Penicillin dust exposure and penicillin resistance among pharmaceutical workers in Tehran, Iran

Ali Asghar Farshad¹, Mojtaba Enferadi¹, Shahnaz Bakand¹,
Rouhangiz Jamshidi Orak¹, Roksana Mirkazemi²

¹Occupational Health Research Center (OHRC), Iran University of Medical Sciences, Tehran, Iran, ²Hooman Research Collaborators Institute, Tehran, Iran

Background: Antimicrobial resistance (AMR) adversely impacts the prevention and treatment of a wide range of infections and is considered as a serious threat to global public health. Occupational-related AMR is a neglected area of research.

Objective: To assess exposure to penicillin dust, penicillin active materials, and to report the frequency of penicillin resistance among pharmaceutical workers in Tehran, Iran.

Methods: A quasi-experimental study was conducted among workers on a penicillin production line in a pharmaceutical company ($n = 60$) and workers in a food producing company ($n = 60$). Data were collected via survey, air sampling, and throat swab.

Results: The mean overall concentrations of penicillin dust and penicillin active material were 6.6 and 4.3 mg/m³, respectively, in the pharmaceutical industry. *Streptococcus pneumoniae* (*S. pneumoniae*) was detected in 45% (27) individuals in the exposed group, 92.6% of which showed penicillin resistance. Resistance was significantly higher among workers in penicillin production line ($p = 0.014$).

Conclusions: High level of AMR among workers in penicillin production line is a health risk for the workers as well as society as a whole through the spread of drug resistant micro-organisms.

Keywords: Penicillin dust, Antimicrobial resistance, Pharmaceutical industry, Iran

Introduction

Antimicrobial resistance (AMR) is a serious global health concern. The effectiveness of antibiotics is threatened by the emergence of AMR, which impairs the treatment of common infectious diseases.¹ AMR is defined as “resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.”¹ AMR risks lives and can result in prolonged illnesses and high health care expenditures.¹ Many studies report AMR in hospitals^{2,3} and in the general population.^{4,5} The Middle East was recognized as a region with extensive emergence of antibiotic resistance by the World Health Organization (WHO) in its report on surveillance of AMR in 2014.⁶

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals on Penicillin failed to address AMR resulting from occupational exposure.⁷ Also, WHO guidelines regarding AMR have failed to address occupational exposure to antibiotics as a potential source of AMR.⁶ Workers in pharmaceutical companies, particularly, those working on the penicillin producing

end-products line, are at risk of exposure to penicillin via inhalation and dermal contact. Exposure may occur during fermentation, chemical synthesis of derivatives, and formulation of end-products. In the fermentation process workers may be exposed to penicillin dusts, solutions, and aerosols while performing activities such as loading, sampling, maintenance, packing, and storage.⁷

The health effect of occupational exposure to antibiotics, mainly penicillin, has been previously studied. Asthma, other respiratory diseases,⁸ dermatitis, and allergies^{9–14} have been reported to be associated with exposure to antibiotics, mainly penicillin. However, most studies investigate AMR as a result of dermal contact to antibiotics and not airborne exposure to antibiotics.⁷ Few studies reported quantitative monitoring of penicillin dust and AMR in pharmaceutical industries^{7,15}. Sarker et al. assessed the level of antibiotic resistance among occupationally exposed and compared the degree of bacterial resistance between pharmaceutical workers ($n = 20$) and non-pharmaceutical workers ($n = 20$) in Bangladesh. Results indicated that all of the isolated species of bacteria showed a significant AMR in pharmaceutical workers compared with non-pharmaceutical subjects.¹⁶

Correspondence to: Ali Asghar Farshad, Occupational Health Research Center (OHRC), Iran University of Medical Sciences, Hemmat Highway, Tehran, Iran. Email: fdgir@yahoo.com

Figure 1 Study flowchart.

