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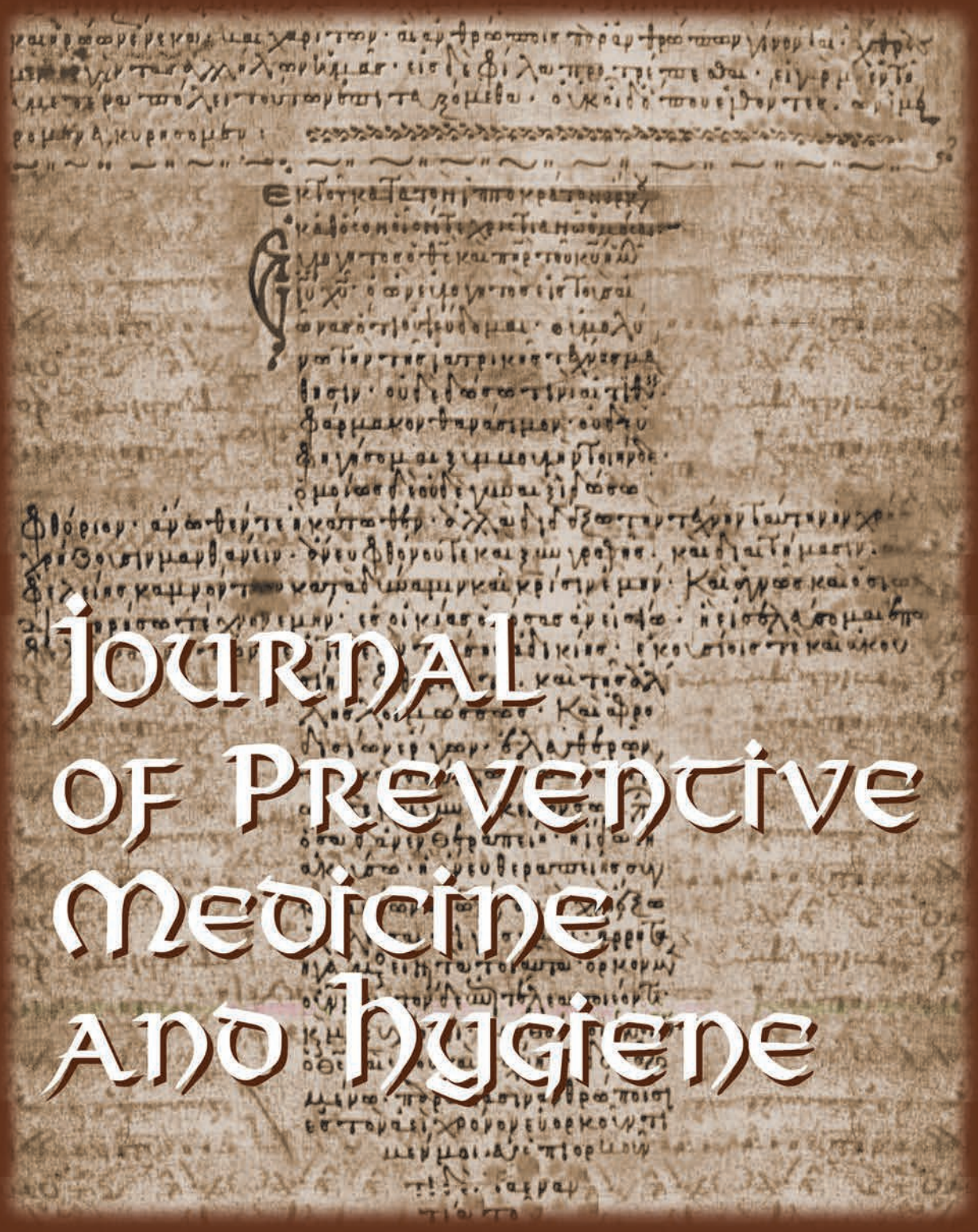

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Review

Influenza vaccination in HIV-positive subjects: latest evidence and future perspective

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Key words

Influenza vaccination • HIV-1 RNA levels • CD4+ count

Summary

Annual influenza vaccination is recommended for persons with human immunodeficiency virus (HIV) infection. Recent reports indicate that immunizations may increase HIV replication in infected individuals. Generally, vaccination against influenza is well tolerated in both children and adult individuals with HIV and does not induce significant changes in viral load and CD4+ cell counts. The observed increase in viral replication is usually transient and a clear, measurable progression of the underlying HIV disease is hard to be determined. Several studies reported immunogenicity data in HIV+ population, by comparing different influenza vaccines, adjuvanted or not, and different administration routes. Data are encouraging because an adequate immune response is shown, although split/subunit vaccines do not elicite an efficient immune response in these subjects. New strategies have been evaluated to increase the immune response in immunocompromised patients.The aim of this review is to evaluate tolerability, safety, immunogenicity and efficacy of vaccines actually approved for human use and to consider latest evidence and future perspective in HIV positive subjects.

Introduction

Influenza in HIV positive patients

Influenza illness is a worldwide, public health problem of major concern. It is a highly contagious, ubiquitous disease that can lead to severe complications, especially in the elderly, debilitated or chronically ill patients, children and in immunosuppressed subjects, including those infected with the human immunodeficiency virus (HIV) and transplant recipients [1, 2]. It is difficult to estimate hospitalizations and deaths due to influenza and its complications because infections are not often confirmed virologically or specified on hospital discharge forms or death certificates [3]. For influenza disease a significant burden lies on all individuals, but hospitalization and treatment occur more frequently in high-risk patients. In addition to the clinical burden, influenza also poses a considerable economic burden. There are extensive economic analyses of the influenza burden in the literature. One study estimated a total economic burden of seasonal influenza in the United States (using 2003 population and dollars) to be $87.1 billion, including $10.4 billion in direct medical costs [4]. In addition to the direct costs of medical care, the indirect costs of influenza are substantial due to the increase morbidity. The burden of influenza varies with the age and underlying health of the patient. Estimates of the cost of influenza in the USA, France and Germany have shown that indirect costs can be five– to 10–fold higher than direct costs [5]. In particular, influenza remains a common cause of respiratory illness in adults with HIV, despite the use of novel high retroviral therapies and increase of flu vaccine coverage rate, that lead the mortality rate from 2.2 million (in 2005) to 1.8 million (in 2010) [6, 7]. The studies conducted by Neuzil et al. and Lin et al. confirmed high numbers of hospital admissions and high mortality from influenza in patients with HIV/AIDS not on Highly Active Anti Retroviral Therapy (HAART) [8, 9]. Neuzil et al., in another study reported that cardiopulmonary hospitalisations in influenza infection of patients with Acquired Immunodeficiency Syndrome (AIDS)/HIVwere very high in the pre-HAART era, with a rate of 48 per 1000 persons; in the post-HAART era hospitalisation rates decreased by 53% but remained more higher than that of the U.S. population and similar to that of the population at risk [10].

Immunization against influenza can effectively reduce the annual clinical and economic burden of influenza. Nevertheless, despite efforts to vaccinate those at highest risk of severe influenza-related complications, many still go unvaccinated [11, 12]. A study in eleven European countries showed that the highest immunization coverage for the population considered at high risk, was reached in the Netherlands (about 80% of vaccinated subjects), while the lowest rate belongs to Greece with only 25%. This data may be explained by several considerations: first, factors such as education can guide people towards a particular choice in favor of vaccination or not; second, in some countries the reimbursement for the cost of vaccination is partial; third, a smaller number of doses distributed could obviously result in a smaller number of subjects vaccinated [12]. The Advisory Committee on Immunization Practices considers HIV-infected persons to be at increased risk for influenza and recommends annual vaccination [13]. In view of mortality , morbidity and complication risk, already in 1986 there was a rec-

ommendation for influenza vaccination of patients with human T- lymphotrophic virus type III AIDS-related, and since 1988 the CDC recommended vaccination in children with acquired immunodeficiency syndrome. Current guidelines recommend that individuals infected by HIV receive yearly influenza vaccination. Since most previous studies on influenza vaccines in HIV infected individuals focused on their immunogenicity rather than on their clinical effectiveness, it is crucial to set up close post vaccination influenza monitoring to check the persistence of immune response and effective immune protection against viral strains circulating during seasonal epidemics [14-16].

The Strategic Advisory Group of Experts (SAGE) on immunization reviewed evidence on influenza disease burden, vaccine performance (efficacy and safety), and the feasibility and cost-effectiveness of implementing vaccination programmes for population groups at higher risk. In 2012, WHO published updated recommendations for seasonal influenza vaccination based on a systematic literature review performed by SAGE [17-21].

SAGE confirmed the recommendations to consider as priority groups for influenza vaccination individuals > 6 months with chronic heart or lung diseases, metabolic or renal disease, chronic liver disease, chronic neurological conditions and immunodeficiencies.

Prospective studies have looked at the long-term effect of influenza vaccination, confirming the safety and tolerability of currently used influenza vaccines, but questions remain about the immunogenicity and effectiveness of these vaccines in HIV infected patients. New roads could be opened through the use of new vaccines, such as MF59® adjuvant and those administered intradermally, that could overcome problems such as poor immune response and suboptimal effectiveness [22, 23].

The aim of this review is to evaluate tolerability, safety, immunogenicity and efficacy of vaccines actually approved for human use and to consider latest evidence and future perspective in HIV- positive subjects.

Tolerability and safety

Several studies were performed to evaluate tolerability and safety of influenza vaccination in HIV positive patients showing a good tolerability profile. In different studies reported symptoms resolved without sequelae in few days. There is lack of data regarding adverse events at long-term [23, 24].

Main evidence emerged by safety and tolerability evaluation of available vaccines in the last decade; serious adverse events, systemic and local reactions are reported below.

Serious adverse events

Serious adverse reactions were defined as any untoward medical event that at any dose result in death or is life-threatening, requires hospitalisation, results in disability or congenital anomaly [25]. From global analysis of more than 20 studies that evaluated safety and tolerability profile, no serious adverse events (SAEs) are tight associated with influenza vaccination in HIV- infected patients. Reported adverse events during follow-up of the studies were not associated with influenza vaccination but usually related to syndromes or treatment associated with HIV.

Trivalent Influenza Vaccines (TIV) were the first and the most used vaccine for immunization of HIV positive subjects. As emerged from literature data of the last two decade, TIV showed a good safety profile and no SAEs were reported [26, 27]. Durando et al., compare two influenza virus subunit vaccines with or without MF59® adjuvant showing absence of serious adverse event, except for a case of transitory ischemic attack in a men, episode that was demonstrated to be not correlate to vaccination [28]. Cooper et al., in his study, using a trivalent killed split not adjuvanted influenza vaccine in HIV infected adults, showed that vaccination is well tolerated without increase reactogenicity as consequence of higher antigen dose or boosting dose. In his study the population is divided into three groups, the first of which received one dose of influenza vaccine (0.5 mL or 15 μg hemagglutinin [HA]) in October and November 2008 followed by a booster dose 28 days later, while the second gets a double dose (30 μg HA) at the same time interval, followed by a double dose of booster 28 days later and finally, the third group received a single dose of vaccine [29].

Several studies conducted in HIV infected individuals immunized with A(H1N1) 2009 pandemic inactivated, unadjuvanted vaccine showed that vaccines were safe and well tolerated in this population and no SAEs were reported. Crum-Cianflone et al. evaluated a monovalent non adjuvanted 2009 influenza A/H1N1 vaccine comparing SAE in HIV positive and uninfected subjects showing that only 1 partecipant (HIV- uninfected patients) developed a serious adverse event that consist in angioedema on day 1 post vaccination and resolved after 17 days with antihistamine therapy [30]. It also occurred eight hospitalization but no one related to vaccination (seven in HIV-positive patients and one in healthy subjects) [31-41]. It has been demonstrated in studies involving a total of 892 children and 111 adults that administration of live attenuated influenza vaccine (LAIV) vaccine is safe and well tolerated and not serious adverse events related to vaccination were recorded. Furthermore, the safety profile is very similar to that previously reported in studies including other populations. Current influenza vaccination guidelines do not recommend LAIV immunization in persons with known or suspected immunodeficiency diseases, but the cited studies demonstrated that this vaccine should be evaluated for a role in immunizing HIV infected people [42-47].

Data from existing studies showed that virosomal influenza vaccination is well tolerated and no complaints of severe adverse reactions are usually reported in both children and adult HIV positive individuals [26].

Gabutti et al., and Durando et al., in their study do not show adverse serious events associated with the vaccination during the follow up period in HIV populations vaccinated both with MF59® influenza vaccine and with

subunit vaccine containing 15 µg of HA per strain and administered intramuscularly [26, 28].
In the study by Launay et al., three adverse reactions are reported after 42 days post vaccination, with monovalent 2009 Influenza A/H1N1v vaccine adjuvanted with AS03®, consisting of hospitalization following the second dose of adjuvanted vaccine, one recurrent episode of depression and one increase in serum alanine transaminase value associated with other treatment [48]. Palma et al., evaluating safety and immunogenicity of monovalent adjuvanted A/H1N1 pandemic influenza vaccination reported no deaths or serious adverse event during the follow-up [49]. No correlation between SAE and influenza vaccination was observed. Many studies report that the pandemic vaccine with or without adjuvant is safe and well tolerated [32-35, 38, 39, 48, 50-52].
Gelinck et al. also reported no adverse events in the study which compares the influenza vaccine containing 0.1 ml of the 2005/2006 trivalent influenza vaccine administered intradermally and 0.5 ml administered intramuscularly in immunocompromised patients. The frequency of events is more higher in subjects who received the vaccine intramuscularly [22]. The same observation were reported by Ansaldi et al., in a study in which intradermal vaccination low-antigen – 9 µg HA per strain- and vaccine intramuscular containing a standard dose of antigen -15 µg- were administered to HIV positive patients and compared. The study, although the low population size, shows good safety for both vaccines and no SAE [53].

Systemic reactions

Systemic reactions occur after a few hours of vaccination and may last for 24-36 hours. They may be linked to various causes such as the action of endotoxins, replication "in vivo" of microorganisms , the toxicity of the adjuvant and the reactivity of the immune system. They are usually mild, but in some cases can be so severe as to require supportive therapy.
Durando et al., comparing two subunit influenza vaccines with or without MF59® adjuvant, in patients with immunodeficiency acquired, reports such as systemic event most widespread headaches and fever in both groups with percentages of 25.9% and 28.4% [28].
In different studies, adverse systemic effect in patient vaccinated with virosomal influenza vaccine are comparable to subunit influenza vaccine group. In particular Evison et al., reported in a population of immunosuppressed adults vaccinated with a subunit or a virosomal influenza vaccine that the fatigue was the most frequently reaction, followed by headache and malaise in both vaccine group [54].
Systemic reactions typically occur after a few days post vaccination and are more frequent in subjects receiving an adjuvanted vaccine. They are mild or moderate and of short duration.
Indeed, Gabutti et al., comparing two influenza vaccine containing 15 µg of superficial haemagglutinin antigen for strain, MF59®-adjuvanted influenza vaccine (group A) versus a conventional subunit vaccine (group B), reports fever in 5% of patients of group A and 10% of subjects of groups B [26].
Palma et al., reports in his study as most frequent systemic reactions headache, fatigue and chills. 8% of subjects reports fever , 11% fatigue after the first dose. Fever is not reported after the second dose, while fatigue reported by 6% of subjects [49].
Gelinck et al., comparing 156 immunocompromised patients and 41 healthy controls that were randomized to receive either 0.5mL of the 2005/2006 trivalent influenza vaccine intramuscular or 0.1mL intradermal, estimated the frequency of adverse reactions after intramuscular vaccination with symptoms going from muscle pain to fever with values ranging from 11-48% [22].

Local reactions

Local reactions are defined as reactions that occur at the site of inoculation of the vaccine and determine redness, pain, erythema, pruritus. In general the local reactions are more frequent in subjects vaccinated with adjuvanted or intradermally administered influenza vaccines.
LAIV were well tolerated and have a similar safety profile compared with TIV; nasopharyngeal symptoms were minor and of short duration.
Durando et al., comparing two subunit vaccines with or without MF59® adjuvant, in patients with immunodeficiency acquired, reports such as local event most widespread pain an induration, respectively 54.3% and 22% [28].
Among the adverse local effect in patient vaccinated with virosomal influenza vaccine, the pain is the most frequent local reaction, followed by swelling and redness. Reported adverse events were comparable with those recorded in the groups immunized with conventional vaccines.
Some studies that use an adjuvanted vaccine (MF59®) and where the population was immunodepressed (HIV positive or those with chronic illnesses) reported local reactions of mild or moderate entity [24, 41, 42]. In the study by Launay et al., use of adjuvanted vaccine with aluminum salts determine a higher rate of reactions (71%) in HIV positive subjects compared to the control group (21%) [48]. Gabutti et al., comparing the safety and immunogenicity of a subunit vaccine versus MF59®-adjuvantated vaccine in HIV-positive patients, reported pain and redness in 28% of patients vaccinated with adjuvantated vaccine and 10% of subjects vaccinated with the subunit vaccine [26].
The most frequent local effect were pain -18%-, swelling and redness -2%- at injection site. Were classified as mild and resolved in few days post vaccination, as reported by Palma et al. [49].
Ansaldi et al. in his study reported pruritus in 29% ID vs 4% IM, redness 46% vs 8%, swelling 43% vs 12%. All local events were mild or moderate and resolved without sequelae [53].
The same conclusions are reached by Gelinck et al. in their study in which they evaluated the administration of a trivalent vaccine by intradermal route (0.1 ml) or by intramuscular (0.5 ml), they reported erythema and pain

at the injection site 48 hours after vaccination showing these reactions more frequently in subjects vaccinated intradermally and in the control group compared to immunocompromised patients. In general, all subjects in the control group and 69% of immunocompromised individuals who responded to all three antigens showed a local skin reaction [22].

HIV-RNA and CD4+ cell count post-vaccination

Several studies published between 1995 and 2012 reported controversial data both in favour and against the evidence of increase of viral load and a decrease of CD4+ cell count secondary to the administration of influenza vaccination in HIV infected persons with or without correlation to the immune response. Differences in used vaccines, in sample sizes and features of HIV infected populations (i.e. demographic characteristics, risk factors, stage of HIV disease, patients under anti-retroviral treatment or naıve) enrolled in the various studies as well as timing of sampling assays and different sensitivity of laboratory methods for quantification of viral load, could explain at least part of these conflicting reports [32, 41, 43].

Many authors reported an increase in viral load following influenza immunization, this data appears to be related to detectable viral load at baseline and no treatment of HAART therapy, although it is not always observed [24, 27, 55-59, 61-63]. The rebound of viral load is attributed to activation of quiescent HIV infected CD4+ cells and the up regulation of HIV viral replication [52, 58-62].

Günthard et al. and Staprans et al. showed that effects of trivalent influenza vaccine on viral replication in HIV positive adults determined transient increase of plasma HIV-RNA levels [58, 64]. Therefore, the simultaneous decrease in pro-viral DNA and memory phenotype CD4+ cells in association with increased plasma HIV RNA after vaccination in patients with < 400 RNA copies/ml at baseline suggested that in vivo mobilization of the latently infected cell reservoir may occur during potent antiretroviral therapy [58]. The same conclusion has been reported by Fuller et al. and Madhi et al. [56, 65].

Study conducted in HIV infected children reported controversial data about increase of viral load after immunization with trivalent influenza vaccine.

Kosalaraska et al. showed an increase in HIV-RNA levels in children aged ≥ 6 months to < 18 years: authors stated that increase in plasma HIV-RNA was a transient phenomenon and did not have any clinical significance [66]. Machado et al. showed no increase neither in viral load nor in CD4+ cell count in a population of children with a mean age of 12 years [67].

In the study by Tasker et al. CD4+ cell count and viral load are evaluated in HIV positive subjects vaccinated with LAIV influenza vaccine. They showed an increased HIV replication and a decrease in CD4%: according to the authors, this effect is probably due to the absence of treatment with antiretroviral therapy [63].

Levin et al., showed, instead, no significant increase from baseline in plasma HIV viral load and no change in CD4% in HIV infected children aged ≥ 5 months to < 18 years old [44]. Studies in HIV-positive adults immunized with a monovalent unadjuvanted influenza vaccine (H1N1) administered with a single dose, reported no significant change in plasma HIV RNA levels or CD4+ cell count [30, 32].

Tanzi et al. evaluating effects of a virosomal influenza vaccine on viral replication and T-cell activation in HIV–infected children, receiving HAART, observed no increase in plasma HIV-1 RNA or HIV-1 pro-viral DNA and the immunophenotype analyses demonstrated that CD4+ cell counts and percentages and activated lymphocytes remain stable for about a month after immunization [68].Same results have been obtained by Zuccotti et al., Zanetti et al. and Esposito et al. [24, 69, 70]. In the study by Amendola et al., the mean viral RNA levels did not change in HIV infected and uninfected adults as well as no difference have been showed in HIV proviral DNA levels [25].

However, more recent and better designed studies have not documented a substantial increase in the replication of HIV, immune stimulation resulting from influenza vaccination did not significantly change the levels of plasma virus, CD4+ cell counts, or activation-induced apoptosis in HIV-infected individuals. An increase in the T-cell response to influenza and spontaneous apoptosis, and increase in plasma HIV-1 RNA level following influenza vaccination are rare and transient phenomenon [43-45, 52, 56, 60, 61].

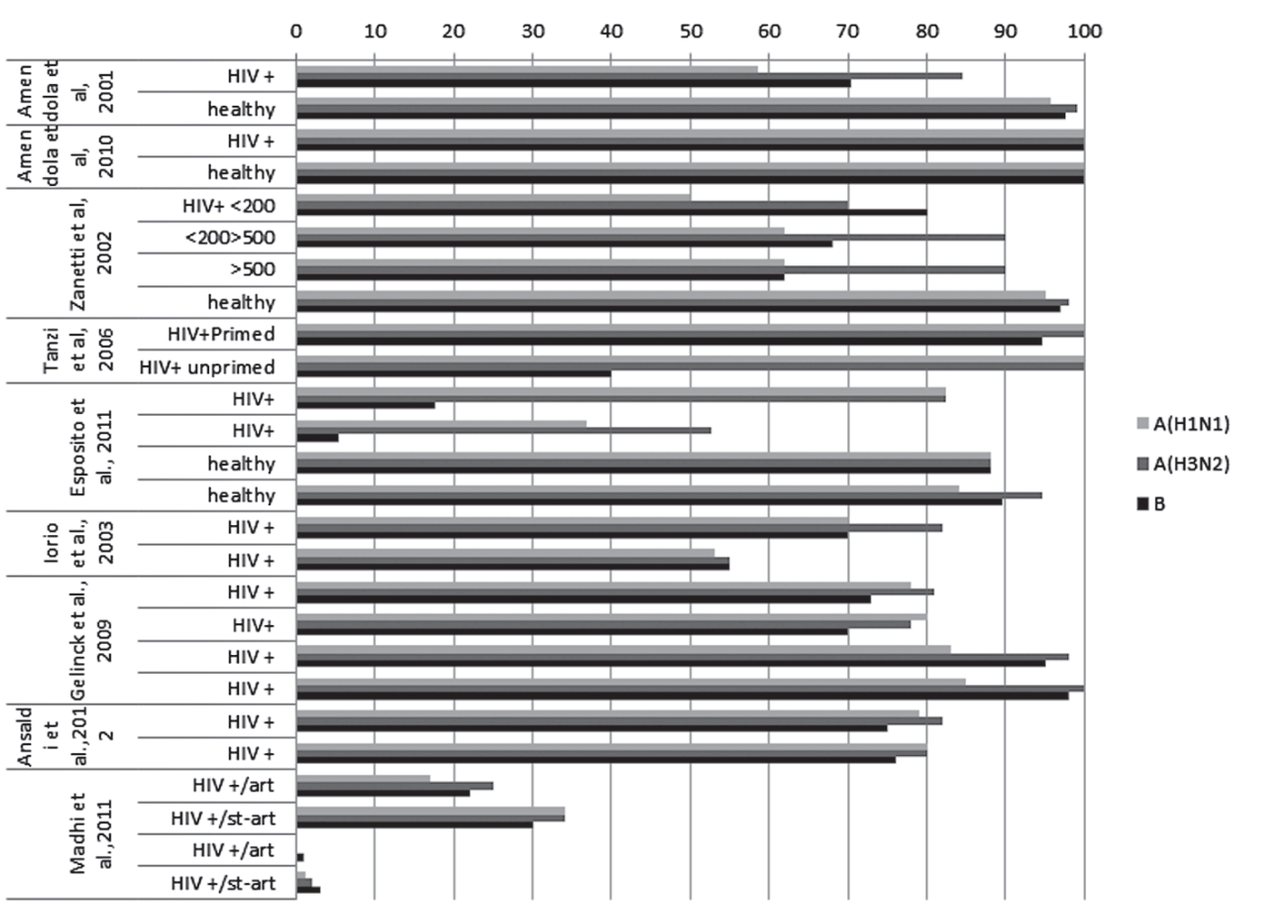
Different studies evaluated the effects of adjuvanted seasonal and pandemic influenza vaccine on HIV viral load and CD4+ cell count in HIV positive subjects. Vaccines used in this studies were adjuvanted with oil-in-water emulsion, in particular with MF59® and AS03®, the only adjuvants approved for human use. Gabutti et al. by comparing groups mean lymphocyte count for time points after immunisation didn't reveal any statically significant changes in HIV positive adults immunized with MF59 adjuvant or conventional influenza vaccine, with the exception of subjects with lymphocyte counts < 200 cells/mm^3, vaccinated with conventional subunit vaccine, whose counts showed a progressive increase after immunization [26]. Durando et al. in HIV positive adults showed a decrease of HIV RNA and an increase of CD4 cells in subjects immunized with adjuvant vaccine compared to patients immunized with conventional not adjuvanted influenza vaccine [28]. Iorio et al. reported, no substantial change in viral load and transitory increase of HIV replication in subjects immunized with a conventional vaccine although the study population were immunized with the same formulation of the above-mentioned study [71]. Palma et al., in HIV positive children and adults immunized with a monovalent pandemic adjuvanted influenza vaccine, showed no altered CD4 count and HIV viral load levels [49]. As regard as influenza vaccines adjuvanted with AS03®, Calmy et al., Tremblay et al. and Launay et al. observed a transient increase of HIV-1 RNA replication within days of the vaccination, but neither increased risk of disease progression nor long-term effects on CD4+ cell

counts, viral load, or progression to AIDS or death have been reported [48, 51, 52].
Lack of data exists in the literature regarding the effect of influenza vaccination with intradermal delivered; therefore, further studies of this preparation are needed.

