

Poliomyelitis: Current Status in Iran and Worldwide

Rahim Vakili¹, Zahra Emami Moghadam², Seyed Mohsen Soltani³, Ali Khakshour⁴, Gholamreza Khademi¹, *Masumeh Saeidi⁵

¹Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

² Faculty Member, Department of Community Health and Psychiatric Nursing, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran.

³Resident of Neurology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

⁴Department of Pediatrics, Faculty of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran.

⁵Students Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Poliomyelitis (polio) is a highly infectious viral disease, which mainly affects young children. The virus is transmitted by person-to-person spread mainly through the faecal-oral route or, less frequently, by a common vehicle (e.g. contaminated water or food) and multiplies in the intestine, from where it can invade the nervous system and can cause paralysis. Initial symptoms of polio include fever, fatigue, headache, vomiting, stiffness in the neck, and pain in the limbs. In a small proportion of cases, the disease causes paralysis, which is often permanent. There is no cure for polio, it can only be prevented by immunization. Of the 3 types of wild poliovirus (type 1, type 2 and type 3), type 2 wild poliovirus transmission has been successfully stopped (since 1999). Today, despite a concerted global eradication campaign, poliovirus continues to affect children and adults in Afghanistan, Pakistan and some African countries (Nigeria). In Iran, the last laboratory-confirmed indigenous polio case was reported in 1997. Until poliovirus transmission is interrupted in these countries, all countries remain at risk of importation of polio, especially in the 'poliovirus importation belt' of countries from west Africa to the Horn of Africa.

Key Words: Poliomyelitis, Prevalence,



Fig.1: The Geographical Position of Iran vs. Pakistan and Afghanistan

*Corresponding Author:

Masumeh Saeidi, Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad Iran. Email: Masumeh_Saeedi@yahoo.com

Received date: May 12, 2015 ; Accepted date: May 20, 2015

Introduction

Poliomyelitis is a highly infectious disease caused by wild poliovirus types 1, 2 and 3. The virus is transmitted from personto-person through ingestion of infected fecal matter. Following infection, the virus is shed intermittently in excrement for several weeks with little or no symptoms in majority of cases. The initial symptoms of poliomvelitis include fever, fatigue, headache, vomiting, neck stiffness and pain in the limbs. Less than 1% of the infected develop irreversible persons paralysis. Poliomyelitis mainly affects children less than five years. 5%-10% of those paralyzed by the virus die as a result of breathing complications (Table. 1). Oral Poliovirus Vaccine (OPV) is used as the primary vaccine in interrupting Wild Polio Virus (WPV) transmission, administered through immunization routine or during Supplementary Immunization Activities (SIA). When given multiple times this vaccine almost always protects a child for life.

Table 1: Outcomes	s of poliovirus infection	
-------------------	---------------------------	--

Outcome	Proportion of cases ^[1]
No symptoms	90–95%
Minor illness	4–8%
Nonparalytic aseptic meningitis	1–2%
Paralytic poliomyelitis	0.1–0.5%
- Spinal polio	79% of paralytic cases
— Bulbospinal polio	19% of paralytic cases
— Bulbar polio	2% of paralytic cases

Polio invades the nervous system and can cause irreversible paralysis in a matter of hours. When a child is infected with wild

poliovirus, the virus enters the body through the mouth and multiplies in the intestine. It is then shed into the environment through the faeces where it can spread rapidly community, through а especially in situations of poor hygiene and sanitation. If a sufficient number of children are fully immunized against polio, the virus is unable to find susceptible children to infect, and dies out. Most infected people (90%) have no symptoms or very mild symptoms and usually go unrecognized. In others, initial symptoms include fever, fatigue, headache, vomiting, stiffness in the neck and pain in the limbs (1-5).

Poliomyelitis has existed for thousands of years, with depictions of the disease in ancient art. The disease was first recognized condition as a distinct by Michael Underwood in 1789(1) and the virus that causes it was first identified in 1908, by Karl Landsteiner (6). Major outbreaks started to occur in the late 19th century, in Europe and the United States (1). In the 20th century it became one of the most concerning childhood diseases in these areas (7). The first polio vaccine was developed in the 1950s by Jonas Salk (8). It is hoped that vaccination efforts and early detection of cases will result in global eradication of the disease by 2018 (9). In 2013; however, there were reports of new cases in Syria (10) and in May 2014, the World Health Organization (WHO) declared a public health emergency of international concern due to the outbreaks of disease in Asia, Africa and the Middle East(11).