Penicillins are a class of antibiotics produced by some members of the genus *Penicillium*.^{17,18} Penicillin was one of the first medications used against many bacterial infections caused by staphylococci and streptococci and still are used widely. Penicillin group of antibiotics include penicillin G (intravenous use), penicillin V (oral use), procaine penicillin, and benzathine penicillin (intramuscular use). Penicillin is a solid powder that can be dispersed via air during handling in production plants. Several derivatives of penicillin are currently produced in Iran.

The present study is the first to assess the level of exposure to penicillin dust (airborne and aerosol) and penicillin resistance among pharmaceutical workers in Tehran, Iran. This study was conducted in response to a complaint to the Ministry of Health and Medical Education (MoHME) by penicillin production line workers about frequent prolonged infectious diseases that were unresponsive to common antibiotics. The research team was assigned by MoHME to investigate the case. The objective of this study was to measure exposure to penicillin dust and active penicillin materials among pharmaceutical production line workers and to compare the level of drug resistance exposed and unexposed workers.

Materials and methods

Research was conducted with an occupationally exposed group and a control group (non-occupationally exposed). Data were collected between January and March of 2013 in Tehran, Iran.

Participants

The exposed group consisted of workers in penicillin production line ($n = 60$) in a pharmaceutical company. The exposed group included 41 males and 19 females that worked in a similar environment and workplace conditions. Sixty workers in a food production industry were selected as control group for comparing the level of AMR

among the two groups. The two groups were matched based on age, sex and work duration. There was no shift work in both groups. The control group consisted of 42 males and 20 females that worked in similar environment, but had no history of work in pharmaceutical companies. Both industries were located in similar areas of Tehran, but with enough distance to assume that food industry workers were not exposed to penicillin dust.

Data collection tools

Data were collected via questionnaire, air samples measurements to determine the concentration of penicillin dust and the concentration of active penicillin materials, and individual throat swabs samples to measure the level of AMR.

Data collection forms

The questionnaire included demographic information (age, sex, education), exposure to penicillin dusts, use of prescribed antibiotics or self-prescription of antibiotics, reported prolonged infectious diseases with no response to antibiotics, and history of antibiotic use in the past month. Prolonged infectious diseases with no response to antibiotics were defined as an infection that persisted after completion of the whole antibiotic course prescribed by a physician. Questionnaires were self-administered for both groups. Researchers clarified any questions that respondents had while filling the forms.

Air sampling

Individual air sample collection was performed based on NIOSH Manual of Analytical Methods (1994)¹⁹ and the technique used by Shmunis et al.²⁰ Individual sampling pumps (Gilian model HFS 513 A), milipor filter with a pores diameter of 0.8 μm (Schleicher & Schuell, Germany), 37 mm cassette with 5 μm PVC filter (Gilian) were used to collect the air samples. The calibration of sampling pumps was done by standard rotameter. The calibration flow rate was set at 2.4 LPM. One sample was taken for each worker at the breathing zone level.

Sampling stations were selected after field observation of penicillin production work procedures. The clean room where drug vials are filled, space around mixing equipment and filling machines (while air conditioners were on) were selected as sampling stations. Individual air samples were collected in the breathing zone of workers. The pumps were installed on belts and the samplers were attached to the collar or dresses of workers. Sixty individual samples were taken from the exposed group. Filter moisture removal was performed by desiccator for 24 h. There were two production lines in the penicillin production industry: an older line with fermentation and filling equipment purchased more than 30 years ago and a newer production line. In the older system, powder containing penicillin was filled from funnels to small containers on a rotating disk. The rotating disk then transferred the powder

to vials. In the newer production line, powder travelled via funnels to containers in a sealed encasement and then from container into vials. Samples were collected in both production lines.

The sampling stations, type of sampling, the holder filter number, temperature and moisture level, date, and time were registered for each sample. Vaisala HUMICAP® Humidity and Temperature Transmitter Series HMT310 (made in Finland) was used to measure temperature and humidity.

