Analysis of Adverse Drug Events in Pulmonary Mycobacterium avium Complex Disease Using Spontaneous Reporting System

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Research Article

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Abstract

Background: In Japan, *Mycobacterium avium* complex lung disease (MAC-LD) is the most common in nontuberculous mycobacterial lung disease. Patients often experience adverse events, resulting in the discontinuation of treatment, which causes treatment failure. The Japanese Adverse Drug Event Report (JADER) database is a database of adverse events and reflects the clinical practice in Japan. We can collect large-scale data cost-effectively and detect signals of potential adverse events such as reporting odds ratio (ROR) by using spontaneous reporting systems.

Methods: We included cases of MAC-LD between April 2004 and June 2017. We investigated sex, age, and medications that may have caused the adverse events, outcomes, and time of onset. We calculated the safety signal index as the ROR. Time-to-event analysis was performed using the Weibull distribution.

Results: The total number of adverse effects of CAM, EB, and RFP was 2780, with 806 patients. In the overall adverse events, hematologic and lymphatic disorders were the most common adverse events, with 11%, followed by eye disorders (10.6%), and hepatobiliary disorders (8.9%). The outcomes were as follows: recovery, 40.1%; remission, 27.1%; non-recovery, 11.2%; and death, 7.2%. Regarding the most common onset time of CAM, EB, and RFP was within 120 days at 40%, 181–300 days at 43.6%, and within 120 days at 88.5%. For CAM, the RORs of infections and infestations, hepatobiliary system disorders, and immune system disorders were 4.13 (95% CI, 2.3–7.44), 2.61 (95% CI, 1.39–4.91), and 2.38 (95% CI, 1.04–5.44). For EB, the ROR of eye disorders was 215.79 (95% CI, 132.62–351.12). For RFP, the RORs of renal and urinary tract disorders and investigations were 7.03 (95% CI, 3.35–14.77) and 6.99 (95% CI, 3.22–15.18). The β value of EB was 2.07 (95% CI, 1.48–2.76), which was classified as wear-out failure type.

Conclusions: For MAC-LD, adverse events of EB occur after 180 days, whereas the adverse events of CAM and RFP occur early in the course of treatment.

Background

The incidence of nontuberculous mycobacterial lung disease (NTM-LD) is increasing worldwide (1). In Japan, *Mycobacterium avium* complex lung disease (MAC-LD) is the most common NTM-LD (2, 3), and its mortality rate is increasing (4). MAC-LD generally progresses slowly in immunocompetent hosts and affects their quality of life (5).

In Japan, CAM, EB, and RFP are the standard regimen for MAC-LD, but this is the result of using the same regimen for *Mycobacterium avium* Complex bacteremia in the late stages of HIV (6, 7). Patients often experience adverse events during long-term chemotherapy for MAC-LD, resulting in the discontinuation of treatment (8–12), which causes treatment failure (13). Therefore, we need to understand the actual situation of adverse events to improve the therapeutic outcome of MAC-LD. But it is difficult to calculate the exact frequency of adverse events because it is hard to follow patients concisely for a long term.

In Japan, since 1967, there has been a system for medical institutions and pharmaceutical sales companies to report adverse events presumed to be caused by drugs to the Ministry of Health, Labour and Welfare. The Japanese Adverse Drug Event Report (JADER) database of the Pharmaceuticals and Medical Devices Agency (PMDA) is a database of adverse events since 2004 and is available on the PMDA website. It has been noted that we can collect large-scale data cost-effectively and detect signals of potential adverse events such as reporting odds ratio (ROR) by using spontaneous reporting systems (14). ROR is the proportion of spontaneous reports about a drug that is related to a specific adverse event divided by the proportion of corresponding adverse events to all other drugs, and we can quantify the safety signals. The JADER database reflects the clinical practice in Japan. Several studies using the JADER database have been reported in various diseases.

Few studies have summarized the adverse event reports of MAC-LD treatment in Japan in general. In this study, we summarized the adverse events of clarithromycin (CAM), ethambutol (EB), and rifampicin (RFP) using the JADER database; investigated sex, age, outcome, and onset; and calculated ROR and Weibull distribution. We aimed to understand the actual adverse events associated with MAC-LD.