Classification

The term "poliomyelitis" is used to identify the disease caused by any of the three serotypes of poliovirus. Two basic patterns of polio infection are described: a minor illness which does not involve the Central Nervous System (CNS), sometimes called abortive poliomyelitis, and a major illness involving the CNS, which may be paralytic or non-paralytic (12). In most people with a normal immune system, a poliovirus infection is asymptomatic. Rarely, the infection produces minor symptoms; these may include upper respiratory tract infection (sore throat and fever), gastrointestinal disturbances (nausea, vomiting, abdominal pain, constipation or, rarely, diarrhea), and influenza-like illness(1).

The virus enters the central nervous system in about 1% of infections. Most patients with CNS involvement develop nonparalytic aseptic meningitis, with symptoms of headache, neck, back, abdominal and extremity pain, fever, vomiting, lethargy, and irritability (13, 14). About one to five in 1000 cases progress to paralytic disease, in which the muscles become weak, floppy and poorly controlled, and, finally, completely paralyzed; this condition is known as acute flaccid paralysis (15). Depending on the site of paralysis, paralytic poliomyelitis is classified as spinal, bulbar, or bulbospinal. Encephalitis, an infection of the brain tissue itself, can occur in rare cases, and is usually restricted to infants. It is characterized by changes in mental status, confusion. headaches, fever, and, less commonly, seizures and spastic paralysis (16).

People most at risk

Polio mainly affects children under 5 years of age.

Transmission

Poliomyelitis is highly contagious via the fecal-oral (intestinal source) and the oraloral (oropharyngeal source) routes. In endemic areas, wild polioviruses can infect virtually the entire human population. It is seasonal in temperate climates, with peak transmission occurring in summer and

autumn. These seasonal differences are far less pronounced in tropical areas. The time between first exposure and first symptoms, known as the incubation period, is usually 6 to 20 days, with a maximum range of three to 35 days. Virus particles are excreted in the feces for several weeks following initial infection. The disease is transmitted primarily via the fecal-oral route, by ingesting contaminated food or water. It is occasionally transmitted via the oral-oral route, a mode especially visible in areas with good sanitation and hygiene. Polio is most infectious between seven and 10 days before and after the appearance of symptoms, but transmission is possible as long as the virus remains in the saliva or feces (17-20).

Factors that increase the risk of polio infection or affect the severity of the disease include: immune deficiency, malnutrition, physical activity immediately following the onset of paralysis, skeletal muscle injury due to injection of vaccines or therapeutic agents, and pregnancy. Although the virus can cross the maternal-fetal barrier during pregnancy, the fetus does not appear to be affected by either maternal infection or polio vaccination. Maternal antibodies also cross the placenta, providing passive immunity that protects the infant from polio infection during the first few months of life (21-27).



Prevention

There is no cure for polio, it can only be prevented. Polio vaccine, given multiple times, can protect a child for life. Polio vaccine protects children by preparing their bodies to fight the polio virus. Almost all children (99 children out of 100) who get all the recommended doses of vaccine will be protected from polio. There are two types of vaccine that can prevent polio: Inactivated Poliovirus Vaccine (IPV) and Oral Poliovirus Vaccine (OPV). Only IPV has been used in the United States since 2000; OPV is still used throughout much of the world (1, 3, 28).

Materials and Methods

The current study is a review survey which was conducted to evaluate of current status of polio by studying WHO website, Centers for Disease Control and Prevention (CDC) website and scientific texts about this subject. To evaluate the texts, the singular or combination forms of the following keywords were used: "Polio", "Vaccine", "Immunization", "Children", "Worldwide" and "WHO regions". То evaluate the electronic databases the following websites were searched: Google, Ministry of healthcare, Google Scholar, Scopus and PubMed. Also, library search was performed by referring to the journal archives of libraries, and evaluating the available Persian and English references, and also articles of research-scientific journals, and articles of the annual seminar of Imnunization and Public health.