Determination of the levels of total dust

The filter weight was measured before and after sampling by a weighing machine with an accuracy of 0.00001 mg (Shimadzu Corporation). Weighing was performed three times for each filter before each measurement. If the measurements differed, calibration was repeated. The following formula was used to calculate dust concentration.

$$C = [(W_2 - W_1) \times 1000] / V_{\text{STP}}$$

Where: C = concentration (mg/m³); W_2 = Weight of filter after sampling (mg); W_1 = Weight of filter before sampling (mg); V_{STP} = the volume of sampled air in standard situation (L).

The adjustment for calculating standard air volume in different temperature and air pressure was based on the formula:

$$V_{\text{STP}} = V \times P / P_0 \times [(273 + 25) / (273 + t)]$$

Where: V_{STP} = the volume of sampled air in standard situation (L); V = the volume of sampled air (L); P_0 = Atmospheric pressure at sea level (760 mm Hg); P = Atmospheric pressure at sampling situation (mm Hg); $273 + 25$ = The standard temperature in occupational health (°K); t = The temperature at the time of sampling (°C).

Analysis of active penicillin material in the dust

To calculate the penicillin active material concentration in the total dust, each filter was placed in a glass-sealed container and stored in five ml mixture of water, acetonitrile, and monobasic potassium phosphate for 30 min in shaker. The solution was then transformed to a high performance liquid chromatography (HPLC). The HPLC was Agilent 1100 series, model ISS-100 equipped with UV detector (56, 47, and 37). The flow rate was set at 1 ml/min and there were three injections for each sample. The mobile phase composition was 14 g potassium phosphate monobasic and 6 g tetrabutylammonium adjusted to pH 7.5 ± 0.05 .

The retention time was nine minutes and the injecting volume for sample and standard solution was 20 µL. The area under peak curves of HPLC analysis for sample and standard solutions was used to calculate the penicillin active concentration based on the formula:

$$\% \text{ Penicillin} = 50C(G_s/W_u)(r_u/r_s)$$

Where: C = concentration of penicillin in standard solution (mg/mL); G_s = percentage of penicillin in standard solution; W_u = sample weight (mg); r_u = the area under peak curve for sample (milli absorbance units mAU); r_s = the area under peak curve for standard solution (milli absorbance units mAU).

The concentration of penicillin in the air sample was calculated based on the below formula:

$$C = (A \times 1000) / V_{\text{STP}}$$

Where: C = the penicillin dust concentration (mg/m³); A = Concentration of penicillin active material in injected sample (mg); V_{STP} = Volume of sampled air in standard situation (L).

Time Weighted Average (TWA) was calculated based on the result of individuals sampling and the below formula

$$\text{TWA} = (C_1 T_1 + C_2 T_2 + \dots + C_n T_n) / (T_1 + T_2 + \dots + T_n)$$

Where: C = concentration of penicillin (mg); T = time duration of (h).^{21,22}

Determining the level of antimicrobial resistance

To assess AMR, bacteria of the species *Streptococcus pneumoniae* (*S. pneumoniae*) were isolated from throat swabs. Samples were cultured and *S. pneumoniae* species was separated from the culture. The separated species were cultured again to test the level of drug resistance. Disk diffusion (Kirby Bauer) method was used for detection of resistance level. A volume of bacteria was dissolved in sterile physiologic serum to reach to turbidity in the solution equal to 0.5 McFarland. The bacterial suspensions, adjusted to 0.5 McFarland, were streaked across the entire surface of the Müller-Hinton-Agar. Antibigram disks were placed in the culture with 12 mm distance from each other and the plate walls. It was kept in incubator for 24 h and in 37 °C. The level of resistance to penicillin was based on the diameter of the growth inhibition zone (diameter less than 20 mm was considered as a resistant case).²³

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 19.0 for windows (IBM Corporation, New York, United States) was used for data analysis. Descriptive statistics, Mann-Whitney U test and Fisher exact test were used to describe the data and test for differences between the exposed and control groups. The level of significance was set at 0.05.

