Immunity to Tetanus in the 3–20 year age group in Italy

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In Italy, systematic mandatory tetanus immunization of children started in 1968. In 1989, immunity against tetanus was assessed in a random sample of 758 healthy subjects aged 3–20 y, from four Italian cities. There were 257 subjects 3–5 y old all residing in Southern Italy and 501 subjects 11–20 y old from both the South and North. The overall prevalence of non-immune subjects was 19.1%, without difference by sex. The rates of subjects lacking protective antibody titres was 25.3% in children 3–5 y old (all coming from South and the islands), 11.5% in those 11 y old, and 18.9% in the 18–20 y age-group, respectively. Subjects 11–20 y old residing in the South and the islands were more likely to be non-immune that those residing in the North (20.2% vs 6.0%; P < 0.01). Socio-demographic indicators such as lowest paternal education and largest family size were both unassociated with lack of protective antibodies.

These findings indicate that an high rate of children in South of Italy do not have protective antibody levels, probably as consequence of lack of compliance with the vaccination programme. More efforts should be addressed to decrease geographical inequalities in the delivery of health care.

Keywords: immunity; Italy; tetanus

Introduction

Immunization with tetanus toxoid has been compulsory for all children in Italy since 1968. Primary vaccination consists of three doses: a single dose given in the third, fifth and eleventh month of life. A booster dose is administered at 5–6 y of age and then every 10 y. In order to ensure that people susceptible to tetanus are vaccinated, documentation of primary vaccination against tetanus is required upon enrollment in primary school.

Vaccination rates are frequently considered a surrogate measure of protection. Serum levels of protective antibody provide more accurate estimates.

The aim of this study was to evaluate the prevalence of protective levels of tetanus antibody in a national sample of subjects 3–20 y old. The effect, if any, of sociodemographic factors such as family size and father’s years of schooling on immunity status were also considered.

Materials and methods

Study population

The study population included 758 apparently healthy subjects (403 males and 355 females), 3–20 y old, residing in four Italian cities; one middle-sized city in the North (Padua), two large cities in the South (Bari and Palermo), and the city of Cagliari, which is the largest city in the Sardinia island. Subjects were recruited from kindergartens, primary schools (fifth grade), and high schools (last year), using a systematic cluster sampling.²

Briefly, all kindergarten, fifth grade of primary schools and last year of high schools were identified within each city; they were assigned to one of three lists according to level. A single class in each list was considered a cluster. Because in the fifth grade of the primary schools and in the last year of the high schools there were no subjects who were 6–10 y old or 12–17 y old, we did not study these age groups. Because schooling through 14 y of age is mandatory in Italy, children in fifth grade of primary schools are representative of the entire population of Italian children.

The sampled subjects were thus stratified in three age-groups: 3–5 y olds, 11 y olds, and 18–20 y olds. In Padua subjects were selected from 11 y of age (fifth grade of primary school), while in other cities from 3 y of age. We did not study the 3–5 y age group in Padua, where infant vaccine coverage is very high, because virtually all children in this age-group were expected to have protective antibody titres.

The study period was the year 1989. All subjects were thus born after the introduction of compulsory vaccination in 1968.

Laboratory test

After parent’s informed consent, a blood sample was taken from each participant. Sera were stored at −20 °C and subsequently tested in a single laboratory for tetanus antitoxin by passive haemagglutination (HA) method using turkey erythrocytes sensitized with absorbed tetanus antitoxin (Tetan test, Istituto Sieroterapico Milanese, Milan, Italy). Tetanus antitoxin concentrations were expressed in International Units/ml, using the reference serum given in the kit after titration against the International Standard for Tetanus Antitoxin. Antibody levels ≥ 0.11 IU/ml (HA titer > 1024) were considered to be protective.²³

The passive haemagglutination test used in our assay is a technique largely employed for serological purposes.²³ It is considered as a valid alternative to neutralisation assay for tetanus antitoxin determination in serum samples.²³ The
neutralisation test might provide more specific information about protection, but it should be performed in vivo and therefore it is time-consuming and inappropriate for epidemiological surveys.

**Statistical analysis**

Differences in proportions were evaluated by $\chi^2$ test. A $P$ value $< 0.05$ was considered to be significant. Odds Ratios (OR) were calculated considering as reference category that of the most favourable level of exposure (lowest family size and highest number of years of father’s schooling). Confidence limits of 95% of OR were calculated according to the Woolf method.²

**Results**

Out of the 758 subjects investigated, 145 (19.1%) had tetanus antitoxin titre below the protective level ($< 0.1 \text{ IU ml}^{-1}$). A similar rate (19.1%) of females and males tested non-immune. The rate of subjects lacking protective antibody titres was 25.3% in children 3–5 y of age (all coming from South and the islands), 11.5% in those were 11 y olds, and 18.9% subjects 18–20 y olds, respectively (Table 1).

Subjects 11–20 y old residing in the South and the islands were more likely to be non-immune than those residing in the North (20.2% vs 6.0%; $P < 0.001$) (Table 2).