Immunogenicity

Typically, to evaluate the immunogenicity of influenza vaccines are considered the following parameters:
Geometric mean titres (GMTs), mean- fold increase in titres (MFI; ratio of post to pre- vaccination titre), seroprotection rate, defined as the percentage of subjects achieving a significant increase in titre from a non-negative pre-vaccination titre (≥ 1:10) or a rise from < 1:10 to ≥ 1:40 in those who were seronegative), and seroconversion rate defined as either a negative pre-vaccination titer (≤ 10) to a post-vaccination titer ≥ 40, or at least a fourfold increase between pre-and post-vaccination titers where the pre-vaccination titer is ≥ 10. The Committee for Medicinal Products for Human Use (CHMP; formerly CPMP) criteria for approval of influenza vaccine in adults younger than 60 years includes that at least one of the following criteria are met: seroprotection rate > 40%, MFI > 2.5 or seroconversion rate > 70% [72]. As recommended by the WHO the test used to assess the immunogenicity of influenza vaccine are the inhibition of hemagglutination (HI) and microneutralization (MN) assay [17].
The HI assay has been used as the primary means to measure serum antibody responses to influenza vaccines due to the ease of conducting the assay and a generally accepted correlation with seroprotection. However, the information imparted by a demonstration of neutralization capacity is different from that of HI, which measures disruption of binding to red cells without assessing prevention of infection. Although definitive human studies are lacking, animal models suggest that neutralization capacity predicts prevention of infection, while HI correlates with prevention of disease [45, 46]. In clinical trials of vaccines, MN assays may be more sensitive in detecting antibody and demonstrating seroconversion [54, 73] , including in immunocompromised subjects. HIV infection is associated with deficiencies in both humoral and cell-mediated immunity, which can alter the course of common infections and influence vaccine immunogenicity [74]. Generally in HIV-infected patients immunogenicity correlates directly with CD4+ cell count and inversely with HIV viral load [57, 58].
Most studies emphasized the importance of a high CD4+ cell count, treatment HAART therapy and use of adjuvant influenza vaccine to increase vaccine response rate; The immune response is closely correlated to the degree of immunosuppression [28, 35, 71, 75]. Hatayema et al.,

Fig. 1. Seroprotection rate in studies involving HIV + population.



instead, in his study observed no correlation between plasma HIV RNA levels and HI antibody response [31]. Figure 1 shows the seroprotection rates of some studies reported in this review.

Conventional and LAIV influenza vaccines

As regard as non-adjuvanted A(H1N1)2009 pandemic vaccine, several studies evaluated antibody responses elicited by this vaccine in different populations of HIV infected individuals. Most of study participants followed an antiretroviral therapy with an high median CD4+ T-cells counts and fully suppressed HIV-RNA levels. Despite a good safety and tolerability profile, antibody responses elicited by conventional pandemic vaccine were insufficient to confer adequate protection in this immunosuppressed, hyporesponsive, at high risk subjects [30, 41].

The collected data regarding the administration of influenza unadjuvanted vaccine are controversial: Lagler et al. and Hatakeyama et al., reported in HIV positive adults a low immune response after two doses of pandemic influenza vaccine, while Bickel et al. and Cooper et al., demonstrate the effect of a booster dose of pandemic influenza vaccine in HIV-positive adults plays a fundamental role to increase the immunogenicity in immunodepressed population [31, 39, 41, 76]. Some authors evaluated the effect of a single dose of non-adjuvanted pandemic vaccine obtaining controversial results: some authors reported an adequate immunogenicity while others suggested that new strategies would be evaluated [30 32, 34, 36, 37, 40, 77]. As regards the evaluation of the immunogenicity of non-adjuvanted pandemic vaccine in children, Phongsamart et al., Flynn et al. and Hakim et al. reported an adequate immune response after two doses. Phongsamart et al., in his study showed a low level of cross reacting antibody to seasonal H1N1 [33, 35, 38].

Immunogenicity evaluations of LAIV in HIV infected population derived from a few studies.

In HIV infected children further evaluations of LAIV are needed, because conflicting data exist about antibody responses to vaccination. Two comparative studies showed that TIV elicited a seroconversion rate higher than LAIV, although the proportions of subjects with protective titers were similar between groups. In particular Weinberg A et al., demonstrated that TIV was more immunogenic than LAIV both against homotypic and heterosubtypic viruses, using microneutralization and haemagglutination inhibition assays. A study by King JC et al., showed a similar seroconversion rate after two doses of LAIV immunization both in HIV infected and uninfected children. In HIV infected adults only one study reported data about immunogenicity elicited by LAIV vaccine, but the low size of study population does not allow appropriate conclusions [42, 46].

A limited number of studies reported results of immunogenicity for virosomal influenza vaccination, in populations of adults and children. All studies reported that HIV positive subjects show lower immune responses to influenza vaccination in comparison with immunocompetent individuals. Seroconversion rates of HIV infected populations elicited by virosomal influenza vaccines do not differ significantly from that produced by trivalent conventional vaccines.

Tanzi et al., showed that use of the virosomal influenza vaccine is moderately immunogenic in HIV infected children. Because there are no EMEA defined criteria for children, immunogenicity was evaluated using criteria for adult. Humoral immune response were adequate for all three influenza strains in primed children and adequate for the two A strains in groups of the unprimed [68].

Oil-in-water emulsion adjuvanted influenza vaccines

Immunogenicity of MF59 adjuvanted influenza vaccine has been evaluated in different HIV positive populations. The different studies were designed and carried out in different manners: in literature there are comparative and not comparative, prospective trials, and populations involved varied from infected/uninfected children to infected/uninfected young adults and adults. Several studies showed that MF59 adjuvanted influenza vaccine had good safety and immunogenicity profiles similar or better than conventional influenza vaccine. All studies underlined that CD4+ cell count and HAART treatment play a key role in determining antibody response in influenza vaccination. Three studies reported a comparison between MF59 adjuvanted and conventional non adjuvanted seasonal influenza vaccine in HIV positive adults.

In the study by Durando et al. an assessment of humoral and cell-mediated immune responses elicited by the two influenza vaccines was made. Immunocompromised individuals vaccinated with MF59 adjuvanted vaccine showed a better antibody response and also a statistically significant increase in the frequency of proliferating T cells at 30 days after immunization, compared with patients vaccinated with non adjuvanted vaccine. HIV-negative subjects mounted a stronger antibody response than HIV-positive subjects [28].

The same results were obtained by Iorio et al. by comparing the immune response elicited by the same vaccines in HIV patients under antiretroviral therapy [14]: MF59 adjuvanted influenza vaccine induced a better immune responses as compared with conventional vaccine in HIV positive HAART treated subjects [71].

Gabutti et al. compared the antibody responses elicited by an MF59 adjuvanted and a conventional subunit influenza vaccine in 37 HIV positive patients population, showing not significant differences between the two immunised groups and as regard as the three different influenza strains. An important aspect of the study was the prolonged persistence of specific antibodies versus all the vaccine strains: 51.7% of MF59 patients and 59.7% of subunit patients showed a seroprotective level of antibodies even 180 days after immunization [26].

During the last three years, several studies evaluated the performance of MF59 adjuvanted pandemic vaccine in HIV positives children and adults [49, 75, 78, 79, 81]. Both in adults and in children the immune response

stimulated by a single or two doses of pandemic MF59 adjuvanted influenza vaccine was comparable in HIV infected patients and in healthy controls. In the study by Kajaste-Rudnitski et al. the seroconversion rate observed after a single dose of MF59®-adjuvanted influenza vaccine was lower in the HIV positive individuals as compared with HIV negative controls; however, the seroprotection rates were similar in both study groups [80]. Soonawala et al. reported the induction of cross reactive antibodies to pH1N1 after vaccination with seasonal TIV in HIV infected adults: authors hypothesized that HIV infected patients could produce larger quantities of cross reactive antibodies after vaccination because of a less well regulated B-cell immune response [75]. Palma et al. and Viganò et al. evaluated the immunogenicity of MF59®-adjuvanted pandemic influenza vaccine in HIV positive children and young adults, showing adequate levels of seroprotection already after a single dose; however, authors suggested a two-dose vaccination schedule in this population, in order to optimize and obtain a long-term antibody response [49, 81].

Thus, MF59®-adjuvanted influenza vaccine should be considered for use in HIV positive adults and children, because it could improve the effectiveness of influenza vaccination programmes in this population, who are at high-risk of influenza-related complications.

Another oil-in-water emulsion used as adjuvant in influenza vaccine is the AS03 adjuvant system. The AS03® adjuvant consisted of a 10% oil-in-water emulsion based adjuvant system, containing 5% *dl*-α-tocopherol (11.86 mg) and squalene (10.69 mg) in the oil phase and 2% of the non-ionic detergent Tween®80 (4.86 mg) in the aqueous phase. Recently, the AS03® adjuvant has been adopted in the licensed formulation of a H1N1 2009 pandemic vaccine. Some authors [51, 82] reported seroprotection rates lower after one dose of AS03 adjuvanted vaccine (61% to 75%) in HIV infected adults [51, 82, 83], while a second dose determines an increase up to 97.7% [76, 84]. According to these authors this difference could be attributed to the different timing of immunization during the pandemic outbreak, in relation to higher baseline or follow-up seroprotection rates. Concerning the seroconversion rates, other studies reported values of 88% to 95.3% after a single dose in HIV positive patients [48, 84, 85]. The collected data regarding the administration of a single dose of influenza AS03 adjuvanted vaccine are controversial: Manuel et al., reported a similar immune response in HIV patients and healthy control, while Kelly et al., showed that immune response correlate with a pre- existing antibodies and a single dose may be insufficient to induce protective immunity [86, 87]. Okike et al., reported that the use of ASO3 adjuvant in HIV positive children have likely played an important role in eliciting the high sero-response rates [50]. In general, the use of AS03 adjuvanted pandemic vaccine in HIV positive immunocompromised patients may lead to the expansion of coverage and increase the immune response [55, 83].

Intradermal influenza vaccines

Between strategies implemented to increase the immunogenicity of influenza vaccination in HIV patients, intradermal approach is also to be mentioned. In persons with impaired immunity intradermal vaccination is of particular interest because of different immunologic advantages.

The dermis harbours a network of antigen presenting cells, constituting up to 2% of all dermal cells, which forms an optimal environment to deliver a vaccine. In the study by Gelinck et al., 39 HIV positives adults received the 2005/2006 trivalent influenza vaccine delivered intradermally according to the CDC guidelines, using an intradermal injection syringe (BD Micro-Fine 0.5 ml U-100 insulin syringe) and needle (29G), also used for intradermal tuberculin injections. The intradermal vaccine dose contained 3 μg of haemaglutinin of the three strains. The intradermal vaccination with a low dose resulted in similar postvaccination titers as compared to standard intramuscular vaccination in the study groups: in particular only the HIV group had higher titers after intradermal vaccination. Results suggested that the intradermal vaccination is more efficient in inducing an immune response compared to intramuscular vaccination in HIV infected patients [22].

The superiority of the immune response elicited by the intradermal vaccine is shown by the values of the rates of seroprotection, seroconversion, and MFI/GMRT all higher than the vaccine administered intramuscularly to the controls. Ansaldi et al., in his study compared immunogenicity of licensed intradermal trivalent inactivated split vaccine delivered by licensed microsystem device with a lower antigen content (9 μg HA per strain) against the conventional intramuscular (15μg) influenza vaccine in a population of 54 HIV infected adults. Both vaccines meet the criteria for MFI and seroprotection rate but not for seroconversion against the B virus, there are no differences in terms of post-vaccination GMT /MFI, seroprotection and seroconversion rates comparing the two vaccines. The results of this trial showed that the licensed low antigen content ID vaccine was safe and immunogenic in HIV positive adults, although the small sample size of the study [53].

Conclusions

Influenza is a major cause of death, hospitalization and disability in immunocompromised population, resulting in an health and economic burden that may be reduced implementing annual vaccination as recommended by WHO guidelines.

The considerable experience accumulated about influenza vaccination refers a good safety and tolerability profile, in fact the adverse events reported are usually mild and resolve in a few days after their appearance.

About the vexed question of viral load increase, conflicting data are reported in literature. However, when this increase occurs, it is of transient nature and typically did not associate in CD4+ T cell counts changes.

Some studies reported immunogenicity data in HIV+ population, in which are compared different influenza vaccines, adjuvanted and not, and different administration routes.
The data are encouraging because an adequate immune response is shown, although split/subunit vaccine do not elicited an efficient immune response in these subjects.
New strategies were evaluated to increase the immune response in immunocompromised patients, as increase dosage, multiple dose vaccination, use of vaccine adjuvant, immunostimulant patches (the skin, especially its epidermal layer, is an accessible and competent immune environment and an attractive target for vaccine delivery, through transcutaneous delivery or immunostimulant patches) and different routes of vaccine delivery transcutaneous immunization, a topical vaccine application, combines the advantages of needle-free delivery while targeting the immunologically rich milieu of the skin [64, 70, 88, 89]. The administration of an MF59®- adjuvanted influenza subunit vaccine has been shown to improve immunogenicity and to elicited good immune responses and protective antibody [28, 91, 92]. Several studies estimated safety, tolerability and immunogenicity of intradermal influenza vaccine, the majority of which were conducted in elderly population; only one study was conducted on a population of immunocompromised patients. A dose-response relationship together with more efficient antibody response for intradermal vaccine was demonstrated using only a fifth of the normal dose evaluating the humoral response of intradermal influenza vaccination versus intramuscular vaccination. Local skin reactions can be used as predictors for the success of vaccination by identifying patients who may need a booster [54].
In general, the immunogenicity studies have shown encouraging results for the HIV positive subjects with antibody titres protecting, data on safety and tolerability are encouraging reporting only a few cases of serious effects on the population considered (about 10% of patients).
Definitely the most promising data concern the use of vaccine adjuvants, in particular with MF59®, and the use of new vaccine intradermal administration should be more extensively examined.
In the light of data reported in this review, there still is much to do about vaccination in immunocompromised patients. More extensive effectiveness studies are needed, to assess the impact of influenza vaccination and to prevent complications associated with it.

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Short review

Health promotion or pharmacological treatment for chronic diseases?

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Key words

COPD • DM • Hypertension • Obesity • Smoking • Non-communicable diseases

Summary

Over the last years medicine has progressed very rapidly. Communicable diseases, which were the leading causes of mortalities, are not anymore, especially in developed countries. Currently, non-communicable diseases are more prevalent, and most of them are related to changes in our daily habits and degenerative processes. Most of these diseases are chronic, need continuous care and treatment with limited improvement and high costs. The General Assembly of the United Nations in its resolution 65/238 recognized the primary role and responsibility of Governments in responding to the challenge of non-communicable diseases and the essential need for the efforts and engagement of all sectors of society to generate an effective response. Special emphasis has been concentrated on pharmacological treatments for most of chronic non-communicable diseases with the challenge to discover new drugs for treating, in most cases, chronic irreversible degenerative diseases associated with aging. Little care was given to non-pharmacological lines of treatment.

Introduction

Over the last years medicine has progressed very rapidly. Communicable diseases, which were the leading causes of mortalities, are not anymore, especially in developed countries. Currently, non-communicable diseases are more prevalent, and most of them are related to changes in our daily habits and degenerative processes. Most of these diseases are chronic, need continuous care and treatment with limited improvement and high costs [1-3].

The General Assembly of the United Nations in its resolution 65/238 recognized the primary role and responsibility of Governments in responding to the challenge of non-communicable diseases and the essential need for the efforts and engagement of all sectors of society to generate an effective response [2].

Special emphasis has been concentrated on pharmacological treatments for most of chronic non-communicable diseases with the challenge to discover new drugs for treating, in most cases, chronic irreversible degenerative diseases associated with aging. Little care was given to non-pharmacological lines of treatment [3].

Arterial hypertension

Worldwide hypertension is the most frequent chronic disease among aged population It is estimated that 35% of the general population over 40 years old suffer idiopathic arterial hypertension and need treatment for life [4, 5]. Over the last years pharmacological treatment has revolutionized rapidly. Angiotensin-converting-enzyme inhibitors (ACEIs) have replaced beta-blockers in many cases. The current scientific debate is about indications, effectiveness, safety and cost-effectiveness of angiotensin receptor blocker (ARB) and AECI. Recently ARB is taking its place between known antihypertensive drugs especially in patients with other chronic diseases like renal insufficiency [6, 7]. Non-pharmacological measures for treatment of hypertension are well-known and include diet control with low salt diet and cholesterol diet, tobacco cessation, weight control and physical exercises [8-11]. It is estimated that 30% of hypertensive patients can control their blood pressure following non-pharmacological measures without the need for any antihypertensive drugs. Little attention is given to these basic non-pharmacological measures [12].

Diabetes mellitus

Over the last 30 years the number of Diabetes Mellitus (DM) patients and its prevalence are rapidly rising [13]. Ginter and Simko (2010) reported that in the second half of the 20th century it became obvious that a relentless increase in DM type 2 affecting the economically affluent countries is gradually afflicting also the developing world [14]. Oral antidiabetics drugs are various and are very effective in DM type 2. However, all these drugs have several side effects, which are usually related to other underlying pathologies in the same patient [15]. DM type I is treated with insulin, which has been revolutionized over the last 10 years, with various forms of insulin and modes of administration [14, 16].

Non-pharmacological measures for control of blood glucose in diabetics, like diet and weight controls and regular physical exercise are hardly adopted by these patients [13, 16, 17].

Obesity

Obesity is the new epidemic of the 21st Century. It is estimated that in Western Countries > 40% of the general population are over weight. The raising incidence and prevalence of this morbidity is alarming. Junk food, high carbohydrate and fat diet and lack of physical exercise are the main risk factors for this epidemic [13].
Of no doubt diet control and physical exercise could resolve this health problem [18]. Over the last years, several drugs were used to control weight, like Thyroxin and Metformine and new drugs like Litramine. Most of studies have shown that these drugs are not completely safe and could produce several side effects. Complications related to the use of these drugs are reported [13]. Other measures to treat obesity include surgical intervention like stomach reduction, liposuction and intestinal anastomosis. Recent debates discuss severe complications and mortalities related to these surgical operations [19].

Chronic obstructive pulmonary diseases

Smoking is the epidemic of the 20th Century. After 1950s tobacco smoking prevalence reached 45% of the general population in many western Countries [20]. Currently chronic obstructive pulmonary diseases (COPD) is the second cause of mortalities in most Western Countries. Most of COPD patients are ex-smokers or even current smokers [21]. Treatment of COPD has been revolutionized over the last few years. Treatment measures include bronchodilators with sympathomimetics and antiparasympathomimetics, together with corticosteroids in the form of oral, injection and inhalation therapy. Side effects related to corticosteroids use like iatrogenic hypertension, and iatrogenic DM are well known [22]. Tiotropium is one of the specific treatments to delay the progress of the disease and to improve the pulmonary functions. Recent meta-analysis reported a 52% increased risk of mortality associated with tiotropium mist inhaler in patients with COPD [23]. Although weight reduction, physical exercise and pulmonary exercise in specific have been proved to be effective and improve pulmonary function tests by 30-40%, the use of pharmacological treatment in COPD is by far more numerous than non-pharmacological measures [22].

Discussion and conclusions

In 2010, the Spanish National Health Service (NHS) paid for 958 million prescriptions. Most of these prescriptions were realized at primary healthcare. According to the Spanish NHS, areas requiring improvement in primary care prescription include over-treatment of patients in low risk situations, poor patient information, polymedication and the appreciable percentage of preventable adverse effects [24].
Over the past few decades, developed countries have achieved remarkable improvements in terms of their life expectancy, with growing number of third age population. Most older patients do have several concomitant chronic conditions and receive treatment mainly at primary healthcare by General Practitioners/Family Physicians. Multiple co-morbidities of older patients are usually associated with increased use of health care resources, multiple health care providers, polymedication and an overall increased risk of adverse events [25].
A recent retrospective observational study performed in Croatia from March 2005 to December 2008, showed that polymedication leaded to serious adverse drug reactions and deaths. This study reported 2076 adverse drug reactions, 1209 of which (58.2%) involved more than one drug [26].
In conclusion, we currently look for pharmacological and surgical measures to treat most of chronic non-infectious diseases, as rapid and easy measures ignoring their side effects and costs, rather than adopting healthy habits and non-pharmacological measures.

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ORIGINAL ARTICLE

An opportunistic pre-diabetes screening program offered with existing hypertension screening

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Key words

Diabetes mellitus • Hyperglycemia • Screening • Prevention

Summary

Diabetes mellitus refers to a group of metabolic diseases that share the hallmark characteristic of hyperglycemia. Generally, Diabetes is categorized as type I, or type II. Type I results from the body's failure to synthesize insulin, and requires insulin injections. Type II, also known as adult-onset or non-insulin dependent diabetes mellitus (NIDDM), occurs when the body's cells fail to use insulin properly due to a defective insulin receptor, and may also be combined with a relatively reduced insulin secretion. Type II can be managed with healthy lifestyle habits and early detection of high sugar levels. Most local health departments across New York State offer hypertension screening but no pre-diabetes screening programs. The US preventive Services Task Force recommends that asymptomatic adults with sustained blood pressure greater than 135/80 mm Hg should be screened for type II diabetes. Since high blood sugar levels can be controlled, and in some cases reduced, there exist strong benefits in offering pre-diabetic screening for individuals who are hypertensive.

Introduction

60 million adults in United States have been diagnosed with diabetes, are currently undiagnosed with this disease, or have pre-diabetes [1]. Pre-diabetes is a condition in which blood glucose levels are higher than normal, but not high enough for a diagnosis of diabetes. Clinically the range for a fasted blood glucose tests indicating pre-diabetes ranges from 100 mg/dL to 125 mg/dL, and may also be referred to as impaired glucose tolerance (IGT). Type II is the most common form affecting nearly 95% of the U.S. diabetic population [2]. This translates to an alarming 9% prevalence of this disease among the adult population. Diabetes has long been recognized as the leading cause of blindness, renal abnormalities, and non-traumatic amputations [3]. Furthermore, the risk for death is twice as much for an individual with diabetes, than one without diabetes. Diabetes is the sixth leading cause of death and diabetes is often underreported as a cause of death [4]. Diabetes cost $132 billion, of which $40 billion were due to indirect causes such as disability, absenteeism, and premature mortality.

Although genetics play a role in the development of type II diabetes, the environment, and one's lifestyle contribute to this process. The Center for Disease Control (CDC's) Diabetes Program [5] says that as Americans, "we are eating ourselves into a diabetes epidemic". Almost half of all that have been diagnosed with type II have also been diagnosed as obese [6]. In the state of New York, 5.7% and 17.4% of the population had diabetes and were obese respectively. In 2009, the prevalence increased to 8.9% and 24.6%, for diabetes and obesity respectively [7].

There exists a public health opportunity to promote initiatives that aim to modify eating habits, physical activity, and offer pre-diabetes screening programs to those who have one or more risk factors for diabetes. First and foremost, our aim should be to encourage healthy behavior as this is the most cost effective and sustainable method to reduce the diabetic crisis. The landmark results of the Diabetes Prevention Program, a 27 center randomized clinical trial across the United States [8], has shown that lifestyle changes have been shown to be more effective than medication [9] and extreme lifestyle interventions may reduce the risk of developing diabetes type 2 by 50% [10].

How do we change the behavior of the population as a whole? It is our duty to inform the public about the relationships between obesity, poor physical activity, smoking, hypertension, and all other risk factors that may predispose one to developing type II diabetes. Unlike other chronic diseases, type II diabetes can be managed, and nearly eliminated with proper diet, exercise, treatment, and early detection. To that end, we must include screening programs that range from targeted to opportunistic for our local population. Screening allows us to identify those who may be at risk (pre-diabetic), and those that have been living with undiagnosed diabetes, in turn providing opportunity for early interventions. The residual effect of decreasing the incidence of diabetes is astronomical. Not only would it reduce health care costs, it would dramatically reduce the prevalence of other chronic diseases. Cardiovascular disease is the leading cause of death in this country and 75% of cases have also been diagnosed with type II diabetes [11].

Opportunistic screening

Several county health departments in New York currently provide free blood pressure screenings at numerous locations throughout the county. The US preventive Services Task Force [12] recommends that asymptomatic adults with sustained blood pressure greater than 135/80 mm Hg should be screened for type II diabetes. The American Diabetic Association has set forth guidelines for screening procedures; however these parameters can be adjusted for a local population and available resources within a specific health network. Medicaid and Medicare cover diabetic testing, and by 2014, all insurance plans are mandated to cover preventive services, of which diabetic screening would be included [13, 14]. The test of choice is the Fasting Plasma Glucose Test, it is inexpensive, and produces quick and reproducible results. Clinical practice recommendations by the American Diabetic Association's (ADA) Standards for Medical Care [15] deem fasted sugar levels greater than or equal to 126 mg/dL as diabetic, and anything between 100 to 125 mg/dL as pre-diabetic. Given the uncontrolled nature of health department visits and that at the time of visit an individual will most likely not be in a fasted state; the value of concern for a random blood glucose test is anything greater than 126 mg/dL.