Ethical considerations

Ethical approval for this study was obtained from the Medical Ethics Committee of Iran University of Medical Sciences in Tehran-Iran. The study procedures and objectives were explained to the participants and all study participants provided written informed consent prior to their participation.

Table 1 Characteristics of the exposed group and control group

Characteristics	Exposed group	Control group
	Mean (SD)	
Age	36.0 (4.9)	35.4 (4.9)
p value	1.000	
Work history in penicillin production line	10.9 (3.9)	0 (0.0)
p value	1.000	
	Number (%)	
Sex		
Female	19 (31.7)	18 (30)
Male	41 (68.3)	42 (70)
p value	1.000	
Education		
Diploma	54 (90)	52 (86.7)
Secondary high school	4 (6.7)	8 (13.3)
Primary	2 (3.3)	0 (0.0)
p value	0.875	
Exposure to penicillin		
Yes	60 (100)	0 (0.0)
No	0 (0.0)	60 (0.0)
p value	1.000	
Antibiotic use in last month		
Yes	1 (1.7)	0 (0.0)
No	59 (98.3)	60 (100)
p value	1.000	
Self-medication (antibiotic)		
Yes	1 (1.7)	6 (10.0)
No	59 (98.3)	54 (90.0)
p value	0.000	
Self-report of antibiotic resistance (prolonged infectious diseases with no response to antibiotics)		
Yes	60 (100)	5 (16.7)
No	0 (0.0)	55 (83.3)
p value	0.000	

Results

Characteristics of participants

Table 1 shows the characteristics of participants in the exposed and control groups. Mean age of the exposed group was 36.0 ± 4.9 (standard deviation) years and mean age of the control group was 35.4 ± 4.9 years. Mean work history in penicillin production line was 10.9 ± 3.9 years for exposed group, while no one in the control group had experience of working in the pharmaceutical industry. Most participants had educational level of diploma (90% in exposed group and 86.7% in control group). All penicillin production line workers were exposed to penicillin dust, compared with none in the control group. There was one report of antibiotic use in the last month in the exposed group but none in the control group. There were six reported cases of self-medication (antibiotics) in the control group and one case in the exposed group. All workers in the exposed group self-reported antibiotic resistance in the previous year, defined as a prolonged infectious diseases with no response to antibiotics, while five cases in the control group self-reported prolonged infectious diseases with no response to antibiotics in the previous year.

Table 2 Concentration of penicillin dusts, active penicillin materials and TWA among workers in older and newer production lines

	Number	Mean $\pm$ SD (mg/m ³)	<i>p</i> value*
<i>Concentration of penicillin dusts</i>			
Overall production line	60	6.6 $\pm$ 1.3	0.0001
Older production line	36	7.67 $\pm$ 0.13	
Newer production line	24	5.10 $\pm$ 0.04	
<i>Concentration of penicillin active material</i>			
Overall production line	60	3.7 $\pm$ 0.7	0.0001
Older production line	36	4.30 $\pm$ 0.09	
Newer production line	24	2.87 $\pm$ 0.03	
<i>TWA</i>			
Older production line	36	7.66 $\pm$ 0.14	0.0001
Newer production line	24	5.1 $\pm$ 0.05	

*Mann–Whitney U test.

Penicillin concentration and TWA

The level of total dust concentration in the older and the newer production lines showed that the mean total dust concentration was 7.67 mg/m^3 in the older production line and the mean total dust concentration was 5.10 mg/m^3 in the newer production line. The difference was statistically significant ($p = 0.0001$) (Table 1).

Based on individual air sampling, the level of penicillin active material concentration in the older and the newer production lines were significantly different in the mean concentration of penicillin dust ($4.3 \pm 0.09 \text{ mg/m}^3$ vs. 2.9 ± 0.03 , respectively) ($p = 0.0001$) (Table 2).

