Letter

DOI: 10.5582/bst.2018.01201

Prescription surveillance for early detection system of emerging and reemerging infectious disease outbreaks

Tamie Sugawara[1], Yasushi Ohkusa[1], Hirokazu Kawanohara[2], Miwako Kamei[3,*]

[1] *National Institute of Infectious Diseases, Tokyo, Japan;*
[2] *EM Systems Co. Ltd., Osaka, Japan;*
[3] *School of Pharmacy, Nihon University, Chiba, Japan.*

Summary **Based on prescriptions filled at external pharmacies, prescription surveillance (PS) in Japan has been reporting the estimated numbers of influenza and varicella patients and people prescribed certain drugs since 2009. Every morning, this system estimates the numbers of patients from the numbers of prescriptions filled nationwide for neuraminidase inhibitors, anti-herpes virus drugs, antibiotic drugs, antipyretic analgesics, and multi-ingredient cold medications. Moreover, it can detect "unexplained" infectious diseases that are not explained as infectious diseases monitored by other surveillance systems. Such "unexplained" infectious diseases might be emerging and re-emerging infectious diseases including bioterrorism attacks, which are reportedly difficult to diagnose, at least in early outbreak stages. To ascertain the system's potential benefits, this study examined schemes to detect "unexplained" infectious diseases using PS information. The numbers of patients prescribed the respective drugs are first regressed on the known infectious diseases, time trends, and dummies for day-of-the-week, holidays, and days following a holiday. Known infectious diseases are defined as covered by the National Official Sentinel Surveillance for Infectious Diseases under the Infection Control Law. After the numbers of patients from PS are compared with the predicted numbers of patients, their probabilities of occurrence are calculated. We examined the system's prospective operation from January 2017 through July 2018. The criterion we used to define aberrations varied, from 0.01 to 10^{-7}. For criteria of 0.01 and 10^{-7} we found 254 and 15 aberrations, respectively. We confirmed its feasibility and effectiveness.**

Keywords: Prescription surveillance, pharmacy, emerging and reemerging infectious disease, bioterrorism attack, National Official Sentinel Surveillance for Infectious Diseases

In Japan, the National Official Surveillance for Infectious Diseases (NOSSID) is operated based on a related Law. Except for some severe diseases, it requires only the sentinel medical institution to report the number of patients weekly. For many common pediatric infectious diseases, 3,000 sentinel pediatric care facilities, which account for about one-tenth of all pediatric care facilities throughout Japan, report the number of cases each week by NOSSID. For influenza, 2,000 internal medicine care facilities were added (*1*). The sentinel reports are regarded as reliable information because it based on physician's diagnosis. Nevertheless, these reports are published weekly after a ten-day delay following diagnosis. For that reason, they probably cannot indicate emerging or re-emerging infectious diseases early.

Prescription surveillance (PS), as operated in Japan by the Japan Medical Association, Japan Pharmaceutical Association, School of Pharmacy, Nihon University, and EM Systems Co. Ltd., is a nationwide syndromic surveillance. Since 2009, it has been reporting the estimated number of influenza and chicken pox patients, and the numbers of patients prescribed drugs of certain types, based on prescriptions at pharmacies (*2-7*). It estimates the numbers of patients every day from the number of prescriptions by prefecture by age group. As of the end of April 2015, approximately ten

**Address correspondence to:*
Dr. Miwako Kamei, School of Pharmacy, Nihon University, 7-7-1 Narashinodai, Funabashi-shi, Chiba 274-8555, Japan.
E-mail: kamei.miwako@nihon-u.ac.jp

thousand pharmacies were participating, collectively accounting for about 20% of all pharmacies. The estimated numbers of patients are presented on the web page the following morning (*http://prescription.orca.med.or.jp/kanjyasuikei/*).

It is apparently useful to detect aberrational increases of patients with some symptoms that cannot be found by NOSSID. To examine its potential, we proposed and examined schemes to detect "unexplained" infectious diseases using PS information.

PS estimates the numbers of patients by multiplying the reciprocal of the pharmacy PS participation rate and the reciprocal of the proportion of prescriptions at external pharmacies in the prefecture by the total number of prescriptions issued in the prefecture. The numbers of patients prescribed neuraminidase inhibitors (NI), anti-herpes virus drugs (AHV), antibiotic drugs (AB), antipyretic analgesics (AP), multi-ingredient cold medications (MIC), and antidiarrheal and intestinal drugs (AD) have been recorded. Antibiotics are classified into five types: penicillin (ABP), cephem (ABC), macrolide (ABM), new quinolone (ABQ), and others (ABO) (*2,3*).

