Journal of Food and Drug Analysis, Vol. 20, No. 3, 2012, Pages 597-602 doi:10.6227/jfda.2012200305

Off-Label Antibiotic Use in the Pediatric Population: A Population-based Study in Taiwan

KUANG-HUA HUANG[1], YI-CHUNG HSIEH[1], CHIH-TUN HUNG[2] AND FEI-YUAN HSIAO[3]*

[1.] Department of Health Service Administration, China Medical University, Taichung, Taiwan, R.O.C.
[2.] Department of Health Care Administration, Central Taiwan University of Science and Technology, Taichung, Taiwan, R.O.C.
[3.] Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, R.O.C.

(Received: July 26, 2011; Accepted: March 15, 2012)

ABSTRACT

This study investigated the epidemiology and determinants of off-label antibiotic use in children in Taiwan. This was a retrospective, population-based study using the 2002-2005 Taiwan's National Health Insurance Research Database (NHIRD). The study subjects consisted of children under 12 years old. The prescriptions of antibiotics were retrieved from the pharmacy claims of NHIRD. Multivariable logistic regression models were used to assess the associations between patients' and providers' demographics and off-label use of antibiotics. Among 66,446 antibiotic prescriptions identified, off-label use accounted for 33.33%. The percentages of off-label use varied with time trend, dispensing type, patient characteristics, physician characteristics and institution characteristics. Off-label use of antibiotics is very common among Taiwanese children, especially in the cases whose prescriptions were issued by senior and experienced physicians, as well as those from private, non-teaching or regional hospitals. Off-label use can seriously affect pediatric drug safety and health, and are worthy of more concern and discussion. In addition, the study in the future would still need to explore the possible root causes of off label use.

Key words: antibiotics, pediatrics, off-label use, pharmacy

INTRODUCTION

The vast majority of antibiotic prescriptions in the pediatric population were prescribed for upper respiratory infection (URI)[1-4]. However, misuse of antibiotics for viral respiratory infections not only cannot relieve diseases but also can result in bacterial resistance. In Taiwan, the rate of bacterial resistance is one of the highest on a global scale[5,6]. Inappropriate use of antibiotics in the pediatric population can also cause adverse drug reactions (ADRs) and even adverse drug events (ADEs) such as emergency visits, hospitalizations or extension of hospital stay. These could add to the medical care utilization and expense[7,8]. Study has shown that the incidence of ADRs was approximately 1.7% in the pediatric outpatient department and was extremely high (9.5%) in hospitalized children[9]. While several types of inappropriate prescriptions, including duplicated prescriptions and overdose, and determinants of inappropriate prescriptions have been reported in the adult population[10], studies in the pediatric population were relatively limited. Unlike the adult population, off-label use, meaning licensed medications being prescribed outside their indications, may be the major cause of inappropriate prescriptions in the pediatric population. A study conducted in five European hospitals indicated that 39% of medications prescribed to the pediatric population were of off-label use[11]; other studies also showed that the incidences of off-label use and un-licensed drug use in the pediatric population were 11% in England, 33% in France, 29% in the Netherlands[12-14] and 80% in neonatal intensive care units in Australia[15]. Furthermore, one study in Germany revealed an association between off-label use of mediations and increased incidences of ADR in children[16].

While off-label use of drugs in the pediatric population has been discussed worldwide, such information is still lacking in Asian countries. Using Taiwan's National Health Insurance Research Database (NHIRD), this study attempted to investigate the epidemiology and determinants of off-label antibiotic use in children in Taiwan.

* Author for correspondence. Tel: +886-2-23123456 ext. 88347; Fax: +886-2-23951113; E-mail: fyshsiao@ntu.edu.tw

MATERIALS AND METHODS

This was a retrospective, population-based study using the 2002-2005 systematic sampling cohort of Taiwan's NHIRD. Initiated in 1995, the National Health Insurance (NHI) program covered nearly all inhabitants (99.6% coverage rate at the end of 2009) in Taiwan[17]. Therefore, the NHIRD is considered as a nationally representative claim database. The database has been described in detail elsewhere[18] and has been reviewed routinely by the Bureau of NHI of Taiwan. On a monthly basis, 0.2% of claims of ambulatory visits were extracted by a systematic method to create the systematic sampling cohort we used[19]. Prescriptions containing antibiotics for children under 12 years old were retrieved from the pharmacy claims in the NHIRD. Antibiotics were identified according to the first four digits of the pharmacological classification code (code: 0812) in prescription claims in the NHIRD. The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) revised by the World Health Organization (WHO) in 1992 was used to identify disease diagnoses and drug indications.