TWA exposure to penicillin dust for workers in the older production line was $7.7 \pm 0.1 \text{ mg/m}^3$ and $5.1 \pm 0.05 \text{ mg/m}^3$ for workers on the newer production line. There was a significant difference in TWA exposure to penicillin dust between the two lines ($p = 0.0001$) (Table 2).

Prevalence of penicillin resistance

Table 3 shows drug resistance level for the exposed and control groups. *S. pneumoniae* was detected in 45% (27) of the exposed group, and 92.6% of the *S. pneumoniae* positive cases were drug resistant. *S. pneumoniae* was detected in 35% (21) of the control group, and 71.4% of the *S. pneumoniae* positive cases were drug resistant (Figure 1). This difference was statistically significant ($p = 0.014$).

Table 4 shows the association between drug resistance and gender and age of participants in both groups. Gender and age were not statistically associated with penicillin resistance ($p = 0.771$ and $p = 0.679$, respectively). Table 5 shows comparison of the drug resistance level between the two pharmaceutical production lines. *S. pneumoniae* was detected in 17 (51.5%) of workers in the older production line (94.1% drug resistant) and among eight (33.3%) workers in the newer production line (87.5% drug resistant). Drug resistance was not significantly different between the two production line groups ($p = 0.243$).

Table 3 Comparing drug resistance level among pharmaceutical workers and food production workers (control group)

Groups	Samples with detected <i>S. pneumoniae</i>	Samples with drug resistance
	Number (% of total)	Number (% of samples with detected <i>S. pneumoniae</i>)
Penicillin exposed group	27 (45%)	25 (92.6)
Control group	21 (35%)	15 (71.4)
<i>p</i> value #		0.014

#Fisher exact test.

Table 4 Association between age and sex and drug resistance in both groups

Characteristics	Resistance	Non resistance	<i>p</i> value
	Mean $\pm$ SD	Mean $\pm$ SD	
Age	37.2 $\pm$ 5.0	36.6 $\pm$ 4.2	0.771*
Gender	Number (%)	Number (%)	
Male	28 (84.8)	5 (15.2)	0.679#
Female	11 (78.6)	3 (21.4)	

*Mann–Whitney *U* test.

#Fisher exact test.

Table 5 Comparing drug resistance level in older and newer penicillin production line

	Older production line (<i>n</i> = 33)	Newer production line (<i>n</i> = 23)
<i>S. pneumoniae</i>	17 (51.5)	8 (33.3)
Detected (% of total)		
Drug resistance (% of applicable cases)	16 (94.1)	7 (87.5)
<i>p</i> value#		0.243

#Fisher exact test.

Discussion

The WHO, in its report on AMR surveillance, emphasized AMR as a complex global public health challenge that requires complex strategies to prevent its emergence and spread.⁶ Occupational-related AMR is a neglected area of study that should be considered from both aspects of safety and health of workers and as a strategy for combating global AMR. This study is one of handful to measure the level of exposure to penicillin dust and the only study to our knowledge to compare penicillin resistance among pharmaceutical workers with a control group in Iran.

This study showed that the level of penicillin resistance was significantly more among pharmaceutical workers compared with the age and sex matched food industry workers. This can be attributed to exposure to low volume of penicillin for a long duration. A study on exposure of pharmaceutical workers on the development of antimicrobial drug resistance that compared drug resistance among 20 male workers from five local pharmaceutical companies and 20 male subjects not involved in the pharmaceutical field showed that all the isolated species of bacteria from pharmaceutical workers exhibited higher degree of

multi-drug resistance compared with non-pharmaceutical subjects.¹⁶

In this study, the percentage of penicillin resistance was nearly 93% in pharmaceutical workers and 71.4% among food industry workers, indicating a high level of resistance in both groups. A similar result were reported by study of Sarker et al.¹⁶ in Bangladesh that showed 100% resistance to amoxicillin for pharmaceutical workers and 66.7% resistance for non-pharmaceutical workers. A surveillance by WHO on drug resistance has reported 33.9% *S. pneumoniae* resistance or non-susceptibility to penicillin in Iran, which is a much lower resistance level in comparison with the prevalence reported in this study.⁶

