The seroprevalence of diphtheria among adults in Izmir-Turkey

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Abstract
A serological survey to determine the immunity to diphtheria in the adult population in Izmir-Turkey was conducted according to the recommendations of the World Health Organization. A total of 339 blood samples were collected from subjects aged between 20 and 81, and diphtheria antitoxin levels were measured by the enzyme linked immunosorbent assay method. Titers below 0.1 IU/ml were considered to show insufficient immunity. Of the studied population, 56.3% had showed insufficient immunity against diphtheria. Diphtheria protection rates showed a gradual age-related decrease. The lowest immunity rate was observed in 40–49-year age group (30.6%) (p < 0.05). There was no significant difference in the rate of immunity between subjects in terms of sex, levels of education, urban–rural region (p > 0.05). These results emphasize the need for booster immunization of adults. The present vaccination policy should include re-vaccinations of the adult population every 10 years in order to provide a complete protection of the population.

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1. Introduction
In 1990s, after the separation of the Union of Soviet Socialist Republics, an epidemic of diphtheria emerged in Newly Independent States (NIS), and mainly in Russia, which surprised the whole world [1]. The most striking point in this epidemic is that although diphtheria is a childhood disease in pre-vaccination period it affected the adults widely in this case [2,3]. Turkey, which is neighboring those countries, was also affected from this epidemic [4].

Diphtheria toxoid was first introduced in 1937, however routine vaccination started in 1964. Diphtheria incidence in Turkey declined after a national campaign in 1985 due to high vaccination coverage achieved. However, incidence of 0.02/100 000 increased four folds in 1993, because of outbreaks in neighbor countries. For this reason, childhood immunization schedule was changed due to the epidemic. The schedule was consisted of three doses of diphtheria and tetanus toxoids and pertussis vaccine (DTP) at the 2nd, 3rd, 4th months and two booster doses included one DTP at the 18th month and one diphtheria and tetanus toxoids (pediatric formulation, DT) at the age of 7. After this epidemic, an additional booster diphtheria and tetanus toxoids (adult formulation, Td) was scheduled at 11-years old. In 2003, danger of epidemic disappeared and the vaccine postponed to the age of 14. There is still no routine diphtheria vaccination program for adults in Turkey.

Diphtheria vaccination coverage, which is about 80% in general in Turkey, shows great differences in accordance with regions. While the vaccination coverage is 80–85% in the northern and western regions, in the eastern regions it is lower (60–65%). The cases of diphtheria reported are mainly in the southeast part of the country.

In this research, inspired by the epidemic which emerged in neighboring countries where especially adults were...
affected, the aim has been to evaluate rates of immunity to diphtheria for adults and determining the factors affecting the situation, and needs analyses of booster vaccine in adulthood in Izmir-Turkey.

2. Patients and methods

2.1. Study population

The cross-sectional study was carried out at Dokuz Eylul University, the Faculty of Medicine in Izmir, in the western region, which has one of the highest vaccination rates in Turkey. According to census in 2000, about 3.4 million people live in Izmir, which is the third biggest city in Turkey, 3/4 of which live in urban areas and childhood immunization rate is 95%. Socio-economical status and health service are better than that of eastern region. There is no significant difference between immunization rates of urban and rural regions.

The number of patients was set based on level of reliability which was calculated around 95% considering the envisaged diphtheria immunization rates. For this purpose, 339 patients, who consulted to the centre laboratory in July–August 2003 to give blood samples to be tested after being examined in any one of the clinics of the Dokuz Eylul University Hospital, were interviewed and asked their oral permission to fill out a questionnaire. The patients were chosen by haphazard sample method. Questions in the form included age, sex, education level, lived in (urban/rural), diphtheria vaccination status and past diphtheria history.

2.2. Serological investigation

As the patients were giving blood to be tested, laboratory nurse also took 4 ml blood to be used in this research. The serum samples were separated by centrifugation and stored at −70 °C until tested.