In order to investigate the epidemiology of antibiotic use in the pediatric population, all identified prescriptions were further grouped based on the following categories:

I. Dispensing type: non-released (dispensed in pharmacy department at prescribing hospitals/clinics) and released (dispensed in NHI contracted pharmacies) prescriptions.

II. Diagnosis: URIs (upper respiratory infections) and non-URIs. URIs included prescriptions with ICD-9-CM codes of 460.xx (Acute nasopharyngitis [common cold]), 462.xx (Acute pharyngitis), 464.xx (Acute laryngitis and tracheitis), 465.xx (Acute upper respiratory infections of multiple or unspecified site), 466.xx (Acute bronchitis and bronchiolitis), 487.xx (Influenza) and 490.xx (Bronchitis, not specified as acute or chronic). Prescriptions with diagnoses other than URI were defined as non-URI prescriptions.

III. Off-label use: off-label use of antibiotics was screened out according to the indication criteria based on the Micromedex Health Care Series Drug Database. When none of the three diagnosis codes listed in the NHIRD outpatient records was the Food and Drug Administration (FDA) labeled indications for an antibiotic prescription, it was defined as an "off-label use of antibiotic".

The multivariable analysis was conducted by logistic regression to examine determinants of off-label antibiotic use in the pediatric population. Covariates included in the model were dispensing types, patients' characteristics (age and gender), physicians' characteristics (years since issue of licenses), geographic characteristics based on the study by Liu *et al.*[20] on the level of urbanization of Taiwan townships, and institutions' characteristics.

All analyses were performed using the software SAS for Windows 9.1.

RESULTS

We identified 66,446 prescriptions containing antibiotics for patients under 12 years old over the four-year study period (Table 1).

Most (80%) of the identified prescriptions were non-released prescriptions, whereas those prescriptions released to community pharmacies increased over years. Nearly half of these prescriptions (45.7%) were prescribed to children aged 2-5 years old. Most prescriptions came from the pediatrics (33.9%) and otolaryngology (29.8%) departments. Approximately 61% of the antibiotic prescriptions were prescribed for URI. Male physicians (90.6%) and physicians with working experiences ranged from 6 to 15 years (82.8%) accounted for most of the prescribing physicians. Most prescriptions came from private hospitals (90.1%), non-teaching hospitals (88.4%), clinics (84.3%) or highly urbanized regions (76.5%). The rates of antibiotics prescription for URIs decreased from 64.3 to 54.0% during 2002-2005. The Cochran-Armitage trend test showed that the variables included dispensing type, diagnosis, physician's gender, and teaching hospital status had significant differences ($p < 0.0001$).

Approximately one-third of prescriptions were identified as off-label use. Variables significantly associated with off-label antibiotic use were displayed in Table 2. Odds ratios (OR) and 95% confidence interval (CI) were estimated using logistic regression models. As for the time trend, with the 2002 year group as the reference group, the risks of off label use decreased as the time increased.

Patients aged 2-5 years old were at a lower risk for off-label use than infants (under 1 year) (OR = 0.85, 95% CI = 0.80-0.89).

For categorization by diagnosis, risks of off label use were higher for non-URIs compared to URIs (OR = 1.05, 95% CI = 1.01-1.08). Family medicine department were more likely to prescribe an off label use antibiotic (Internal medicine vs. Family medicine, OR = 0.88, 95% CI = 0.80-0.97; Pediatrics vs. Family medicine, OR = 0.66, 95% CI = 0.62-0.70; Otolaryngology vs. Family medicine, OR = 0.81, 95% CI = 0.76-0.87).

As for the physician's age, with the 51 to 60-aged group as the reference group, the 31-50 year old groups were less likely to prescribe an off label use antibiotic (31-40y vs.51-60y, OR = 0.68, 95% CI = 0.63-0.74; 41-50y vs.51-60y, OR = 0.84, 95% CI = 0.78-0.92).

As for physician seniority, with the 11-15 year group as the reference group, physicians with working experience 5 years and under were more likely to prescribe an off label use antibiotic (< 5y vs.11-15y, OR = 1.10, 95% CI = 1.03-1.18). On the contrary, the groups with working experience more than 21 years were more likely to prescribe an off label use antibiotic (> 21y vs.11-15y, OR = 1.28, 95% CI = 1.14-1.44).