An individual that has a random blood glucose test result greater than 126 mg/dL should be scheduled for a fasted test, and proper action will be taken depending on the results of the second test. If the individual is found to be pre-diabetic upon subsequent testing they will be assigned to counseling to reduce their risk of developing diabetes. In addition, the ADA [15] recommends follow up periods every three years for those who are pre-diabetic and over the age of 45. The time of onset of type II diabetes is not confirmed, but studies show that it is around ten years [16]. Therefore an individual who is pre-diabetic should be followed up, at minimum, for three to four screening periods (9-12 years). In most cases, those who are concerned enough about their livelihoods will learn to test their blood sugar a few times a month on their own. Medicaid and Medicare will cover the cost for home testing kits. Kits should also be available for purchase from the local health department at a subsidized cost for those who are uninsured or financially troubled. In the case that someone that is at risk has a negative result; an attempt should be made to re-screen them within six months.

The assumption is that if one is warned of their risk of developing a disease that can be extremely debilitating the longer one has it; one will make changes in their lifestyle and behavior to avoid progression toward a clinically diagnosed state. Numerous programs and campaigns exist to promote these changes, such as Healthy New York, Healthy People 2020, and various programs at local YMCA's. The first step, however, is to identify those who are at risk of having diabetes, those who are pre-diabetic. Since it is not feasible to screen the entire population, the ADA recommends opportunistic screening to those who have one or more risk factors (Tab. I) [17]. In addition, a diabetes questionnaire should be completed by those who will be screened, with the assistance of a health care provider if needed, to supplement the test results [18].

To date, no trail has been done to determine if systematic screening and early treatment of pre-diabetics leads to improved health outcomes compared with clinical diagnosis. To conduct a randomized cohort clinical study would provide useful evidence to evaluate this proposal for diabetes screening. However, major hurdles exist. To provide diabetes screening to one group continuously for up to twelve years, and not to another, brings up ethical concerns that cannot be avoided [17]. In the case that many in the screened group are found to have diabetes, or pre-diabetes, these individuals may seek proper treatment or change lifestyle behaviors to prevent or extend their onset of clinical type II diabetes. Those in the non-screened group may continue to live with undiagnosed treatment, or would not be informed of their pre-diabetic state, and might continue to practice lifestyle habits which are detrimental to the avoidance of type II diabetes.

Several state pilot projects that provide diabetes screening are underway across the country; and the results of a few studies have been published with remarkable results. The Diabetes Prevention Program that provides screening for people covered by Medicaid and Medicare in Minnesota showed an overall reduction of 58% from pre-diabetes to diabetes type II. The state of Minnesota reported that they were able to deliver the Diabetes Prevention Program curriculum, for less than $300 per participant. This included screening, and 16 lifestyle and health structured education sessions to those who were pre-diabetic [19]. The Medicare Diabetes Screening Project [20] in Georgia and New Hampshire has also reported great success by implementation of their own Diabetes Prevention Programs. Outside of the United States, the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screened Detected Diabetes in Primary Care), was a population based study that managed to achieve high levels of participant retention and follow up for over 200,000 people between the ages of 40-69. The find-

Tab. I. Risk factors for type 2 diabetes [16].

❑ Age ≥ 45 years
❑ Overweight (BMI ≥ kg/m^2.)
❑ Family history of diabetes (i.e., parents or siblings with diabetes)
❑ Habitual physical inactivity
❑ Race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
❑ Previously identified IFT or IGT
❑ History of GDM or delivery of a baby weighing > 9 lbs
❑ Hypertension (≥ 140/90 mmHg in adults)
❑ HDL cholesterol ≤ 35 mg/dl (0.90 mmol/l) and/or a triglyceride level ≥ 250mg/dl (2.82 mmol/l)
❑ Polycystic ovary syndrome
❑ History of vascular disease

* May not correct for all ethinic groups. BMI- Body mass index; GDM-Gestational diabetes mellitus;

ings of the study were that "stepwise screening for type 2 diabetes in primary care is feasible and acceptable [and] identifies individuals with high levels of modifiable risk factors [21].

Conclusions

The aim of this screening program is to identify those with undiagnosed diabetes and those who show signs of a pre-diabetic state. This will allow the health department to refer for early treatment or prevention to delay the onset of diabetes and the various other long-term complications that are related with it. It is obvious that the economic costs of high blood sugar and its consequences are substantial. Although no real world studies have been done on the cost savings of screening versus no screening, several simulations have been run to determine if screening would be economically efficient. It has been shown that screening appears to be cost-saving and cost-neutral from a societal perspective [22]. Providing this service from the health department will promote and spread awareness of services and habits that will reduce the frequency of obesity, lack of physical activity, and poor diet. Overall, this program will provide a service that increases the general health and awareness of the community itself. Although the American Diabetic Association recommends screening with fasted blood glucose tests, it is not commonly performed in everyday clinical practice, even to individuals who shows many risk factors [23]. Thus, in the interest of the community, the public health service, namely the Department of Health, should take initiative in a screening program.

Providing screening for at risk individuals does not require any changes in the health infrastructure, and glucose test kits are readily available at most health care facilities. It is highly likely that the incidence of type II will decrease through systematic screening. Since the screening will be opportunistic, and only offered to people who fulfill one or more of the risk factors, resources will be well spent in this effort.

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ORIGINAL ARTICLE

Piercing and tatooing in high school students of Veneto region: prevalence and perception of infectious releated risk

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Key words

Body art • Piercing • Students

Summary

Introduction. *Body piercing (P) and tattoo (T) is a growing social phenomenon over recent years. Nowadays in Italy little is known about the prevalence, the attitude, the medical and social consequences of these activities. The purpose of this study is to examine the prevalence distribution and the attitude towards P and T and the perception of the risk for infections, in a sample of high school students living in the four Provinces of the Veneto Region (Italy).*
Methods. *An anonymous, self administrate multiple-choice questionnaire about piercing and tattoo practices was distributed during the 2009-2010 academic year to a sample of randomly extracted grades to obtain information about socio-demographic characteristics, family educational level, personal attitude, prevalence and perception of the importance of the sanitary, technical and artistic competence of the operator.*
Results. *The correctly compiled questionnaires were 2712 (95.4%). Males and females were respectively 46.2% and 53.8% (mean age 17 ± 1.7 years). The 20.2% and the 6.4% of all the students had already experienced respectively P and T and resulted "very interested" the 46.7% to P and the 57.4% to T. Esthetical motivations are the main ones referred to use body art. The most part of interviewed subjects (81.6%) think that it is possible to have an infection, but only about 50% of students reported to know specific information about transmission of HIV, Viral Hepatitis and skin infections. The parents' educational levels do not influence the perception of the risk of infection. The majority of interviewed subjects (88.0%) prefers to undergo body art practices in a qualified center. Only the 30% of students recur to a medical help to solve problem of infection.*
Discussion. *The piercing and tattoo prevalence rate in our study (P: 20.2% and T:6.4%) resulted similar to other Italian ones (range reported: P: 20.3-35.1%, T: 4.8-8.6%), showing an increasing trend with age.*
Since a high rate of interviewed students referred a substantial ignorance about the risk of transmission of body art related infectious diseases, it is suitable to promote as soon as possible among the youth educational interventions and counseling.

Introduction

Tattooing (T) and body piercing (P) showed a raise from the 90s and the trend does not show signs of decreasing in the near future. Adolescents and young adults have increasingly acquired body piercing over recent years and medical literature in relation to prevalence of P is partially still limited [1].
Body piercing is ubiquitous and concerns all socio-economic and age groups, with a major concentration between 15-30 years old [2]. In USA it is estimated that 2% of the population (about 6 million of people) have P. In a U.S. study conducted in a college population P showed a prevalence rate between 17 and 33% [2] and in undergraduate university students an overall prevalence of 51% (40% males and 60% females) [3]. The same study reported tattooing as a very common practice with an overall prevalence of 21.8% (23% males and 21% females) was found [3]. In Germany the general population show a prevalence rate for P of 6.8% and for T of 8.5%, with a peak in younger subjects (14-44 years) reaching the 14% for P and 15% for T [4].
In Italy other studies [5, 6] found a prevalence rate between 35,1 and 31.3% for P and 11.3 and 4.8 for T in high school students.
Both procedures occur across the social spectrum and over a wide range of age. They intend to create a permanent body modification according to the social trends or beauty or to display a transgressive and reactive behavior.
Nowadays in Italy little is known about the current prevalence, social distribution, attitude, and medical and social consequences of these activities.
The purpose of this study is to examine the prevalence distribution of piercing and tattoo, the causes of the choice of these practices, the perception of the associated risk for infections, in adolescent living in the Veneto Region (North East of Italy), who attend manifold sort of high school.

Methods

Body piercing has been defined as the "penetration of jewelry into openings made in such body areas as eyebrows, lips, tongues, nose, nipples or genitals". Tattooing is defined as an invasive procedure in which multiple punctures produce an indelible decorative design with pigment introduced into the skin [7].

To evaluate the attitude to the piercing and tattoo (also defined as body art) and the perception of the risk of infections related to these practices, an anonymous, self administrate multiple-choice questionnaire was distributed during the 2009-2010 academic year to a selected group of high school students living in the Veneto Region (Italy).

The Veneto Provinces randomly involved in the study were Verona, Vicenza, Belluno and Venezia; and the high schools sampled were classic, scientific, artistic, pedagogic liceo and professional and technical schools.

From each school two first, third and fifth grades were randomly extracted to obtain a total of six grades for each school.

The validated questionnaire assessed information about: socio-demographic characteristics as age, sex, family educational level (university or high school or middle school) considering the higher educational level reached at least of one parent; personal attitude towards piercing and tattoo practices; prevalence of subjects with piercing and tattoo; the perception of the importance of the sanitary, technical, artistic competence of the operator. Moreover the student's awareness of the potential transmission of some infectious diseases associated with these practices was evaluated.

The data from this study were collected and processed in compliance with the national law on privacy (Law N. 196/2003).

Students were assured the confidentiality of their responses and the participation was voluntary. Approval from parents and teaching staff of each school was obtained before conducting the survey.

To ensure a high response rate, the survey was brief and non intrusive, easy to complete (requiring less than 15 minutes), and administered at the beginning of a class lesson. All questionnaires were immediately collected and their information was entered in a database.

Statistical analysis

Statistical analyses were carried out using EpiInfo 6.01 software supplied by the Centres for Disease Control, Atlanta (GA, USA). Frequencies were compared by χ_2 test (Mantel-Haenszel). P values were considered significant when less than or equal to 0.05

Results

A total of 2843 students participated to the study. The data were analyzed from the 2712 correctly compiled questionnaires (95.4%); the main cause of exclusion in the data base entry was due to the lack of information on birth, sex and grade attended. Among considered students 1252 (46.2%) were males and 1460 (53.8%) were females; age range was between 13 and 22, mean age 17 ± 1.7 years. Their socio-demographic characteristics are reported in Table I.

In the most part of families (89%) both parents are present, while in 9.8% there is a single parent. They are only son in 23.3% of cases.

Considering the higher educational level achieved by least of one the family parent, the 25.2% reported university degree, and 53.4% and 21.3% attained respectively a middle (high school) and low (till junior high school) schooling.

Among the school students and in relation to male or female sex, ones who "experienced" and ones who answered to be "very interested" about piercing and tattoo didn't show any significative difference in relation to the manifold sort of high school (Figs. 1 a, b).

Positive attitudes toward P were found in 29.0% of males and 54.5% of females respectively ($p < 0.0001$)

Tab. I. Socio-demographic characteristics of the 2,712 enrolled students.

	Males (%)	Females (%)	Total (%)
Years			
< 14	0.3	0.1	0.2
14	28.3	30.0	29.4
15	7.5	4.3	5.4
16	25.8	29.5	28.2
17	8.7	6.0	6.9
18	22.7	26.2	25.0
> 18	6.9	3.8	4.9
Class			
First	37.4	36.2	36.6
Third	27.8	29.2	28.7
Fifth	34.8	34.6	34.7
Nationality			
Italian	95.3	95.7	95.6
Other	4.7	4.3	4.4
Residential area			
Downtown	22.4	19.8	20.7
Suburb	25.4	23.2	24.0
Municipal district >15.000 inhabitant	10.5	9.8	10.0
Municipal district <15.000 inhabitant	41.7	47.2	45.2
Residential city			
Belluno	22.2	22.7	20.7
Verona	28.7	28.0	29.6
Vicenza	27.2	24.2	26.0
Venezia	21.9	25.1	23.7

Fig. 1 a, b. Prevalence rate of attitude of students regarding piercing and tattoo by sex and type of school attended.

Fig. 1a. Piercing

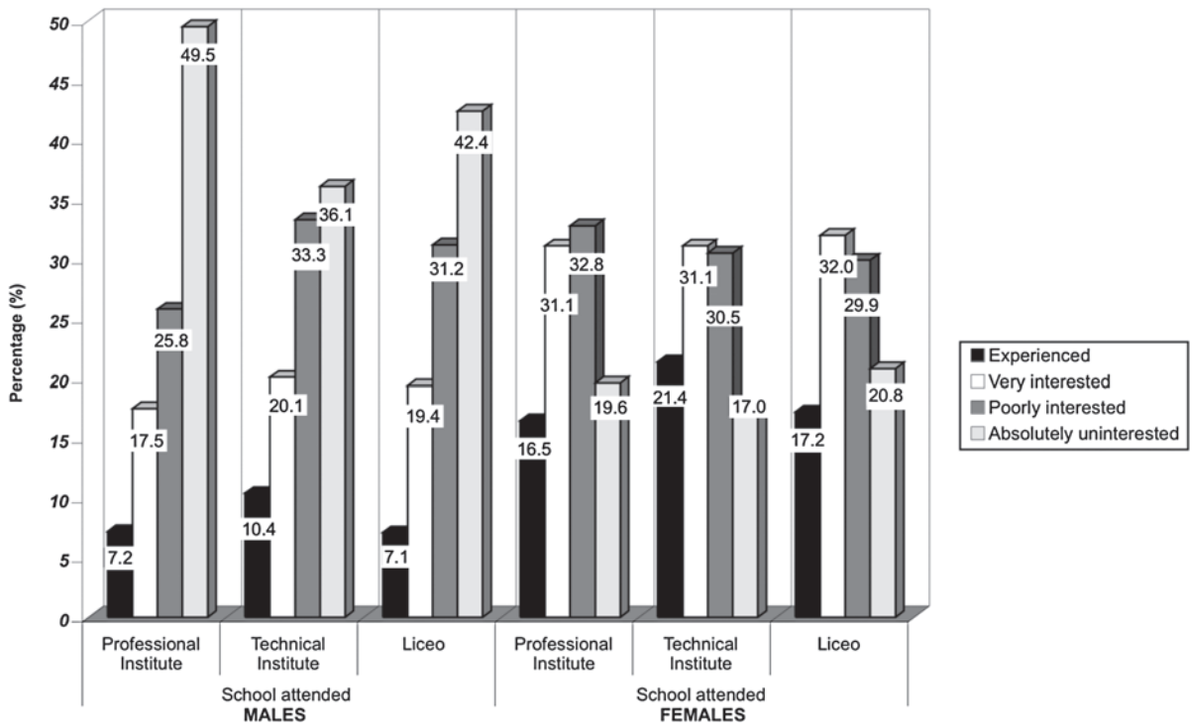


Fig. 1b. Tattoo

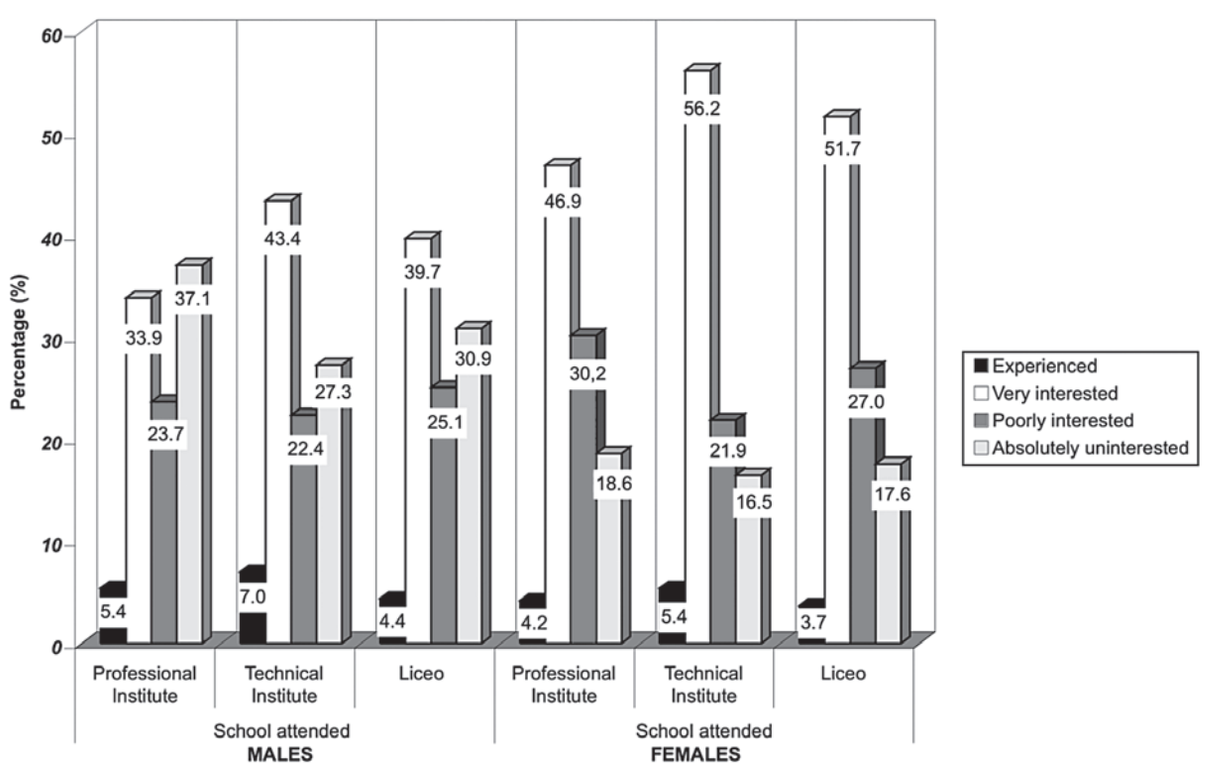
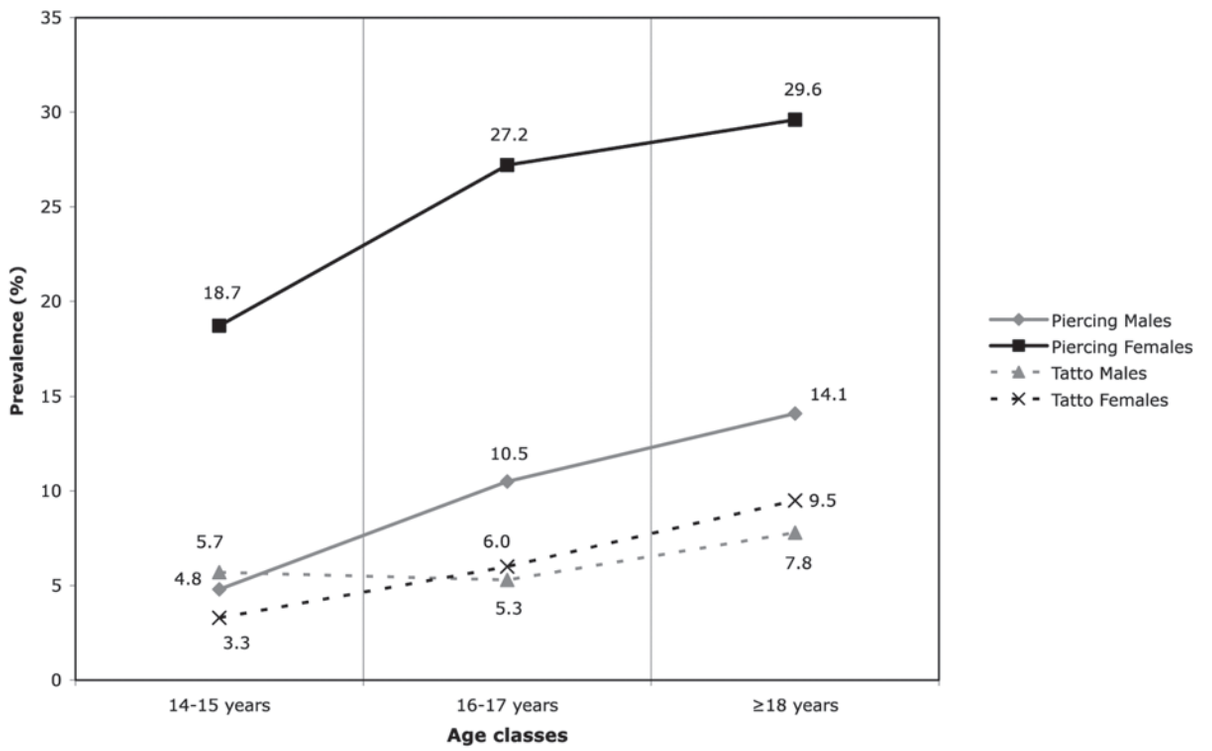


Fig. 2. Prevalence rate of students who have experienced piercing and tattoo by age and sex.



(Fig. 1a), and for T in 46.7% and 57.4% of males and females respectively ($p < 0.0001$) (Fig. 1b).

The 20.2% and the 6.4% of all the students respectively experienced P and T. An increasing trend with age was found in both sexes and for both kind of practices ($p < 0.0001$); with a particular higher prevalence in females (range 18.7-29.6%) for P (Fig. 2).

Piercing removal was considered on average in 21.1% of subjects who experienced it (males: 28.7%, range 15.0-31.6%; females: 19.5%, range 12.9-23.4%) and in 12.0% of subjects who experienced tattooing (males: 17.6, range 13.0-28.0%; females: 9.1, range 6.5-14.5%).

The reasons to have body art resulted for both sexes by relevance: esthetical motivations (28.2% of cases), transgression (16.1%), curiosity (15.5%), fashion (12.0%), attention drawing of the other sex, to make a personal statement, to emulate a VIP, to belong to their own group.

The main cause for willing students not to have body at performed on them was parent prohibition, while personal dislike for the subject was the main cause for unwilling ones (Tab. II).

As regard to infections, the most part of interviewed subjects (81.6%) think that it is possible to get an infection. but when specific notices were asked about HIV, Viral Hepatitis and skin infections only about 50% of them – more often females – appeared truly aware of the risk (Tab. II).

For both sexes parents' educational level does not influence the perception of the risk of infection (Fig. 3).

The most part of interviewed subjects prefers to undergo body art practices in a qualified center (88.0%), followed to friends (9.5%) or other choices (2.5%). In a qualified center the students consider sanitary characteristics to be important -as the use of latex gloves (96.9%), of single-use needles (97.0%), of sterilized instruments (97.7%)- followed by artistic performance (94.3%).

Discussion

Tattooing and piercing are perceived as body art decoration, growing in popularity and increasingly belonging the generational conformity [1, 8] thus this phenomenon is worthy of an immediate attention.

In fact, the principle motivation to undergo to these practices in our studied population was above all related above all to embellish themselves (esthetical motivations and to be fashionable), while transgression appears only in 16% of responses.

This study represent a report on the practice of piercing and tattoo in young people aged 13-22 years in four provinces of Veneto Region (North East Italy), attending a wide range of Italian high school. In Italy some schools like artistic and pedagogic liceo are mostly attended by females (respectively 66.6% and 84.5%) [5, 9] and this may explain the higher prevalence of female sex in our study.

The piercing and tattoo prevalence rate in our study (P: 20.2% and T: 6.4%) resulted similar to other Italian ones (P: range 20.3-35.1% and T: range 4.8-8.6%) [5, 10],

Tab. II. Student's attitude (rate) to piercing and tattoo regarding: personal interest, generic and specific perception of risk of infection, infection problem solving.