Anti diphtheria IgG levels were determined by using enzyme immunoassay (ELISA) method (Genzyme Virotech GmbH, Russelsheim, Germany). The results were obtained in terms of IU/ml, up to the international standards by using a standard curve that the Virotech Diphtheria ELISA had checked with the Diphtheria Antitoxin Human Serum (S1/534) of the Institute for Biological Standards and Control, WHO International Laboratory for Biological Standards in Great Britain. The results were evaluated according to literature as follows [5]:

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1 IU/ml</td>
<td>Insufficient protection</td>
</tr>
<tr>
<td>≥0.1 IU/ml</td>
<td>Full protection</td>
</tr>
</tbody>
</table>

2.3. Statistical analysis

The results were evaluated by using Statistical Package for the Social Sciences (SPSS)-11 computer program and χ²-test was used in statistical analysis.

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Protectivity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>49</td>
<td>26</td>
<td>0.002</td>
</tr>
<tr>
<td>30–39</td>
<td>45</td>
<td>15</td>
<td>33.3</td>
</tr>
<tr>
<td>40–49</td>
<td>72</td>
<td>22</td>
<td>30.6</td>
</tr>
<tr>
<td>50–59</td>
<td>82</td>
<td>40</td>
<td>48.8</td>
</tr>
<tr>
<td>60+</td>
<td>91</td>
<td>54</td>
<td>59.3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>123</td>
<td>56</td>
<td>45.5</td>
</tr>
<tr>
<td>Female</td>
<td>216</td>
<td>101</td>
<td>46.8</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>275</td>
<td>130</td>
<td>47.3</td>
</tr>
<tr>
<td>Rural</td>
<td>64</td>
<td>27</td>
<td>42.2</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>99</td>
<td>51</td>
<td>56.9</td>
</tr>
<tr>
<td>High school</td>
<td>107</td>
<td>50</td>
<td>45.5</td>
</tr>
<tr>
<td>University</td>
<td>133</td>
<td>56</td>
<td>42.1</td>
</tr>
</tbody>
</table>

3. Results

Of the participants, 123 were men (36.3%) and 216 were women (63.7%), and their average ages were 49.33 ± 15.28 (20–81 ages). After examining the diphtheria antibody levels of the subjects of the test, it was found out that 182 (53.7%) of them did not have protection against diphtheria, and 157 (46.3%) of them had full protection.

The diphtheria protectivity rates of subjects according to their characteristics are shown in Table 1.

After comparing protection levels according to age groups, significant difference was obtained among the groups in terms of protection rates. As a result of analysis to see among which groups this difference emerges, protection at the ages of 40–49 was found to be lower than the other age groups (p < 0.05). When Fig. 1 is examined, it is observed that protection at the ages of 30–39 is low, it gets higher at the ages of 50–59 and the highest level is over 60. However, no significant differences were observed statistically in terms of age.
protection among the groups other than the age group of 40–49 ($p > 0.05$).

Of the subjects, 69.9% ($n = 237$) replied that they did not know their vaccination status, thus the protection rates were not evaluated in terms of their vaccination status. No subject had a past diphtheria history.

4. Discussion

The results of the serologic studies both in developed and developing countries bring to mind that adult population is greatly susceptible to diphtheria and booster vaccination is necessary even after childhood because of the decrease in immunity [5–8]. In many countries, diphtheria booster is included to adult immunization programs every 10 years [9,10]. It has also been accepted that soldiers and the ones traveling to the regions where the disease is endemic should be vaccinated.