Compared to non-teaching hospitals, teaching hospitals were less likely to issue an off-label use antibiotic (OR = 0.70, 95% CI = 0.61-0.81). On the contrary, non-profit proprietary hospitals as a reference group, private hospitals were more likely to issue an off label use antibiotic (OR = 1.17, 95% CI

Journal of Food and Drug Analysis, Vol. 20, No. 3, 2012

Table 1. Descriptive characteristic of antibiotic prescriptions in the pediatric population, 2002-2005

	2002 (n = 21,697)		2003 (n = 18,261)		2004 (n = 14,765)		2005 (n = 11,723)		Total (n = 66,446)		Cochran-Armitage Trend Test	
Variable	N	%	N	%	N	%	N	%	N	%	value	p
Dispensing type											-39.73	< .0001
Non-released prescription	19,047	87.8	14,617	80.0	11,192	75.8	8,295	70.8	53,151	80.0		
Released prescription	2650	12.2	3,644	20.0	3,573	24.2	3,428	29.2	13,295	20.0		
Patient age												
≤ 1 year old	2,953	13.6	2,256	12.4	1,686	11.4	1,260	10.8	8,155	12.3		
2-5 years old	10,154	46.8	8,141	44.6	6,908	46.8	5,153	44.0	30,356	45.7		
6-12 years old	8,590	39.6	7,864	43.1	6,171	41.8	5,310	45.3	27,935	42.0		
Patient gender											1.32	0.1874
Male	11,799	54.4	9,857	54.0	8,046	54.5	6,463	55.1	36,165	54.4		
Female	9,898	45.6	8,404	46.0	6,719	45.5	5,260	44.9	30,281	45.6		
Diagnosis											-19.36	< .0001
URIs	13,944	64.3	11,552	63.3	8,709	59.0	6,325	54.0	40,530	61.0		
Non-URIs	7,753	35.7	6,709	36.7	6,056	41.0	5,398	46.1	25,916	39.0		
Medical department visited												
Family Medicine	1,757	8.1	1,609	8.8	1,167	7.9	897	7.7	5,430	8.2		
Internal Medicine	909	4.2	728	4.0	603	4.1	343	2.9	2,583	3.9		
Pediatrics	7,036	32.4	5,901	32.3	5,059	34.3	4,498	38.4	22,494	33.9		
Otolaryngology	6,524	30.1	5,552	30.4	4,322	29.3	3,396	29.0	19,794	29.8		
Non-Specialist	4,492	20.7	3,624	19.9	2,762	18.7	1,867	15.9	12,745	19.2		
Others	979	4.5	847	4.6	852	5.8	722	6.2	3,400	5.1		
Physician's age												
≤ 30 years old	167	0.8	100	0.6	90	0.6	52	0.4	409	0.6		
31-40 years old	8,317	38.3	6,501	35.6	5,121	34.7	4,001	34.2	23,940	36.0		
41-50 years old	9,268	42.7	8,111	44.4	6,483	43.9	5,153	44.0	29,015	43.7		
51-60 years old	3,087	14.2	2,742	15.0	2,341	15.9	1,914	16.4	10,084	15.2		
≥ 61 years old	858	4.0	798	4.4	730	4.9	590	5.0	2,976	4.5		
Physician's gender											6.37	< .0001
Male	19,793	91.2	16,615	91.0	13,331	90.3	10,438	89.1	60,177	90.6		
Female	1,904	8.8	1,637	9.0	1,434	9.7	1,272	10.9	6,247	9.4		
Physician's seniority												
≤ 5 years	2,111	9.7	1,327	7.3	940	6.4	630	5.4	5,008	7.5		
6-10 years	13,695	63.1	10,807	59.2	7,589	51.4	5,109	43.6	37,200	56.0		
11-15 years	4,302	19.8	4,490	24.6	4,617	31.3	4,388	37.4	17,797	26.8		
16-20 years	1,012	4.7	1,140	6.2	1,087	7.4	1,179	10.1	4,418	6.7		
≥ 21 years	577	2.7	497	2.7	532	3.6	417	3.6	2,023	3.0		
Teaching hospital status											-8.36	< .0001
Yes	2,397	11.1	1,848	10.1	1,875	12.7	1,597	13.6	7,717	11.6		
No	19,300	88.9	16,413	89.9	12,890	87.3	10,126	86.4	58,729	88.4		
Ownership												
Public	570	2.4	437	2.4	436	3.0	420	2.8	1,863	2.8		
Private	19,745	91.4	16,686	91.4	13,157	89.1	10,284	90.1	59,872	90.1		
Non-profit proprietary	1,382	6.4	1,138	6.2	1,172	7.9	1,019	8.7	4,711	7.1		
Accreditation level												
Medical center	703	3.2	533	2.9	523	3.5	476	4.1	2,235	3.4		
Regional hospital	1,236	5.7	955	5.5	969	6.6	830	7.1	4,030	6.1		
District hospital	1,267	5.8	1,058	5.8	1,069	7.2	766	6.5	4,160	6.3		
Clinics	18,491	85.2	15,675	85.8	12,204	82.7	9,651	82.3	56,021	84.3		
Urbanization level												
High	16,897	77.9	13,842	75.1	11,087	75.1	9,033	77.1	50,859	76.5		
Moderate	3,621	16.7	3,353	18.4	2,761	18.7	2,060	17.6	11,795	17.8		
Low	1,179	5.4	1,066	5.8	917	6.2	630	5.4	3,792	5.7		
off-label use												
Yes	7,447	34.3	6,062	33.2	4,967	33.6	3,669	31.3	22,145	33.3		
No	14,250	65.7	12,199	66.8	9,798	66.4	8,054	68.7	44,301	66.7		