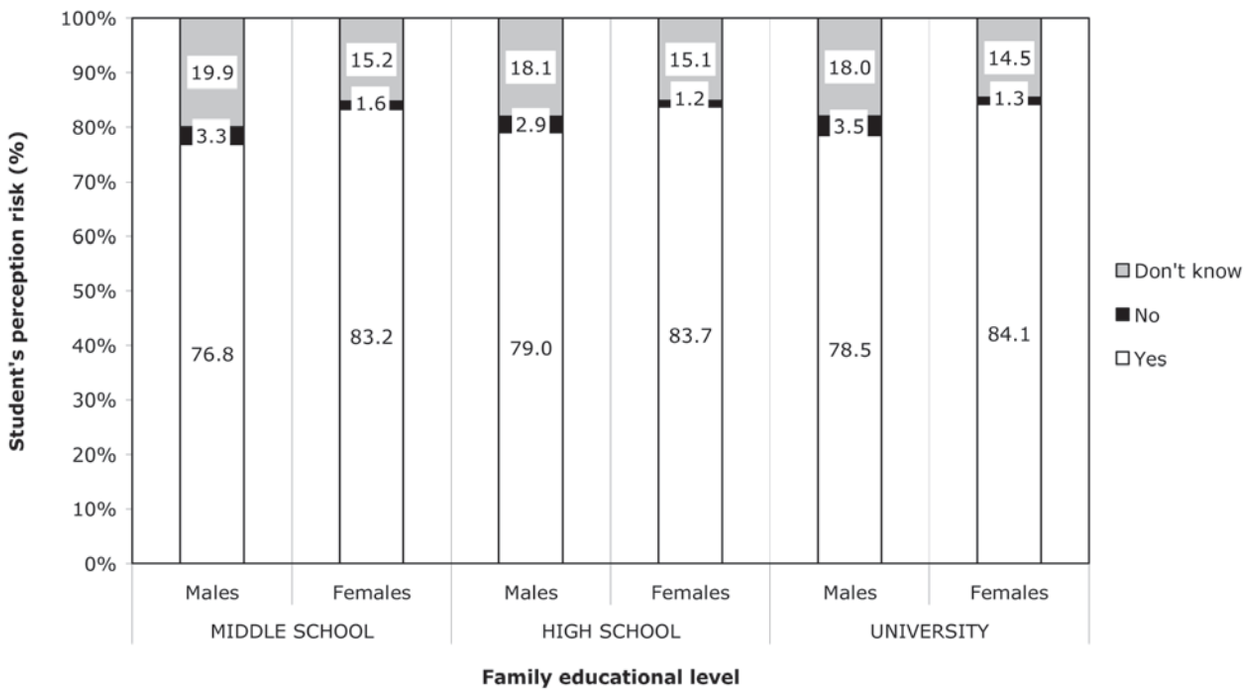
		Piercing		Tattoo	
		Males	Females	Males	Females
STUDENT'S ATTITUDE					
Does not want					
Do not like it		54.4	53.3	48.3#	43.1#
Do not approve it		26.1	21.9	26.3	23.1
May not					
Parents proibition		47.1#	54.6#	33.3#	46.3#
Fear		7.7	19.7	5.9	18.0
PERCEPTION OF RISK OF INFECTION					
Generic risk					
Yes		77.7*	83.6*	77.7*	83.7*
No		3.3	1.4	3.3	1.4
Non responders		19.0	15.0	19.0	14.9
Specific risk					
	Yes	52.4	54.8	50.2*	60.7*
HIV	No	35.5	34.9	37.4	28.3
	Don't know	12.1	10.3	12.3	11.0
	Yes	45.4	46.9	44.8#	49.9#
Viral hepatitis	No	39.8	39.4	40.0	35.9
	Don't know	14.7	13.7	15.1	14.2
	Yes	54.0#	69.5#	73.5*	81.7*
Skin infections	No	22.2	19.5	12.7	8.2
	Don't know	13.8	11.1	13.8	10.1
Infection problem solving					
Medical help		28.4	35.6	42.9	41.7
Self-medication		78.9	71.8	68.3	70.8

* $p < 0.0001$; # $p < 0.005$

and international investigations performed on high school students reports similar or higher body art prevalence: between 17-50% for piercing and 7.9-20% for tattoo [2, 3, 8, 11]. The difference in piercing prevalence reported in some studies may be due to the different interpretation of the earlobe piercing: some of them consider only cartilage as piercing site in females, while others take in account all the ear [3, 12, 13]. The questionnaire for our study did not discriminate between piercing and earlobe earrings. The low piercing prevalence found in our and other Italian studies may be explained since earlobe earring is very common in our geographical area and females do not consider it as a piercing, excluding therefore themselves from piercing users. A rise on the prevalence of subjects with body art with time can be also expected as our study shows that on average the 25.4% and the 45.6% of subjects are interested respectively to piecing and tattoo practices. Indeed both for piercing and tattoos a significative increase with age in this as in other studies was found [1, 5, 8, 10- 12].

An high rate (over 80%) of students perceives a generic risk of infection. Nevertheless when specific data are collected about the possible transmission of HIV, Viral Hepatitis and skin infections, respectively the 49.5%, 52.7% and the 21.2% of them answer "no" or "don't know". This point out that the major part of youth don't

Fig. 3. Student's perception of the infection risk (rate) and family educational level.



really know the specific route of transmission and then the pattern of the prevention of the possible related infections [1, 5, 14].

The demonstration that some serious infections are strictly correlated with those body art practices underlines then the importance of legislative and educational interventions [6, 12, 15-21]. This study shows that even if youth report to prefer qualified centers to undergo body art practices and in theory considers the use of safe instruments of great importance, the inappropriate knowledge on prevention of infections compromises the ability of a critical and aware choice and behavior [1].

The perception of the risk of infection doesn't appeared to be related to the family schooling level, even if a light and not significant decrease in piercing and tattoo was found with the higher level of parent's education [9]. This fact may indicate that in this period of life the extrafamiliar milieu is held in high regard, as it also appears from reported motivation to have body art.

This is why a great attention is due particularly to youth with a dedicated incisive informative and educational campaign to promote knowledge on health risks related to body art.

Prevention may be done though the acquaintance of related health risks and though the choice of a professional operator with a regular qualification as requested by specific guidelines of the Italian National Health Council (Circular letter of 5February 1998 n. 2.8/156 and Circular letter of 16 July 1998 n. 2.8/633) and of Regione Veneto Guidelines (DGR 2401, 14/10/2010) [22]. Other relevant points for the risk of infection and others complications are represented by the chosen body site [22- 25] and by poor knowledge about what to do in case of problems. When pierced people have health concerns, most of them return to their body piercer (decorator, operator) or try to seek help from a friend or the internet rather than medical advice [2]. This is also what emerges in our study, where respectively only 34.3% and 42.1% of pierced and tattooed students recur to medical help.

Prevention is defined as the promotion of health by the individual and the community, and therefore includes identifying unhealthy or risky behaviors and intervening to correct them or to minimize their effects.

Primary infection prevention activities intervene before the event, aiming to prevent it happening, and in case of body art practice by controlling the victim's exposure to the microorganism, with strategies that seek to change attitudes, lifestyles and behaviors of individuals and groups, as to educate communities and individuals on awareness and safety practices. Benefits can include, for example, a reduced incidence of infectious events, sometimes severe or fatal.

Prevention can positively improve the quality of health, and thus the quality of life, of both the individual and the community as a whole, supporting then personal and social development. There are also specific health and economic benefits: prevention activities save resources and contribute to the rationalization of medical care in public health systems.

In conclusion, the study underlines that educational interventions and counseling have to be organized for a wide range of age, but a better outcome can be obtained when the target is represented by young subjects if they are made aware before they put themselves at risk by performing any kind of body art.

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ORIGINAL ARTICLE

Pseudomonas aeruginosa infection among cystic fibrosis and ICU patients in the referral Children Medical Hospital in Tehran, Iran

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Key words

Pseudomonas aeruginosa • Cystic fibrosis • Cross-infection

Summary

Introduction. *Pseudomonas aeruginosa is one of the important causes of hospital-acquired infections in Intensive Care Unit (ICU) and considered as a major determinant of morbidity and mortality in patients affected by cystic fibrosis (CF). The aim of this study was to investigate clonal diversity among randomly picked P. aeruginosa isolates of CF and the other hospitalized patients in ICU.*

Methods. *Cultivation, identification, and antimicrobial susceptibility testing of P. aeruginosa isolates were performed using standard techniques. The genetic similarity of the strains was investigated by amplification of the Enterobacterial Repetitive Intergenic Consensus-polymerase chain reaction (ERIC-PCR) sequence.*

Results and discussion. *Among 49 isolates, sixteen were isolated from 11 patients affected by CF and 33 came from an epidemiological investigation of 25 P. aeruginosa infected patients of ICU. Five clusters were generated for all isolates analyzed through ERIC-PCR genotyping. Two major clusters (B and C) were discovered in P. aeruginosa isolates of ICU and CF patients during the whole period of this study. Fifteen unique antibiogram patterns obtained from all isolates and multi-resistant P. aeruginosa (MRPA) were identified in 23 isolates (47%). MRPA isolates were detected in all clusters (except A) while pan-resistant isolates were recovered only in cluster C.*

The high prevalence of related or identical isolates in CF and non-CF patients can be due to transmission of particular dominant clones in ICU ward. Therefore, enhanced infection-control may become necessary to prevent further spread of clonal strains.

Introduction

Pseudomonas aeruginosa is one of the important causes of hospital-acquired infections in intensive care unit (ICU) and considered as a major determinant of morbidity and mortality in patients affected by cystic fibrosis (CF) [1-3].

Surveillance of nosocomial *P. aeruginosa* infections has revealed trends of increasing antimicrobial resistance [4]. The emergence of transmissible *P. aeruginosa* strains at hospital and its spread to other *P. aeruginosa*-negative patients raise concerns especially in ICU settings, where the number of antibiotic agents with good activity is limited [5, 6]. Several studies describe the patient-to-patient transmission of this bacteria from centers related with CF patients [7, 8].

At our hospital, CF patients are cared in gastroenterology ward and *P. aeruginosa*-positive and *P. aeruginosa*-negative patients are not separated from each other in this ward. In addition, these patients move to other wards especially ICU during their hospitalization. The aim of this study was to investigate epidemiology of antimicrobial resistance and clonal diversity among randomly picked *P. aeruginosa* isolates of CF and the other hospitalized patients in ICU.

Material and methods

Between January and December 2010, randomly picked *P. aeruginosa* isolates of infected patient in ICU and patients affected by CF were collected from the tertiary referral Children Medical Hospital in Tehran, Iran. The patients investigated in this study were all prone *to P. aeruginosa* infection. An infected patient was defined as a patient with clinical symptoms of infection, and from whom a clinical culture yielded a dominant growth of *P.aeruginosa*. Clinical information on *P. aeruginosa* patient isolates was collected from medical records. Information included age, sex, length of hospital stay, history of transfer from another wards, clinical outcome and microbiological data.

A number of CF patients had more than one isolates and some of them were isolated while they were transferred to the ICU. In addition several cultures were obtained

Tab. I. Patient details, origin and date of isolation, outcome and microbiological data of all the *P. aeruginosa* isolates.

Patient*	Isolates	Age (month)	Gender	Ward	Type of specimen	Length of hospital stay(Day)	Time of isolation after hospitalization(Day)	Outcome	ERIC-PCR pattern	Antibiogram pattern
1	a	11	M	PICU	Trachea tube	21	4	Death	D	12
2	a	12	M	PICU	Wound	30	6	Discharge	B	3
3	a	12	F	PICU	Ear secretion	58	5	Discharge	C	15
4	a	7	M	PICU	Trachea tube	34	20	Discharge	E	11
5	a	2.5	F	PICU	Urine	29	2	Discharge	C	15
6	a	10	F	PICU	Urine	30	21	Death	C	15
7	a	6	F	PICU	Wound	11	10	Death	A	6
8	a	3	M	PICU	Urine	21	5	Death	B	7
9	a	11	F	PICU	Trachea tube	5	2	Discharge	B	8
10	a	3	F	PICU	Wound	22	12	Death	B	7
	b				Eye		22		B	4
11	a	7	F	PICU	Trachea tube	15	5	Discharge	B	4
12	a	120	M	PICU	Urine	13	2	Discharge	B	3
13	a	2	M	PICU	Trachea tube	5	3	Death	B	11
14	a	9	M	PICU	Trachea tube	39	4	Discharge	B	4
	b				Wound		17		B	3
15	a	108	F	PICU	Trachea tube	54	2	Discharge	B	2
16	a	24	M	PICU	Trachea tube	4	3	Discharge	A	7
	a				Blood		4		E	10
17	b	4	F	PICU	Alveolar aspirate	28	14	Discharge	A	3
	c				Sputum		8		A	3
	d				Alveolar aspirate		8		C	12
18	a	8	M	PICU	Trachea tube	18	2	Discharge	C	2
	b				Urine		14		C	1
	a		F				3		B	7
19	b	36	F	PICU	Wound	40	5	Discharge	C	14
	c		F				20		C	12
20	a	4	M	PICU	Urine	25	1	Discharge	C	15
21	a	31	F	PICU	Urine	26	5	Discharge	B	3
22	a	36	M	PICU	Blood	58	1	Dischrge	C	15
23	a	120	M	PICU	Trachea tube	19	4	Discharge	B	3
24	a	24	M	PICU	Pharynx	15	6	Discharge	C	14
25	a	3	F	PICU	Wound	51	3	Death	C	15
26	a	12	F	PICU	Wound	14	14	Death	C	15
	a			Gastroenterology	Alveolar aspirate		4		B	6
27	b	192	F	Gastroenterology	Sputum	56	40	Death	B	7
	c			Gastroenterology	Sputum		46		B	6
	a			PICU	Trachea tube		2		B	5
28	b	72	M	PICU	Tracheal aspirate	12	7	Death	B	13
	c			PICU	Trachea tube		11		B	11
29	a	5	F	PICU	Sputum	10	1	Dischage	C	15
30	a	45	M	Gastroenterology	Sputum	14	2	Dischage	B	8
31	a	120	M	Gastroenterology	Sputum	12	2	Death	B	7
32	a	10	M	PICU	Wound	10	9	Death	C	15
33	a	5	F	Gastroenterology	Urine	11	1	Dischage	B	9
34	a	7	M	Gastroenterology	Urine	36	2	Death	C	15
35	a	72	M	PICU	Trachea tube	7	2	Death	B	3
	b			Gastroenterology	Sputum		7		C	15
36	a	48	F	Gastroenterology	Sputum	7	1	Dischage	B	10

*Isolates number of 26 to 36 isolated from CF patients. PICU: Pediatric Intensive Care Unit

Fig. 1. Dendrogram of genotype analysis derived from 49 *P. aeruginosa* isolates. The scale at the top represents the genetic distance between the isolates..

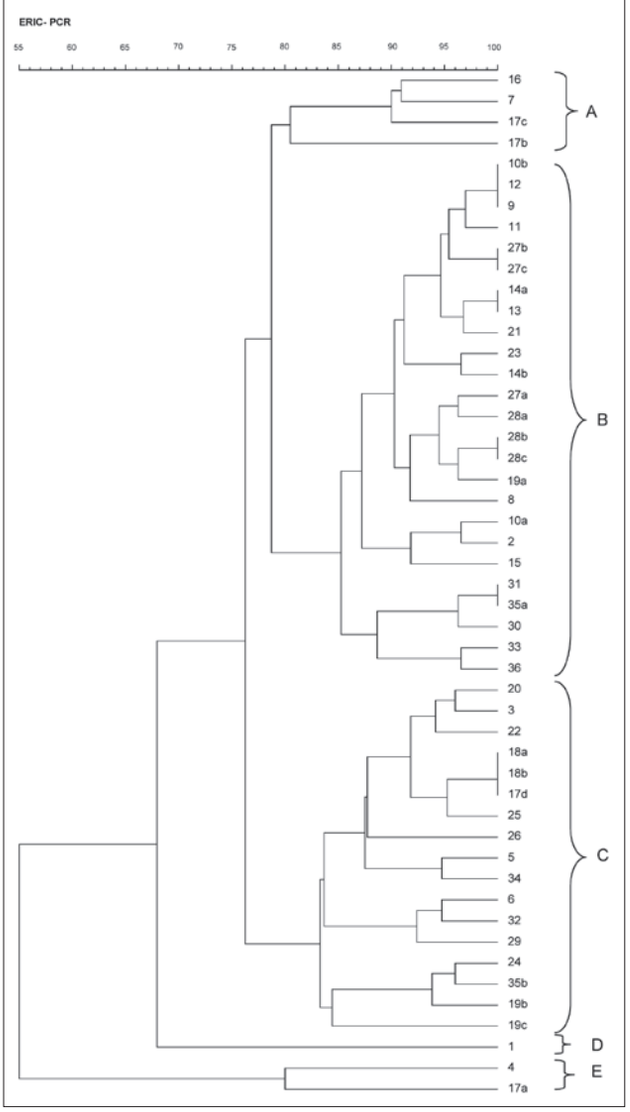
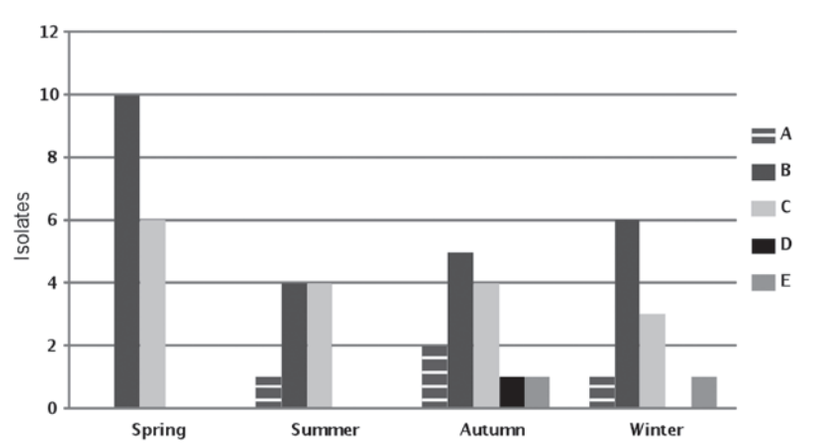


Fig. 2. Distribution of different clusters during 2010.



from some patients as long as they stayed in the ICU. Cultivation, identification, and antimicrobial susceptibility testing of *P. aeruginosa* isolates were performed using standard techniques [9].

Multi-resistant *P. aeruginosa* (MRPA) was defined as strains resistant to ≥ 3 of the following classes of antibiotics: antipseudomonal penicillins, antipseudomonal oxyimino-b-lactams, fluoroquinolones, aminoglycosides, and carbapenems [10].

The genetic similarity of the strains was investigated by amplification of the Enterobacterial Repetitive Intergenic Consensus-polymerase chain reaction (ERIC-PCR). sequence [11]. Comparison of banding patterns was performed using Gelcompar II, version 6.5 (Applied Maths, Sint-Matens-latem, Belgium). Cluster analysis was accomplished with the unweighted pair group method using average linkages (UPGMA). ERIC-PCR was performed for *P. aeruginosa* isolates and relatedness among genetic clones was defined as 80% similarity as belonging to one clone.

Results

During one year, 36 patients aged 3.5 to 192 month (average 33.4) were entered to this study. Table I illustrated the patient details, origin and date of isolation, outcome, ERIC-PCR and antibiogram pattern of all isolates.

Among 49 isolates, sixteen were isolated from 11 patients affected by CF and 33 came from an epidemiological investigation of 25 *P. aeruginosa* strains isolated from infected patients of ICU.

P. aeruginosa isolates were recovered from trachea tube (26%), urine (18%), wound (16%), sputum (18%), alveolar aspirate (8%), blood (4%), tracheal aspirate (2%), ear secretion (2%), and eye (2%).

Average length of hospital stay in all patients was 24 days. Of the 36 patients, 14 died during the study (case fatality rate, 39%); whereas half of them were from CF patients (case fatality rate, 64%). MRPA were identified in 23 isolates (47%) and consistently detected during the study period. Among all isolates, 11 considered as pan-resistant isolates that 5 of them belonged to CF patients.

Five clusters were generated for all isolates analyzed through ERIC-PCR genotyping, which were designated alphabetically from A to D (Fig. 1). Cluster B and C comprised both ICU and CF isolates while cluster A, D and E had only isolates of ICU ward. Eleven isolates of cluster B were identical whereas cluster C comprised of only 3 identical isolates.

MRPA isolates were detected in all clusters (except A) while pan-resistant isolates were recovered only in cluster C.

Cluster B and C was seen during the study period (4 seasons) (Fig. 2). Cluster A was introduced during summer and remained present during the rest

Tab. II. Antibiogram patterns of 49 *P. aeruginosa* isolates.

Pattern number	Isolates*	CF	FEP	CP	MEM	CAZ	PTZ	IMP	GM	AM
1	18b	S	S	S	S	S	S	S	S	S
2	15,18a	S	S	S	S	R	S	S	S	S
3	2a,12,14b,17b,17c,21,23,35a	R	S	S	S	S	S	S	S	S
4	10b,11,14a	R	S	S	S	R	S	S	S	S
5	28a	S	S	S	R	S	S	S	R	S
6	7,27a,27c	R	R	S	S	S	S	S	S	S
7	8,10a,16,19a,27b,31	R	R	S	S	R	S	S	S	S
8	9,30	R	R	S	R	R	S	S	S	S
9	33	R	R	R	R	R	S	S	S	S
10	17a,36	R	R	S	R	R	R	S	S	S
11	2c,10b,28c	R	R	R	S	R	S	R	S	S
12	1,17d,19c	R	R	R	R	R	R	S	S	S
13	28b	R	R	S	S	R	S	R	R	R
14	19b,24	R	R	R	R	R	S	R	R	R
15	2b,5,6,20,22,25,26,29,32,34,35b	R	R	R	R	R	R	R	R	R

CF, Cephalothin; FEP, Cefepime; CP, Ciprofloxacin; MEM, Meropenem; CAZ, Ceftazidime; PTZ, Piperacillin-tazobactam; IMP, Imipenem; GM, Gentamycin; AM, Amikacin

* Isolate number of 26 to 36 belongs to CF patients

of the study. During the autumn, one patient appeared in cluster D and E. However, cluster D emerged in the third season, detection of this cluster during the winter did not occur.

In our study, 15 unique antibiogram patterns obtained from all isolates (Tab. II). Most of the isolates were resistant to antipseudomonal oxyimino-b-lactams. The highest percentage of susceptibility was seen in aminoglycosides (71%) followed by piperacillin-tazobactam (67%), imipenem (63%), ciprofloxacin (59%), and meropenem (55%). Different antibiogram patterns were displayed in a number of isolates even with ≥ 95% similarity.

Discussion

Our hospital is a tertiary referral center in which the ICU setting includes mixed patients such as CF patients and transmission of *P. aeruginosa* strains between CF and the other hospitalized patients in ICU is probable,Therefore genotyping of *P. aeruginosa* isolates seems to be essential to clarify our hospital epidemiology. The spread of infection from patients with CF is a definite risk in children's wards especially in ICU [12, 13]. In this study, molecular typing suggests cross-transmission between CF and non-CF patients. According to our results, infections were predominantly caused by strains with cluster B and C. presence of these patterns during the whole period of this study suggesting that these clones are adapted to our hospital. Cluster B was identified in 25 strains (51% of all typed isolates) and highly appeared in the first 3 months of 2010 and circulated until end of the study.

Our analysis demonstrated that CF isolates are genotypically closely related to non-CF isolates. The two major clusters (B and C) in our study were discovered in both patient populations that suggest probable occurrence of cross-infection between these patients.

Studies about *P. aeruginosa* cross-infection demonstrated controversy evidence of clonal spread in CF centers. Some studies have revealed convincing evidence of clonal spread at CF holiday camps or centers [14-18]. Another study at the Vancouver CF Centre did not represent any evidence of significant cross-infection with *P. aeruginosa* [19].

Emergence of MDR expect to become more prevalent in many hospitals [20, 21]. There is no doubt that cross-transmission plays an important epidemiological role in MRPA isolates [22, 23], so prevention of the acquisition of these isolates are essential due to limited therapeutic options and increased mortality [24]. On the other hand, prevalence of strains with resistance to all antimicrobial agents is a major risk for hospitalized patients especially in CF patients because of rare *P. aeruginosa* eradication and subsequently occurrence of chronic infection [25, 26].

P. aeruginosa has capacity to develop resistance to essentially antimicrobial agents [27] and may require treatment with less commonly used antibacterial agents such as colistin [4].

Our results support other studies [28] that mentioned aminoglycosides are clinically effective against *P. aeruginosa* isolates when administrated intravenously or by nebulization.

Finally, in our study the high prevalence of related or identical isolates in CF and non–CF patients can be due to transmission of particular dominant clones in ICU ward. This suggests cross-infection can occur between CF and non-CF patients. Therefore, enhanced infection-control including strict segregation policies, basic hygiene measures and continued microbiological surveillance may become necessary to prevent further spread of clonal strains.

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ORIGINAL ARTICLE

Impact of immigration on burden of Tuberculosis in Umbria: a low-incidence Italian region with high immigrants rates

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Key words

Tuberculosis • Surveillance • Epidemiology

Summary

Introduction. *In Italy, Tubercolosis (TB) has increasingly become a disease for specific population subgroups such as immigrants. The objective of this paper is to describe the trend in TB incidence from 1999 to 2008 in Umbria: a low-incidence Italian region with high immigrants rates.*
Methods. *Data were obtained from the Regional Information System for Infectious Diseases. Using a linear regressions model we estimated trends for number of cases and incidence rates; with a logistic regression model we estimated the effect of a set of covariates on the probability of being affected by TB.*
Result. *590 TB cases were reported of whom 254 (43%) were foreign. In 2008 39.7 new cases per 100.000 were registered among foreign-born subjects. TB incidence among Italians was 3.8/100.000 Italians. But a linear regression analysis showed a statistically significant decreasing trend in the notification rate among foreign-born people (coef: -7.32, r2:0.57, p < 0.05). The probability to be affected by extra-pulmonary is significantly larger in foreign patients (OR = 0.72, CI = 0.48-1.07). Foreign unskilled workers report a higher probability to be affected by TB (OR = 19.05, CI = 6.01-60.4).*
Discussion. *Increasing immigration rates may affect TB epidemiology. The analysis of incidence trends is an important tool for monitoring tuberculosis disease control and to identify specific sub-group at risk.*

Introduction

During the last 50 years, the improvement of socio-economic, hygienic and therapeutic conditions have allowed a progressive decrease in the incidence of Tuberculosis (TB) in industrialized countries [1, 2]. However, the increase in HIV, the appearance of new marginalized people, especially in some urban areas and, in particular, immigration from high TB incidence countries have recently contributed to reverse this downward trend [3, 4]. In 2006, in the United States 57% of all reported TB cases were among foreign-born persons and in 2007 the TB case rate for foreign-born persons was 9.9 times greater than the rate for US-born persons [5, 6]. In most European countries there was a steady decline in the number of notified cases of native-born between 2001 and 2008, whereas case notifications of foreign-born generally increased, especially in lower-incidence countries [7]. In 2008 TB incidence among Italians was 3.8/100.000 Italians, TB incidence among foreign born persons was 52.1/ 100.000. The annual proportion of foreign-born cases on the total TB notifications increased from 20.3% in 1999, to 48.7% in 2008 [8, 9]. As the global burden of TB falls principally on developing countries, estimates of the role of immigration on the epidemiology of TB in low-prevalence countries are important for the design of appropriate strategies in disease control.

In this paper, the aim is to describe the trend in tuberculosis incidence from 1999 to 2008 in the central Italian region Umbria, highlighting the main differences in TB incidence between native-born and not Italy-born in this Region featured by a high immigration rate.

Methods

We conduct a retrospective study within the Surveillance System for Infectious Diseases in Umbria, a region with about 900.000 inhabitants and about 10% of resident immigrants, the second highest Italian Region for presence of foreign [8]. Data were obtained from the Regional Information System for Infectious Diseases, based on mandatory physician notifications. From the database, we extracted year of notification, gender, age, citizenship, occupational status, professional position, sector of activity of patients and the site of the disease (pulmonary, extra-pulmonary and disseminated).
Data on HIV co-infection of incident cases could contribute significantly to TB surveillance, but it would been required record linkage between two independent data sources.
Foreign-born were differentiated in “regularly registered” and “not regularly registered”. Not regularly registered have been estimated according to the procedure reported in the report on foreigners’ health status in 2007 of the National Observatory of health at regional level [10], that

Tab. I. TB total cases and shares according to origin of patients by site of disease, Umbria region, Italy: 1999-2008.