Results

Iran

The National Polio Eradication initiative in Iran was launched in 1990. Future to the establishment of the Expand program on Immunization in 1984 and its integration with the primary health care services (in 1986), efforts were made to increase the

coverage of all EPI Vaccines in the context of PHC. This resulted in high vaccine coverage against all EPI target diseases including Polio by 1989, and hence paving the way for polio eradication initiative which was launched in 1990. Stopping poliovirus transmission has been pursued combination through а of routine immunization and supplementary immunization campaigns which are guided by high quality surveillance. In the first years when the global polio eradication program was initiated approximately 50 polio cases were reported from Iran annually but the last laboratory confirmed indigenous polio case was reported in 1997, and importation of wild poliovirus from neighboring endemic countries (Afghanistan and Pakistan) was stopped in December 2000. Thus the country has remained poliofree for the past 17 years.

The existence of an excellent primary health care system based on health houses, health posts, and rural and urban health centers which is accessible to more than 95% of total population, is a cornerstone for the achievement and maintenance of polio eradication in Iran. Routine Immunization against Polio has been mandatory since 1984. The routine OPV3 has reached and maintained coverage of close to 100% since Supplementary 2002. immunization activities (SIAs) including NIDs, Sub-NIDs and mopping up operations have been crucial to the success of polio eradication in the country. NIDs were successfully implemented annually during the period 1994 – 1998. Since 1997 sub-NIDs have been carried out in high risk areas every year for prevention of reemergence of wild polio virus due to circulation of virus in Afghanistan and Pakistan and risk of importation of poliovirus from these endemic countries (29).

At current, polio cases have decreased by over 99% since 1988, from an estimated 350 000 cases in more than 125 endemic countries then, to 416 reported cases in 2013. These included only 160 cases in endemic countries; international spread from endemic areas into polio-free areas accounted for the remainder. In 2014, only parts of 3 countries (Afghanistan, Pakistan and Nigeria) in the world remain endemic for the disease-the smallest geographic area in history. Of the 3 strains of wild poliovirus (type 1, type 2, and type 3), wild poliovirus type 2 was eradicated in 1999 and case numbers of wild poliovirus type 3 are down to the lowest-ever levels with the no cases reported since November 2012 from Nigeria (30-32).

Afghanistan

No new cases of Wild Poliovirus type 1 (WPV1) have been reported until 5 May 2015. The most recent case had onset of paralysis in Gulestan district of Farah province on 5 May. The total number of WPV1 cases for 2015 remains 2, and 28 for 2014. Most of the cases from 2014 were linked with cross-border transmission from neighbouring Pakistan (30).

Nigeria

No new Wild Poliovirus type 1 (WPV1) cases were reported until 5 May 2015. Nigeria's total WPV1 case count for 2014 remains 6. The most recent case had onset of paralysis on 24 July in Sumaila Local Government Area (LGA), southern Kano state. No new type 2 circulating Vaccine-Derived Poliovirus (cVDPV2) cases were reported this week. No cases have been reported in 2015. The most recent case had onset of paralysis on 16 November in Barde Local Governmental Area of Yobe state. The total number of cVDPV2 cases for 2014 in Nigeria remains 30 (31).

Pakistan

One new case of wild poliovirus type 1 (WPV1) was reported this week in North Waziristan district in the Federally Administered Tribal Areas. This most recent case had onset of paralysis on 6 May 2015. The total number of WPV1 cases for 2015 is now 24 (and remains 306 for 2014). No new type 2 circulating vaccine-derived poliovirus (cVDPV2) cases were reported in the past week. No cases have been reported in 2015. The number of cVDPV cases reported in 2014 remains 22 (Tables. 2, 3) (32).

Total Cases	20	15	2014		Total in 2014	
	WPV	cVDPV	WPV	cVDPV	WPV	cVDPV
Globally	25	0	84	14	359	55
In endemic countries*	25	0	74	14	340	52
In non- endemic countries	0	0	10	0	19	3

Table 1: Wild poliovirus type 1 and Circulating vaccine-derived poliovirus cases (WHO, 26 May 2015).

* Nigeria, Pakistan, Afghanistan.

