September 28, 2016 | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in serogroup 1 (genotype 1) |
| **VIEKIRAX** | Ombitasvir hydrate/ Paritaprevir hydrate/ Ritonavir | Manufacturer and distributor: AbbVie GK | September 28, 2016 | Improvement of viremia in patients with chronic hepatitis C in serogroup 2 (genotype 2) |
| **GRAZYNIA** | Grazoprevir hydrate | Manufacturer and distributor: MSD K. K | September 28, 2016 | Improvement of viremia in patients with chronic hepatitis C in serogroup 2, Additional indication |
| **REBETOL** | Ribavirin | Manufacturer and distributor: MSD K. K | September 28, 2016 | Improvement of viremia in patients with chronic hepatitis C in serogroup 2, Additional indication |
| **INAVIR** | Laninamivir octanoate hydrate | Manufacturer and distributor: Daiichi Sankyo | August 26, 2016 | Prophylaxis of influenza A or B virus infections |
| **GENVOYA** | Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir alafenamide fumarate | Manufacturer and distributor: Gilead Sciences | June 17, 2016 | Treatment of HIV-1 infection |
| **MALARONE** | Atovaquone/Proguanil hydrochloride | Manufacturer and distributor: GlaxoSmithKline K. K | March 28, 2016 | Treatment and prevention of malaria |
| **PRIMAQUEINE** | Primaquine phosphate | Manufacturer and distributor: Sanofi S.A. | March 28, 2016 | Treatment of malaria caused by Plasmodium vivax and P. ovale |
| **Biken** | Freeze-dried live attenuated varicella vaccine | Manufacturer and distributor: The Research Foundation for Microbial Diseases of Osaka University | March 18, 2016 | Prevention of herpes zoster in individuals 50 years of age and older |
| **KITASATO DAIIICHI SANKYO** | Adsorbed cell culture-derived influenza vaccine (H5N1) | Manufacturer and distributor: Daiichi Sankyo Distributor: Kitasato Pharmaceutical Industry | March 18, 2016 | Prevention of pandemic influenza (H5N1) |
| **TRIBIK** | Adsorbed diphtheria-purified pertussis-tetanus combined vaccine | Manufacturer and distributor: The Research Foundation for Microbial Diseases of Osaka University Distributor: Mitsubishi Tanabe Pharma Corporation | February 29, 2016 | Prevention of pertussis, diphtheria and tetanus |
| **VAXEM HIB** | Hemophilus influenzae type b | Manufacturer and distributor: | January 22, 2016 | Prophylaxis of Hemophilus influenzae type b |

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| Brand | Manufacturer and distributor | Approval Date | Price | Indications |
|-------|------------------------------|---------------|-------|-------------|
| REMICADE | Infliximab | December 21, 2015 | $648 (100mg bottle) | Treatment of acute-phase Kawasaki's disease in patients who have not responded sufficiently to conventional therapies |
| VIEKIRAX | Ombitasvir hydrate/Paritaprevir hydrate/Ritonavir | September 28, 2015 | $204/pill | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in serogroup 1 (genotype 1) |
| CIPROXAN | Ciprofloxacin | September 24, 2015 | $0.3 (100mg/pill) $0.4 (200mg/pill) $17 (200mg/100ml) $21 (300mg/150ml) $19 (400mg/200ml) | Treatment of sepsis, pneumonia, etc. |
| HARVONI | Ledipasvir acetone/Sofosbuvir | July 3, 2015 | $509/pill | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in serogroup 1 (genotype 1) |
| DIFLUCAN | Fluconazole | May 26, 2015 | $3 (50mg capsule) $4 (100mg capsule) $17 (0.1% 50ml bottle) $22 (0.2% 50ml bottle) $36 (0.2% 100ml bottle) | Treatment of vaginitis and vulvovaginitis caused by Candida |
| ALDREB | Colistin sodium methanesulfonate | March 26, 2015 | $77 (150mg bottle) | Treatment of infections caused by colistin-sensitive Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Pseudomonas aeruginosa and Acinetobacter |
| SYNFLORIX | Pneumococcal 10-valent conjugate vaccine adsorbed | March 26, 2015 | NA | Prophylaxis of pneumonia and pneumococcal invasive diseases |
| KAKETSUKEN | Cell culture-derived influenza emulsion HA vaccines (prototype) | March 26, 2015 | NA | Prevention of pandemic influenza |
| SOVALDI | Sofosbuvir | March 26, 2015 | $395 (400mg pill) | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in serogroup 2 (genotype 2) |
| COPEGUS | Ribavirin | March 26, 2015 | $6 (200mg/pill) | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in serogroup 2 (genotype 2) |
| DAKLINZA | Daclatasvir hydrochloride | March 20, 2015 | $74 (60mg/pill) | Improvement of viremia in patients with chronic hepatitis C or compensated cirrhosis type C in serogroup 1 (genotype 1) |
| TRIUMEQ | Dolutegravir sodium, Abacavir sulfate, Lamivudine | March 16, 2015 | $64/pill | Treatment of HIV infection |

Note: Additional indication indicates the use of the drug for an indication not certified by peer review.
| VENOGLOBULIN | Polyethylene glycol treated human normal immunoglobulin | Manufacturer and distributor: Japan Blood Products Organization | February 2, 2015 | $347 (5g/100ml bottle) $702 (10g/200ml bottle) | Prevention of acute otitis media, acute bronchitis, or pneumonia caused by Pneumococcus or Hemophilus influenzae in patients associated with a decrease in serum IgG2 levels | Additional indication |

*Price per drug was converted into US dollars using the 2019 average monthly exchange rates of ¥109.0 per $1.

Price per drug was used as of February 19, 2022.

Drug price for vaccines was not determined and was open priced in Japan. So, it was not available.
Supplemental Material 5. Geographical characteristics of payment distribution
5A: The number of infectious disease specialists in 2021; 5B: The number of infectious disease specialists per million population in 2021; 5C: total personal payment values to the infectious disease specialists from 2016 to 2019; 5D: average personal payment values per infectious disease specialist from 2016 to 2019.