Methods

Study population

JADER data were downloaded from the PMDA website (http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp) in November 2018. We included cases of MAC-LD between April 2004 and June 2017. Duplicate data with the same outcome as drugs with the same identification number were excluded. Patients with NTM-LD were excluded from the study because they may include diseases other than MAC-LD. We investigated sex, age, and medications that may have caused the adverse events, outcomes, and time of onset. Patients whose sex, age, and outcomes were not described were considered unknown.

Cases in which only the year was described were excluded. In cases where the year and month were described but the day was not, the day was set to 15.

This study was conducted in accordance with Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases (15).

Statistical Analysis

We calculated the safety signal index as the ROR using the standard method with a 2 × 2 contingency table. If the lower limit of the 95% confidence interval (CI) was greater than 1.0, the drug was considered single-positive. Time-to-event analysis was performed using the Weibull distribution to calculate shape parameter β. The Weibull distribution represents the distribution of failure rates over time and is the estimated failure rate. Failure rate corresponds to the occurrence of adverse events. If $\beta < 1$, the incidence decreases with time and is classified as an early failure type. If $\beta = 1$, the side effect appears at a constant

rate and is classified as an accidental failure type. If $\beta > 1$, the incidence increases with time and is classified as a wear-out failure type.

If the onset of adverse events was more than 1095 days (3 years) after the start of treatment, the onset time was 1095 days. We used JMP 11 (SAS Institute Inc., Cary, NC, USA) for the analysis.

Results

The total number of adverse effects of CAM, EB, and RFP for MAC-LD registered in the JADER database in November 2018 was 2780, with 806 patients. Figure 1 shows the overall sex and age of patients. Males, females, and unknown accounted for 40.6% (327/806), 58.9% (475/806), and 0.4% (4/806) of patients, respectively. The most commonly reported age was in the 70s for both sexes. The total numbers of patients aged 50 years or older, including those classified as elderly, were 66.7% (218/327) for males and 91.2% (433/475) for females, accounting for the majority.

Figure 2 shows the overall adverse events and outcomes. Hematologic and lymphatic disorders were the most common adverse events, with 11% (132/1200), followed by eye disorders (10.6%, 127/1200), and hepatobiliary disorders (8.9%, 107/1200). The outcomes were as follows: recovery, 40.1% (481/1200); remission, 27.1% (325/1200); non-recovery, 11.2% (134/1200); and death, 7.2% (85/1200). For each adverse event, death occurred most frequently in respiratory, thoracic, and mediastinal disorders at 19.2% (15/78), followed by metabolic and nutritional disorders at 13.5% (10/74).

Clarithromycin

Females accounted for 63.9% (39/61). The numbers of patients aged 40 years or younger were 55.0% (11/20) for males, while the numbers of patients aged 50 years or older were 82.1% (32/39) for females (Fig 3a). Infections and infestations were the most common adverse events at 14.4% (13/90), followed by hematologic and lymphatic disorders at 13.3% (13/90), hepatobiliary disorders at 12.2% (11/90), and gastrointestinal disorders at 11.1% (10/90). Regarding outcome, recovery, remission, non-recovery, and death were observed in 23.3% (21/90), 45.6% (41/90), 5.6% (5/90), and 6.7% (6/90) of the patients, respectively. The most common onset time was within 120 days at 40% (20/50) (Fig. 4a, 5a).

Ethambutol

Females accounted for 75.0% (57/76). The numbers of patients aged 50 years or older were 100% (18/18) for males, and 98.2% (56/57) for females (Fig 3b). Eye disorders were the most common adverse events at 66.7% (56/84), followed by nervous system damage (10.7%, 9/84). Regarding outcome, recovery, remission, non-recovery, sequelae, and death were observed in 8.3% (7/84), 13.1% (11/84), 35.7% (30/84), 7.1% (6/84), and 0.0% (0/90) of the patients, respectively. Particularly, in eye disorders,

44.6% (25/56) of patients did not recover, and 5.4% (3/56) were left with sequelae. The most common onset time was 181–300 days at 43.6% (21/48) (Fig. 4b, 5b).

Rifampicin

Females accounted for 59.4% (19/32). The numbers of patients aged 50 years or older were 92.3% (12/13) for males, and 94.7% (18/19) for females (Fig 3c). Renal and urinary tract disorders were the most common adverse events at 22.5% (9/40), followed by investigations at 20.0% (8/40), and hematological and lymphatic disorders at 12.5% (5/40). Regarding outcome, recovery, remission, non-recovery, and death were observed in 47.5% (19/40), 22.5% (9/40), 2.5% (1/40), and 7.5% (3/40) of the patients, respectively. The most common onset time was within 120 days at 88.5% (23/26) (Fig. 4c, 5c).