Countries	2	015	2014		Total in 2014		Onset of paralysis of most	
							recent case	
	WPV	cVDPV	WPV	cVDPV	WPV	cVDPV	WPV	cVDPV
Pakistan	23	0	67	10	306	22	20-Apr-15	13-Dec-14
Afghanistan	2	0	4	0	28	0	5-May-15	N/A
Nigeria	0	0	3	4	6	30	24-Jul-14	16-Nov-14
Somalia	0	0	0	0	5	0	11-Aug-14	N/A
Equatorial Guinea	0	0	3	0	5	0	03-May-14	N/A
Iraq	0	0	2	0	2	0	07-Apr-14	N/A
Cameroon	0	0	3	0	5	0	09-Jul-14	N/A
Syria	0	0	1	0	1	0	21-Jan-14	N/A
Ethiopia	0	0	1	0	1	0	05-Jan-14	N/A
South Sudan	0	0	0	0	0	2	N/A	12-Sep-14
Madagascar	0	0	0	0	0	1	N/A	29-Sep-14

Table.2: Case breakdown by country

Circulating vaccine-derived poliovirus (cVDPV): Madagascar is cVDPV1, all others cVDPV2. NA: onset of paralysis in most recent case is prior to 2014. cVDPV is associated with ≥ 2 AFP (Acute flaccid paralysis) cases or non-household contacts. VDPV2 cases with ≥ 6 (≥ 10 for type1) nucleotides difference from Sabin in VP1 are reported here.

Outbreaks in polio-free countries

In 2014, a total of 19 WPV cases were reported in six previously polio-free countries, a 93% decrease from 2013, when 256 WPV cases were reported in five polio-free countries. Α large outbreak in the Horn of Africa following an importation of WPV of Nigerian origin accounted for 54% of WPV cases globally in 2013; the most recent case related to this outbreak occurred in Somalia on August 11, 2014. In late 2013 and early 2014, an outbreak affected Cameroon and Equatorial Guinea in Central Africa after a WPV importation of Nigerian origin. Onset of the most recent outbreak-related case was on July 9, 2014, in Cameroon. An exportation of WPV from Pakistan led to an outbreak including 36 cases in Syria and two in Iraq during 2013–2014; the most recent case related to this outbreak occurred on April 7, 2014, in Iraq (33).

Discussion

Four of six WHO regions have been certified as free of indigenous WPV, and endemic transmission of WPV continued in only three countries in May, 2015. In 2013, the global polio eradication effort suffered setbacks with outbreaks in the Horn of Africa, Central Africa, and the Middle East: however, significant progress was made in 2014 in response to all three outbreaks. Nonetheless, the affected regions remain vulnerable to WPV re-importation from endemic areas and to low-level, undetected WPV circulation. Continued response activities are needed in these regions to further strengthen AFP surveillance and eliminate immunity gaps through highquality SIAs and strong routine immunization programs.

Progress in Nigeria since 2012 has brought the goal of interrupting the last known chains of indigenous WPV transmission in Africa within reach. Elimination of all poliovirus transmission in Nigeria in the near term is feasible, through intensified efforts to 1) interrupt cVDPV2 transmission, 2) strengthen routine immunization services, and 3) increase access to children in insecure efforts areas. Similar should be implemented in all countries in Africa, where 9 months have passed without a reported WPV case, and 6 months have passed since the last reported cVDPV2 case. Undetected circulation or reimportation of WPV into vulnerable countries such as those affected by the Ebola epidemic in West Africa, which suffered damage to routine health systems and deferment of polio SIAs, threatens recent progress in Africa.

Most (86%) WPV cases in Afghanistan in 2014 resulted from importation from Pakistan; however, the detection of orphan viruses highlights the need to strengthen the quality of both polio vaccination and AFP surveillance (34). Efforts are also needed to increase population immunity by intensifying routine polio immunization activities to ensure high coverage among infants with at least 3 OPV doses.

Conclusion

Estimated coverage in 2013 (the latest year for which complete data are available) among infants aged <1 year with 3 doses of oral poliovirus vaccine delivered through (OPV3) routine immunization programs was 90% in Afghanistan, 67% in Nigeria, and 66% in Pakistan, with substantial subnational variation. OPV3 coverage was 97% in the WHO Western Pacific Region, 96% in the European Region, 90% in the Region of the Americas, 82% in the Eastern Mediterranean Region, 77% in the

African Region, and 76% in the South-East Asia Region (35-39).