To predict the numbers of patients taking those drug by well-known infectious diseases, we used the data for influenza, RS virus infection (RS), pharyngoconjunctival fever (PCF), group A streptococcal pharyngitis (A-SP), gastrointestinal infections (GI), varicella, hand, foot and mouth disease (HFMD), erythema infectiosum (EI), exanthem subitum (ES), pertussis, herpangina, mumps, and mycoplasma pneumonia(MP) from NOSSID. Except for RS, NOSSID provides numbers of patients per sentinel per week as the incidence of each disease. For RS, NOSSID provides only the total number of patients per week.

First, from known infectious diseases and calendar information, we predicted the numbers of patients prescribed each drug. The dependent variable was the number of patients prescribed drug i on day t. Explanatory variables were the NOSSID reported number of patients of disease j: the latest available data in day t. Because NOSSID publishes data in the prior week on Friday at noon, the latest available data are two weeks prior on Monday–Friday, and one week prior on Saturday and Sunday. Furthermore,

Table 1. Criteria and numbers of detected aberration

Criterion	Number of detected aberration
10^{-2}	254
10^{-3}	126
10^{-4}	66
10^{-5}	40
10^{-6}	30
10^{-7}	21
10^{-8}	15

Note: Total number of days and drug types was 5790. "Criterion" means that if the *p*-value was less than criterion, then we inferred that type of drug on that day as an aberration.

Table 2. Detected aberrations when the criterion was 10^{-5}

Year	Month	Day of week	Hol	Holw	ABP	ABC	ABQ	ABO	AP	MIC
2017	1	Mon	Yes						> 8	
2017	1	Mon	Yes						> 8	
2017	5	Mon	Yes	Yes	7.2					
2018	1	Fri			5.2					
2018	1	Tue	Yes						7.1	
2018	1	Mon	Yes						> 8	
2018	1	Tue							> 8	
2018	1	Wed							7.3	
2018	1	Thu							6.7	
2018	1	Fri							> 8	
2018	1	Mon	Yes						> 8	
2018	1	Mon	Yes						> 8	
2018	2	Mon	Yes						> 8	
2018	2	Tue	Yes						5.3	
2018	6	Fri				> 8		> 8		
2018	6	Fri				> 8	6.5	> 8		
2018	6	Sat				6.5		7.1		
2018	6	Tue				5.5		5.7		5.9
2018	6	Wed				6.1		6.7		
2018	6	Thu				5.8		6.2		
2018	6	Fri				7.4		> 8		
2018	7	Fri				5.2		6.4		7.1
2018	7	Fri						5.4		> 8
2018	7	Wed								5.0
2018	7	Fri				6.2	5.1	6.8		> 8

Note: No aberration of neuraminidase inhibitors (NI), anti-herpes virus drugs (AHV), macrolide (ABM), and antidiarrheal/intestinal drugs (AD) was detected. ABC, cephem; ABO, other antibiotic drugs; ABP, penicillin; ABQ, new quinolone; AP, antipyretic analgesics; Hol, one for a day following a holiday or Sunday, otherwise zero; Holw, one for a day following two consecutive holidays or Sunday, otherwise zero; MIC, multi-ingredient cold medications.

explanatory variables included dummy variables of the epidemiological week, day of the week, holiday, and the day following a holiday, the day following two consecutive holidays, summer vacation (13-15 August), and the new year vacation (1-3 January).

Next, we calculated the probabilities at which they occurred if the numbers of patients from PS greater than the predicted number. If the *p*-value was lower than a criterion, it was regarded as aberration. We examine criteria from 10^{-2} to 10^{-7}. We applied this analysis prospectively from January 2017 through July 2018 using data from 1 October, 2010 to the day prior for prediction.

Table 1 presents association among criteria and the numbers of aberrations. When the criterion was 0.01, 254 aberrations were found. Its proportion was 4.4%. Conversely, when we used the criterion of 10^{-7}, the number of aberrations decreased to 15, which is 0.26%.

Table 2 presents calendar information and the probability of detected aberrations if criterion was 10^{-5}. In total, 40 aberrations were found in 25 days: ABP had 2 aberrations; ABC had 9; ABQ had 2; ABO had 10; AP had 12; and MIC had 5. No aberration was detected in NI, AHV, ABM, or AD.

Of 25 days, 7 were Monday, 4 were Tuesday, 3 were Wednesday, 2 were Thursday, 8 were Friday, and 1 was Saturday. Nine aberrations occurred on a day following a holiday. Only one aberration was detected on a day following two consecutive holidays.

Overall, we conclude that aberration seemed not to be biased to a particular day of the week or a day following a holiday. Therefore, we confirmed its feasibility and effectiveness. We expect to perform it prospectively and share the results to support public health countermeasures against bioterrorism attack.

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(Received August 24, 2018; Revised October 23, 2018; Accepted October 25, 2018)