Reporting odds ratio

The RORs for CAM, EB, and RFP are shown in Table 1.

For CAM, the RORs of infections and infestations, hepatobiliary system disorders, and immune system disorders were 4.13 (95% CI, 2.3–7.44), 2.61 (95% CI, 1.39–4.91), and 2.38 (95% CI, 1.04–5.44), respectively. For EB, the ROR of eye disorders was 215.79 (95% CI, 132.62–351.12). For RFP, the RORs of renal and urinary tract disorders and investigations were 7.03 (95% CI, 3.35–14.77) and 6.99 (95% CI, 3.22–15.18), respectively.

Weibull Distribution

We calculated the Weibull distribution of EB in 28 patients with known onset of adverse events. The β value of EB was 2.07 (95% CI, 1.48–2.76), which was classified as wear-out failure type (Table 2).

Discussion

The Official ATS/ERS/ESCMID/IDSA Clinical Practice Guidelines recommend treatment with 3-drug regimen including a macrolide for macrolide-sensitive MAC-LD (16)In this study, we firstly reported the problematic adverse events of treatments for MAC-LD by using a large database in Japan.

For all three drugs, the majority of adverse events were reported by patients aged over 50 years. In a previous study, the majority of MAC-LD cases in Japan were reported in those in their 50s or older (3). Of the 1200 adverse event reports, the total number of deaths, non-recovery, and sequelae was 19.4% (233/1200), which cannot be ignored. This result may be influenced by the bias that minor side effects that are not clinically recognized are unlikely to be reported; therefore, severe side effects may have been reported relatively more frequently. However, a systematic review showed that serious adverse events are

also underreported (17). Thus, we believe that serious adverse events, such as death, non-recovery, and sequelae, are common.

By calculating the ROR, we found that the most frequent adverse events of CAM were infections and infestations, hematologic and lymphatic disorders, hepatobiliary disorders, and immune system disorders. A study investigated the adverse events of switching from CAM to azithromycin (AZM) for MAC-LD when CAM was discontinued due to side effects (18). Patients who switched from CAM to AZM did not have more adverse events, and the most common adverse event that led to discontinuation was skin rash. Kadota et al. investigated the effect of CAM-based regimens for MAC-LD in Japan (19). Adverse events occurred in 47.2% of CAM-based regimens, with 33.6% of adverse events related to CAM. The frequency of adverse events was not related to the total dose of CAM, doses per body weight, or age. The most common adverse events were skin rash, anorexia, hepatic dysfunction, diarrhea, and leukopenia. These results were not consistent with the results of this study because the regimens included drugs other than CAM, EB, and RFP. Kwon et al. compared the rate of treatment discontinuation due to adverse events of CAM and AZM for MAC-LD (20). The most common adverse event that resulted in treatment discontinuation was gastrointestinal disorders. The frequency of adverse events varies among studies because of the difficulty of studying only CAM. In this study, the onset of adverse events within 120 days was 40%. This suggests that attention should be paid to the occurrence of adverse events early in treatment. This study is novel in that we show that adverse events of CAM tend to occur early in the course of treatment.

In this study, the most common adverse events occurred between 181 and 300 days after the start of treatment, indicating that attention should be paid to the adverse effects of EB, especially 6 months after the start of treatment. Adverse events of EB develop depending on doses, and risk factors include high doses per body weight and daily administration (21–24). In a case series of 70 patients with EB-induced eye toxicity, 36 patients developed eye toxicity between 2 and 6 months, and 26 patients developed eye toxicity more than 6 months after the start of treatment (25). Therefore, the duration of treatment was also a risk. In a retrospective study of MAC-LD treatment in Japan, the median onset of eye toxicity was as long as 278 days, which is a frequent cause of drug discontinuation (96.2%) (9). In a retrospective review comparing patients who received standard treatment including EB and those who discontinued EB due to adverse events, the treatment failure rate tended to be higher in the group of patients who discontinued EB (13). To avoid discontinuation of treatment, patients receiving EB should always be assessed for doses per body weight. In this study, 42.9% (36/84) of patients experienced non-recovery or sequelae, whereas 0.0% died. This may reflect the current situation in which patients are more aware of the adverse events of EB, are more regularly assessed for adverse events, and are more promptly treated when adverse events occur. In addition, using the Weibull distribution, we found that the onset time of eye disorder in EB was the wear-out failure type. This indicates that the incidence of adverse events increases over time. We should keep in mind that the treatment of MAC-LD requires long-term administration of EB, and that the frequency of adverse events increases with the duration of treatment.