						Pulmonary			Extra-pulmonary			Disseminated		
Year	Italy		Not Italy		Total	Italy	Not Italy	Total	Italy	Not Italy	Total	Italy	Not Italy	Total
	nr.	%	nr.	%	nr.	%	%	%	%	%	%	%	%	%
1999	55	79.7	14	20.3	69	70.9	57.1	68.1	25.5	42.9	29.0	3.6	0.0	2.9
2000	52	63.4	30	36.6	82	75.0	56.7	68.3	25.0	40.0	30.5	0.0	3.3	1.2
2001	38	54.3	32	45.7	70	78.9	78.1	78.6	21.1	15.6	18.6	0.0	6.3	2.9
2002	23	52.3	21	47.7	44	78.3	61.9	70.4	21.7	38.1	29.6	0.0	0.0	0.0
2003	30	50.9	29	49.1	59	50.0	89.7	69.5	50.0	10.3	30.5	0.0	0.0	0.0
2004	30	57.7	22	42.3	52	70.0	81.8	75.0	23.3	13.6	19.2	6.7	4.6	5.8
2005	20	45.5	24	54.5	44	80.0	95.8	88.6	20.0	0.0	9.1	0.0	4.2	2.3
2006	31	59.6	21	40.4	52	67.7	81.0	73.1	25.8	14.3	21.2	6.5	4.8	5.8
2007	26	45.6	31	54.4	57	88.5	80.7	84.2	11.5	12.9	12.3	0.0	6.5	3.5
2008	31	50.8	30	49.2	61	67.7	76.8	72.1	25.8	23.3	24.6	6.5	0.0	3.3
Total	336	56.9	254	43.1	590	72.3	76.8	74.2	25.3	20.1	23.1	2.4	3.2	2.7

considered irregular immigrants to be 20% of regular ones for every year, except for 2003, when a national decree massively legitimized irregular immigrants, where it was considered to be 10% of the regular ones. We compared odd-ratios according to origin of patients by age group (0-19, 20-39, 40-59, 60-79 and 80 years or more), type of profession (skilled and unskilled workers) and occupational status (occupied, unemployed and retired). For each comparison we performed a chi-squared test to check for the presence of heterogeneous odd-ratios. Moreover, we calculated: number of TB cases, shares of pulmonary, extra-pulmonary and disseminated TB, and incidence rates (/100.000 population per year) for both the groups of patients. We also estimated trends for number of cases and incidence rates using a linear regressions model. We report the estimated coefficients, their confidential intervals (95% Confidence Interval [CI]) and a p-value labelling the observed significance level for the t-statistic. Since information about individuals not affected by TB was not collected in our original sample, we also use the "Everyday Life Aspects" (ELA), conducted by the National Statistical Institute (ISTAT) to retrieve information for healthy individuals. We extracted from the entire dataset only those observations corresponding to Umbria region for the years 2002-2008, with exception for 2004, year in which the ELA survey was not conducted. Using a logistic regression model, we estimated the effect of a set of covariates on the probability of being affected by TB for native-born and foreign-born groups. Statistical analysis was performed using Stata (Version 12).

Results

Over the decade examined (1999-2008) a total of 590 TB cases notified were reported. Overall 333 (56.4%) of 590 patients with TB are male, 219 (37%) are ≥ 60 year old and the median age is of 47 years in the entire sample; 254 (43.1%) cases were foreign-born. The median age of foreign-born individuals is of 31 years, much lower than that reported by Italy born subjects, 66 years. 73.7% of not-Italy-born cases were aged 15–39 years, compared to 17.9% of native-born cases. 74.2% of reported TB cases was diagnosed with pulmonary disease, 23.1% had a diagnosis of extra-pulmonary TB and only 2.7% with disseminated TB. Extra-pulmonary TB was light common among Italian patients (Tab. I). Total TB cases were, on average, 59 per year and no significant time trends were found. Foreign-born TB subjects showed an increase of 114.3% during the study period (from 14 in 1999 to 30 in 2008). The annual proportion of not Italy-born cases on the total TB notifications increased from 20.3% in 1999, to 49.2% in 2008. Over the last four years the proportion of foreign born cases has reached that of native-born and in 2005 and 2007 also reported higher values (54.6% and 54.4% respectively) (Tab. I). But a linear regression analysis showed a statistically significant decreasing trend in the number of not Italy-born cases (coef: -2.68, r2:0.09, $p < 0.05$) and a concurrently statistically significant decreasing trend in the incidence rate among foreign-born people (coef: -7.32, r2:0.57, $p < 0.05$) (Tab. II).

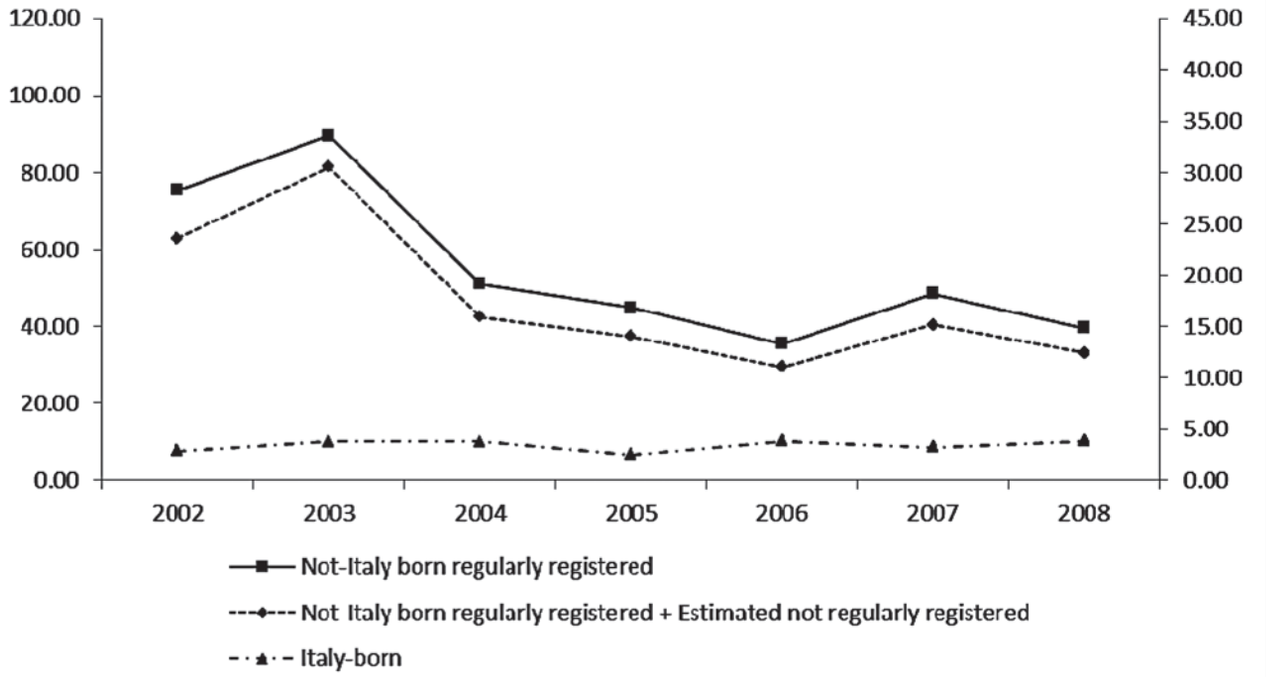
Tab. II. Trend of TB cases and incidence rate according to origin of patients.

	TB case		TB Incidence rate	
	Coef	R^2	Coef	R^2
Italy-born	-2.68**	0.49	0.07	0.50
	(1.00)		(0.073)	
Not Italy-born	0.59	0.09	-7.32**	0.57
	(0.741)		(2.144)	
Total	-2.08	0.27	0.12	0.38
	(1.157)		(0.125)	

Standard errors in parentheses

*** p < 0.01, ** p < 0.05, * p < 0.1

Fig. 1. TB incidence rates (/100.000 population per year) in the Italy born (left scale) and not-Italy born (right scale) population: denominators with and without estimated not regularly registered presences. Umbria region, Italy: 1999-2008.



TB incidence rate for the whole population decreased from 8.4 new cases /100.000 inhabitants in 2002 to 6.9 in 2008. TB incidence was found to be higher for the not-Italy born population. In 2008, 39.7 new cases per 100.000 were registered among foreign-born subjects and 33.1/100.000 adding 20% of estimated irregular presences to the denominator. TB incidence among Italians was 2.9 /100.000 population in 2002 and 3.8 in 2008 (Fig. 1). This difference remained when rates were standardised for age group and sex ranging from 3.6 to 5.0/100.000 for native born males and 76.0 to 29.9/100.000 for foreigner males and from 1.9 to 2.4/100.000 for native females and 69.1 to 44.8/100.000 for foreigner females (data not showed).

In tables 3 we report odd-ratios for site of disease according to origin of patients by age group, type of profession and occupational status. It shows that native-born subjects aged 0-19 present a significantly higher probability to contract pulmonary TB compared to foreigners (Odds Ratio [OR]: 0,17; CI 95% 0,02-1,55). Extra-pulmonary TB, instead, seem to be more associated with young age classes of immigrants (0-19 and 20-39), where number of cases is also consistently larger (OR: 6,00; CI 0,64-55,95). We also report odd-ratios for site of disease according to origin of patients by type of profession (manual and non-manual). For each site, the majority of TB cases are recorded by manual workers. The probability to be affected by pulmonary TB is smaller, but not significantly different, for Italian patients (OR = 1.29, CI = 0.88-1.91). The probability to be affected by extra-pulmonary TB, instead, it is found to be significantly larger in foreign patients (OR = 0.72, CI = 0.48-1.07). Finally we distinguish between employed, unemployed and retired individuals. In this case, no significative differences are found between Italy born and not-Italy born subjects, but the retired group confirmed, as previously highlighted for the age classes, that the elder Italian population is more likely affected by pulmonary TB compared to foreigners (OR = 0.43, CI = 0.12-1.56) and that the opposite result holds in case of extra-pulmonary TB (OR = 2.55, CI = 0.71-9.14). For the other groups, respectively employed and unemployed, only the unemployed seem to report some differences in the probabilities to be affected by pulmonary (OR = 1.46, CI = 0.67-3.19) and extra-pulmonary TB (OR = 0.59, CI = 0.26-1.32). Moreover, we compared TB cases, for native-born and foreign-born separately, with the average individual living in Umbria. Table IV reports the coefficients from the logit model on the probability to be affected by TB conditioned on some socio-demographics characteristics and the associated odds-ratio. The coefficients estimated using the Italy born sub-sample increase their magnitude with age of patients and turn from negative to positive in correspondence of the reference age class (40-59) with associated odds-ratio respectively lower than one for age classes below and greater than one for age classes above the reference age class. Italian patients belonging to age classes 0-19, 60-79 and ≥80 years have respectively a probability of 0.15, 2.05 and 5.32 times higher to contract TB, respect to the reference age class. Only the 20-39 age class shows a non-significant coefficient. Foreign born subjects present a quite different relation between age classes and the probability to be affected by TB. In this case, the coefficients associated with age classes tend to decrease with age, the highest probability of contracting the disease is estimated in correspondence of individuals with 20-39 years, 2.69 times higher to be affected by TB. After this threshold the probability

Tab. III. Odd ratios for site of disease according to origin of patients (not Italy born/Italy born) by age group, type of profession and occupational status.

	Pulmonary TB			Extra-Pulmonary TB			Disseminated TB		
Age group (years)	Not Italy born	Italy-born	OR 95% CI	Not Italy born	Italy-born	OR 95% CI	Not Italy born	Italy-born	OR 95% CI
Age group									
	N	N		N	N		N	N	
0-19	14	12	0.17* (0.02-1.55)	7	1	6.00* (0.64-55.95)	0	0	-
20-39	131	38	0.80 (0.35-1.79)	31	8	1.09 (0.46-2.56)	8	1	2.27 (0.28-18.6)
40-59	40	58	1.48 (0.55-3.95)	7	14	0.74 (0.27-1.99)	0	1	-
60-70	9	93	1.14 (0.33-3.89)	4	41	1.07 (0.31-3.68)	0	6	-
≥ 80	1	42	0.25 (0.02-2.92)	2	21	4.00 (0.34-46.68)	0	0	-
Total	195	243	1.29 (0.88-1.91)	51	85	0.79 (0.54-1.16)	8	8	1.33 (0.49-3.60)
Type of profession									
	N	N		N	N		N	N	
Non-manual	4	29	-	0	6	-	0	1	-
Manual	191	214	1.3 (0.89-1.91)	51	79	0.72* (0.48-1.07)	8	7	1.38 (0.49-3.87)
Total	195	243	1.29 (0.88-1.91)	51	85	0.79* (0.54-1.16)	8	8	1.33 (0.49-3.60)
Occupational status									
	N	N		N	N		N	N	
Employed	101	69	1.26 (0.64-2.51)	19	16	0.82 (0.4-1.71)	3	3	0.71 (0.14-3.59)
Unemployed	76	26	1.46 (0.67-3.19)	23	13	0.59 (0.26-1.32)	5	1	1.97 (0.22-17.4)
Retired	5	136	0.43 (0.12-1.56)	5	55	2.55* (0.71-9.14)	0	4	-
Total	182	231	1.26 (0.87-1.84)	47	84	0.74* (0.50-1.10)	8	8	1.33 (0.49-3.60)

Note: Non-manual workers category: managers and white collars, entrepreneurs and self- employed. Manual workers category: blue collars, other employed and self-employed workers.

Tab. IV. Logit model Coefficients and Odds Ratio for TB cases.

VARIABLES	(1) Not Italy-born			(2) Italy-born		
	Coeff.	Odds-ratio	CI 95%	Coeff.	Odds-ratio	CI 95%
Male	0.17	1.18	[0.82;1.71]	1.96***	7.13***	[4.48;11.34]
	(0.189)	(0.22)		(0.237)	(1.689)	
0-19	-0.90**	0.41***	[0.19;0.85]	-1.89***	0.15***	[0.06;0.4]
	(0.375)	(0.152)		(0.497)	(0.075)	
20-39	0.99***	2.69***	[1.75;4.16]	-0.50	0.61	[0.33;1.13]
	(0.221)	(0.596)		(0.315)	(0.191)	
60-79	-1.37***	0.25***	[0.11;0.58]	0.72***	2.05***	[1.25;3.36]
	(0.425)	(0.107)		(0.252)	(0.516)	
≥ 80	-2.09**	0.12***	[0.02;0.92]	1.67***	5.32***	[3.01;9.43]
	(1.021)	(0.125)		(0.291)	(1.551)	
Unskilled worker	2.95***	19.05***	[6.01;60.4]	0.30	1.35	[0.75;2.45]
	(0.589)	(11.215)		(0.302)	(0.408)	
Retired	-1.39**	0.25***	[0.08;0.8]	3.56***	35.21***	[21.61;57.72]
	(0.597)	(0.148)		(0.251)	(8.851)	
Unemployed	1.42***	4.13***	[2.78;6.13]	1.74***	0.74	[2.86;11.39]
	(0.202)	(0.833)		(0.353)	(0.225)	
Constant	-7.06***			-6.80***		
	(0.629)			(0.388)		
Observations		7,909			7,912	
Pseudo R-squared		0.187			0.259	

Standard errors in parentheses

*** p < 0.01, ** p < 0.05, * p < 0.1

decreases to 0.25 and 0.12 times for elder individuals (50-79 and ≥ 80 respectively). According to the other socio-demographics characteristics considered we can highlight the following differences: male individuals are more likely to be affected by TB in the Italy-born sample (OR = 7.13, CI = 4.48-11.34), while in the not-Italy born sample have the same probability as females; unskilled workers present a higher probability to be affected by TB than skilled ones. Moreover, not-Italy unskilled workers report a higher probability (OR = 19.05, CI = 6.01-60.4) than Italy born ones (OR = 1.35, CI = 0.75-2.45). The retired group has a much higher probability of contracting the disease in the Italy born subjects (OR = 35.21, CI = 21.61-57.72) than in the not-Italy born subjects (OR = 0.25, CI = 0.08-0.8). Unemployment is significant only for the foreign-born group, reporting a higher probability to be affected by TB (OR = 4.13, CI = 2.78-6.13).

Discussion

Regional TB incidence rate estimation (in 2008: 6.9 cases per 100.000 population in Umbria) is quite lower than other northern and central region and Italy (Italian mean 7.4 cases per 100.000 population) [11-13]. In developed countries, TB has increasingly become a disease for specific population subgroups; in particular, immigrants are a population group at risk and their presence may affect the TB epidemiologic situation in host countries [4, 12, 14]. The increase of foreign-born TB cases in Umbria region appears to be correlated with progressively increased immigration, while in aggregate TB incidence has shown a progressive reduction. Our results are in accordance with trends at the national level [10, 13] and the demographic characteristics of non- Italy-born and Italy–born cases differed, reflecting the differing epidemiology of disease in these populations. This study provides a clear description of the current epidemiology of TB in foreign-born people in Umbria, which will help inform appropriate public health action and health service provision. During 2005-2008, 49.5% of TB cases in Umbria were foreign born, yet this group constituted only 7.3% of the population. This trend is partly explained by the decreasing number of cases in the indigenous population, but also by migration patterns and the changing global epidemiology of TB. Given that the immigrants increase in Umbria by 171% from 2002 to 2008, it is possible to explain the increasing risk of TB in this area of Italy. This effect is not even completely under control although in Umbria TB incidence in foreign born population decreased in the last years. It is known that incidence among the not-Italy born is likely to largely reflect the prevalence of disease in their country of origin.

Other factors such as the conditions of migration and socio-economic conditions could make ethnic-minority groups living in less-deprived areas still at higher risk of disease. Immigration conditions in the host country is often indicative of living in crowded places, being homeless or in prison, all well-known risk factors for TB infection, reactivation, transmission and TB disease progression [15, 16].

Limitations in estimating TB incidence must be mentioned. Denominators for the immigrant population which only considers documented foreign-born subjects in Umbria (not including immigrants without a legal residence permit) leads to overestimate TB incidence. TB incidence rates decreased, in fact, adding the estimate of irregular presences to the denominator (Fig. 1).

But not regularly registered immigrants are not easily quantified and no official data are available in the Umbria region. In addition, differentiating between native-born and foreign-born cases doesn't allow including young foreigners who were born in Italy. This study being based on notified cases, as a unique source of information, is another limiting aspect. Although the surveillance system is considered efficient in Italy, it can be hampered by under-reporting and inconsistency. Most interestingly, even if healthcare assistance is offered also to "not regularly registered" immigrants, foreign-born subjects without legal residence permit might be reluctant to access to healthservice, this attitude leading to underestimation of TB cases and being a matter of public health concern [17]. In our study, as reported in other developed areas [15, 18, 19], TB among immigrants is mostly found in young adults. This could be partially linked to the immigration of predominantly young people but it also reflects true epidemiologic differences in TB patterns of transmission in low-incidence countries like Italy and countries of origin of immigrants. In this context, it is more complex to demonstrate whether TB in immigrants is a consequence of an infection acquired in the country of origin [18, 20] or in the host country [21, 22], as specific molecular investigations are needed but were not available for this study.

Relating to TB disease sites, differences in the likelihood of extra pulmonary TB depending on immigration status remain largely unclear [23]. Available data show a significant higher risk of extra pulmonary TB for immigrants in the age group 0-19 and 20-39 years (Tab. III). One aspect for concern is that extra pulmonary TB forms are more likely to be under-reported or not suspected by health specialists often inadequately trained in TB diagnosis.

According to European Action Plan to fight Tuberculosis, new recommendations for TB control activities were also developed in Italy and in Umbria Region. It aimed to tackle the increase in tuberculosis, and to outline measures for control including better clinical services, screening and surveillance. The delayed effect between infection and progression to disease means that cases detected by screening for tuberculosis in migrants before (pre-entry) or upon entry to Italy are likely to account for only a small proportion of all cases diagnosed in foreign-born populations. The evidence from numerous studies suggests that a one-off approach of new entrant screening for active disease is likely to be of limited value. This emphasises the need for communities and health care practitioners to maintain awareness of the risk of TB, not only in recent entrants, but also among those who have been resident for many years and minority ethnic groups. Prompt diagnosis and effective treatment remain priorities in terms of TB control for all persons, irrespective of their country of origin or migration status.

Conclusions

TB surveillance among specific at-risk subgroups should be made a priority as immigration flow to Italy is increasing at a fast rate. In Umbria despite the clear gap, we recorded an impact of TB lower than the national average both in the native population than in foreigners. This is probably due to the particular demographic aspects of Umbria region (such as absence of metropolitan areas) and to its organization of the public health system.

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ORIGINAL ARTICLE

Determinants of utilization of traditional bone setters in Ilorin, North Central Nigeria

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Key words

Determinants • Utilization • Traditional Bone Setter (TBS) • Ilorin West

Summary

Background. *Traditional bone setting (TBS) practice is an important part of health care delivery in many developing countries and has been in Nigeria for long. Despite the complications that arise from the cultural practice, TBS services is still in high demand by a significant number of people. This study was conducted to determine the factors that influence the utilization of TBS practice.*
Methods. *A descriptive cross-sectional study was carried out using a semi structured questionnaire to gather information from 400 randomly selected residents of Ilorin West LGA in north central Nigeria. Multistage sampling technique was used in selecting the respondents.*
Results. *The respondents were between the ages of 18-72 years with a mean age of 36.3 ± 12.3. Three hundred and three (77.3%) of the respondents know of TBS practice as a way of getting treatment for bone injuries. More than two third 210 (69.3%) of the respondents who know TBS practice as a form of treatment for bone injuries think that TBS therapy is preferable to Orthodox medicine in handling bone injuries. Reasons for preference are that it is cheap 134 (63.8%), acceptable 123 (58.6%) and accessible 109 (51.9%) to them. More than half (52.3%) of the respondents had patronized TBS treatment at one time or the other. Main reason for patronage of TBS was influence from family members and friends (53.6%). However, factors that influence the respondents decision to utilize TBS treatment include attitude of health workers 310 (77.5%), delay in hospitals 284(71.0%) fear of amputation 272 (54.35) and fear of operation 217(54.3%) in hospitals. There was a statistically significant ($p < 0.05$) relationship between respondents age, sex, marital status, occupation, ethnicity as well as the income level of the respondents and the utilization of TBS.*
Conclusions. *Utilisation of TBS is quite popular among the studied population because it is believed to be cheap, acceptable and accessible to them and a high proportion of the respondents utilize TBS notwithstanding that they live in a community where they have better access to orthodox medical care. Influence from family and friends is the main reason for consulting TBS. Regulations should be made concerning the advertisement of TBS practice by relevant agencies and the public should be made aware through health education on the dangers of TBS treatment.*

Introduction

Traditional healers were practicing long before orthodox medicine was introduced to the developing world [1]. The first orthodox hospital was built in Lagos, Nigeria in 1873 [2]. Prior to this, traditional medicine was the only available form of health care. Presently both orthodox and traditional medicines co-exist side by side and are patronized by patients [3].
Traditional bone setting is a specialization in Traditional Medicine passed from father to child but some non-family members receive training via apprenticeship [4]. A traditional bonesetter (TBS) is a lay practitioner of joint manipulation. He or she is a practitioner who takes up the practice of healing without having had any formal training in accepted medical procedures [5]. Modern day healthcare has evolved greatly following advances in technology and medical research. Despite the availability of these services, traditional bone setting has continued as an alternative health care service. It is practiced in many communities of the world, especially in developing countries in the continents of Asia, South America and Africa with less developed healthcare resources and plays an important role in their healthcare delivery system. According to an estimate, between 10 to 40% of patients with fractures and dislocations in the world are managed by unorthodox practitioners [5].
In Nigeria however many people believe that TBS know more about bone disorders than orthodox practitioners probably due to cultural beliefs, ignorance and poverty; as such a good number of patients that cut across class, profession and religion patronize them irrespective of age and gender. Up to 85% of patients with fractures present first to the TBS before coming to the hospital and therefore this mode of care delivery cannot be overlooked in Nigeria [6].
In most developing countries where Traditional bone setting is practiced, many failures of bone setting procedures have been reported due to the use of irrational methods adopted by Traditional bonesetters (TBS) that are not scientifically based. These methods of treatment lack the knowledge of anatomy, physiology, radiology and basic principles of infection prevention/control and soft tissue care which have led to limb and life threatening complications [6]. These complications range from acute compartmental syndrome, tetanus, deformities, chronic

osteomyelitis, gangrene, amputation and death [7], and have become a major concern on morbidity and mortality. Oginni calculated a high failure rate of 66.7% among patients who voluntarily opted out of TBS treatment [8]. In Hyderabad district, India, a study reported 43% mal-union and non-union along with other complications from TBS [9]. In Gambia, Bickler et al found out that bonesetters gangrene occurred almost exclusively in children from rural areas most of which underwent proximal extremity amputation [10]. Many complications from mismanaged fractures by TBS have been reported in various parts of Nigeria [6, 7]. The complications account for about 50-60% of limb gangrene necessitating amputation in our hospitals [11]. Nwankwo et al. reported 4 deaths (26.7%) from 15 patients who developed limb gangrene following TBS treatment [12]. Eighty three percent of patients in a study had complications like mal-union and non-union, most of whom became disabled or deformed [7].

A study in Ilorin, Kwara State highlighted eight cases mismanaged by TBS in which four of the cases were children under ten years. Out of the four children, three of them lost their right upper limb through above elbow amputation while the fourth child lost his right lower limb through above knee amputation. The other four were young adults; two of which lost their lower limbs through above knee amputation and the other two who did not lose their lower limbs were in the hospital for several months and one later died of gas gangrene and septicemia [13]. TBS have also gone beyond the treatment of fractures into areas like congenital anomalies and caring for patients with bone tumors and bone infections [14].