However, the ongoing circulation of poliovirus in the neighboring polio endemic countries poses a threat to polio eradication in Iran. This calls for intensive international, regional and national efforts aiming at interruption of wild poliovirus circulation in the endemic countries of the Region. As the elimination of poliomyelitis in the Eastern Mediterranean Region has been hence delayed and calling for continuation of supplementary immunization activities (SNIDs), this has resulted in community fatigue and reservation of medical professionals against repeated SNIDs. Allocation of adequate financial recourses for eradication of polio continuation activities in the face of "Zero polio cases" for more than one decade is another challenge to be addressed by the national authorities.

Conflict of Interest: None.

References

1. Atkinson W, Hamborsky J, McIntyre L, Wolfe S (eds.). "Poliomyelitis". Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book) (PDF) (11th ed.). Washington DC: Public Health Foundation; 2009. pp. 231–44.

2. World Health Organization. "Poliomyelitis Fact sheet N°114". WHO.int. October 2014. Accessed, 3 November 2014.

3. "Post-Polio Syndrome Fact Sheet". http://www.ninds.nih.gov/. April 16, 2014. Accessed, 4 November 2014.

4. http://www.polioeradication.org/Data andmonitoring/Poliothisweek.aspx#sthash.45 zKqU9P.dpuf.

5. http://www.polioeradication.org/Data andmonitoring/Poliothisweek.aspx#sthash.

6. Edited by Thomas M. Daniel Frederick C. Robbins. Editors. Polio (1st ed.). Rochester, N.Y.: University of Rochester Press; 1999. p. 11. ISBN 9781580460668.

7. Wheeler, Derek S., Wong, Hector R., Shanley, Thomas P. (eds.). Science and practice of pediatric critical care medicine. London: Springer; 2009. pp. 10– 11. ISBN 9781848009219.

8. Aylward R. "Eradicating polio: today's challenges and tomorrow's legacy". Ann Trop Med Parasitol 2009;100 (5–6):401–13.

9. "Global leaders support new six-year plan to deliver a polio-free world by 2018". WHO.int. 25 April 2013. Accessed,4 November 2014.

10. "Polio in the Syrian Arab Republic - update". WHO.int. 26 November 2013. Accessed, 4 November 2014.

11. "WHO statement on the meeting of the International Health Regulations Emergency Committee concerning the international spread of wild poliovirus". WHO.int. 5 May 2014. Accessed, 4 November 2014.

12. Falconer M, Bollenbach E. "Late functional loss in nonparalytic polio". American journal of physical medicine & rehabilitation / Association of Academic Physiatrists2000;79(1):19–23.

13. Chamberlin SL, Narins B (eds.). The Gale Encyclopedia of Neurological Disorders. Detroit: Thomson Gale; 2005. pp. 1859–70. ISBN 0-7876-9150-X.

14. Leboeuf C. The late effects of Polio: Information For Health Care Providers. (PDF). Commonwealth Department of Community Services and Health. ISBN 1-875412-05-0. Archived from the original (PDF) on 25 June 2008. Accessed, 23 August 2008.

15. Frauenthal HWA, Manning JVV. Manual of infantile paralysis, with modern methods of treatment. Philadelphia Davis; 1914. pp. 79–101. OCLC 2078290.

16.Jesse B. Hall, Gregory A.Schmidt. Principles of Critical Care (3rd ed.).McGraw-Hill Professional; 2005. p. 870.ISBN 0-07-141640-4.

17. Kew O, Sutter R, de Gourville E, Dowdle W, Pallansch M. "Vaccine-derived polioviruses and the endgame strategy for global polio eradication". Annu Rev Microbiol 2005; 59: 587–635.

18. Parker SP (ed.). McGraw-Hill Concise Encyclopedia of Science & Technology. New York: McGraw-Hill; 998. p. 67. ISBN 0-07-052659-1.

19. Racaniello V. "One hundred years of poliovirus pathogenesis". Virology 2006; 344 (1): 9–16.

20. Ohri, Linda K.; Jonathan G. Marquess. "Polio: Will We Soon Vanquish an Old Enemy?". Drug Benefit Trends 1999; 11 (6): 41–54.