Using the ROR, we found that the most frequent adverse events when the suspect drug was RFP alone were renal and urinary tract disorders. In this study, we also found that most of the adverse events of RFP occurred within 120 days of administration. Few studies have examined the onset of adverse events of RFP alone, and we consider the results of this study to be important. Covic et al. investigated 60 cases of acute renal failure after RFP administration (26). The amount that induced renal failure and the total dose were not related to the severity of renal failure, and dialysis was directly correlated with the length of anuria. The common histological finding was tubulointerstitial nephritis (26). Muthukumar et al. reported 25 cases of acute renal failure due to RFP (27). Symptoms in 24 patients developed between 1 to 24 hours, which are consistent with this study's result. Among 12 patients who underwent kidney biopsy, 7 patients had acute interstitial nephritis. In addition, 1 patient had crescentic glomerulonephritis, and 3 patients had mesangial proliferation. Another review of 48 RFP-associated renal failure cases also showed the most common histological finding was acute tubular necrosis (28). Kim et al reported a case who developed minimal change disease while taking RFP (29). These findings revealed that RFP can cause various types of kidney injuries. Moussa et al. compared the blood concentration of RFP in patients with tuberculosis who experienced adverse events (30), and there was no difference in blood concentration. Since there may be little relationship between the dose and occurrence of adverse events, we should note decreased urine output and anuria regardless of the dose of RFP.

In this study, we investigated the actual adverse events associated with MAC-LD using spontaneous reports. We found that adverse events caused by CAM and RFP tended to occur within 120 days of treatment initiation, whereas those caused by EB tended to occur after 180 days. In addition, the use of the JADER database made it possible to determine the situation in Japan in general and to collect a large number of cases compared with previous studies that summarized adverse events. This study has some limitations. First, reporting bias is unavoidable because the JADER database is based on voluntary reports. Second, a previous study showed that the quality of reports differed depending on the facilities or occupations in the JADER database (31), and the quality of the reports was not evenly distributed. Third, although ROR is suggested to be less biased than the proportional reporting ratio, which is a ratio of reporting proportions, there are still various biases (32). We need to accumulate more cases to understand the actual situation of adverse events.

Conclusions

For MAC-LD, adverse events of EB occur after 180 days, whereas the adverse events of CAM and RFP occur early in the course of treatment.

Abbreviations

AZM azithromycin

CAM clarithromycin

EB ethambutol

JADER Japanese Adverse Drug Event Report

MAC-LD *Mycobacterium avium* complex lung disease

NTM-LD nontuberculous mycobacterial lung disease

PMDA Pharmaceuticals and Medical Devices Agency

RFP rifampicin

ROR reporting odds ratio

Declarations

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Japanese Adverse Drug Event Report (JADER) repository, http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp

Data statement

This study was conducted using the Japanese Adverse Drug Event Report (JADER) database provided by the Pharmaceuticals and Medical Devices Agency (PMDA). The information, results, and interpretation of this study do not constitute an expression of any opinion of the PMDA.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

HN conceived of the presented idea. HN, RT and YT developed the theory and performed the computations. HN and YT verified the analytical methods. TO and HN wrote the main manuscript text. All authors discussed the results and contributed to the final manuscript.

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Tables

Table 1
Reporting odds ratio of adverse events of every drug.

Drug	Adverse event	n	ROR	95% CI
CAM	Infections and infestations	13	4.13	2.3–7.44
	Blood and lymphatic system disorders	12	1.95	1.06–3.58
	Hepatobiliary disorders	11	2.61	1.39–4.91
	Gastrointestinal disorders	10	1.5	0.78–2.89
	Respiratory, thoracic, and mediastinal disorders	8	1.41	0.68–2.92
	Immune system disorders	6	2.38	1.04–5.44
	Metabolic and nutritional disorders	5	1.8	0.73–4.44
EB	Eye disorders	62	215.79	132.62–351.12
	Nervous system disorders	10	1.42	0.73–2.75
RFP	Renal and urinary disorders	9	7.03	3.35–14.77
	Investigations	8	6.99	3.22–15.18
	Blood and lymphatic system disorders	5	1.81	0.71–4.62

CAM, clarithromycin; EB, ethambutol; RFP, rifampicin; ROR, reporting odds ratio; CI, confidence interval.