The health and socioeconomic effects resulting from the cultural practice is enormous. Despite the shortcomings of the TBS practice, more than 70% of the Nigerian population at present live outside the vicinity of modern hospitals and rely almost exclusively on the traditional medicine healers for their healthcare services [15], thus the terrible consequences of TBS remain an important and complex issue in the healthcare system in Nigeria. Because of the persistence of TBS complications and the constant use of their services by the public, the objective of this study was therefore aimed at determining the factors that influence utilization of traditional bone setting practice in North Central Nigeria.

Methodology

Ilorin, the capital of Kwara state is located in North Central Nigeria at the geographical and cultural confluence of the North and South of Nigeria. The study was conducted in Ilorin West Local Government Area (LGA), one of the three LGAs in Ilorin metropolis. It has a population of 365,221 [16] delineated into 12 wards, with at least 3 communities in each ward.

A descriptive cross sectional design was used for the study. Multistage sampling technique was used to recruit the subjects from 6 districts/wards and 12 communities in the study area. A total of 400 respondents were interviewed using a semi structured questionnaire. In selecting the required house within each selected community, grid method [17] was used by spinning a bottle at the center of the communities to determine the index house. Thereafter, every other houses with eligible respondents were included in the study until the desired sample size was attained. The questionnaire elicited information on the respondents' sociodemographic/economic characteristics, if they have ever used TBS and their reasons for utilization. Factors that influence their decision to patronize TBS were also elicited.

Analysis was done using Epi Info version 3.5.3. Cross tabulations of variables were constructed and F –test and chi-square with p-values were calculated to determine statistical significance if any. Significant p-value was predetermined at $p < 0.05$. The data was collected from July - September 2011.

Tab. I. Socio-demographic characteristics of respondents.

Variables	Frequency (N = 400)	Percentage (%)
Age (years)		
< 20	37	9.3
21-30	103	25.8
31-40	158	39.5
41-50	52	13.0
51-60	24	6.0
61 and above	26	6.5
Sex		
Male	232	58.0
Female	168	42.0
Marital Status		
Married	242	60.5
Single	129	32.3
Widowed	23	5.8
Separated	6	1.5
Ethnic Group		
Yoruba	261	65.3
Igbo	37	9.3
Hausa	26	6.5
Others	76	19.0
Religion		
Islam	208	52.0
Christianity	171	42.8
Traditional	21	5.3
Educational level		
None	13	3.3
Quranic	27	6.8
Primary	23	5.8
Secondary	97	24.3
Tertiary	240	60.0
Occupation		
Civil servant	118	29.5
Trading	92	23.0
Student	78	19.5
Artisan	51	12.8
Unemployed	31	7.8
Farming	11	2.8
Others	19	4.9

Results

The respondents mean age was 36.3 ± 12.3. The modal age group for the study was 31-40 years constituting 158 (39.5%) of all the respondents. There was a male preponderance with 232 (58%) males. Two hundred and forty two (60.5%) of the respondents were married; two-third 261 (65.3%) belong to the Yoruba ethnic group; 208 (52%) were Moslems; while 171 (42.8%) were Christians. Three hundred and thirty seven (84.3%) of the respondents had secondary education and above; 27 (6.8%) had Quranic education; 23 (5.8%) had primary education while 13 (3.3%) had no form of education. Respondents were mostly Civil servants 118 (29.5%), while 31 (7.8%) are unemployed (Tab. I). About half 151 (50.3%) of the respondents in this study earn an income of less than fifty thousand naira (< N50, 000.00) per month but more than N10,000.00 per month. This implies majority of the respondents earn more than $2.00 a day, the required amount by WHO to sustain a daily living.

Majority 303 (77.3%) of the respondents know TBS practice as a form of therapy for treating bone injuries. As reported in Table II, more than half 209 (52.3%) of the respondents who know TBS practice as a form of therapy for bone injuries have patronized TBS treatment at one time or the other while 60 (28.7%) have used TBS treatment in the last 12 months of this study. Conditions that prompted visit to TBS were dislocations 131 (62.7%), broken bones 106 (50.7%) and infections 36 (17.2%). One hundred and nineteen (56.9%) had received one form of treatment prior to TBS treatment (Tab. II). About 63 (52.9%) had been to orthodox hospitals prior to TBS treatment.

The respondents' main reason for consulting TBS was influence from family and friends 112 (53.6%). Two hundred and fifty nine (64.8%) of the respondents in this study can advice a person with bone injury to visit TBS instead of orthodox treatment (Tab. III). Attitude of health workers 310 (77.5%), delay in hospitals 284 (71.0%), fear of amputation 272 (68.0%) and fear of operation in hospitals 217 (54.3%) are factors that would influence respondents decision to patronize TBS treatment. There was a statistically significant relationship

Tab. II. Practice of traditional bone setting.

Variables	Frequency	Percentage (%)
Ever patronized TBS treatment (N=400)		
Yes	209	52.3
No	191	47.8
Patronized TBS treatment in the last 12 months (N=209)		
Yes	60	28.7
No	149	71.3
Conditions that prompted visit to TBS* (N=209)		
Broken bone	106	50.7
Dislocation	131	62.7
Infection	36	17.2
Received treatment prior to TBS treatment		
Yes	119	56.9
No	90	43.1
Treatment received prior to TBS treatment (N=119)		
Orthodox treatment	63	52.9
Self medication	50	42.1
Others	6	5.0
Reasons for visit to TBS (N=209)		
Influence from family members	91	43.5
Influence from friends	21	10.1
Delay in hospitals	69	33.0
Fear of operation or amputation	17	8.1
Others	11	5.3
Never patronized TBS before but would visit TBS in case of bone injury (N=191)		
Yes	78	40.8
No	77	40.3
Don't know	36	18.8
Can advice a person to visit TBS (N=400)		
Yes	259	64.8
No	141	35.3

*Multiple responses

Tab. III. Factors that influence respondents decision to patronize TBS Treatment (N = 400).

Factors	Yes		No	
	Frequency	(%)	Frequency	(%)
Cultural belief	144	36.0	256	64.0
Superstition	80	20.0	320	80.0
Delay in hospitals	284	71.0	116	29.0
Fear of operation in hospitals	217	54.3	183	45.8
Fear of amputation in hospitals	272	68.0	128	32.0
Use of Plaster of Paris (POP)	67	16.8	333	83.3
Attitude of health workers	310	77.5	90	22.5
Cost of treatment	116	29.0	284	71.0

* Multiple response

Tab. IV. Influence of income level on utilization of TBS.

	Utilization of TBS	
	Yes (%)	No (%)
Income level		
< N10,000.00	42 (72.4)	16 (27.6)
< N50,000.00	80 (53.0)	71 (47.0)
> N50,000.00	60 (65.9)	31 (34.1)
	p = 0.0170	

between respondents age, sex, marital status, occupation, ethnicity as well as the income level of the respondents and the utilization of TBS as all test of associations were statistically significant ($p < 0.05$) (Tabs. IV, V).

Discussion

Treatment of bone injuries using traditional methods is an age old art which has been confined into the backstage due to access to western biomedicine, adequate education, employment opportunities and economic growth in most families especially in the urban communities in Nigeria [18]. However, despite documented complications that arise from the cultural practice [6, 7, 15] there is still a high demand for TBS services by people of various class, profession and religion irrespective of age and gender.

The respondents in this study are aged 18-72 years with majority of them between 31-40 years age group. This age group belongs to the productive age group of the population. Studies [7, 19] have shown that this age group, the working population are mostly involved in bone trauma due to involvement in injury prone activities. Three hundred and three (77.3%) of the respondents know TBS treatment as a form of therapy for bone injuries. This may be due to promotional information on TBS practice through which this study found out was gotten mainly through Radio and Television. This is not surprising as there is a high level of uncontrolled radio coverage. This finding is in tandem with that of Bamidele et al. [18] who stated that in recent times there has been renewed interests of residents of urban communities as a result of the pronouncements on radios and TV by Alternative Medical Therapists with claims that their 'wares' can cure all diseases ever known to mankind.

More than one third (64.8%) of the respondents in this study would advice a person with bone problem to seek TBS care instead of orthodox therapy. This may be because TBS practice is intricately interwoven with the culture of the respondents - a socio-economic and socio-cultural heritage as described by Elujoba et al. [20]. This is in line with the fact that the practice of TBS is common among Yorubas, the predominant ethnic group among the respondents in this study and in Ilorin as confirmed by the findings of Oyebola [4] and Suleiman et al. [21]. The main reason for preference by this group is because it is cheap (63.8%), acceptable (58.6%) and accessible (51.9%) to them. This finding corroborates the findings by Udosen et al. [22] and Dada et al. [19] that it is popular belief that TBS is cheaper in the treatment of bone injuries. This may be due to the fact that TBS allow multiple little payments and payments in kind. An earlier study in Nigeria by Osujih [23] also reported that in developing countries where in addition to the dearth of orthodox medical services, institutions and personnel, Alternative Medical Therapy is cheaper, socio-culturally accessible and acceptable.

Respondents in this study also belief that TBS give better attention (60.4%) and offer quicker services (71.0%) than orthodox health care workers. This may be due to delays in hospitals which in this study was found to account for 62.4% of respondents reasons for preference, attitudes of health workers and poor quality of service in some hospitals [19]. Solagberu [24] reported on a group of patients who visited the hospital after initial failure of TBS treatment that their main motives for visiting the bonesetter first were lower cost and belief in faster healing. Majority (54.8%) felt TBS are very competent or competent (20.5%) while 9.9% believe they are incompetent. Sixty six percent of the respondents felt TBS are indispensable (cannot do without). These findings are similar to that of Thanni [25] where 40% of the respondents felt TBS are competent or very competent, 23% believe they are incompetent while 37% believe they are indispensable (cannot do without) and 32.8% believe they are desirable (can do without, though useful).

It is noteworthy that majority of the respondents in this study had tertiary level of education and majority are gainfully employed. These are factors that should influence utilization of the several orthodox healthcare facilities in the study area. However, more than half (52.3%)

Tab. V. Association between selected sociodemographic characteristics and utilization of TBS.

Variables	Utilization of TBS				
	Yes (%)	No (%)	X_2	df	p-value
Age (years)					
< 20	15 (40.5)	22 (59.5)	22.3397	5	0.0005
21-30	42 (40.8)	61 (59.2)			
31-40	89 (56.3)	69 (43.7)			
41-50	40 (76.9)	12 (23.1)			
51-60	10 (41.7)	14 (58.3)			
61 and above	13 (50.0)	13 (50.0)			
Sex					
Male	137 (59.1)	95 (40.9)	10.243	1	0.00014
Female	72 (42.9)	96 (57.1)			
Marital status					
Married	151 (62.4)	91 (37.6)	28.7741	3	0.0000
Single	50 (38.8)	79 (61.2)			
Widowed	8 (34.8)	15 (65.2)			
Separated	0 (0.0)	6 (100.0)			
Occupation					
Artisan	32 (62.7)	19 (37.3)	45.2975	6	0.0000
Civil Service	80 (67.8)	38 (32.2)			
Farming	6 (54.5)	5 (45.5)			
Student	22 (28.2)	56 (71.8)			
Trading	45 (48.9)	47 (51.1)			
Unemployed	21 (67.7)	10 (32.3)			
Others	3 (15.8)	16 (84.2)			
Ethnicity					
Hausa	12 (46.2)	14 (53.8)	11.2190	3	0.0106
Igbo	14 (37.8)	23 (62.2)			
Yoruba	152 (58.2)	109 (41.8)			
Others	31 (40.8)	45 (59.2)			

of the respondents in this study have patronized TBS treatment at one time or the other. The conditions that prompted their visit to TBS were mainly dislocations (62.7%) and fractures (50.7%). OlaOlorun et al. [7] reported 85% of femoral fractures presented to TBS while Dada et al. [19] documented 155 musculoskeletal injuries treated by TBS with the resultant complications. The main reason for patronage of TBS by the respondents was influence from family members and friends (53.6%). The influence of this group is important because of the existing social system in Africa where family and friends will normally contribute towards defraying the cost of treatment. In Solagberu's study in Ilorin [24] 74.9% of the studied population were urged to visit the TBS by this group of people. Other reasons for patronage by the respondents in this study are delay in hospitals (33.0%), and fear of operation and amputation (8.1%). These reasons are similar to those findings of Dada et al. [19], Nottidge et al. [26] and Udosen et al. [22]. While the orthodox practitioners have little control over the above stated reasons for patronage of TBS, it is noteworthy that some of the activities of the orthodox practitioners like strike actions also contributed to these problems [19]. Nonetheless, the result of these studies further raises the issue of lack of confidence in modern orthopaedic practice by the general population.

This study also showed that 52.9% of the respondents who had patronized TBS treatment had first visited hospitals. Oyebola [4] was impressed by the fame the TBS enjoyed in their locality as patients voluntarily discharge themselves from orthodox hospitals to receive treatment from TBS. This may be due to influence from family and friends on the patients cultural belief, unnecessary bottlenecks in hospitals, attitude of health workers and work stoppages which are valid factors that may influence voluntary discharge from hospitals. The major factors in this study that influence the respondents decision to patronize TBS are attitude of health workers (77.5%), delay in hospitals (71.0%) and fear of amputation in hospitals (68.0%). This is similar to the findings of Ogunlusi et al. [3].

There is an association between the income level of the respondents and the utilization of TBS as test of association was statistically significant ($p < 0.05$). Respondents who earn less than N10, 000.00 per month utilize TBS more (72.4%) than other income earners. This is expected considering the fact that they earn less than $2.00 a day; the WHO amount required for daily sustenance and will consider TBS services to be cheaper. This corroborates with the findings of Dada et al. [19] that patients patronize TBS because they think it is cheaper than orthodox medicine, possibly because TBS allow multiple payment options.

Utilization of TBS by respondents in this study is also affected by their age, sex, marital status, occupation and ethnicity, as test of associations were statistically significant ($p < 0.05$). Utilization is highest among males than females. This may be due to the fact that males are more adventurous and engage in more injury prone activities than females. Respondents that are married utilize TBS more than those that are single, separated or widowed. This may be due to the influence of the heads of households or spouses involved in decision making in the household. The practice of TBS is more common among respondents that belong to Yoruba ethnic group. This may be due to the cultural heritage of TBS practice among this ethnic group as confirmed by the findings of Oyebola [4] and Suleiman et al. [21].

Conclusion and recommendations

More than half of the respondents had patronized TBS treatment at one time or the other. Influence from family members and friends are one of the main reasons for use of TBS or voluntary discharge from hospitals for TBS treatment by the respondents. Other factors that encourage utilization of TBS by respondents were attitude of health workers, delay in hospitals and fear of operation and amputation. More so, the age, sex, marital status, occupation, ethnicity as well as the income level of the respondents were found to influence the utilization of TBS.

The public must be enlightened on the dangers associated with patronizing traditional bone setters with their attendant complications. Orthodox healthcare services should be made affordable and accessible to prevent delays and aid quicker attention which may reduce the rate of "leaving hospitals to the traditional bone centres against medical advice". Equally important is the need to train and retrain orthodox health care personnel on the need for excellent communication skills with clients to reduce the perception of "unfavorable attitude of health workers" on the part of the clients.

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ORIGINAL ARTICLE

Correlation between physical activity and sedentary behavior with healthy and unhealthy behaviors in Italy and Tuscan region: a cross sectional study

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Key words

Physical health status • Quality of peer relationships • Health complaints

Summary

Introduction. *Regular physical activity (PA) has associated with various positive health aspects such as a decreased risk of chronic or generic illnesses, furthermore, a sedentary lifestyle has been associated with health problems such as obesity. To examine the relationship between patterns of PA, screen-based media use (SBM) and social health indicators within a specific demographic group and highlight the regional vs. national differences in these relationships.*
Methods. *The data is drawn from the Health Behaviour in School-Aged Children (HBSC) database, a national cross-sectional survey in a representative sample (N = 3920) of students aged 11-13-15 years and compared to those of the Tuscan region (N = 3381). Variables considered other than PA and SBM use includes positive health indicators such as physical health status, quality of family and peer relationships, fruit consumption, breakfast consumption as well as negative health indicators, such as health complaints, smoking and alcohol use.*
Results. *Some positive health indicators showed a positive correlation with PA. Students adopting healthy behaviours often met the Physical Activity Guide Line (PAGL). On the contrary, negative health indicators were associated with PAGL in a negative way.*
In general SBM was positively related to several of the negative health indicators and vice versa.
SBM was related in a positive fashion to tobacco use that represents a protective factor.
Discussion. *The results show that met PAGL is associated with positive health indicators and that high levels of SBM use is associated with negative health indicators. The study also emphasizes the relationship between PA, SBM use and social factors. Increasing PA and decreasing SBM use should be an aim in general health behaviour promotion.*

Introduction

Regular physical activity (PA) has been associated with various positive health aspects such as a decreased risk of chronic or generic illnesses: coronary heart disease, obesity, cancer, type 2 diabetes, sexual dysfunction and cognitive impairment [1, 2].
There has been evidence that the inclusion of regular PA as part of a healthy lifestyle is related in a positive way to other health indicators such as perceived health status [3, 4], self-image [4-8], quality of life [9], and quality of peer relationships [10, 11].However, the extent of influence of the family on PA [12, 13] and the potential relationship of adolescent PA to quality of family relations has not been investigated.
Furthermore, a sedentary lifestyle has been associated with health problems such as obesity. In fact, research shows that prolonged hours spent watching TV or playing computer games has a direct impact on the level of daily energy expenditure and as such, it has been suggested that a causal relationship between sedentary behaviors and obesity exists [14].
The primary mechanism for overweight is an imbalance between energy intake and expenditure. Excess sedentary behaviour contributes to one side of this equation [15, 16]. There is also evidence that the effects of sedentary behaviour accumulates over the course of childhood [17]. It appears that sedentary contributes to weight status independently of the PA level [16, 18].
The relationship between PA and negative health indicators such as health complaints, physical aggression, or alcohol abuse has not been sufficiently studied. Currently there is some evidence that suggests that the participation in sports activities might be related to certain health risk behaviors [19-22]. To the contrary there is also evidence that shows that PA is not related to physical aggression [23, 24], smoking [21, 25-27] and alcohol use [12, 21, 25]. Moreover, it has emerged that PA involvement in adolescents may help prevent future alcohol abuse in adult age [28].
Screen-based media (SBM) use has been the center of increased interest recently. It is theorized that SBM may be a potential independent factor that could have a direct impact on chronic health problems. Current recommendations suggest that children should not have any more than two hours of television viewing per day [29,30]. Research shows that young people who watch television frequently seem to be more prone to have a lower self-esteem [7], lower perceived health status [3],

poorer school grades [7], and a higher prevalence of smoking [3]. Television viewing has been associated with bullying [31], higher consumption of energy-rich foods [32] and lower consumption of fruit and vegetables [33]. Moreover SBM has been related to the presence of a higher number of somatic symptoms [34], alcohol and illicit drug use [13].
Dimensions of inequalities include age, gender and family affluence. There is a general increase in television viewing with age in just over half of countries involved in HBSC (Health Behaviour in School-Aged Children) survey. Television watching is significantly associated with family affluence in over half of countries that participate in the HBSC study [35, 36].
Clinical studies document that regular meal consumption can potentially reduce the risk of obesity and chronic disease through mechanisms involved in energy balance and metabolism [37, 38].
Breakfast is often considered the most important meal of the day and regular breakfast consumption is inversely associated with overweight and risk behaviors [39].
The consumption of fruit and vegetables is considered a good proxy for a healthy diet. Fruit and vegetables are a dietary protective factor for tobacco related cancers as well as for cardiovascular disease. Epidemiologic studies demonstrate a consistent relationship between a higher consumption of fruit and vegetables and a lower risk of cancer [40].
The main objective of this research is to analyze the extent of the relationship between PA and SBM and other positive and negative health indicators, highlighting the positive and negative patterns of interrelationship in a sample of Italian and Tuscan adolescents. It was hypothesized that there would be a positive correlation between PA and the positive health indicators and a negative correlation with the negative health indicators. For SBM opposite results were expected.
It was also expected that the trends that emerged in the national sample would be replicated in the analysis focusing on Tuscan adolescents, which would suggest the consistency of the pattern across different samples with similar demographics.

Methods

The HBSC survey is an international cross-sectional study conducted in collaboration with the World Health Organization's Regional Office for Europe. The main objective of HBSC is to increase understanding of those factors and processes that may have effects on adolescent health.
Participation was voluntary, and anonymity and confidentiality were ensured, parental permission to participate was obtained before the administration. Questionnaires were administered in classrooms by trained personnel [41].
The present study analyzed data from the nationally representative HBSC surveys conducted in Italy and in the Tuscan region. The study population consists of students aged 11-13-15 years, selected during the 2005/06 school year.
The questionnaires and all the methodology for the survey were approved by the Ethics Committee of the Italian Ministry of Education, Universities and Research. All questions used in the HBSC were considered included only after standardization and validation at the international level, to ensure the homogeneity of the instrument [41].

Physical activity

PA is described as "any activity that raises your heart rate and that possibly leaves you out of breath". Respondents behavior were considered positive if they have met the physical activity guide line (PAGL) (at least 60 minutes of PA seven days a week) [42].

Screen-based media use

SBM use was assessed asking the students how many hours per day they spent watching television (including DVDs), using the computer, play station or similar devices [43, 44]. A score of no more than two hours a day in front of the TV/PC was considered a positive behaviour. The SBM score was created by summing the mean number of hours per day of all screen based activities.

Positive health indicators

Critical aspects related to physical, psychological and social health were assessed through the development of indicators. Physical status was investigated through the body mass index (BMI), the consumption of fruit and the frequency per week of having breakfast. The perception of physical health status was considered to reflect both physical and psychological health. Social health was reflected in the quality of family and peer relationships.

Body Mass Index

BMI was calculated from weight and height, using the following formula: weight (kg)/height (m^2). BMI classes of the children were set using the Cole et al. method [45]. This method permits specific cut-off points for males and females at every age as recommended by the International Obesity Task Force (IOTF). The BMI was considered positive if students fell in the categories "underweight" or "normal-weight".

Fruit consumption

Consumption of fruit was assessed through a single question (How many times a week do you eat fruit?) with seven response options ("never", "less than once a week", "once a week", "2-4 times a week", "5-6 times a week", "once a day every day" and "more than once a day"). Behaviour was considered positive if the response was "more than once a day".

Frequency of breakfast

To assess the frequency of breakfast consumption, students were asked to indicate the number of days they

have breakfast on school days. Breakfast was defined as having something more than just a glass of milk, tea or fruit juice. Response categories ranged from "never" to "all days of school" a week. Having breakfast "five times a week" or "on all school days" was considered a positive behavior.

Physical health status

Respondents were asked to rate their physical health status on a four-point scale ("excellent", "good", "fair", "poor). Respondents that perceived their physical health status as "Good" or "excellent" were considered physically healthy.

Quality of family relationships

Students indicated on a four-point scale how easy it is to talk to their father, stepfather (or mother's partner), mother and step-mother (or father's partner) about things that bother them. The quality of family relations was considered as good when at least two of the responses given were "easily" or "very easily".

Quality of peer relations

The quality of peer relations was measured on a five-point Likert type scale Students were asked to indicate how much they agree with the phrase "Other students accept me as I am". The response options were ("strongly agree", "agree", "neither agree nor disagree", "disagree", "strongly disagree"). The quality of peer relationships was considered to be positive if they responded "strongly agree" or "agree" with the feeling of being under consideration.

Negative health indicators

Negative health indicators are indicators that describe perceived health problems (health complaints) and health risk behaviors (tobacco use, alcohol use).

Health complaints

Students indicated the frequency with which they experienced each of the following seven symptoms: headache, stomachache, backache, feeling low, irritability or bad temper, feeling nervous, difficulty in falling asleep, feeling dizzy. The frequency was measured on a five-point scale ("about every day", "more than once a week", "about once a week", "about once a month", "rarely or never"). Students with at least one symptom every day were considered as those that have health complaints.

Tobacco use

Cigarette smoking was assessed with a single question asking respondents how often do they currently smoke. Responses were registered on a four-point scale ("every day", "at least once a week but not every day", "less than once a week", "I do not smoke"). Behaviour was considered healthy is they responded that they do not smoke or that they smoke "less than once a week".

Alcohol use

The use of alcohol was assessed through a single item asking "How often do you drink alcoholic drinks like beer or wine?", on a five-point scale (every day, every week, every month, rarely, never). Respondents that declared that they "never" drink alcohol were considered as those with a healthy lifestyle.

Statistical Analysis

Categorical variables were expressed as number of cases (%), continuous ones as mean (SD).
For a comparison between proportions of independent groups the chi-square and Z test were used, whereas for comparison of continuous variables between independent groups the t-test was used.
In order to verify the existence of possible risk factors, a logistic regression model was implemented including as covariates the variables under study, adjusted for age and sex.
Estimates of relative risk were provided through the use of odds ratio and confidence intervals at 95%.
Results with a $p < 0.05$ were considered statistically significant.
All analyses were repeated separately for males and females and performed through the SPSS software (version 16.0) and Stata (version 9.0).

Results

In Table I the number of respondents for Italy and Tuscany by grade and gender are presented. The differences for age and sex were minimal (Tab. I).
Italian students spending more than two hours in front of the TV/PC were significantly younger ($p < 0.00001$) than their Tuscan counterparts; however, in both sam-

Tab. I. Unweighted prevalence of students (number of cases and %) by gender and age (mean and SD).