In this study conducted in Izmir-Turkey, 46.3% of the 339 participants were observed to have protection and 53.7% of them were susceptible to diphtheria. According to age groups studied, protection against diphtheria starts to decrease after the age of 30, and reaches to its lowest level at the ages of 40–49. Protection rates at the ages of 40–49 were significantly lower than the other age groups ($p < 0.05$) (Table 1). The protection level starts to rise at 50–59 years of age and reaches to the highest level at 60 and over. The results showing that protection decreases with ageing and begins to increase after 50 are similar to many studies in the literature [11–14]. However, according to Turkey’s population count of 2000 the citizens at the age of 50 and over makes up of only 25% of the population over age of 20, meanwhile our research group’s half was consisting of 50 and over aged subjects (173/339). Since the immunity rates are higher at this group, the rate of total immunity might have been observed higher than the actual. In the studies performed in many different cities of the Turkey, diphtheria protection rates were found higher ($62–65\%$) than our study’s rates. The lowest immunity rates were determined in 20–29 years, 30–44 years, and 40–49 years age ranges in Ciftci’, Beyazova’ and Egemen studies, respectively [15–17].

When the age group with the lowest immunity rate was studied, it is noticed that it is changeable according to countries and usually related to the starting date of the routine childhood immunization [5,8,13–14,18–20]. In this study, it was found that protection rates were lower in the ages of 40–49, and increased after 50s again; results are compatible with the starting date, which is 1960s. As it is also noticed in our research, due to their natural immunity developed during their possible diphtheria epidemic, elderly people in some countries are still considered to be immune to diphtheria while adults who gained immunity to diphtheria through vaccination in childhood lose their immunity as they grow older. It is stated that age groups having lowest immunization rates shift to older ages in Poland, where serological studies are performed in 10–15 years of intervals [20].

In our research, when the genders of the participants are considered in terms of their protection rates against diphtheria, no significant difference was found ($p > 0.05$). It is an expected result because men are not immunized against diphtheria when they join the army. In researches carried out in many countries such as Holland, Sweden, England, Israel and the United States of America the protection rates against diphtheria in men were higher than in women [6–8,21]. The high level is associated with the administering of routine Td to men in the army. Similar to our study, in some studies no difference has been recorded between the two sexes with respect to their protection levels against diphtheria [22,23]. When our sample subjects evaluated, even though the number of females are higher than the number of the males, we do not think this affects the results since there are no significant differences among male and female immunity rates.

Protection rates against diphtheria could change according to regions within the same country depending on the disease among the regions, being a carrier and the difference of immunization rates. Since the frequency of diphtheria cases and immunization rates between both rural and urban areas and among regions are different, protection against diphtheria might be expected to be different. In this study, any difference of protection rates between rural and urban areas is not observed. However, our study sample may not be representative of the general population as high immunity rates might be obtained due to study population which have better socio-economical level. In an Italian study, protection rates in the northern region which have high socio-economical level were found to be higher than that in southern region and it emphasizes that difference could originate from high vaccination coverage [23]. In Germany, in a study performed, adult population diphtheria protection rates are found higher in East Berlin than west part (34.4%; 20.3%) [24]. To demonstrate regional differences, similar seroepidemiological studies should be also performed in the Turkey’s other regions.

When protection rates were compared with respect to the participants’ education levels, it has been found out that there is no significant difference among the groups ($p > 0.05$) (Table 1). This is an expected result since there were no vaccination programs for the participants after a 5-year primary school education in those years. However, it can be predicted that primary school graduates will have higher rates of protection against the disease as they are now immunized at the 8th grade of compulsory primary school education.

5. Conclusion

In Turkey, in accordance with the post-epidemic precautions, the additional Td vaccine included in the immunization program at the 8th grade in primary schools is a significant application to move the protection to a further adult period. In this way, protection in adulthood will be lengthened to further ages, and a long-lasting immunity will be maintained.
by subsequent booster administering. When the difficulty of booster administering application in every 10 years is considered, the increase of immunization rates against diphtheria in the society could be managed by at least vaccinating the groups under risk and administering Td instead of tetanus toxoid (TT) in every case of risky injuries. As in other countries, vaccination calendars should be revised in this way and the necessary amendments ought to be done.

Acknowledgement

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References