Table 2
Weibull distribution of ethambutol.

Drugs	n	β	95% CI
EB	28	2.07	1.48–2.76

EB, ethambutol; CI, confidence interval.

Figures

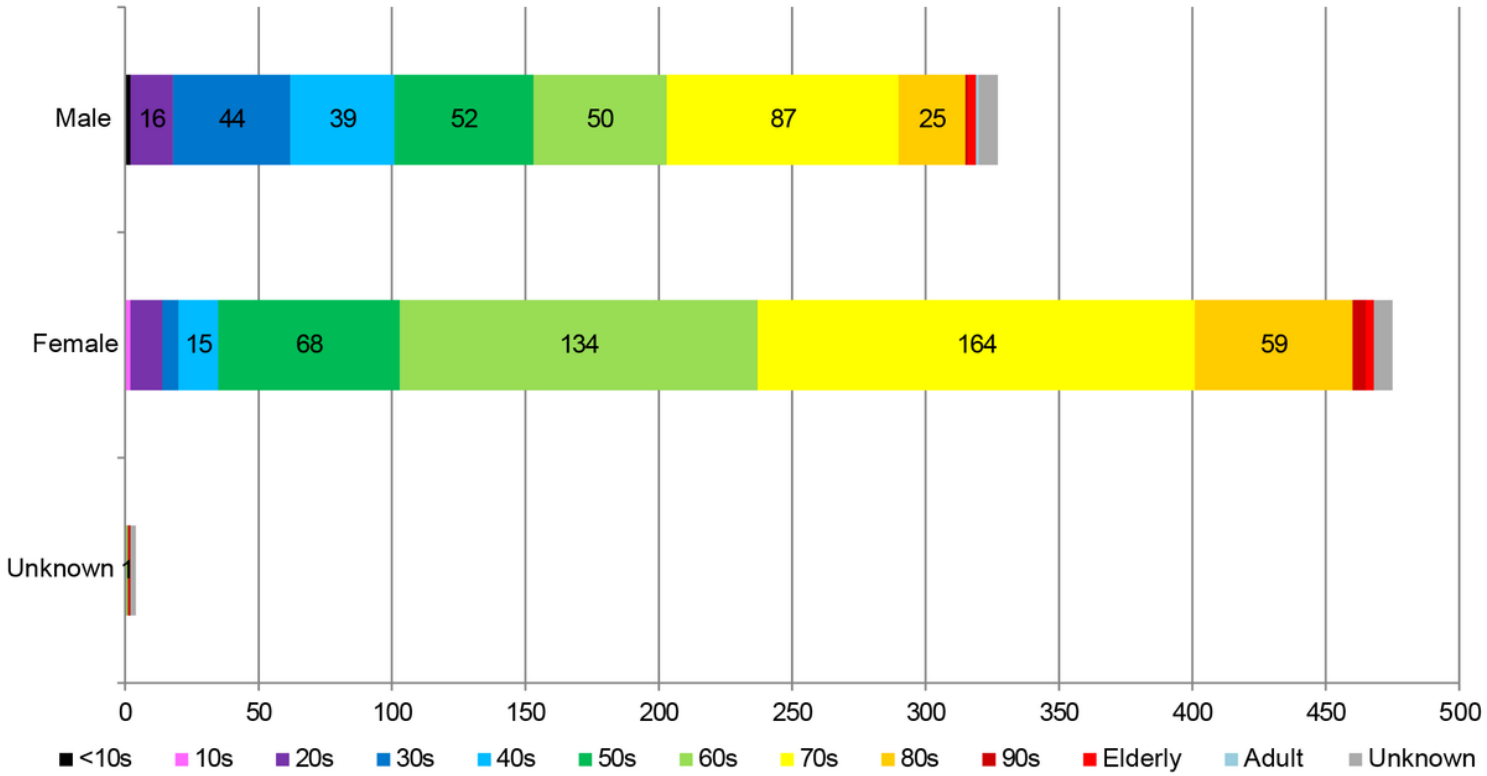

Figure 1

Patient's characteristics in *Mycobacterium avium* complex lung disease (MAC-LD) in the Japanese Adverse Drug Event Report database. Horizontal axis shows the number of MAC-LD cases. Each bar chart is divided by the number of cases according to age.