Table 2. Logistic regression analysis on inappropriate pediatric antibiotic prescriptions

	Off-label use	
Incidence	**33.33%**	
Variable	O.R.	(95% C.I)
Year (Ref. group: 2002)		
2003	0.93*	(0.892-0.971)
2004	0.94*	(0.901-0.987)
2005	0.85**	(0.810-0.896)
Prescription type (Ref. group: Released prescription)		
Non-released prescription	1.02	(0.974-1.063)
Patient age (Ref. group: ≤ 1 year old)		
2-5	0.85**	(0.804-0.894)
6-12	0.97	(0.919-1.023)
Patient gender (Ref. group: Female)		
Male	1.01	(0.981-1.047)
Diagnosis (Ref. group: URIs)		
Non-URIs	1.05*	(1.009-1.083)
Medical department visited (Ref. group: Family medicine department)		
Internal medicine	0.88*	(0.799-0.971)
Pediatrics	0.66**	(0.617-0.704)
Otolaryngology	0.81**	(0.762-0.867)
Non-specialist	0.88**	(0.825-0.941)
Others	1.78**	(1.627-1.953)
Physician's age (Ref. group: 51-60 years old)		
≤ 30	0.97	(0.770-1.214)
31-40	0.68**	(0.626-0.744)
41-50	0.84**	(0.777-0.917)
≥ 61	0.95	(0.876-1.039)
Physician's gender (Ref. group: Female)		
Male	0.95	(0.894-1.009)
Physician's seniority (Ref. group: 11-15 years)		
≤ 5	1.10*	(1.027-1.177)
6-10	1.13*	(1.049-1.215)
16-20	1.10*	(1.003-1.209)
≥ 21	1.28**	(1.142-1.442)
Teaching hospital status (Ref. group: No)		
Yes	0.70**	(0.608-0.805)
Ownership (Ref. group: Corporate hospital)		
Public hospital	1.09	(0.957-1.233)
Private hospital	1.17*	(1.044-1.319)
Accreditation type (Ref. group: District hospital)		
Medical center	0.73**	(0.623-0.863)
Regional hospital	1.02	(0.897-1.170)
Clinics	0.75**	(0.687-0.815)
Urbanization (Ref. group: Moderate)		
High	0.84**	(0.786-0.905)
Low	0.98	(0.905-1.057)
C value	0.598	
X^2	1,786.9817**	

*$p < 0.05$; **$p \leqq 0.001$

Journal of Food and Drug Analysis, Vol. 20, No. 3, 2012

= 1.04-1.32).

As for the accreditation type, medical center and clinic were less likely to issue an off label use antibiotic (medical center vs. district hospital, OR = 0.73, 95% CI = 0.62-0.86; clinic vs. district hospital, OR = 0.75, 95% CI = 0.69-0.82).

As for the urbanization, with the moderate urbanization group as the reference group, off-label use antibiotic was less likely from the high urbanization group (high vs. moderate urbanization, OR = 0.84, 95% CI = 0.79-0.91).

DISCUSSION

I. *Distribution of Pediatric Antibiotic Prescriptions*

This was a retrospective, population-based study using NHIRD. Because NHIRD is a claim-based database, prescriptions not reimbursed by the Bureau of NHI, such as over-the-counter drugs and prescription drugs paid out-of-pocket, were not included in our analyses.