The results of this study showed that the mean concentration of total dust, active penicillin dust and TWA in older production line were 7.67, 4.30 and 7.66 mg/m³, respectively, and in newer production line were 5.10, 2.87 and 5.1 mg/m³, respectively. There is no standard set for exposure limit to penicillin dust. OSHA considered 15 mg/m³ and ACGIH considered 10 mg/m³ for nuisance dusts, which contains no asbestos and quartz less than 1%.¹⁹ Shmunès et al. showed a significant increase in incidence of allergic symptoms in workers exposed to 0.1 to 9.9 mg/m³ penicillin as compared to below 0.1 mg/m³.¹⁹ Hanke & Patnode,²⁴ found excessive prevalence of asthma and respiratory symptoms in penicillin exposed workers at a total dust concentration of 0.29 mg/m³ (0.12–0.45 mg/m³). Exposure level to penicillin dust in the present study was much higher than that reported by Shmunès et al.²⁰ and Hanke and Patnode.²⁴

This study showed that the concentration of penicillin dust was significantly higher in the older production line compared to the newer production line. This can be attributed to the differences in filling system of vials in the two lines. Binks in his study on occupational toxicology and control of exposure to pharmaceutical agents at work showed that without proper control measures, workers are exposed to active pharmaceutical ingredients in the primary manufacture.²⁵

The results of this study showed no significant difference in drug resistance level between the older and the newer production line workers, possibly as a result of the small sample size, or because no difference existed, as drug resistance is mainly due to chronic exposure to penicillin, regardless of the volume of exposure.

It is noteworthy to mention that penicillin active material dust consisted around half of the total dusts. This finding highlights the needs for measures to eliminate dust level in the penicillin production line of the industry.

Study limitations

In this study, all the study subjects were from only one pharmaceutical company, which may limit generalizations to other Iranian pharmaceutical industries. Another limitation is the lack of measurement for penicillin dusts in food industry group. As there was no source of

penicillin in the food production industry, it was assumed that there should not be any penicillin in the dusts of this factory, and therefore it was not measured. Confounding variables including the frequency and duration of previous intake of penicillin for therapy of infections, and the prevalence of underlying illnesses such as diabetes, cardiovascular diseases, respiratory diseases, and genito-urinary tract infections were not studied. In addition, there is no standard and universally accepted sampling device for pharmaceutical dust.²⁵

Conclusion

This study found high penicillin dust exposure and occupational-related AMR among workers in the penicillin production line. This is a risk to both individual workers, their families, and to society. More attention to occupational-related AMR among workers in pharmaceutical industries is recommended and additional safety precautions for occupationally exposed groups should be implemented.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