	Grade			
	11 years old	13 years old	15 years old	Total
Italy (n-%)	1242 (31.7%)	1343 (34.3%)	1335 (34.1%)	3920
Males mean age by grade (SD-%)	11.51 (0.30)	13.49 (0.32)	15.45 (0.33)	1974 (50.36%)
Females mean age by grade (SD-%)	11.53 (0.29)	13.48 (0.31)	15.48 (0.32)	1946 (49.64%)
Tuscany (n-%)	988 (29.2%)	1218 (36.0%)	1175 (34.8%)	3381
Males mean age by grade (SD-%)	11.63 (0.40)	13.68 (0.59)	15.79 (0.59)	1664 (49.3%)
Females mean age by grade (SD-%)	11.62 (0.43)	13.62 (0.50)	15.69 (0.56)	1712 (50.7%)

Tab. II. Prevalence of Physical Activity (PA) and Screen-Based Media Use (SBM) by gender and grade.

	Meet Physical Activity Guide Line (PAGL) and Screen-Based Media Use (SBM) (> 2 hours for day)							
	11 y-old				13 y-old			
	Boys		Girls		Boys		Girls	
	PAGL*	SBM*	PAGL	SBM*	PAGL*	SBM	PAGL*	SBM
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Italy	**23.2** (19.9-26.4)	**55.3** (51.5-59.1)	**13.6** (10.9-16.3)	**66.7** (63.0-70.4)	**23.2** (20.1-26.4)	**50.9** (47.1-54.6)	**9.0** (6.8-11.1)	**51.8** (48.1-55.5)
Tuscany	**17.9** (14.5-21.3)	**61.6** (57.2-66.0)	**10.0** (7.4-12.6)	**74.0** (70.2-77.8)	**12.9** (10.2-15.6)	**50.3** (46.3-54.3)	**7.4** (5.3-9.5)	**52.5** (48.5-56.5)

*p < 0.05, Z Test

ples boys reported less SBM than girls (Italy: 50.6% vs. 58.0% respectively, p < 0.0001; Tuscany: 53.5% vs. 58.3% respectively, p < 0.0001).

There is a general reduction in meet PAGL as age increase in both samples (Tab. II). The prevalence of students that meet PAGL is significantly higher in the Italian sample than in the Tuscan one (15.2% vs. 10.9%, p < 0.05).In both samples the prevalence of students that meet PAGL is significantly higher in boys than girls (Italy: 20.5% vs. 9.8% respectively, p < 0.0001; Tuscany: 14.9% vs. 7.9% respectively, p < 0.0001).

SBM use and positive health indicators

As expected, SBM was negatively related to PA in both samples. However, the relationships were modest, and do not suggest that these two behaviors are opposite ends of the same dimension. SBM use increase over the course of childhood. In Tuscany negative family relationships represented a risk factor for spending more than two hours a day in front of a screen for boys (OR = 2.35, p < 0.05). As shown in Table III in Italy, when males and females were considered separately, perceived health and frequency of breakfast consumption had a negative impact on SBM use representing risk factors for SBM use of > 2 hours a day, especially for girls (OR = 1.40, p < 0.05 and OR = 1.26, p < 0.05, respectively).

Considering the distribution of observed indicators related to a positive SBM score (spending < 2 hours a day in front of the screen), the results of the Italian sample are consistent with those of the Tuscan sample, however it includes two other variables as well, an improvement in the family relationship (p < 0.003), and in the physical health status for all children (p = 0.009). Tuscan students that perceived their health as good and had a higher frequency of breakfast consumption, primarily girls, showed a positive SBM behaviour, instead for boys a positive

Tab. III. Odds ratio ($CI_{95\%}$) for the observed variables, in total and by gender related to SBM (>2 hours for day).

	Italy			Tuscany		
	Boys	Girls	Total	Boys	Girls	Total
Age	1.070 (0.998-1.148)	1.049 (0.978-1.126)	1.049 (0.998-1.102)	1.070 (0.998-1.148)	1.220* (1.118-1.331)	1.158* (1.088-1.231)
Gender			0.710* (0.614-0.821)			1.024 (0.998-1.051)
BMI (cat)	0.748 (0.525-1.064)	0.913 (0.600-1.391)	0.779 (0.597-1.016)	0.748 (0.525-1.064)	1.899* (1.005-3.622)	1.295 (0.846-1.980)
Fruit consumption	0.868 (0.682-1.104)	1.095 (0.856-1.399)	0.974 (0.821-1.156)	1.350 (0.979-1.861)	1.095 (0.856-1.399)	1.178 (0.945-1.470)
Breakfast frequency	0.981 (0.791-1.217)	1.264* (1.029-1.551)	1.211 (0.997-1.470)	1.940 (0.965-1.735)	1.138 (0.876-1.478)	1.211 (0.997-1.470)
Physical health status	1.013 (0.667-1.536)	1.400* (1.019-1.922)	1.177 (0.881-1.574)	1.013 (0.667-1.536)	1.160 (0.815-1.653)	1.177 (0.881-1.574)
Family relationships	1.028 (0.826-1.279)	1.256 (0.373-1.738)	1.495 (0.923-2.421)	2.351* (1.217-4.543)	0.805 (0.373-1.738)	1.495 (0.923-2.421)
Peer relationships	0.952 (0.746-1.214)	0.838 (0.670-1.047)	0.952 (0.779-1.165)	0.952 (0.746-1.214)	0.838 (0.670-1.047)	00.952 (0.779-1.165)
Health complaints	1.169 (0.962-1.421)	1.444* (1.155-1.948)	1.268* (1.093-1.707)	1.169 (0.962-1.421)	1.500* (1.155-1.948)	1.403* (1.153-1.707)
Tobacco use	0.919 (0.653-1.293)	0.746* (0.521-0.993)	0.728* (0.538-0.986)	0.919 (0.653-1.293)	0.746 (0.521-1.067)	0.728* (0.538-0.986)
Alcohol use	1.423* (1.145-1.768)	1.340* (1.007-1.784)	1.381* (1.163-1.641)	1.381 (0.940-2.030)	1.219 (0.657-2.262)	1.226 (0.986-1.523)

*Chi square test, p < 0.05

15 y-old				All age group				All	
Boys		Girls		Boys		Girls			
PAGL	SBM	PAGL	SBM	PAGL*	SBM	PAGL*	SBM	PAGL*	SBM
% (95% CI)	% (95%CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
14.7 (11.9-17.4)	**45.5** (41.6-49.3)	**6.9** (4.9-8.9)	**56.1** (52.2-60.0)	**20.5** (18.7-22.2)	**50.6** (48.4-52.8)	**9.8** (8.5-11.1)	**58.0** (55.8-60.1)	**15.2** (14.1-16.3)	**54.2** (52.7-55.8)
12.0 (9.3-14.6)	**50.3** (46.1-54.4)	**6.5** (4.5-8.5)	**50.8** (46.7-54.7)	**14.0** (12.3-15.7)	**53.5** (51.1-55.9)	**7.9** (6.6-9.1)	**58.3** (55.9-60.6)	**10.9** (9.8-11.9)	**55.9** (54.2-57.6)

SBM behaviour was associated with good family relationships (p = 0.003) and positive fruit consumption behaviour (p = 0.03).

SBM use and negative health indicators

With regard to the negative health indicators considered, the results for SBM use were very similar. In both samples the students with less health complaints and less alcohol use spent less than two hours a day in front of the TV/PC (p < 0.0001), in Tuscany they tended also to smoke less cigarettes. In both samples respondents reporting more health complaints resulted to be more at risk for SBM use of more than two hours a day (OR = 1.26, p < 0.05), while use of tobacco resulted to be a protective factor for SBM use of more than two hours a day (OR = 0.72, p < 0.05). Only in the Italian sample alcohol use resulted to be a risk factor for SBM use of more than two hours a day (OR = 1.38, p < 0.05). The associations, in the Italian sample, between negative health indicators and SBM use were primarily due to a significant relationship in girls.

PA and positive health indicators

The pattern of results that emerged for positive and negative health behaviour indicators and their relation to PAGL showed some differences in the two samples. Although the associations were similar in both samples, it was only in the Italian sample that students met PAGL declared to have a significantly better physical health status (p < 0.005), in particular among girls, and a better quality of peer relationships (p < 0.012). Students that met PAGL had a significantly better consumption of fruit in both Italy and Tuscany (p < 0.00001), this effect seems to be slightly bigger in Italian boys compared to Tuscan boys and in Tuscan girls compared to Italian girls. As can be seen in Table IV, consuming less fruit, for both males and females, was a risk factor for not meeting the PAGL in both the Tuscan and Italian sample (Tuscany: OR = 1.65, p < 0.05; Italy: OR = 2.45, p < 0.05).

Tab. IV. Odds ratio ($CI_{95\%}$) for the observed variables, in total and by gender related to "PAGL".

	Italy			Tuscany		
	Boys	Girls	Total	Boys	Girls	Total
Age	1.131* (1.034-1.236)	1.190* (1.057-1.341)	1.144* (1.066-1.227)	1.040 (0.907-1.192)	1.069 (0.917-1.331)	1.057 (0.995-1.169)
Gender			2.344* (1.389-2.894)			1.765* (1.319-2.363)
BMI (cat)	1.338 (0.857-2.091)	0.723 (0.364-1.434)	1.114 (0.770-1.612)	0.664 (0.295-1.493)	1.567 (0.355-5.828)	0.871 (0.446-1.700)
Fruit consumption	1.569* (1.187-2.074)	1.846* (1.289-2.644)	1.653* (1.327-2.060)	2.128* (1.404-3.225)	2.878* (1.844-4.492)	2.454* (1.815-3.319)
Breakfast frequency	1.041 (0.793-1.366)	0.804 (0.571-1.127)	0.954 (0.772-1.177)	1.041 (0.793-1.366)	1.111 (0.571-1.792)	1.069 (0.772-1.479)
Physical health status	1.624 (0.883-2.989)	0.977 (0.665-1.688)	1.337 (0.782-2.286)	1.624 (0.883-2.989)	1.056 (0.665-2.043)	1.337 (0.782-2.286)
Family relationships	0.983 (0.748-1.293)	0.758 (0.519-1.108)	0.900 (0.691-1.125)	3.686 (0.868-15.65)	0.758 (0.519-1.108)	1.634 (0.691-3.864)
Peer relationships	1.204 (0.878-1.650)	1.085 (0.747-2.435)	1.222 (0.869-1.718)	1.204 (0.878-1.650)	1.085 (0.747-2.435)	1.222 (0.869-1.718)
Health complaints	0.935 (0.733-1.193)	0.912 (0.626-1.330)	0.935 (0.763-1.145)	0.571* (0.375-0.868)	0.912 (0.626-1.330)	0.694* (0.510-0.945)
Tobacco use	1.103 (0.700-1.739)	0.840 (0.449-1.552)	1.013 (0.700-1.466)	0.595 (0.297-1.195)	1.159 (0.449-1.552)	0.841 (0.509-1.389)
Alcohol use	0.869 (0.663-1.138)	0.746 (0.416-1.341)	0.959 (0.675-1.361)	1.117 (0.718-1.739)	0.746 (0.416-1.341)	0.959 (0.675-1.361)

*Chi square test, p < 0.05

Only males that met PAGL had a significantly better BMI (Italian boys p = 0.023; Tuscan boys p = 0.012).

Physical activity and negative health indicators

Considering the pattern of association of PA and negative health behaviour indicators, the results do not show a significant relationship between cigarette smoking and/or alcohol use and having less than 60 minutes of physical activity seven days a week. However, it is interesting to note that in the Tuscan sample, more health complaints was a protective factor for PAGL (OR = 0.694, p < 0.05), mainly for boys (Tab. IV).
In the Tuscan sample, meeting the PAGL was associated with less alcohol use (p = 0.04).

Discussion

In this analysis regular PA has been consistently associated with positive health indicators. To the contrary high SBM use was associated with worse physical health, quality of life, quality of family relationships and breakfast frequency. Even though the extent of some of these relationships was small, the fact that the results was constant considering various health behaviours and across different geographical areas lead to the conclusion that PA and SBM use may be considered as general indicators of physical, psychological and social health.
The results provide a solid base for the promotion of PA and a reduction in the use of SBM in adolescents. The potential general positive effects regular PA as part of a healthy lifestyle includes amongst others a general sense of well-being, which in turn might promote a higher quality of psychological and social functioning [6, 10]. PA has proven to also have positive effects on mood [5] and cognitive functioning [46], which lead to believe that also the personal and social spheres of life might benefit from PA.
The negative indicators associated with SBM use may be related to the fact that the use of SBM promotes a more passive lifestyle. Moreover, TV viewing signifies that adolescents are not engaging in other activities such as social interactions, or focusing on personal or social issues. An active involvement with the environment rather than a passive observation thereof has been linked with a more developed sense of competency in youth [47].
The patterns of PA and SBM use have shown clear relationships with fruit consumption and breakfast frequency. These relationships were among the most significant in both samples considered. Children, who eat breakfast regularly, generally spend less than two hours a day in front of TV/PC. Breakfast omission in physically active children contrasts with their increased energy requirements and, in accordance with our study, often it is replaced by televisions programs [37], this finding can be particularly worrying given the relationship between high energy intake and TV viewing in increasing overweight.
Both in Tuscany and Italy there is a strong association between PA and fruit consumption, the results support a transfer effect where very active children are also more likely to eat more fruit. Although increased fruit intake is an important aspect of obesity prevention, it needs to be coupled with a decreased consumption of food with a high fat and high sugar content and increased PA. More research is needed to understand the mechanisms and moderators (e.g., gender) which influence the relationship between PA and nutrition behavior.
In Italy the quality of peer relationships was positively related to PA. It has been clearly demonstrated that peer interactions are environments for PA and peer influences represent a motivating factor for PA [48]. The relationship was not significant considering SBM use, although peer interactions and use of the media are ubiquitous elements of adolescence, and it is possible that engagement with peers is a reflection of engagement in the adolescent culture [49].
When considering the negative health indicators, it emerged that time spent watching TV/PC was related to two of the three negative health indicators in an independent way in the Tuscan sample and a third (alcohol use) in the Italian sample. These results are consistent with previous studies [22]. Tobacco use is a clear exception, representing a protective factor for SBM use. This finding can be explained by arguing that higher SBM use means more time spent in front of the TV/PC, activities typically confined to a home environment where the possibility of smoking is limited.
A more complex scenario emerged when observing PA and negative health indicators. In Tuscany, but not in Italy, PA was positively related to health status, children meeting PAGL registered less health complaints. The trend appears to be opposite, as shown in other studies, where PA and sport activities is associated with physical injuries [22].
No significant relation emerged when meeting PAGL and cigarette consumption was considered in different age and gender groups. This was true for both samples. Similar studies suggest that engaging in PA in adolescence is associated with lower rates of smoking during adolescence and adulthood [3, 28].
Adherence to PAGL, perceived health status and the quality of peer relationships were found to be better in Italian youth; Tuscan youth reported slightly more SBM use, regular breakfast consumption, fewer health complaints and a higher quality of family relationships.
The overall pattern of the relationship between PA and SBM use with positive and negative health indicators was fairly consistent across the two samples considered. PA seems to influence physical health status positively in both samples but on a significantly higher level in Italian one. It is possible that there is a PA threshold that requires a minimum amount of PA for this to have an impact on the physical health status [7] or may be limited only to vigorous PA [8]. It emerged that students in Italy were more active than their Tuscan counterparts, and as such it may appear that there are more students with PA levels above the set threshold. This threshold effect might also be influenced by gender differences insinuating that there might be different threshold for males and females. In fact, 4 out of the 11 relationships tested in this study involving PA, in both Italy and Tuscany, showed a significant for males but not for females. Gender differences also emerged in SBM use. SBM use

was associated with more health complaints in female students. The results show the importance of considering gender differences when exploring the relationships between PA and SBM use. There was a negative relationship between SBM use and physical health status in both samples considered. However this relationship was more noticeable in the Tuscan sample. Given the lack of evidence available exploring the relation between SBM use and health indicators we can only speculate about the possible relations. One possible explanation would be that expectations for the level of SBM use are different in these two areas. It can be noticed that the essential pattern is the same across country and region, which means that the primary conclusions of this study are applicable to both samples. On the other hand these geographical areas share many cultural similarities, this said, such regional similarities may have been taken into account for potential differences across studies.

Conclusions

The study has various limits that need to be taken into account in the interpretation of the results. The data are cross-sectional, as such it do not indicate a causal relationship between PA and SBM use and the various other health indicators considered. In some cases the relationships between PA and SBM and the other health indicators are rather weak, even though statistically significant. An additional aspect to take into consideration is that the data collected for this survey has been self-reported by participants. Data collected through self-report may signify that some errors could be introduced attenuating the statistical relationships, this suggests that the actual relationships between the variables considered in the study might be even stronger. However, the large sample size and the rather consistent trend of results across countries indicate that these are solid effects and but studies replicating these results in other samples is needed to confirm the generalisability of these results. The current research in the field considering the correlation of PA and SBM with other health behaviour is limited to variables like aggression and substance use. The results of this study show that in adolescents PA is positively correlated with various health, psychological and social outcomes. The analysis carried out on PA and SBM, showed that the adolescent use of SBM adversely predicted these positive and negative findings, independently of PA behaviors.
The results also suggest that interventions targeting one of either PA or SBM in order to influence the other might not be effective. Although SBM is a sedentary behaviour the results suggest that it is not to be collocated on the opposite end of the dimension of PA. As such interventions aiming specifically at SBM use and PA are suggested as this might prove to be more effective.
Research was extended to the identification of psychological and behavioral health benefits of PA and risks related to SBM use. Such research could suggest a potential mechanism for these relationships, and shed light on potential public health concerns and educational efforts to motivate adolescents to engage in more PA while discouraging excessive SBM use. Region-specific differences should be taken into consideration for future studies of these relationships and the potential causes for such differences.

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ORIGINAL ARTICLE

Asymptomatic malaria parasitaemia using rapid diagnostic test in unbooked pregnant women in rural Ondo-south district, Nigeria

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Key words

Booking • Insecticide-treated • Malaria • Net • Pregnancy

Summary

Background. *Malaria is a major contributor of maternal and peri-natal morbidity and mortality. The disease may be asymptomatic despite sequestration of parasitized red blood cells in the placental micro-circulation with antecedent complications. In such condition, it may also be difficult to identify the malaria parasite by the peripheral blood film microscopy, thus the need for use of simple but reliable tool for malaria parasite diagnosis.*
Objective and method. *To determine the prevalence of asymptomatic malaria parasitaemia using the Rapid Diagnostic Test in pregnant unbooked women seen in a primary health centre during a malaria control campaign programme in rural Ondo-south, District Nigeria.*
Results. *Prevalence of asymptomatic malaria parasitaemia was 25.9%. Only 3 (3.5%) of the 85 women had the long lasting insecticide-treated nets. There was no significant association between malaria parasitaemia, and the age group, parity and gestation age.*
Conclusion. *Given the high prevalence of asymptomatic malaria in pregnancy, routine screening for malaria at booking and scaling-up of other malaria control strategies such as the use of long lasting insecticidal-treated nets and intermittent preventive therapy for pregnant women are recommended.*

Introduction

Malaria poses enormous public health burden worldwide [1]. Pregnant women and children under the age of 5 years are at risk of severe disease and mortality. The burden of malaria in pregnancy in sub-Saharan Africa is caused mainly by *Plasmodium falciparum* [1]. In malaria holo-endemic areas, malaria in pregnancy may remain asymptomatic despite sequestration of parasitized red blood cells in the placental micro-circulation with antecedent complications [2]. These complications include chronic anaemia, post-partum haemorrhage and death. The impact on the foetus is usually from maternal infection of the placenta and maternal anaemia resulting to low birth weight, prematurity, still birth, abortions, intra-uterine growth restriction, as well as congenital malaria [1, 2].
Prevalence rates for malaria parasitaemia in pregnancy (using microscopy) in hospital-based surveys in different parts of Nigeria included 3.1% in Sokoto in the north-west [3], 9.0% in Jos in the north-central [4] 27.4% in Lagos in the south-west [5] and 39.1% in Awka in the south-east [6].
Most of the available data were from urban areas, whereas most of Nigeria is rural [7]. This anomaly partly derives from the difficulty in conducting microscopy in rural areas because microscopists are few and power supply is erratic. However, Rapid Diagnostic Test (RDT), now recommended by the World Health Organization (WHO) for diagnostic purposes where microscopy is unavailable [8, 9] is not yet widely used in surveys in Nigeria.
The objective of this study therefore was to determine the prevalence of asymptomatic malaria parasitaemia in pregnant unbooked women in a rural area using the RDT. The findings from this study will add to the body of knowledge of asymptomatic malaria parasitaemia in pregnant women living in rural areas as well as give information on the usefulness of RDT for malaria diagnosis.

Materials and methods

This was a cross sectional descriptive study and was carried out in June 2011. The study site was Primary Health Care (PHC), Odo-Aiye; a rural community in Okitipupa Local Government Area (LGA) located in Ondo-south District, south-west Nigeria. The LGA lies within the equatorial evergreen rain forest of Nigeria where malaria is stable with no seasonal variation [1]. The major occupations of the inhabitants are farming, timber felling and lumbering [7].
Ethical clearance was obtained from the Ethics and Research Committee, University of Benin Teaching Hospital, Benin City, Nigeria. Verbal permission to conduct the study in the PHC was obtained from the Director

of the PHC. The written informed consent was read, interpreted and explained in the local dialect by trained research assistance to the participants; following which each participant then gave a verbal consent before being recruited in the study.

Recruitment of subjects was during the campaign for malaria control at the PHC, Odo-Aiye. Participants for this study included all pregnant women who were in attendance during the malaria campaign program. Pregnant women who though were present during the program but had already booked at the PHC or in any other organized health facility were excluded from this study. Pregnant women who had fever or who received antimalaria drugs in the preceeding two weeks to the study and those who were on intermittent preventive treatment (IPT) were also excluded from the final analysis of the study. Fever was defined as axillary body temperature ≥ 37.5°C or history of fever in preceeding 7 days to this study [1].

A total of 116 pregnant women attended the campaign program. In line with aforementioned criteria, 31 were excluded from the study because they had booked in the PHC; of whom 4 had received IPT for malaria and another 4 had fever during the period of recruitment for this study.

A validated questionnaire was administered to the participants by one of the authors and assisted by a trained research assistance who verbally translated the required information in the questionnaire to respondents where necessary. The questionnaire contained questions about the participants' demography, whether or not she had long lasting insecticide-treated net (LLIN), and whether she slept under the net. Family social class was obtained by the method proposed by Olusanya, Okpere and Ezimokhai [10], using level of education of the participant and the occupation of her husband. In this method of classification of social class, specific scores (0, 1, and 2 for the woman's level of education; and 1, 2 and 3 for her husband's occupation) was allotted to each participant and the sum of these scores was used to describe social class as I, II, III, IV, and V. Participants with scores I and II were classified as upper class, III-middle class; IV and V as lower class. The gestational age of the participants was calculated from the first day of the last menstrual period (LMP).

Each subject was then tested for malaria using the RDT kit for malaria parasite- *Plasmodium falciparum* (pf). The RDT was a one step invitro diagnostic test for qualitative detection of pf antigen known as the histidine-rich protein II (HRP-II) in capillary blood [11]. The RDT kit used for this study was the Standard Diagnostic (SD) Bioline malaria antigen pf test (Kyonggi-do, Korea). Each pack of the RDT kit used in this study was from lot number 082048 (reference number 05FK50) and contained 25 cartridge kits or test devices, 25 un-opened alcohol swabs, 25 appropriately calibrated pipette loop and 25 sterile lancets. One pack was meant for testing malaria parasite for 25 people and a new test cartridge or test device was used for each participant. Internal evaluation of the RDT kits which was certified by WHO showed that the SD Bioline RDT kit has 100.0% sensitivity for blood with > 50 parasite/μL and 98.0% specific for *P. falciparum*. The kits had storage temperature range of one to 40°C which was within the average environmental temperature in Ondo and the other southwestern region of Nigeria.

Malaria parasite test was performed by one of the authors who had received certified training on the use of RDT for malaria diagnosis. Procedure for the test was as follows: the pulp of the fourth finger of the subject was cleaned with an alcohol swab and when it was air dried, the cleaned area was pierced with the sterile lancet. A capillary pipette loop was used to collect 5.0 μL of blood (a black line calibrated on the pipette loop provided in the test kit). The blood was then transferred to the sample window on the test kit cartridge. Four drops of provided buffer was then added to the buffer well window on the cartridge. Each test kit was read between 15-30 minutes. Malaria positive was by the presence of two colour bands ('T' Test line and 'C' Control line) within the result window, no matter which band appeared first and no matter the intensity of the colour band. Negative result was by presence of only one colour band 'C' (Control line) within the result window. If the control band failed to appear within the result window or no colour band at both the 'T' and 'C' regions, the result was considered invalid and the test was repeated for that particular subject using a new test device.

Women with positive malaria parasite received the recommended anti-malarials in line with the national guideline for treatment of malaria in pregnancy.

Data analysis

The data obtained for this research was entered into the Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc Chicago, Illinois, USA) spread sheet where analysis was also done. The major outcome variable was the presence of malaria parasitemia. Associations with this variable were tested using chi-square and student t tests as appropriate. The level of significance of each test was set at $p < 0.05$.

Tab. I. Demographic data of the subjects.

Demographic data	n = 85 (%)
Age	
18-24 years	30 (35.3)
25-31 years	46 (54.1)
32-38 years	8 (9.4)
39-45 years	1 (1.2)
Educational status	
No formal education	7 (8.2)
Primary	22 (25.9)
Secondary	54 (63.5)
Tertiary	2 (2.4)
Social class	
Upper	1 (1.2)
Middle	9 (10.6)
Lower	75 (88.2)

Results

Mean (± SD) age of the 85 pregnant women recruited for this study was 26.1 ± 4.7 years (age range 18-40 years); mean gestational age was 27.1 ± 8.1 weeks (range 6-40 weeks). Forty-five (52.9%) were in the third trimester, 35 (41.2%) were in second trimester and 5 (5.9%) were in the first trimester. Forty-eight (56.5%) were multipara, 20 (23.5%) were primigravidae and 17 (20.0%) were grand multiparous women. Fifty-four (63.5%) of the women had secondary education, 22 (25.9%) had primary, 2 (2.4%) had tertiary education and 7 (8.2%) had no formal education. Table I shows the age group and social class of the respondents. Majority (88.2%) of the women were from the lower social class and most were 31 years and below.