Our study revealed that the incidence of off-label use antibiotic was 33.33%, indicating that children in Taiwan are readily exposed to an environment with high rates of off-label drug use. This is especially the cases in non-teaching, district and private hospitals.

In addition, our study found that those prescriptions released to community pharmacies increased over years. One explanation might be the introduction of physician-owned pharmacies, also called "gateway pharmacies", which are usually next door to physicians' clinic, in 2002 in Taiwan[21]. Although gateway pharmacies might not be avoidable in less urbanized areas[21], potential adverse outcomes, such as off-label use, resulted from the link between profits from pharmaceutical sales and physician prescribing behavior, may worth more attention.

Overall, the rates of antibiotics prescription for URIs decreased from 64.3 to 54.0% during 2002-2005. This was possibly due to the Bureau of NHI's revision on drug reimbursement policies of antimicrobial agents in 2001: "If URI patients have common cold or viral infections, use of antibiotics is prohibited. If antibiotics are necessary, clinical evidence of bacterial infection is mandatory"[22]. Previous high incidences of antibiotic prescriptions for URIs may have been controlled. However, findings from our study suggested that approximately 76.5% of antibiotic prescription were prescribed in highly urbanized regions, possibly due to the large number of institutions and population in urban areas. Implementation of strategies to prompt proper antibiotic use may be warranted in these regions.

II. *Determinants of Off-Label Antibiotic Prescriptions*

Incidences of off-label use were higher in infants, which was similar to findings from international study in pediatric patients indicating that non-licensed or off-label drug usages are the most common among neonates[22]. These results showed that infants, which are the most vulnerable, are in fact exposed to a largely insecure drug environment, which is an issue worthy of further investigation and regulation.

Compared to family medicine specialist, pediatricians were less likely to prescribe an off-label use antibiotic. Pediatricians might have more expertise knowledge and training on pediatric drug usage, in turn leading to lesser incidences of off-label use prescriptions.

Physicians aged from 31-50 years old were less likely to prescribe off-label use antibiotics than those aged 51-60 years old. This was possibly due to that young physicians are keen on learning new medical information and are more familiar with drug indications.

Off-label use antibiotics were more likely from non-teaching hospitals than teaching hospitals, thus indicating that teaching hospitals not only have lower antibiotics utilization rates[23], but also are able to avoid off-label use antibiotics. Compared to corporate hospitals, off-label use antibiotics were more likely from private institutions. This was possibly due to that corporate hospitals are mostly large hospitals with abundant resources and equipped with sophisticated medical information systems to assist physicians. Such hospitals, compared to public or private hospitals, exerted better control over off-label use antibiotic.

Off-label antibiotic prescriptions were less likely from highly urbanized regions, possibly because physicians in such regions have access to more medical information to assist drug decision-making. Physicians working in highly urbanized regions also have greater opportunities to attend in-service training, academic seminars and other education compared to physicians in suburban regions.

This study also found that released prescriptions were less likely off-label use prescriptions compared to non-release prescriptions. Pharmacist can serve as a checking point and cooperate with physicians to promote better drug safety for the general public.

CONCLUSIONS

Our study found that the incidence of off-label use of antibiotics were 33.33%. The phenomena of Off-label use of antibiotics is very common among Taiwanese children, especially in the cases whose prescriptions were issued by senior and experienced physicians, as well as those from private, non-teaching or regional hospitals. Health authorities should therefore focus especially on the determinants of prescribing behaviors of such physicians and hospitals. In addition, the study in the future would still need to explore the possible root causes of off label use which would improve the drug safety for the pediatric population.

ACKNOWLEDGMENTS

The authors are grateful for the research funding from the the National Science Council, Executive Yuan (program No.: NSC 97-2410-H-039-001) and China Medical University

(program No.: CMU96-150). This study is based on part of the data from the NHIRD provided by the Bureau of NHI, Department of Health and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of Bureau of NHI, Department of Health or National Health Research Institutes.