Figure 2

Outcome of adverse events in all three drugs: clarithromycin, ethambutol, and rifampicin. Vertical axis shows the types of adverse events. Horizontal axis shows the number of cases by adverse event. Each bar chart is divided by the number of cases according to outcome.

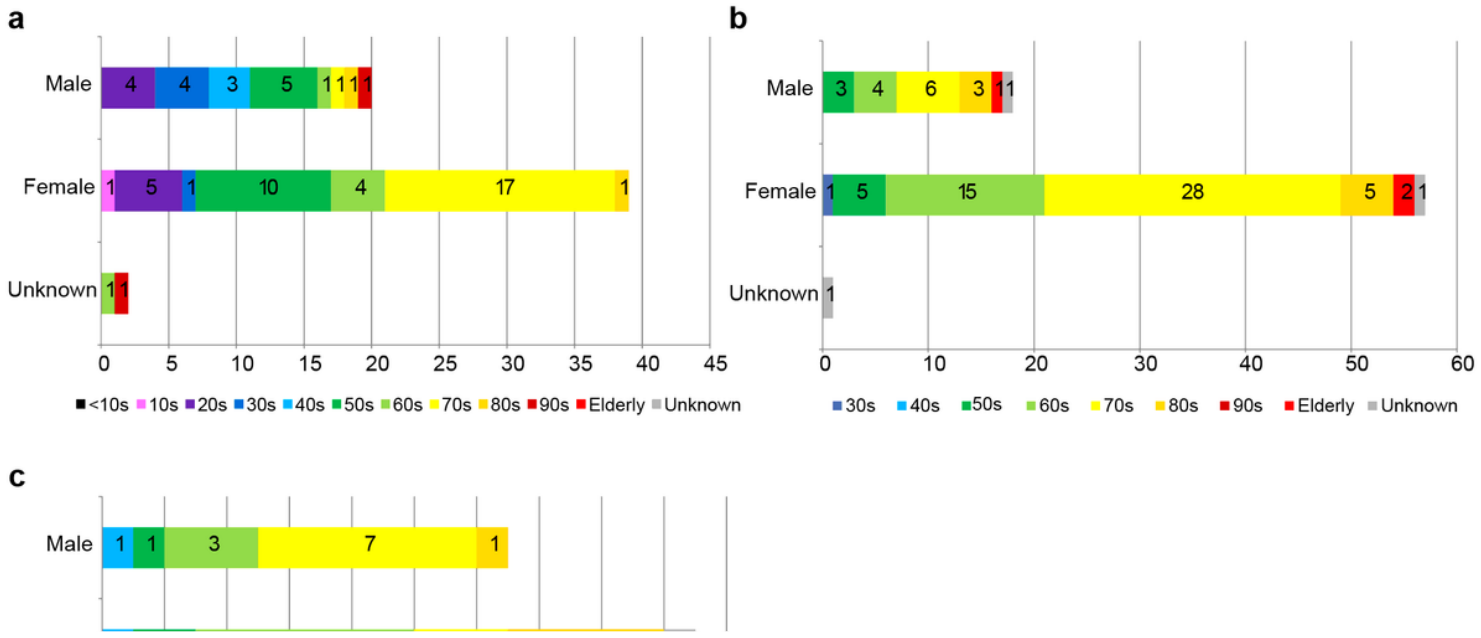

Figure 3

Age and sex of cases who experienced adverse events in each drug. Vertical axis shows sex. Horizontal axis shows the number of patients who experienced adverse events by sex. Each bar chart is divided by the number of patients according to age. (a) Clarithromycin. (b) Ethambutol. (c) Rifampicin.

Figure 4

Outcome of adverse events in each drug. Vertical axis shows the types of adverse events. Horizontal axis shows the number of patients who experienced adverse events by the type of them. Each bar chart is divided by the number of patients according to outcome. (a) Clarithromycin. (b) Ethambutol. (c) Rifampicin.

Figure 5

Onset of adverse events in each drug. Vertical axis shows the onsets of adverse events. Horizontal axis shows the number of patients who experienced adverse events by onset. Each bar chart is divided by the number of patients according to the type of adverse event. (a) Clarithromycin. (b) Ethambutol. (c) Rifampicin.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.tif