21. Davis L, Bodian D, Price D, Butler I, Vickers J. "Chronic progressive poliomyelitis secondary to vaccination of an immunodeficient child". N Engl J Med 1997; 297 (5): 241–5.

22. Chandra R. "Reduced secretory antibody response to live attenuated measles and poliovirus vaccines in malnourished children". <u>Br Med J</u> 1975; 2 (5971): 583–5.

23. Horstmann D. "Acute poliomyelitis relation of physical activity at the time of onset to the course of the disease". J Am Med Assoc 1950; 142 (4): 236–41.

24. Gromeier M, Wimmer E. "Mechanism of Injury-Provoked Poliomyelitis". J. Virol 1998; 72 (6): 5056– 60.

25. Evans C.Factors Influencing the Occurrence of Illness During Naturally Acquired Poliomyelitis Virus Infections. Bacteriol Rev 1960; 24 (4): 341-52.

26. Joint Committee on Vaccination and Immunisation (Salisbury A, Ramsay M, Noakes K (eds.) (2006). Chapter 26:Poliomyelitis. in: Immunisation Against Infectious Disease, 2006 (PDF). Edinburgh: Stationery Office. pp. 313–29. ISBN 0-11-322528-8.

27. Sauerbrei A, Groh A, Bischoff A, Prager J, Wutzler P. "Antibodies against vaccine-preventable diseases in pregnant women and their offspring in the eastern part of Germany". Med Microbiol Immunol 2002; 190 (4): 167–72.

28. World Health Organization. Poliomyelitis: intensification of the global eradication initiative. Geneva, Switzerland: World Health Organization; 2012.

29. Sadrizadeh B, Zahraei SM. Poliomyelitis Eradication in Iran: Opportunities and Challenges. J Compr Ped. 2013; 3(3):91-2.

30. http://www.polioeradication. org/Dataandmonitoring/Poliothisweek.aspx#s thash.45zKqU9P.llZsf3oO.dpuf.

31. http://www.polioeradication. org/Dataandmonitoring/Poliothisweek.aspx#s thash.45zKqU9P.llZsf3oO.dpuf.

32. http://www.polioeradication. org/Dataandmonitoring/Poliothisweek.aspx#s thash.45zKqU9P.llZsf3oO.dpuf.

33. Centers for Disease Central and Prevantion. Global Health - Polio. Updates on CDC's Polio Eradication Efforts. Available at:

http://www.cdc.gov/polio/updates/. Accessed, 5 May 2015.

34. World Health Organization. WHO vaccine-preventable diseases: monitoring system 2014 global summary. Switzerland: World Health Geneva, Organization; 2015. Available at http://apps.who.int/immunization_monitoring /globalsummary/timeseries/tscoveragepol3. html. Accessed 5 May 2015.

35. World Health Organization. Global Polio Eradication Initiative. Polio this week as of 5 May 2015. Geneva, Switzerland: World Health Organization; 2015. Available at http://www.polioeradication.org/Dataandmon itoring/Poliothisweek.aspx. Accessed 5 May 2015.

36. World Health Organization. Statement on the 4th IHR Emergency Committee regarding meeting the spread of wild poliovirus. international World Geneva. Switzerland: Health Organization; 2015. Available at http://www.who.int/mediacentre/news/statem ents/2015/. Accessed 27 February-2015.

37. Farag NH, Alexander J, Hadler S, Quddus A, Durry E, Wadood MZ, et al. Progress toward poliomyelitis eradication—Afghanistan and Pakistan, January 2013–August 2014. MMWR Morb Mortal Wkly Rep 2014; 63(43):973–7.

38. Vakili R, Ghazizadeh Hashemi A, Khademi Gh, Ajilian Abbasi M, Saeidi M. Immunization Coverage in WHO Regions: A Review Article. Int J Pediatr 2014;3(2.1): 111-18.

39. Ghazizade Hashemi SA, Bayyenat S, Purbafrani A. Taghizade Moghaddam H, Saeidi M. Comparison of Immunization in Iran and Turkey between Years 1980-2013. Int J Pediatr 2014;2(3.3):75-83.