REFERENCES

1. Ochoa, C., Inglada, L., Eiros, J. M., Solis, G., Vallano, A. and Guerra, L. 2001. Appropriateness of antibiotic prescriptions in community-acquired acute pediatric respiratory infections in Spanish emergency rooms. Pediatr. Infect. Dis. J. 20: 751-758.
2. Gonzales, R., Steiner, J. F. and Sande, M. A. 1997. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. JAMA 278: 901-904.
3. Mainous, A. G., Hueston, W. J. and Clark, J. R. 1996. Antibiotics and upper respiratory infection: do some folks think there is a cure for the common cold. J. Fam. Pract. 42: 357-361.
4. Chang, S. C., Chang, H. J. and Lai, M. S. 1999. Antibiotic usage in primary care units in Taiwan. Int. J. Antimicrob. Agents 11: 23-30.
5. Ho, M., McDonald, L. C., Lauderdale, T. L., Yeh, L. L., Chen, P. C. and Shiau, Y. R. 1999. Surveillance of antibiotic resistance in Taiwan, 1998. J. Microbiol. Immunol. Infect. 32: 239-249.
6. Chang, S. C., Hsieh, W. C. and Liu, C. Y. 2000. High prevalence of antibiotic resistance of common pathogenic bacteria in Taiwan: the Antibiotic Resistance Study Group of the Infectious Disease Society of the Republic of China. Diagn. Microbiol. Infect. Dis. 36: 107-112.
7. Fick, D. M., Cooper, J. W., Wade, W. E., Waller, J. L., Maclean, J. R. and Beers, M. H. 2003. Updating the Beers criteria for potentially inappropriate medication use in older adults. Arch. Intern. Med. 163: 2716-2724.
8. Fu, A. Z., Jiang, J. Z., Reeves, J. H., Fincham, J. E., Liu, G. G. and Perri, M. 2007. Potentially inappropriate medication use and healthcare expenditures in the US community-dwelling elderly. Med. Care 45: 472-476.
9. Impicciatore, P., Choonara, I., Clarkson, A., Provasi, D., Pandolfini, C. and Bonati, M. 2001. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br. J. Clin. Pharmacol. 52: 77-83.
10. Hill, P. 2005. Off licence and off label prescribing in children: litigation fears for physicians. Arch. Dis. Child. 90: i17-i18.
11. Conroy, S., Choonara, I. and Impicciatore, *et al*. 2000. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. BMJ 320: 79-82.
12. McIntyre, J., Conroy, S., Avery, A., Corns, H. and Choonara, I. 2000. Unlicensed and off label prescribing of drugs in general practice. Arch. Dis. Child. 83: 498-501.
13. Chalumeau, M., Treluyer, J. M. and Salanave, B. *et al*. 2000. Off label and unlicensed drug use among French office based pediatricians. Arch. Dis. Child. 83: 502-505.
14. `T Jong, G. W., Eland, I. A., Sturkenboom, M. C., van den Anker, J. N. and Stricker, B. H. 2002. Unlicensed and off label prescription of drugs to children: population based cohort study. BMJ 324: 1313-1314.
15. O'Donnell, C. P., Stone, R. J. and Morley, C. J. 2002. Unlicensed and off-label drug use in an Australian neonatal intensive care unit. Pediatrics 110: e52.
16. Neubert, A., Dormann, H. and Weiss, J. *et al*. 2004. The impact of unlicensed and off-label drug use on adverse drug reactions in pediatric patients. Drug Saf. 27: 1059-1067.
17. Bureau of National Health Insurance. Statistical annual report, Daan, Taipei, Taiwan. http://www.nhi.gov.tw/
18. Hsiao, F. Y., Yang, C. L., Huang, Y. T. and Huang, W. F. 2007. Using Taiwan's national health insurance research databases for pharmacoepidemiology research. J. Food Drug Anal. 15: 99-108.
19. National Health Insurance Research Database. Data subsets, Chunan, MiaoLi, Taiwan. http://w3.nhri.org.tw/nhird/
20. Liu, C.Y., Hung, Y. T., Chuang, Y. L., Chen, Y. J., Weng, W. S., Liu, J. S. and Liang, K. Y. 2006. Incorporating Development Stratification of Taiwan Townships into Sampling Design of Large Scale Health Interview Survey. Journal of Health Management 4: 1-22.
21. Lee, Y. C., Huang, K. H. and Huang, Y. T. 2007. Adverse Pharmaceutical Payment Incentive and Providers' Behavior: The Emergence of the GP-owned Gateway Pharmacies in Taiwan. Health Policy and Planning. 22: 427-435.
22. Choonara, I. and Conroy, S. 2002. Unlicensed and off-label drug use in children: implications for safety. Drug Saf. 25: 1-5.
23. Gaur, A. H., Hare, M. E. and Shorr, R. I. 2005. Provider and practice characteristics associated with antibiotic use in children with presumed viral respiratory tract infections. Pediatrics 115: 635-641.