Cases of tetanus reported from official notifications have been decreasing over the last decades in Italy from 644 in 1955 to 90 in 1993 (Figure 1). Cases are mostly reported among elderly people.⁸

Although the transformation of Italian society from an agricultural to an industrial one after World War II contributed to a decrease in tetanus incidence, immunization has been the principal tool for controlling the disease. It is of general opinion that the compulsory vaccination programme is satisfactorily complied with in Italy; tetanus vaccination coverage is estimated to be as high as 90%.⁹

Our results, referring to a cohort of subjects born after 1968 and thus who should have received a full course of tetanus vaccination, contradict this. In fact we have found that as many as 19.1% of subjects lack protective antibodies levels. Moreover, stratifying the sample by area of residence we can see that in the North the rate of non-immune subjects 11–20 y old was as low as 6%, while in the South and the islands the corresponding figure was 20.2%; most importantly 25.3% of children 3–5 y old in the South was sero-negative.

Primary vaccine failure seems unlikely because tetanus toxoid is a very effective antigen, with a rate of subjects having protective antibody levels after only two immunizations ranging from 98.7–100%.¹⁰,¹¹ Moreover in a randomly selected sample of Danes 25–30 y of age who had received a primary series of three immunizations against tetanus but no booster vaccinations, 90% of those vaccinated less than 20 y earlier still had protective levels.¹²

Given the results of the Danish study, children who receive three or more tetanus immunizations should not lose their protective levels for many years.

It is thus likely that the low rates of tetanus immunity among subjects residing in South of Italy may be related to a lack of compliance with the vaccination programme.

**Table 1** Age-specific prevalence of non-immune subjects by sex

<table>
<thead>
<tr>
<th>Age-groups (years)</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>(%)</td>
<td>$n$</td>
</tr>
<tr>
<td>3–5a</td>
<td>43/151 (28.5)</td>
<td>22/106 (20.7)</td>
<td>65/257 (25.3)</td>
</tr>
<tr>
<td>11</td>
<td>11/100 (11.0)</td>
<td>12/100 (12.0)</td>
<td>23/200 (11.5)</td>
</tr>
<tr>
<td>18–20</td>
<td>23/152 (15.1)</td>
<td>34/149 (22.8)</td>
<td>57/301 (18.9)</td>
</tr>
<tr>
<td>Total</td>
<td>77/403 (19.1)</td>
<td>68/355 (19.1)</td>
<td>145/758 (19.1)</td>
</tr>
</tbody>
</table>

*a Only South and the islands.

**Table 2** Age-specific prevalence of non-immune subjects by area of residence

<table>
<thead>
<tr>
<th>Age-groups (years)</th>
<th>North</th>
<th>South and the islands</th>
<th>$\chi^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1/50 (2.0)</td>
<td>22/150 (14.7)</td>
<td>&lt; 0.02</td>
<td></td>
</tr>
<tr>
<td>18–20</td>
<td>8/100 (8.0)</td>
<td>49/201 (24.4)</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9/150 (6.0)</td>
<td>71/351 (20.2)</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3** Prevalence of non-immune subjects by socio-demographic factors

<table>
<thead>
<tr>
<th></th>
<th>$n$ (%)</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family size:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Number of subjects in a household)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 4</td>
<td>29/155 (18.7)</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>48/288 (16.7)</td>
<td>0.87 (0.51–1.49)</td>
</tr>
<tr>
<td>Years of father’s education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12</td>
<td>52/259 (20.1)</td>
<td>1</td>
</tr>
<tr>
<td>8–12</td>
<td>39/251 (15.5)</td>
<td>0.73 (0.45–1.19)</td>
</tr>
<tr>
<td>&lt; 8</td>
<td>54/269 (20.1)</td>
<td>1.0 (0.64–1.56)</td>
</tr>
</tbody>
</table>

Lowest paternal education and largest family size were both unassociated with lack of protective antibodies (Table 3).
Our findings are in agreement with the figures of a recent study among a national sample of subjects 18–22 y old, born after 1968, showing a rate of non immune subjects significantly higher in the South than in the North (15.0% vs 5.5%). They are further supported by a survey in the Naples area (South of Italy), where only 21.2% of the children attending a primary school had received a full course of tetanus vaccination.

We believe that this phenomenon is a reflection of differential North-South health care delivery rather than a socio-cultural problem of different attitudes and knowledge of the two population groups; in fact, indicators of socio-cultural level such as family size and years of parent’s education do not affect immunity status.

Despite reductions in inequality in the health sector in Italy over the last few decades, more efforts should still be addressed to decrease regional differences.

It would be advisable for the health authorities to identify those children who enter primary school without having completed the entire vaccination cycle in order to adequately immunize them. In order to achieve this aim current health education campaigns in the field of childhood immunization should include tetanus vaccination as a component and should be addressed not only to the general public but also to the general practitioners, pediatricians and educators.

References


Figure 1 Reported cases of tetanus in Italy, 1955–1993