The prevalence of malaria parasitaemia in this study was 22 (25.9%). There was no significant difference in mean age of infected (26.5 ± 5.1 years) and non-infected subjects (25.9 ± 4.6 years); (t = 0.46, p = 0.65, 95%CI = -1.78, 2.85).

Only 3 (3.5%) out of the 85 women owned LLIN; and only one of the three slept under a LLIN. Reason given by the other two who did not sleep under the net was that the net was difficult to mount. Malaria parasitaemia was not significantly associated with age, parity, gestational age and social class (Tab. II).

Discussion

The high prevalence of asymptomatic malaria in pregnancy in this study supports similar findings in other stable malarial transmission areas [1, 3-6]. Susceptibility to *Plasmodium* parasitaemia has been linked to the level of antibodies to placental sequestrated parasites [2]. The most preferentially adherence is to the chondroitin sulphate-A (CSA) receptors expressed by the syncytiotrophoblasts in the placenata [12]. This adherence is common in primigravidae and women in second pregnancy as the anti-adhesion antibodies against CSA binding parasites usually develop in women after successive pregnancies [2]. The consequence of untreated asymptomatic malaria parasitaemia in pregnancy is enormous [3-6], therefore adequate and prompt implementation of malaria control policy for pregnant women should be intensified to protect these women and their un-born babies from the antecedent complications of malaria disease.

In most African countries, pregnant women usually book for antenatal care by the 2nd trimester [13], there is the need for malaria parasite screening as a routine test at booking to identify and treat asymptomatic malaria parasitaemia with the recommended anti-malarial drug before the commencement of IPT. Some authors have also suggested that in areas with high prevalence of asymptomatic malaria in pregnancy, it may be more appropriate to institute intermittent screening for malaria parasite using simple tools such as the RDT as well as treat the individual with presence of asymptomatic malaria parasitaemia as alternative to IPT especially in areas where sulphadoxine-pyrimethamine (SP) resistance is very high [14].

Malaria detection using RDT is a major break-through in malaria control [8]. Though this study did not compare the prevalence of malaria parasitaemia by RDT and microscopy, the prevalence found (25.9%) was comparable to 27.4% observed in a study among pregnant women using microscopy in Lagos, in the same south-west Nigeria [5]. Malaria screening and diagnosis in pregnancy using RDT especially at booking may also be a cost effective malaria control strategy in pregnancy and should be an integral component of malaria control in pregnancy in holo-endemic regions.

Only 3.5% of the pregnant women had the LLIN. The use of the LLIN is now one of the most important preventive tools against malaria. LLIN has been shown to reduce the number of infective mosquito bites by 70.0 – 90.0% in a variety of ecologic settings as well as reduce the prevalence of malaria in children and adults [15, 16]. Unfortunately, most women of reproductive age group in Nigeria do not possess the LLIN and the few who had the LLIN barely sleep under the net [15].

Tab. II. Malaria parasitaemia and age group, gestation, parity and social class of the subjects.

	Malaria Parasitaemia			
	Positive (%)	Negative (%)	χ^2	p-value
Age group				
18-24 years (n = 30)	5 (16.7)	25 (83.3)		
25-31yeras (n = 46)	14 (30.4)	32 (69.6)	4.69	0.20
32-38 years (n = 8)	2 (25.0)	6 (75.0)		
39-45 years (n = 1)	1 (100.0)	0 (0.0)		
Trimester of gestation				
First (n = 5)	2 (40.0)	3 (60.0)		
Second (n = 35)	12 (34.3)	23 (65.7)	3.35	0.19
Third (n = 45)	8 (17.8)	37 (82.2)		
Parity				
Primigravida (n = 20)	7 (35.0)	13 (65.0)		
Multipara (n = 48)	10 (20.8)	38 (79.2)	1.62	0.45
Grand multipara (n = 17)	5 (29.4)	12 (70.6)		
Social class				
Upper (n = 1)	0 (0.0)	1 (100.0)		
Middle (n = 9)	3 (33.3)	6 (66.7)	0.62	0.73
Lower (n = 75)	19 (25.3)	56 (74.7)		

Limitations of the study

The observations were not sufficient to permit statistical significance in the observed differences. In addition, microscopy on the specimens could have offered an opportunity to assess the validity of the RDT results in the community.

Conclusions

This study showed that one-quarter of the pregnant women had asymptomatic malaria parasitaemia and that RDT can be an invaluable instrument for malaria diagnosis in rural areas. The authors therefore recommended routine malaria parasite screening for all pregnant women at booking as well as scaling-up the availability of LLIN for vector control and the RDT kits for malaria diagnosis in rural areas. Health education on the use of LLIN as important tool for control of malaria should be intensified in malaria control National Advocacy, Communication, and Social Mobilization Strategic Framework and Implementation Plan in Nigeria.

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ORIGINAL ARTICLE

Baking soda and salt in bakeries of Mehrdasht (Najafabad), Isfahan, Iran: a survey on a typical rural population in a developing country

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Key words

Baking soda • Salt • Bread • Bakeries • Iran • Sodium bicarbonate

Summary

Background. *Bread is a valuable source of proteins, minerals and calories. Baking soda prevents the absorption and digestion of bread and more salt used in production of bread also causes different diseases. This study was conducted to determine the amount of soda and salt in bakeries.*
Method. *Cross-sectional descriptive study was carried out on 50 bakeries district during 2009. 400 samples were collected in four steps randomly. The standard PH < 6.2 indicative of no consumption of baking soda in bread and salt less than 2g/100 g was considered as the reference.*
Results. *The PH less than 6.2 was seen in 91.5% of samples and analyzed by random effect analysis. In 64.5% of samples, the amount of salt was more than the standard.*
Conclusion. *The amount of baking soda used in the bakeries was not high; bakers either had no enough knowledge about the amount of salt or had more other reasons. Drastic measures are recommended.*

Introduction

Bread is one of the major contributors of human diet [1] that playing an important role in the primary energy needs of Iranian families [2], is considered as the most important source of energy, pr*f*otein, minerals and vitamins [3-5]. Almost 60-65% of the protein and calories and near 2.3 g of minerals come from bread [6], which is in the case of its complete fermentation, most nutrients of natural wheat and flour can be metabolized, digested and quickly absorbed by the body because of phytic acid that combines with minerals such as iron and calcium and making them insoluble in water and thus preventing the absorption of wheat minerals.
Phytic acid can be inactivated during baking process. For this, enzymes, called phytases, inactivate during fermentation, thus enhance the nutrient absorption [7]. Phytase can be effective only when it is used with yeast or sourdough and let it be left for an appropriate length of time [8, 9] and in breads made with the aid of baking soda because of the absence of phytase enzyme, the minerals of bread can not be digested and absorbed.
Yeast is a living and single-celled organism that converts starch and sugar into alcohol and carbon dioxide during a complex process and makes the digestion easy for the human digestive system through breaking down the long chains of starch [10]. Carbon dioxide and alcohol produced by yeast form bubbles that make the dough rise, and give bread its spongy texture. Moreover, the alcohol and acid produced during fermentation process remove the pathogenic microorganisms from bread and enhance its hygienic production. Having low PH level due to producing acid and colloidal state of gluten can make the durability of bread longer.
The yeast containing a lot of proteins, minerals and vitamins is routinely added to bread for its better processing. The most distinguishing advantage of yeast for consumers is adding a pleasant taste and aroma to bread which is due to creation of aromatic acids produced by yeast [7].
Another commercial alternative for processing food is adding baking soda to dough which due to its lack of fermentation causes some disorders in digestion and absorption of effective minerals and bivalent, thus leading to gastroenteritis [11]. Using baking soda in bread increases the absorption of heavy metals (e.g. lead and mercury) which in long-term can make severe disorders [12]. Despite the numerous advantages of yeast, studies have shown that only 45-55 percent of the bakeries in Iran actually use industrial yeast or leaven and the amount of baking soda in bread varies from 2-47%.
Considering the importance of properties and advantages of using the yeast and disadvantages of using baking soda in bread processing, the strict supervision on eliminating the soda in bread production is considered an important priority in health center policies. Since bread is a highly consumed food in our community, the existence of large and uncontrolled amount of salt in bread may also lead to cardiovascular diseases, hypertension [13]. Moreover, other diseases (e.g. gastric cancer, osteoporosis, and bronchial hyperactivity) are also caused by in-

creased salt intake [14]. Nowadays, most bakers (40%) have no information on the amount of salt added to a known amount of flour [15-17]; few of them (26.5%) in cases use salt less than and other cases more than the standard limit [17]. The average salt used in Mashhad bakeries was 1.95g in 100 g [18] and in Isfahan 2.66 g per 100 g which are more than the standard limit [19]. Therefore, regarding the high average consumption of bread among low-income, traditional and rural families and the notion that the magnitude of some problems related to malnutrition (e.g. iron deficiency) can be decreased by improving the quality of flour and bread and also the scarcity of such studies in small towns and rural areas, the aim of the present study was to determine the amount of baking soda and salt used in bread bakeries of Mehrdasht.

Tab. I. Frequency distribution of the amount of PH and salt used in bakeries.

Salt < 2% in bread samples		PH < 6.2 in bread samples		Number of samples	Frequency Type of bread
Percent	Number	Percent	Number		
(40.2)	74	(93.4)	172	184=n	Taftoon
(37.5)	30	(90)	72	80=n	machine-made
(25)	4	(100)	16	16=n	Sangak
(25)	2	(100)	8	8=n	Barbari
(18.75)	6	(87.5)	28	32=n	Lavash
(32.2)	18	(96.5)	48	56=n	Home-made
(33.4)	8	(91.7)	22	24=n	Dried
(35.5)	142	(91.5)	366	400	Total

Tab. II. Frequency distribution of the availability of yeast and the numbers of bakeries.

The amount of yeast used in bakeries		Number of bakeries	Number of bakeries Type of bread
Percent	Number		
(86.9)	20	23 = N	Taftoon
(80)	8	10 = N	machine-made Taftoon
(100)	2	2 = N	Sangak
(100)	1	1 = N	Barbari
(75)	3	4 = N	Lavash
(100)	7	7 = N	Home-made
(66.7)	2	3 = N	Dried
(80)	43	50 = N	Total

Materials and methods

This cross-sectional descriptive study was conducted in all bakeries of Mehrdasht district (Najafabad), including Dehaq, Alavijeh and eight other related villages (Ashn, Goldareh, Damab, kheyrabad, Khundab, Hasinjeh, Ali abad and Hussein abad) during 2009-10

From a total number of fifty bakery units taken part in the study and officially active in Mehrdasht, the detailed numbers of units were as follows: Taftoon, 23; machine-made bread, 10; Sangak, 2; Barbari, 1; Lavash,4; dried, 3 and home-made, 7.

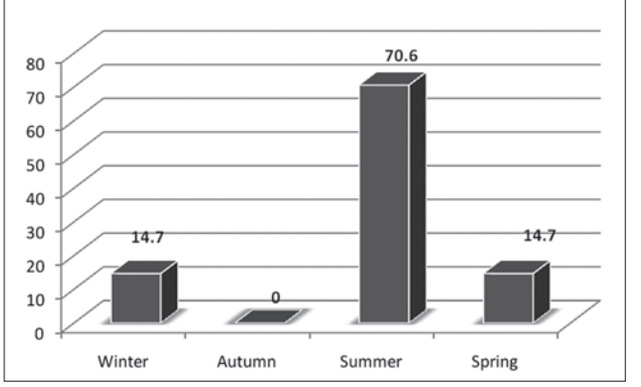
Samples were randomly collected from all bakeries in four steps (2 loaves from first batch) and sent to the laboratory to determine the values of the variables. Sampling was done in random days with no bakers' knowledge of the research intention. The measurement of pH was done in accordance with the standard of Iranian Institute for Standard and Industrial Research (ISIR, 1999 issue No.2628) and using an electrical PH meter [20]. Samples with normal PH (PH < 6.2) were considered as having no baking soda and above the limit containing baking soda. The amount of the salt in samples was determined according to the standard of (ISIRI issue No. 2628), Standard No. 2628. The amount of salt < 2 g/100 g was considered as standard level and more than that as the nonstandard. Presence or absence of yeast (leaven or sourdough) in the bakeries was determined in accordance with the recommendations of Environmental Health Guidelines. The obtained data were analyzed using Random effect and descriptive statistics.

Results

The PH for 91.5% of the samples was less than 6.2. In general, the PH of most samples taken from Lavash bread was above 6.2. This study showed no significant difference between the PH of samples and the type of bread (P = 0.35) The amounts of salt in 142 cases of all samples (35.5%) were standard. The highest amount of salt in bread production was in Taftoon (Oven) in 74 cases (40.2 %) and Lavash (18.75%) (Tab. I.).

Yeast was used in 80% of the bakeries and the lowest level of yeast was seen in dried bakeries (66.7%) (Tab. II). Regarding the frequency distribution of baking soda in different seasons of the year, summer season in 24 cases (70.59%) had the highest frequency for baking soda use with a p > 6.2 in bread samples (Fig. 1) (P < 0.042). There was no significant difference between salt and season (P = 0.51).

Fig. 1. Percent Frequency distribution of PH > 6.2 used in different seasons.



Discussion

The results of this study indicated that the PH in 8.5% of the bread samples taken from the bakeries was greater than 6.2. The PH level of bread in Isfahan, Yazd, Chaharmahal & Bakhtiary, Savad kooh, Kashan, Shahroud, and the total mean in the country were 8% [16], 12% [16], 5% [18], 11.8% [21]), 9.8% [22], 2% [23] and 9.1% [18], respectively were in accordance with the results of this study.

The level of baking soda used in bakeries in Ilam, Tehran, Rafsanjan, Kerman have been reported 27% [17], 17 % [25], 22% [26] and 47.7 [27], respectively. In addition, it has been reported that 25% of Tehran bakeries apparently used baking soda in producing bread and only 45-55% of bakeries used industrial yeast which weren't in accordance with the results of the present study. According to the results of the present study, it seems that the small towns and rural areas, like big cities, have made progress in reducing baking soda in the bread; the results taken are contrary to other studies. The reason for this discrepancy may be that the bakers in Ilam, Tehran and Rafsanjan have inadequate knowledge about the disadvantages of soda or in general about the principles of the production of the most common types of bread baked in each region. In general, today 42% of the bread produced in our country is Lavash [7] and the highest amount of baking soda was used in Lavash, followed by Barbari. Moreover, the results of other studies showed that the amount of baking soda in Lavash bread were in Zahedan 60% [30], Gorgan 88.9 % [28], Islam-shahr 60% [30]. The amount of baking soda used for producing Barbari bread in Kashan was 39.1% [25].

Reportedly throughout our country, the barbari bread with 21.2% had the highest and Taftoon the lowest amount of baking soda [24]. Besides, as Taftoon bakeries were more than the Lavash bakeries in our study; therefore, the reason for the lower amount of baking soda in these bakeries may be attributed to the low number of Lavash bakeries. Only 10% of the bakeries in this study were Lavash (8%) and Barbari (2%) and then the remaining (46%) were Taftoon bakeries. And the apparent fact is that despite the lower numbers of Lavash and Barbari bakeries, those types of bread even contained more baking soda. Hence, considering the disadvantages of using baking soda instead of yeast (e.g. digestive disorders, disorder in calcium, phosphorous, and iron absorption) [7] and the level of knowledge of bakers regarding the disadvantages of soda, enough knowledge only in 28%; moderate to weak in 27% [28], the suggestion on providing trainings the appropriate use of baking soda in bread should be considered, especially for Lavash bakeries and in other stages through the acquired trainings, the knowledge of the bakers about the disadvantages of baking soda can be evaluated by repeated visits and supervision under legal considerations. The results of this study indicated the amount of salt used in 64.5% of samples exceeded the standard level.

In similar studies have been conducted in Mashahd, the average salt use (1.95g /100 g) reportedly exceeded the standard level [30]. In similar studies more than 85% of samples taken from Isfahan had salt more than standard and only 15% less than standard [19]. In addition, the amount of salt used in Sabzevar bakeries was 25 ± 2.07 g/100 g and researchers claimed that the number of samples with the salt level above the standard were relatively high [31].

The amount of salt in bakeries of Sistan and Baloochestan increased from 2.1 to 3.4 g/100 g during 2004-7 that was not only exceeded the standard but also had an increasing trend.

In researches done in Yazd and Rafsanjan, the level of salt (1.3g /100g) [26] was similar to the results of the studies done in Tehran and Yazd [16, 32]. The average amount of salt in Ilam was 1.34g /100g and 14% of bakeries used salt more than standard and also the required amounts of salt in 33.4% and 10.4% of the bakeries were less than and more than standard, respectively. To sum up, 43.8% of the bakers didn't have enough knowledge and skill for determining the standard level of salt for producing bread [33].

Conclusions

It seems that most bakers either do not have enough knowledge about the standard level of salt used for the production of bread or have some other reasons for using salt more or less than the standard (e.g. type of flour) or some other factors which need to be investigated in another series of studies.

To sum up, bakeries require strict supervision on using baking soda and especially salt for the production of bread. Hence, drastic control measures are recommended to control the amount of baking soda in bakeries by relevant agencies.

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Case report

Dermatosis caused by *Corythuca ciliata* (Say, 1932) (Heteroptera, Tingidae). Diagnostic and clinical aspects of an unrecognized pseudoparasitosis

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Key words

Entomodermatoisis • Lace bug • *Corythuca ciliata* • Urban green

Summary

The present article discusses three cases of human infestation by Corythuca ciliata (Lace bugs), a parasite of plane trees. The cases were all in the Piedmont region of northwest Italy and the symptoms involved a large number of hives on the subjects' bodies which were scarcely or not at all itchy and which spontaneously cleared up in all the cases in less than 24 hours. It can be concluded that the Lace bug can be an agent of insect-caused dermatosis and this should be considered in examining subjects who visit or live near wooded areas which are infested.

Introduction

Dermatosis caused by parasites is a dermatological pathology which correlates trophic or defensive activity in insects or arthropods and is in general limited to the dermoepidermal layer. Systemic reactions can occur in patients who have developed Type I allergic sensitization [1, 2]. From a clinical point of view classic entodermatitis is an acute inflammatory reaction with the symptoms typical of Lewis's triad: swelling, rash and itching [3]. The clinical picture is the result of several factors: pharmacological effects of substances in the arthropod's secretions or saliva which are toxic or cause itching, the organism's defensive and protective abilities [4], and the effects due to allergic sensitization.

The onset of dermatitis caused by insects is mainly determined by trophic activity of human and/or animal parasites (parasitical entodermatitis) or, more rarely, by phytoparasites [5], household pests [6] or by other arthropods in general (non-parasitical or pseudo-parasitical entodermatitises) [7, 8].

The best-known dermatitises caused by parasites are those caused by fleas, bedbugs [9] and mosquitoes [10], while those which are non-parasitic and caused by phytoparasites are less well-known [5, 11] and difficult to diagnose because it requires a high degree of general entomological and environmental knowledge.

Corythuca ciliata (Say, 1932) is a heteroptera belonging to the Tingidae family (Lace bug) originating from the Nearctic ecozone and is a parasite of plane trees (Fig. 1). It was first observed in Italy in 1964 in Padua [12] and subsequently has spread all over Italy [13]; it infests (at times heavily) the tree-lined boulevards in cities.

On plants the insect punctures the leaves which results in areas of discoloration; heavily infested plants can sustain diminished photosynthesis and drop their leaves prematurely.

Despite the phytopathological importance, bites on humans from *C. ciliata* have not been reported, but we present here the cases of three such individuals from the Piedmont region of northwest Italy.

Case studies

Case 1

In August 2011 a 23 year old man and 18 year old woman residing in the ASL CN1 Health Services Offices territory presented at the emergency department of the local hospital after having developed a rash during the previous night on the hands, neck and head which was

Fig. 1. Adult specimens of *Corythuca ciliata* (photo M. Dutto).

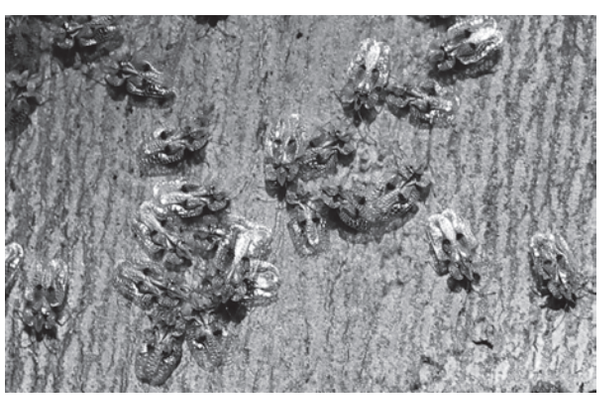
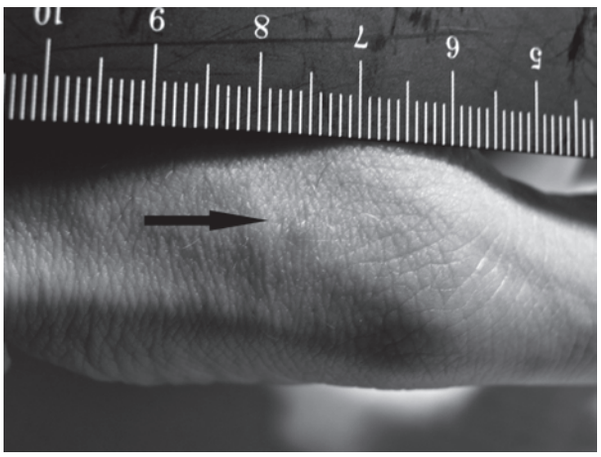


Fig. 2. Single hive caused by *Corythuca ciliata* from subject in Case 1 after approximately 8 hours after onset (photo M. Dutto).



characterized by approximately 100 tiny hives, 1 mm in diameter (Fig. 2). The lesions were irregularly distributed and were not itchy at the moment the subjects came to the ED; nor did they have fever and during anamnesis nothing particular emerged with regards to exposure to or contact with something infectious or chemical.
Given the clinical conditions the subjects were sent to the dermatology department where the attending physician suspected dermatosis caused by insects though due to the lack of symptoms hesitated to prescribe any treatment prior to consulting with an entomologist. The following day the hives had almost completely cleared up in both subjects.
An entomologist investigated the home and areas where the subjects had been in the 24 hours preceding the onset of their symptoms. The subjects' homes were free of *Cimex lectularius*, *Pulex irritans* and *Ctenocephalides felis*, as well as the principle blood-sucking mites (*Argas reflexus* and *Dermanyssus gallinae*). The evening prior to the eruption of hives the subjects had sat for a significant amount of time on a boulevard, under some plane trees, which it turned out were acutely infested with *Corythuca ciliata*. Subsequent examination of the clothes worn by one of the subjects that evening revealed specimens of the insect.

Case 2

A 48 year old woman residing in a second-floor apartment in the center of Turin was examined by her dermatologist in August of 2010 after noticing hives that had appeared and reappeared in the preceding two months on the dorsa of both feet. The hives were 1-2 mm in diameter and were neither itchy nor painful. The subject was in excellent health otherwise, without underlying conditions.
At anamnesis the dermatologist suspected the rash had been caused by insects and recommended that the subject be checked by an entomologist prior to prescribing treatment.
An entomological survey of the situation took into consideration the subject's home and other places she had been when the hives flared up. The absence of hematophagous insects was confirmed, but on the subject's balcony (where she spent a lot of time), there was an extensive quantity of *Corythuca ciliata* specimens, most likely from the adjacent boulevard which was lined with plane trees.
At the suggestion of the entomologist no therapy was prescribed; however it was recommended that the floor of subject's balcony be periodically treated with a permethrin-based product until the infestation on the trees was under control. The subject had no subsequent dermatological flare-ups.

Conclusions

The cases presented here can be classified as insect-caused dermatoses caused by pseudoparasites as the insects involved (*C. ciliata*) are not typically known to be human parasites. In both cases the dermatosis arose from intense plant infestation which resulted in specimens falling onto nearby surfaces which were occupied by the subjects [14]. Insect-caused dermatoses due to pseudoparasites are fairly infrequent events and are distinguished from parasitical dermatoses in that in the former, human reactions are not a result of the insect's primary behavior. These pseudo-parasitoses are typically characterized by being accidental and short-term.
C. ciliata's bite is painless and results in a small (1-2 mm) welt which is usually slightly or not at all itchy. They develop within 2-3 hours of the subject's being bitten but often go unnoticed due to the lack of symptoms. Even the actual moment of the bite usually is unobtrusive enough that it can be unobserved; indeed only one subject (Case 2) complained of discomfort. Signs and symptoms disappear spontaneously within 12 hours without further complications.
Scant reactivity is due to atypical exposure in humans to this insect's bite in addition to the probable inoculation to secretions which in themselves are not particularly toxic. The reaction appears to be a simple inflammatory response to an external irritation.
One problem relative to bites from *C. ciliata* is the diagnosis, which should always involve an entomologist given that the dermatological symptoms are nonspecific and this can lead to inappropriate or ineffective disinfecting of the areas in which the insects are found. Bites from plant parasites can be misdiagnosed and be attributed to mosquitoes [5].
When the suspected cause of dermatosis is entomological it is important to consult with an entomologist who can analyze the case and the environment in order to ascertain what caused the hives [15]. Correct diagnosis is crucial to prescribing the correct therapy as well as deciding the preventative disinfestation measures required in each case.
In diagnosing the typology of dermatitis caused by Lace bugs which infest plane trees a useful clue is to trace back where the subject went prior to the outbreak of the hives and to be aware if it included being in or near

wooded urban areas with plane trees. Pharmacological treatment is not necessary given the that pathology is self-limiting and that the species is not a vector of pathogenic agents. An emollient or moisturizing cream with or without plant extracts (e.g. aloe or calendula) is sufficient.

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