- World Health Organization. Antimicrobial resistance. Fact sheet N°194. 2014a. [cited 2014 Sep 3]. Available from: <http://www.who.int/mediacentre/factsheets/fs194/en/>
- Kumari N, Mohapatra TM, Singh Y. Prevalence of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in a Tertiary-Care Hospital in Eastern Nepal. *J Nepal Med Assoc*. 2008;47:53–6.
- Tiwari HK, Sapkota D, Sen MR. High prevalence of multidrug-resistant MRSA in a tertiary care hospital of northern India. *Infect Drug Resist*. 2008;1:57–61.
- Cardoso MRA, Nascimento-Carvalho CM, Ferrero F, Berezin EN, Ruvinsky R, Camargos PA, et al. Penicillin-resistant pneumococcus and risk of treatment failure in pneumonia. *Arch Dis Child*. 2008;93:221–5.
- van de Sande-Bruinsma N, Grundmann H, Verloo D, Tiemersma E, Monen J, Goossens H, Ferech M. European antimicrobial resistance surveillance system. Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis*. 2008;14:1722–30.
- World Health Organization. Antimicrobial resistance. Global report on surveillance. 2014b. [cited 2014 Jan 12]. Available from: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf
- Moore GA, Nygren O. The Nordic expert group for criteria documentation of health risks from chemicals: 134. Penicillins. 2004. [cited Jan 3]. Available from: http://www.inchem.org/documents/kemi/kemi/ah2004_06.pdf
- D'iaz Angulo S, Szram J, Welch J, Cannon J, Cullinan P. Occupational asthma in antibiotic manufacturing workers: case reports and systematic review. *J Allergy*. 2011;2011:1–9.
- Møller NE, Würden K. Hypersensitivity to semisynthetic penicillins and cross-reactivity with penicillin. *Contact Dermatitis*. 1992;26:351–2.
- Møller NE, Nielsen B, von Würden K. Changes in penicillin contamination and allergy in factory workers. *Contact Dermatitis*. 1990;22:106–7.
- Rembade P, Rudzki E. Occupational allergy in the production of drugs. *Pol Tyg Lek*. 1990;45:82–4.
- Stejskal VD, Forsbeck M, Olin R. Side chain-specific lymphocyte responses in workers with occupational allergy induced by penicillins. *Int Arch Allergy Appl Immunol*. 1987;82:461–4.
- Rudzki E, Rebandel P, Rebandel B. Occupational allergy to antibiotics. *Med Pr*. 1986;37:383–7.
- Rudzki E, Lukasiak B, Leszczyński W. Penicillin hypersensitivity and haemagglutinating antibodies in workers at a penicillin factory. *Acta Allergol*. 1985;20:206–14.
- Haddadin RN, Saleh SA, Ayyash MA, Collier PJ. Occupational exposure of pharmaceutical workers to drug actives and excipients and their effect on *Staphylococcus* spp. nasal carriage and antibiotic resistance. *Int J Occup Environ Health*. 2013;19:207–14.
- Sarker MR, Islam KN, Huri HZ, Rahman M, Imam H, Hosen MB, et al. Studies of the impact of occupational exposure of pharmaceutical workers on the development of antimicrobial drug resistance. *J Occup Health*. 2014;56:260–70.
- Corey SV, Taylor GC. Penicillins, cephalosporins, quinolones. *Clin Podiatr Med Surg*. 1992;9:385–407.
- Kirk RE, Othmer DF, Grayson M. Kirk-Othmer Concise encyclopedia of chemical technology. New York: Wiley; 1985.
- Eller PM, Cassinelli ME, editors. NIOSH manual of analytical methods. 4th ed. Atlanta (GA): DIANE Publishing; 1994. (2) pp. 1–4.
- Shmunis E, Taylor JS, Petz LD, Garratty G, Fudenberg HH. Immunologic reactions in penicillin factory workers. *Ann Allergy*. 1976;36:313–23.
- Boison JO. Chromatographic methods of analysis for penicillins in food-animal tissues and their significance in regulatory programs for residue reduction and avoidance. *J Chromatogr A*. 1992;624:171–94.
- Food and Drug Administration. Guidance for industry, Q7A good manufacturing practice guidance for active pharmaceutical ingredients. 2001.
- Cockerill FR. Performance standards for antimicrobial disk susceptibility testing: approved standard. Clinical and Laboratory Standards Institute, National Committee for Clinical Laboratory Standards. 11th ed. Clinical and Laboratory Standards Institute; 32(3); 2012. [cited 2014 Jan 26]. Available from: <http://antimicrobianos.com.ar/ATB/wp-content/uploads/2012/11/01-CLSI-M02-A11-2012.pdf>
- Hanke W, Patnode R. Health hazard evaluation report No. GHE 80-169-1300. Mylan Pharmaceutical, Morgantown, USA National Institute for Occupational Safety and Health. 1983. [cited 2014 Feb 24]. Available from: <http://www.cdc.gov/niosh/nioshtic-2/00178924.html>
- Binks SP. Occupational toxicology and the control of exposure to pharmaceutical agents at work. *Occup Med*. 2003;53:363–70.